Functional Neuroanatomy of the Basal Ganglia

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OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

- List the **major components of the basal ganglia** and identify:
  - The **major receptive area** of the basal ganglia, the major **sources of input** to the basal ganglia and the nature of these inputs (i.e., excitatory vs inhibitory)
  - The **sources of basal ganglia efferent projections**, the major **targets** of these projections and the nature of these projections (i.e., excitatory vs inhibitory)
  - The major afferent and efferent connections of individual basal ganglia nuclei
- Define the **direct and indirect basal ganglia pathways**, including
  - The **individual nuclei** involved in these pathways, the **sequence** in which these nuclei receive signals and the nature (i.e., excitatory vs inhibitory) of these signals
  - The **net effects** of activation of the direct and indirect pathways on cerebral cortical activity
- List the **three major functional domains** that are influenced by basal ganglia activity

Learning Objectives, continued

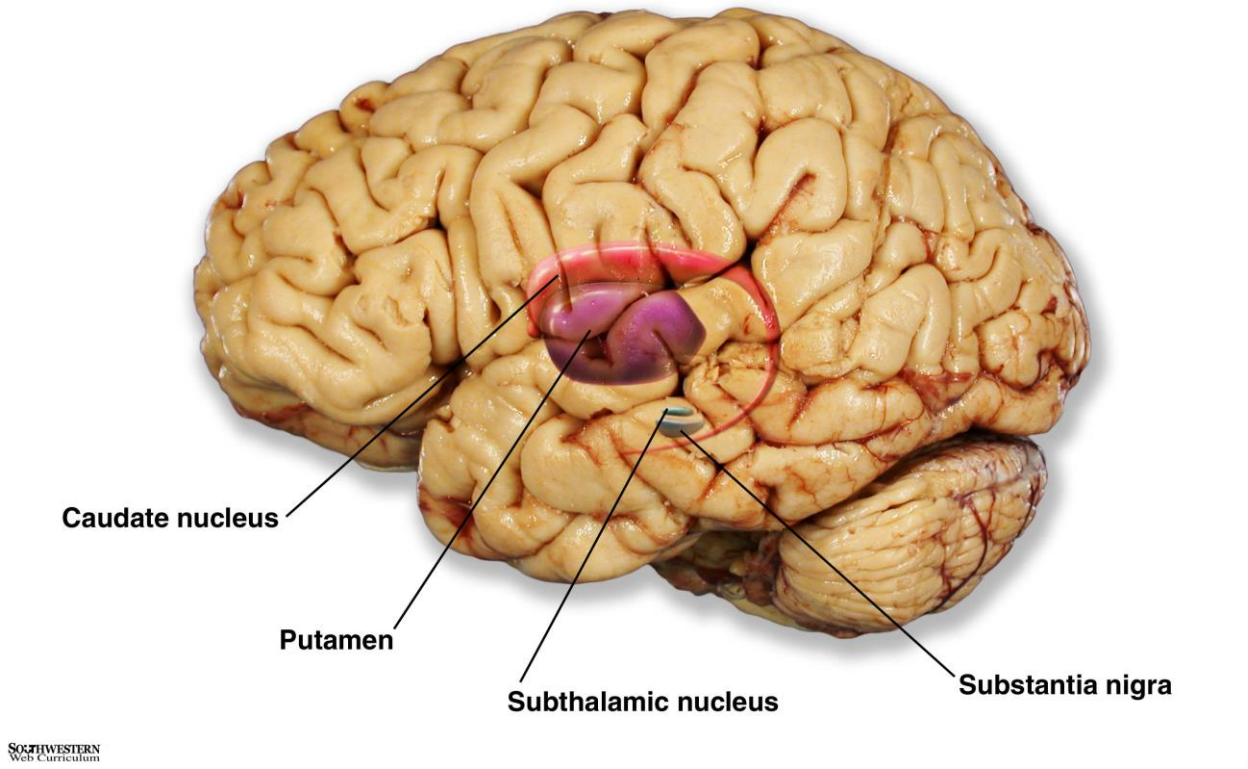
- Identify the neuroanatomical abnormalities that underlie the following basal ganglia disorders and the **derangements in the direct and indirect basal ganglia pathways** that account for the hyper- or hypokinesis encountered in each of these disorders
  - **Hemiballism**
  - **Huntington disease**
  - **Parkinson disease**

Functional Neuroanatomy of the Basal Ganglia

Outline

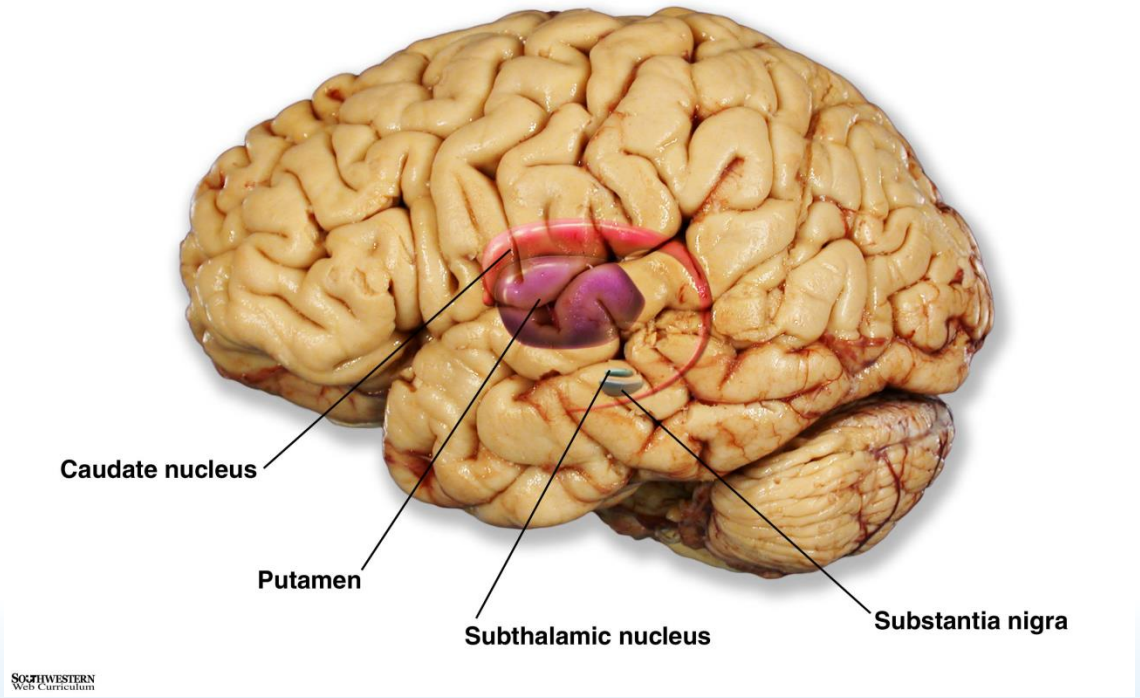
- **Overview** of the components of the components of the basal ganglia, **input** to the basal ganglia, **targets** of basal ganglia projections and basal ganglia **function(s)**
- **Review of individual basal ganglia nuclei** and their connections
- The **direct and indirect** basal ganglia pathways
  - **Functional domains** influenced by basal ganglia pathways
- **Abnormalities in basal ganglia circuitry** associated with selected motor disorders
  - Hyperkinetic disorders
  - Hypokinetic disorders

Relative positions of basal ganglia nuclei



Overview of basal ganglia circuitry

- Basal ganglia **components**
  - Striatum (caudate, putamen, ventral striatum)
  - Globus pallidus (internal and external segments) and ventral pallidum
  - Subthalamic nucleus
  - Substantia nigra pars compacta (SNc) and reticulata (SNr)



nucleus

- Most efferent projections from **globus pallidus (internal segment/GPi) and SNr** via
  - **ansa lenticularis** and **fasciculus lenticularis**

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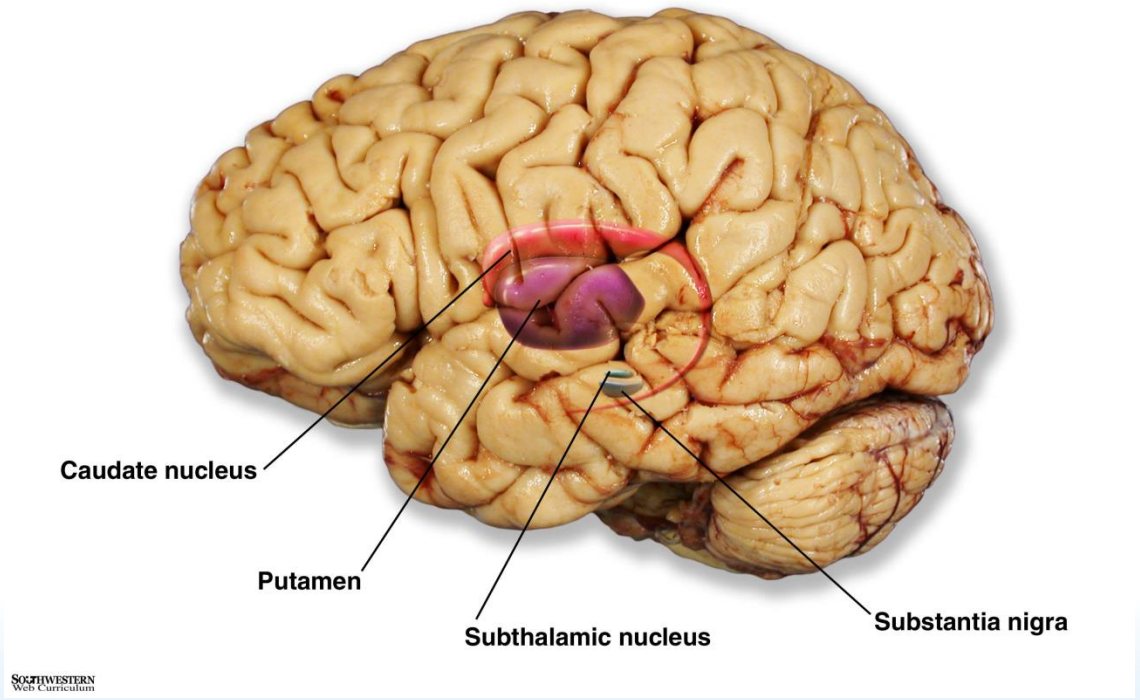
- Basal ganglia **afferents**
  - Major sources = **cerebral cortex** and **thalamus**
  - Most afferent projections received by **striatum**



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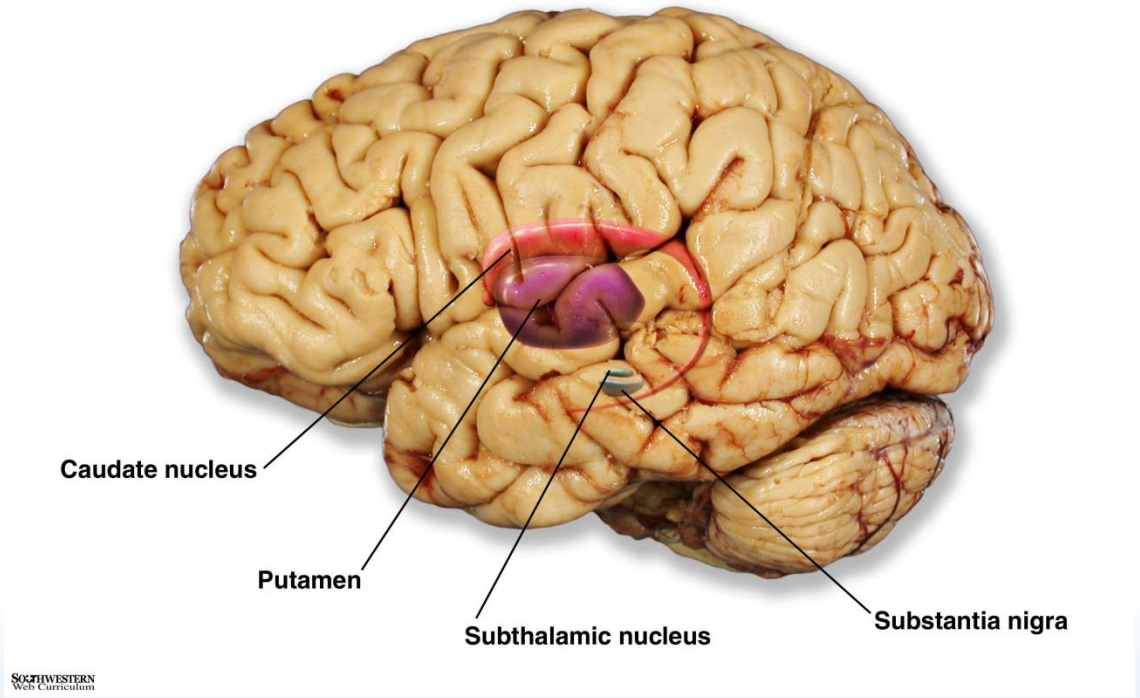
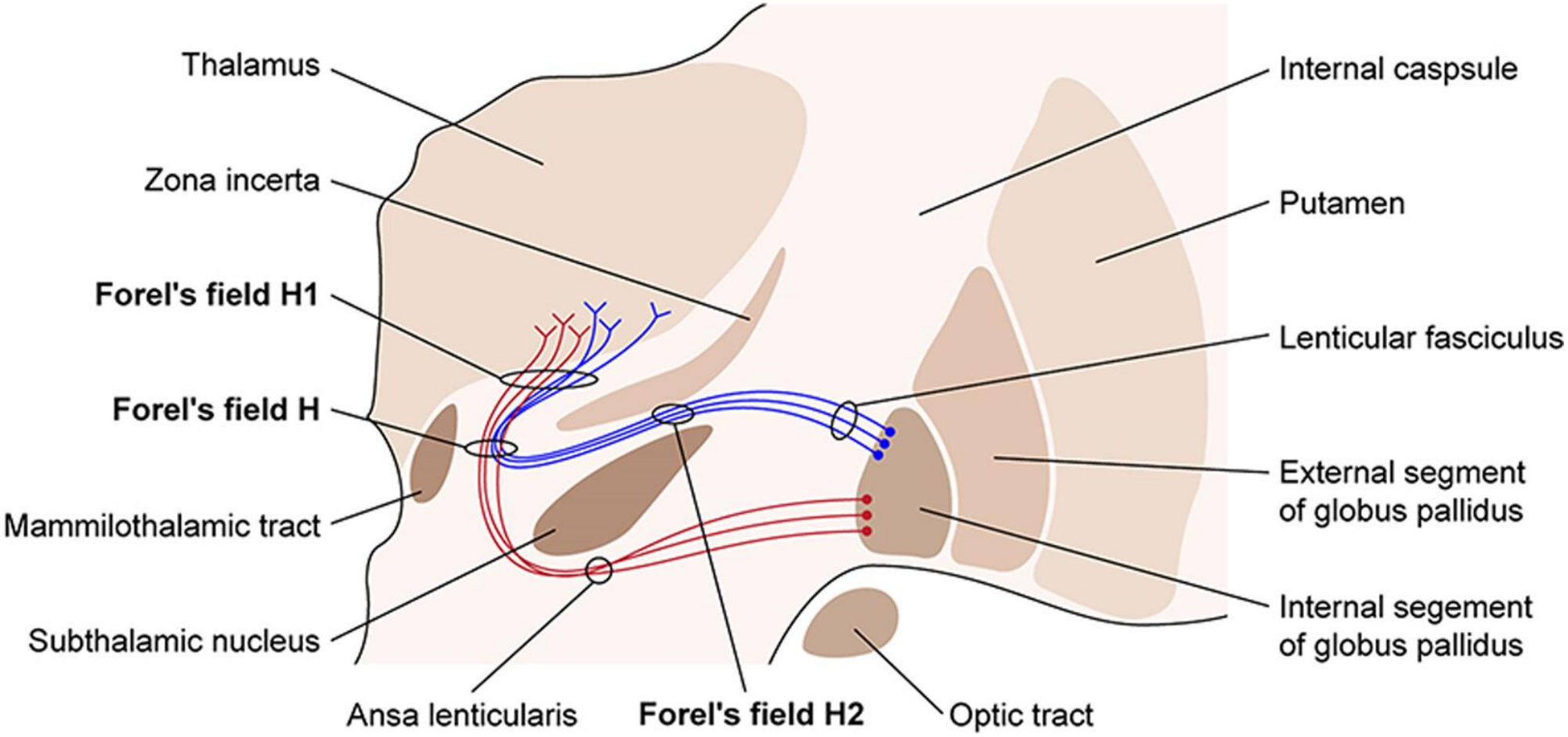
- Basal ganglia **afferents**
  - Major sources = **cerebral cortex and thalamus**
  - Most afferent projections received by **striatum**

- Basal ganglia **efferents**
  - Major target = **thalamus**
    - Additional descending projections to **pedunculopontine nucleus**
  - Most efferent projections from **globus pallidus (internal segment/GPi) and SNr** via
    - **ansa lenticularis** and **fasciculus lenticularis**

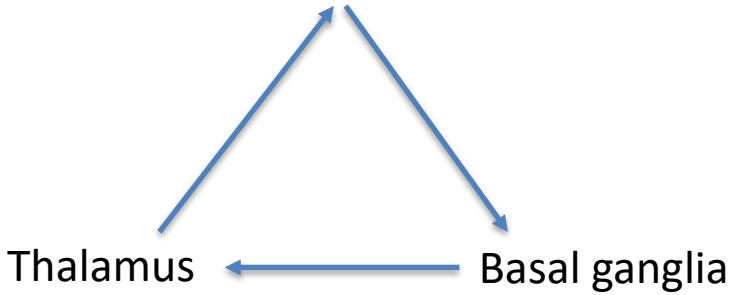


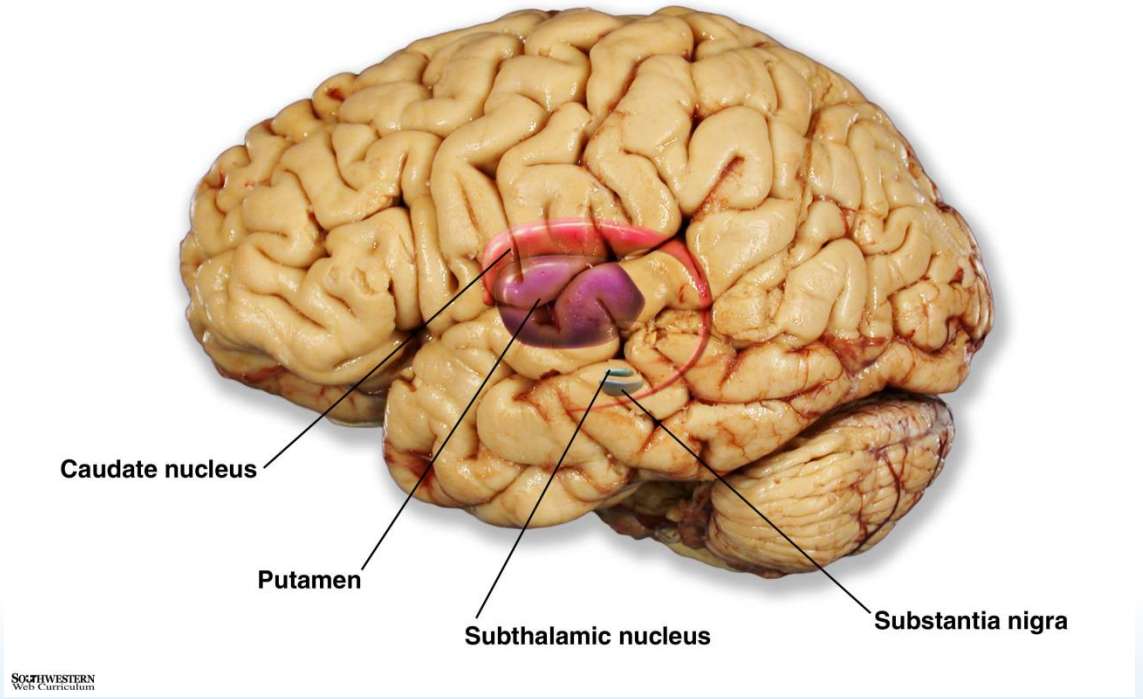


From Horisawa S et al: *Epilepsia Open* 2020; 6:225-229

Overview of basal ganglia circuitry, continued

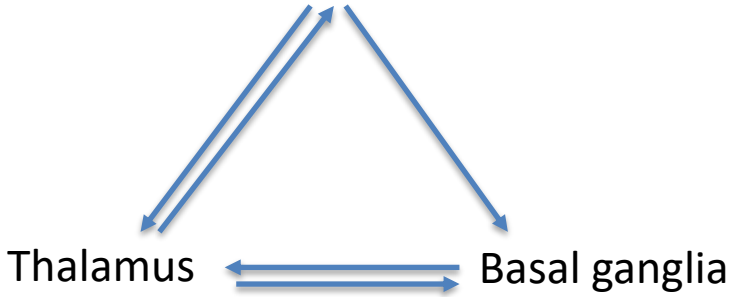
- Cerebral cortex

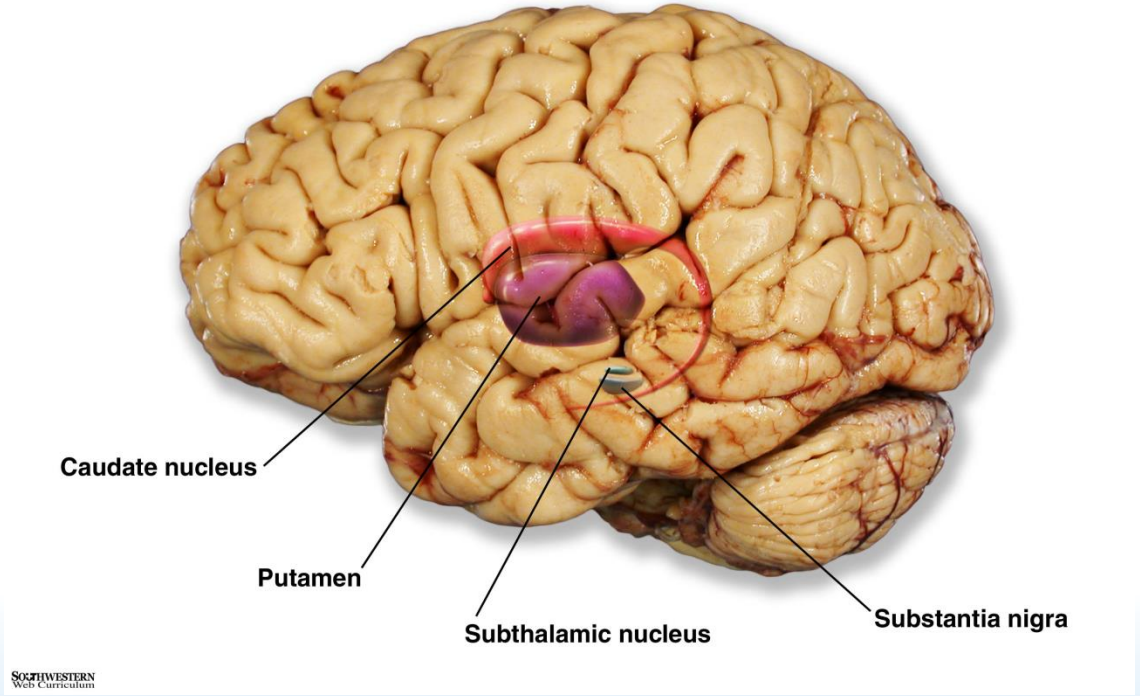




Overview of basal ganglia circuitry, continued

- Cerebral cortex

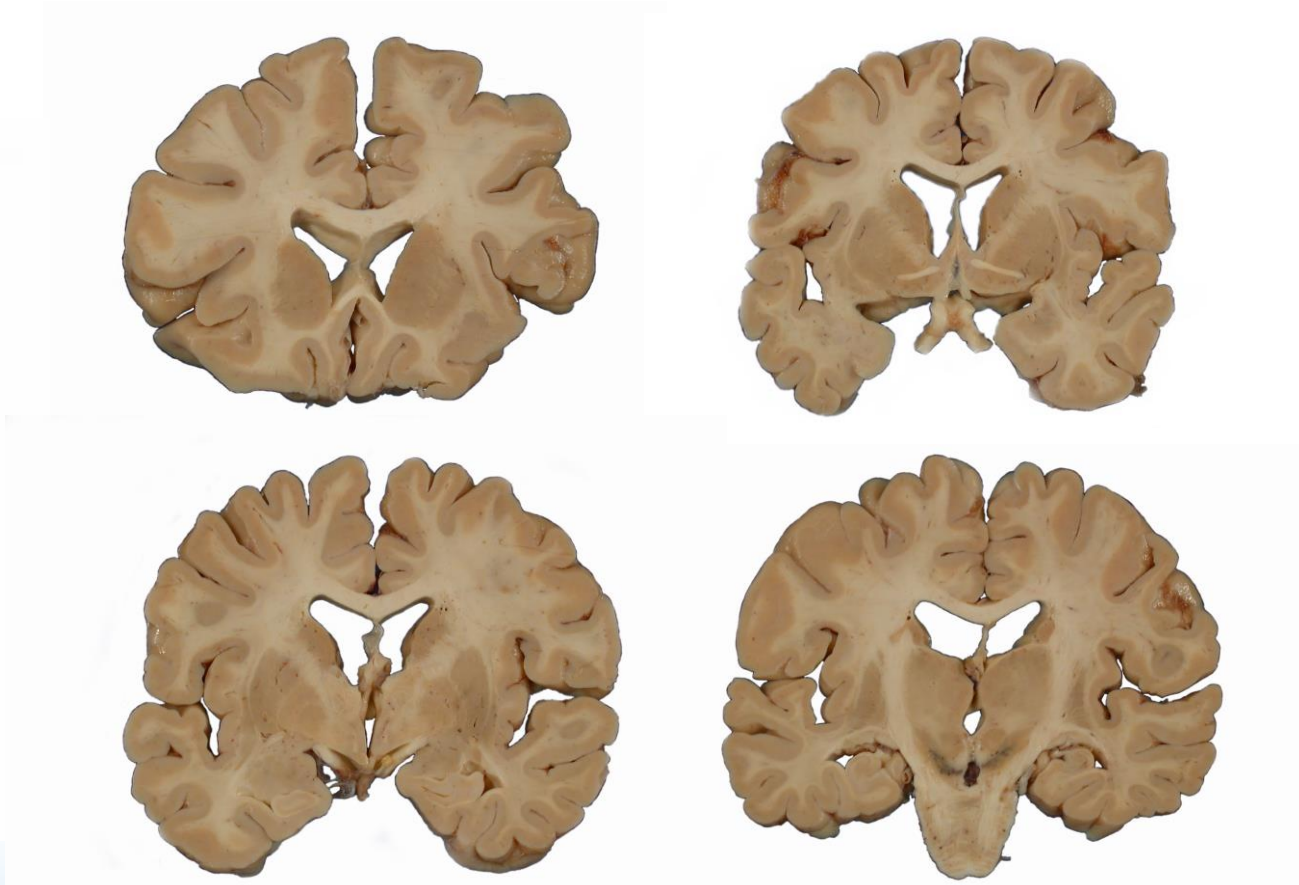


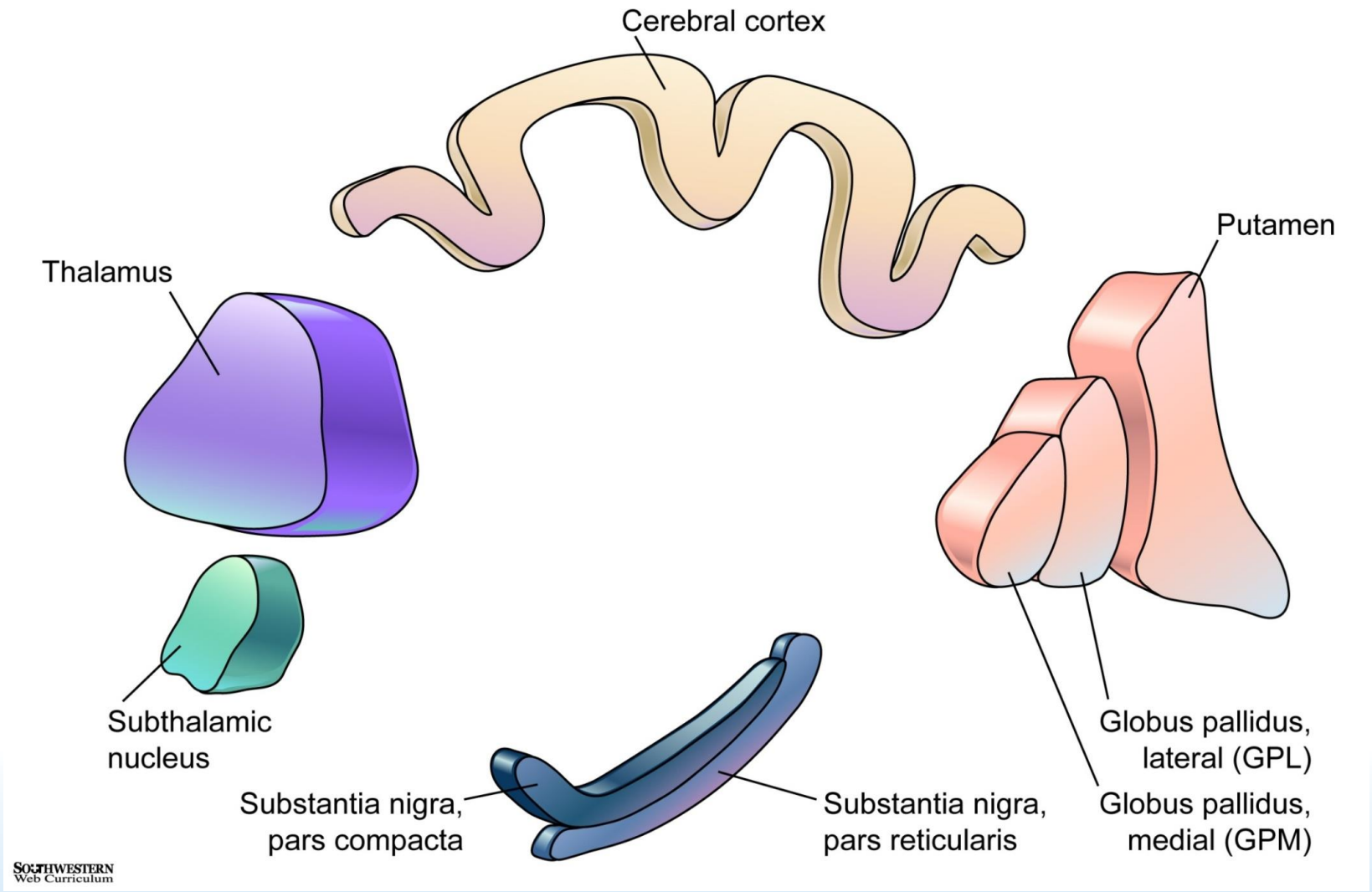


What do the basal ganglia do?

- Represent an important **feedback circuit** to cerebral cortical neurons
- Influence the activity of cerebral cortical neurons via **projections to the thalamus**
- Required for the normal planning, initiation and cessation of **voluntary movements**
- Influence domains beyond classical motor domains
  - **Cognition**
  - **Limbic activities**

Individual nuclei of the basal ganglia




Cerebral cortex
Thalamus
Putamen
Subthalamic nucleus
Globus pallidus, lateral (GPL)
Substantia nigra, pars compacta
Substantia nigra, pars reticularis
Globus pallidus, medial (GPM)
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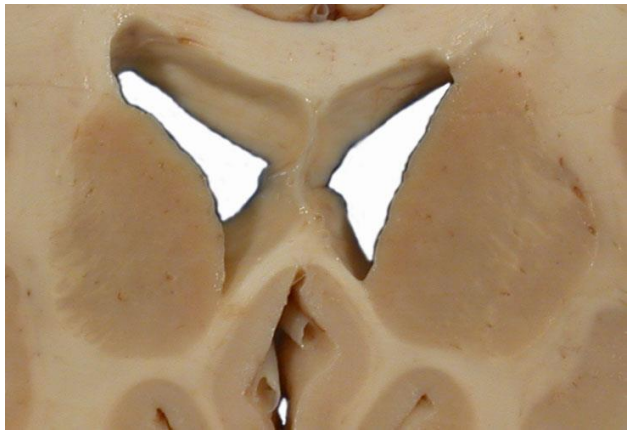
Striatum

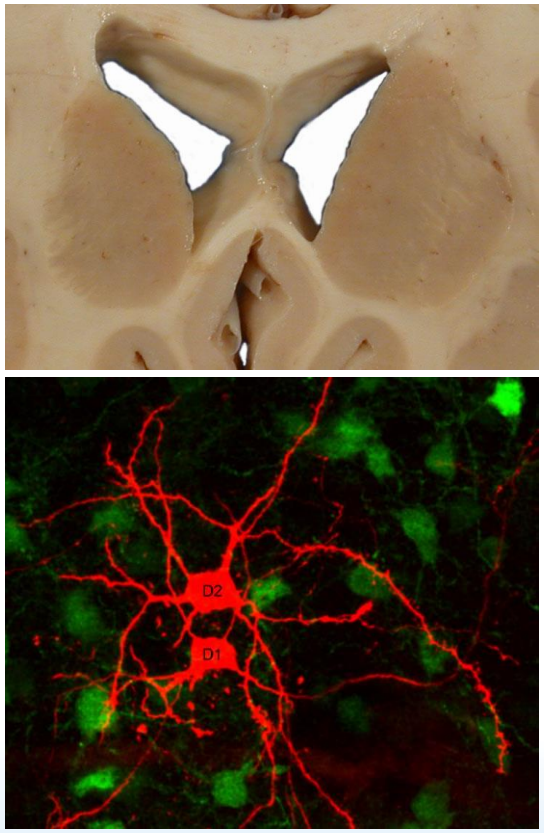
- Composed of **caudate**, **putamen** and **ventral striatum/nucleus accumbens**
- Composed of
  - Medium spiny **GABAergic projection neurons** (~85%)
  - Mixed population of cholinergic and GABAergic **interneurons** (~15%)
- Major **receptive area** of basal ganglia – afferents from
  - Cerebral cortex (glutamatergic)
  - Thalamus (glutamatergic)
  - Substantia nigra and ventral tegmental area (dopaminergic)
- Efferent projections **remain within** basal ganglia (inhibitory)
  - Globus pallidus and ventral pallidum
  - Substantia nigra (SNc and SNr)



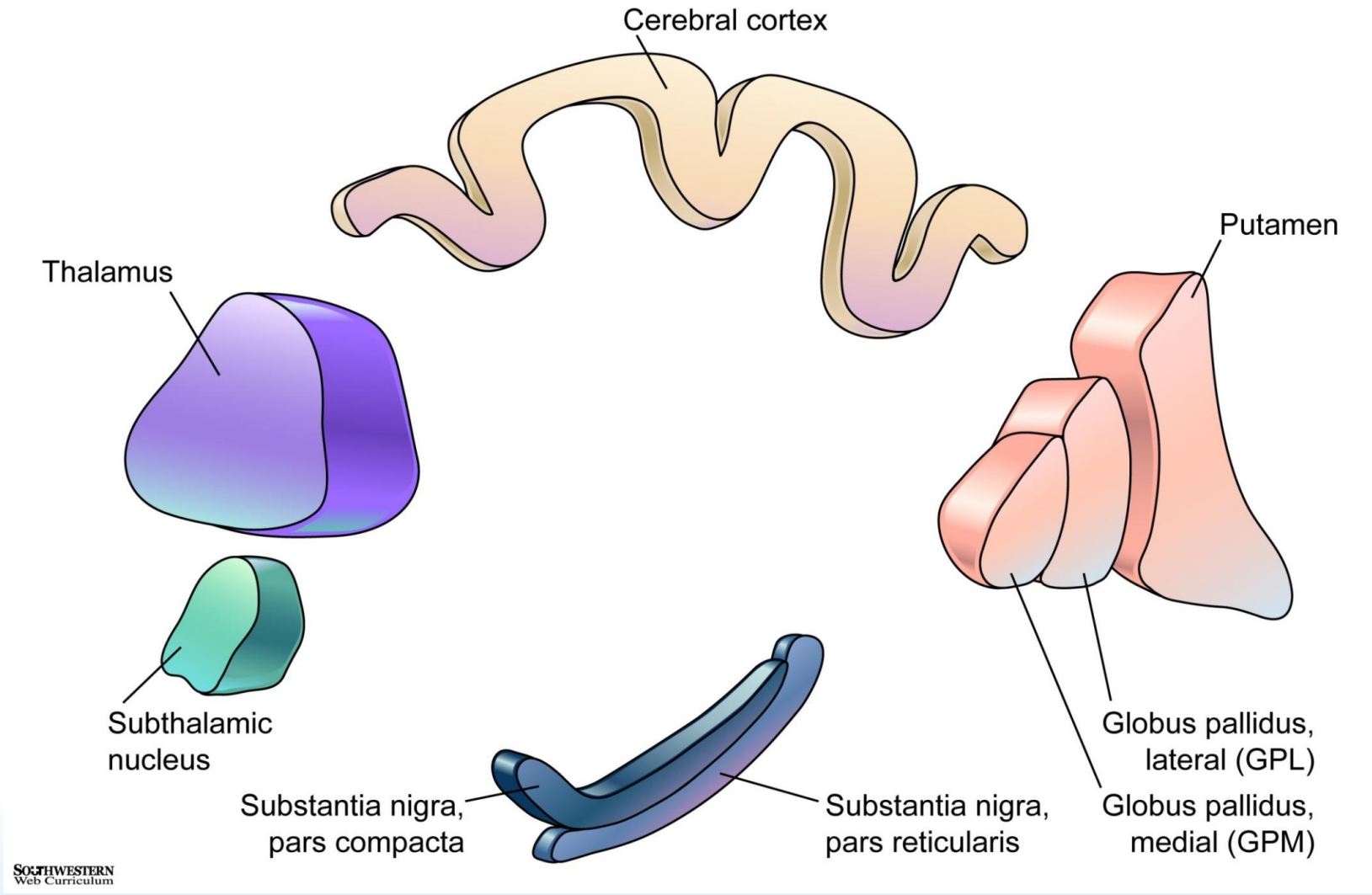
Striatum, continued

Medium spiny projection neurons

- Receive **input** from cerebral cortex, thalamus and pars compacta of substantia nigra (SNc)
- Two subtypes, based on dopamine receptor expression (D1 vs D2)
- **D1** neurons
  - **Excited** by dopamine
  - Co-express GABA and substance P
  - Project to internal segment of globus pallidus (**GPi**) and pars reticulata of substantia nigra (**SNr**)
- **D2** neurons
  - **Inhibited** by dopamine
  - Co-express GABA and enkephalin
  - Project to external segment of globus pallidus (**GPe**)
- Projections (GABAergic) from both subtypes are **inhibitory**



From Taverna S et al. *J Neurosci* 2008; 28:5504-5512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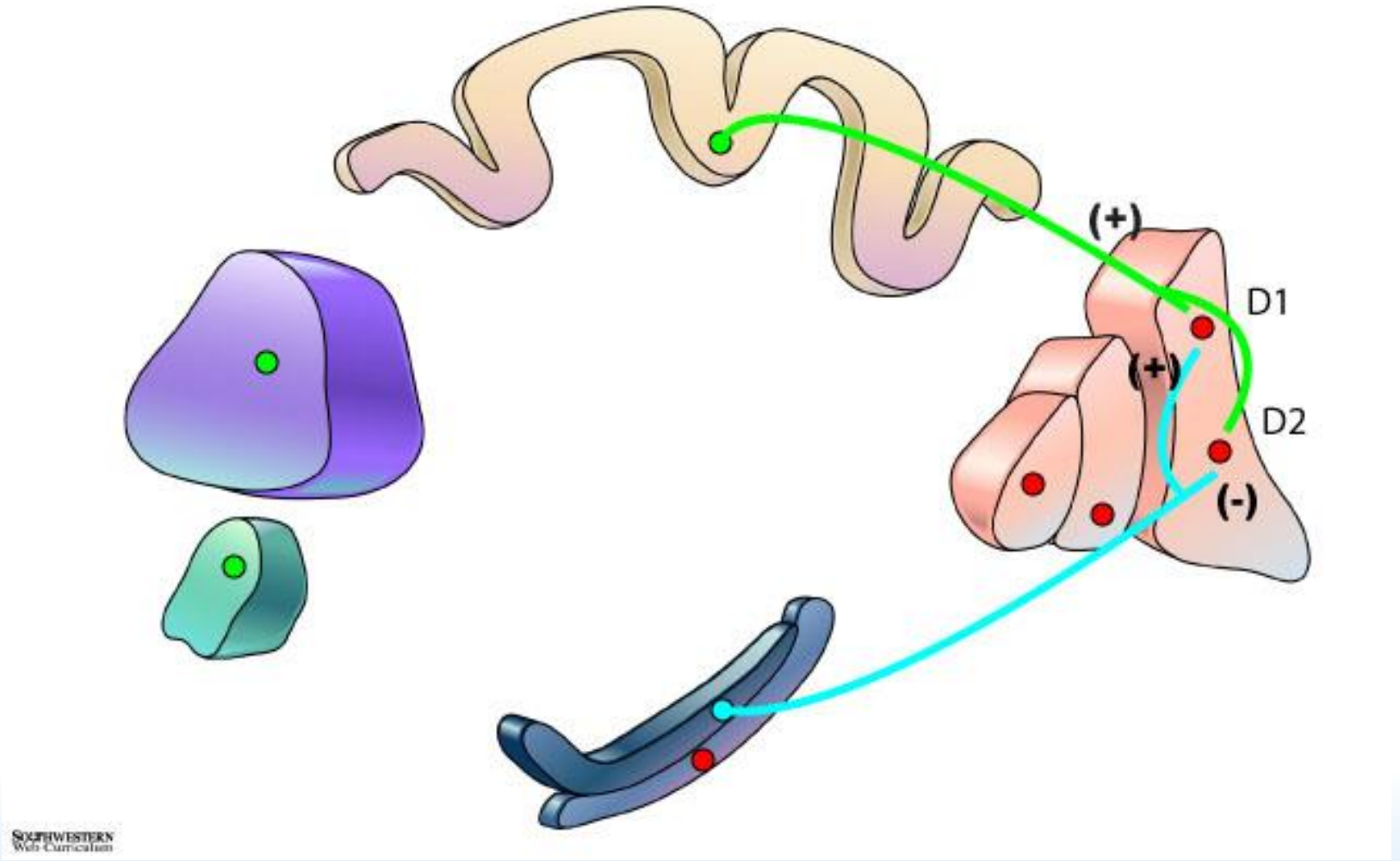
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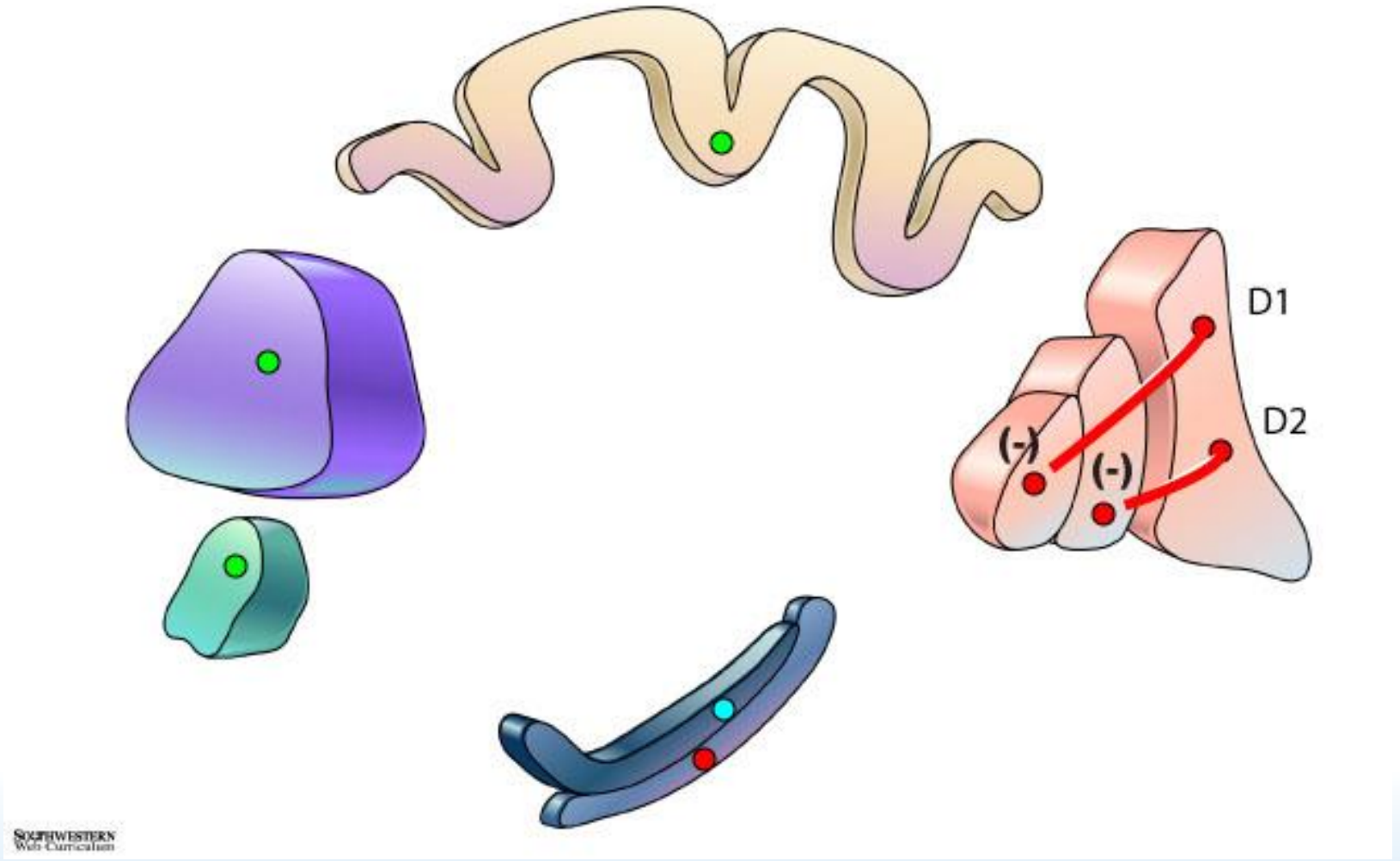
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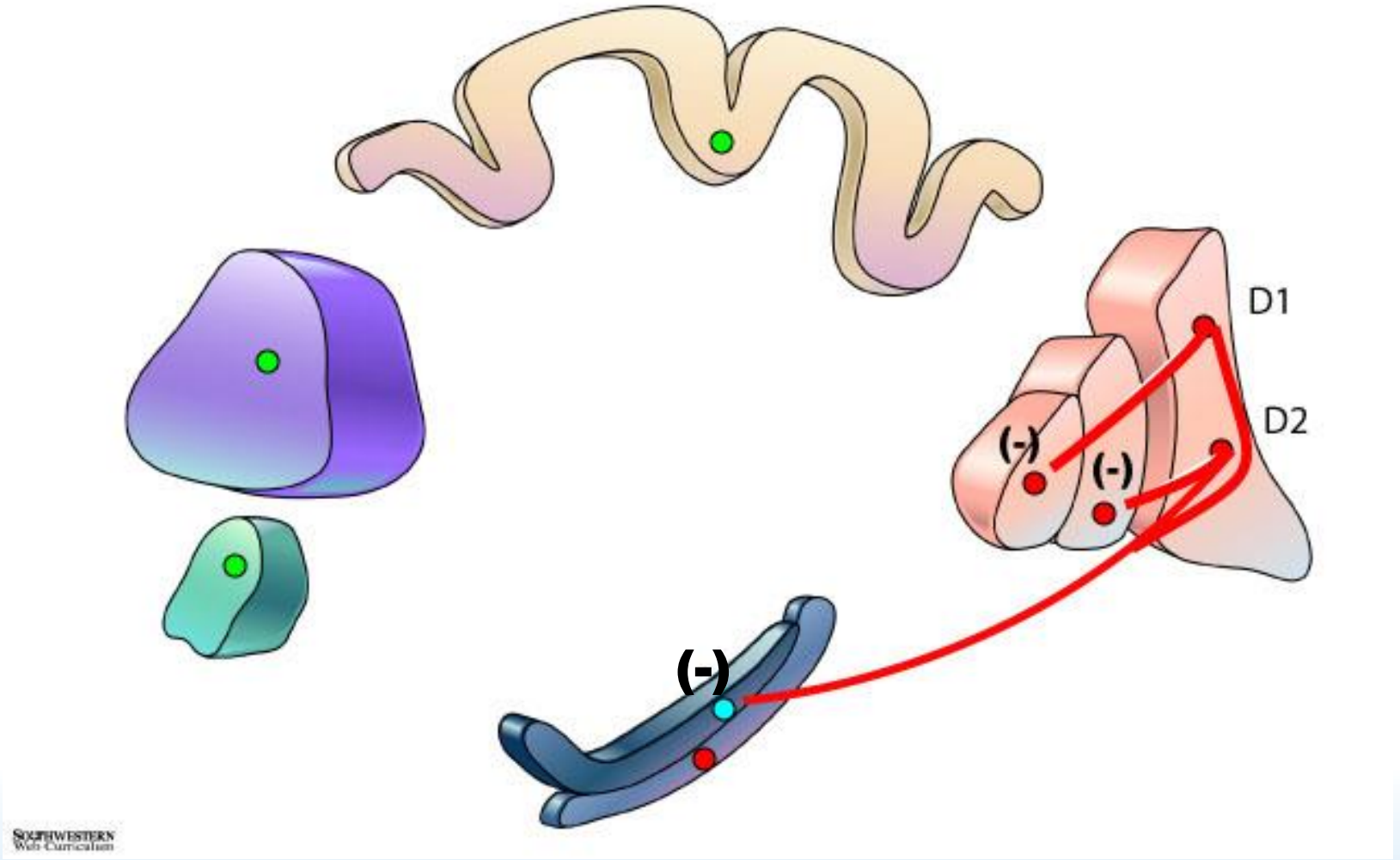
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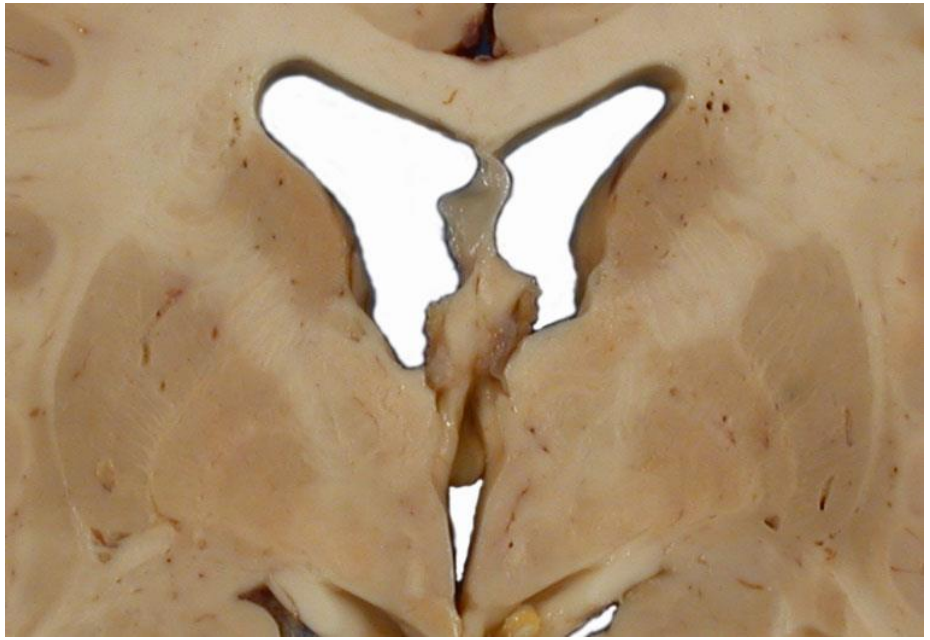
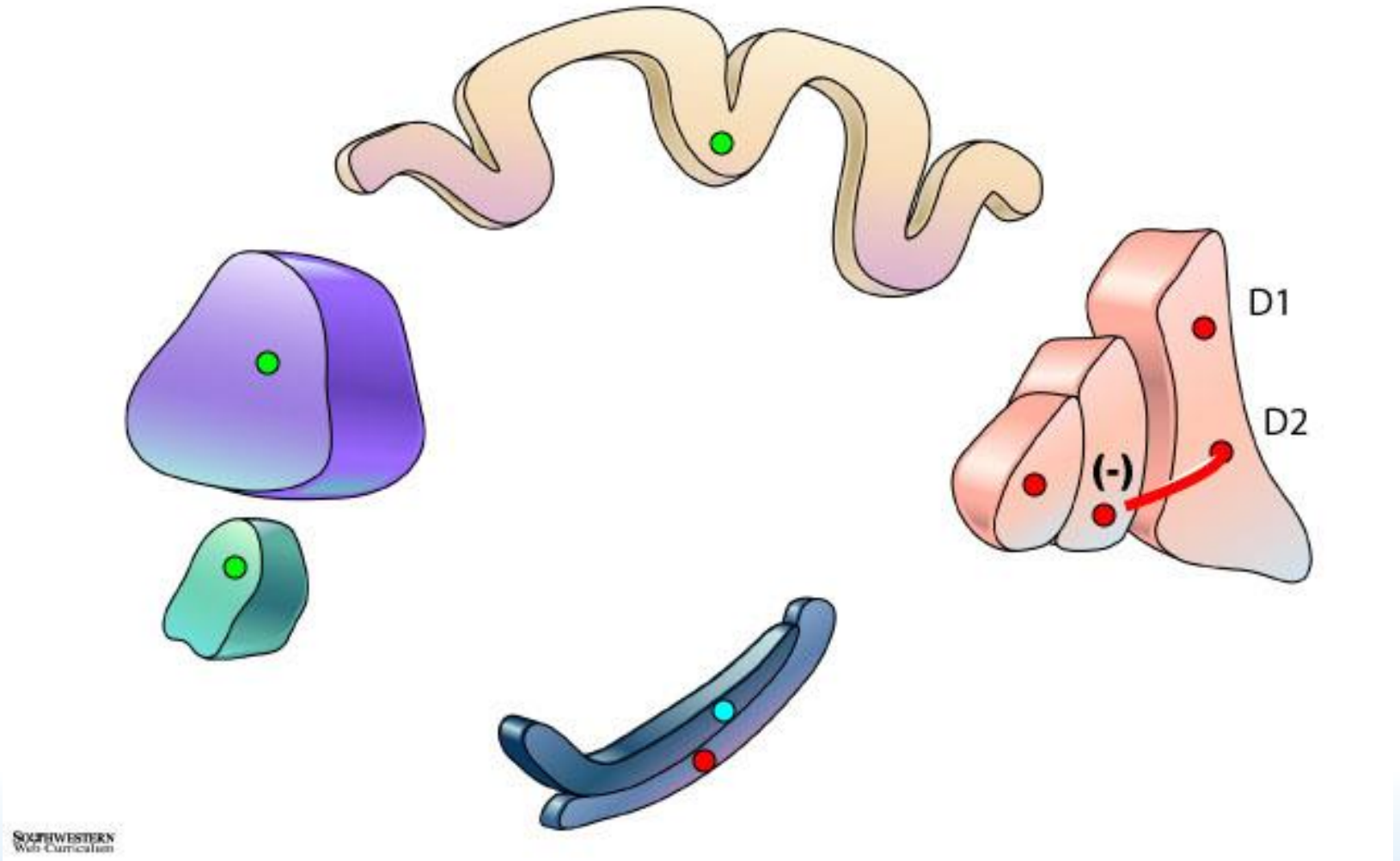
Globus pallidus

- Composed of histologically identical (but functionally different) **external and internal segments**
- Populated by **GABAergic projection neurons**
- External segment (GPe)
  - Receives **inhibitory input from D2 neurons** in striatum
  - Sends **inhibitory projections to subthalamic nucleus**
- Internal segment (GPi)
  - Receives **inhibitory input from D1 neurons** in striatum and excitatory input from subthalamic nucleus
  - Sends **inhibitory projections to thalamus**

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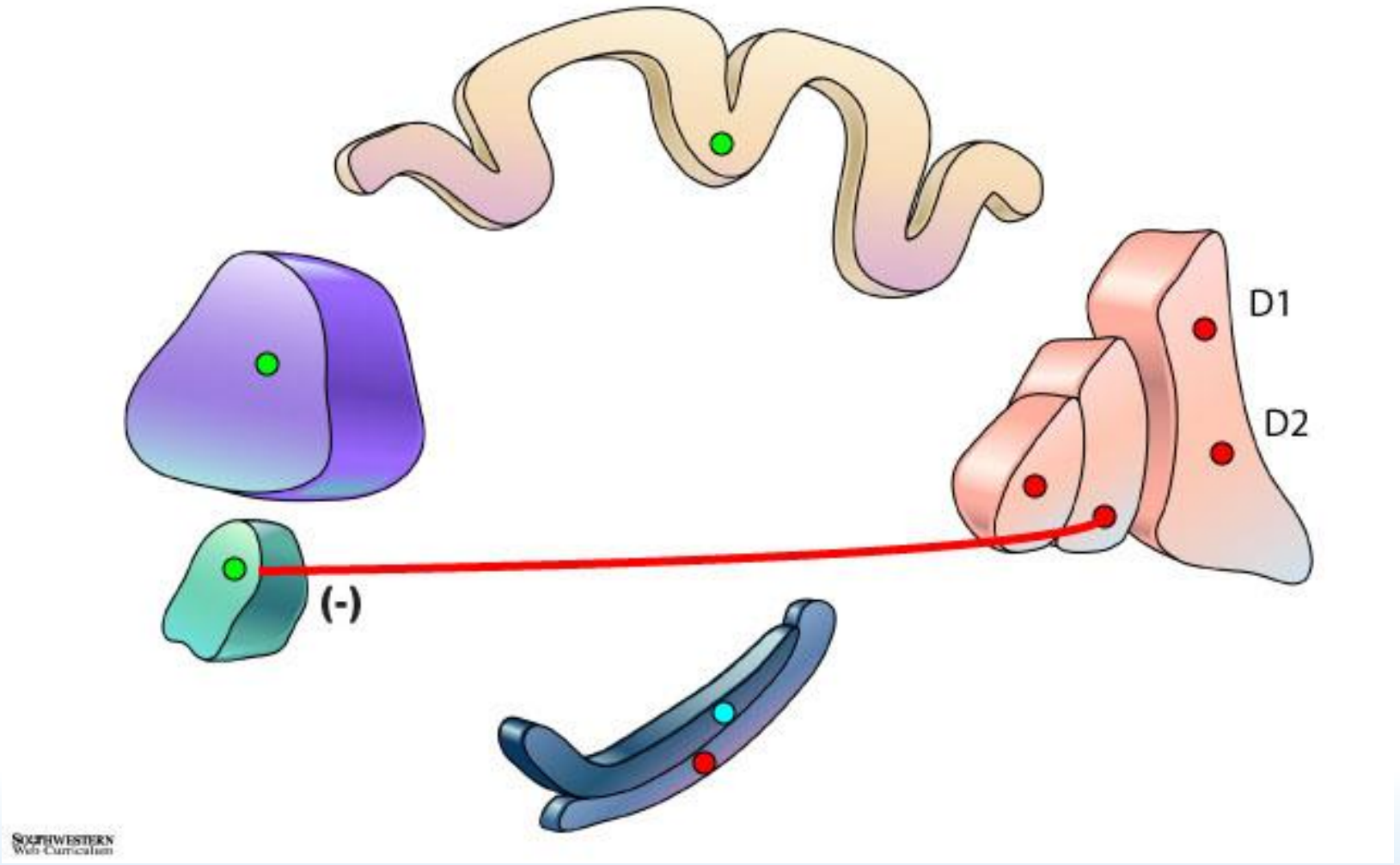
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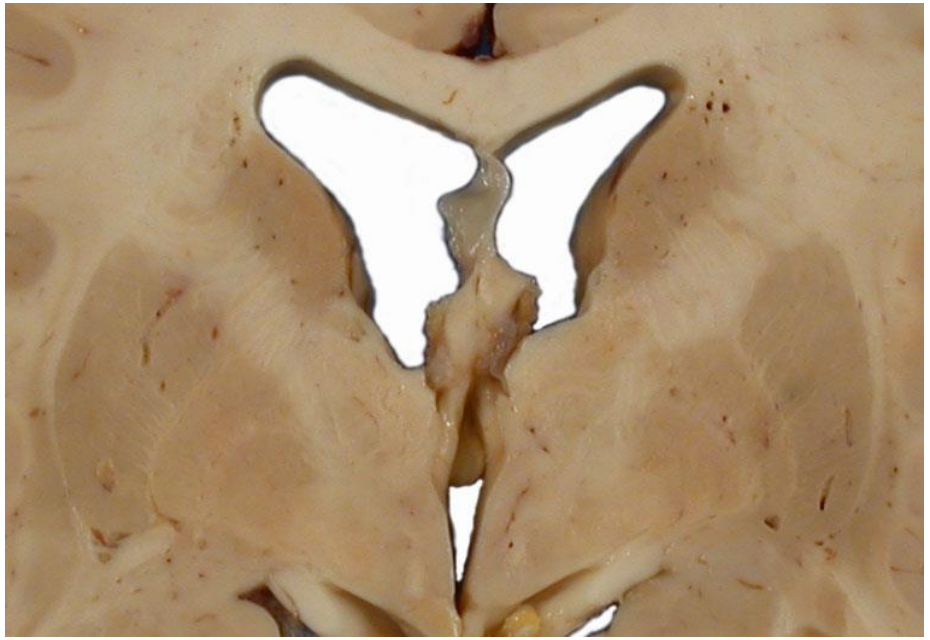
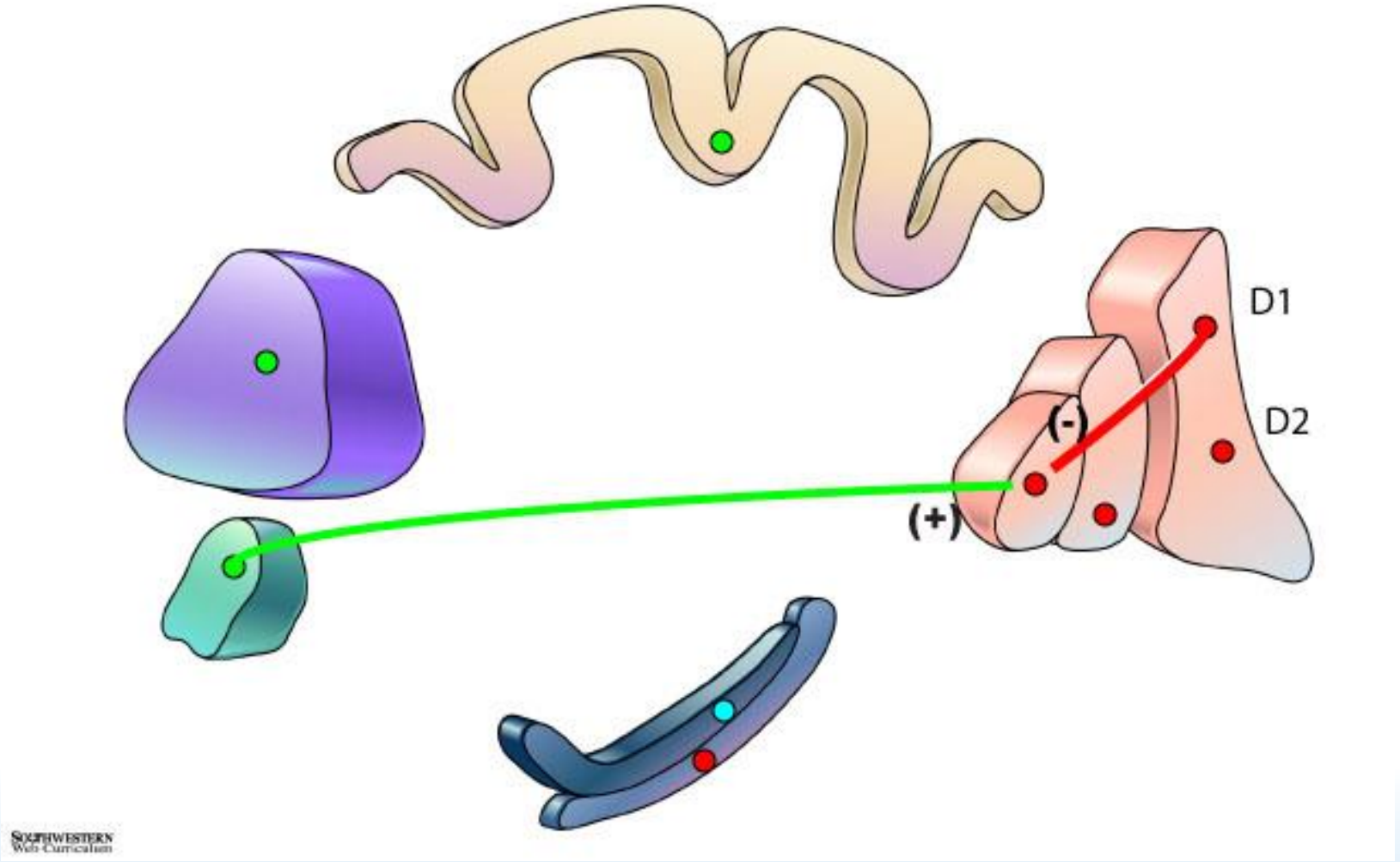
Globus pallidus

- Composed of histologically identical (but functionally different) **external and internal segments**
- Populated by **GABAergic projection neurons**
- External (lateral) segment (GPe)
  - Receives **inhibitory input from D2 neurons** in striatum
  - Sends **inhibitory projections to subthalamic nucleus**
- Internal (medial) segment (GPi)
  - Receives **inhibitory input from D1 neurons** in striatum and excitatory input from subthalamic nucleus
  - Sends most of its projections to **thalamus**

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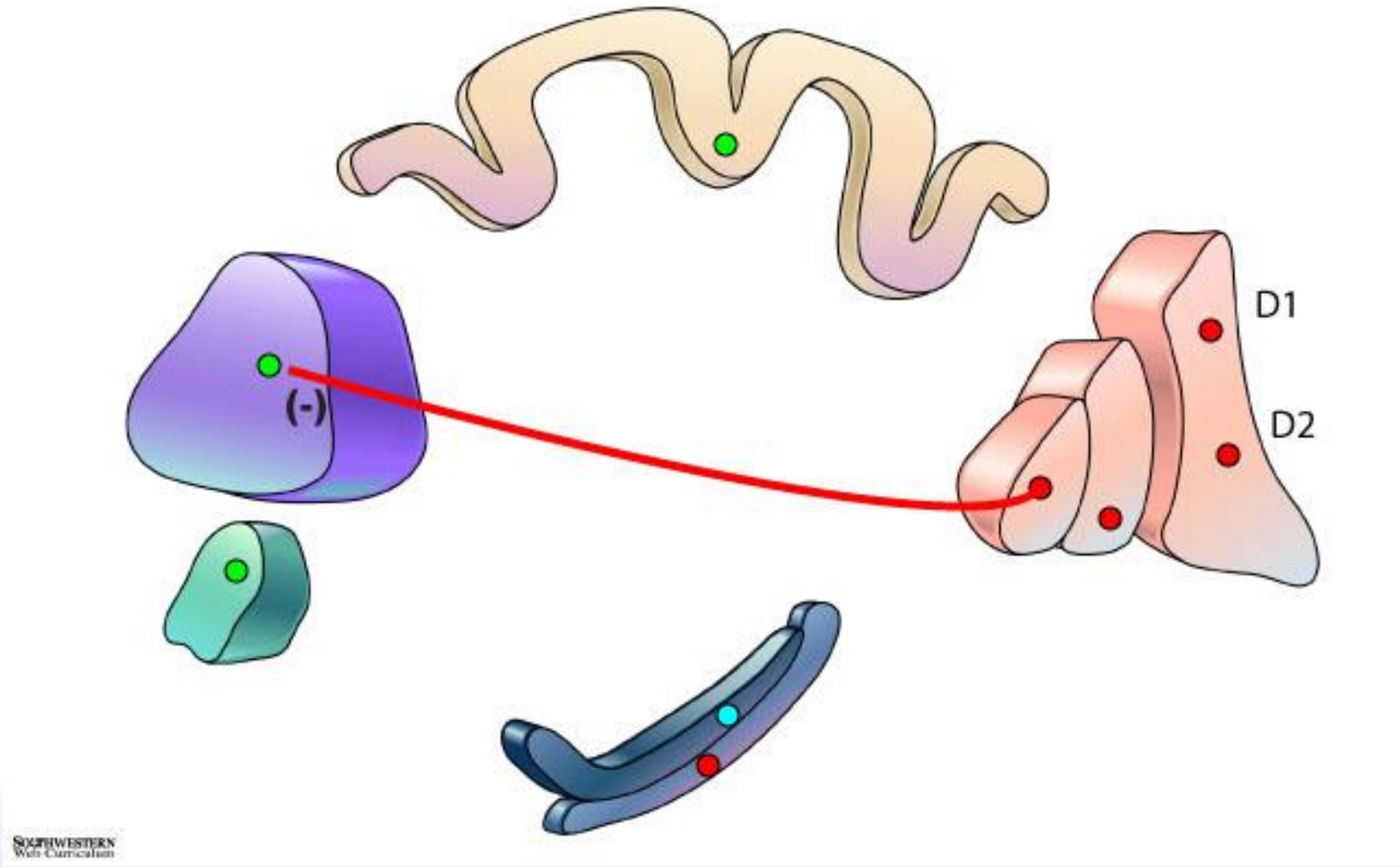
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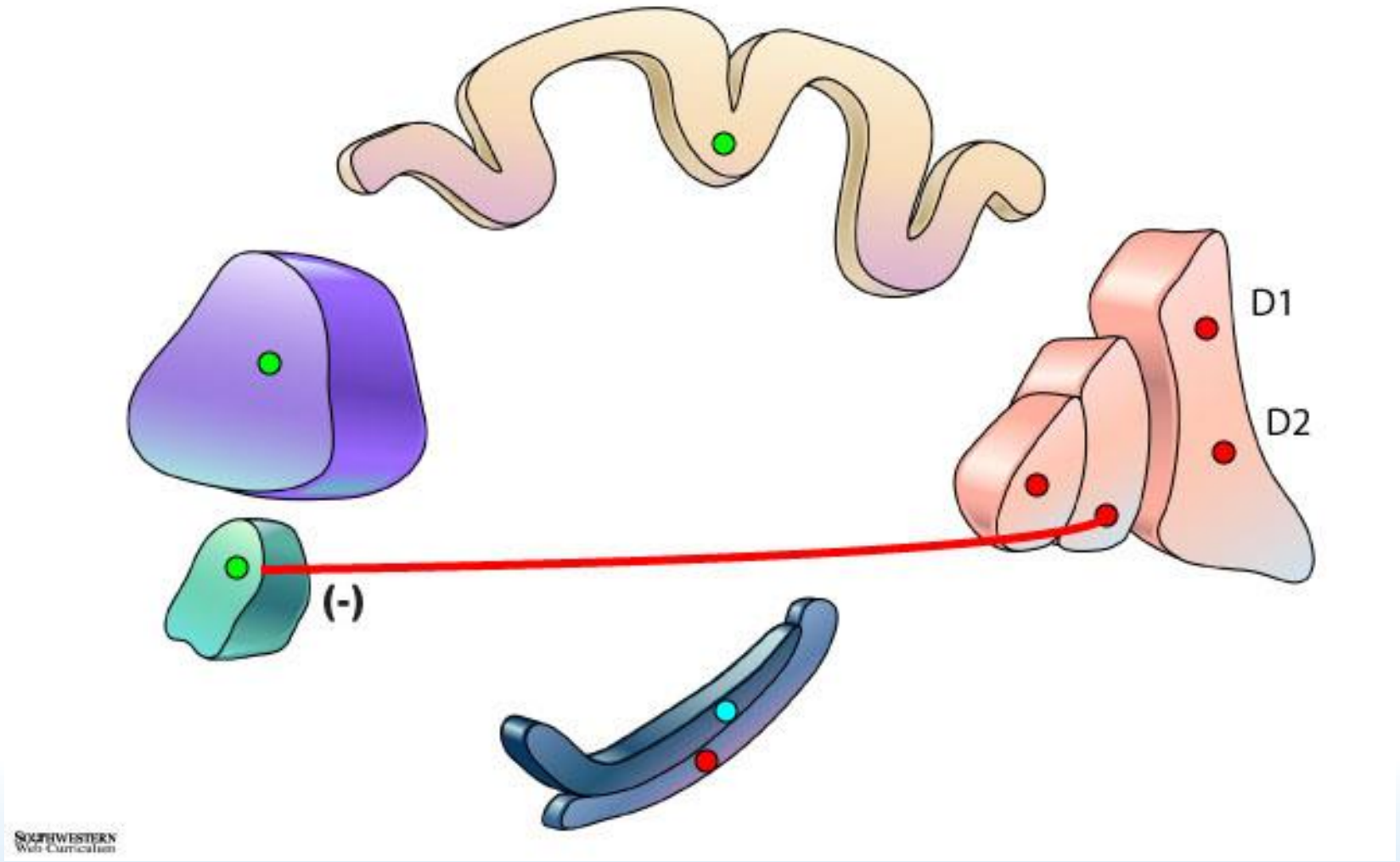
Subthalamic nucleus

- Populated by **glutamatergic** neurons
- Only **exclusively excitatory nucleus** in the basal ganglia
- Receives **input** from
  - **GPe** (inhibitory)
  - **Cerebral cortex** (excitatory)
- Sends excitatory projections to
  - **GPi**
  - **SNr**
- A component of the **“indirect” basal ganglia loops**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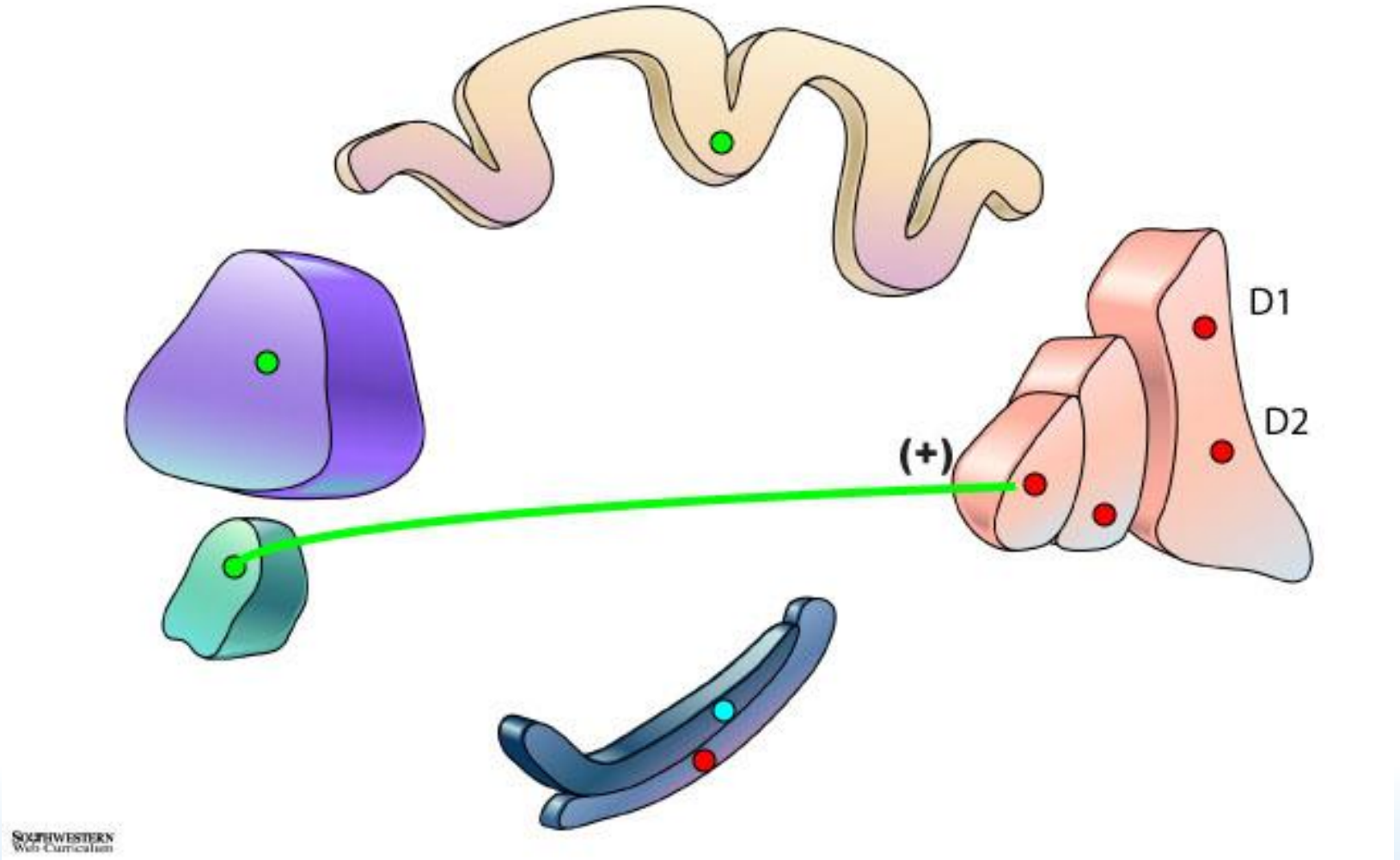
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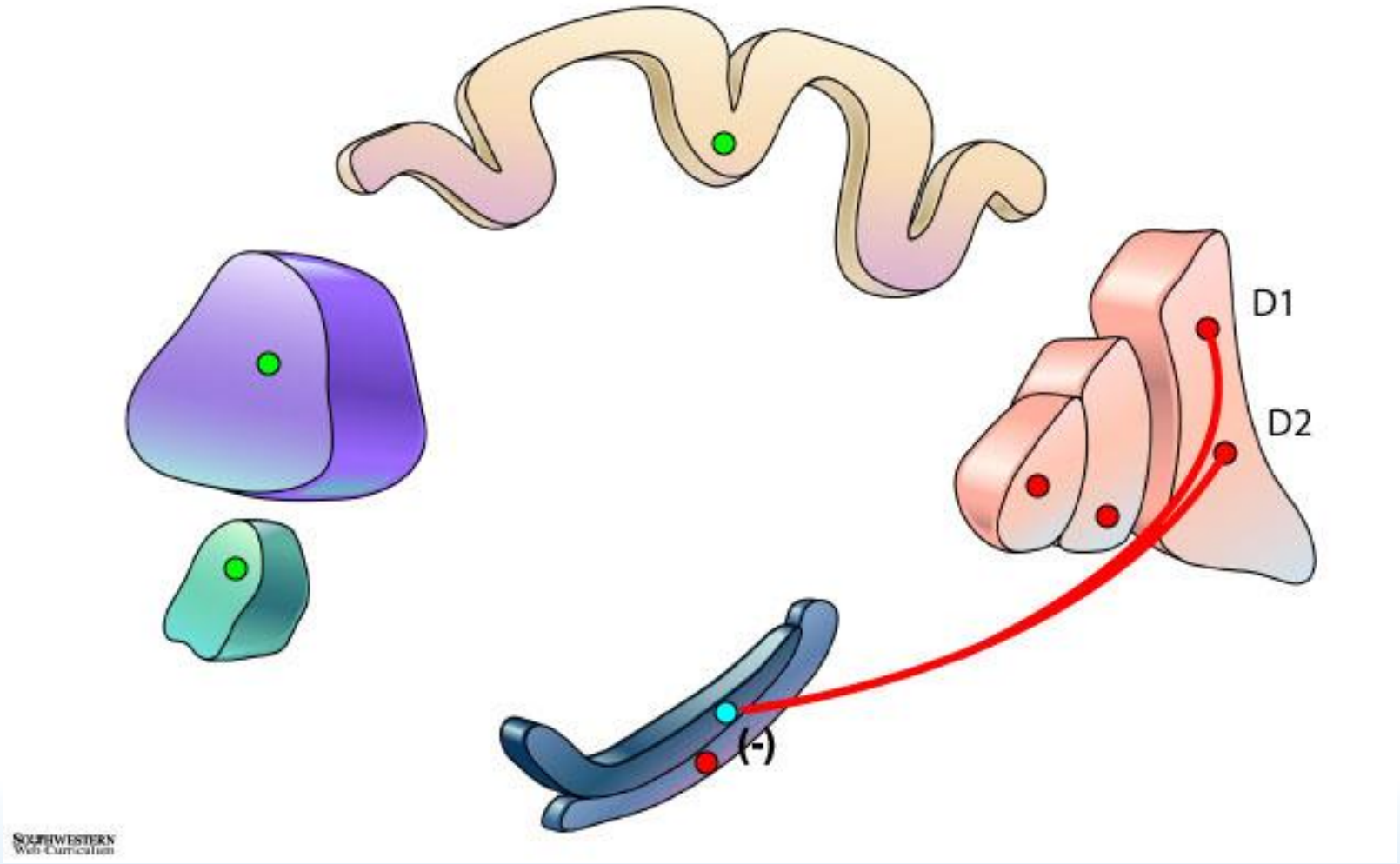
Substantia nigra

- Two subdivisions
  - **Pars compacta (SNc)**
  - **Pars reticulata (SNr)**

- **SNc** populated exclusively by **dopaminergic** cells
  - Most **input** comes from **striatum**
  - Reciprocal **output** to **striatum**
  - Dopaminergic projections modulate the activity of striatal projection neurons (**excitation of D1 neurons** and **inhibition of D2 neurons**)

- For simplification, we can think of the **SNr as identical to the GPi** in terms of neurotransmitters (GABA) and connections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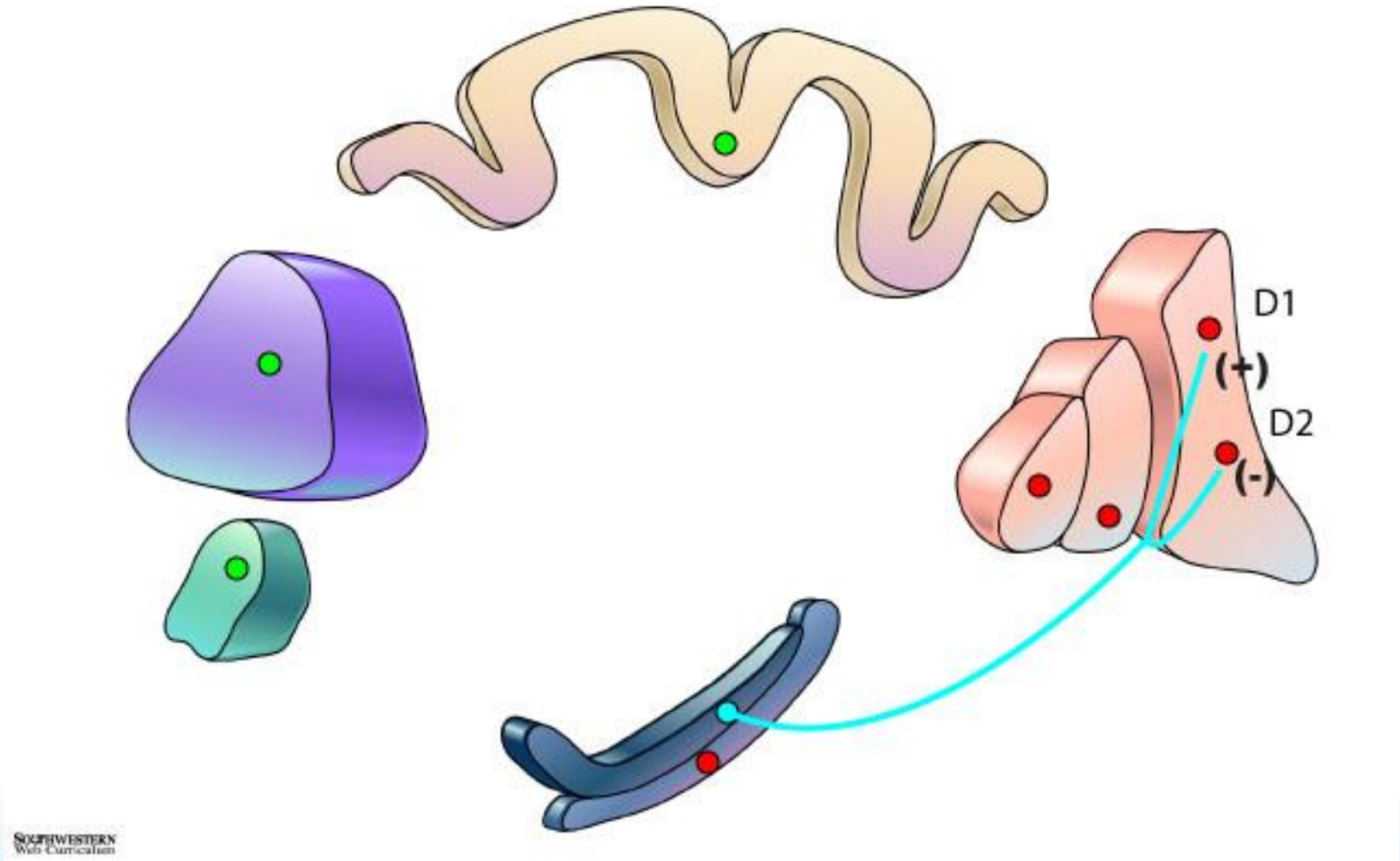
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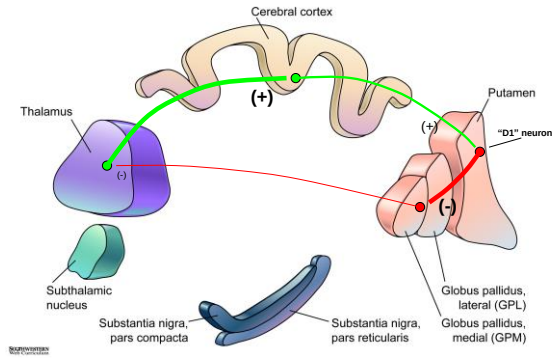
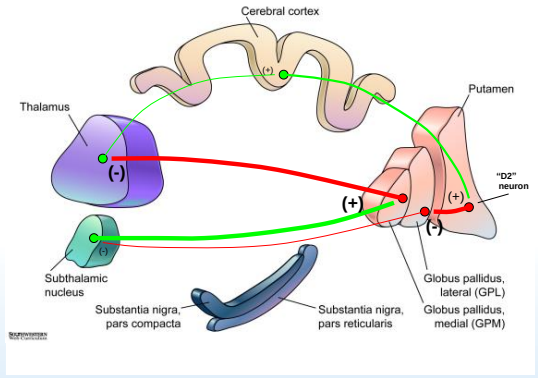
The direct and indirect basal ganglia “loops”

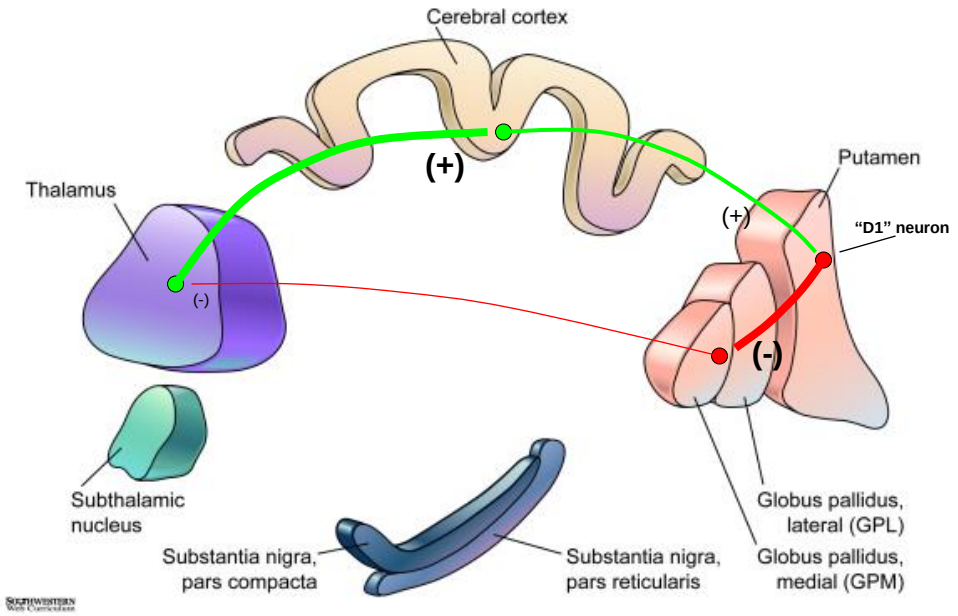
- Pathways for **flow of information through the basal ganglia**
- **Reciprocal** effects on the **thalamus**
- Pathways work together to **modulate the excitatory influence of the thalamus on the cerebral cortex**
  - Thalamocortical projections influence cortical regions in addition to traditional motor areas
- Recent evidence indicates that these pathways are actually interconnected at multiple levels

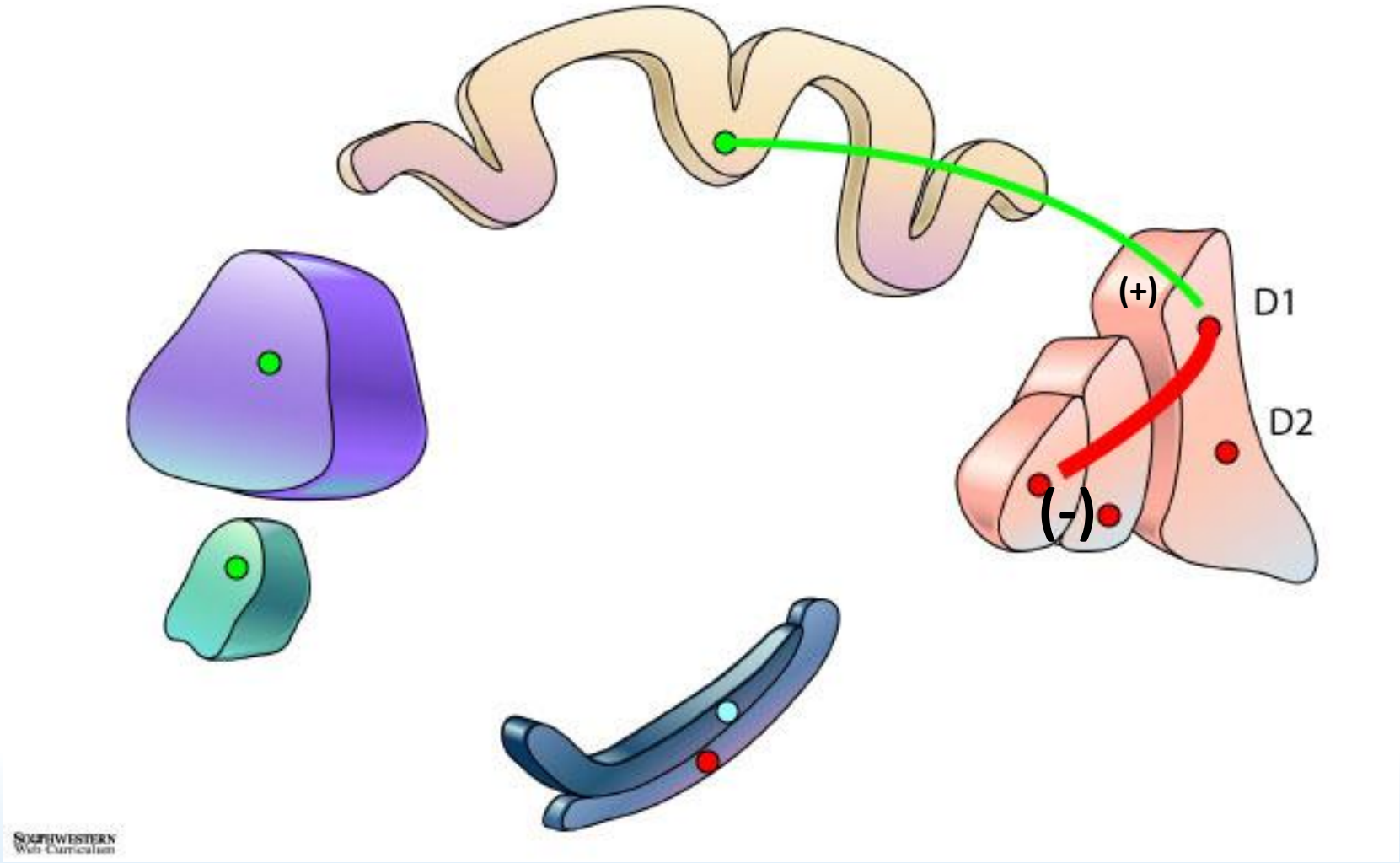




The direct basal ganglia pathway

- Major pathway for **releasing the thalamus from the tonic inhibitory effects of the basal ganglia ("disinhibition")**
- Begins with **excitation of an intermittently active (inhibitory) D1 neuron in the neostriatum**
- **D1** (GABA-ergic) **neurons** in neostriatum project directly to **internal segment of globus pallidus (GPi)**, where they inhibit local neurons
- **Tonic inhibitory influence of GPm on thalamus** is therefore **decreased ("disinhibition"),** and **excitatory thalamic signals to cerebral cortex <u>increase</u>**

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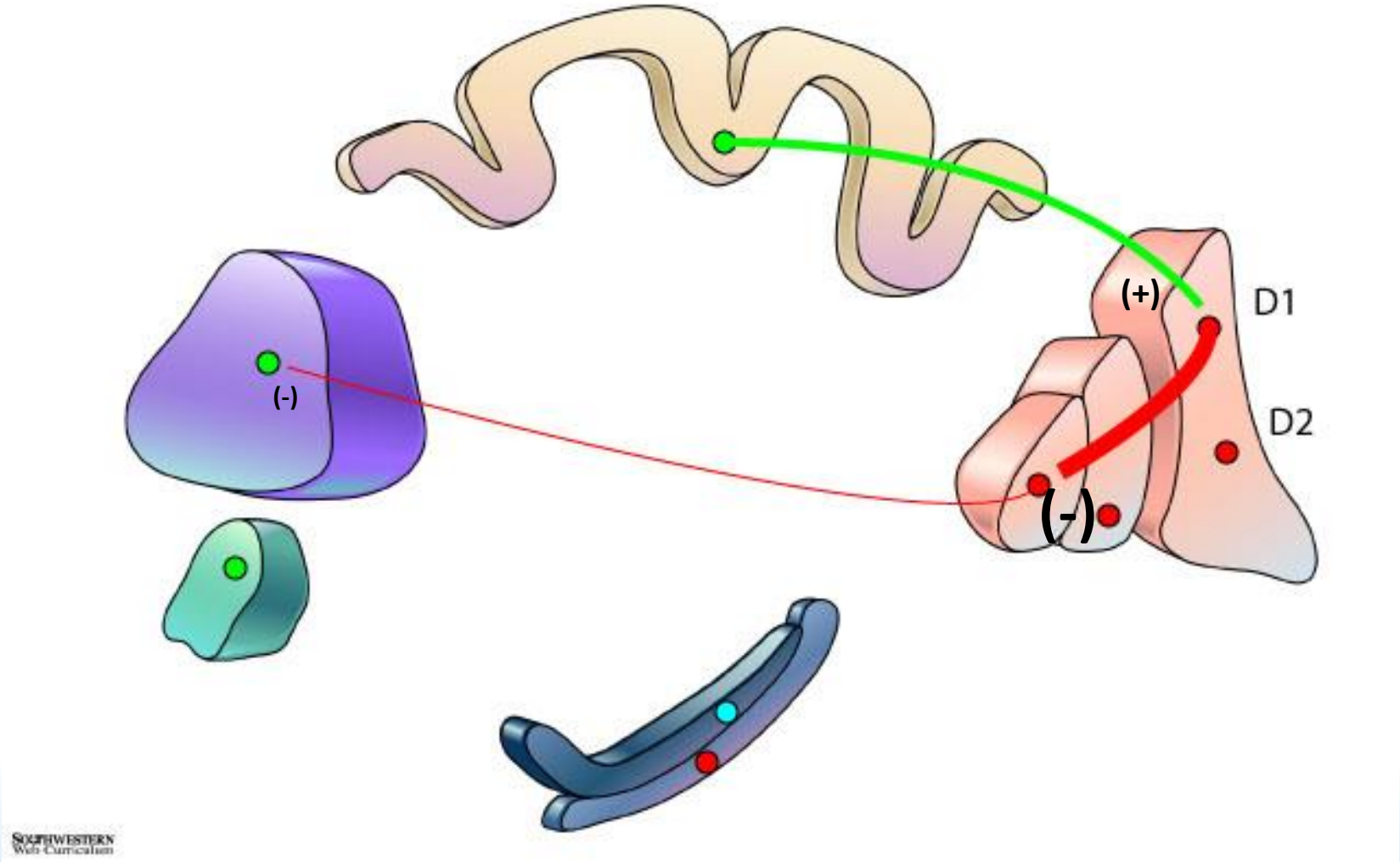
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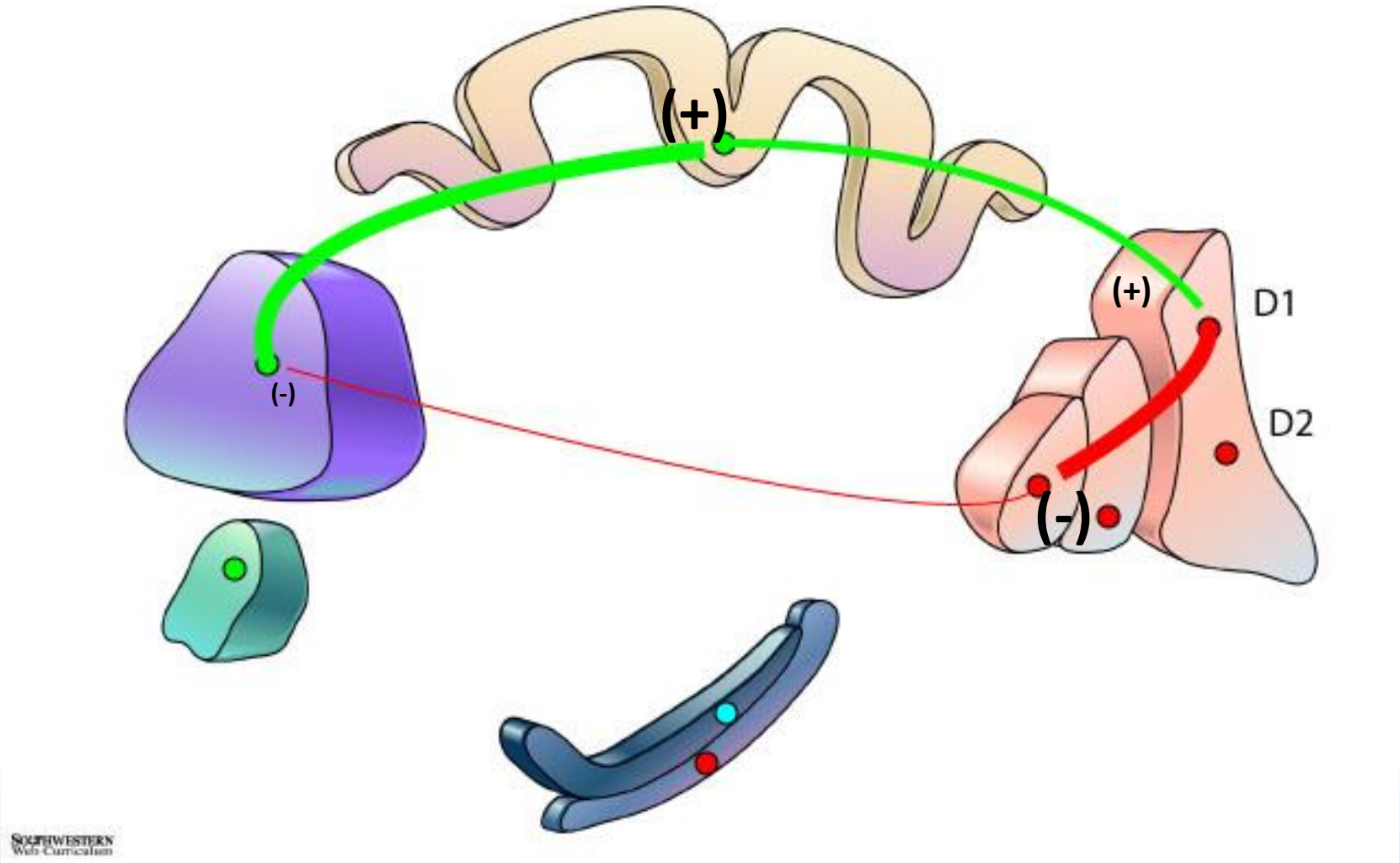
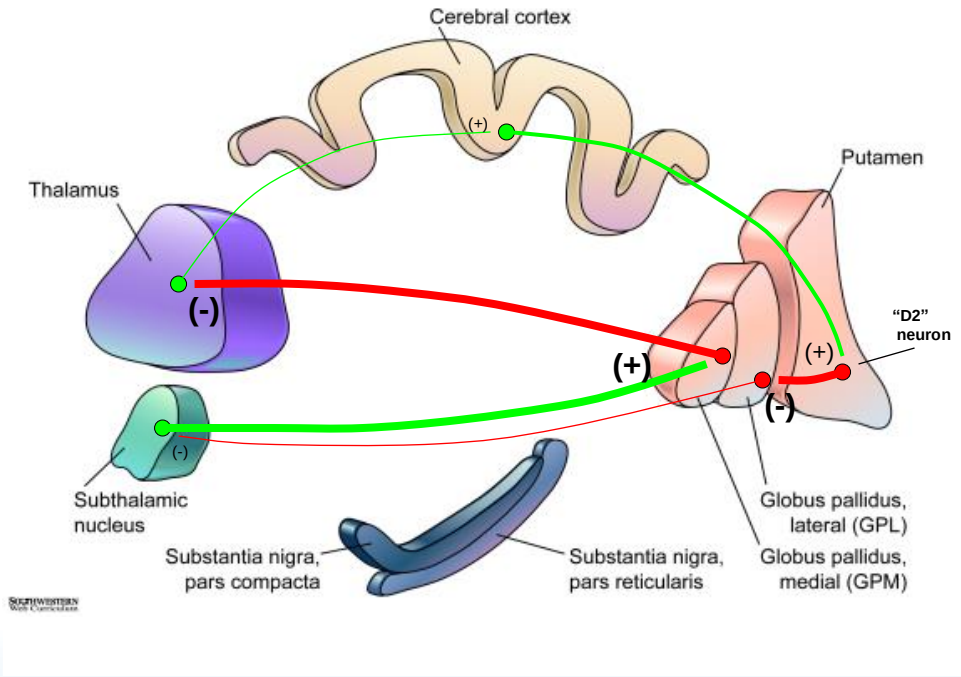
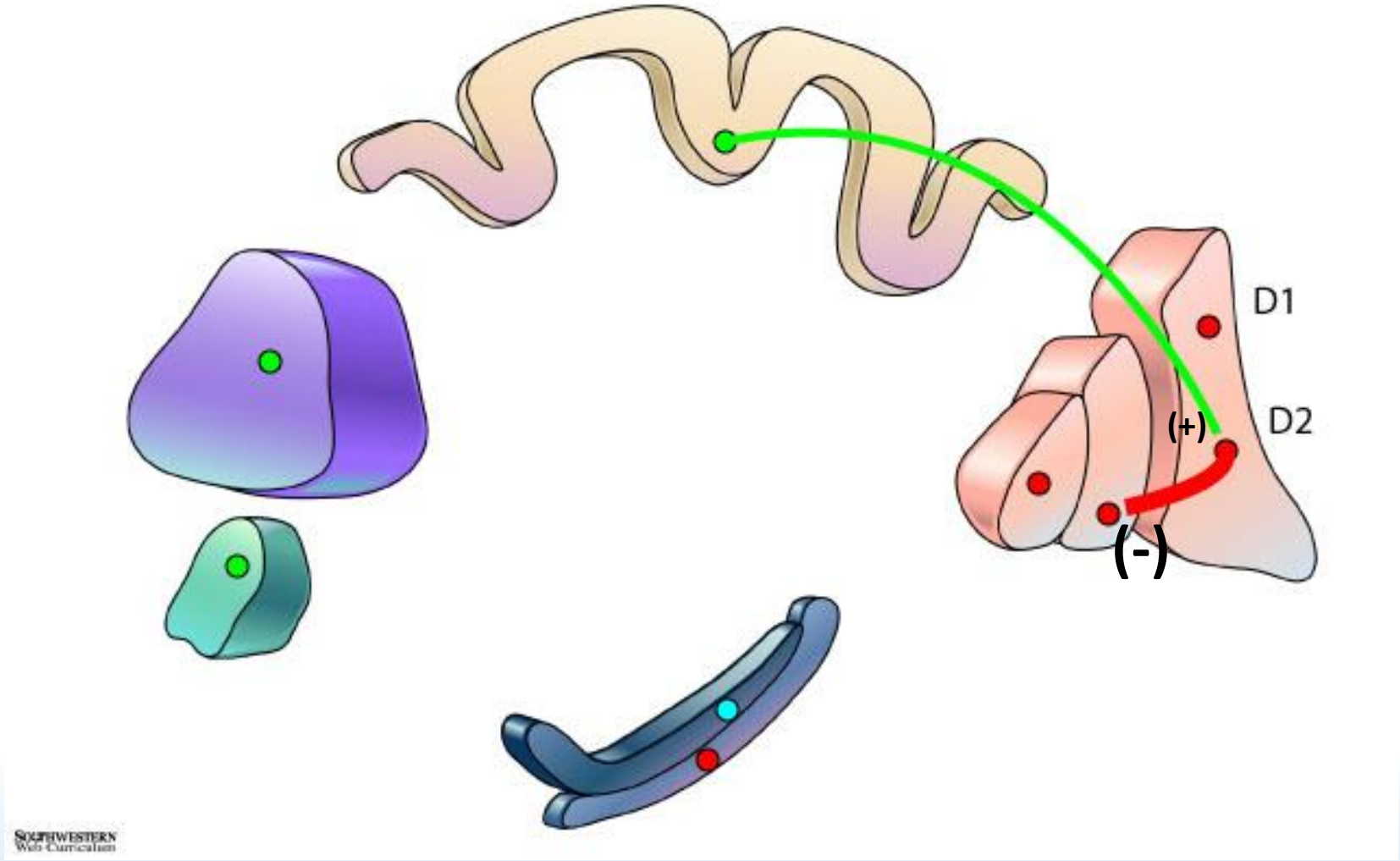


Direct Pathway
decreased thalamic inhibition (“disinhibition”) = increased cortical excitation

Indirect basal ganglia pathway

- **Antagonizes** activity of the **direct pathway**
- Projections include signals from **D2 neurons** in the neostriatum that go through **lateral segment of globus pallidus** and **subthalamic nucleus**
- Effect is to **increase the inhibitory signals from the medial globus pallidus to the thalamus**, which in turn…
- **<u>Decreases</u> excitatory signals from thalamus to cerebral cortex**

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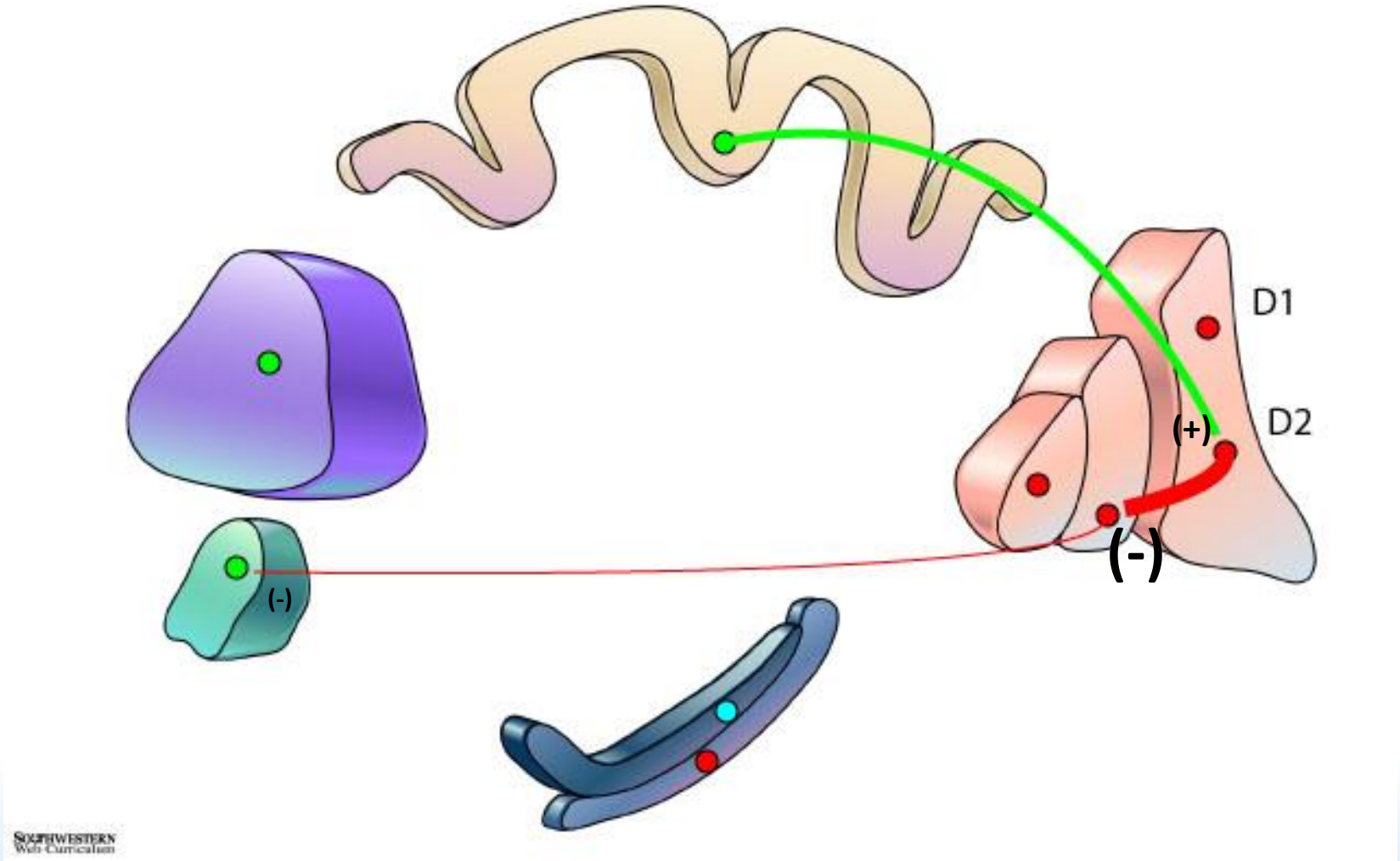
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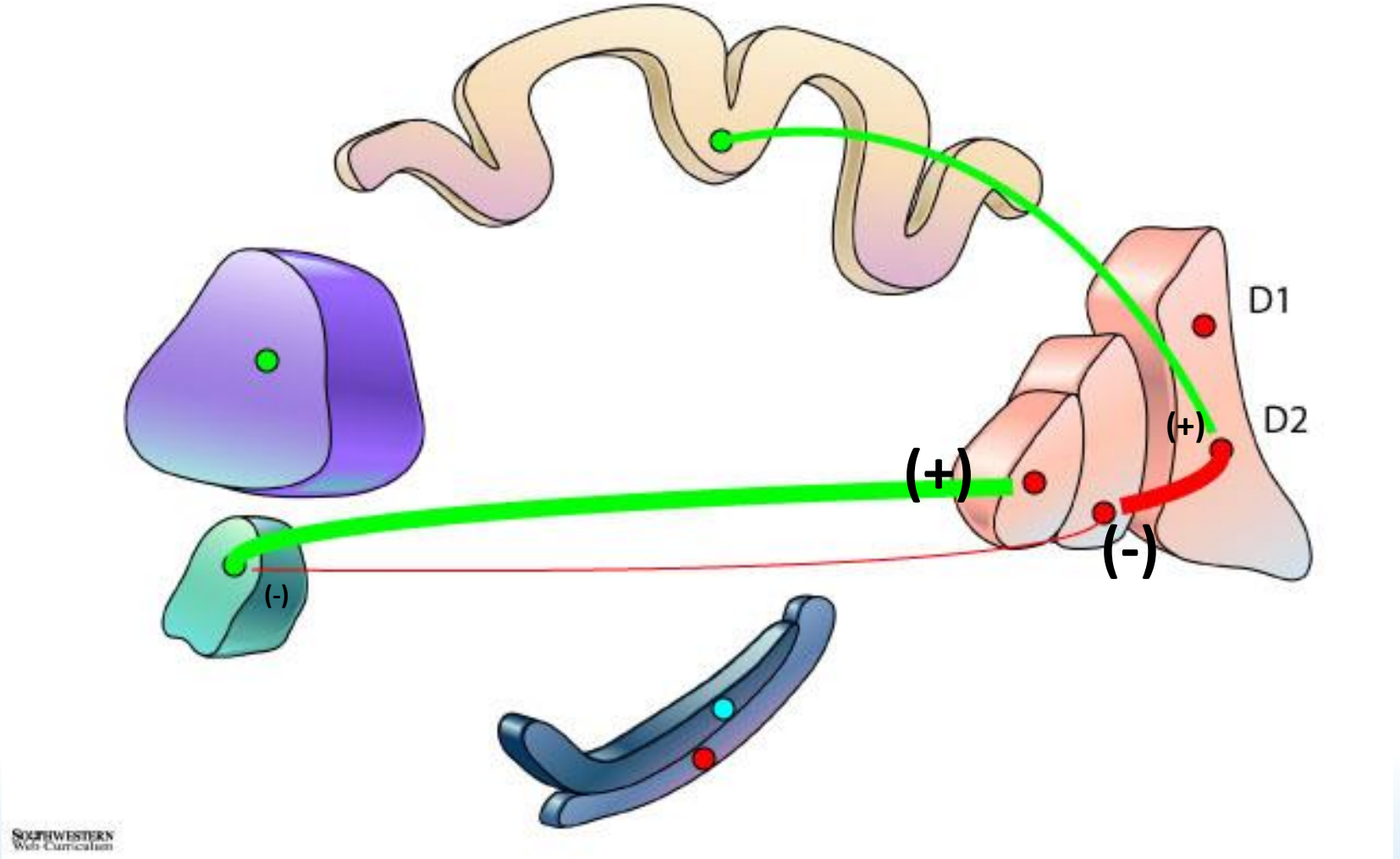
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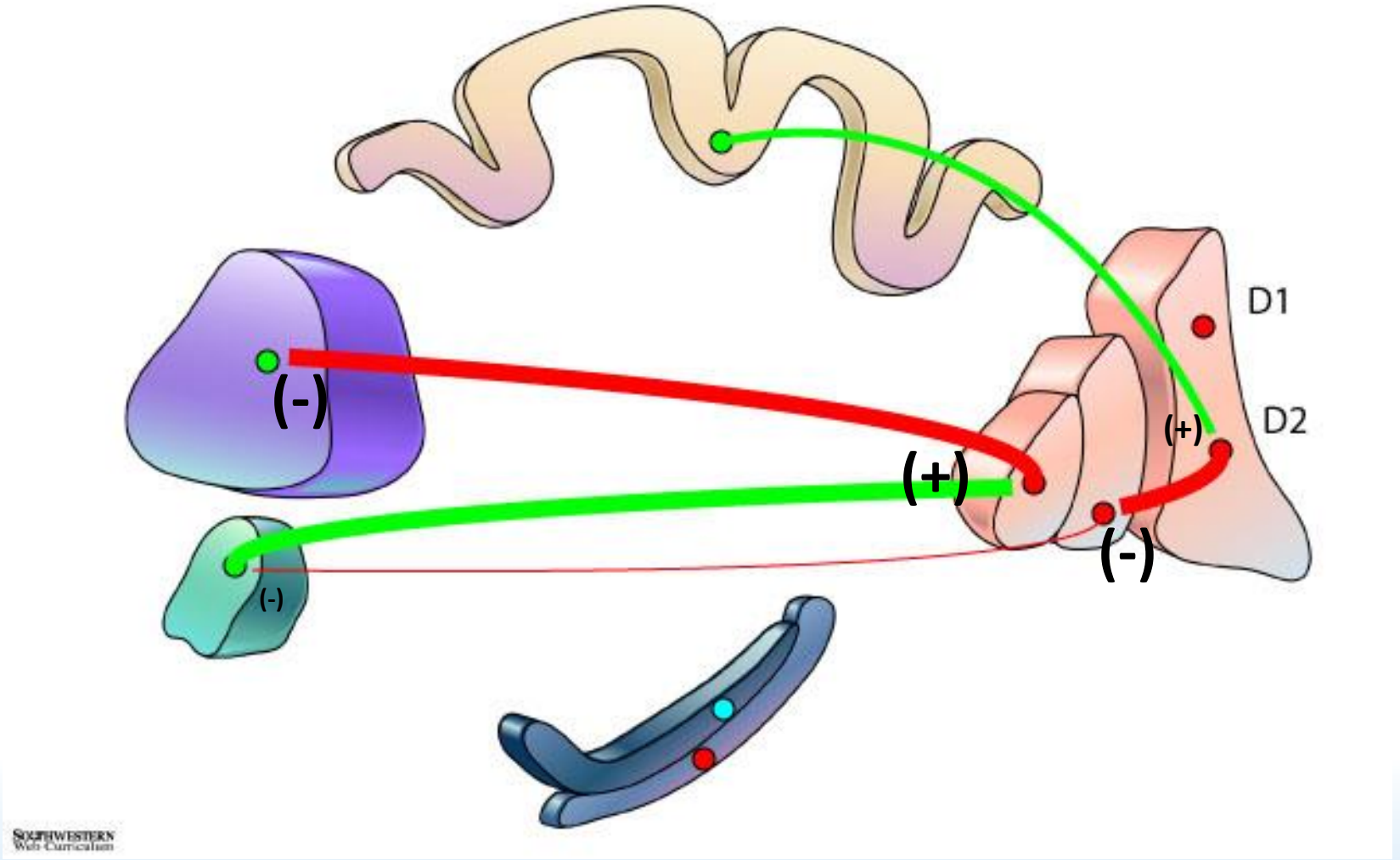
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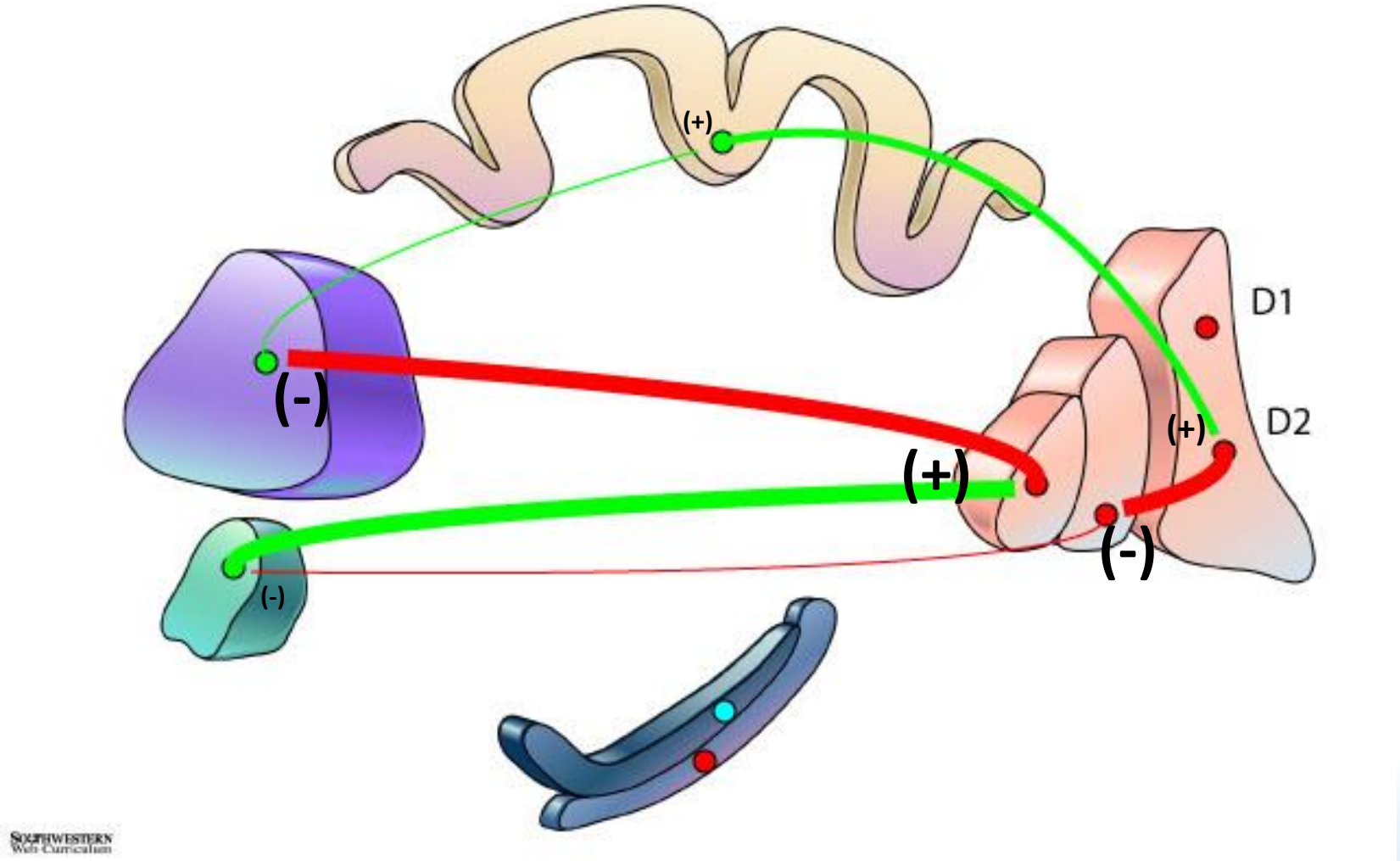
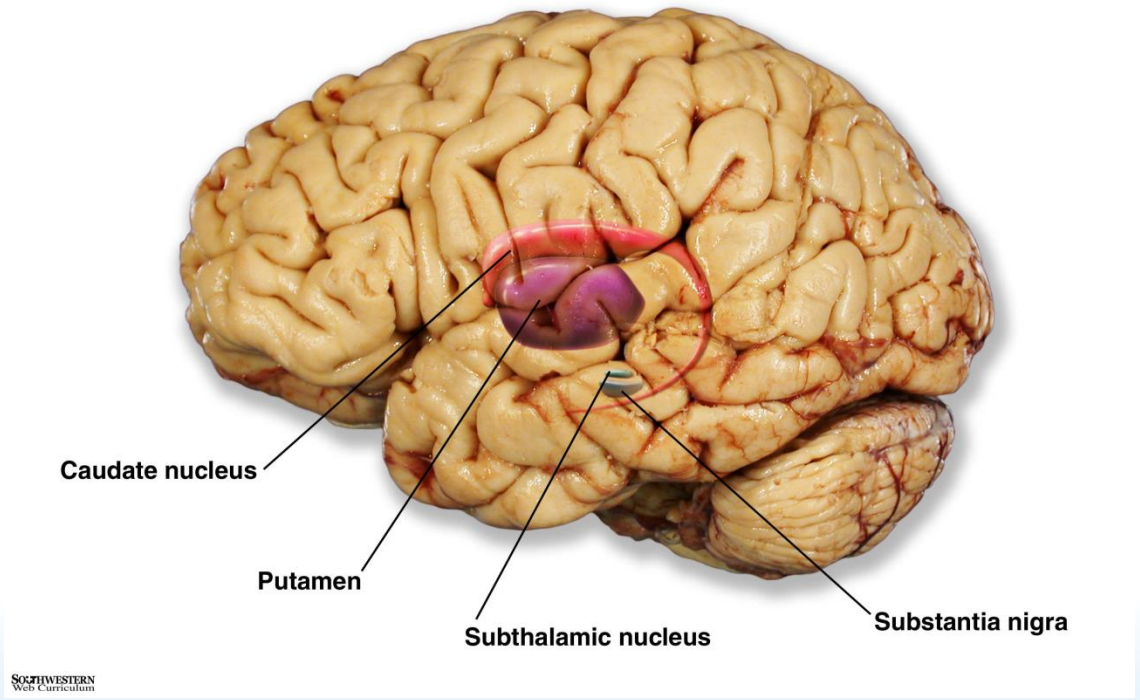


Indirect Pathway
increased thalamic inhibition = decreased cortical excitation

Functional domains influenced by basal ganglia pathways

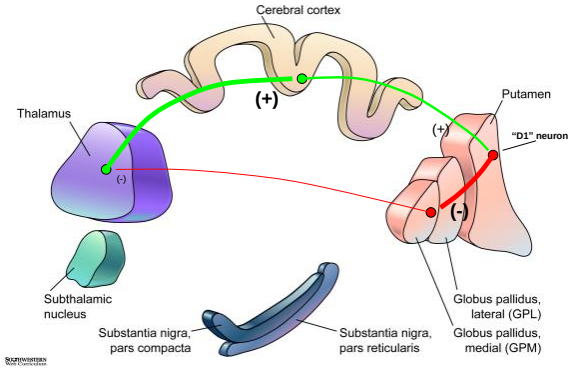
- **Motor** loops
  - Classical motor loop (primary motor cortex/**dorsal striatum**)
  - Premotor (**premotor** cortex and **supplementary motor** cortex/**dorsal striatum**)
  - Oculomotor (**frontal eye fields**/**dorsal striatum**)
- **Associative** loop
  - **Dorsolateral prefrontal** cortex/**dorsal striatum**
  - Cognitive domain – planning future behavior, procedural learning
- **Limbic** loop
  - **Medial and orbital frontal** cortex/**ventral striatum**
  - Mood, emotions, reward-guided behaviors
- **Multiple interconnections** between these functional loops

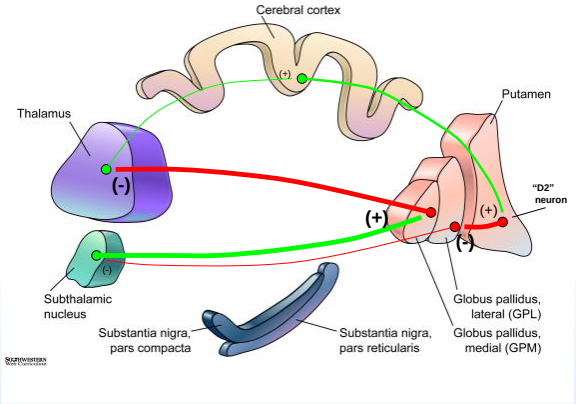


Disorders of the basal ganglia

General considerations

- Historically, have provided important insights into the role of basal ganglia in **normal movement**
- Classical motor abnormalities can be broadly divided into
  - **Hyperkinetic** disturbances
  - **Hypokinetic** disturbances
- Many of motor manifestations can be explained in terms of **derangements in the direct and indirect motor pathways**
- Clinical manifestations of basal ganglia disorders often include **more than pure motor abnormalities**

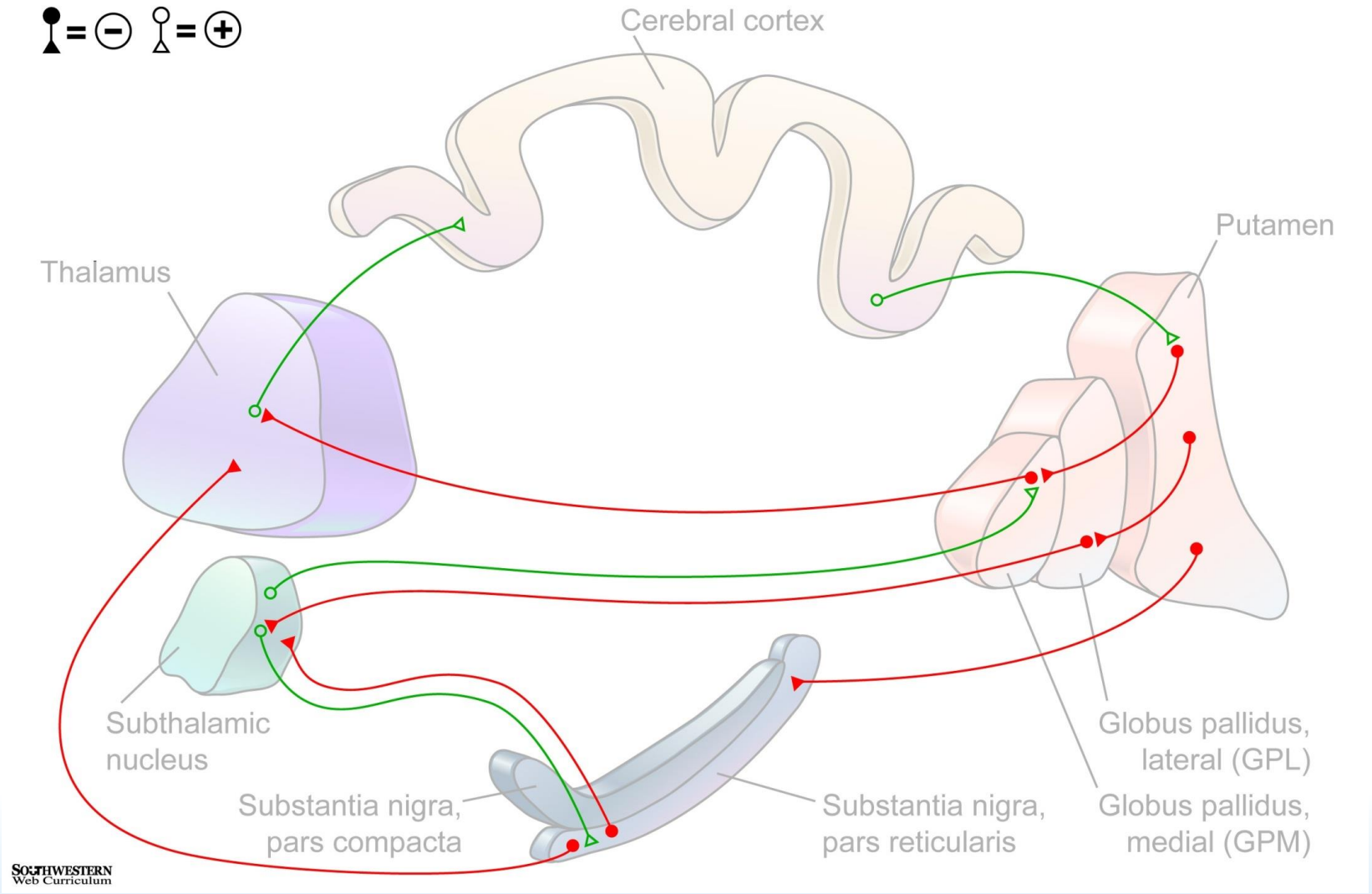




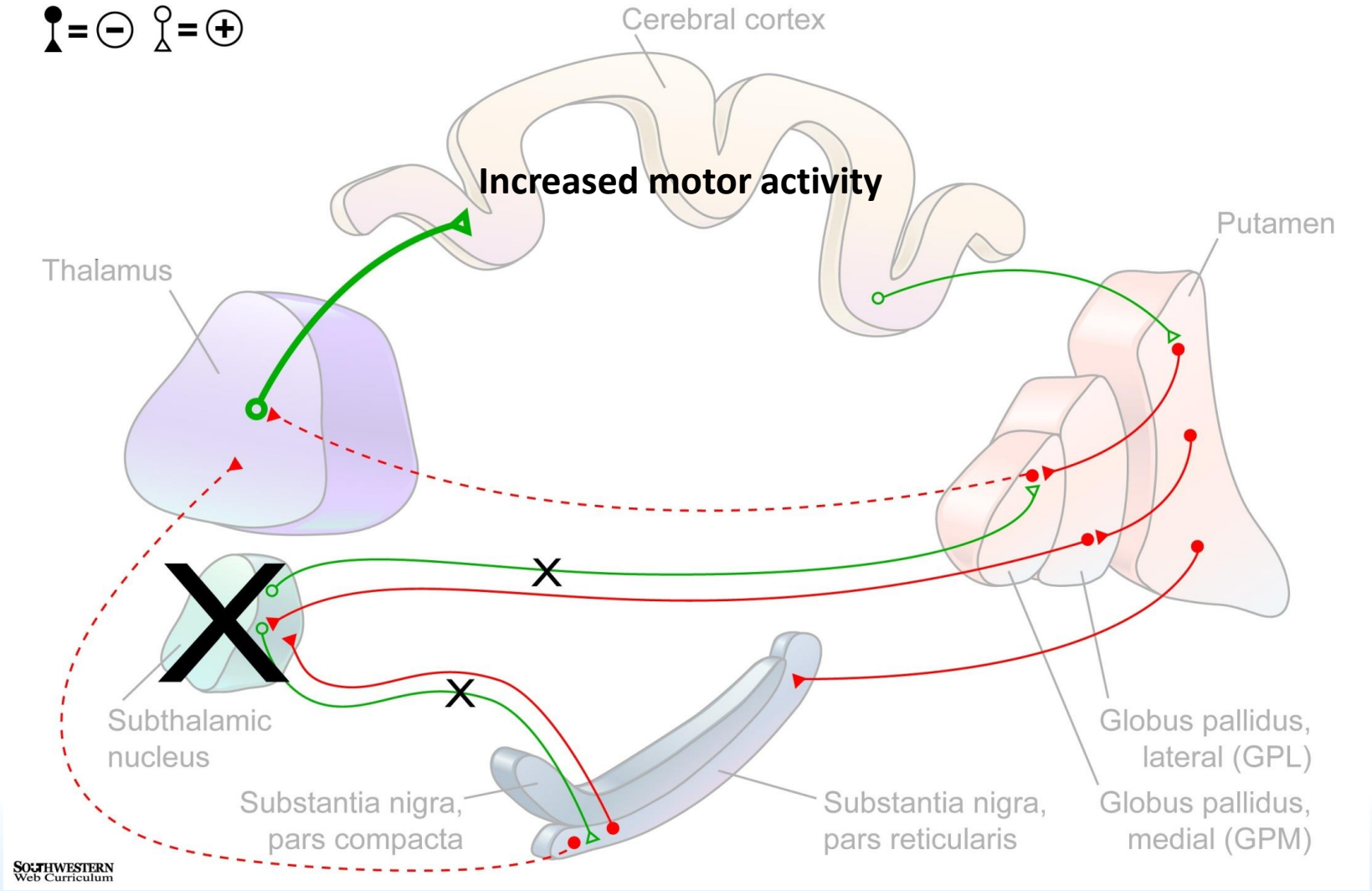
Hemiballism

- A prototypic **hyperkinetic** basal ganglia disorder
- Uncontrolled, spontaneous, flinging movements of an entire limb, often developing acutely
- Classically caused by **injury to contralateral subthalamic nucleus** (usually ischemic)
- What derangements in basal ganglia circuitry account for the unilateral hyperkinesis?

Hemiballism (hemiballismus)

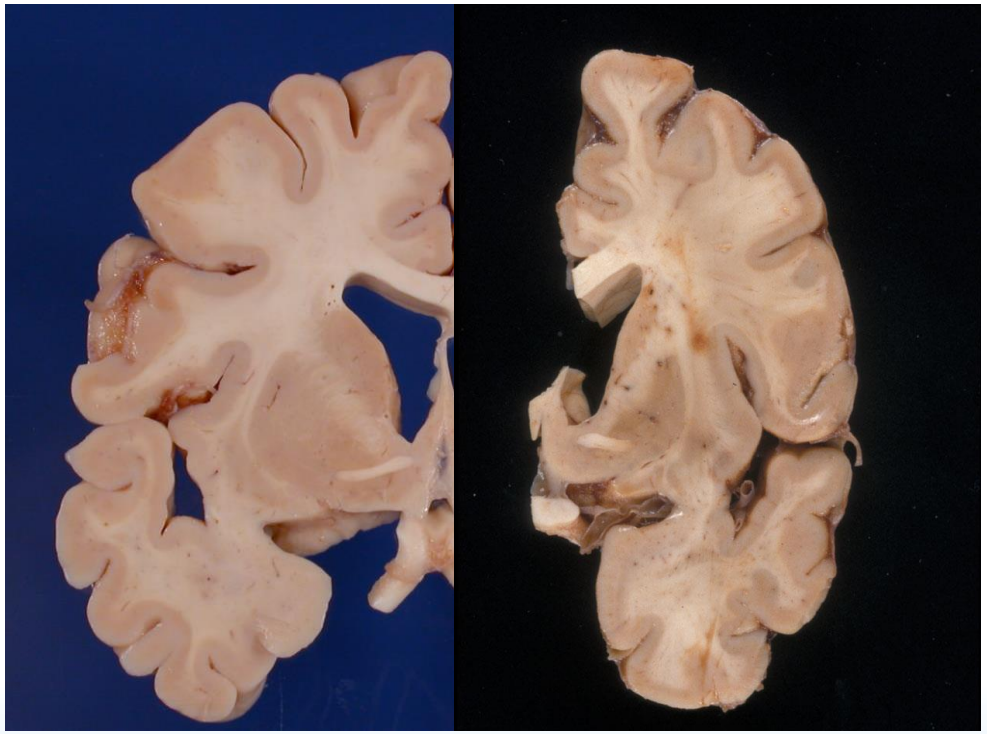


Hemiballism (continued)

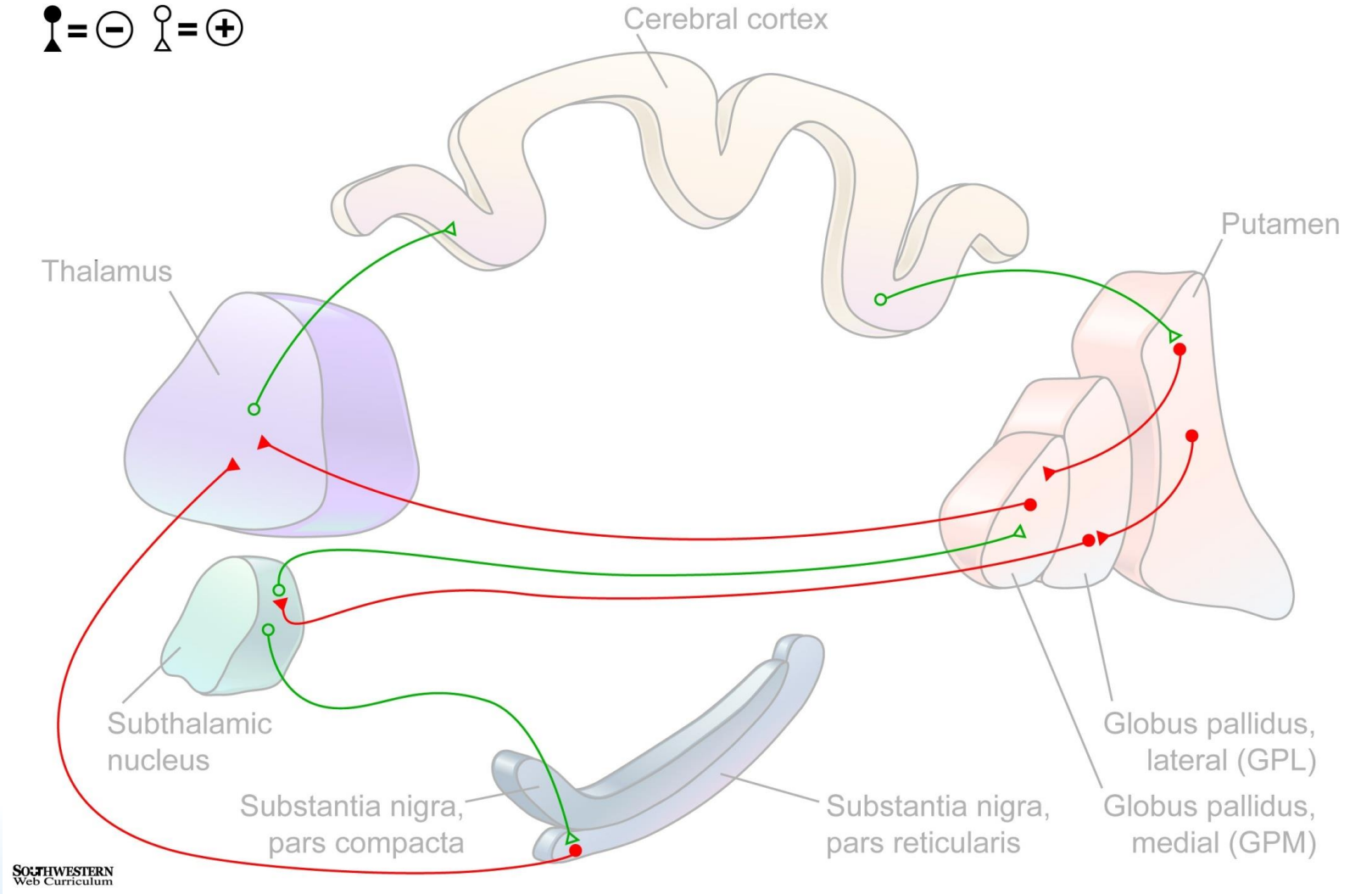


Huntington Disease

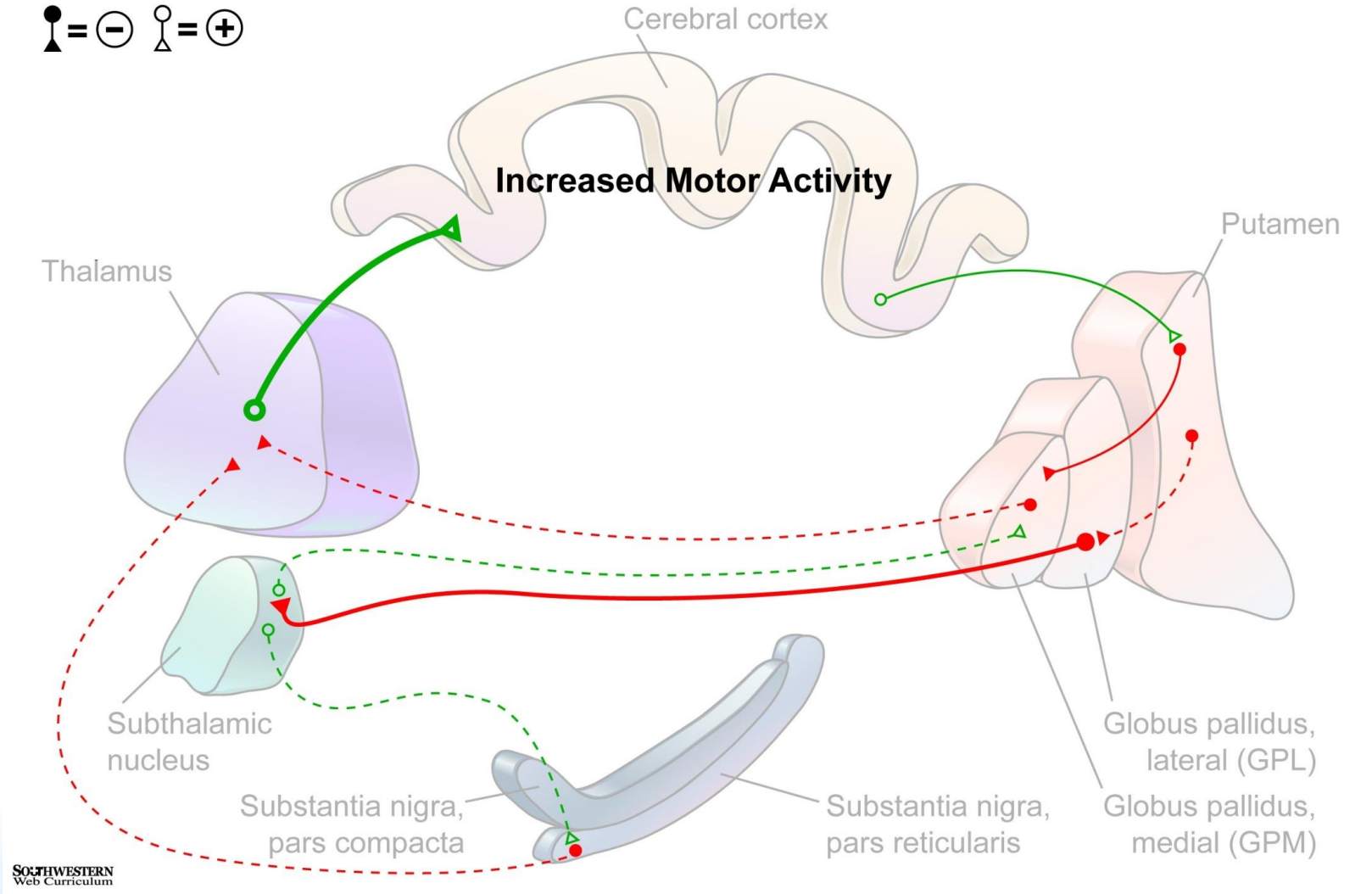
- Abnormal expansion of CAG tandem repeats in ***huntingtin*** gene (chromosome 4p)
  - Normal ~20
  - **HD >40**
- Accumulation of **excess polyglutamine residues** in huntingtin protein
- Progressive loss of GABAergic medium spiny neurons in striatum
  - Preferential loss of **D2 neurons** in classical ("hyperkinetic") cases
  - Loss of both **D2 and D1** neurons in akinetic/rigid variants and in later stages of classical cases
- Manifestations include
  - **Movement disorders** (choreiform movements in classical cases; rigidity in early onset cases or later in course of classical disease)
  - **Neuropsychiatric disturbances** (often antedate motor abnormalities)



Huntington's Disease I

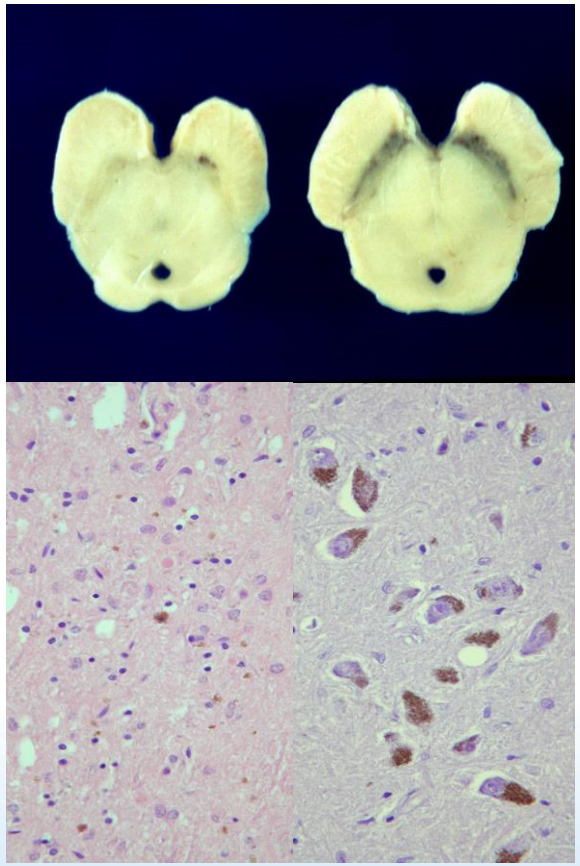


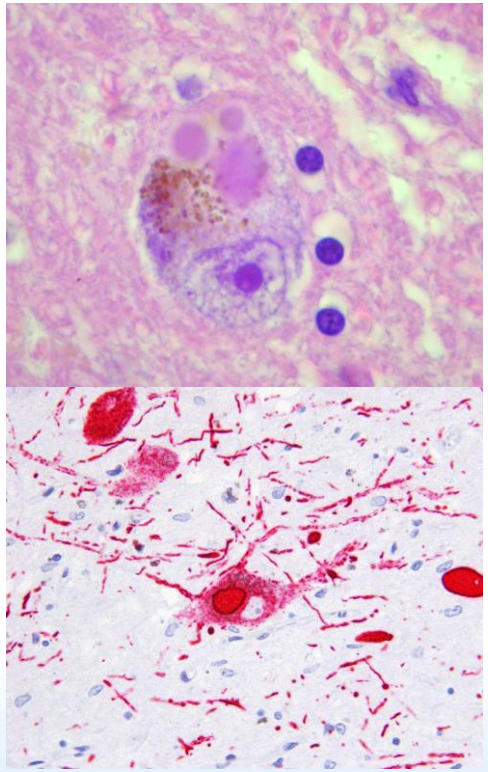
Huntington's Disease II



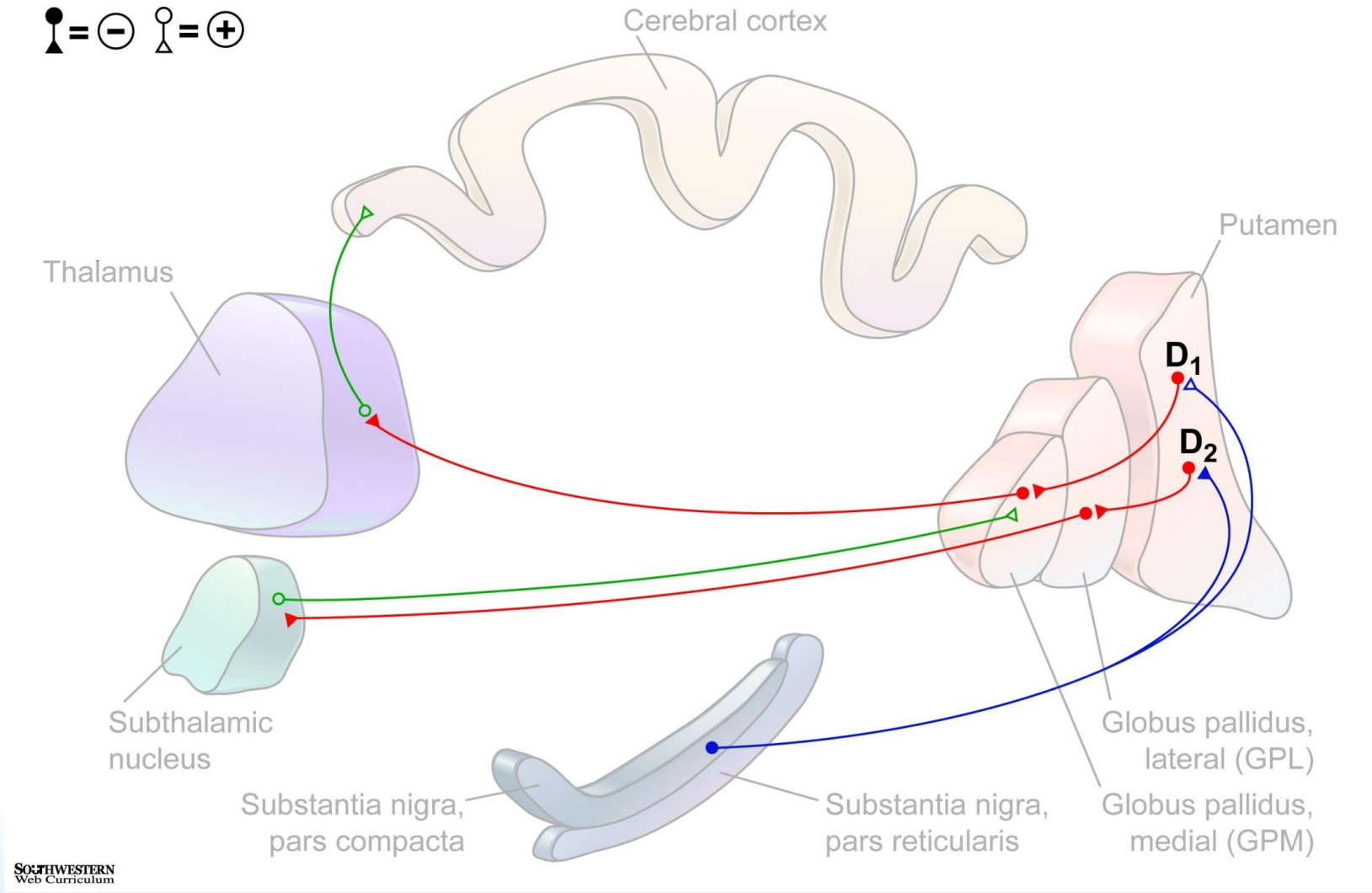
Parkinson's disease (PD)

- A prototypic **hypokinetic** basal ganglia disorder
- One of a growing family of **α-synucleinopathies**
  - Sporadic PD
  - Genetic PD variants
  - Diffuse Lewy body disease
  - Multiple systems atrophy
- Classical PD associated with a **selective loss of dopaminergic projections** to striatal medium spiny neurons (D1 and D2 subsets)
- Manifestations include
  - Hypokinesia / rigidity
  - Postural instability
  - Resting tremor
  - Autonomic dysfunction
  - Behavioral / cognitive disturbances

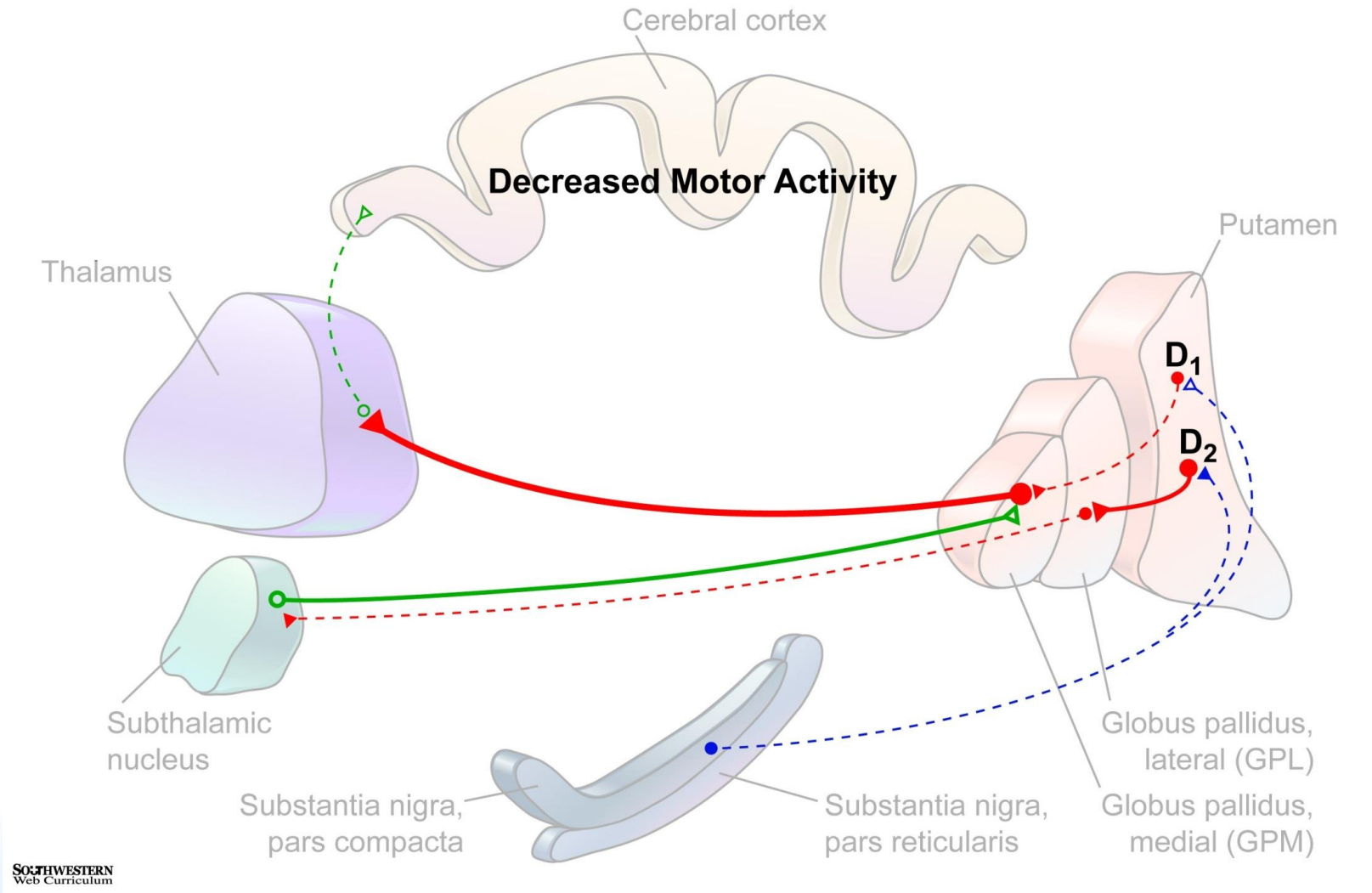




Parkinson's Disease I



Parkinson's Disease II



SOUTHWESTERN Web Curriculum

View from Skyline Drive, Shenandoah National Park