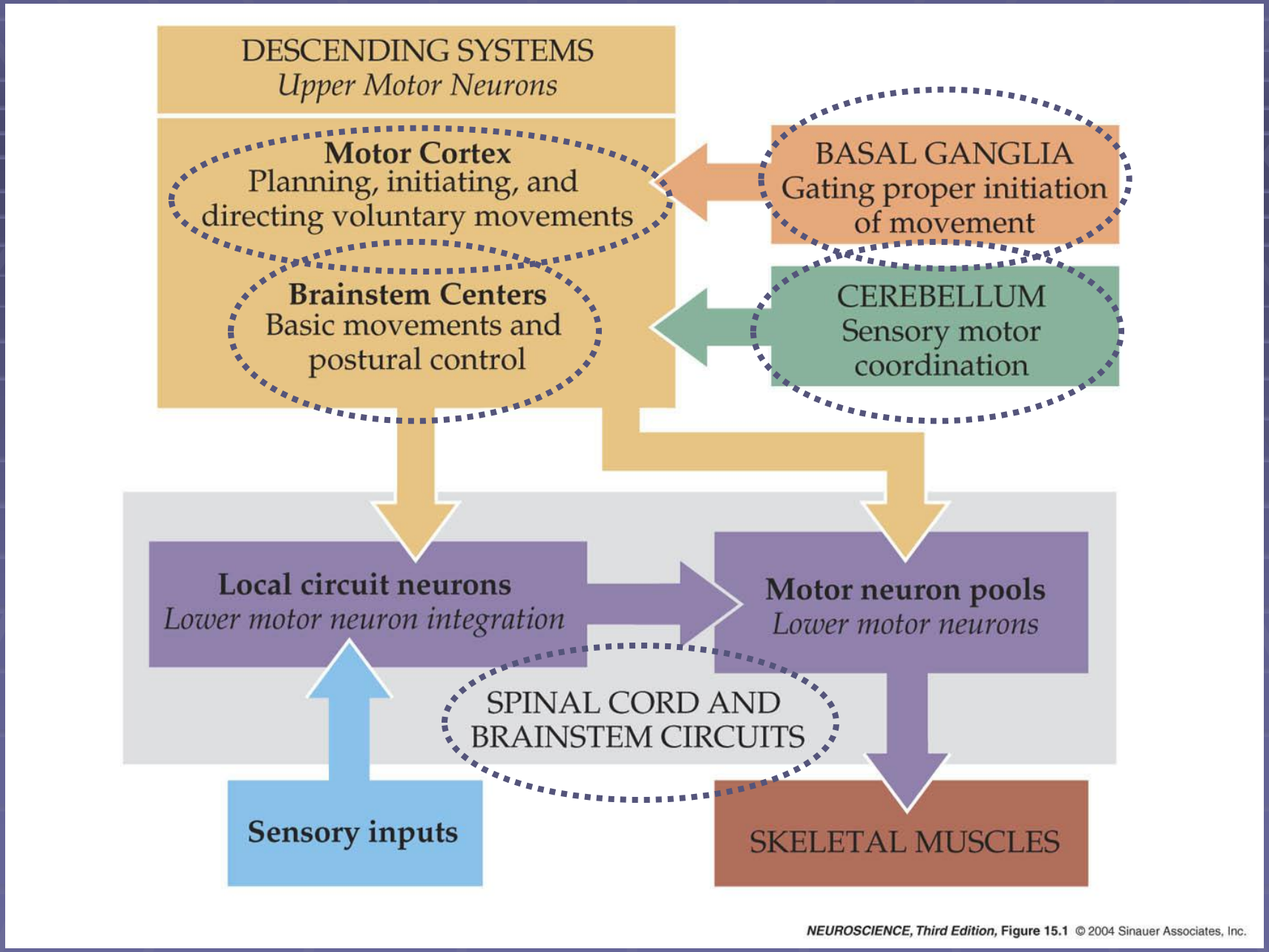
The motor regulator

1) Basal ganglia/nucleus

Neural structures involved in the control of movement



NEUROSCIENCE, Third Edition, Figure 15.1 © 2004 Sinauer Associates, Inc.

Basal Ganglia

- Components of the basal ganglia

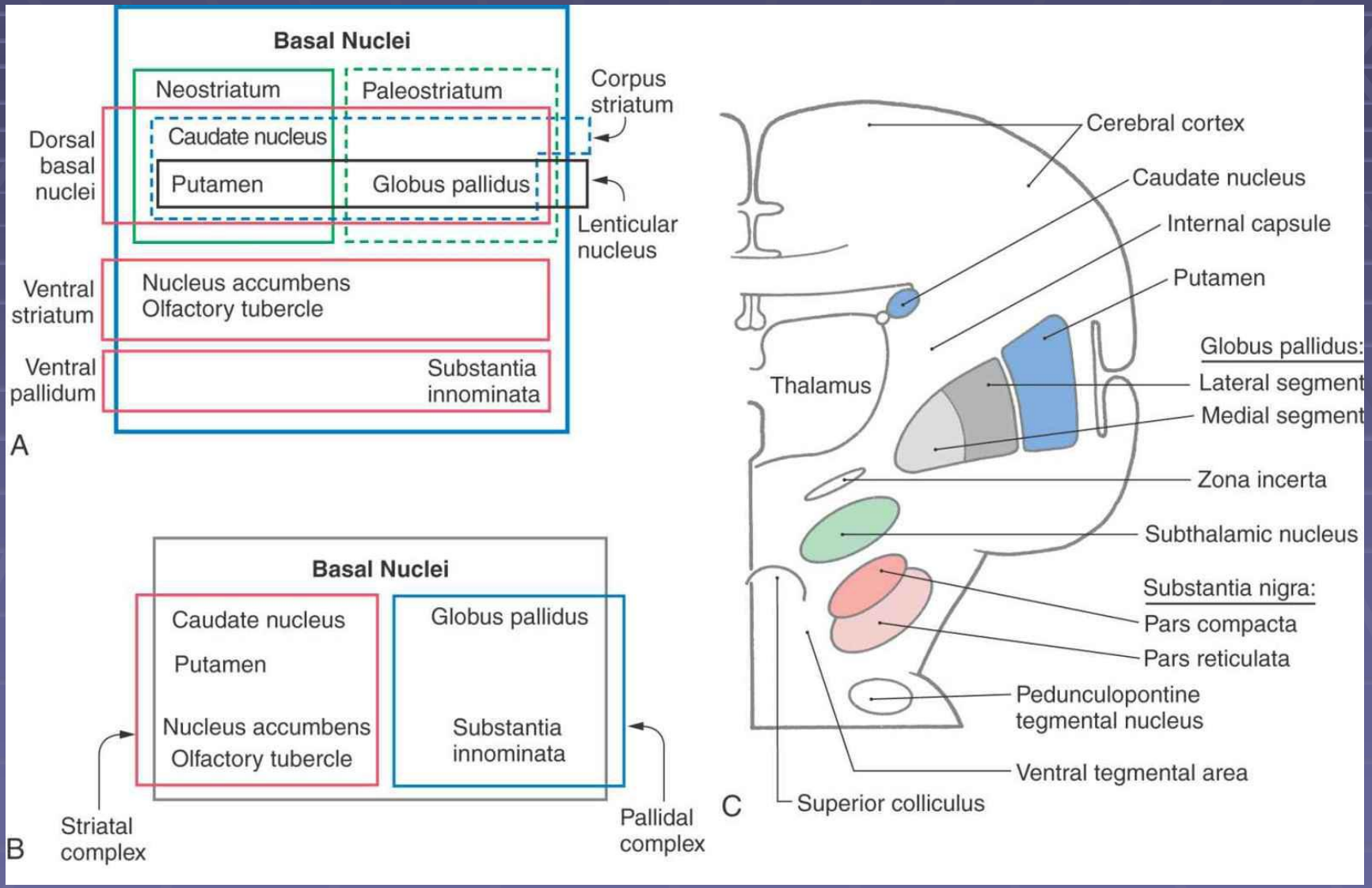
- Function of the basal ganglia

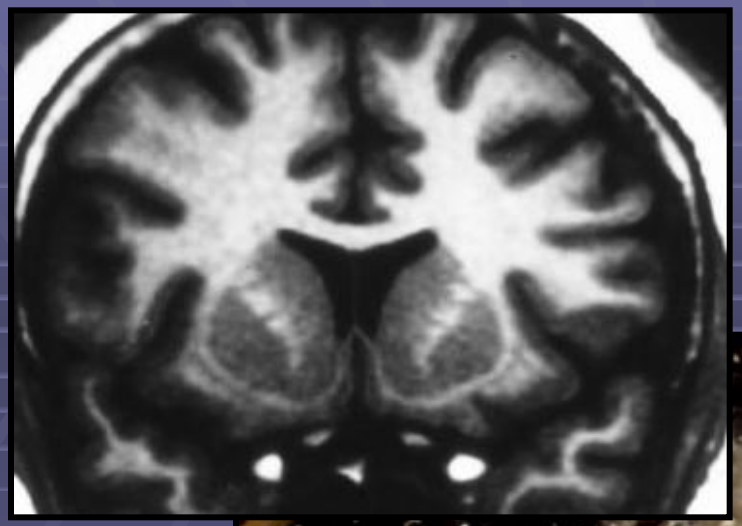
- Connection and circuits

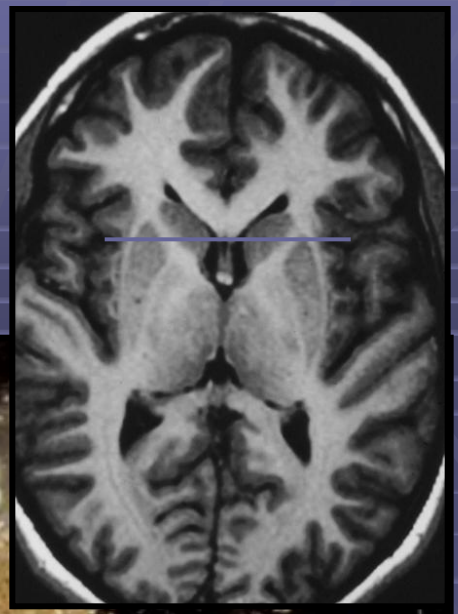
- Functional circuitry of the basal ganglia
  e.g., direct and indirect pathways, transmitters

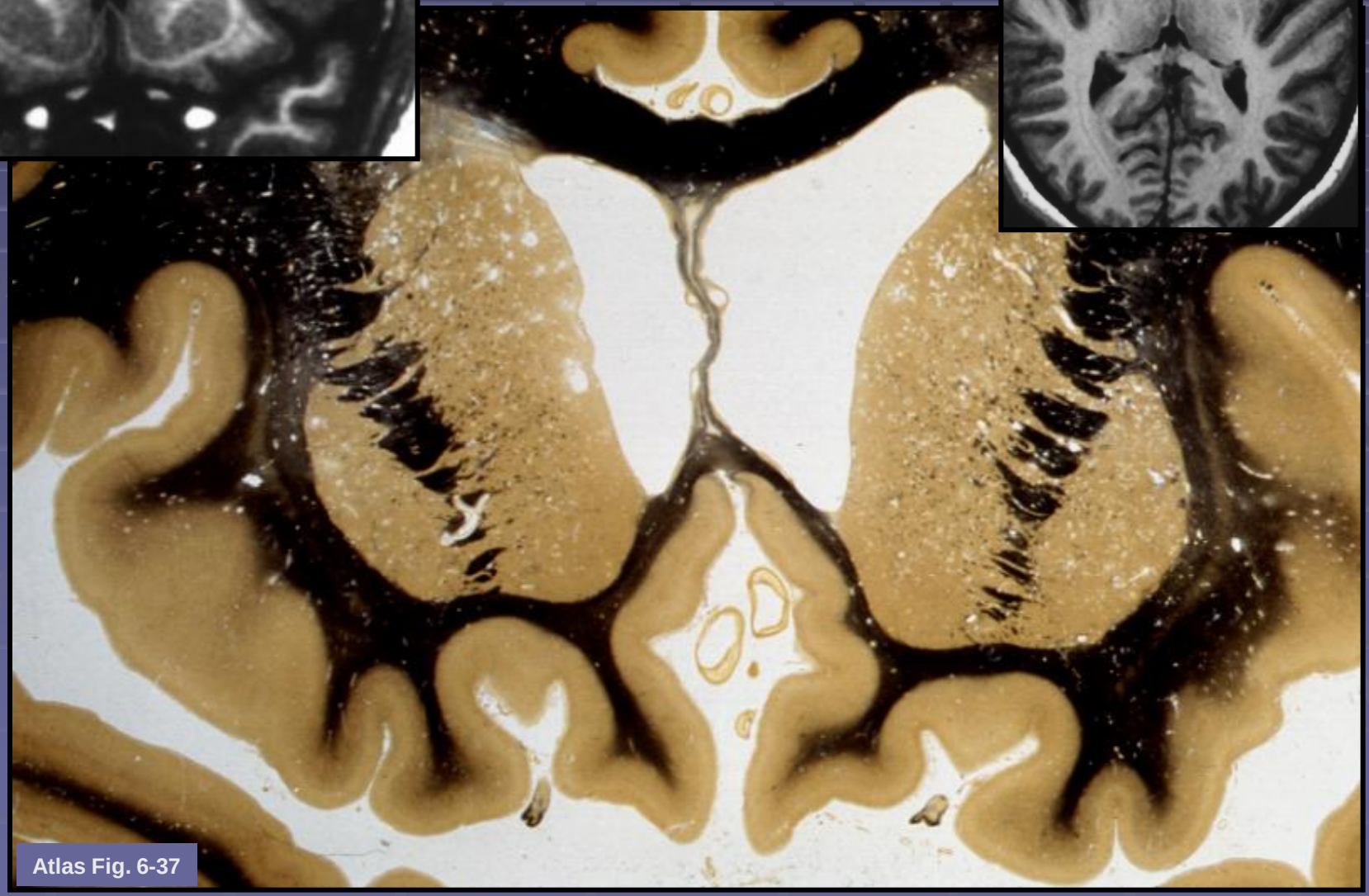
- Symptoms and disorders discussed

Parts

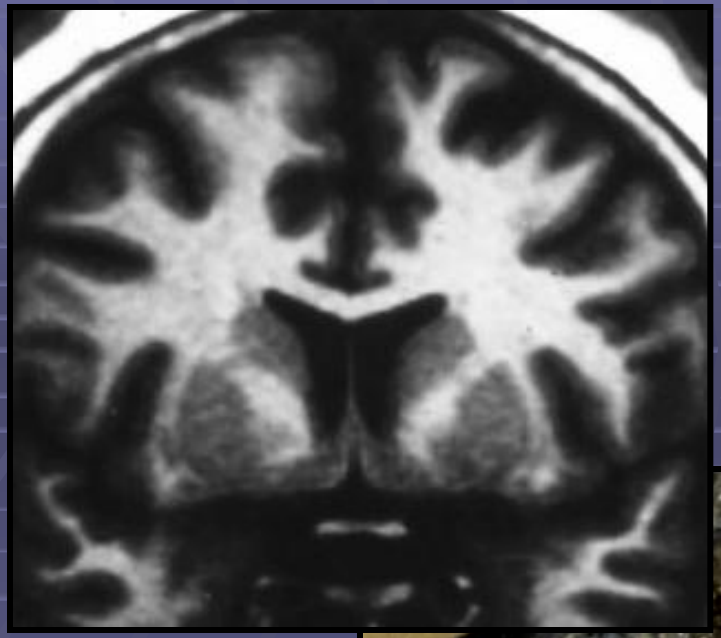

Basal Nuclei
Neostriatum
Paleostriatum
Corpus striatum
Caudate nucleus
Dorsal basal nuclei
Putamen
Globus pallidus
Lenticular nucleus
Ventral striatum
Nucleus accumbens
Olfactory tubercle
Ventral pallidum
Substantia innominata
A
Basal Nuclei
Caudate nucleus
Putamen
Globus pallidus
Nucleus accumbens
Olfactory tubercle
Substantia innominata
Striatal complex
Pallidal complex
B
Cerebral cortex
Caudate nucleus
Internal capsule
Putamen
Thalamus
Globus pallidus:
Lateral segment
Medial segment
Zona incerta
Subthalamic nucleus
Substantia nigra:
Pars compacta
Pars reticulata
Pedunculopontine tegmental nucleus
Ventral tegmental area
Superior colliculus
C

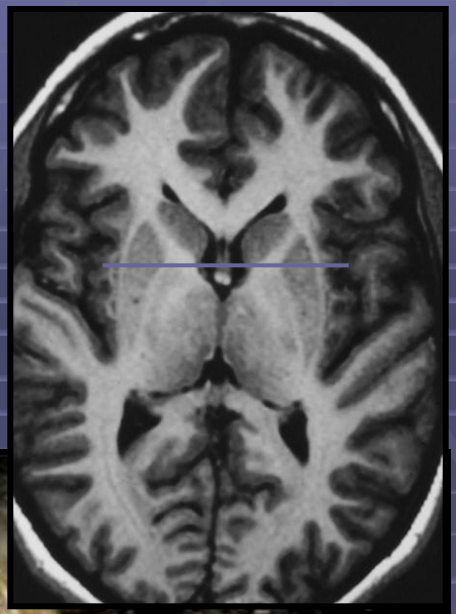


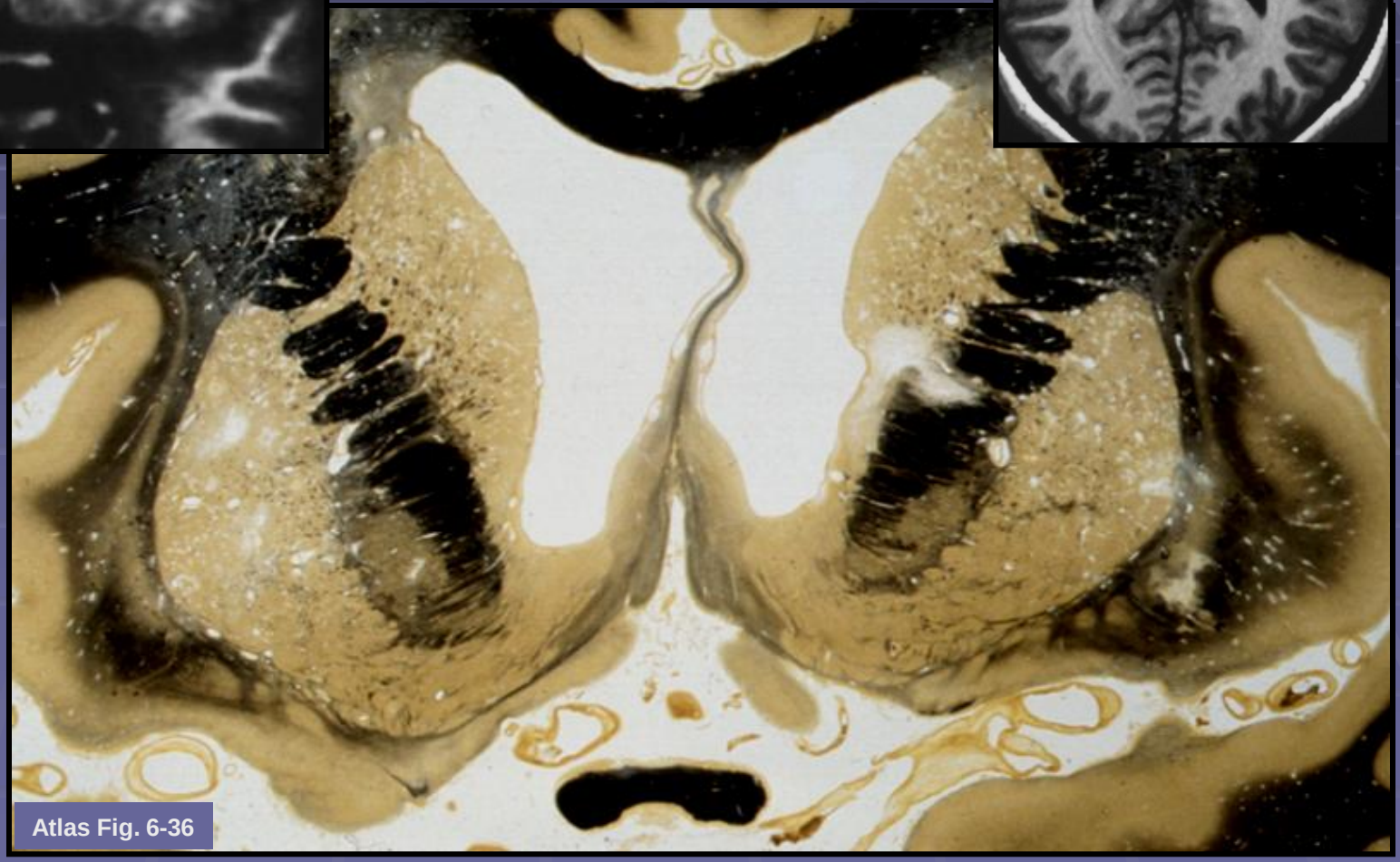




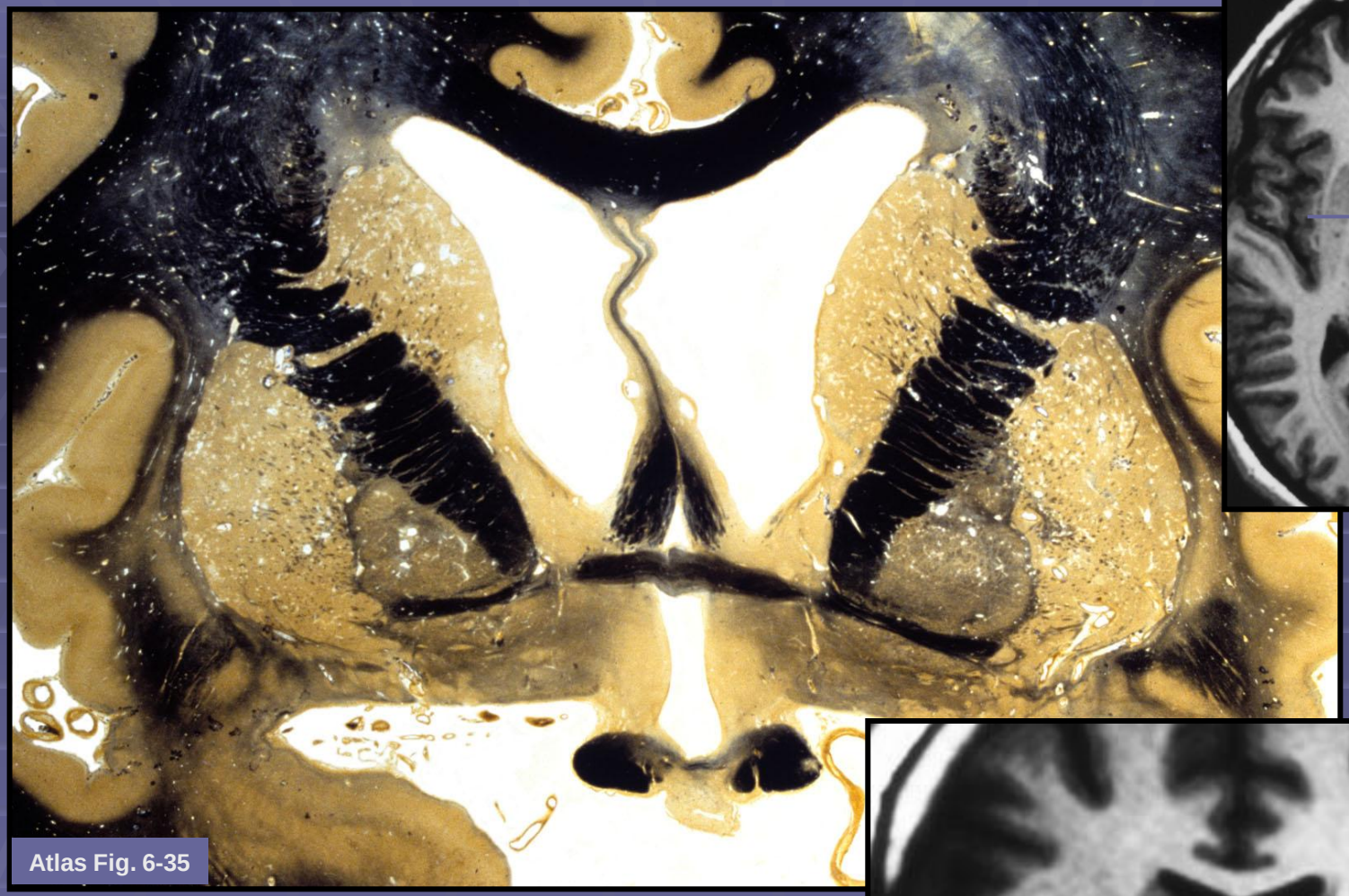
Atlas Fig. 6-37



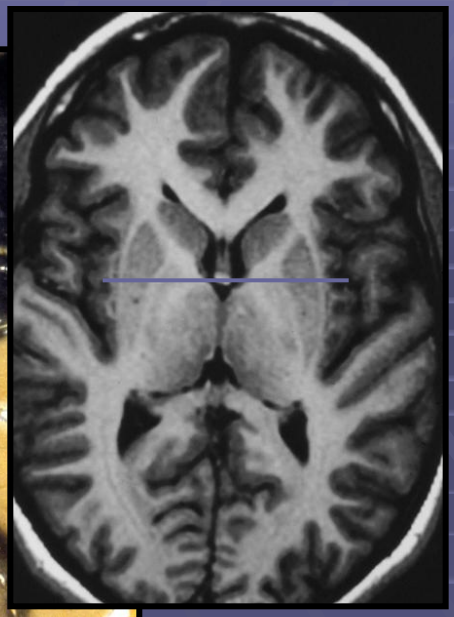


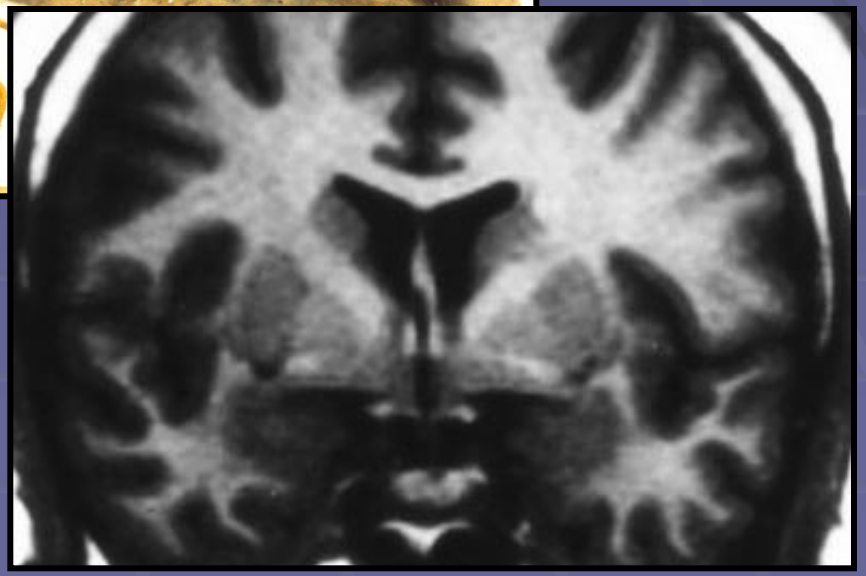


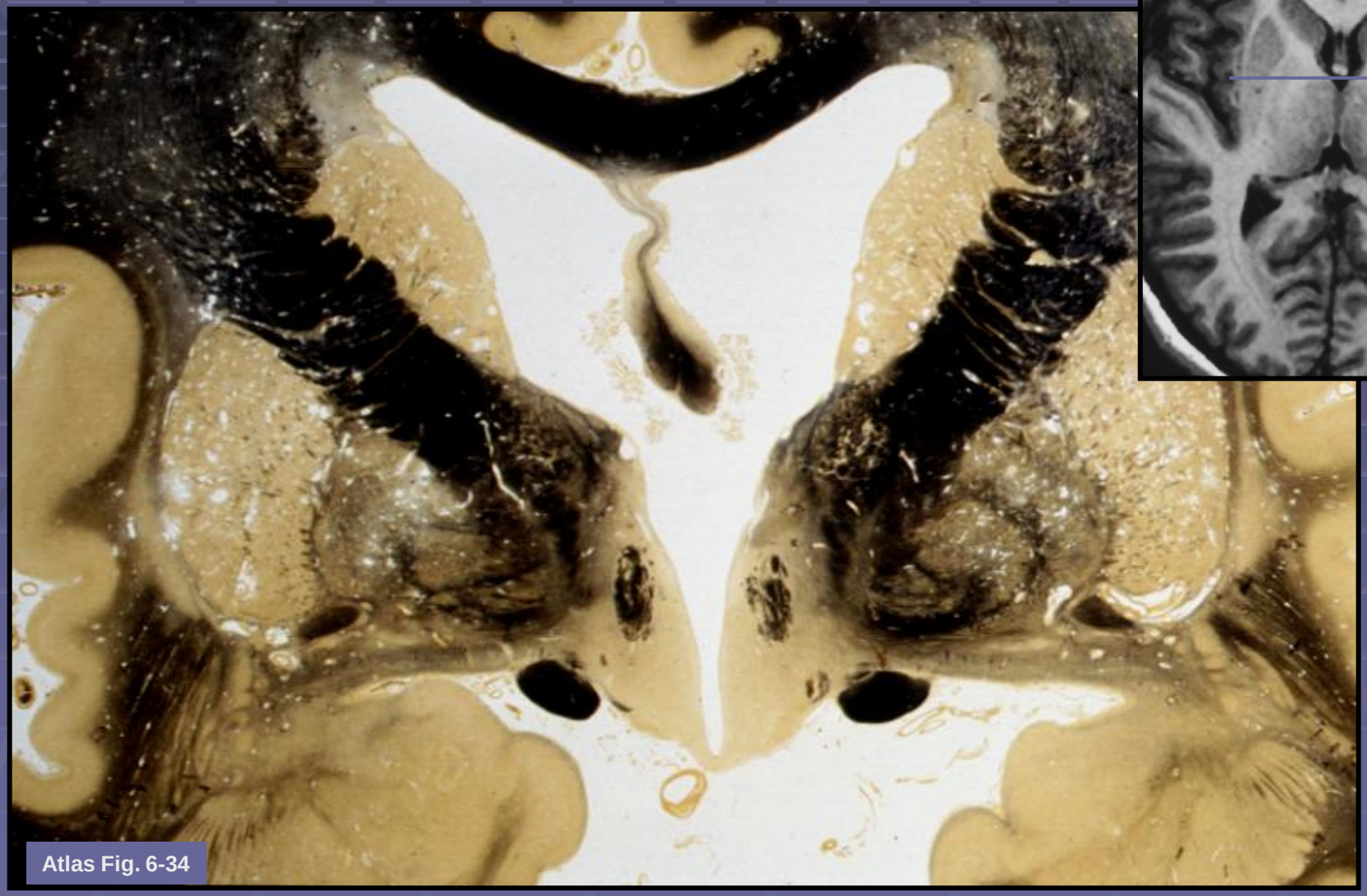
Atlas Fig. 6-36

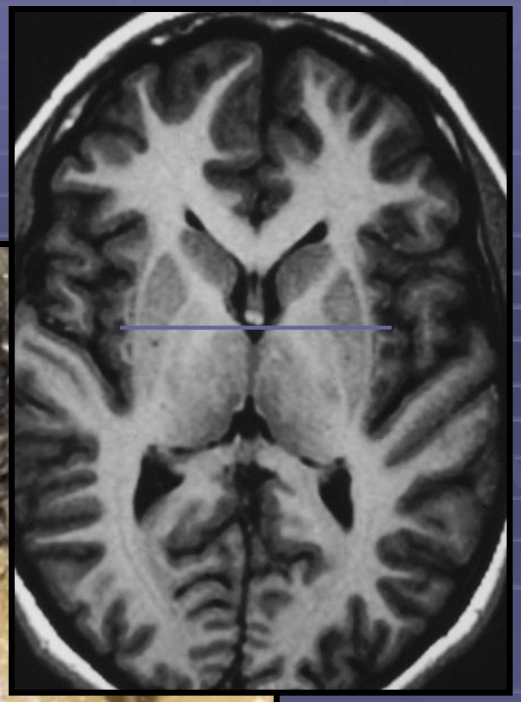


Atlas Fig. 6-35

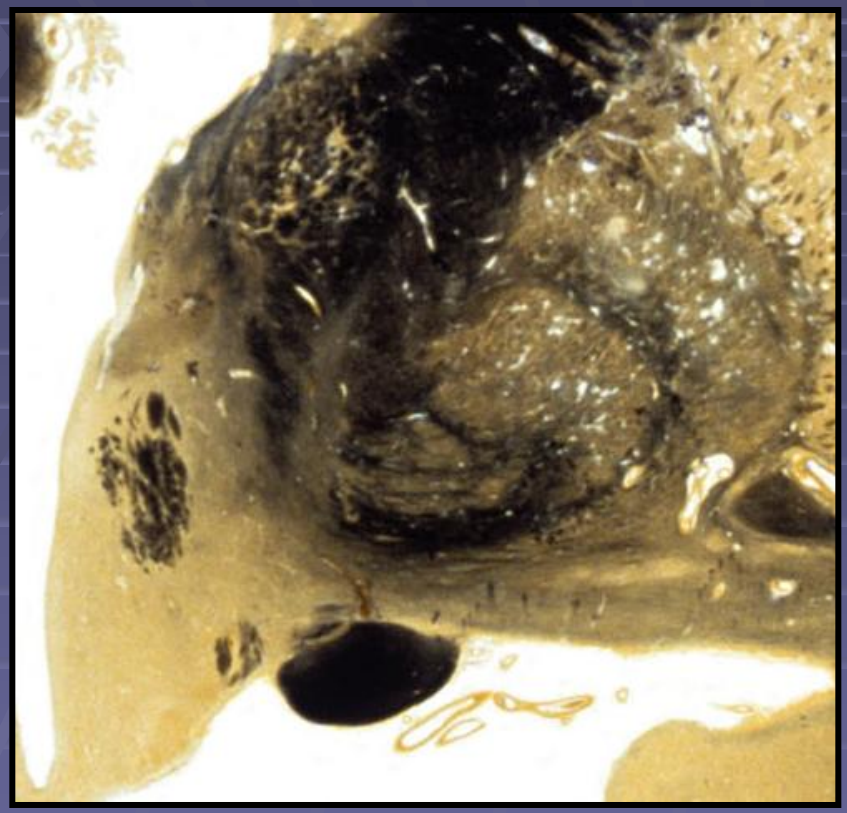


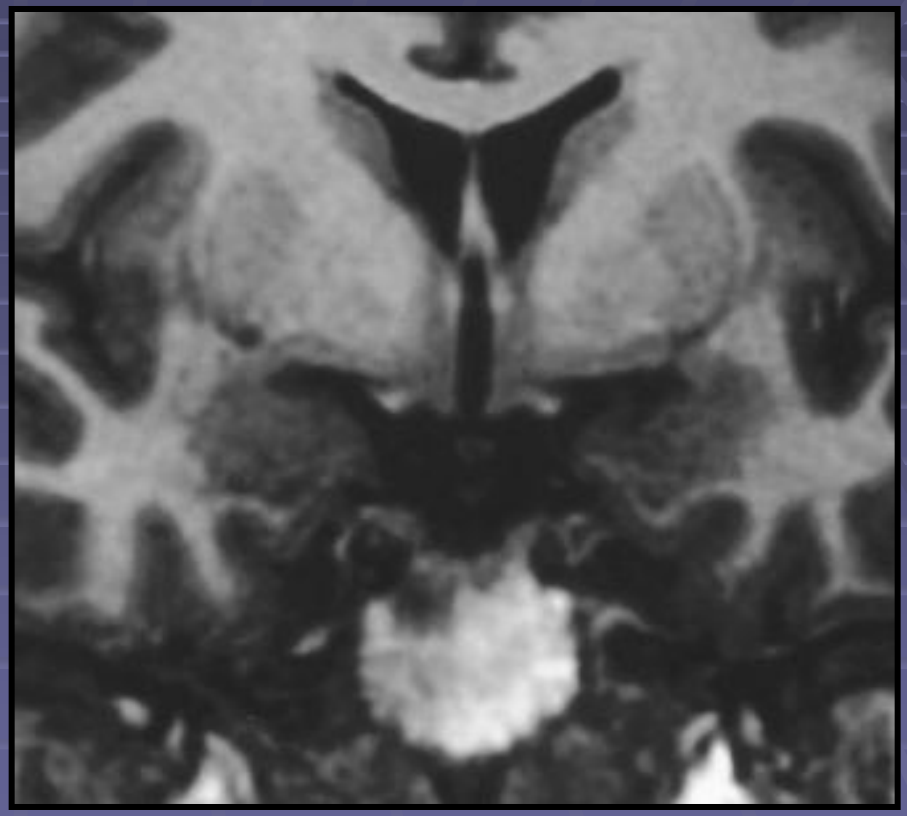


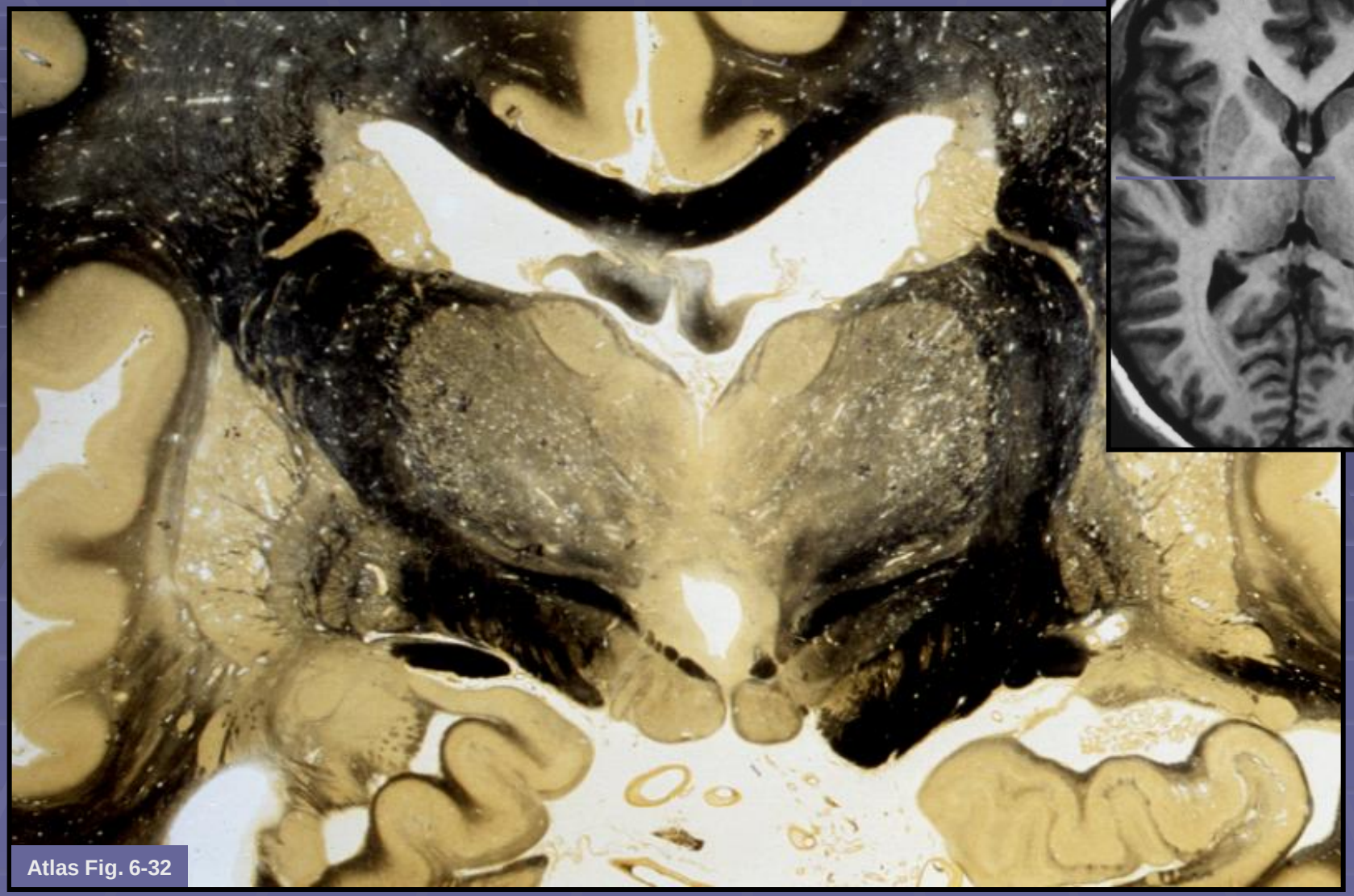




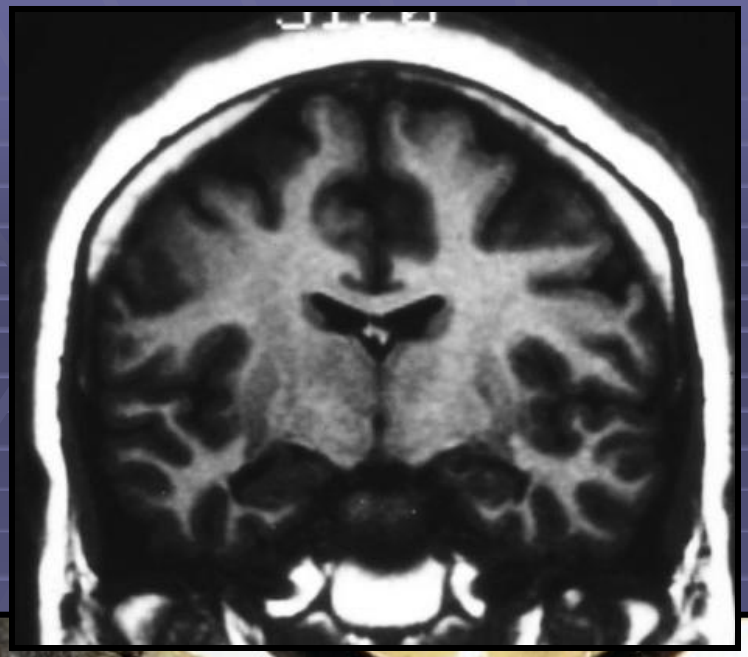
Atlas Fig. 6-34

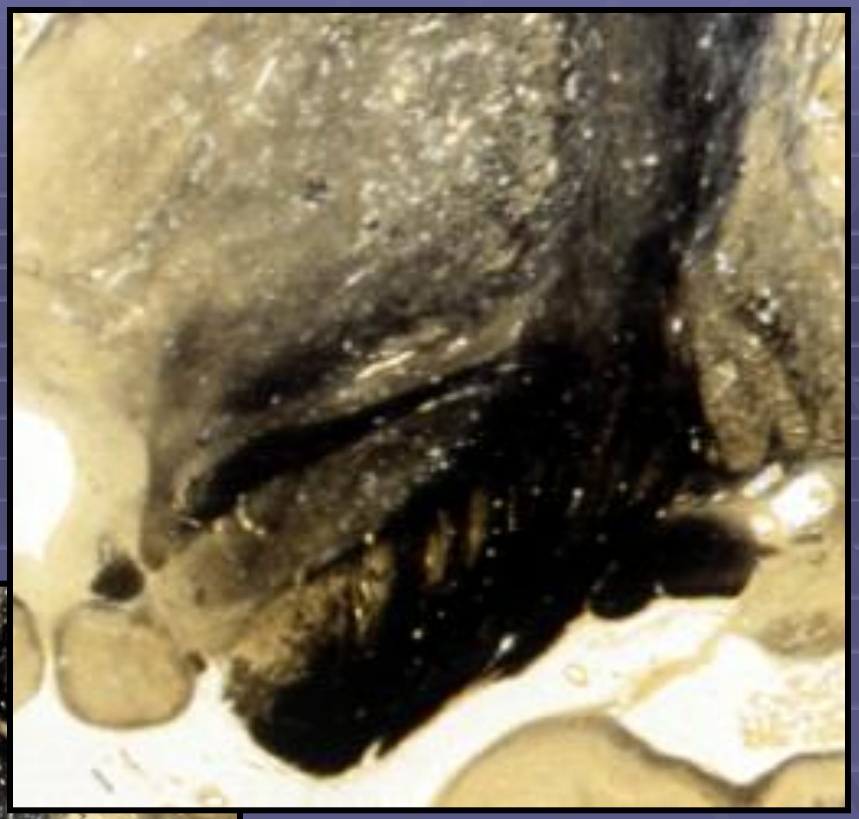


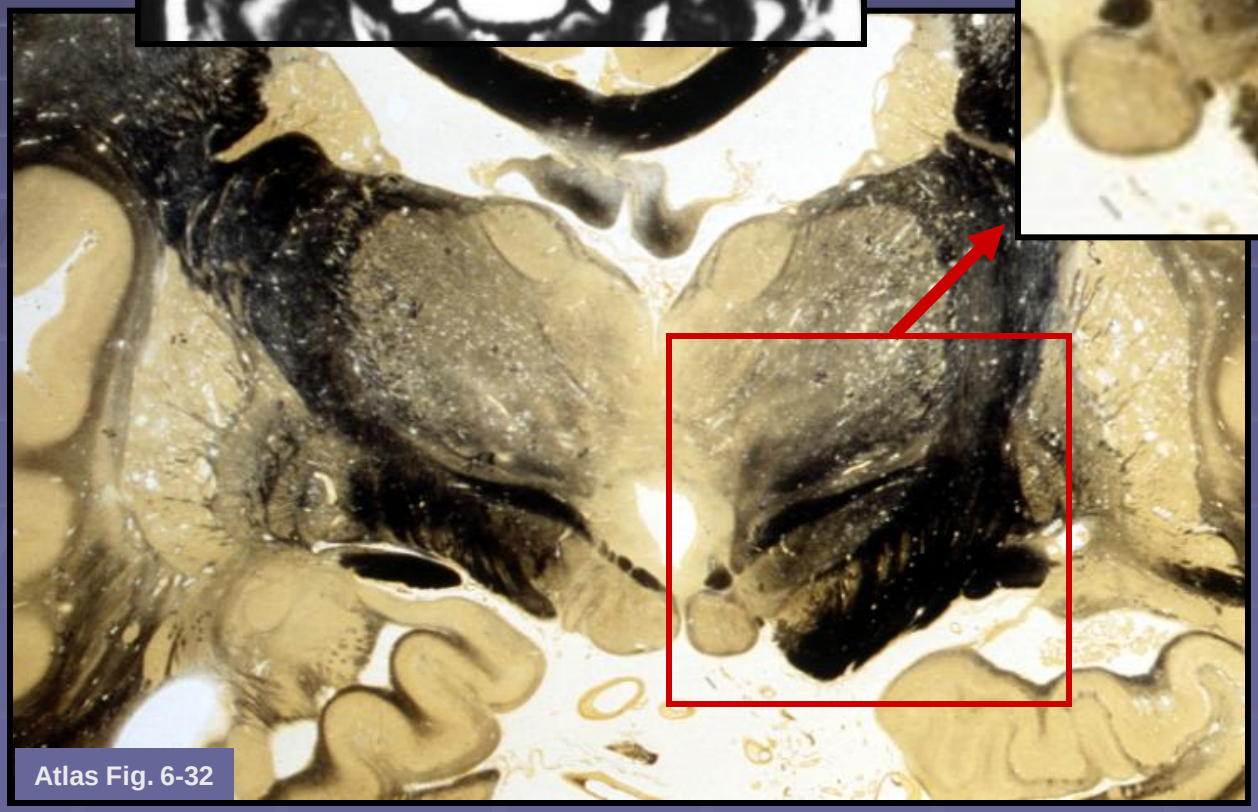




Atlas Fig. 6-32

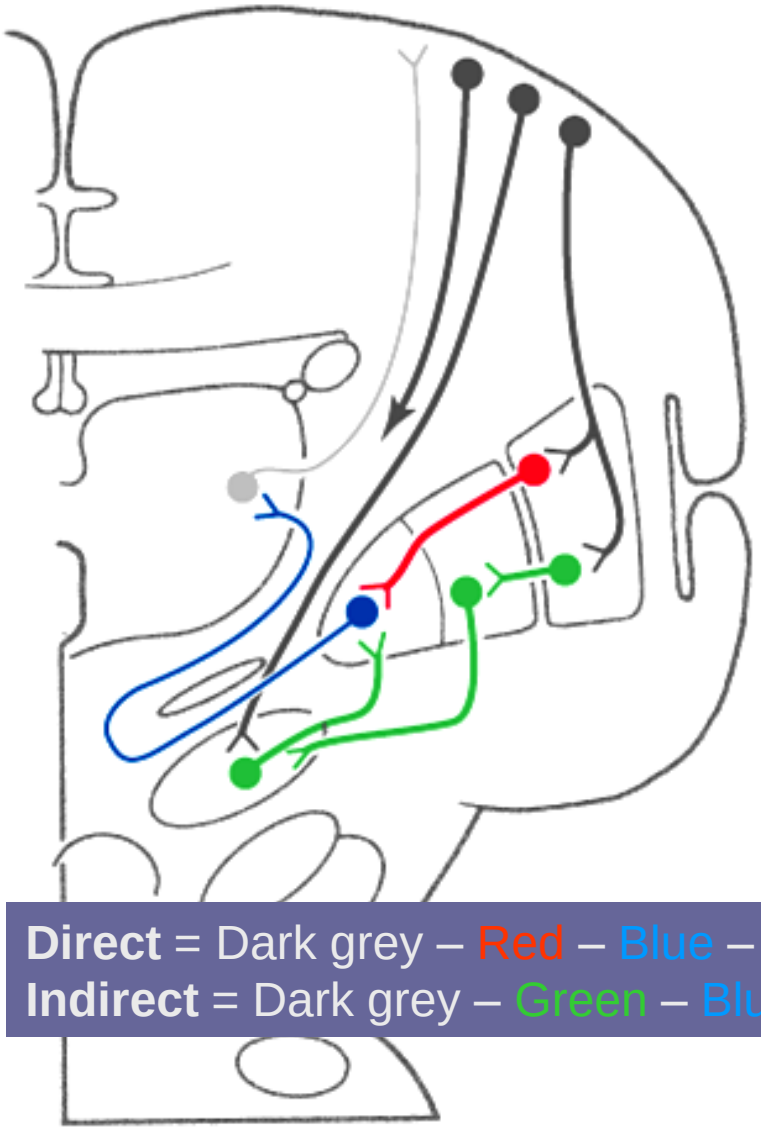






Atlas Fig. 6-32

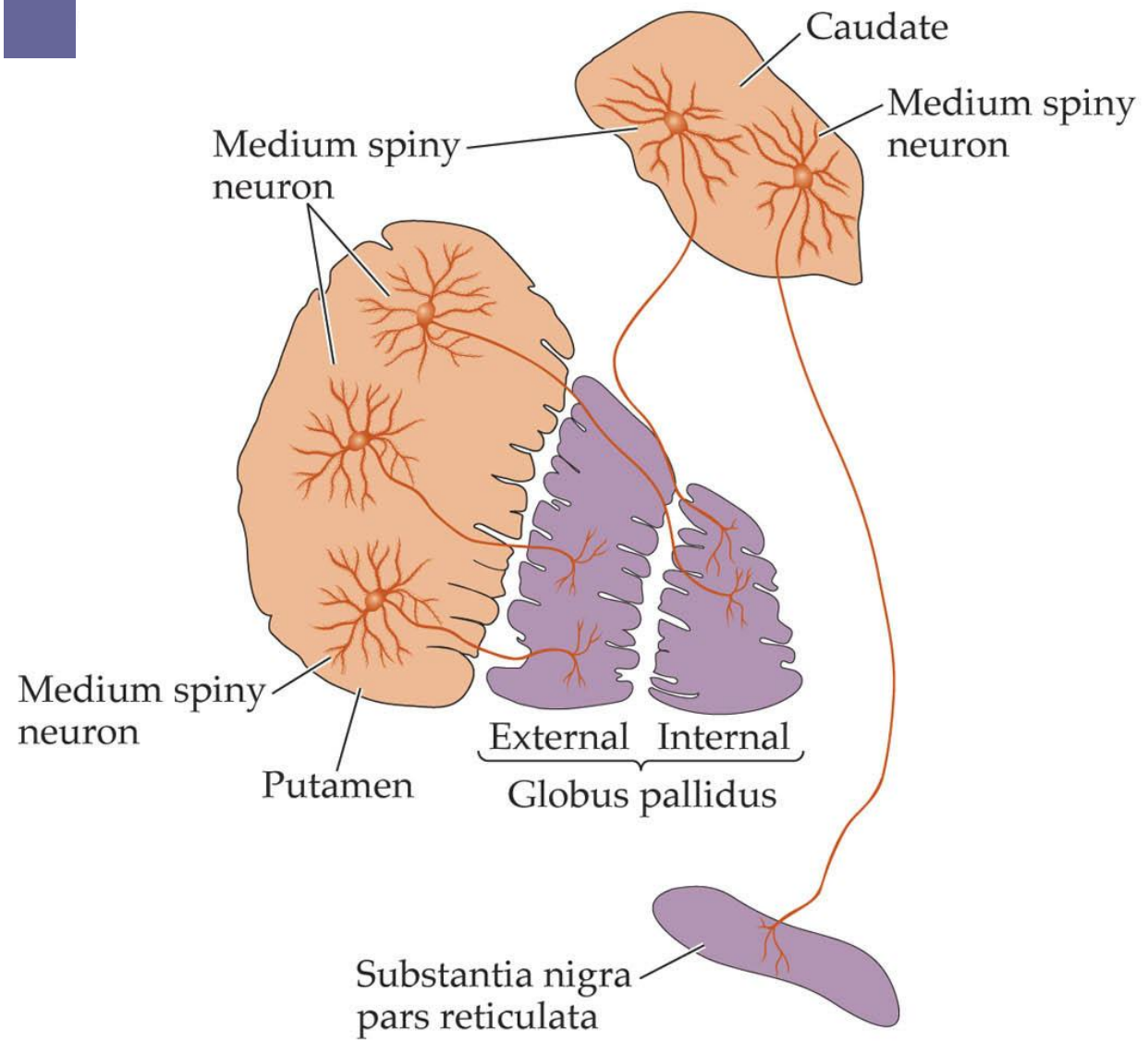
Function of the basal ganglia



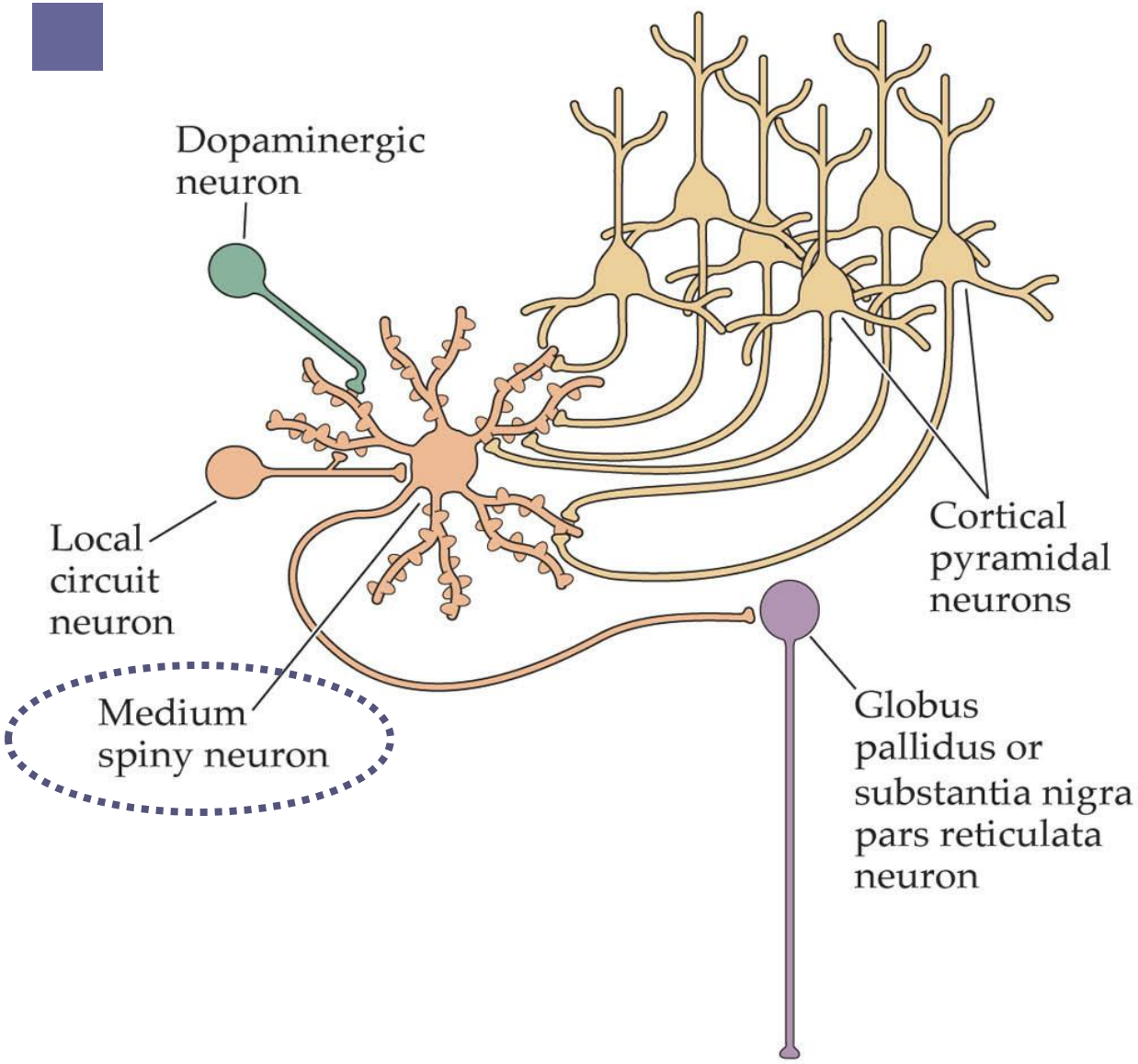
Direct = Dark grey – Red – Blue – Light grey
Indirect = Dark grey – Green – Blue – Light grey

Text Fig. 26-9

Medium spiny neuron projections



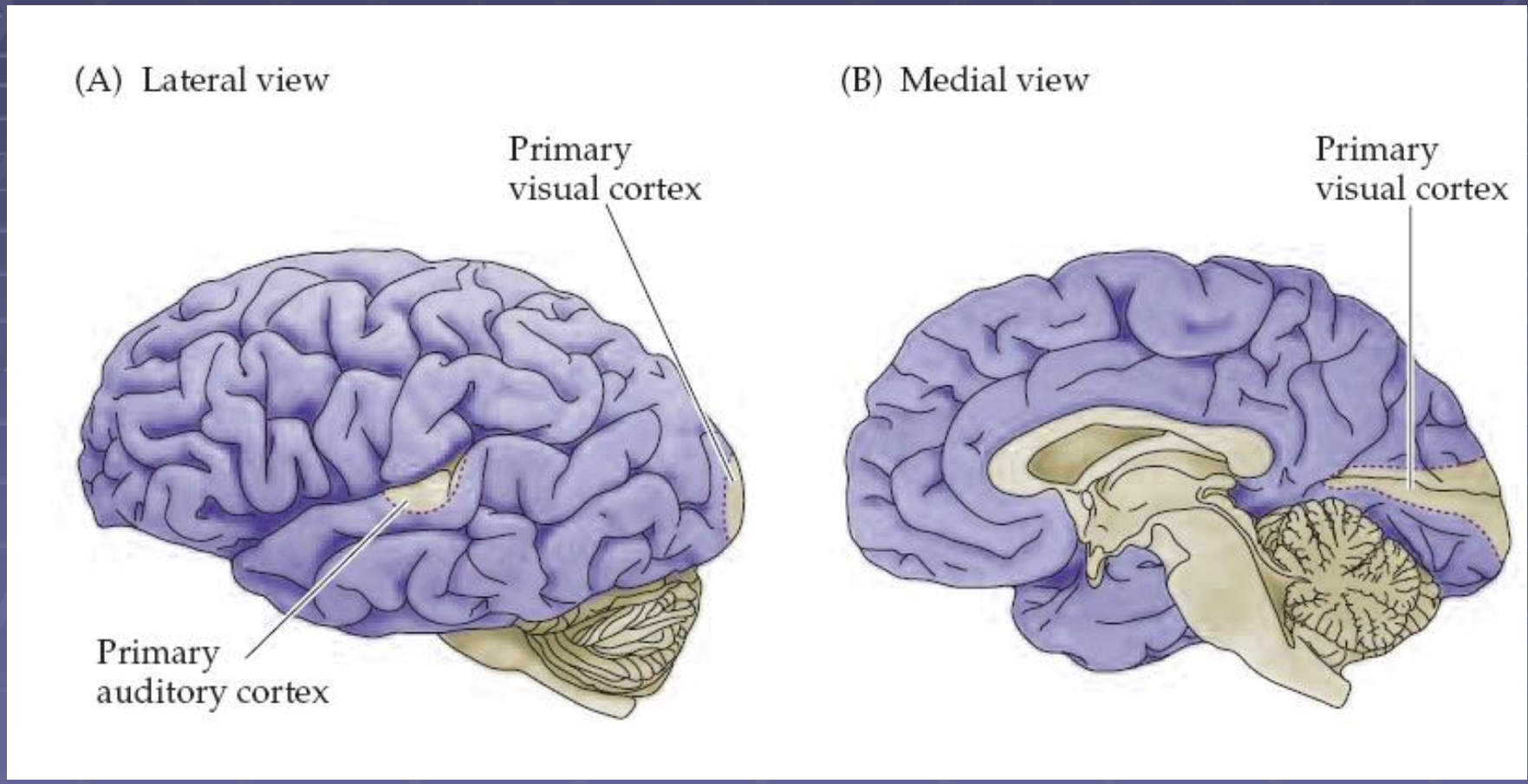
Neurons of the basal ganglia



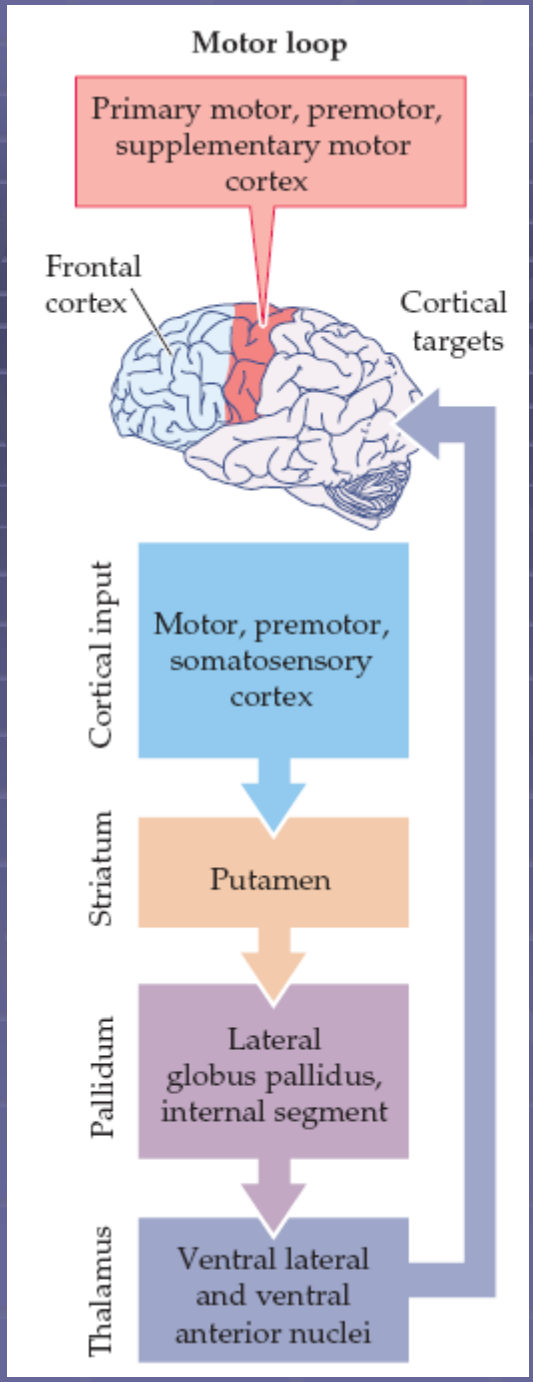
NEUROSCIENCE, Third Edition, **Figure 17.3 (Part 2)**

Connections and circuits

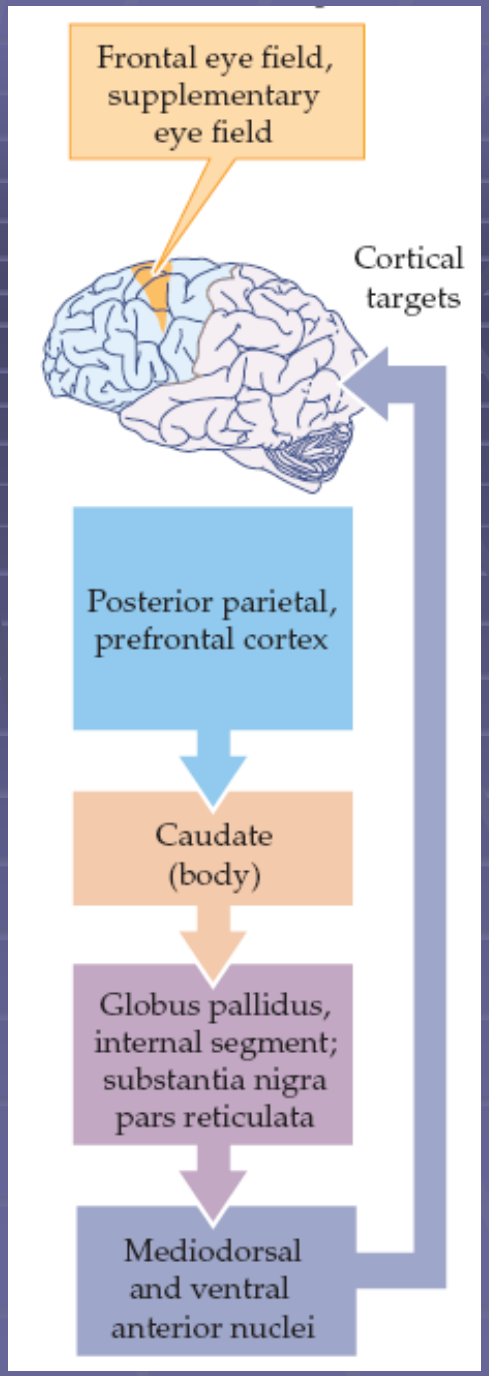
Connections and circuits



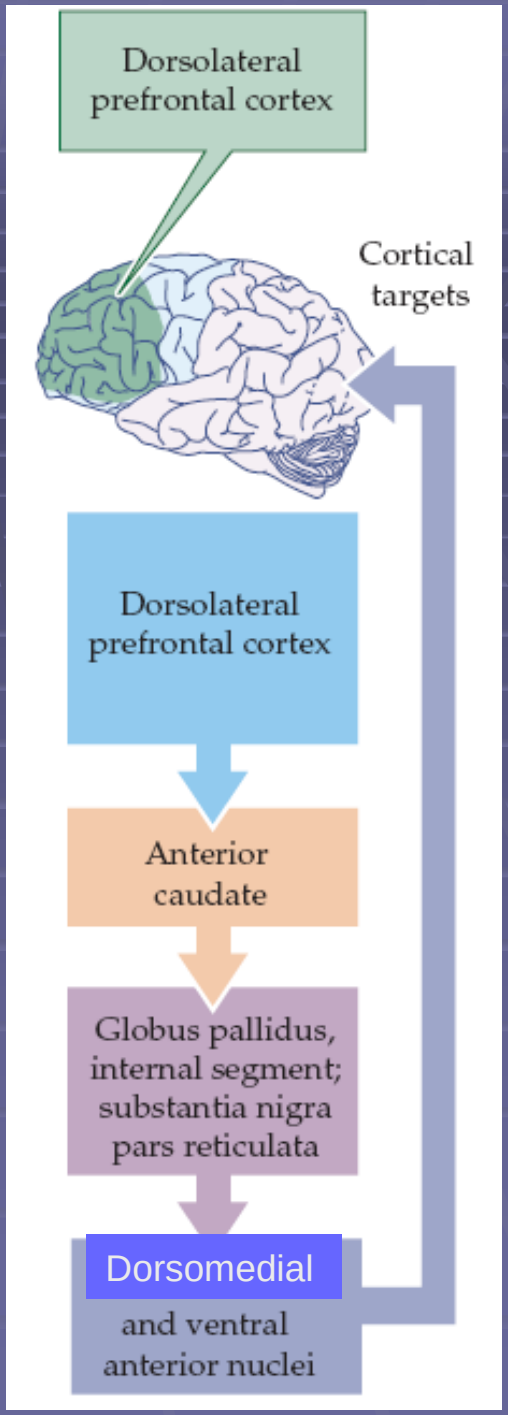
Motor Loop


Motor loop
Primary motor, premotor, supplementary motor cortex
Frontal cortex
Cortical targets
Cortical input
Motor, premotor, somatosensory cortex
Striatum
Putamen
Pallidum
Lateral globus pallidus, internal segment
Thalamus
Ventral lateral and ventral anterior nuclei

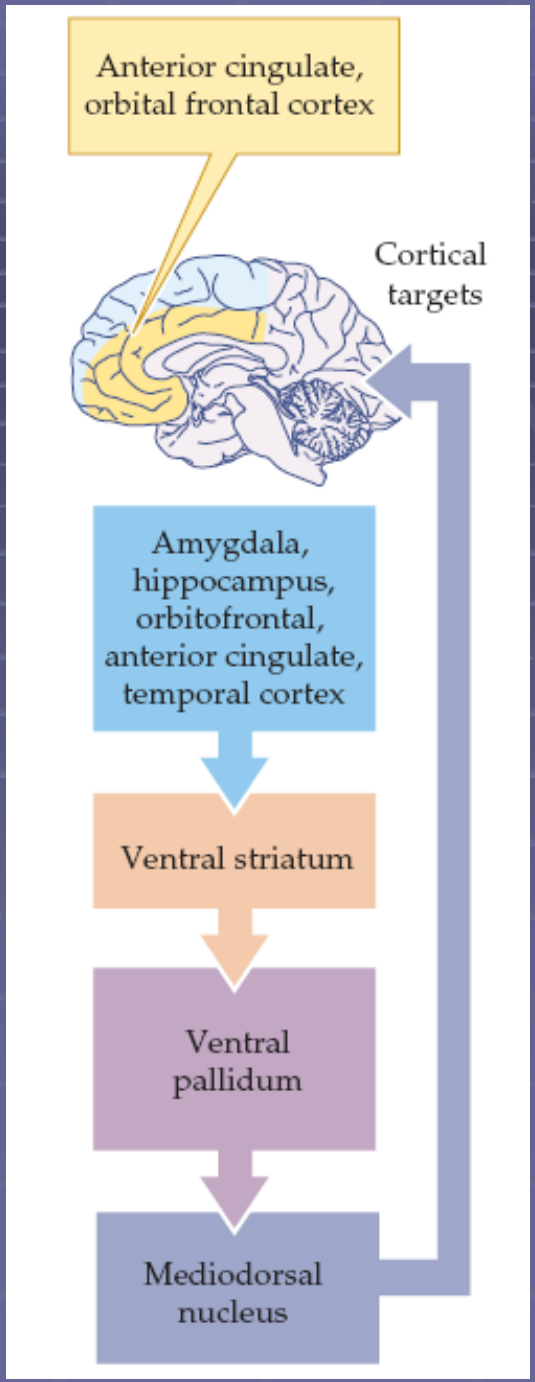
Visuomotor Loop



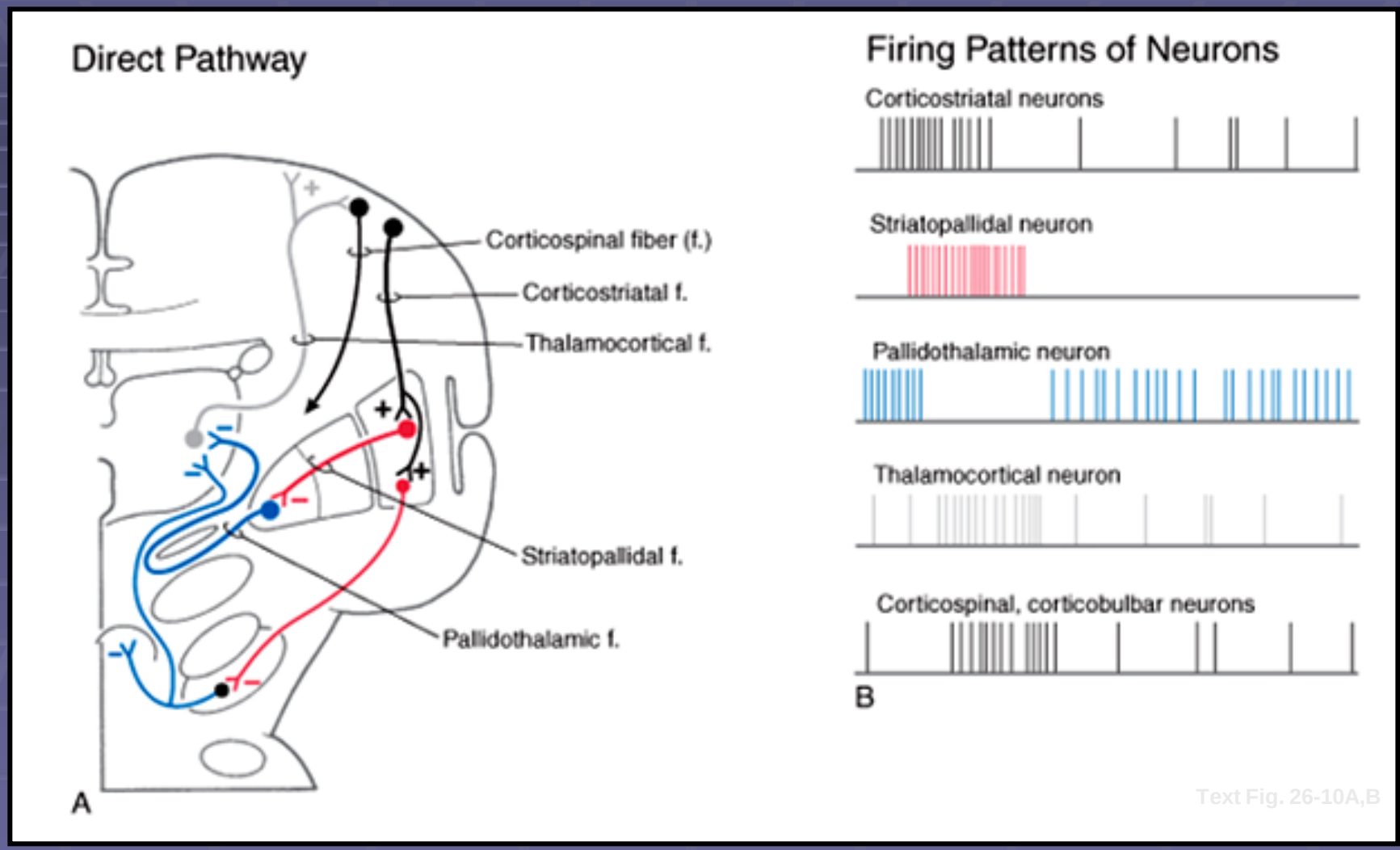
Executive Loop

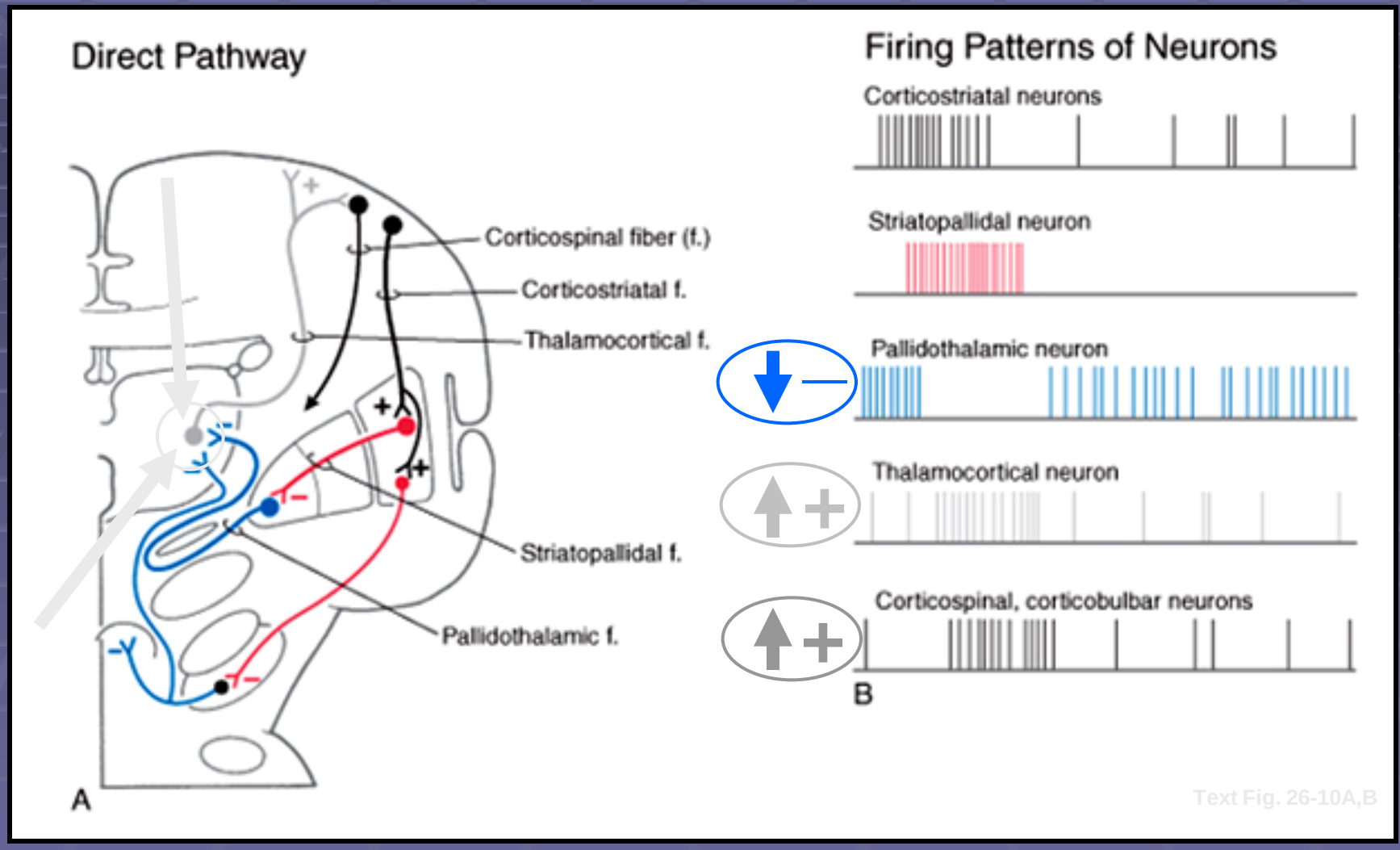


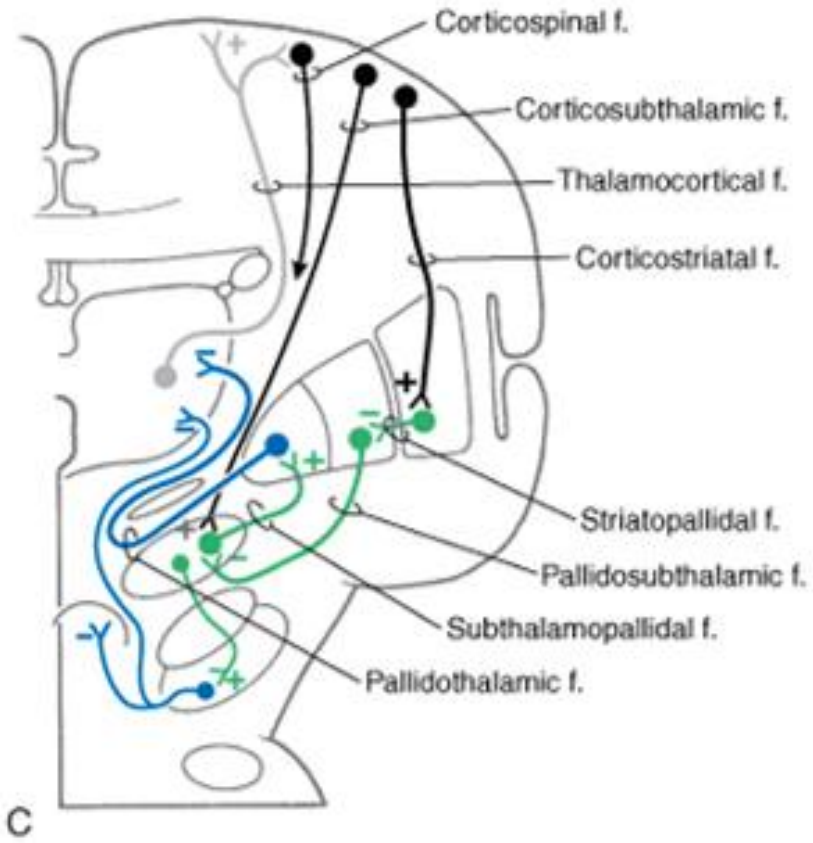
Motivational Loop

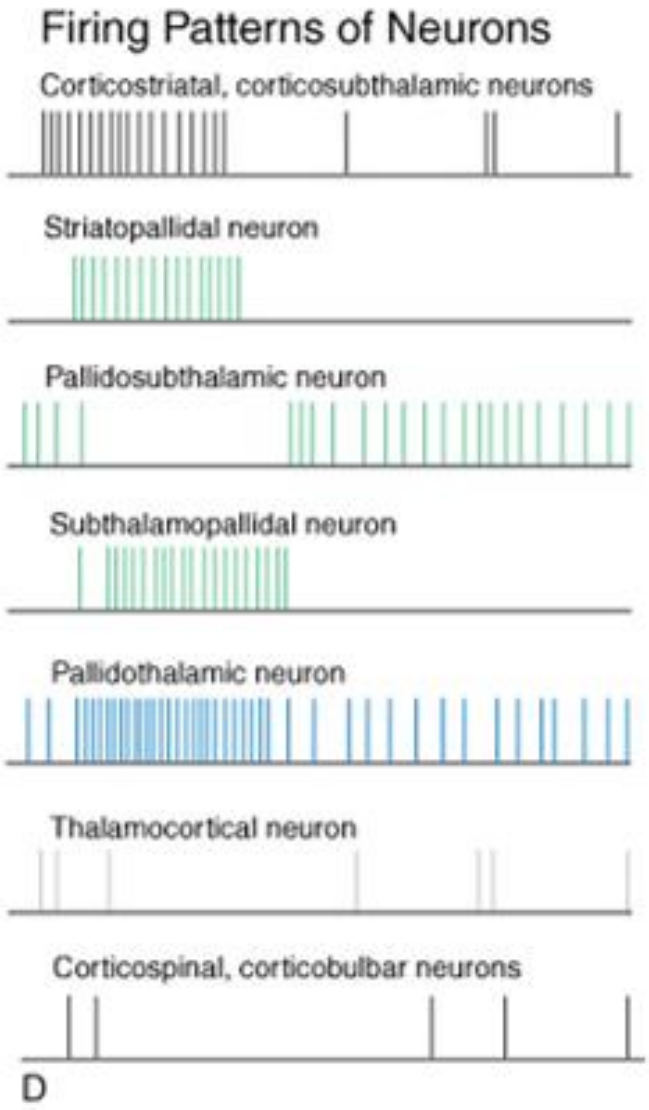


Functional loops

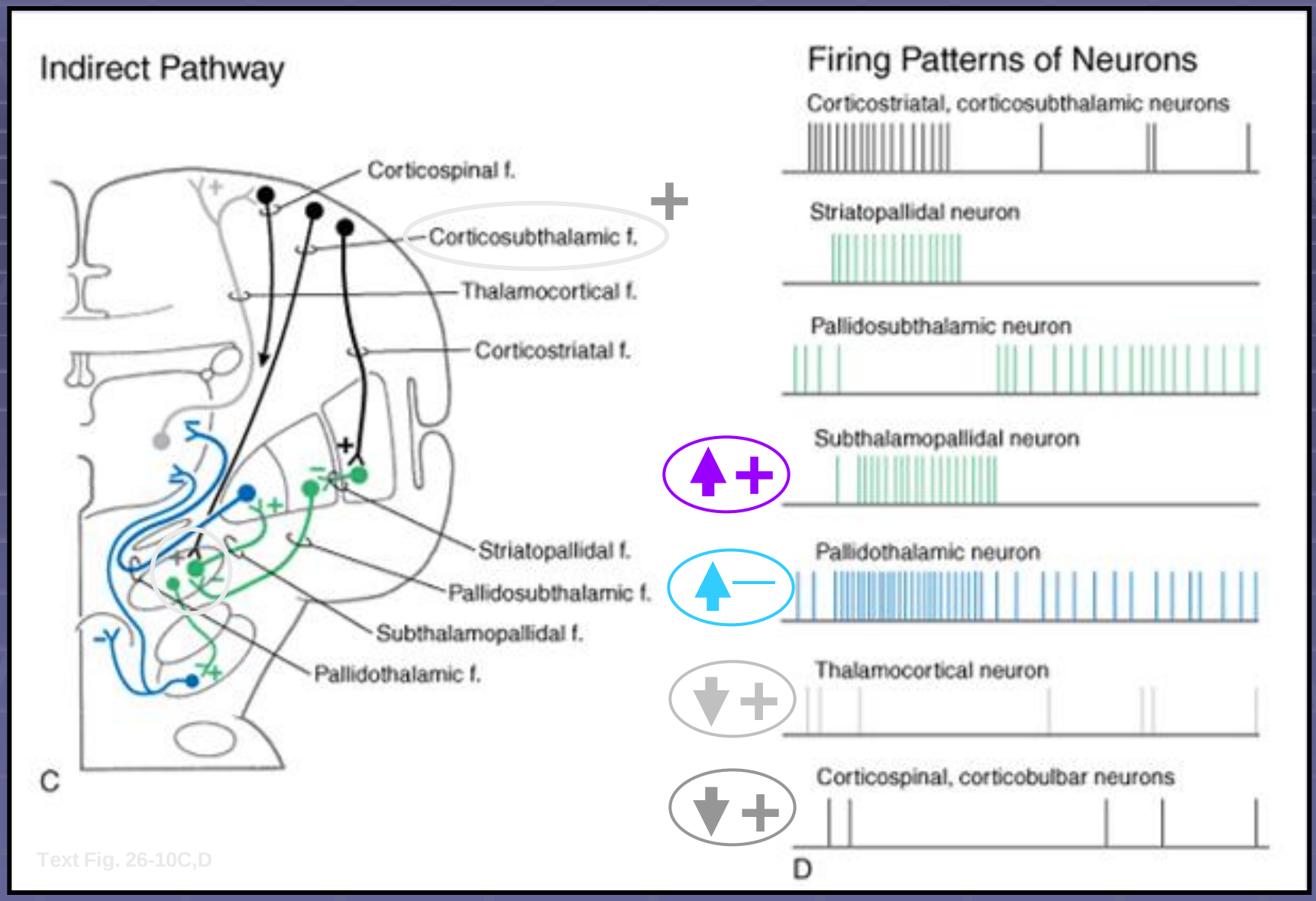

Direct Pathway
Corticospinal fiber (f.)
Corticostriatal f.
Thalamocortical f.
Striatopallidal f.
Pallidothalamic f.
A
Firing Patterns of Neurons
Corticostriatal neurons
Striatopallidal neuron
Pallidothalamic neuron
Thalamocortical neuron
Corticospinal, corticobulbar neurons
B
Text Fig. 26-10A,B


Direct Pathway
Corticospinal fiber (f.)
Corticostriatal f.
Thalamocortical f.
Striatopallidal f.
Pallidothalamic f.
A
Firing Patterns of Neurons
Corticostriatal neurons
Striatopallidal neuron
Pallidothalamic neuron
Thalamocortical neuron
Corticospinal, corticobulbar neurons
B
Text Fig. 26-10A,B





Text Fig. 26-10C,D



Text Fig. 26-10C,D

Modulators (associated nuclei)

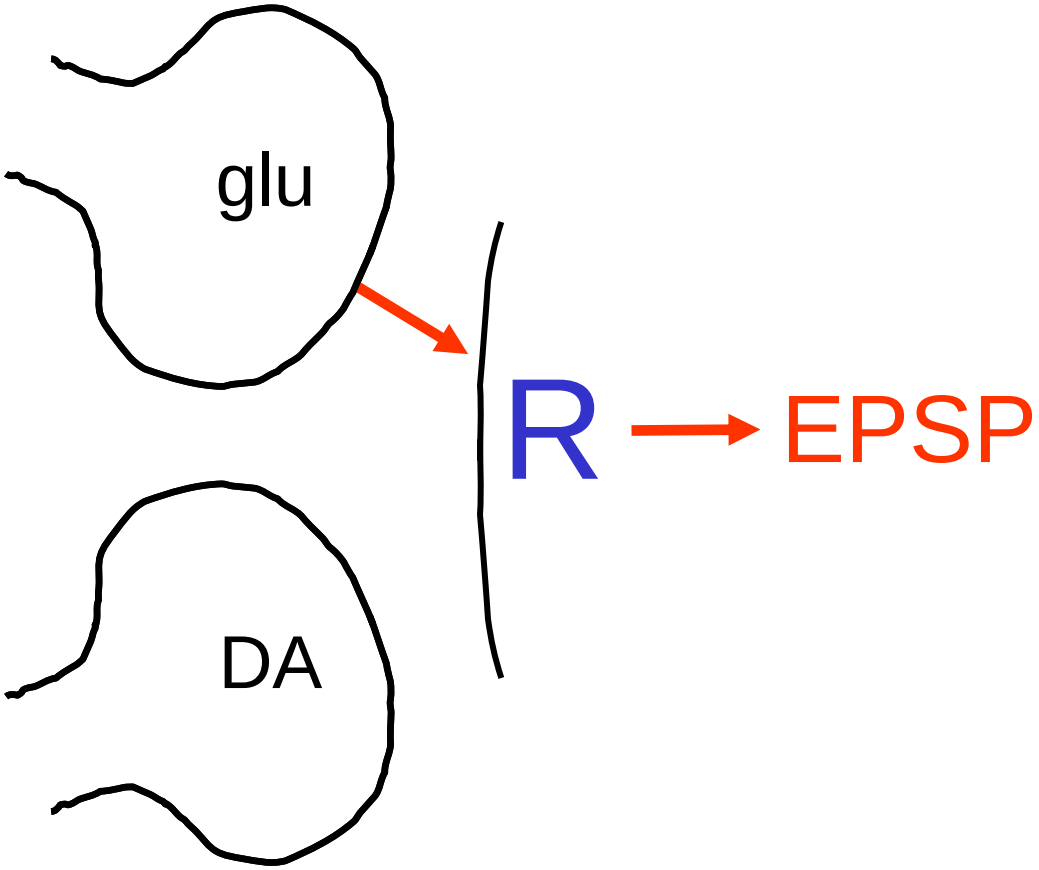
Modulators (associated nuclei)

- Subthalamic Nucleus ?????
- Nigral Complex
- Parabrachial Pontine Reticular Formation
- Zona inserta
- Ventral Basal Nuclei

Modulators (associated nuclei)

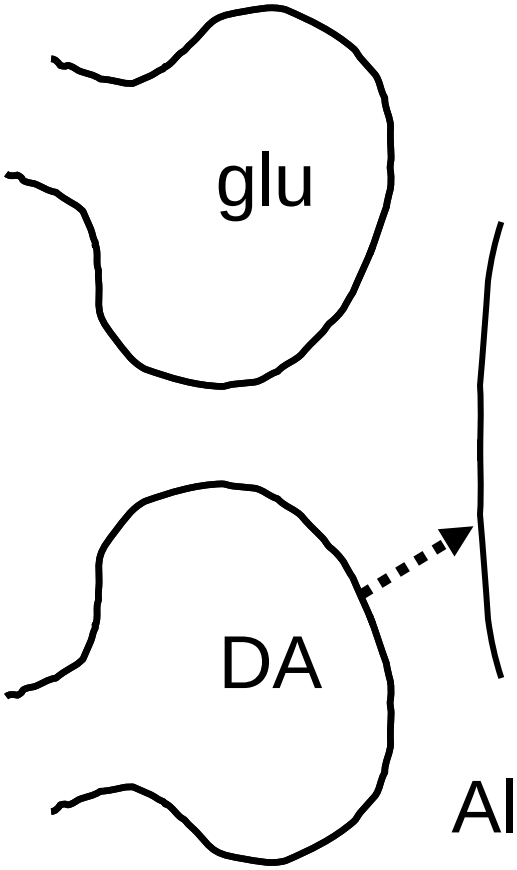
- Subthalamic Nucleus ?????
- Nigral Complex
- Parabrachial Pontine Reticular Formation
- Zona inserta
- Ventral Basal Nuclei

Nigral modulation



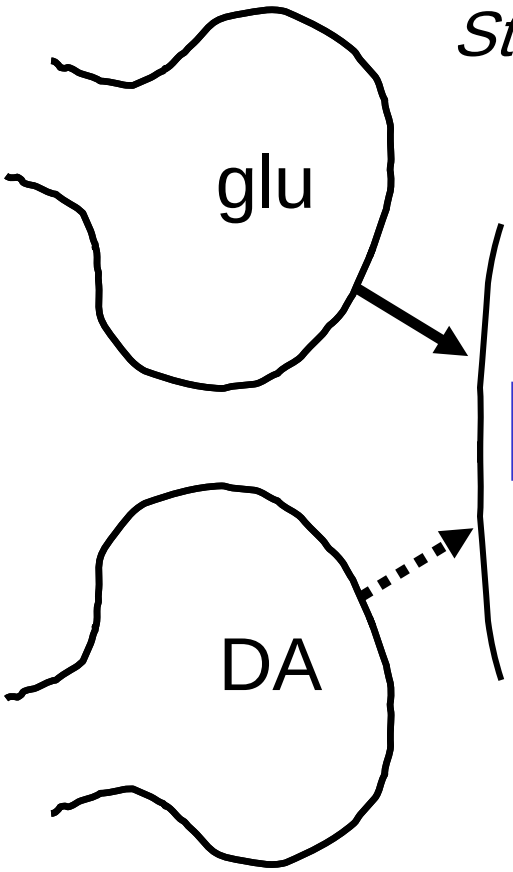
Direct transmission

Direct transmission *vs.* modulation



Almost No direct effect of DA

Direct transmission *vs.* modulation



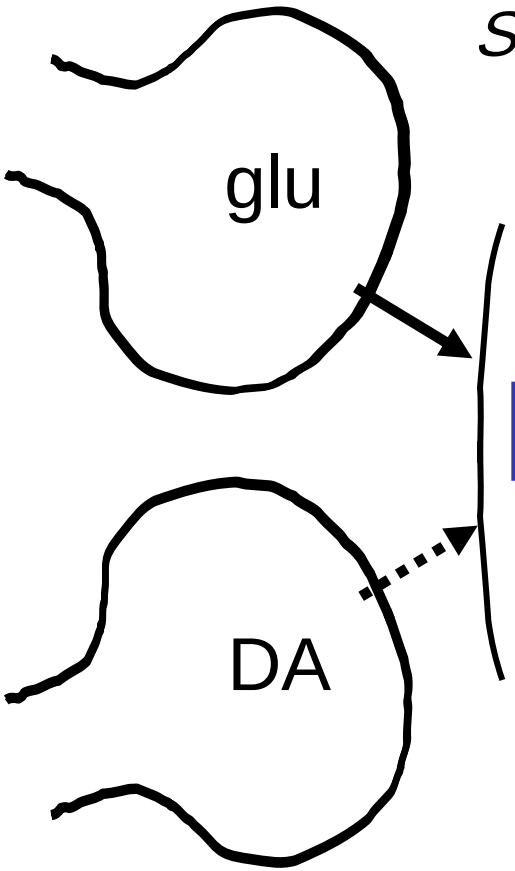
Striatal medium spiny neuron

enhanced
or diminished
response

D1-Rs in the direct pathway:
1) increase GluR phosphorylation
2) alters ionic conductances
to amplify cortical input

Modulation

Direct transmission *vs.* modulation



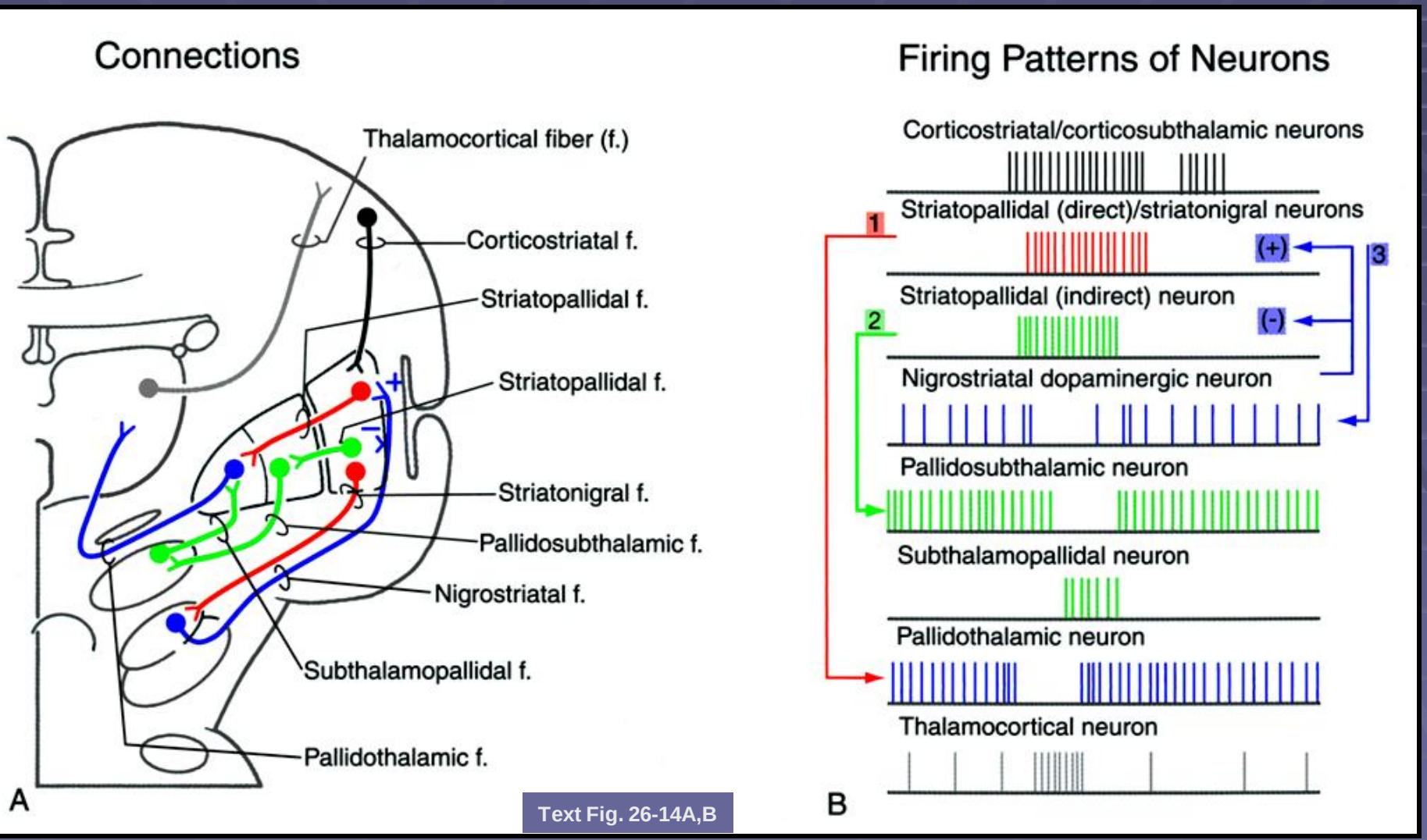
Striatal medium spiny neuron

enhanced
or ***diminished***
response

D2-Rs in the indirect pathway:
1) increase GluR phosphorylation
2) alters ionic conductances
to dampen cortical input

Modulation

Direct and Indirect Pathways (Including the Substantia Nigra

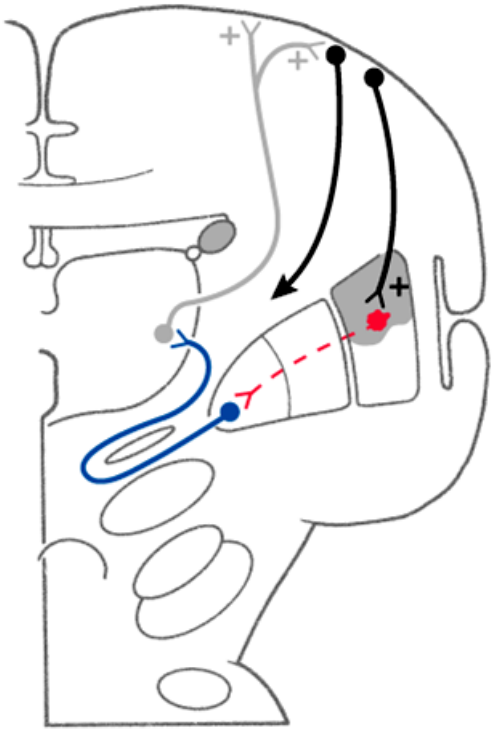


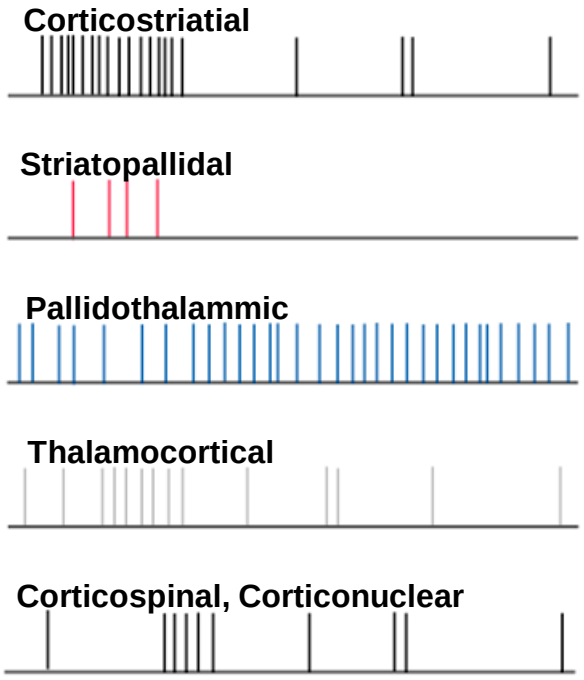
Text Fig. 26-14A,B

Motor behavior is determined by the balance between direct/indirect striatal outputs

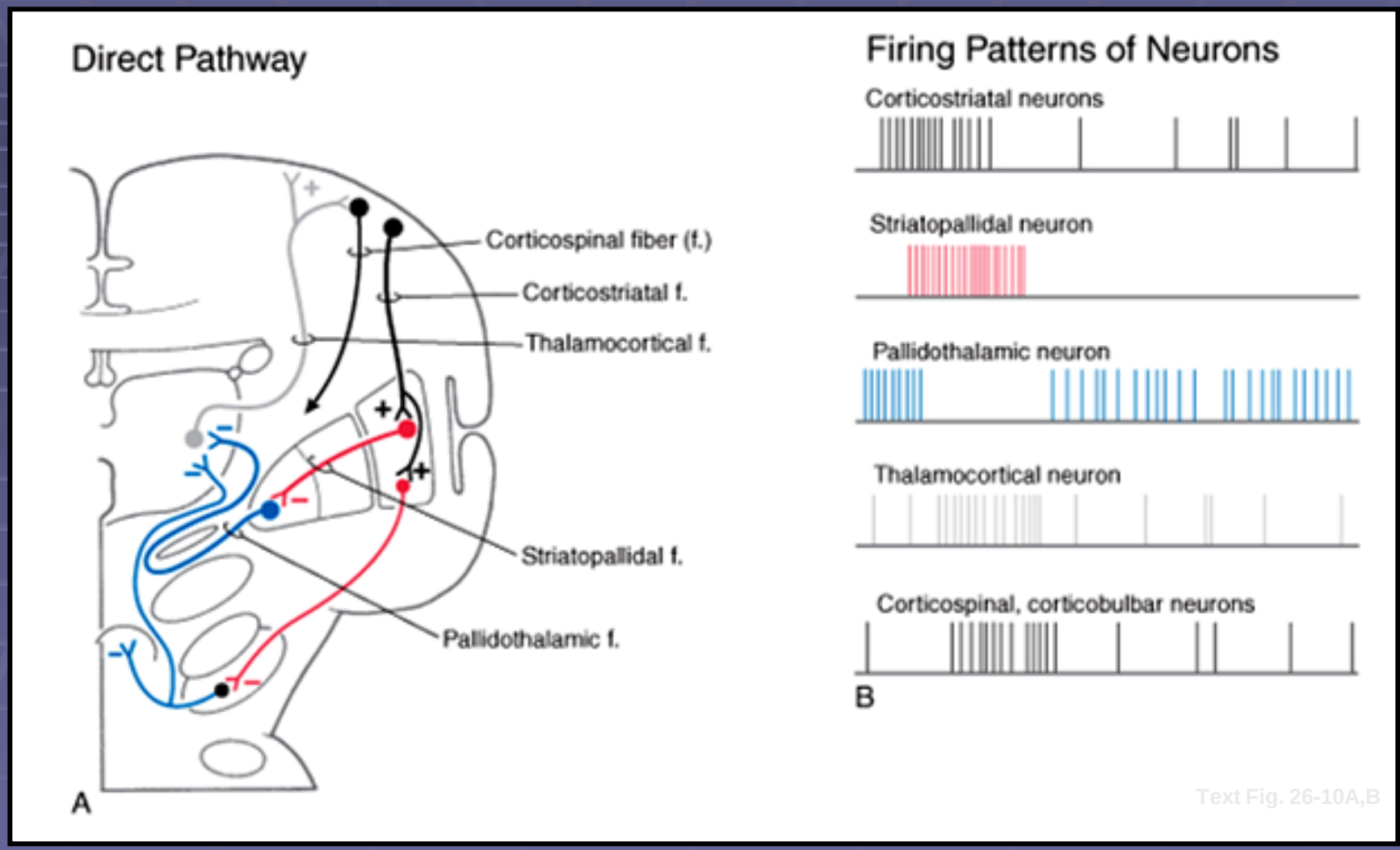
Hypokinetic disorders

- **insufficient direct** pathway output
- **excess indirect** pathway output





Text Fig. 26-12A,B


Direct Pathway
Corticospinal fiber (f.)
Corticostriatal f.
Thalamocortical f.
Striatopallidal f.
Pallidothalamic f.
A
Firing Patterns of Neurons
Corticostriatal neurons
Striatopallidal neuron
Pallidothalamic neuron
Thalamocortical neuron
Corticospinal, corticobulbar neurons
B
Text Fig. 26-10A,B

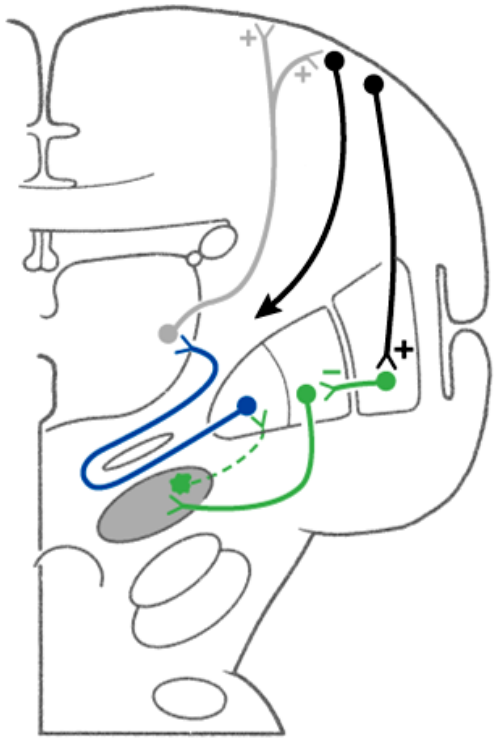
Motor behavior is determined by the balance between direct/indirect striatal outputs

Hypokinetic disorders

- **insufficient direct** pathway output
- **excess indirect** pathway output

Hyperkinetic disorders

- **excess direct** pathway output
- **insufficient indirect** pathway output



Corticostriatal, Corticosubthalamic

Striatopallidal

Pallidosubthalamic

Subthalamopallidal

Pallidothalamic

Thalamocortical

Corticospinal, Corticonuclear

Text Fig. 26-12C,D

Hyperkinetic symptoms
(Choreatic symptoms)

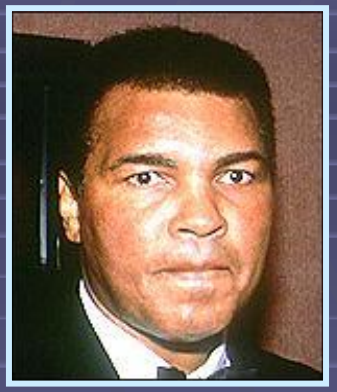
Involuntary (unwanted) movements

- Chorea (dance-like)
- Ballismus
- Dystonia (torsion spasm)
- Athetosis (changeable or writhing movements)
  - Choreoathetosis
  - athetotic dystonia

Basal Ganglia disorders

Parkinson's disease

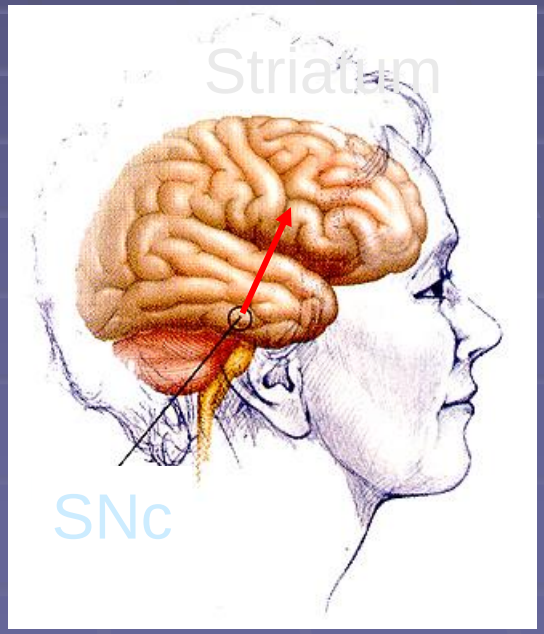
Michael J. Fox



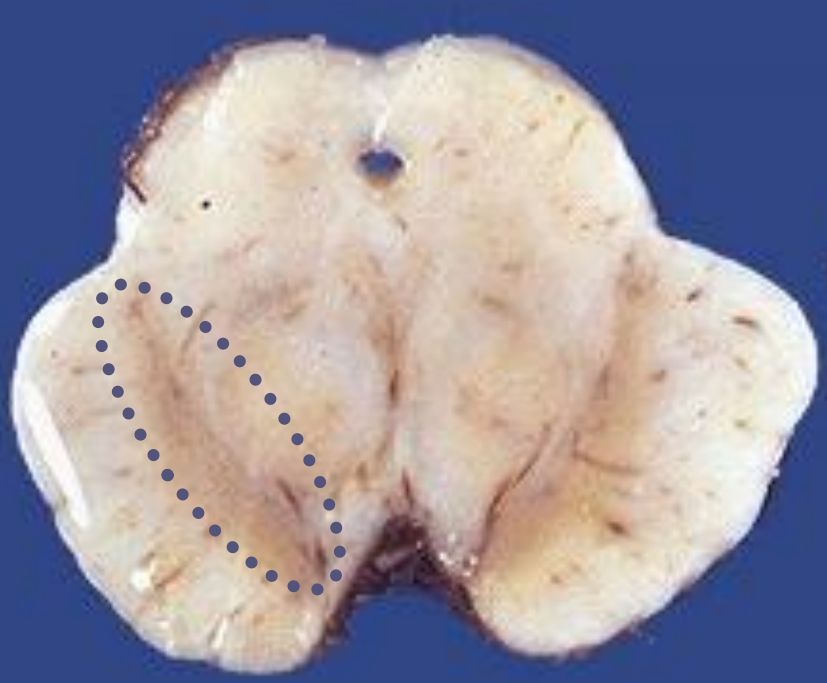
Muhammad Ali

Pathophysiology

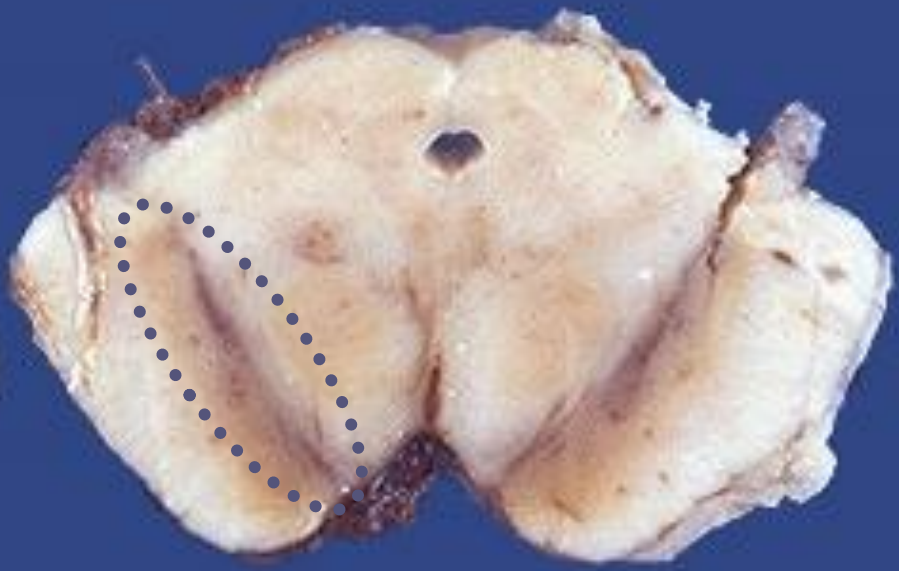
- Primary: loss of nigrostriatal DA projection



Human midbrain

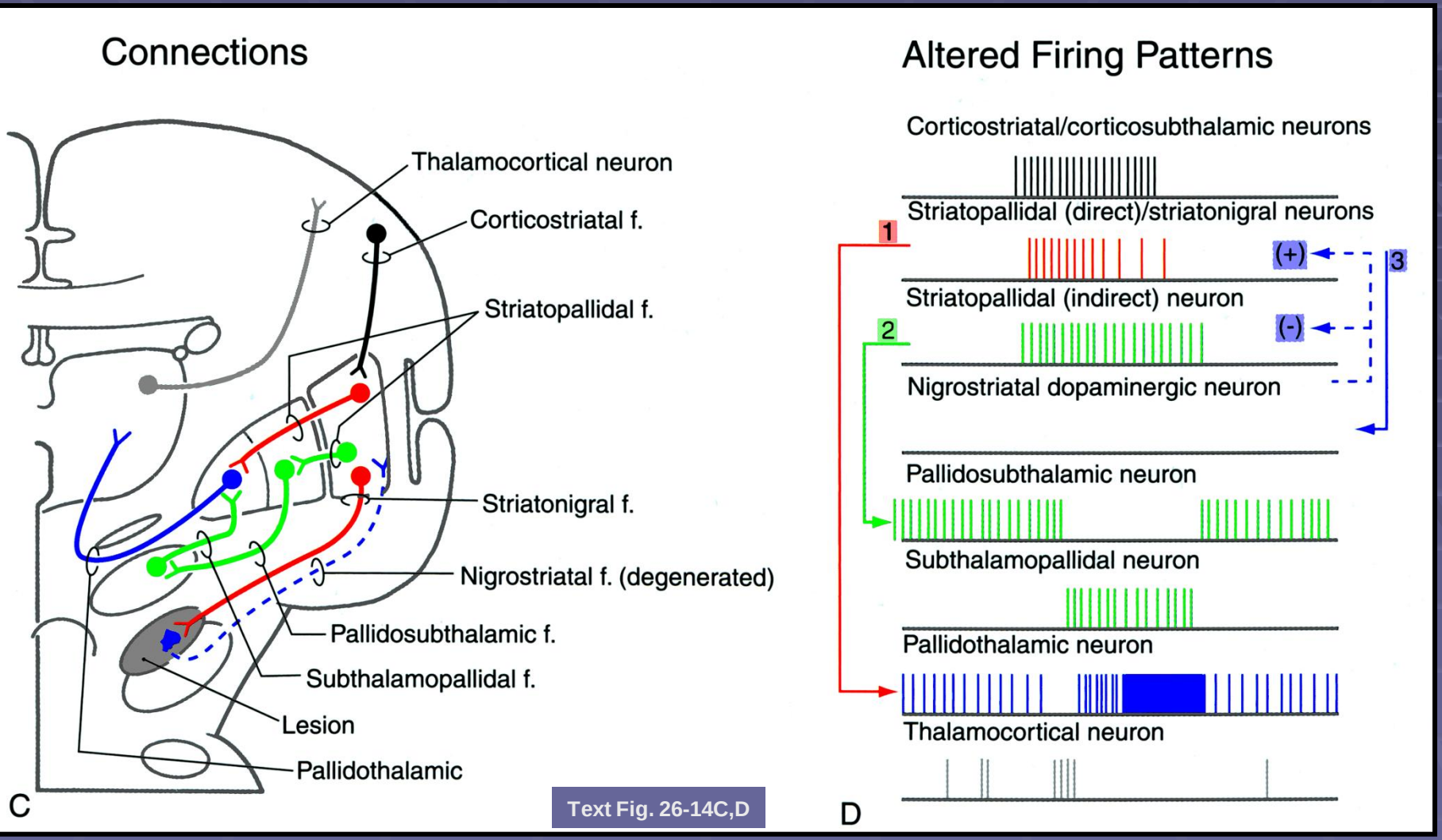


Parkinson's disease



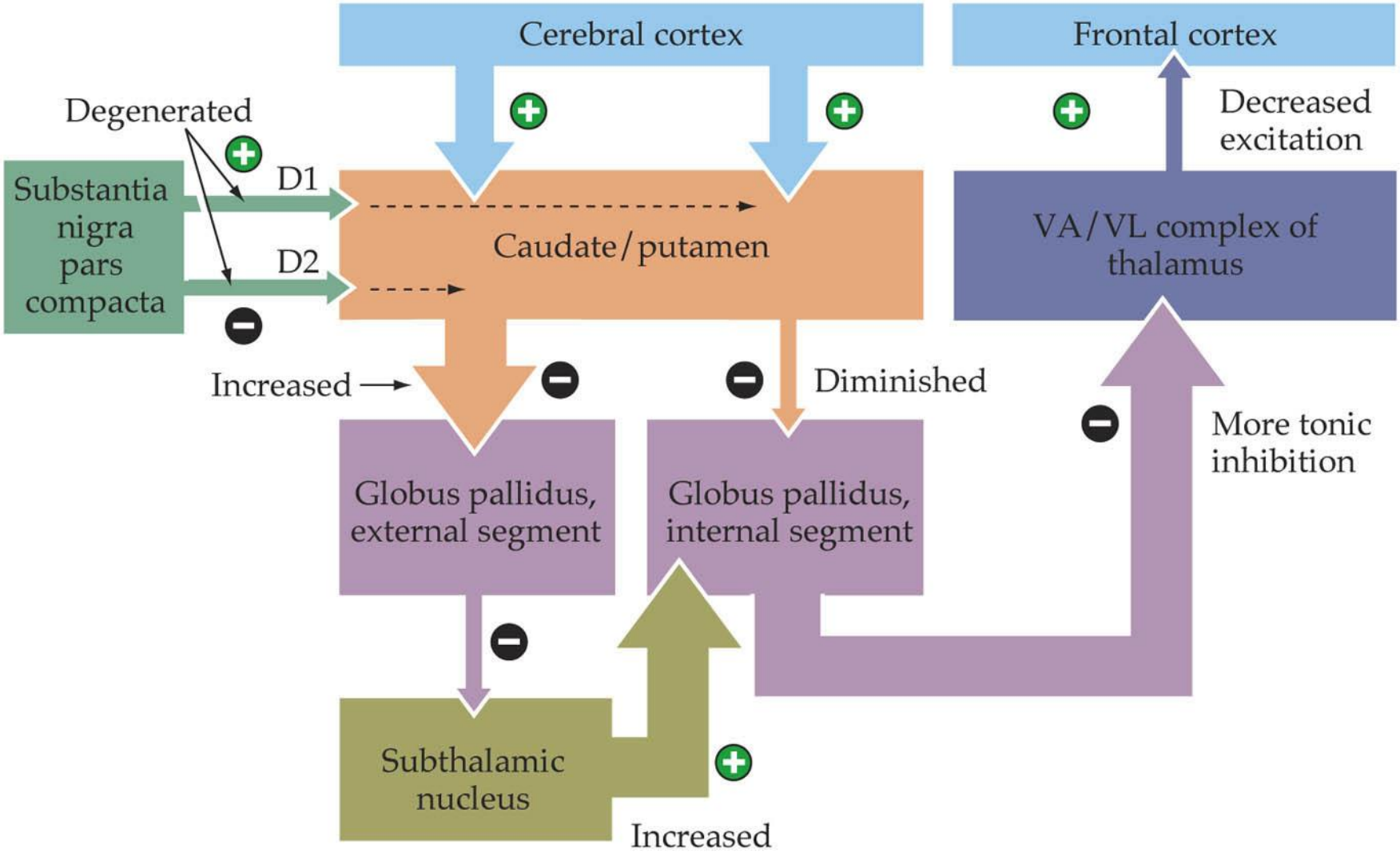
Normal

Loss of Dopaminergic Nigral Connections



Text Fig. 26-14C,D

Parkinson's disease



NEUROSCIENCE, Third Edition, **Figure 17.10 (Part 1)**

Parkinson's disease

- Symptoms
  - Motoric
    - Tremor (~4-5 Hz, resting)
    - Bradykinesia
    - Rigidity
    - Loss of postural reflexes
  - Depression
  - Dementia

Parkinson's disease

Treatment

L-DOPA

This is initially effective, but after 5-10 years, 50% of patients develop DOPA-induced dyskinesia.

Parkinson's disease

Treatment

L-DOPA

This is initially effective, but after 5-10 years, 50% of patients develop DOPA-induced dyskinesia.

Deep brain stimulation

The indirect pathway is increased in Parkinson's. This parkinsonian patient has bilateral STN stimulating electrodes:
high frequency stimulation inactivates the STN.

Parkinson's disease

Treatment

L-DOPA

This is initially effective, but after 5-10 years, 50% of patients develop DOPA-induced dyskinesia.

Deep brain stimulation

SN ***or*** subthalamic nucleus (STN)/ globus pallidus interna (GPi)

high frequency stimulation inactivates the STN or GPi.

Parkinson's disease

Treatment

L-DOPA

Deep brain stimulation

Novel treatments

Anti cholinergic , anti AMPA, & A2

Hyperkinetic disorders: choreatic syndromes

	Causes:
1. Huntington's chorea	*Genetic (autosomal dominant)*
2. Dystonia	*Genetic or idiopathic*
3. Tardive dyskinesia	*Chronic neuroleptic use*
4. DOPA-induced dyskinesia	*Parkinson's therapy*
5. Hemiballismus	*Unilateral vascular accident, typically subthalamic nucleus*
6. Tourette's syndrome	*Excessive D2-subtype DA receptor expression(?)*

Choreatic symptoms

Involuntary (unwanted) movements

- Chorea (dance-like)
- Athetosis (changeable or writhing movements)
- Dystonia (torsion spasm)

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

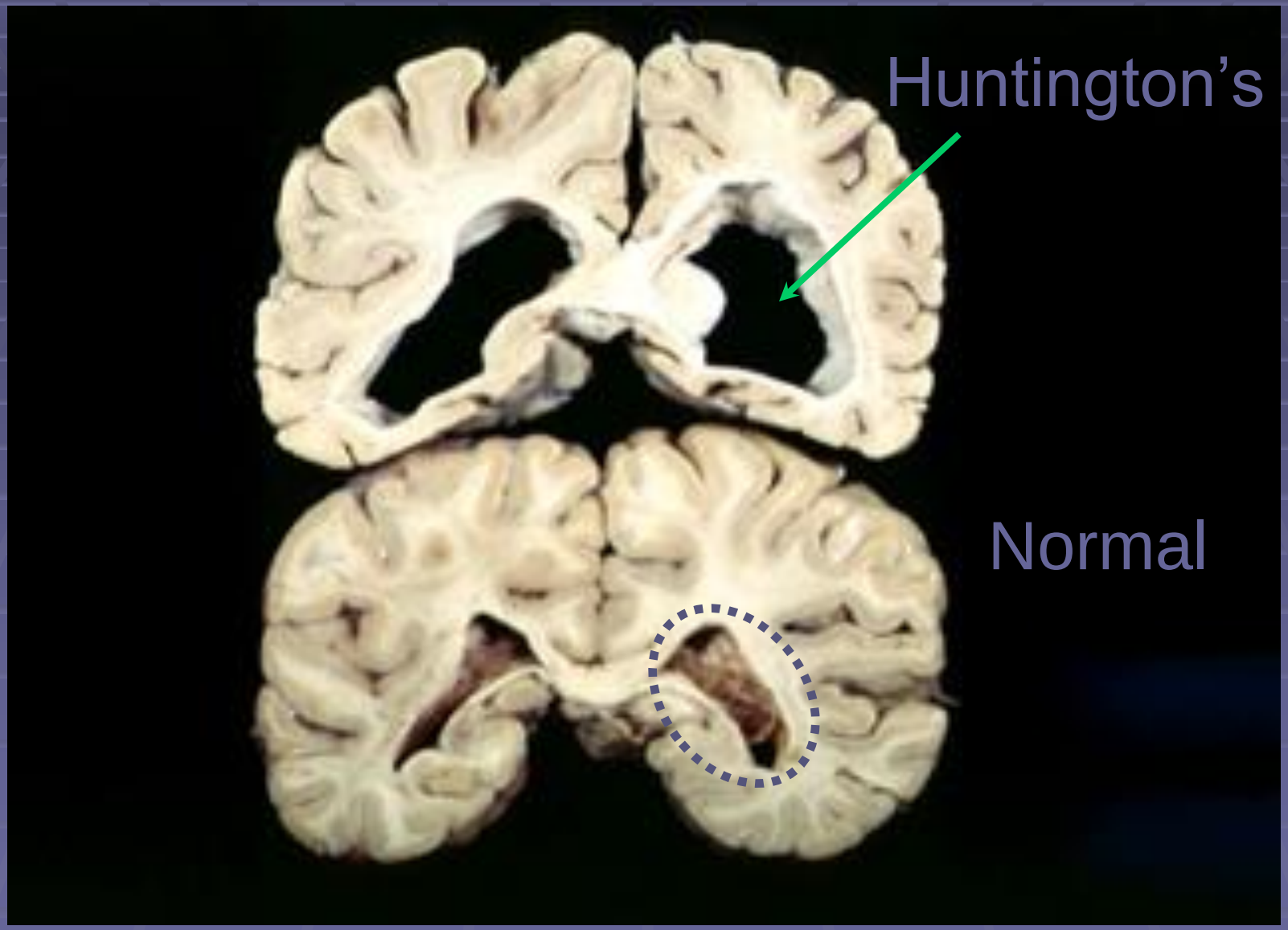
Huntington's disease

Pathophysiology

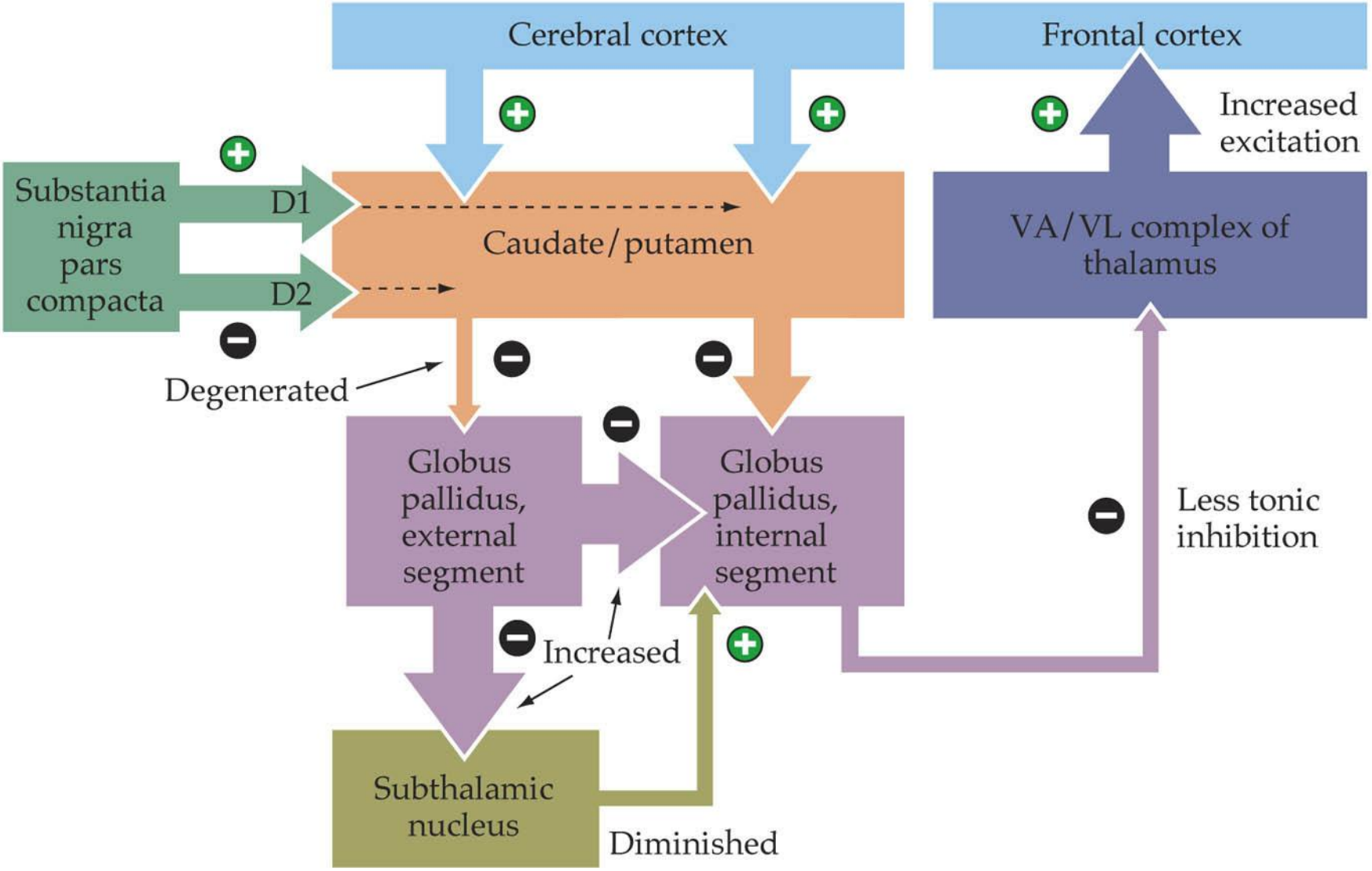
- Atrophy of striatum
- Loss of striatal GABAergic neurons
- Neuropathological sequence
- start , rostral and medial then caudal and lateral

- absentmindedness, irritability, depression, clumsiness, and sudden
- falls. Choreiform

Huntington's disease pathology



Huntington's disease



NEUROSCIENCE, Third Edition, **Figure 17.10 (Part 2)** © 2004 Sinauer Associates, Inc.

Huntington's disease

Choreatic gait

Symptoms

Early motor signs

- chorea (brief, involuntary movements)
- dystonia (abnormal postures)

Dystonic movements

Huntington's disease

- Cognitive abnormalities
  - Executive function (complex tasks)
  - Recent and remote memory (poor retrieval)
- Psychiatric changes
  - Depression
  - Psychosis
- Later decline
  - Immobility
  - Weight loss
  - Death within 10-25 years (often from pneumonia)

Etiology of Huntington's disease

Huntingtin mutation

- Mutation near 5' end contains >>CAG repeats
- Produces protein with excess glutamines near NH_2 terminus

Why cell death?

- Not yet certain
- Excitotoxicity? Glutamate acting via NMDA receptors can kill medium spiny neurons; glutamate antagonists block

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

Cervical dystonia (torticollis)

After botulinum toxin

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

Axial (thoracic and/or lumbar) dystonia

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

*DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

*50% of PD patients on L-DOPA will develop DOPA dyskinesia

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus

Tourette's syndrome

Hyperkinetic disorders: choreatic syndromes

Huntington's disease

Dystonia

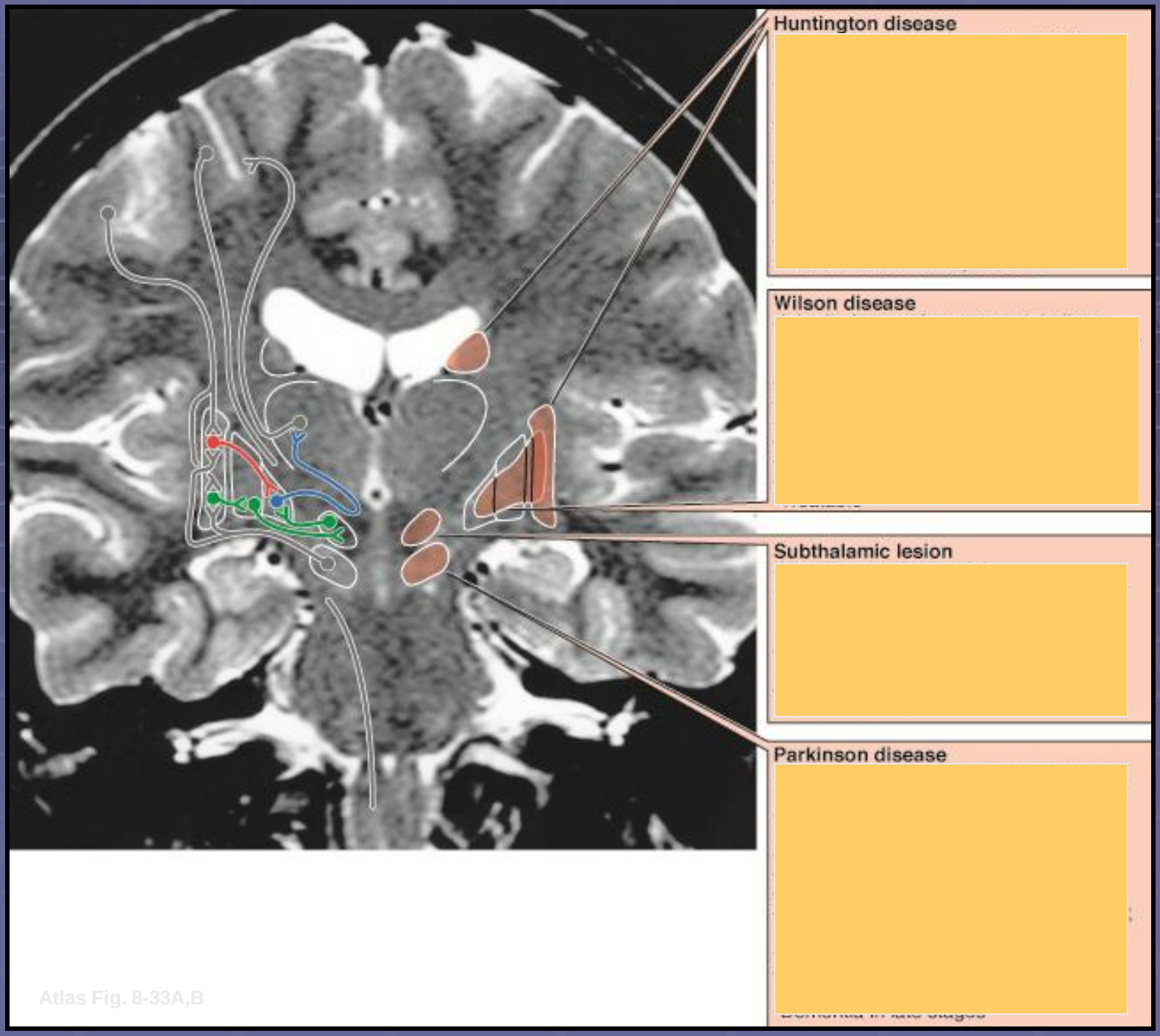
Tardive dyskinesia

DOPA-induced dyskinesia

Hemiballismus – unilateral STN stroke

Tourette's syndrome

After treatment with the D2-R blocker sulpiride


Huntington disease
Wilson disease
Subthalamic lesion
Parkinson disease
Atlas Fig. 8-33A,B

Sydenham Chorea