

**Satellites of the corpus striatum: substantia nigra & subthalamic nucleus (STN):**  
 Inhibitory connections (using GABA) in red, excitatory (using GLU) in blue.

**Fig 30-9**

Courtesy of MIT Press. Used with permission.  
 Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN:9780262026734.

These connections help explain behavioral disorders: Why is it that some basal ganglia diseases cause hyperkinesias (too much movement), others cause loss of movement initiation?

***EXAMPLES:***

- 1) Parkinson's disease, with cell loss in substantial nigra: resting tremor, akinesia
- 2) Huntington's chorea, with cell loss in striatum
- 3) Hemiballism, with lesions of subthalamic nucleus on opposite side: violent, large involuntary flinging movements of arms

***MECHANISM:*** The “double inhibition” pathways are damaged. One outcome is an excessive inhibition of VA/VL cells, so they become hyporactive. Other cells become hyperactive if inhibition is removed.

## Now we return to a more complete view of the striatum, adding the limbic system components

What is the limbic striatum? What structures does it include, and how does it differ from the non-limbic striatum? *(You should review the classes just completed)*

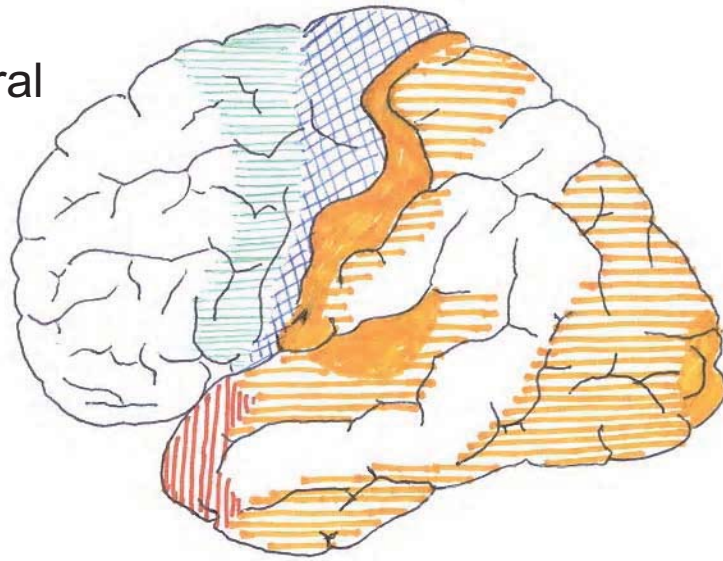
*The “Ventral Striatum” includes nuc. accumbens & the olfactory tubercle.*

*The ventral pallidum includes the Bed Nuc. of the Stria Terminalis, substantia innominata, & magnocellular preoptic nucleus (in anterior-most hypothalamus).*

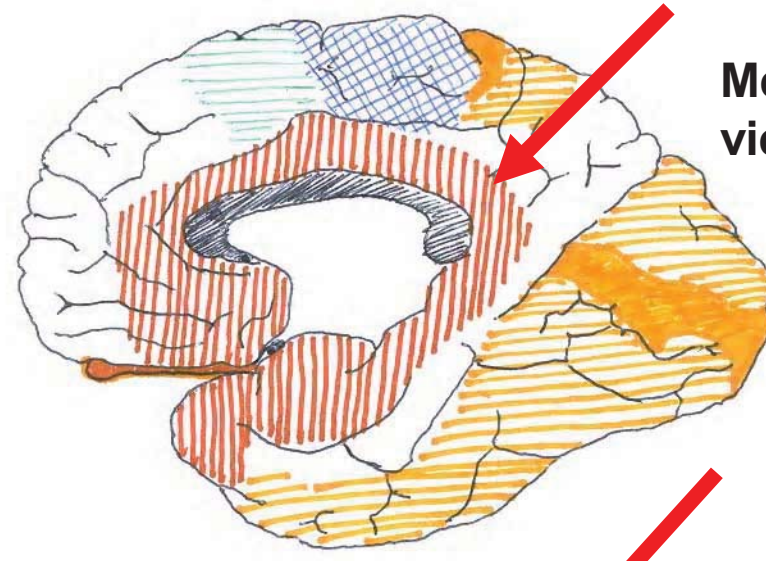
*Major inputs to accumbens: from limbic endbrain structures (especially amygdala & hippocampus), and DA axons from VTA of midbrain.*

*Swanson also includes septal area structures in the limbic striatum and pallidum.*

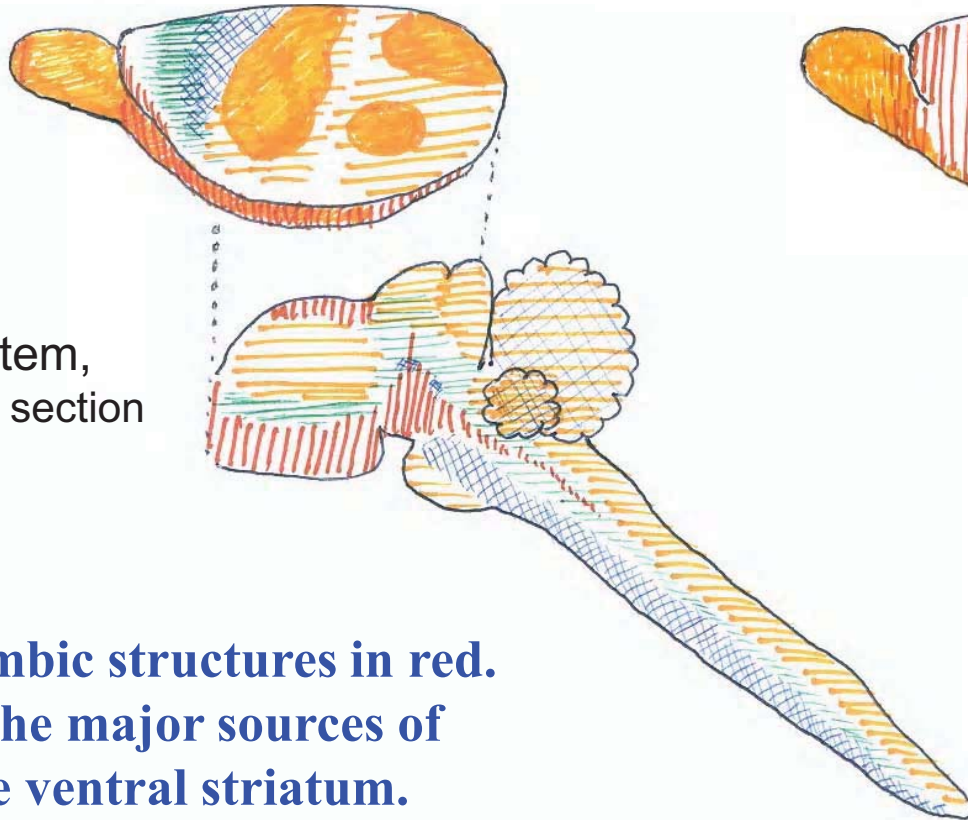
Lateral view







Medial view



Brainstem, sagittal section

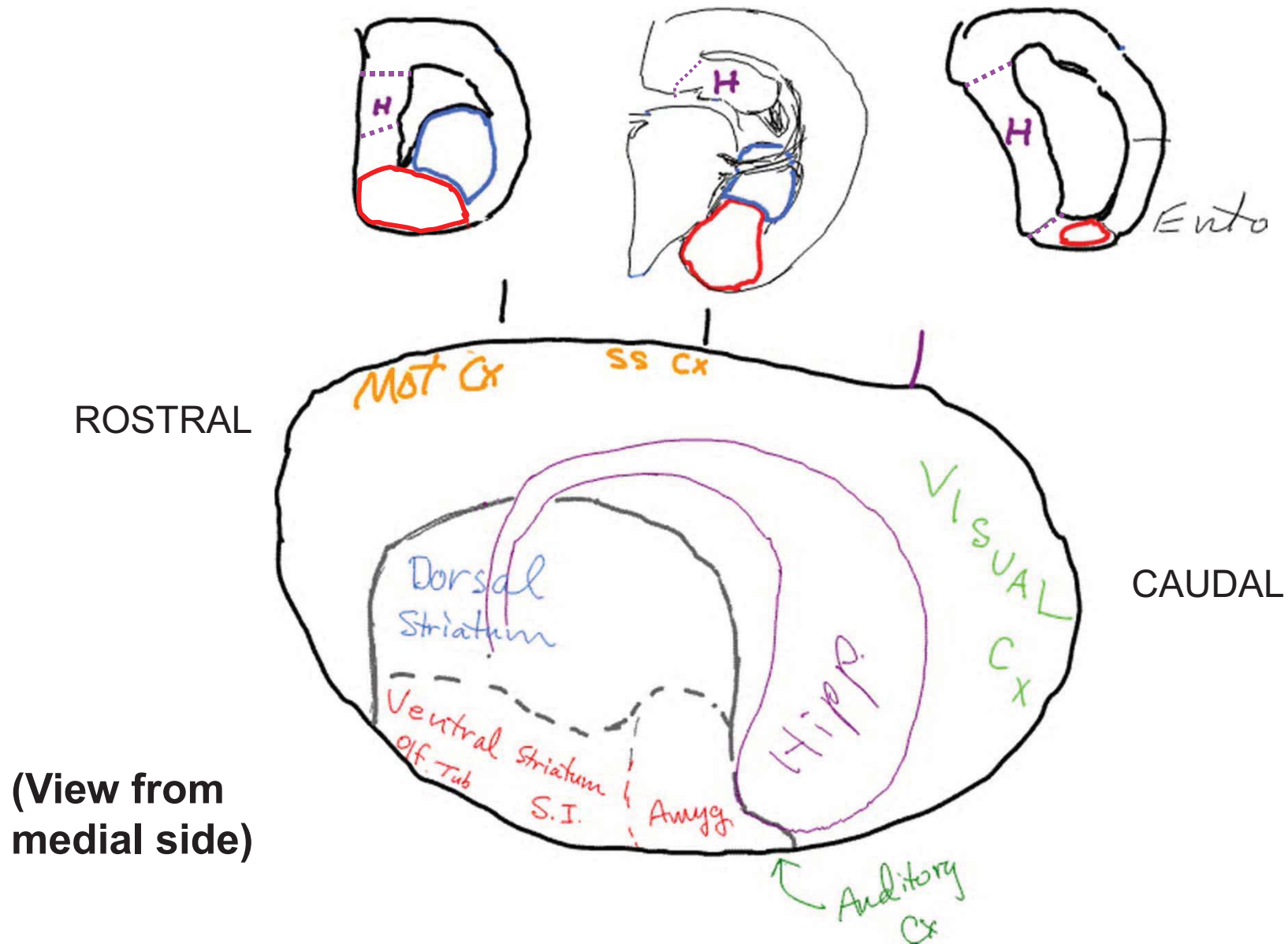


-  Sensory-Perceptual
-  Motor
-  Behavior
-  Motivation

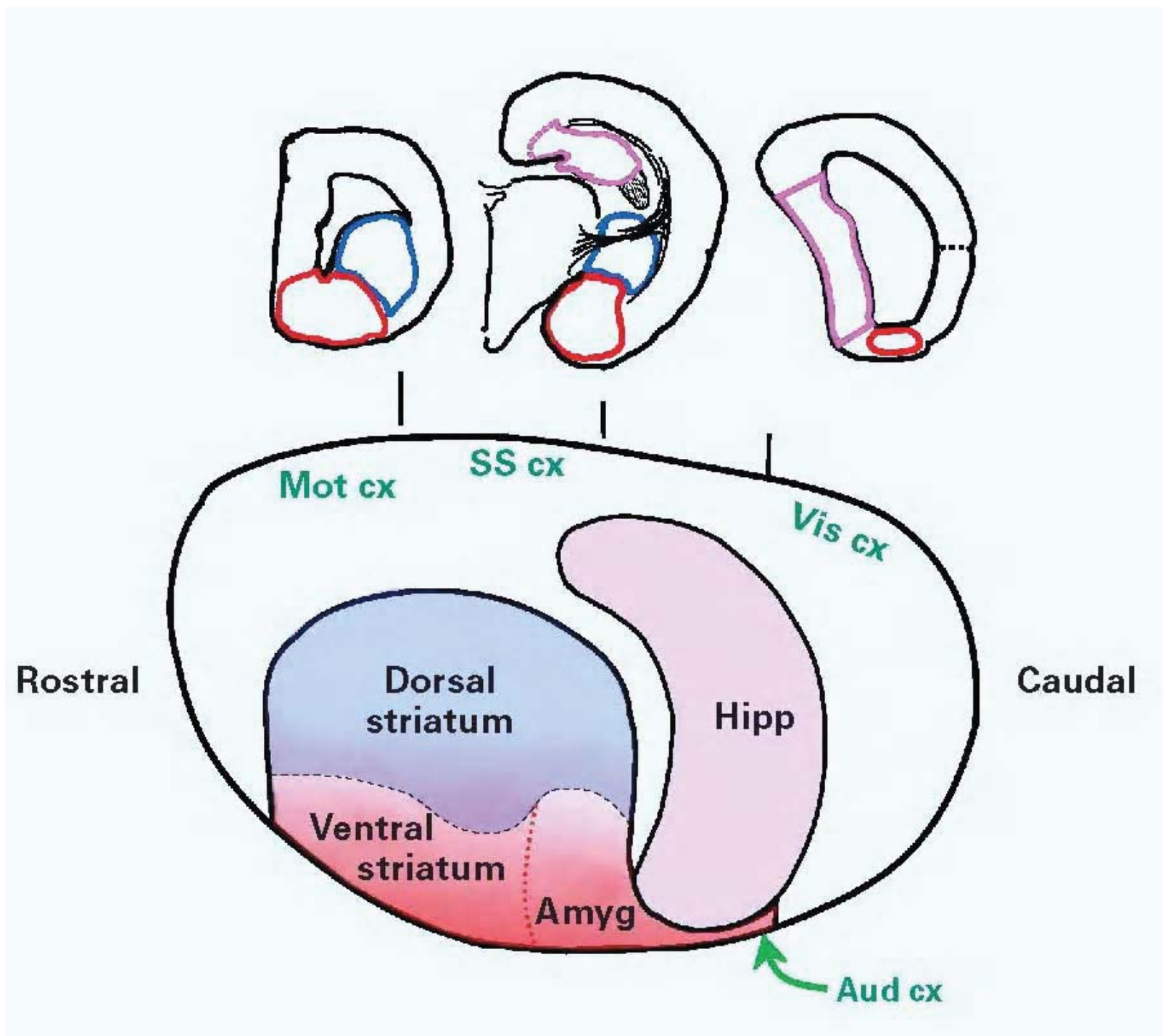
**Note the limbic structures in red. These are the major sources of input to the ventral striatum.**

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# Positions in the hemisphere: **Dorsal striatum**, **ventral striatum including Amygdala**, and **Hippocampus**



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**Fig 30.4**

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**For reference: Larry Swanson's attempt at a more inclusive classification of the basal ganglia.**

## **Swanson's 4 striatal-pallidal divisions**

- The dorsal striatum and pallidum:
  - Striatum: Caudate-Putamen
  - Pallidum: GPe & GPi (the latter is the Entopeduncular nucleus in small rodents)
- Ventral striatum and pallidum:
  - Striatum: Nucleus accumbens, Olfactory tubercle, Fundus striati
  - Pallidum: Substantia innominata, Magnocellular preoptic nucleus
- Medial striatum and pallidum:
  - Striatum: Lateral septal complex
  - Pallidum: Medial septal nucleus/nucleus of the diagonal band
- Caudorostral striatum and pallidum:
  - Striatum: [Baso-]Medial & central amygdala nuclei, Anterior amygdala area, Intercalated amygdala nuclei
  - Pallidum: Bed nucleus of the stria terminalis

Limbic

*See Swanson (2003), p 179*

Note concerning Swanson's groupings:

The last three groups can be included together in the limbic striatum and pallidum



## *Questions, chapter 30*

- 8) Contrast the neocortical projections to the putamen with the neocortical projections to the caudate nucleus.
- 9) The corpus striatum is involved in all, or nearly all, of the functions of neocortical areas. What neuroanatomical findings support this statement?

# Dominant inputs to the dorsal striatum in mammals come from the neocortex

topography of cortico-striatal projections in primates:

Sensorimotor areas to **Putamen;**

Prefrontal areas to **Head of Caudate;**

Posterior areas to **Caudate (tail & medial head)**

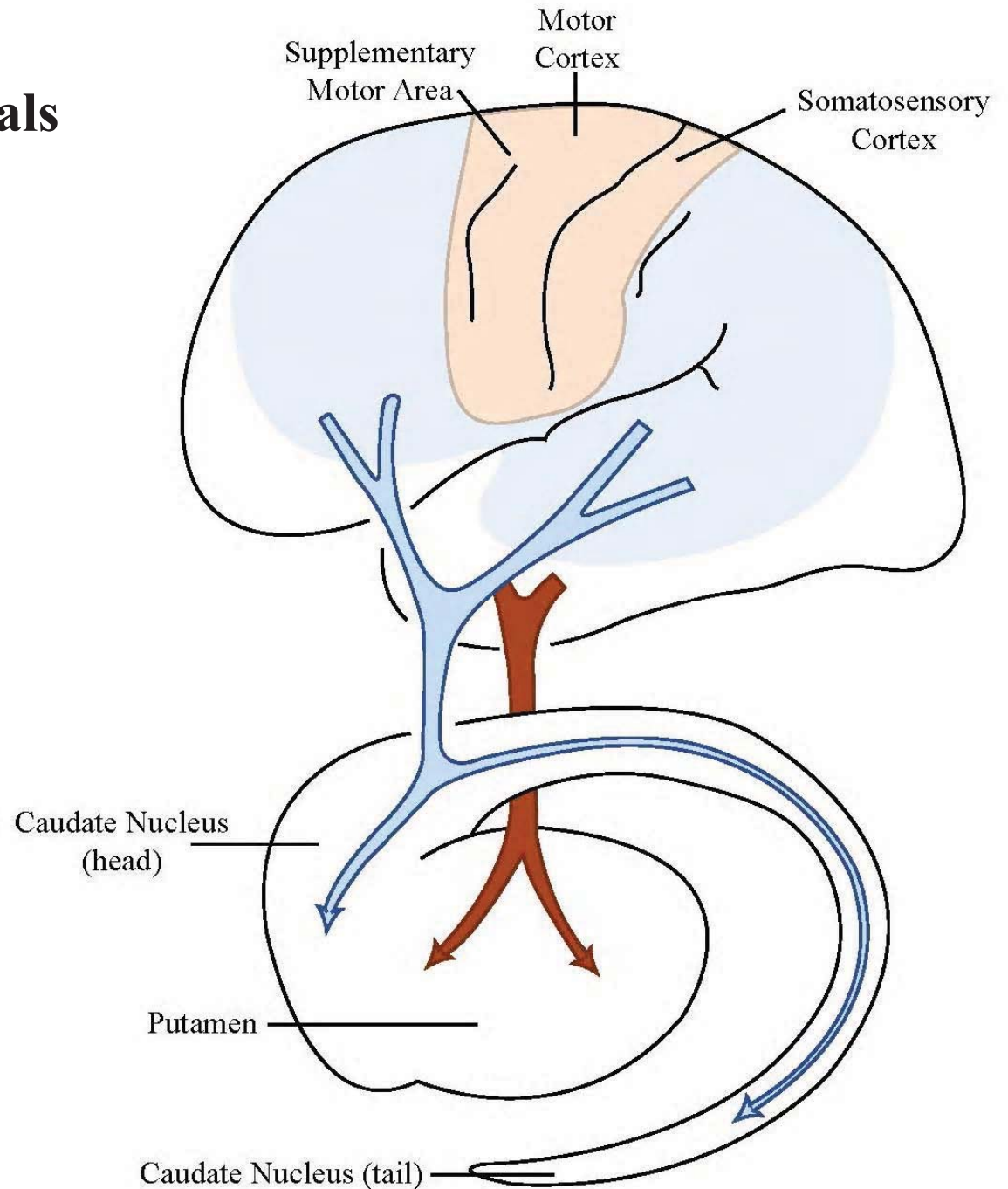


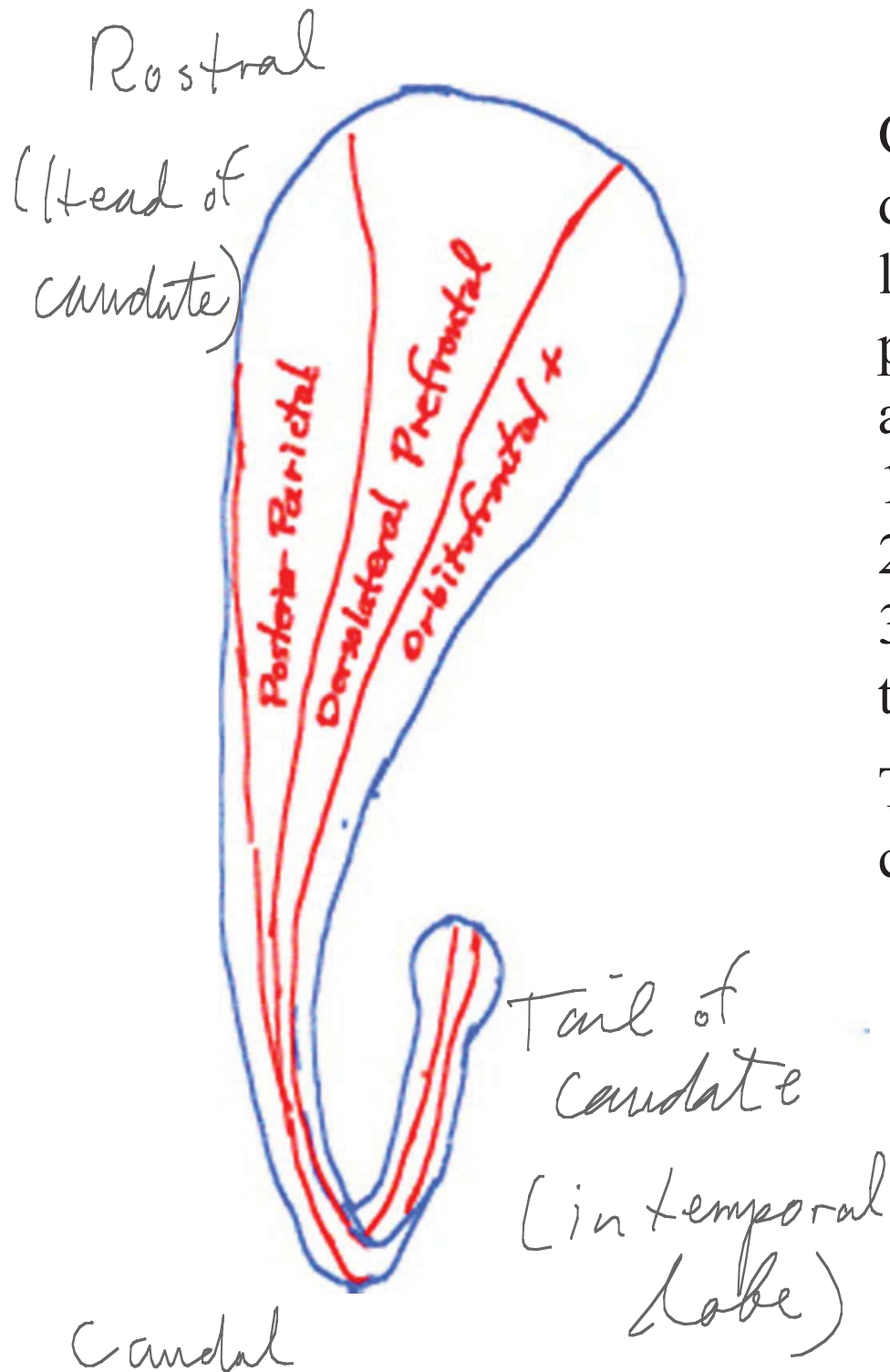
Fig 30-10a

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Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN:9780262026734.

# In rodent brain: cortex to striatum, paleothalamus to striatum

Figure removed due to copyright restrictions. Please see course textbook or:  
Voorn, Pieter, Louk J. M. J. Vanderschuren, et al. "Putting a Spin on the Dorsal-ventral Divide of the Striatum." *Trends in Neurosciences* 27, no. 8 (2004): 468-74.

**Fig 30-10b**

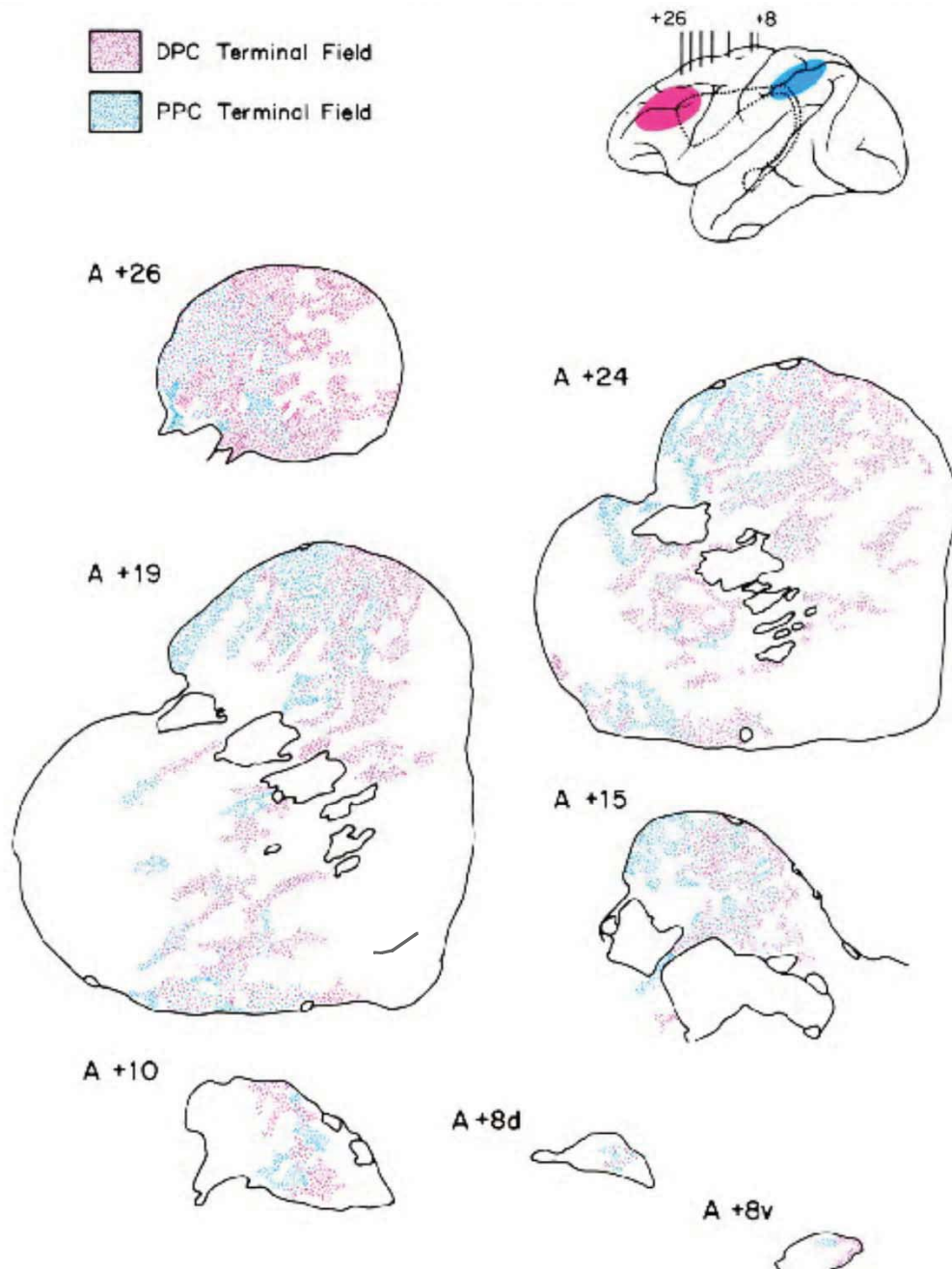


Caudate nucleus of rhesus monkey, dorsal view, showing extensive longitudinal areas that receive projections from multimodal association cortex:

- 1) Posterior parietal → Dorsolaterally
- 2) Dorsolateral prefrontal → Centrally
- 3) Orbitofrontal+anterior-superior temporal → ventromedially

These areas also cross the internal capsule into the putamen.

From Selemon & Goldman-Rakic, 1985



Charts of projections to the dorsal striatum of the rhesus monkey from dorsolateral prefrontal cortex (red) and posterior parietal association cortex (blue).

The projections show areas of overlap, and larger areas of non-overlapping inter-digitation.

From Selemon & Goldman-Rakic, 1985.

C

The topographic projections of neocortex to the striatum makes it easy to understand the discovery of **multiple parallel functional circuits**.

(These may sometime have opposing effects on movement.)

*Brodal p 292-293: 4 or more functional circuits*

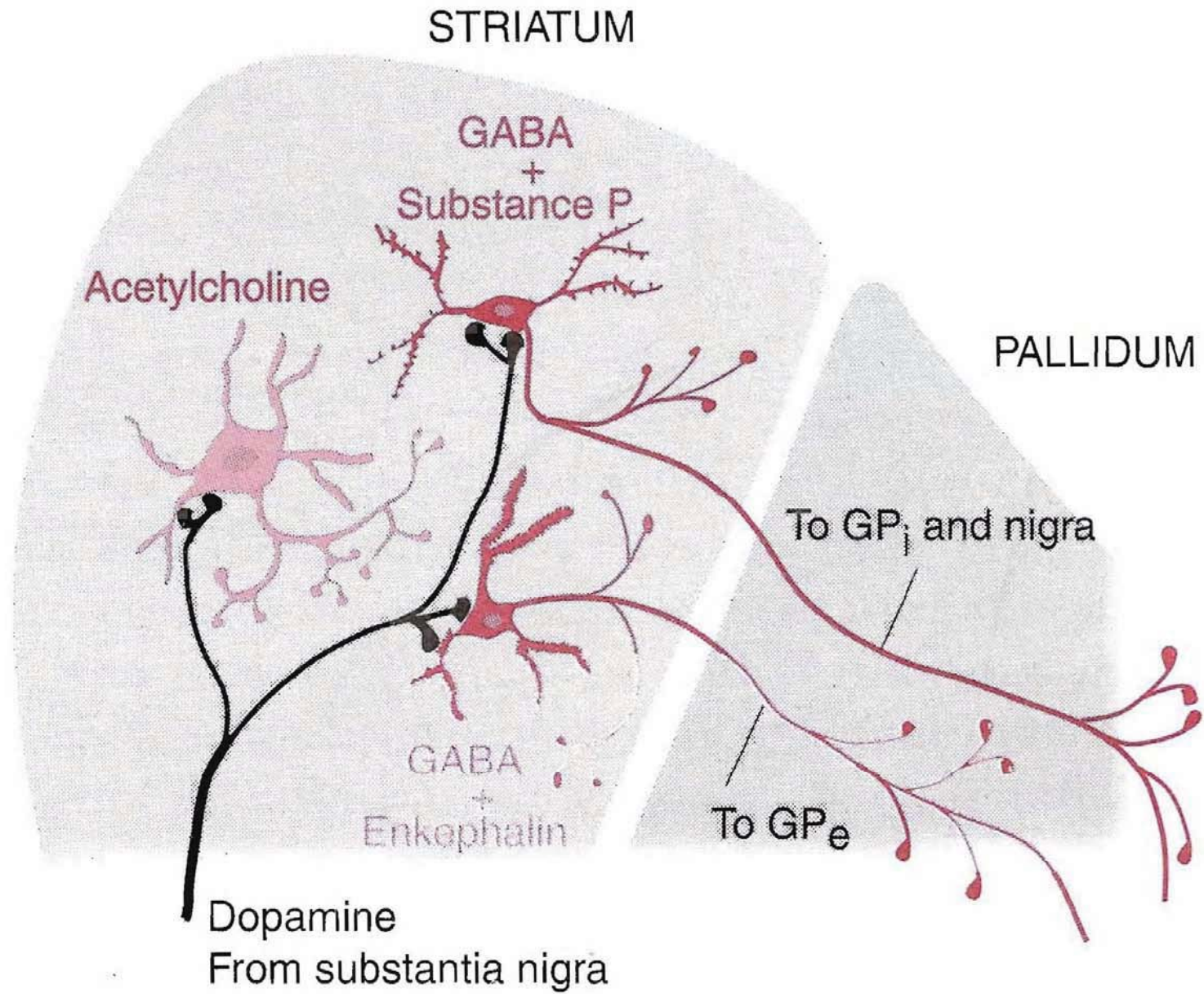
- 1) Motor, somatosensory, & Supplementary motor area [movement]*
- 2) Frontal eye fields; parietal areas [eye movements]*
- 3) Prefrontal [various cognitive functions]*
- 4) Limbic [mood & emotions].*

*This separation of pathways is a bit arbitrary, as there are so many possible “functional pathways” corresponding to the many different cortical areas with different functions.*

## *Questions, chapter 30*

10) What are striasomes?

11) What is the lentiform nucleus? Describe its location in a human brain.



**Fig 30-11**

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## **The large cholinergic interneurons:**

These cells are distributed throughout the dorsal striatum. Whenever there are many axons of cholinergic neurons, there is much cholinesterase.

ACh-ase staining reveals many patches in the striatum that contain very little. These have been called the striosomes—discussed briefly in chapter 30.

# The lentiform nucleus of the human brain (see Nauta & Feirtag)

Describe the approach to the “lentiform nucleus” in dissection of human brain. What covers it? How can that structure be seen when looking at the hemisphere from the side?

cortex of the insula

pry open the Sylvian fissure

“Lentiform nucleus” is a term that includes putamen plus globus pallidus. It is covered by the cortex of the insula (and also by the claustrum)

Figure removed due to copyright restrictions. Please see figure 13.3 of:  
Brodal, Per. *The Central Nervous System, Structure and Function*. 3rd ed.  
Oxford University Press, 2003. ISBN: 9780195165609.

Figure removed due to copyright restrictions. Please see course textbook or:  
Nauta, Walle J. H., and Michael Feirtag. *Fundamental Neuroanatomy*. Freeman, 1986. ISBN: 9780716717232.

**Fig 30-12**

# Temporalization of the cerebral hemisphere

## *What happens to the corpus striatum?*

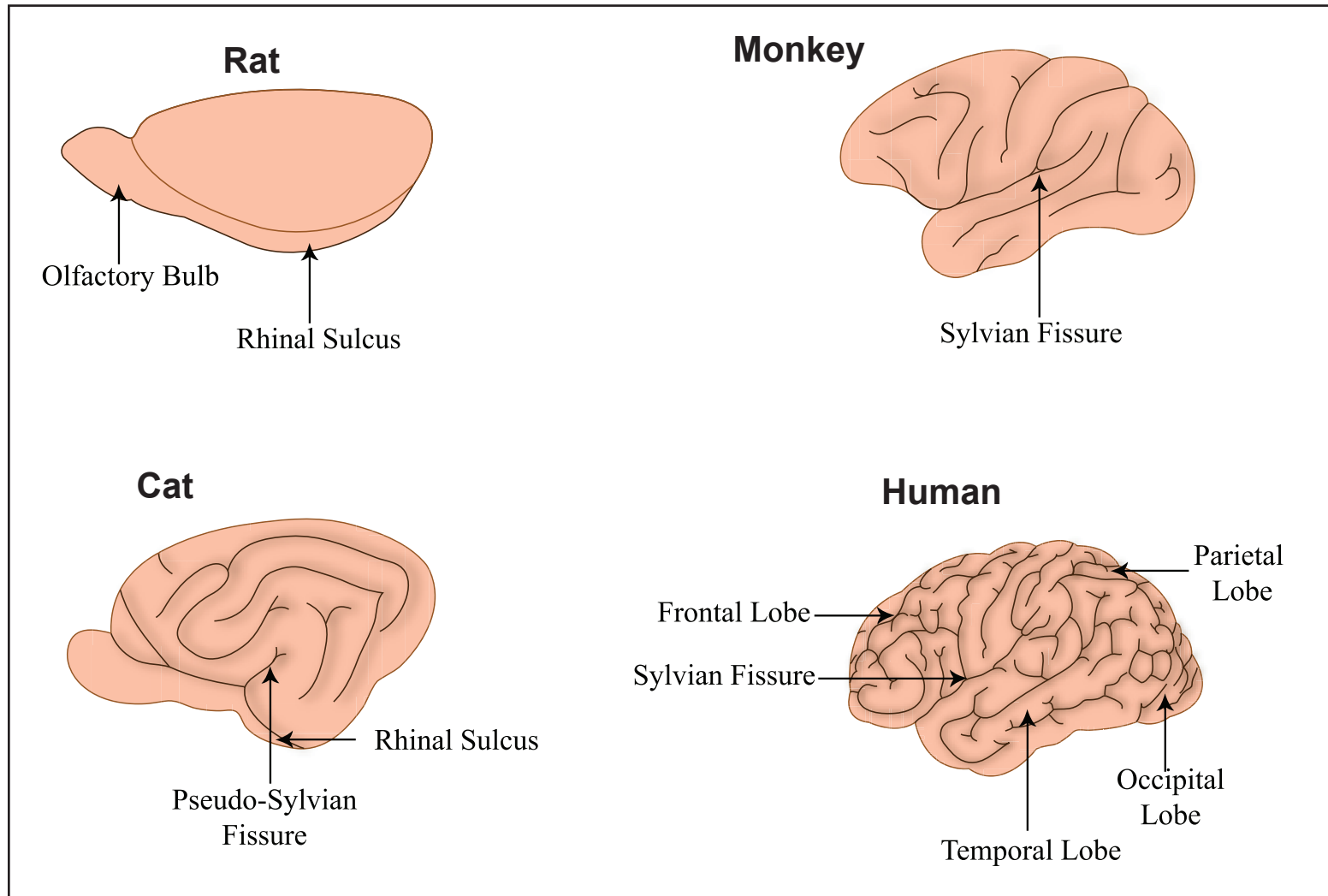
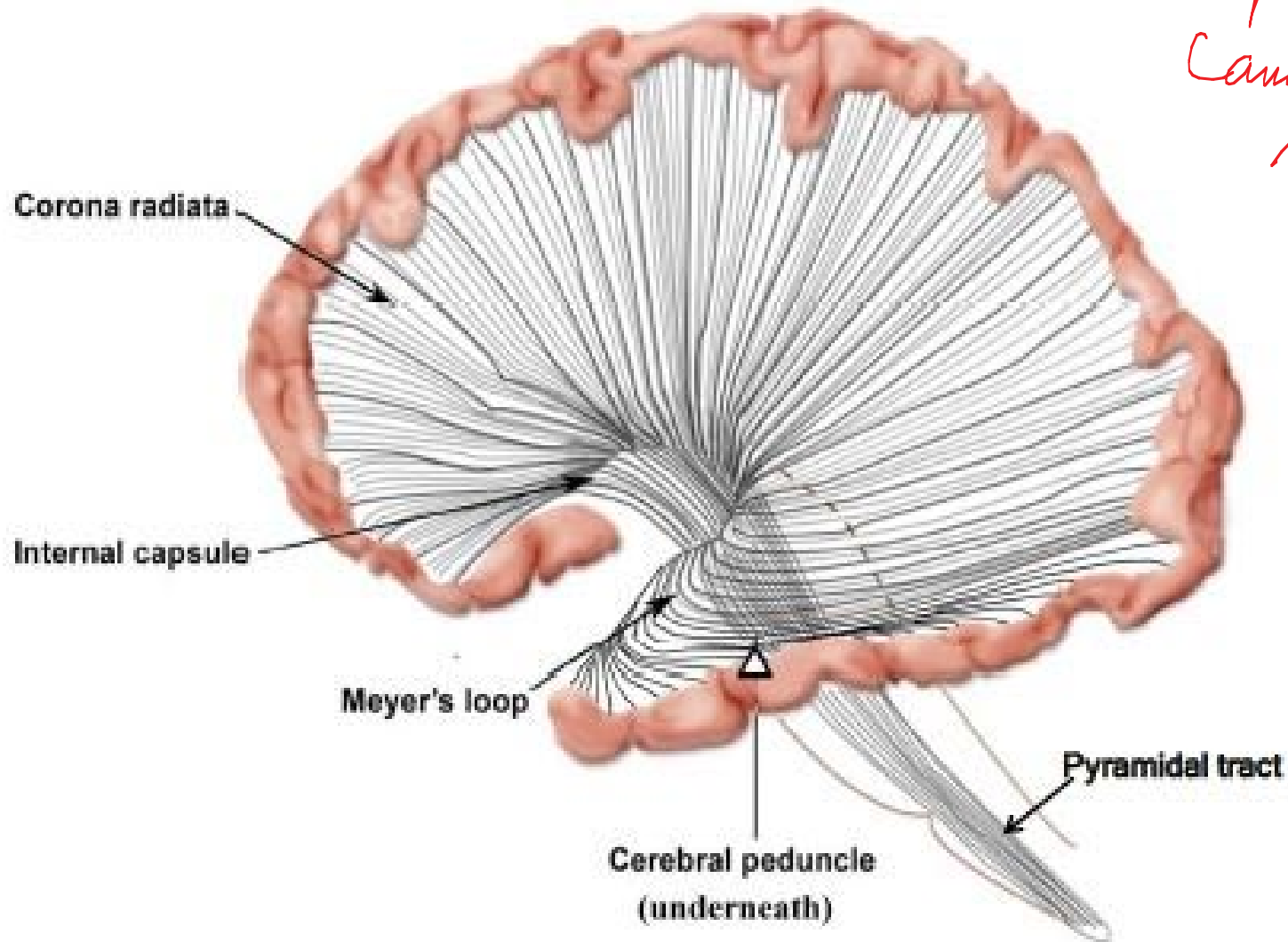


Image by MIT OpenCourseWare.

Lateral view showing  
corona radiata and  
internal capsule.

Caudate is

behind these  
fibers (below  
them in temp-  
le)



Courtesy of MIT Press. Used with permission.  
Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN: 9780262026734.

# Horizontal section of human brain

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Brodal, Per. *The Central Nervous System, Structure and Function*. 3rd ed.  
Oxford University Press, 2003. ISBN: 9780195165609.

**Next:**

## **The striatum in modern medicine: Treatment of Parkinson's Disease by fetal nigral transplants**

But first, a question that requires some integrative thought: **Homework #7 (in part)**

Contrast different routes for sensory information to travel from primary visual cortex to motor output systems. Use information from previous chapters as well as the current one. Try to describe at least three routes.



# **A sketch of the central nervous system and its origins**

G. E. Schneider 2014

**Part 10: Corpus striatum**

**MIT 9.14 Class 34**

- 1. Fetal brain tissue transplantation**
- 2. New neurons for adult brain**  
*(review and extension)*

*Chapter 31 and Intermission (31a)*

# *Readings: topics*

- **Fetal nigral transplantation as a therapy for Parkinson's disease**
- Brain imaging: the dopaminergic system
- New nerve cells for the adult brain
  - (Previously assigned) Turnover of neurons in olfactory bulb (granule cells)
  - Turnover of neurons in the dentate gyrus of the hippocampal formation
  - Stem cells introduced into other brain areas for treating diseases

# First, what is Parkinson's Disease?

- Major cause of symptoms is a loss of dopamine (DA) neurons in the *pars compacta* of the substantia nigra. The degeneration is progressive. When 60-80% of these neurons have been lost, the symptoms of a resting tremor and reduced and altered movement begin to become manifest.
- What enables the brain to compensate for a loss of up to 80%? Most likely there is a collateral sprouting of the axons of remaining cells.
- The most dramatic discovery of a treatment came with the administration of a DA synthesis precursor, L-Dopa, which increases DA production by the remaining intact axons. However, with further loss of such axons, this treatment no longer helps.
- This led to attempts to replace the lost DA cells by implanting fetal nigral cells directly into the striatum of patients.

# Part 1:

## Fetal brain tissue transplantation

- *The surgical procedure*
- *Question about topography of connections made by implanted neurons*

*Questions, chapter 31:*

- 1) Why might the topographic organization of connections not be a critical factor in the functioning of nigrostriatal connections from transplanted tissue?

*Questions, chapter 31:*

- 1) Why might the topographic organization of connections not be a critical factor in the functioning of nigrostriatal connections from transplanted tissue?

The action of dopamine release does not require high information content. It is a neuromodulator.

- 2) Describe the critical nature of donor age in transplant procedures, and why this might be expected.

## *The donor tissue, taken from fetal substantia nigra:*

- Describe the critical nature of donor age in transplant procedures, and why this might be expected.
  - *From Olanow et al. (1996), p. 104:*
    - *Ontogeny of human DA-producing cells*
      - Tyrosine-hydroxylase immunoreactive neurons first appear in the subventricular zone at 5.5-6.5 wk p.c.
      - Neuritic processes first appear at 8 wk p.c.
      - Processes (axons) first reach the striatum at 9 wk p.c.
      - Optimum donor age should be between 5.5 and 9 wk (38-63 days), before differentiation (process development) goes too far. (Disruption of many differentiated processes is likely to kill the cells.)
    - *Data on optimal graft survival: next slide.*

## Data on optimum fetal age of the aborted fetus for source of nigral tissue:

*Tyrosine-hydroxylase-immunostained sections through striatum of rat with grafts of nigra taken from human fetus:*

*A) from fetus of 41 days p.c. showing good survival*

*B) from fetus 72 days p.c. showing poor survival*

*(Olanow et al. '96)*

Figure removed due to copyright restrictions. Please see:  
Olanow, C. W., J. H. Kordower, et al. "Fetal Nigral Transplantation as a Therapy for Parkinson's Disease." *Trends in Neurosciences* 19, no. 3 (1996): 102-9.

# Assessments in living patients

## *Questions, chapter 31:*

- 3) How can imaging of the living brain be used to assess transplant success?
- 4) How has neuroanatomical assessment been done using tissue obtained at autopsy? Describe a result.



*Questions, chapter 31:*

- 3) How can imaging of the living brain be used to assess transplant success?

Use uptake of a radioactive tracer administered in L-Dopa

Fluorodopa uptake, followed by PET imaging (Positron Emission Tomography)

*See Olanow (1996), p. 106*

# Assessments from autopsy material

## *Questions, chapter 31:*

- 4) How has neuroanatomical assessment been done using tissue obtained at autopsy? Describe a result

Neuroanatomical results can be obtained by immunostaining of brain sections for tyrosine hydroxylase, since this enzyme is always present in dopamine neurons.

In general, the autopsy results are in agreement with results from fluorodopa administration followed by PET imaging. See pictures on next slide.

# Tyrosine-hydroxylase-immunostained sections from human brain with surviving graft of fetal tissue from substantia nigra (*Olanow '96*)

Figure removed due to copyright restrictions. Please see:  
Olanow, C. W., J. H. Kordower, et al. "Fetal Nigral Transplantation as a Therapy for Parkinson's Disease." *Trends in Neurosciences* 19, no. 3 (1996): 102-9.

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Olanow, C. W., J. H. Kordower, et al. "Fetal Nigral Transplantation as a Therapy  
for Parkinson's Disease." *Trends in Neurosciences* 19, no. 3 (1996): 102-9.

*Questions, chapter 31:*

- 5) What problem does the size of the human corpus striatum pose for transplant procedures? How far can axons grow from the transplants?

## Problem caused by large brain size

*What problem does the size of the human corpus striatum pose for transplant procedures? How far can axons grow from the transplants?*

Growth rate: 6 – 8  $\mu\text{m/hr}$

(1 mm/7 days @ 6  $\mu\text{m/hr}$ )

Growth distance is very limited:

Commonly only 2.5 mm

*Questions, chapter 31:*

- 6) How is locus of a transplant within the striatum related to possible functional effects?

# Optimal placement of transplants?

*How is locus of a transplant within the striatum related to possible functional effects?*

*Remember the topography of connections from the neocortex:*

What is the difference between the putamen and the caudate nucleus in connections and major functions? Recall the major difference in neocortical inputs to caudate and putamen.

See figure 30.10a



*Questions, chapter 31:*

- 7) Why might the functional improvements after transplants have such a slow onset and slow progression?

# Waiting for results

The improvements can take many months to appear, much longer than predicted by the slow rate of growth of the axons after the implantations. Other aspects of maturation of the neurons apparently require much time in the adult brain tissue.

# Discussion of issues involved

- The transplanted DA cells do not, in all likelihood, get their normal inputs. Tonic effects of DA innervation may be restored, but not phasic changes that must be involved in reward functions
- Parkinson's Disease involves cell groups other than the DA cells of the Substantia Nigra (e.g., norepinephrine cells). What are the functions of these other cell groups?
- Collateral sprouting of non-DA axons may be occurring in the striatum in Parkinson's patients. How well do the new DA axons compete with the abnormal connections?

*Questions, chapter 31:*

- 8) What are alternatives, now or in the future, to transplants of tissue from human fetal substantia nigra?

# Alternatives?

- Xenografts, e.g., from genetically altered pigs
- Implants of non-neuronal cells, e.g., fibroblasts, genetically altered to produce dopamine
- Implants of devices engineered to release dopamine very slowly
- **Stem cells** taken from same patient's body, manipulated so they differentiate into dopamine-releasing cells
- Alleviating some of the symptoms by electrical stimulation or lesions of the striatal tissue, or of other structures connected with the striatum.

*Next slide: What is currently being done*

## Scientific study alters the landscape and leads to changes in treatments

- Little or no effect of transplants except in patients with milder symptoms:
  - Olanow, CW *et al* (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's Disease. *Annals of Neurology* 54: 403-414.
- This has led to greater frequency of "deep brain stimulation" for Parkinson's Disease patients
  - Brain sites usually stimulated: subthalamic nucleus, globus pallidus
  - Online information is easy to find: publications of scientific studies; secondary source descriptions
- Use of stem cells to treat Parkinson's condition in rats (e.g., research at MIT, Jaenisch lab)
  - We will say more about use of stem cells after talking about normal neurogenesis in adult brains

## **Example of another alternative: neurosurgical treatment**

**“Treatment of advanced Parkinson’s disease by posterior  
Gpi pallidotomy: 1-year results of a pilot study...”**

MS Baron, JL Vitek, J Green, Y Kaneoke, ... ..

*Annals of Neurology*. Volume 40 Issue 3, Pages 355 - 366.

Published Online: 8 Oct 2004.

**Goal: Reduce the most debilitating motor symptoms**

# Part 2:

## New neurons in adult brain

- Naturally occurring neurogenesis in adult mammalian CNS:
  - Discovery by Joseph Altman at MIT, in rat endbrain: in olfactory bulb and in dentate gyrus of hippocampal formation)
  - Much later verification for a primate (squirrel monkey)
  - Verification for human dentate gyrus of hippocampal formation
- Stem cell isolation or creation, and their transplantation



*Questions, chapter 31:*

- 9) Where has neurogenesis in the adult mammalian brain been discovered most certainly in research since the 1960s? What types of neurons are involved?

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## 9.14 Brain Structure and Its Origins

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