A sketch of the central nervous system and its origins

G. E. Schneider 2014

Part 9: Hypothalamus & Limbic System

MIT 9.14 Class 29

Core pathways of the limbic system, and remembering meaningful places

(Limbic system 2)

Chapter 26

Limbic system structures

Topics

- Hypothalamic cell groups
- “Papez’ circuit” and the limbic endbrain
- The various structures of the limbic system
- Connections between limbic and non-limbic system structures
- Limbic forebrain activity and mental states
- Review of some major pathways

Questions, chapter 26

1) The hypothalamus has two major divisions, medial and lateral. What is a major difference between these two divisions?

Medial: various distinct cell groups seen in histological sections. No obvious bundles of long axons

Lateral: Axons of medial forebrain bundle throughout. Neurons scattered among these axons.

Hypothalamic cell groups

Per Brodal's chapter 19: questions; discussion

- Which major hypothalamic division can be divided into multiple distinct nuclei?
  - This was done, for example, by Le Gros Clark in 1936: see next slide.
  - See also Larry Swanson's more detailed figure 6.11
  - Comparison of human with rat/mouse/hamster next slides
- How can the remainder of the hypothalamus be characterized? (see previous slide)

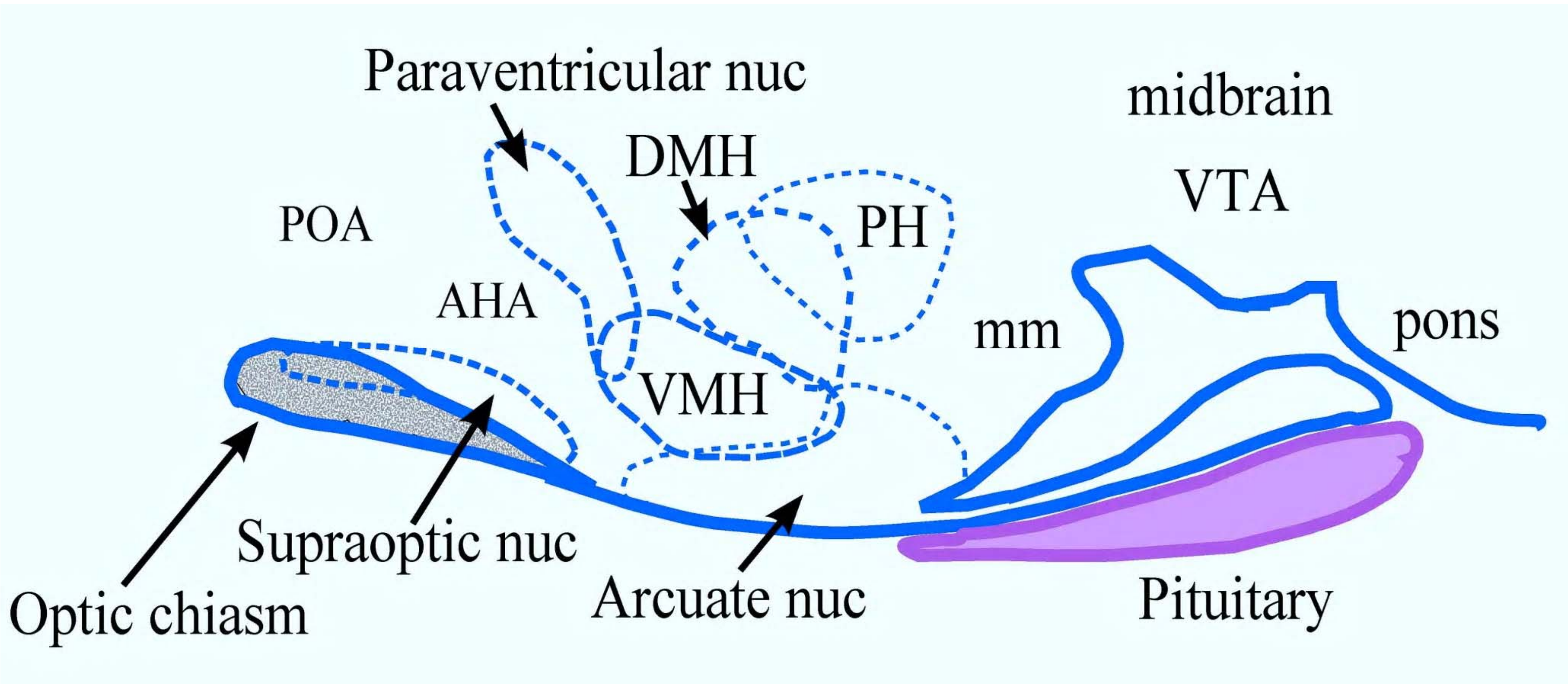
Cell groups of the human medial hypothalamus

Figure removed due to copyright restrictions.
Please see:
Clark, WE Le Gros. "The Topography and Homologies of the Hypothalamic Nuclei in Man." *Journal of Anatomy* 70, no. Pt 2 (1936): 203.

Fig 26.1

"A diagram showing the hypothalamic nuclei projected on to the lateral wall of the third ventricle. This diagram has been made by taking a tracing from a photograph of the brain which was afterwards serially sectioned in a sagittal plane. The extent of the nuclei was reconstructed from the serial sections." *From Le Gros Clark, 1936*

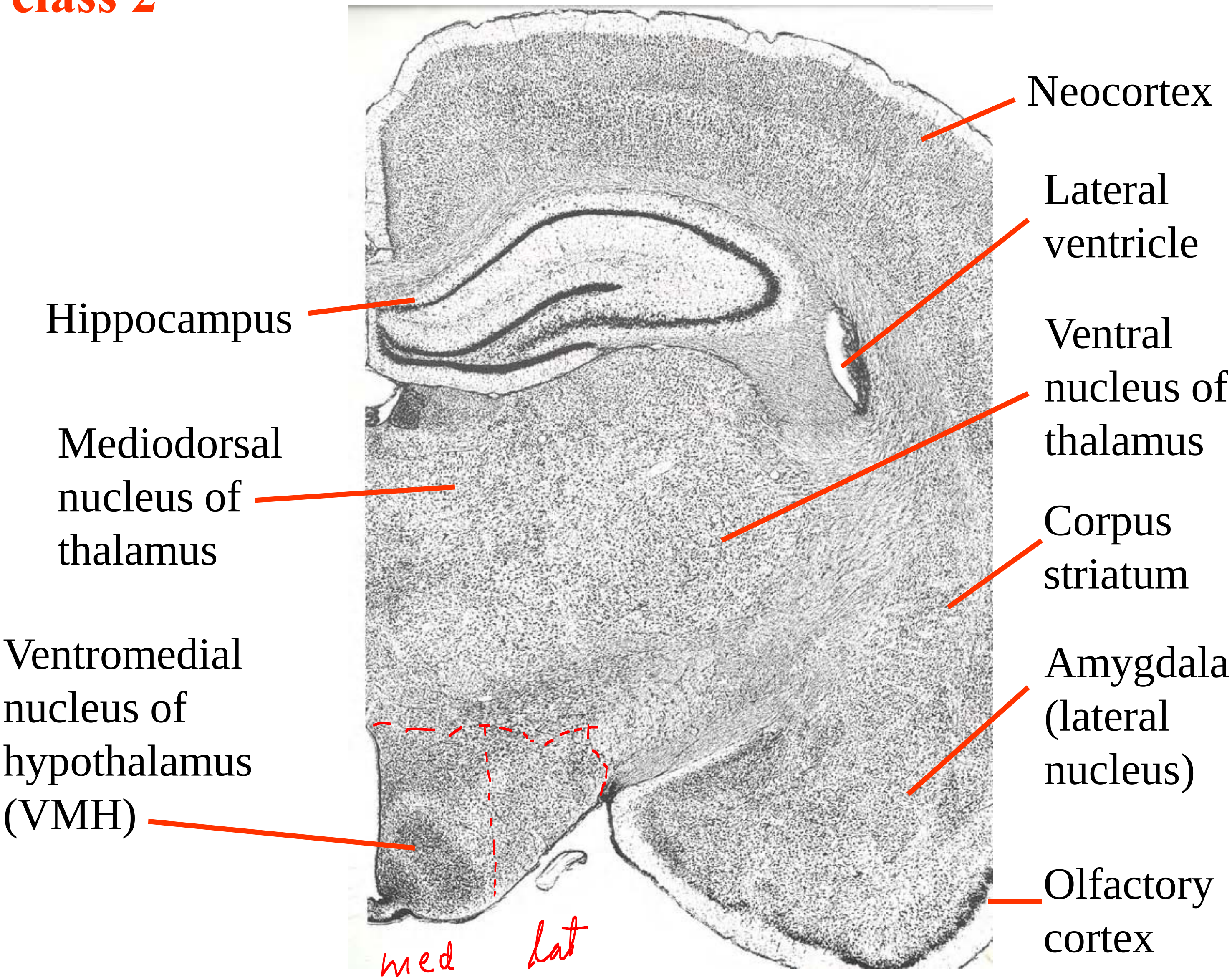
Rat / mouse / hamster: Schematic parasagittal section



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

Fig 26-2

From class 2



Rat brain, coronal section, Nissl stain (cell bodies)

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

From class 2

Rat brain, coronal section, Nissl stain (cell bodies)

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

Questions, chapter 26

2) Information about the internal environment of the body reaches the hypothalamus via two major means. What are they?

1 via bloodstream

2 via sensory pathways

Hormones and the blood-brain barrier:

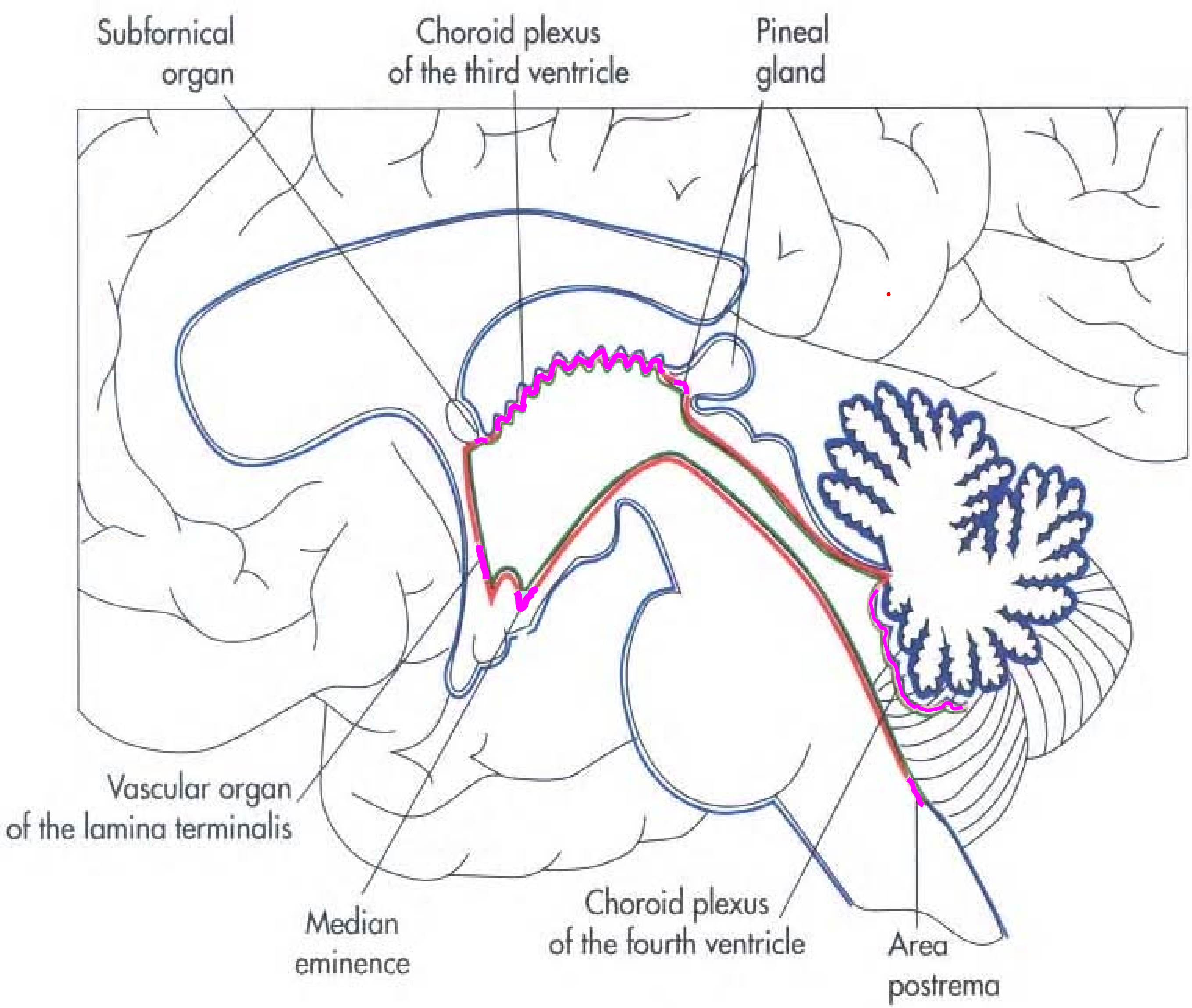
Question on Brodal reading or Schneider ch. 26

How can a circulating hormone like angiotensin II control hypothalamic neurons even though it does not pass through the blood-brain barrier?

weak BBB or no BBB in specific regions:

[***See p 401 box.***] ***What is the subfornical organ?***

Brodal



Shown in pink: Sites in the walls of the third and fourth ventricles where a blood-brain barrier is lacking

Fig 26-3

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

End session 29

HRP, injected into the bloodstream, passes through leaky blood-brain barrier in the median eminence region of the monkey hypothalamus

Fig 26-4

Sensory inputs to hypothalamus

- What is the importance of afferents to the hypothalamus from the nucleus of the solitary tract in the hindbrain?
  - *Vagal inputs re: pain, temperature, stomach distension, etc.*
  - *Other visceral* inputs: from sacral region.
- Describe an alternate pathway from the body below the neck.
  - From dorsal horn neurons: pain sensitivity
- Other inputs
  - Thermoreceptor & osmoreceoptor neurons in hypothalamus
  - Olfactory inputs
  - Inputs direct from retina

See Brodal p 400; Giesler et al.(1994)

Questions, chapter 26

3) Describe the basic Papez’ circuit. Why has there been a revival of interest in this circuit?

Forebrain pathways of special significance:

The Papez' circuit

- The cingulate cortex (a "paralimbic" cortical area above the corpus callosum in mammals) projects to the hippocampal formation. From there, a pathway goes directly to the hypothalamus.
- A pathway goes from the mammillary bodies of the hypothalamus back to the cingulate gyrus *via* the anterior thalamic nuclei. (*See diagrams in following slides*.)
- **The complete loop is called Papez' circuit.**

James Papez and his proposal

- Papez was a neuroanatomist. In 1937 when he published his theory of emotion and the brain, many of the connections he proposed were not certain because the experimental techniques for demonstrating them were lacking.
  - **Papez JW. 1937. A proposed mechanism of emotion**. *J Neuropsychiatry Clin Neurosci.* 1995 Winter;**7**(1): 103-112.
- His basic argument:
  - What had been called the "rhinencephalon" is not dominated by olfaction in humans as had been believed.
  - The medial structures of the hemispheres were associated with feelings and emotional expressions, based on clinical cases.
  - It was also recognized that they have a threshold for seizures that is lower than for other regions. The entire "circuit" is involved in such seizures, so the structures must be highly interconnected.
- His original circuit has been expanded to include various additional structures that we now group into the "limbic system", a term based on Paul Broca's "great limbic lobe", and reintroduced by Paul MacLean.

- **Our understanding of a major function of the pathways has changed**

Why has there been a revival of interest in the circuit described by Papez?

- Discovery of the importance of the hippocampal formation in spatial memories.
- In humans, this role extends to formation of long-term memories for specific events (but not procedural memories – the habits – dependent on corpus striatum.)
- This role adds special importance to the study of hippocampal inputs and outputs.

Starting with the human brain causes confusion!

Main connections of mammillary bodies (nuclei)

How do you find "Papez circuit" in such a confusing picture?

Do not be surprised (or upset) if this schematic picture of the human brain is confusing to you!

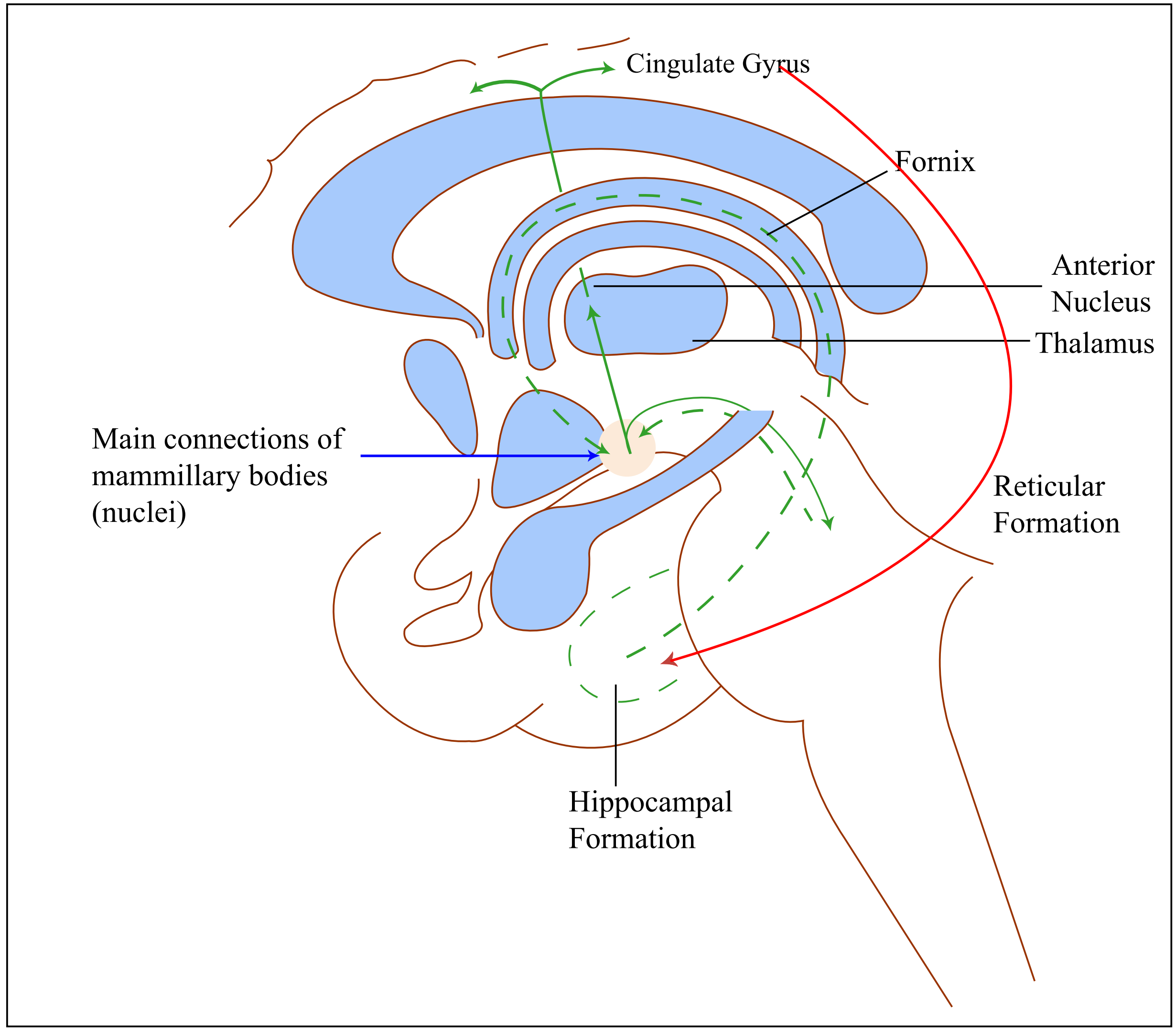
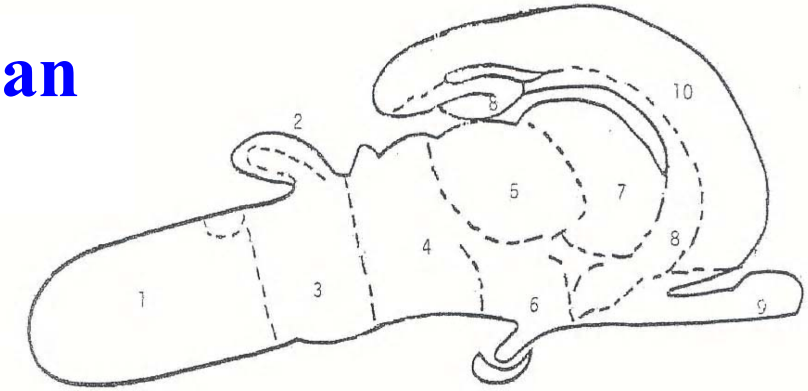


Image by MIT OpenCourseWare.

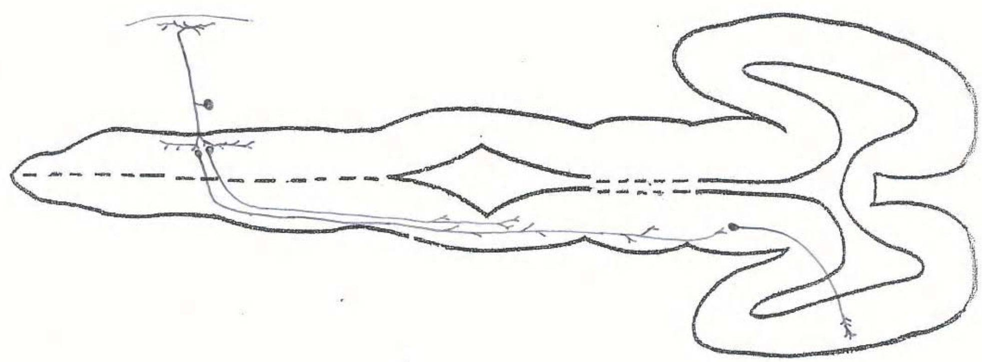
Next: Views of these pathways in rodent brain

Remember the mammalian brain diagrams:

Schematic side view



Top view, embryonic brain (with spinothalamic tract)

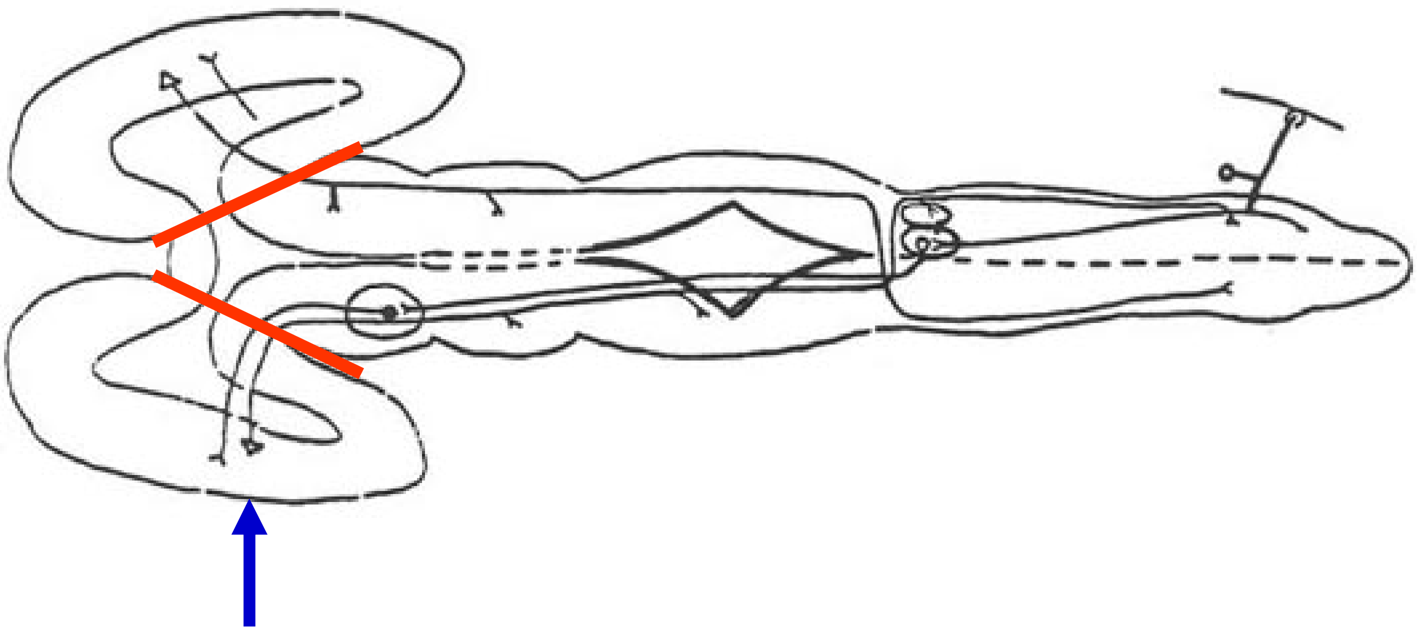


Schneider, G. E. Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind. *MIT Press*, 2014. ISBN: 9780262026734.

NEXT: How we get a more realistic sketch of the embryonic human brain, or adult hamster or rat or mouse brain, with hemisphere separated from the underlying brainstem

First, we turn the brain around, so rostral is to the left.

Next, we cut off the two hemispheres—at the red lines, then discard the left one and move the right one to a position above the brainstem.



Then we look at it from the left side—as indicated by the blue arrow.

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

Doing this for a hamster or mouse brain, we can sketch it as in the following figure.

Students: Read the labels and try to pronounce the names in such pictures, so you can gradually form an image of their locations in the brain.

(top) Medial view of hemisphere of hamster

S = septal area
AC = anterior commissure
BNST = bed nucleus of stria terminalis
SI = substantia innominata

(bottom) Brainstem showing mammillary body and anterior nuclei of thalamus

MD = mediodorsal nuc, thalamus
mt = mammillothalamic tract
mm = mammillary body

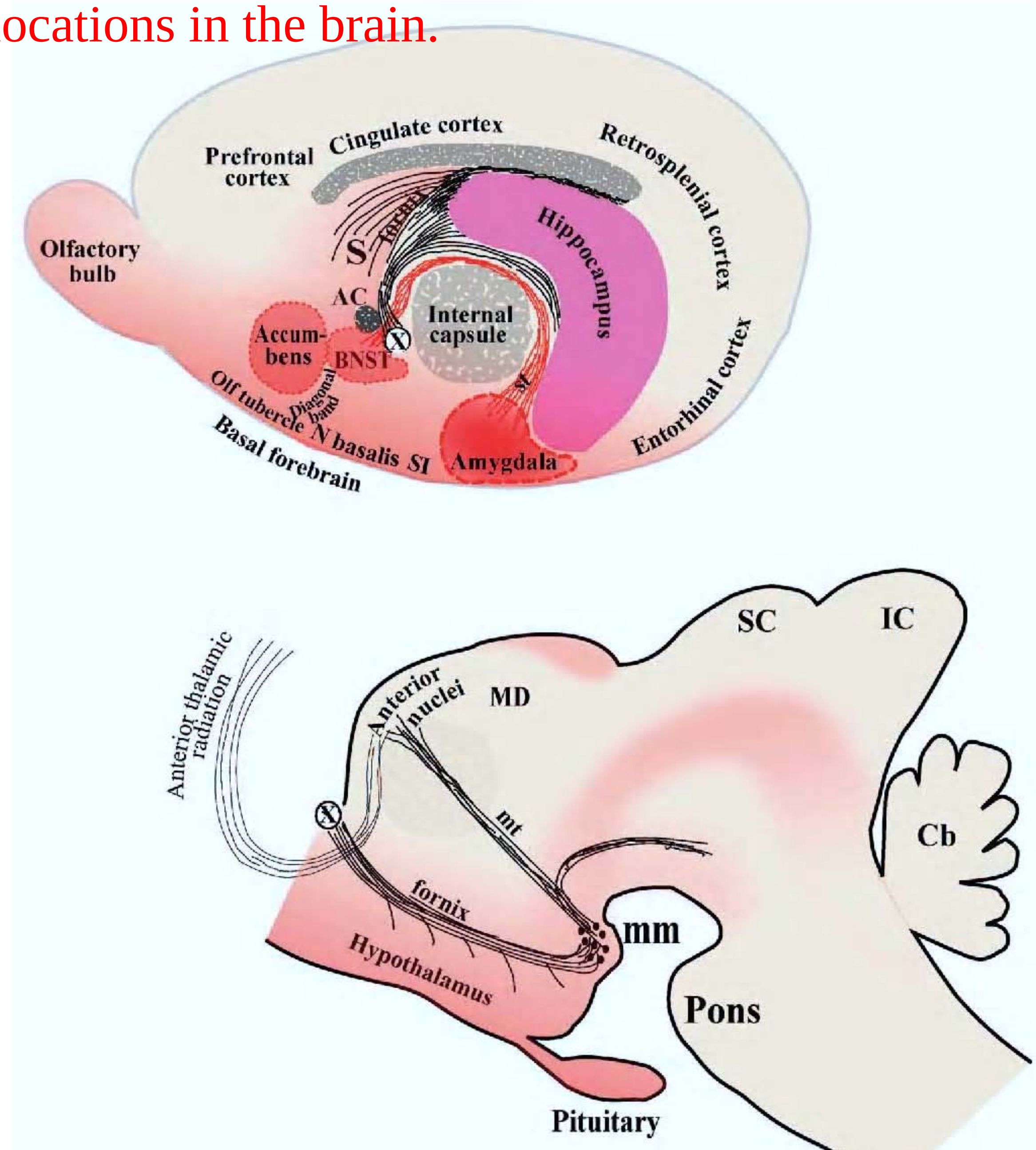


Fig 26.5

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

Cerebral hemisphere, medial view, hamster

OB, olfactory bulb

PF, prefrontal cortex

Cing, Cingulate cortex

RS, retrosplenial cortex (caudal cingulate)

S, septal area

fx, fornix

st, stria terminalis

DB(B), diagonal band of Broca

Am, amygdala

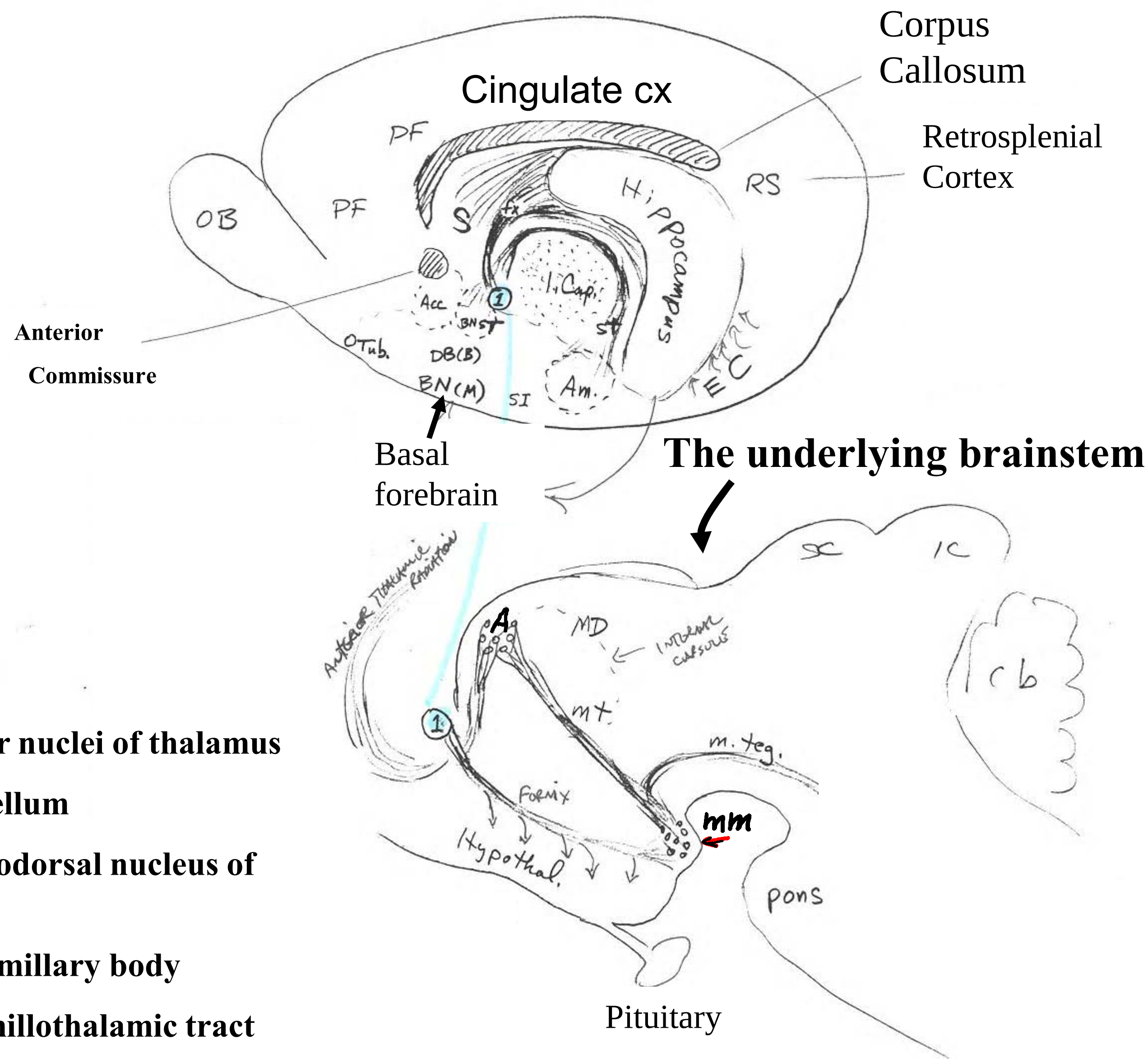
EC, entorhinal cortex

O Tub, olfactory tubercle

SI, substantia innominata

Acc, nuc. Accumbens

BNST, bed nucleus of the stria terminalis



A, anterior nuclei of thalamus

Cb, cerebellum

MD, mediodorsal nucleus of thalamus

mm, mammillary body

mt, mammillothalamic tract

m teg, mammillotegmental tract

SC, superior colliculus

Fig 26-5

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

Where is the “Papez’ circuit in the figure?

The Circuit of Papez

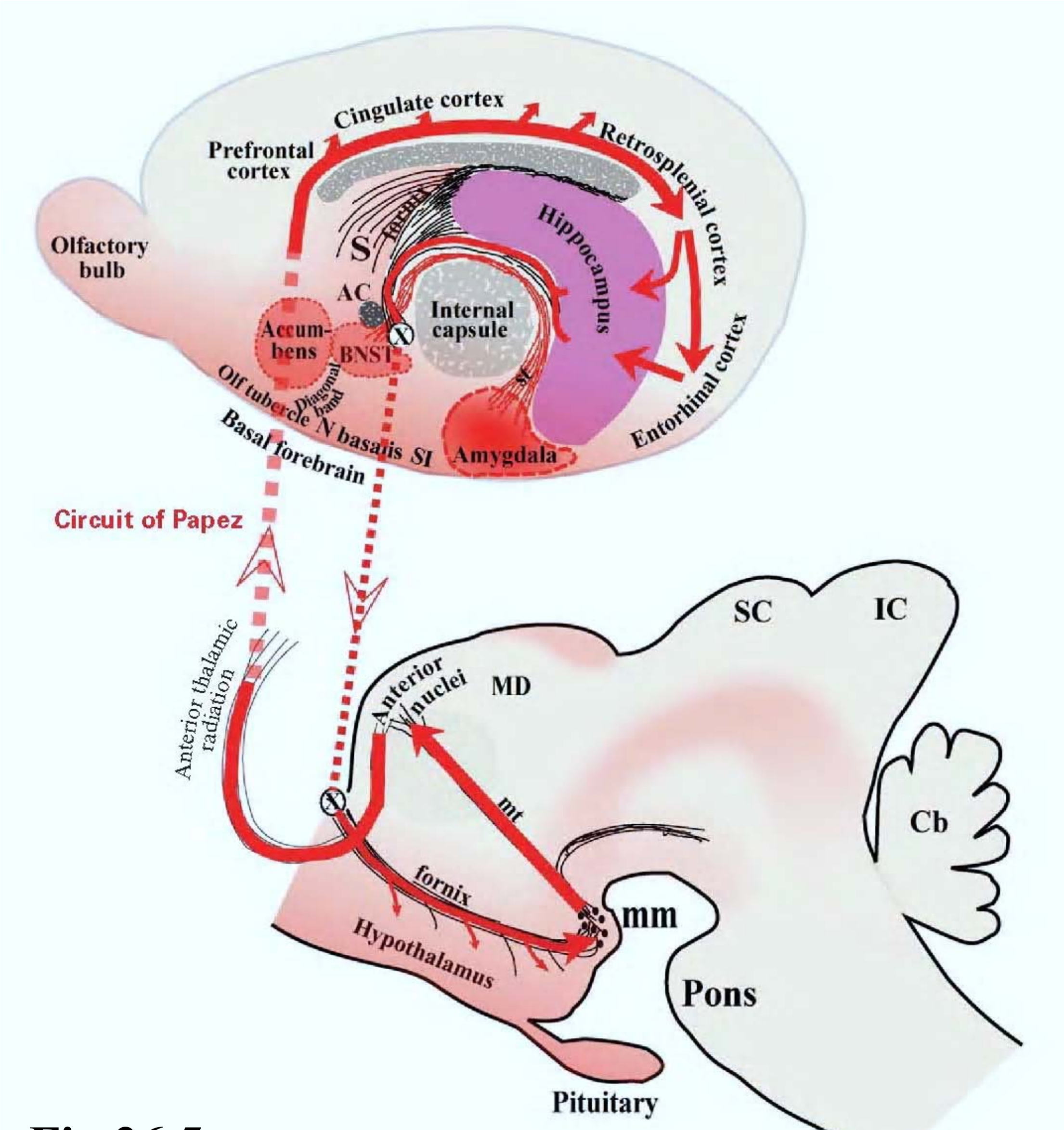


Fig 26.5

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

Papez’ Circuit

OB, olfactory bulb

PF, prefrontal cortex

Cing, Cingulate cortex

RS, retrosplenial cortex (caudal cingulate)

S, septal area

fx, fornix

st, stria terminalis

DB(B), diagonal band of Broca

Am, amygdala

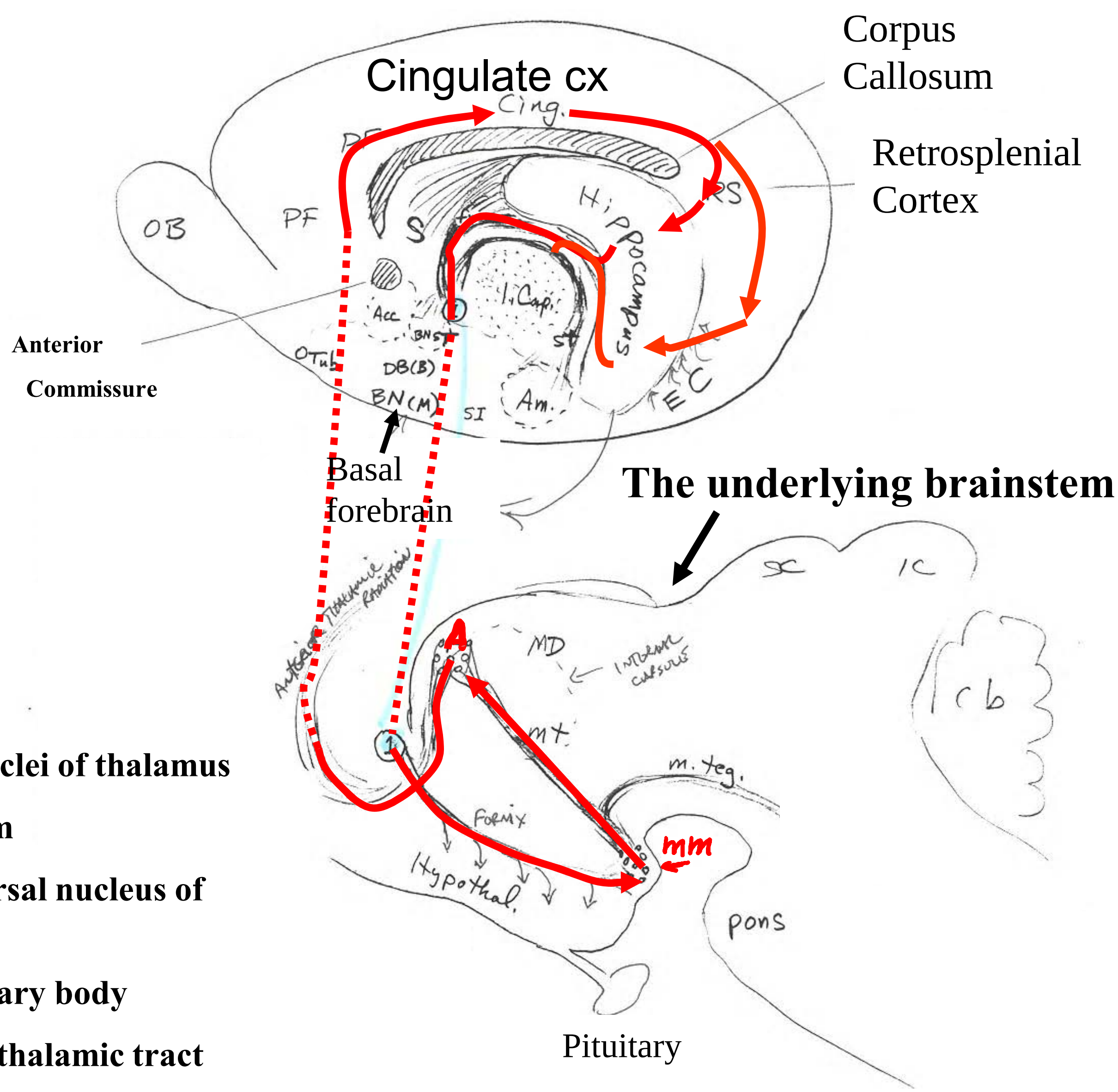
EC, entorhinal cortex

O Tub, olfactory tubercle

SI, substantia innominata

Acc, nuc. Accumbens

BNST, bed nucleus of the stria terminalis



A, anterior nuclei of thalamus

Cb, cerebellum

MD, mediodorsal nucleus of thalamus

mm, mammillary body

mt, mammillothalamic tract

m teg, mammillotegmental tract

SC, superior colliculus

Fig 26-5

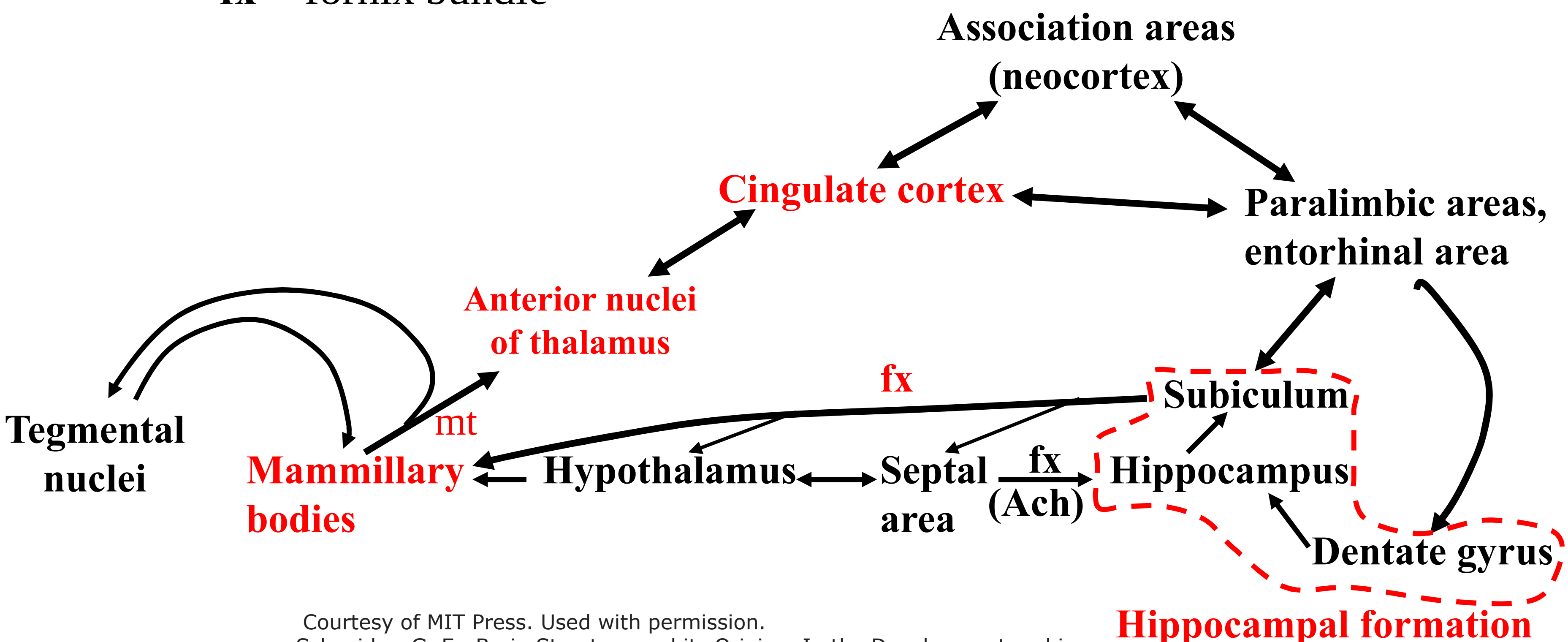
Questions, chapter 26

4) How are the Papez' circuit structures connected to non-limbic neocortical areas?

To answer this, see the following updated diagram of Papez' circuit.

Papez' circuit with additions

mt = mammillothalamic tract
fx = fornix bundle



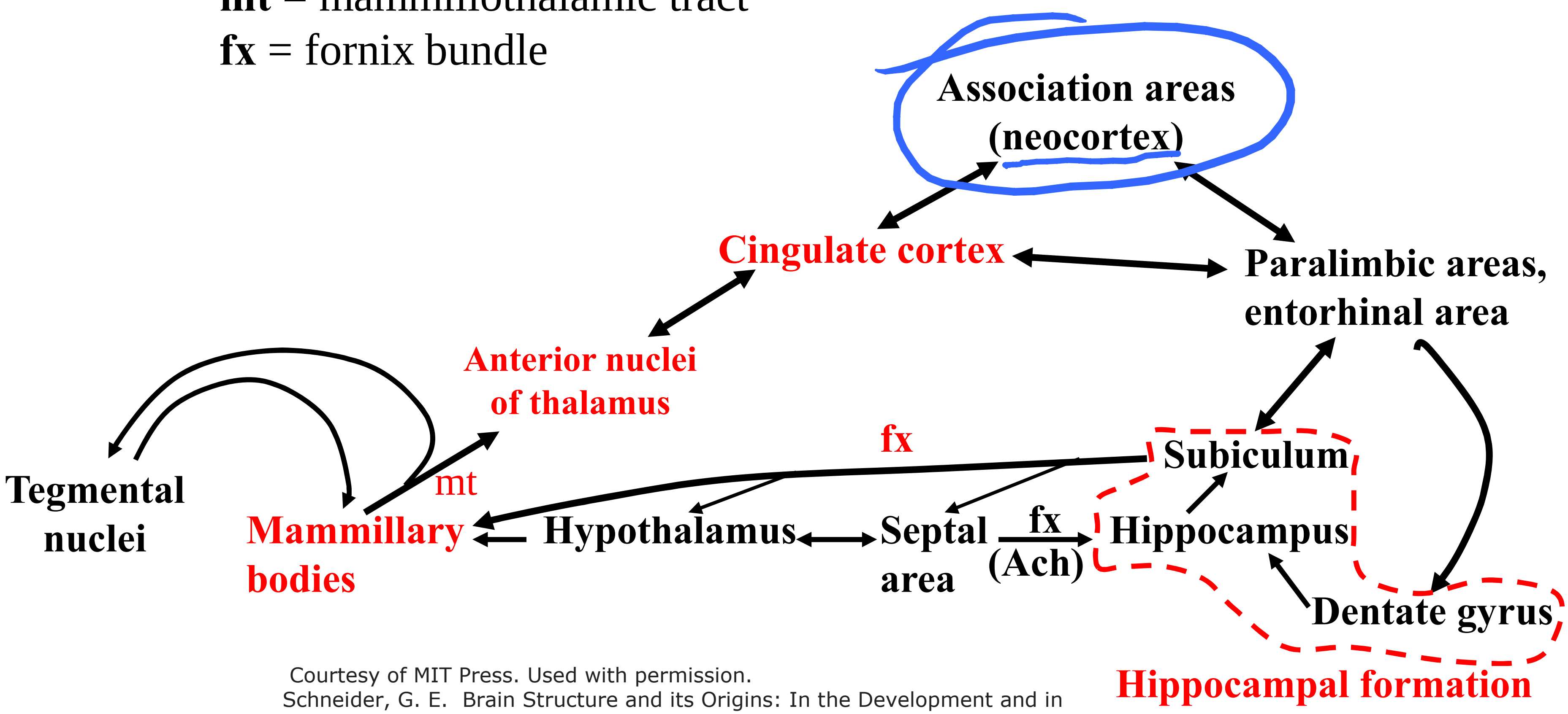
Schneider, G. E. Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind. *MIT Press*, 2014. ISBN: 9780262026734.

Bringing it up to date

Fig 26-7a

Papez' circuit with additions

mt = mammillothalamic tract
fx = fornix bundle



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

Bringing it up to date

Fig 26-7a

What signals are coming from the hippocampus to the mammillary bodies?

- Our "sense of direction" is the direction the head is facing with respect to environmental landmarks; it is signaled from cortical areas through the hippocampus to the mammillary bodies.
- Such head direction (HD) with respect to landmarks is "allocentric" head direction, represented by firing of cells in the mammillary nuclei.
- Changes in head direction modify the activity of the mammillary body cells, so the ascending information signals corrected allocentric direction from moment to moment.

This explains the functional importance of the return pathway

- Any change in head direction (HD) alters activity in the midbrain's tegmental nuclei, which connect with the mammillary bodies.
- The tegmental nuclei receive this information from the vestibular and proprioceptive systems in the brainstem.
- Thus, allocentric HD activity in mammillary body cells is corrected whenever the head turns.
- HD cells are found all along the ascending pathway.
- The place of the animal in its internal map of the environment and its anticipated direction of movement are constantly being updated. For this, information on changes in head direction is crucial.

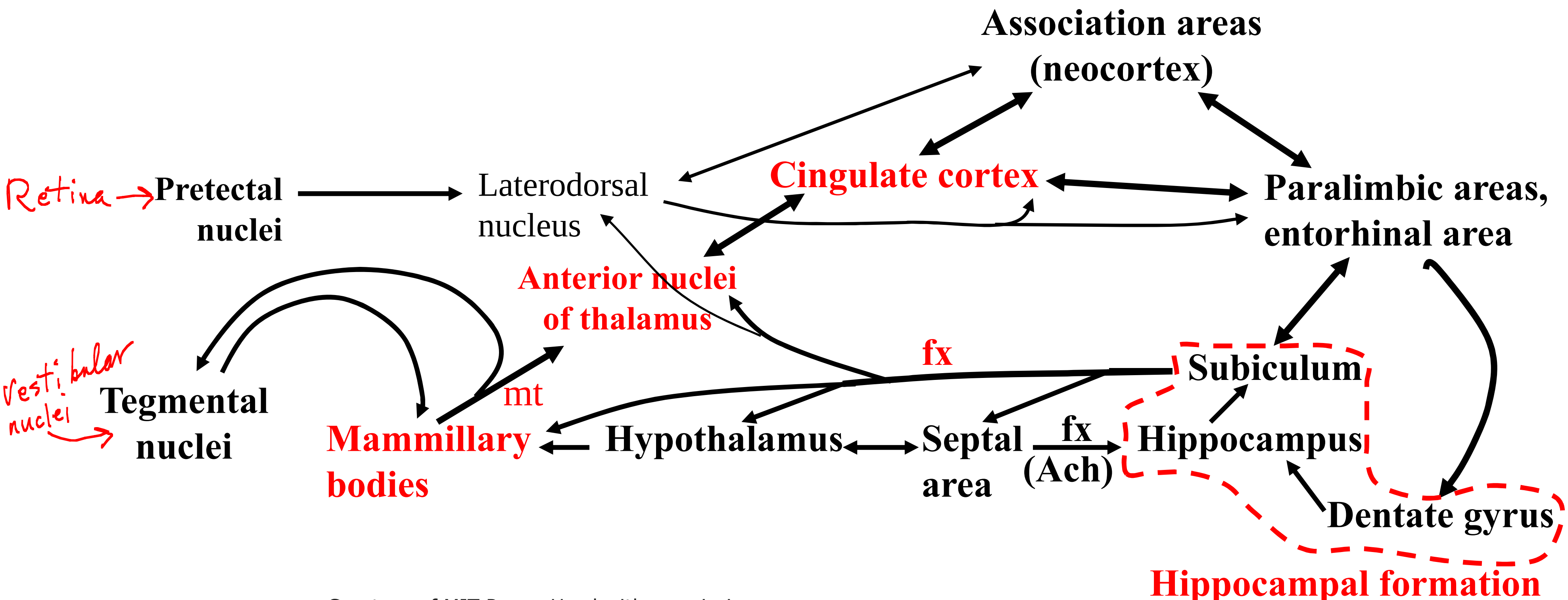
More on the return pathway

- The visual system also detects changes in head direction.
- Lateral shifts in head direction excite cells in the pretectal area.
- The information goes to the anterior part of the lateral nucleus (LD).
- LD projections go to parahippocampal areas.

This can be added to the Papez circuit, as in the next illustration:

Papez' circuit with additions

mt = mammillothalamic tract
fx = fornix bundle



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

Fig 26-7b

Functional significance: additional questions and ideas

- ***Suggestion: the ascending axons of this circuit are continuously activating memories of places that lie ahead, in the direction indicated by the current direction of the head.***

Thus, decisions about direction of locomotion are influenced by memories of those places, including their good or bad values.

- ***Axons in the Papez circuit are of more than one type. Only the ones signaling head direction have been characterized.***

- ***What is the hippocampus sending to other parts of the hypothalamus? It may alter motivational levels according to remembered information about locations in the current frame of reference.***

Questions, chapter 26

5) What is the “basal forebrain”? Name some structures of this region.

(top) Medial view of hemisphere of hamster

S = septal area
AC = anterior commissure
BNST = bed nucleus of stria terminalis
SI = substantia innominata

(bottom) Brainstem showing mammillary body and anterior nuclei of thalamus

MD = mediodorsal nuc, thalamus
mt = mammillothalamic tract
mm = mammillary body

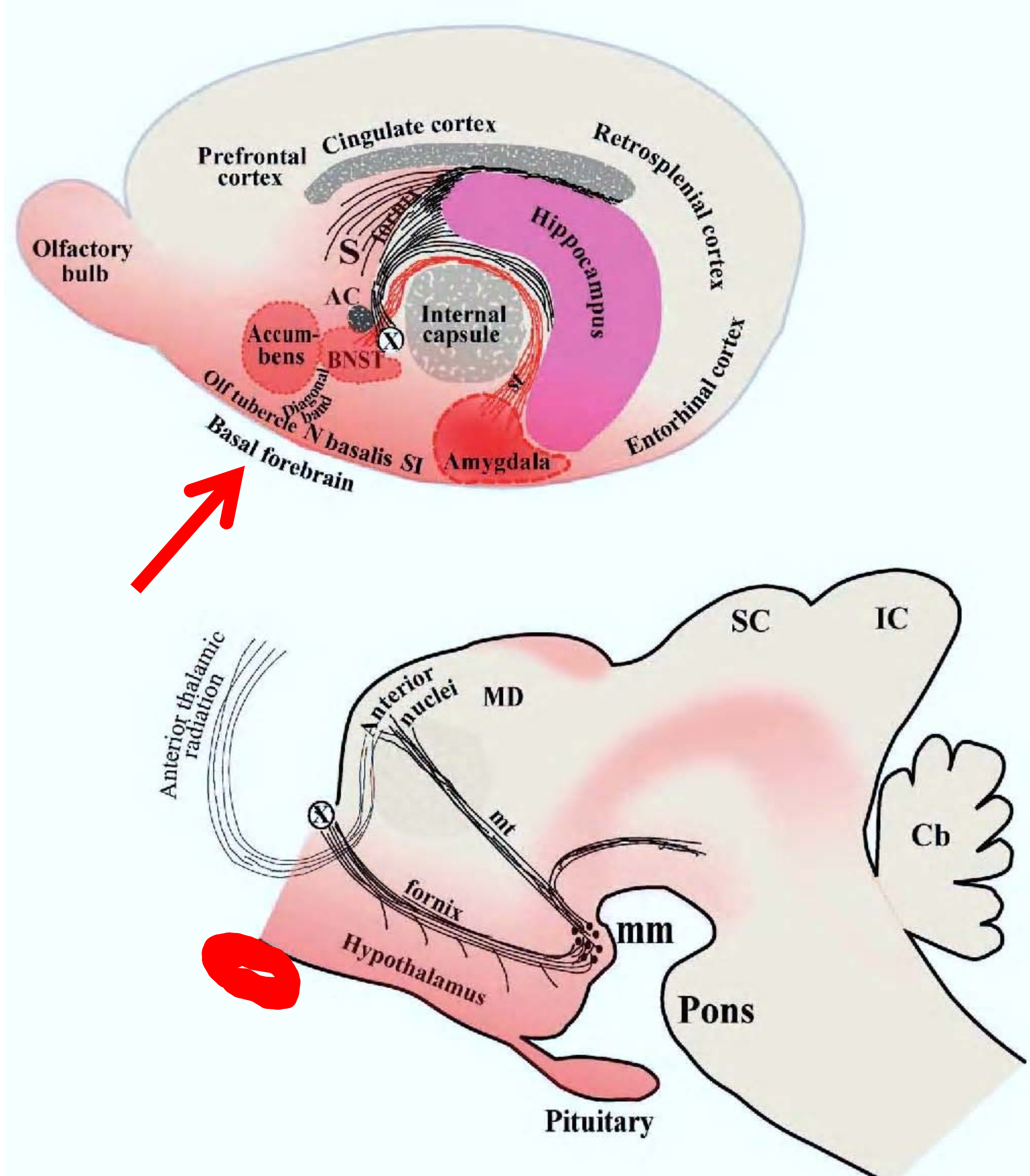


Fig 26.5

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

(top) Medial view of hemisphere of hamster

S = septal area
AC = anterior commissure
BNST = bed nucleus of stria terminalis
SI = substantia innominata

(bottom) Brainstem showing mammillary body and anterior nuclei of thalamus

MD = mediodorsal nuc, thalamus
mt = mammillothalamic tract
mm = mammillary body

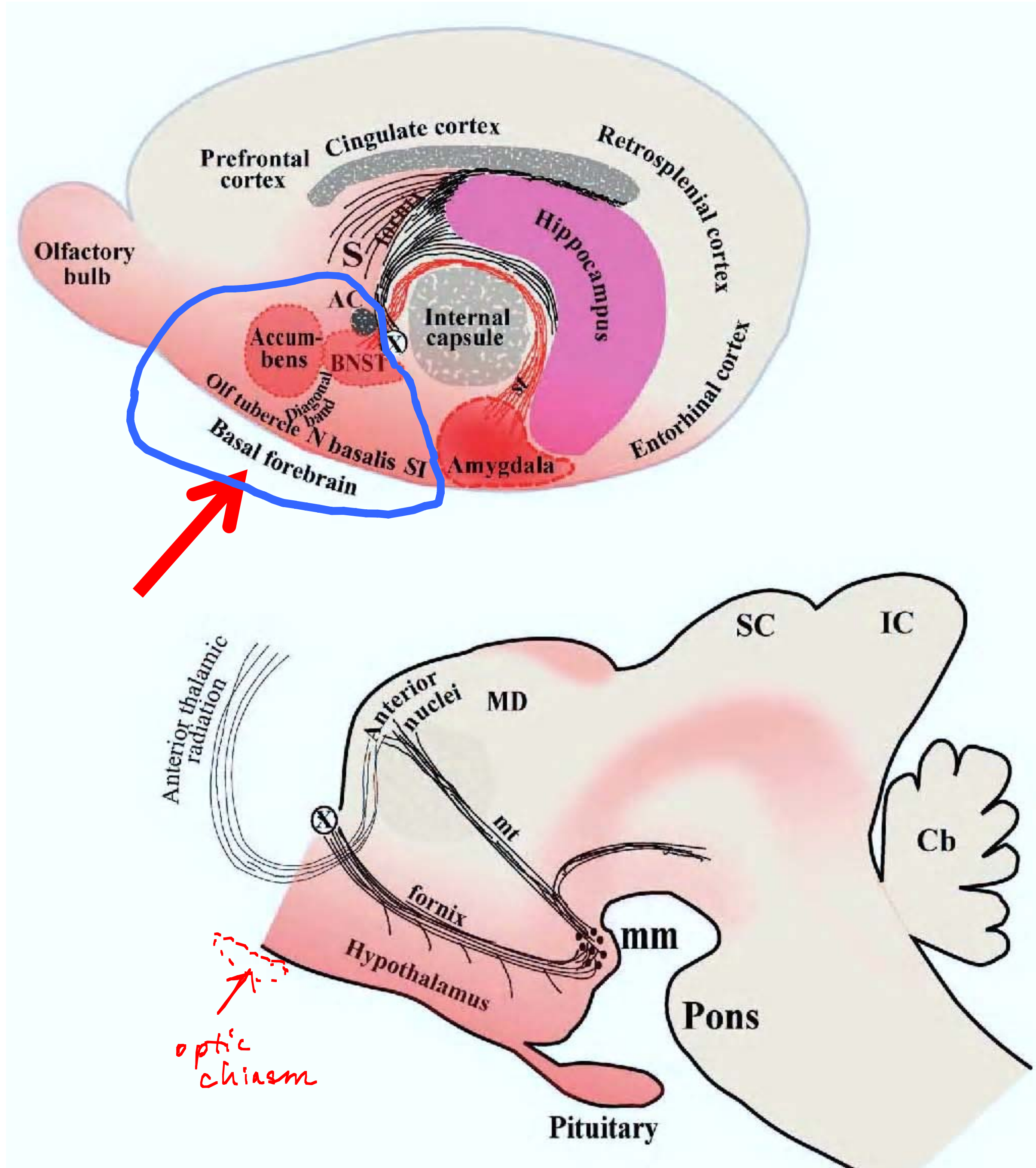


Fig 26.5

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

Frontal sections: the limbic system of rodent

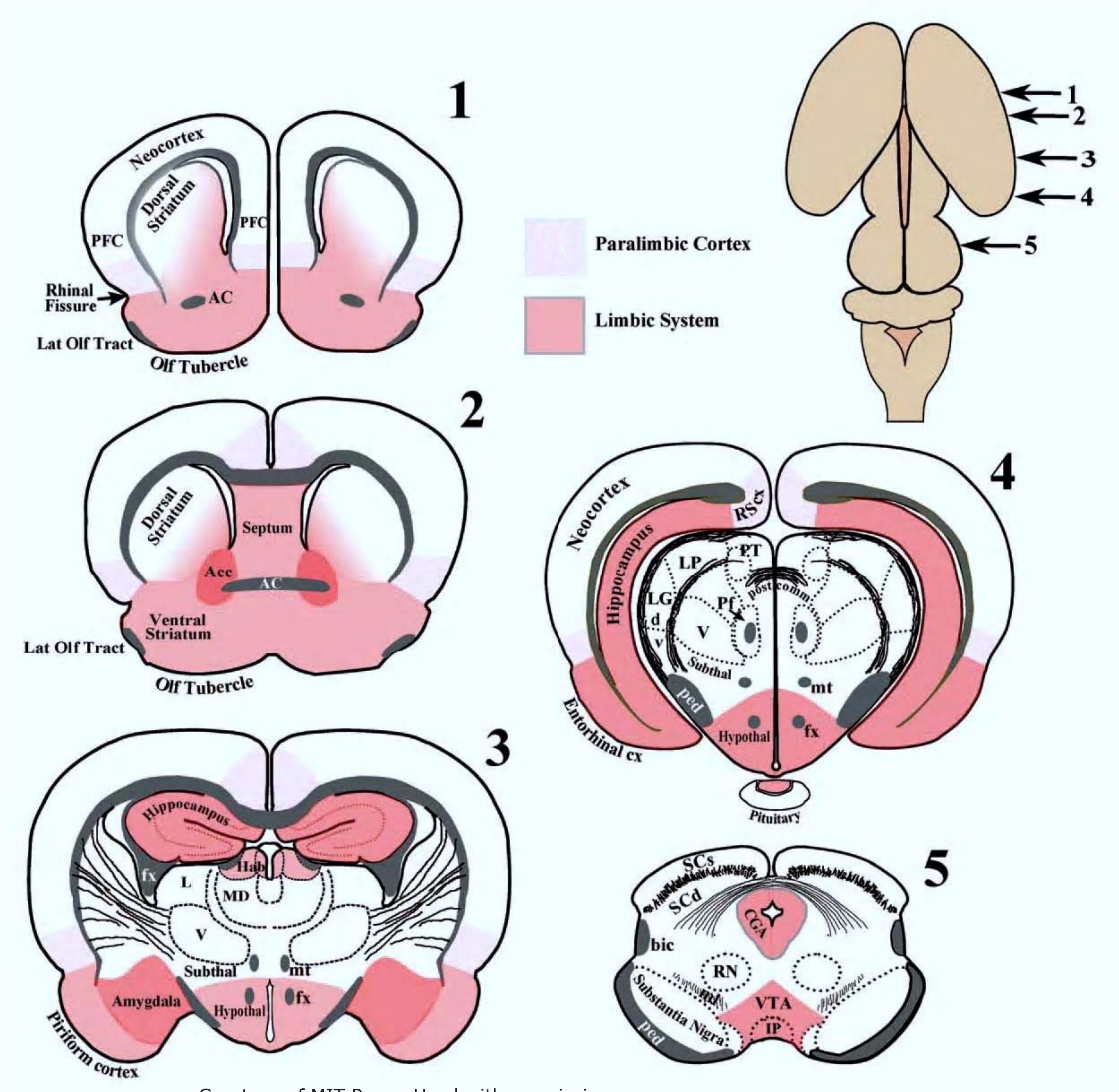


Fig 26.8

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.

Questions, chapter 26

6) Describe two ways that the hypothalamus can influence the neocortex. [slide 42 and next slide]

7) What is a major "reward pathway" in the mammalian CNS?

The dopamine axons from the ventral tegmental area through the lateral hypothalamus to the ventral striatum/ basal forebrain/limbic endbrain structures.

Through the neocortex to the limbic system:

Transcortical pathways from specialized sensory and motor areas through association cortex to limbic system:

Such transcortical connections increased in quantity and importance in larger mammalian brains.

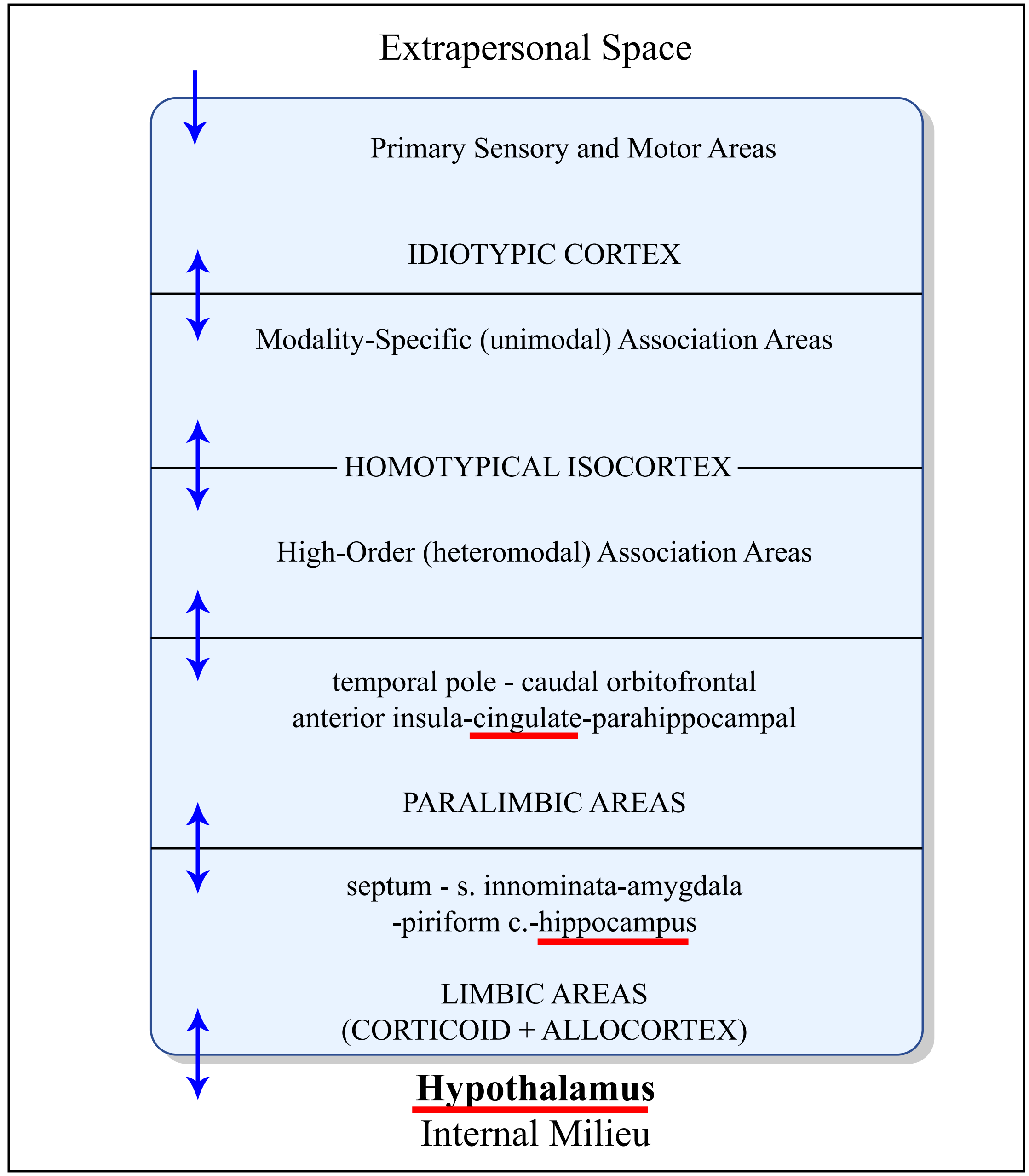


Image by MIT OpenCourseWare.

Would you expect the hypothalamus to influence neocortical activity?

What kind of influences?

Would you expect the hypothalamus to influence neocortical activity?

What kind of influences?

The influences of moods and motivational states on the neocortical processes that result in decision making. (No matter how "cognitive" we may be, we never escape these influences.)

Hypothalamus influences neocortex *via* multiple pathways

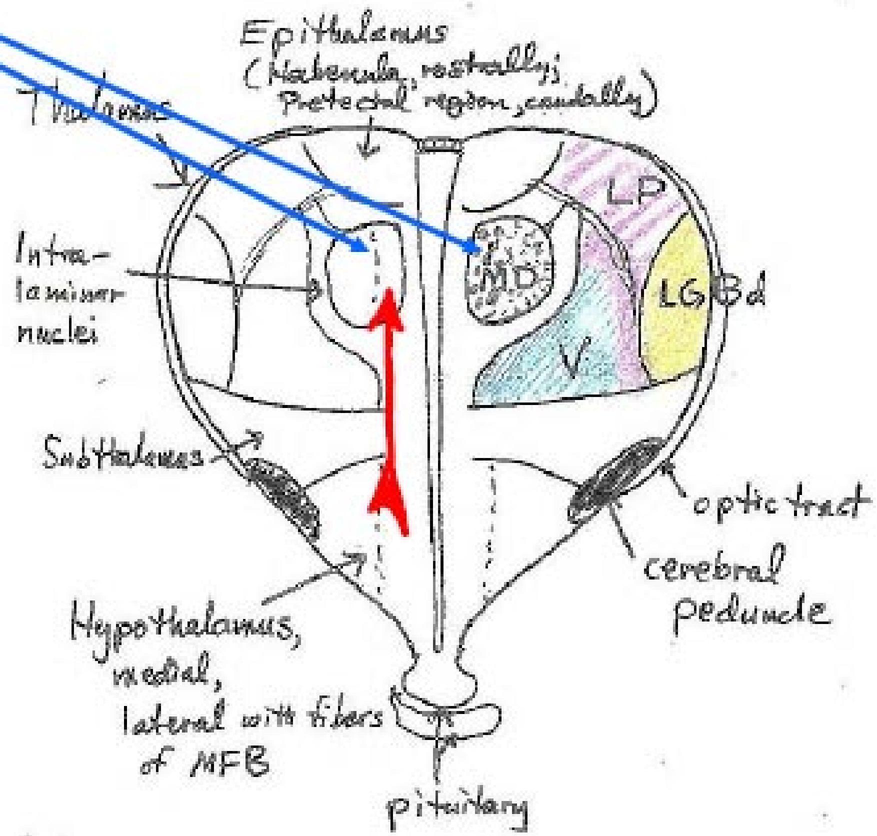
- ***Via* projections to MD** (medial magnocellular part) to Orbital Prefrontal cortex. Olfactory information also reaches neocortex this way. (next slide) also chapter 19 and next slide
- *Via* gating of information processed by other thalamic structures
  also chapters 7, 12, 24
- Papez' circuit:
  - Mammillary nuclei to **Anterior nuc**. of thalamus to Cingulate cortex, which has transcortical connections to Association cortex
  - Hypothal.⟺**Septum**⟺Hippocampus⟹Subiculum⟺Entorhinal & other paralimbic cortex ⟺Cingulate cortex ⟺Assoc.neocortex
- Widespread axon systems: also chapter 17
  - Hypothal.⟹**nuc. Basalis** ⟹*via* ACh axons distributed widely in neocortex
  - **Widespread projections** originating in hypothalamus (Histamine containing; hypocretin/orexin containing)

See "brain states" chapter. Also, see Brodal, Nauta & Feirtag, Mesulam, Swanson.

THE DIENCEPHALON IN FRONTAL SECTION (embryonic human, resembling mature brain of many small mammals):

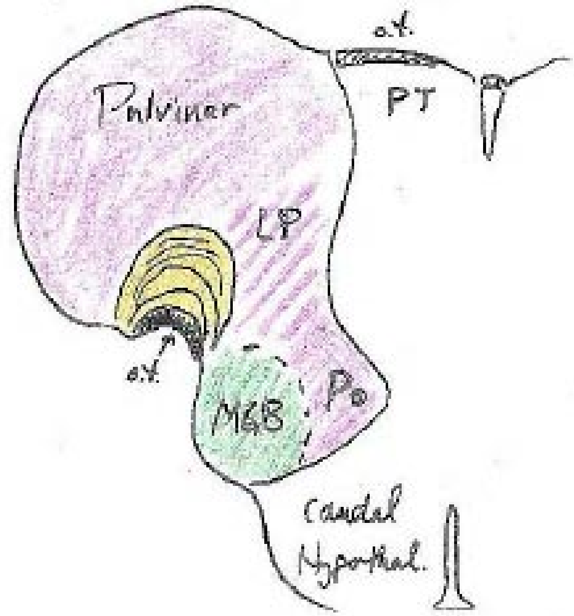
LP = lateral posterior nucleus
MD = mediodorsal nucleus (medial magnocellular, lateral parvocellular divisions)
V = ventral nucleus, at this level the VPL and VPM (ventral posterolateral and ventral posteromedial, representing body and limbs, and face and head, respectively)
LGBd = lateral geniculate body (nucleus), dorsal part. [The ventral part is just below, in the subthalamus.]
MGB = medial geniculate body

Thalamic Nucleus MD



More rostrally: LP becomes L and LD, MD is replaced by the Anterior nuclei (AD, AV, AM), VPL and VPM are replaced by VL and VA (ventral lateral and ventral anterior)

Caudally: Part of LP evolves into the Pulvinar, pushing LGBd out and down; also, the LP is replaced by MGB.



MD projects to the prefrontal neocortex.

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

Mental state and hypothalamus *(Brodal)*:

A person's mental state can influence the endocrine organs *via* the hypothalamus. The hypothalamus can also influence a person's mental state in major ways.

What are some effects of disturbance of the hypothalamus during neurosurgical procedures?

* What underlies "mental state"? This leads to a question discussed by Nauta (next slide).

Mental state and hypothalamus *(Brodal):*

A person's mental state can influence the endocrine organs *via* the hypothalamus. The hypothalamus can also influence a person's mental state in major ways.

What are some effects of disturbance of the hypothalamus during neurosurgical procedures?

Changes in autonomic activity; changes in mood; changes in emotional expression and reported feelings.

* What underlies “mental state”? This leads to another question discussed by Nauta (next slide).

Autonomic *vs* voluntary

What is misleading about the names "autonomic nervous system" and "voluntary (somatic) nervous system"?

Nauta & Feirtag *p 108-109 top.*

Autonomic *vs* voluntary *(Nauta & Feirtag)*

What is misleading about the names "autonomic nervous system" and "voluntary (somatic) nervous system"?

- The "voluntary" motor system, using corticospinal projections, is engaged in unconscious habits as well as conscious voluntary movements.
- The "autonomic" n.s. is subject to some* voluntary control, at least in some individuals with specific training.

* but very limited

Polysynaptic and direct pathways to and from hypothalamus *(Nauta & Feirtag)*

In Nauta's view, what is the relative importance of direct hypothalamus to spinal cord pathways *vs.* polysynaptic pathways? (A similar argument could be made for the spino-hypothalamic pathway.)

Nauta & Feirtag p 115 & fig. 52

Polysynaptic and direct pathways to and from hypothalamus

In Nauta's view, what is the relative importance of direct hypothalamus to spinal cord pathways *vs*. polysynaptic pathways? (A similar argument could be made for the spino-hypothalamic pathway.)

From the hypothalamus, the direct pathways are few and not large quantitatively compared with polysynaptic pathways.

Questions, chapter 26

8) Contrast the effects of sudden disconnection of the hypothalamus from more caudal structures, and more gradual disconnection accomplished in many small steps.

Sudden *vs* staged or slow lesions

Describe Rudolf Thauer's experiments on disconnection of the hypothalamus in rabbits. How do the results support Nauta's view of the importance of polysynaptic pathways controlling visceral activities?

Sudden *vs* staged or slow lesions

Describe Rudolf Thauer's experiments on disconnection of the hypothalamus in rabbits. How do the results support Nauta's view of the importance of polysynaptic pathways controlling visceral activities?

Discussed by Nauta and Feirtag and by Schneider.

Multistaged lesions result in good survival and fewer noticeable effects when compared with one-stage lesions. The midbrain now provides the highest control. However, there are clear reductions in adaptive autonomic responses.

REVIEW:

Contrast the pathways for hypothalamic control of the two divisions of the neurohypophysis (pituitary).

Nauta & Feirtag p. 117 figure; also Brodal fig. 19.6

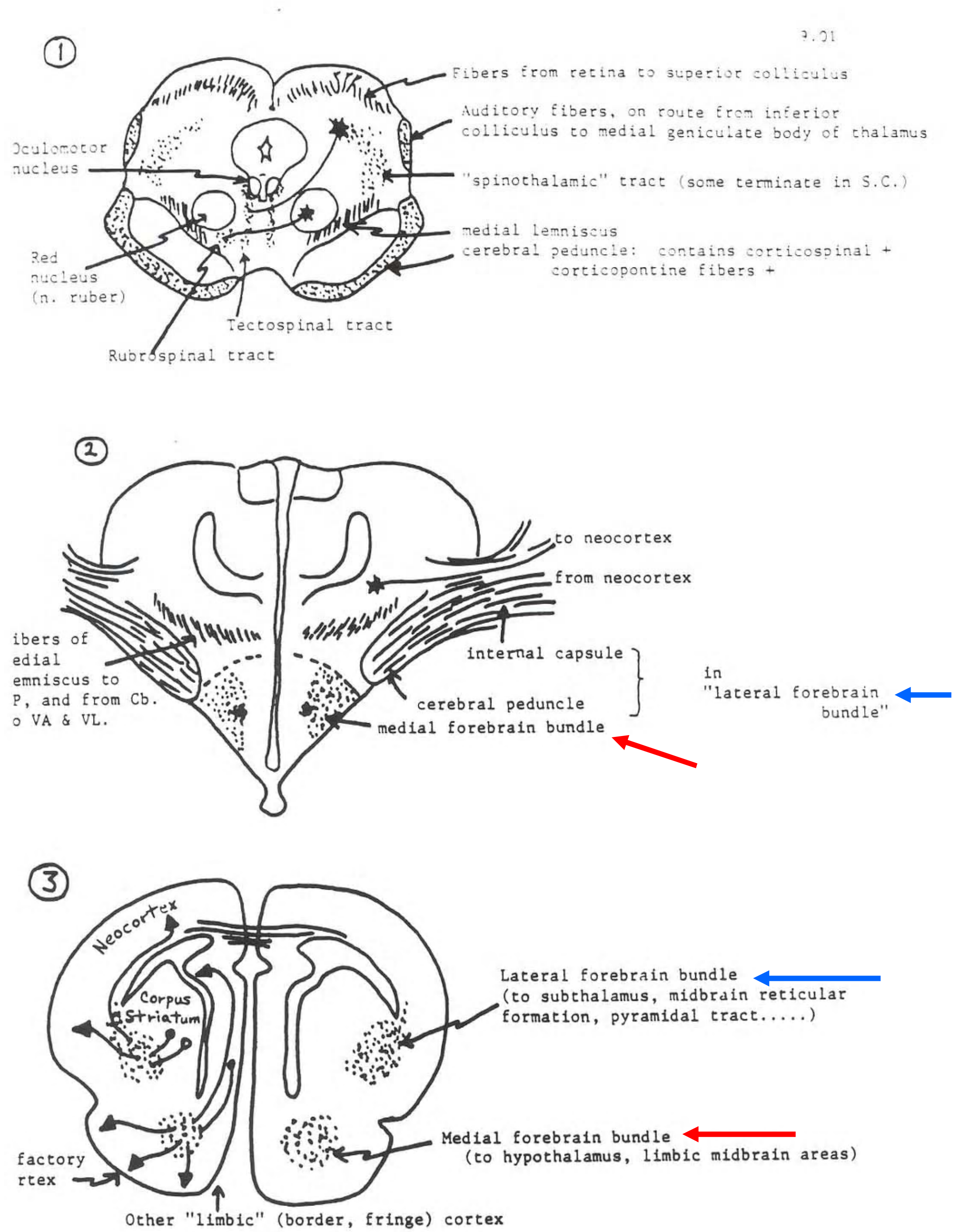
REVIEW:

Brodal 19.6

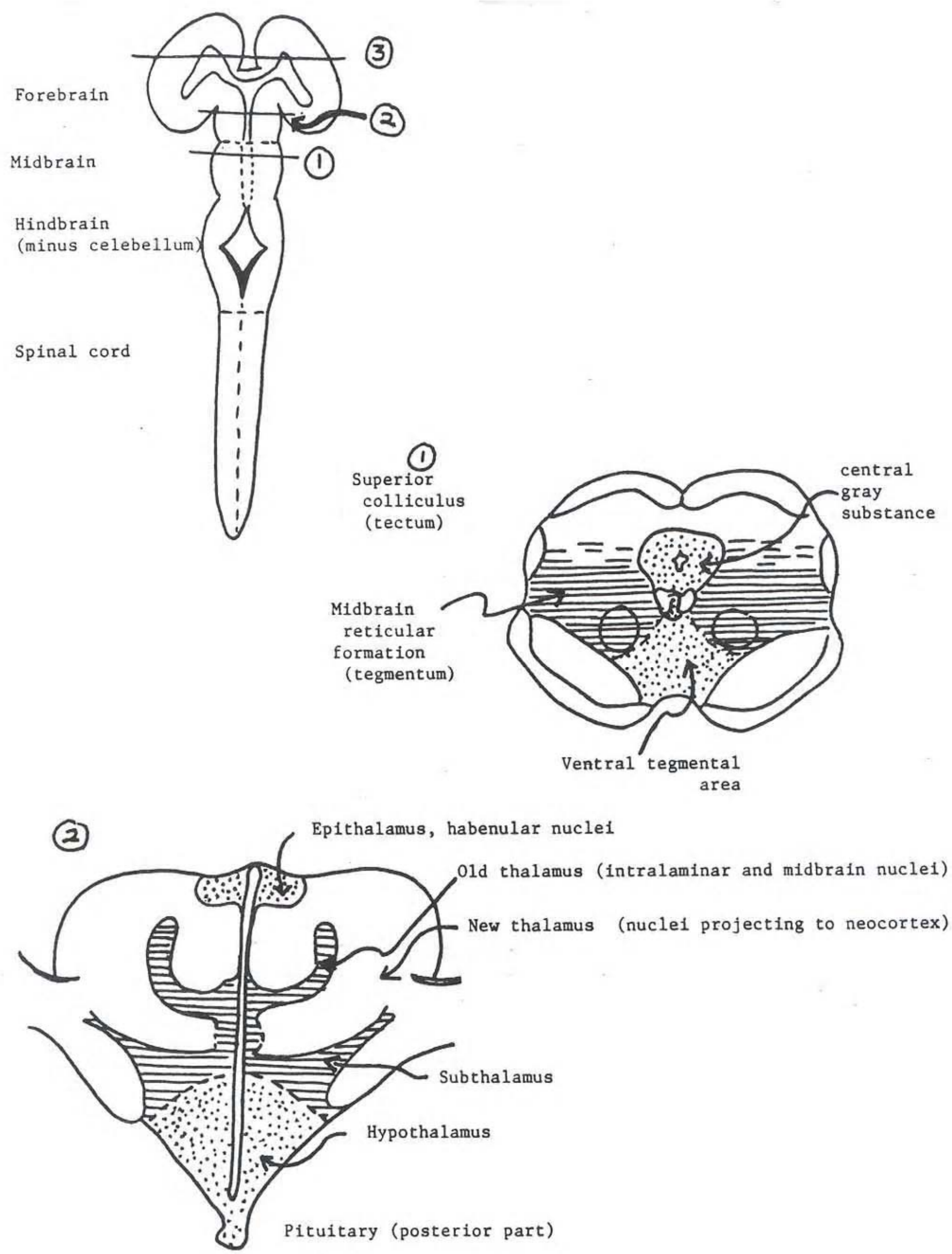
Figure removed due to copyright restrictions.
Please see figure 19.6 of: Brodal, Per. *The Central Nervous System, Structure and Function*. 3rd ed. Oxford University Press, 2003. ISBN: 9780195165609.

REVIEW:

Origins of the major pathways from the limbic and non-limbic portions of the mammalian endbrain



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



REVIEW:

Limbic midbrain areas (Nauta):

stippled

Relation to diencephalon

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

Functional regions within the midbrain's central gray area:

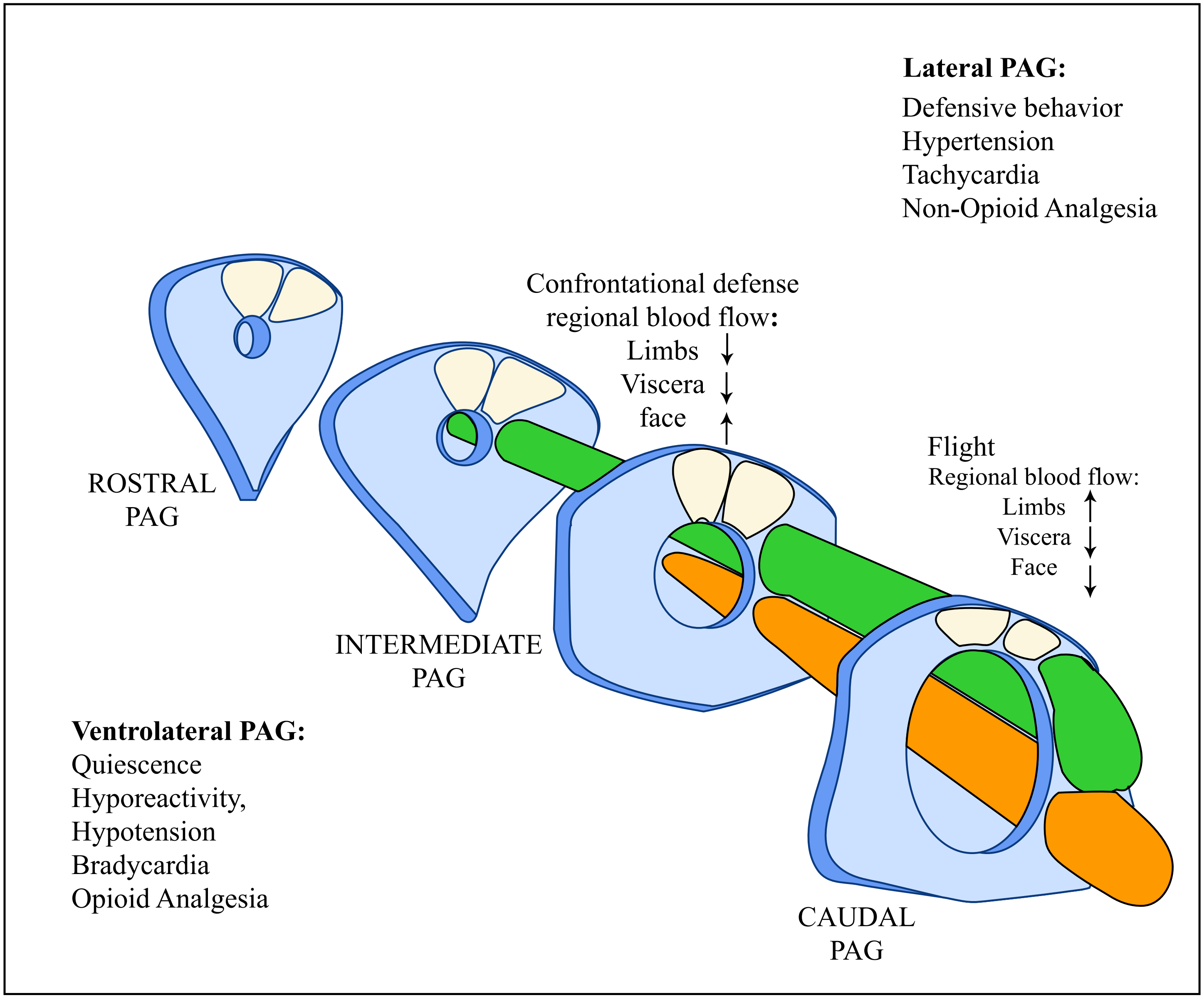


Image by MIT OpenCourseWare.

Also, a "sexual column"

These mechanisms help explain Rudolf Thauer's results.

We stand in the wake of this chattering and grow airy.
How can anyone say what happens, even if each of us
Dips a pen a hundred million times into ink?

- *from* The Steambath, *by Rumi (1207-1273),*
translated by Coleman Barks