End session 14

Questions on chapter 13

21) Describe what happens to regeneration of CNS axons in mammals early in development as the animal grows older. In brief, why does it happen?

Axon regeneration studies:
a very brief introduction

- **Adult mammals *vs*. fish and amphibians**
  - Little axon regrowth in mammals, and birds, much regrowth in fish and amphibians
- **Adult mammalian CNS *vs*. PNS**
  - Little axonal regrowth in CNS, much regrowth in PNS
- **Mammalian CNS regeneration capacity**
  - ➢ **Changes over the course of development**
    - Much regrowth very early; little regrowth at later stages
  - **Differs among different axonal groups**
    - …but most long-axon systems do not show much regeneration capacity

Questions on chapter 13

22) Describe a method that has shown some success for eliciting CNS axon regeneration.

Some CNS axons show some re-growth in implanted segments of peripheral nerve (PN), which can provide a permissive environment including growth factors.

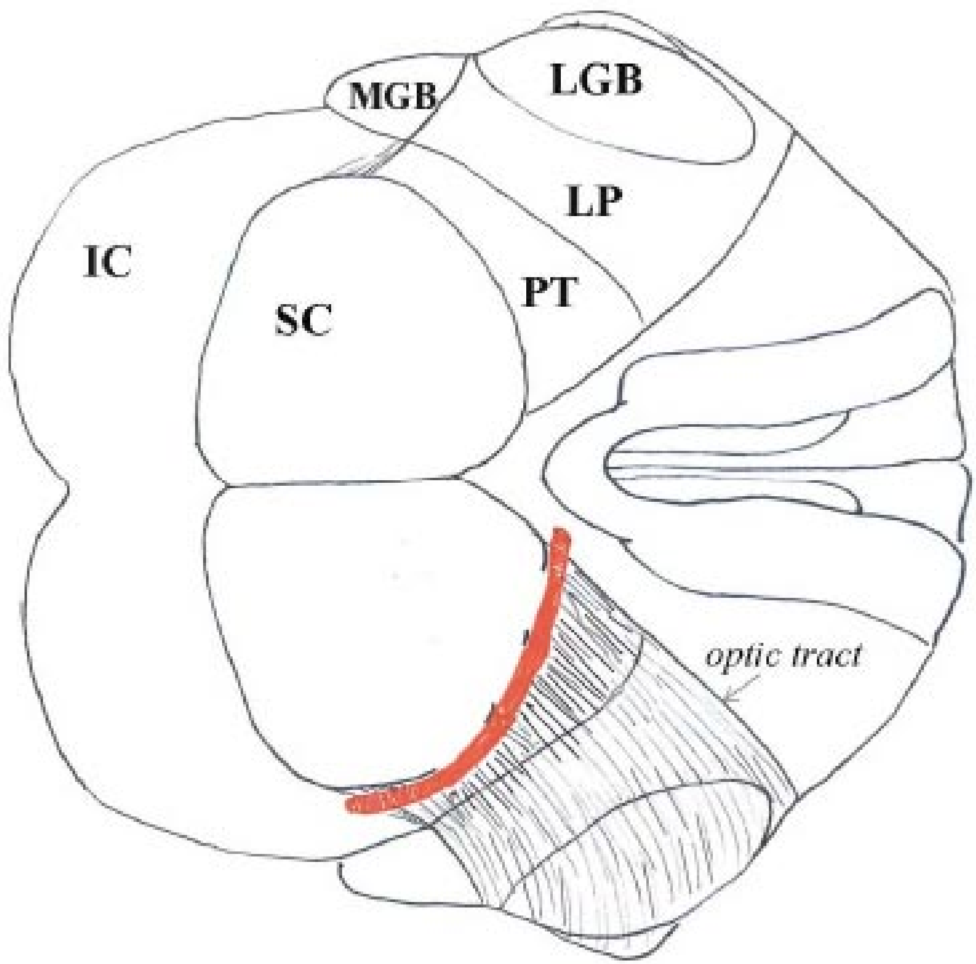
Other methods are the subject of various research projects.

Recent and current research:

- PN bridges. Alternatives: Schwann cells; olfactory ensheathing cells; stem cells.
- New materials used to promote healing and tissue bridge formation (work with bioengineers using nanotechnology)
- Chemical methods for inhibiting scar formation or for breaking it up
- Genetic transfections

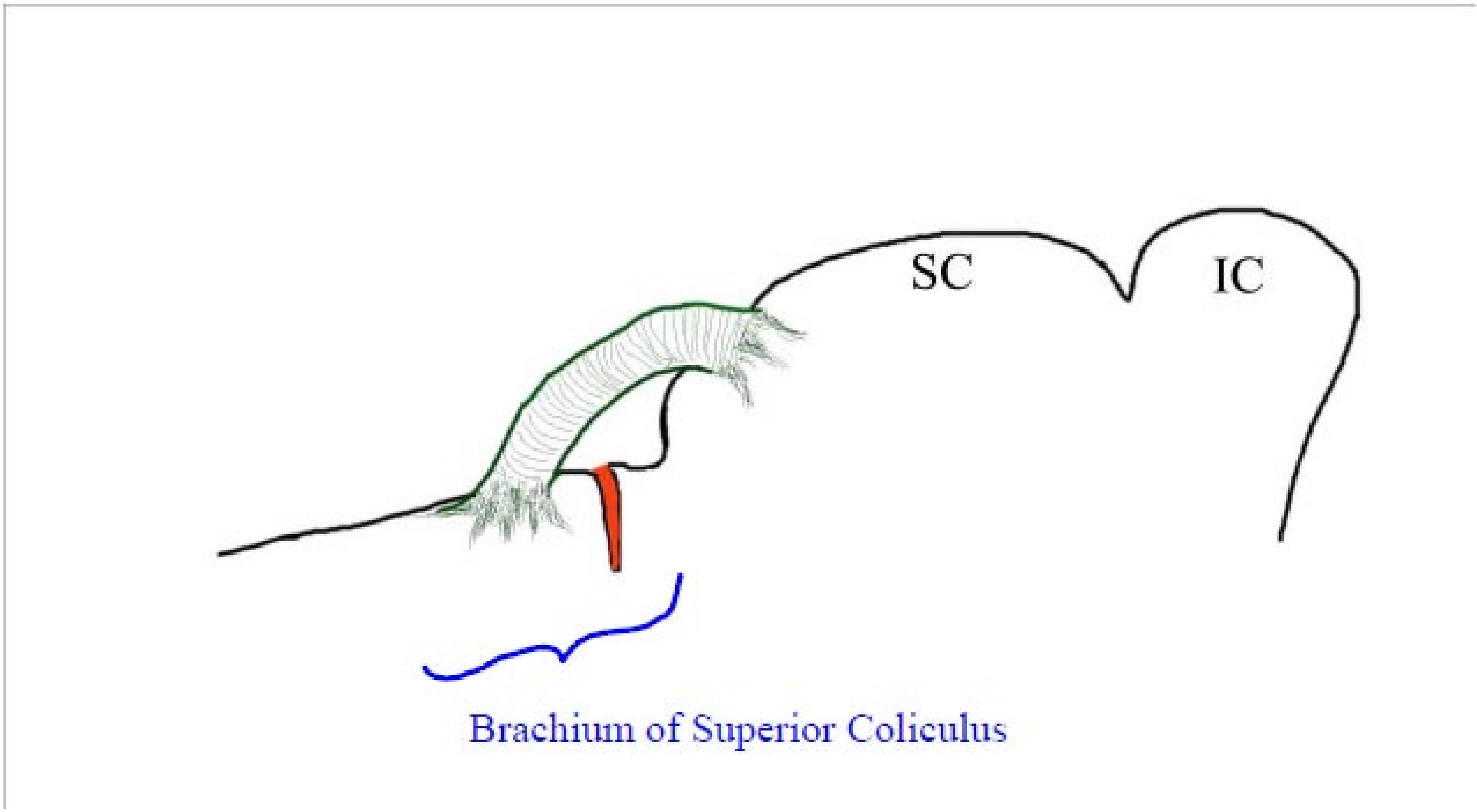
NEXT: a review of experiments in my laboratory

The lesion: Transection of the brachium of the superior colliculus

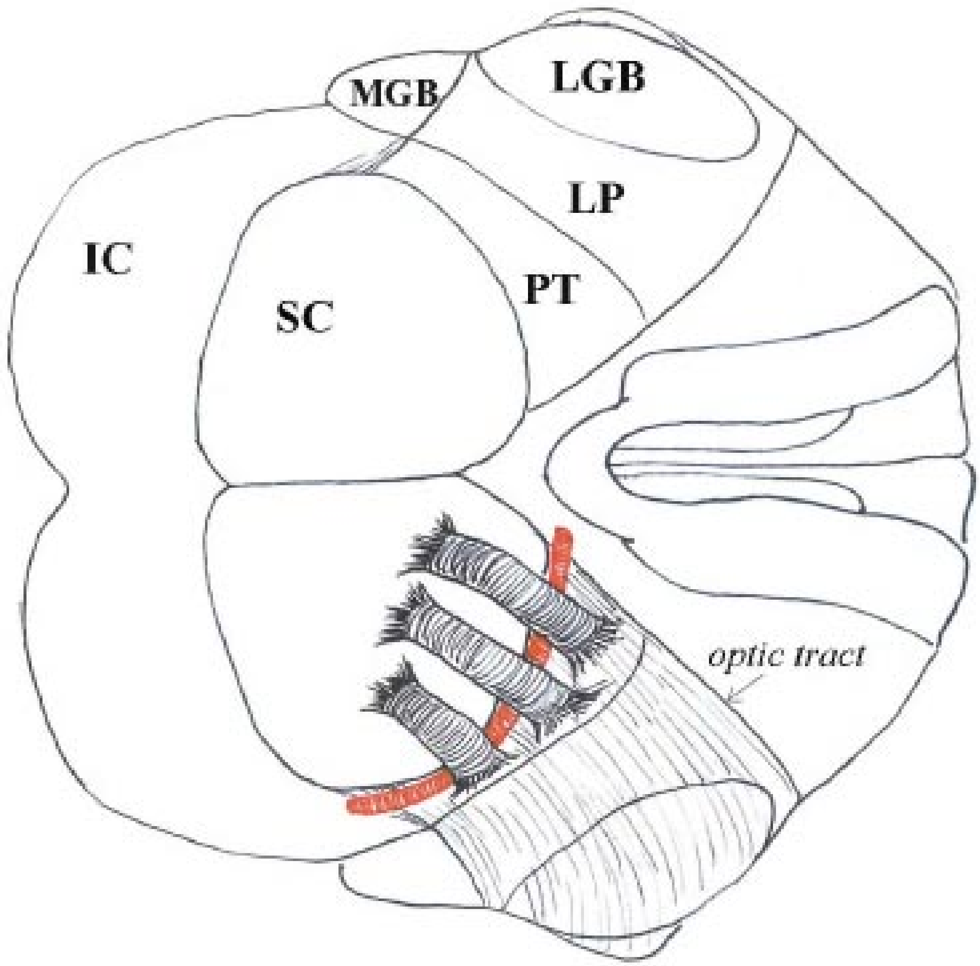


Regeneration through implanted segments of peripheral nerve (PN)

Brachium Bridge



Multiple brachium bridges



Brachium Bridge Video Clip

Hamster HBSC-99-5

Surgery at age 5 ½ months:

- **Transection of right BSC,**
- **Bridges over lesion by PN homografts.**

Behavioral testing at age 6 ½ months:

- **Orienting to stimuli in left visual field (*vs.* right)**

What happens when the PN bridge is connected to the SC on the wrong side of the brain?

Hamster MCO-02

Surgery at age 12 weeks:

- Transection of right optic nerve,
- Re-connection to right SC through PN homograft.
- Removal of left eye. – thus, complete blindness without regeneration

Functionally the wrong side.

Behavioral testing: age 22-25 months.

- Orienting to stimulus in right visual field → turning to left. wrong way!

Brachium Bridge Anatomy

Figure removed due to copyright restrictions.

Green fluorescence shows regenerated axons

Brachium Bridge Anatomy

5.5 months old

Figure removed due to copyright restrictions.

Another method:

Self-assembling peptides: SAP

injections into the lesion site

(Ellis-Behnke and Schneider at MIT)

Initial experiments:
Location of surgery and SAP injection

Figure removed due to copyright restrictions.

1 month post lesion:

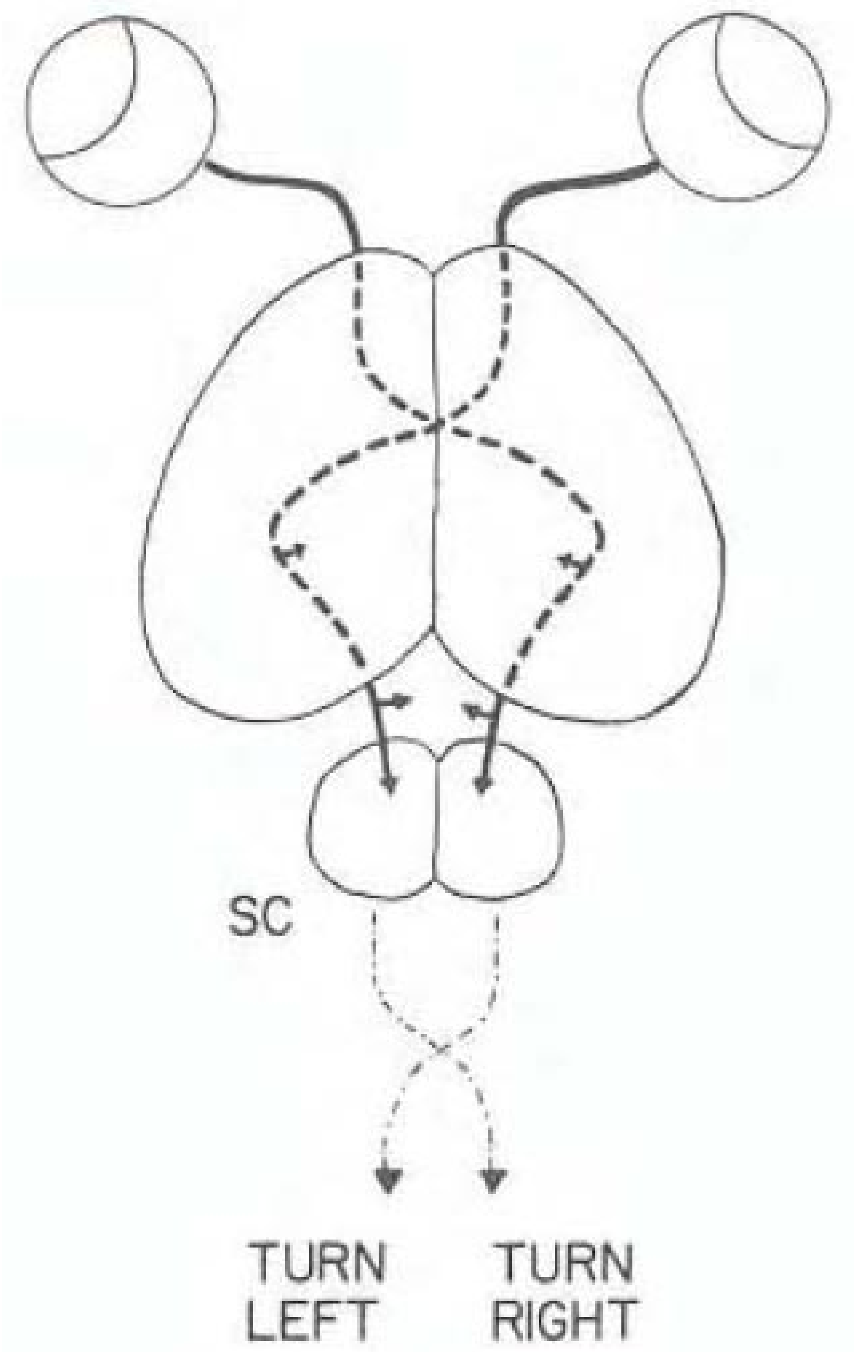
2 Controls 2 SAP alone

Figure removed due to copyright restrictions.

The model for studies of optic-tract regeneration and return of function:

Normal Animal

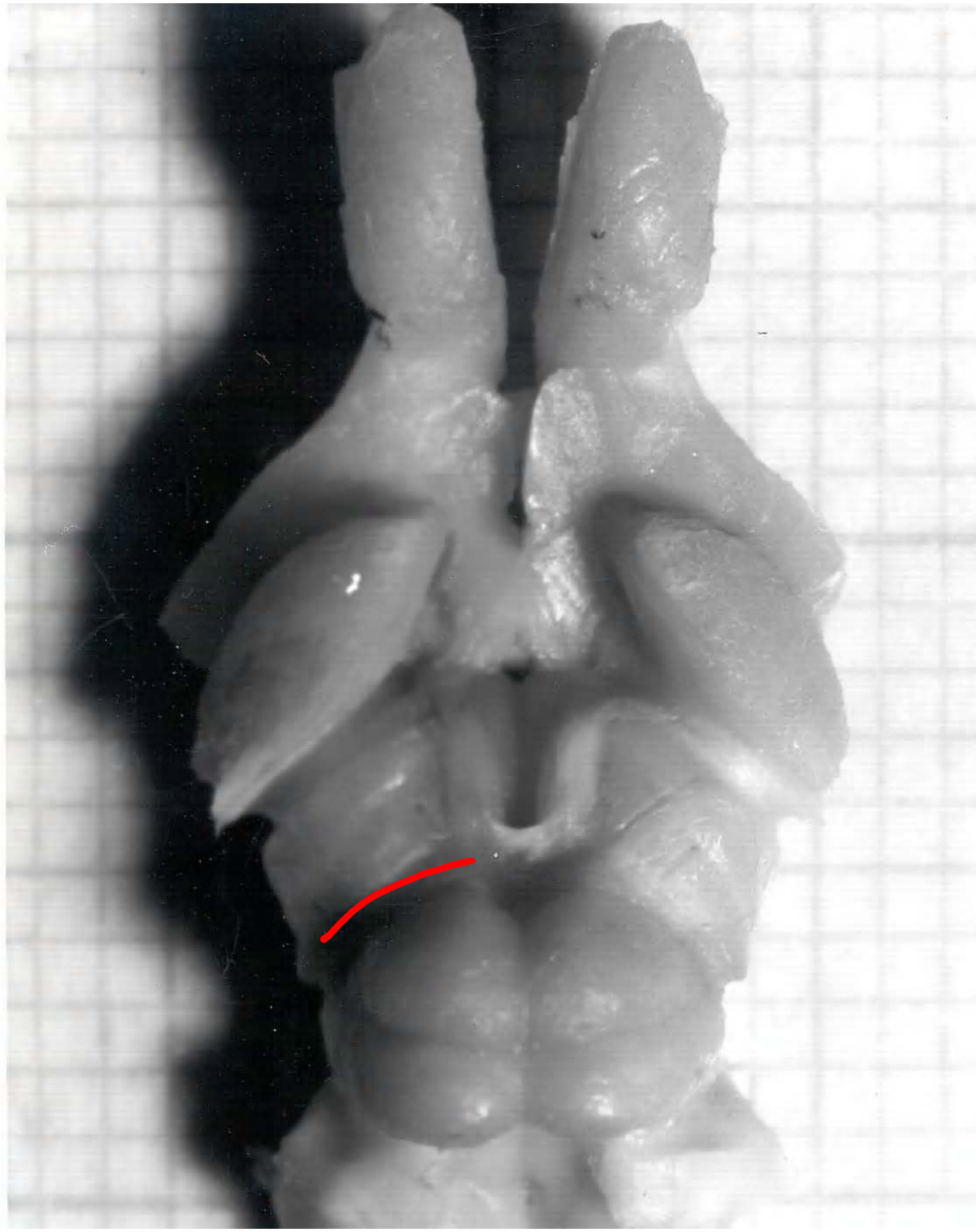
Retina to Contralateral SC



Hamster Brain with the cortex removed

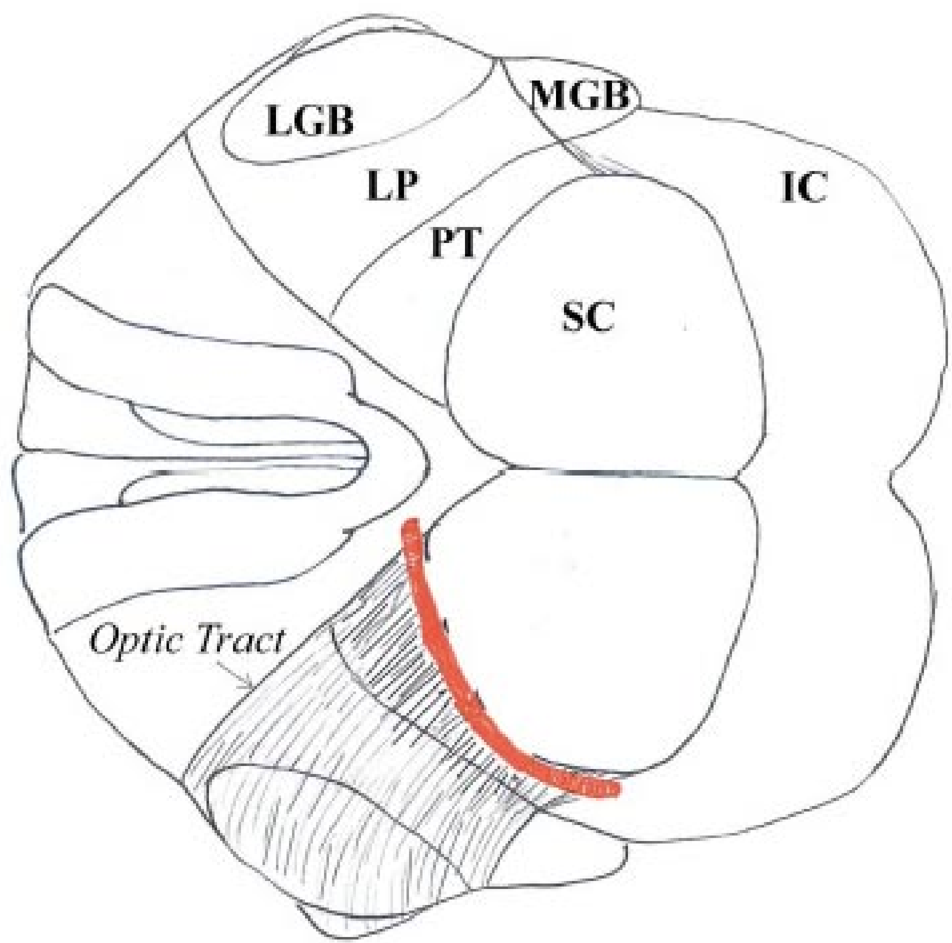
1 mm Grid

Site of Knife cut in red



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.

Brachium Transection



- Regenerated axons in the middle of the lesion site

Figure removed due to copyright restrictions.

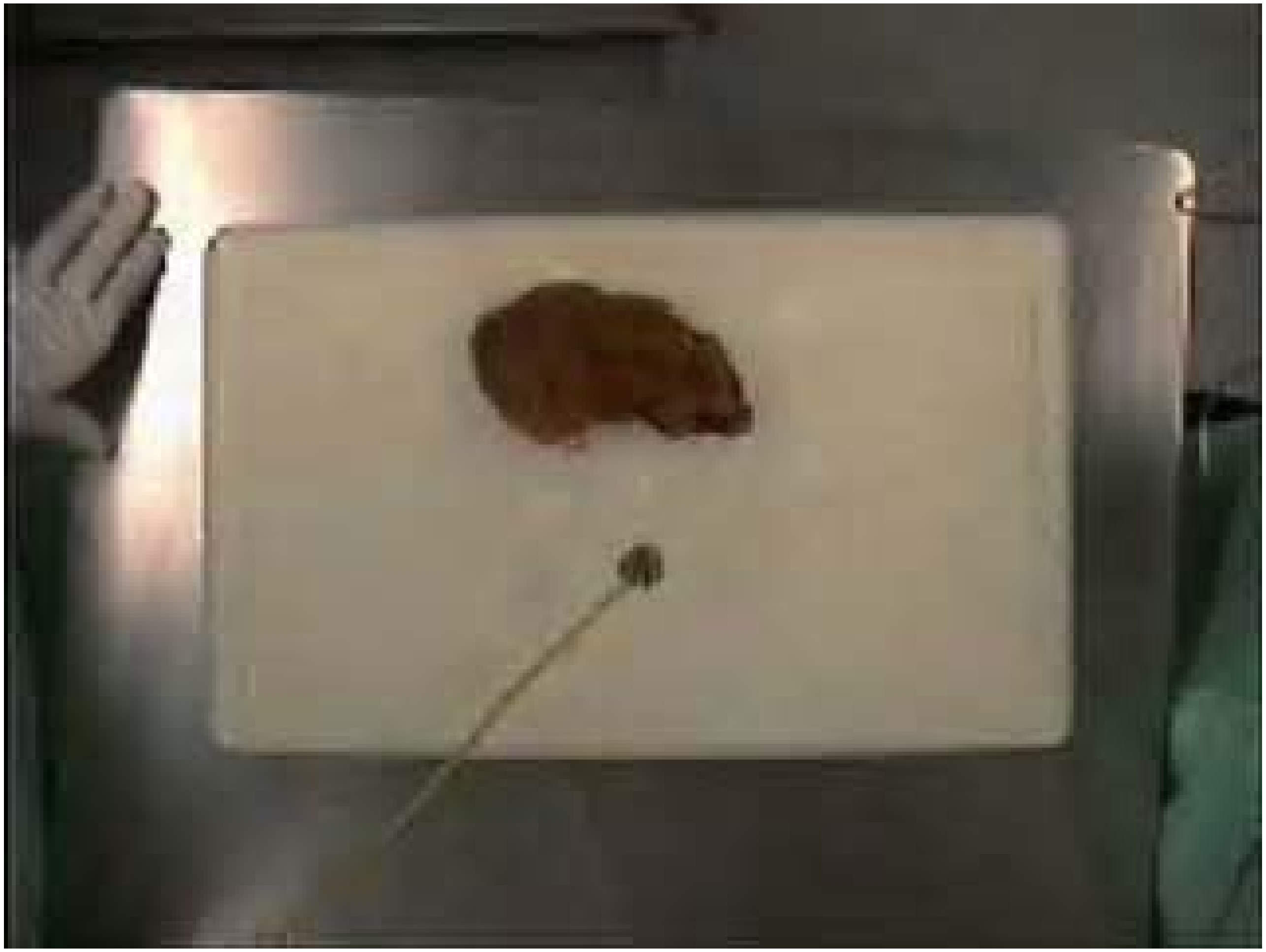
Re-innervation of the SC by axons from retina

Figure removed due to copyright restrictions.

Control, blind in right eye

Animal fails to turn toward stimulus on its right, but turns toward stimulus on its left.

SAP Brachium Bridge, Functional return of vision



Hamster turns towards stimulus on its right after axon regeneration has occurred

Axon regeneration studies in adult mammals:
The problem requires a multi-factor approach

- Need to **Preserve** the damaged cells. (Dying cells don't re-grow axons.) [See also next slide]
- The mature tissue environment contains many inhibitory factors that may be overcome by the right procedures to **permit** axon growth.
- **Promotion** of growth vigor may be needed after the early period of development.
- **Plasticity** of the regenerated connections can play an important role in functional recovery.

These are the <u>4 P's of regeneration</u>, from Ph.D. thesis by Rutledge Ellis-Behnke at MIT.

Important note relevant to regeneration studies:

What happens to an axon after transection?

1) Anterograde degeneration of the axon cut off from its cell body

Thus, regrowth can only occur on the side connected to the cell body.

2) Retrograde degeneration

-- First, changes in the cell body which often but not always eventually lead to death

-- Eventual degeneration of the axon still connected with the cell body, if the cell body fails to survive.

-- Failure to survive caused by lack of trophic factor, taken up by the axonal endings

A sketch of the central nervous system and its origins

G. E. Schneider 2014

Part 6: A brief look at motor systems

MIT 9.14 Class 15

Overview of motor system structure

Functional systems in neuroanatomy

- We have looked at all levels of the central nervous system. Now we begin studies of specific functional systems. First, the motor control systems:
- We do not start with the motor cortex, which came relatively late in vertebrate evolution.
- We first consider the evolution of motor control:
    1) What are the major functional demands? These preceded the vertebrates.
    2) What structures for motor control are present in all vertebrates?
    3) What were the mammalian brain elaborations?
- Organization will be studied by beginning with motor neurons.

REVIEW

Questions, textbook chapter 14

1) The overview of the motor system begins with a description of general purpose movements that are used for many different purposes. Name the three types of movements described.

2) Before a neocortex evolved, the midbrain had evolved structures for controlling the three types of general-purpose movements. Name the structure where the output pathway for each of these movements originates.

REVIEW

Three general-purpose movements:

a functional starting point for studying structures of the motor system

1) **Locomotion: Approach or Avoidance**
   - Escape from predators
   - Foraging or exploring: seeking a goal object
     - This is basic for all drives.
2) **Orienting** of head and body: important for accomplishing the goals of the above
3) **Grasping**: important for consummatory actions
   - With mouth
   - With limbs (reaching and the control of distal muscles)

These movements are used in many different action patterns.

REVIEW:

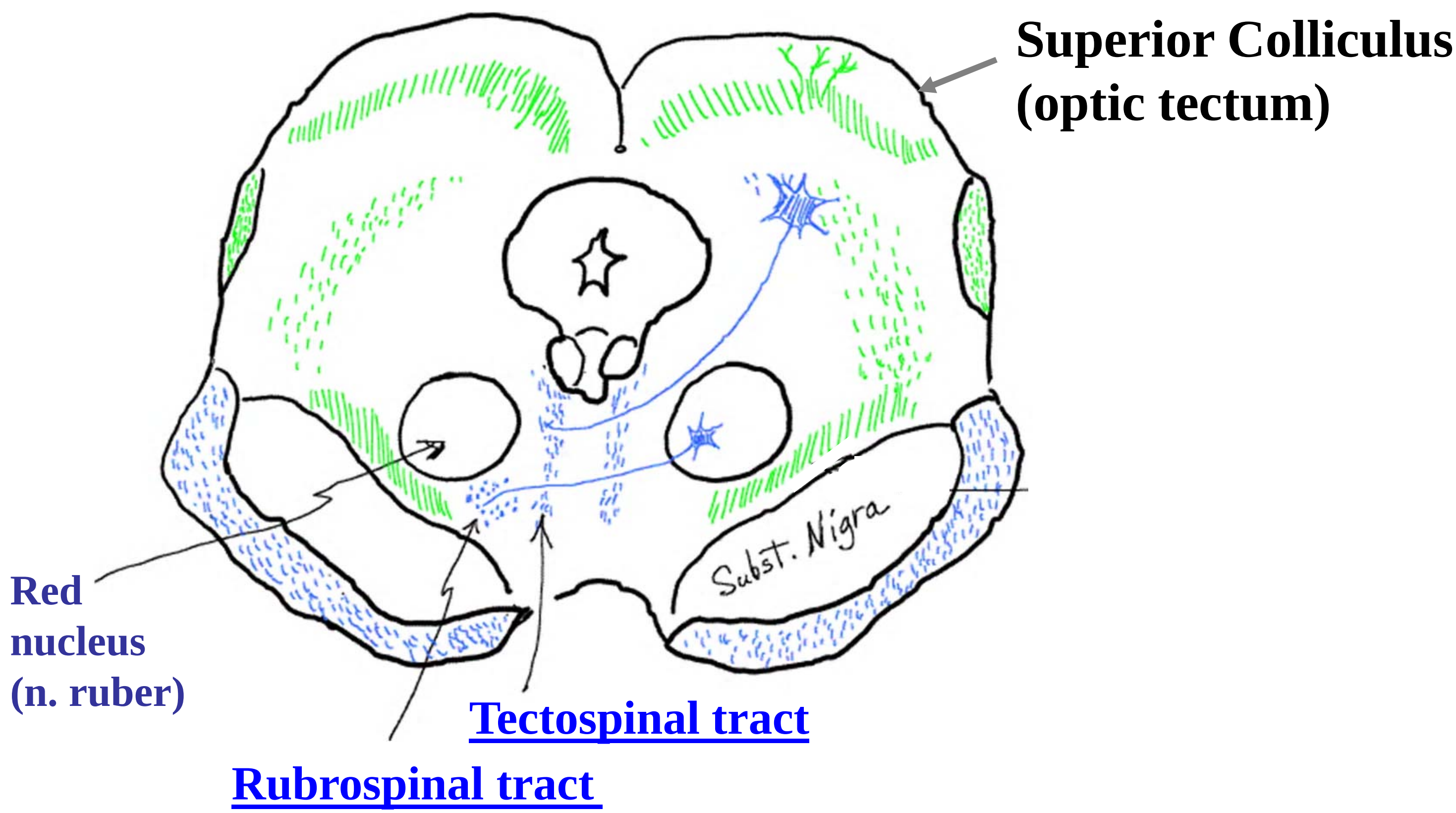
Outputs of midbrain for control of these three types of movement, critical for survival

1) Descending pathways from the MLA (midbrain locomotor area), for
   - Moving towards or away from something
   - Foraging or exploratory locomotion
2) Tectospinal tract, from deep tectal layers, for
   - Orienting by turning of head and eyes
3) Rubrospinal tract, from red nucleus, for
   - Limb movements for exploring, reaching and grasping.

3a) For oral grasping, there are connections from tectum to the motor nucleus of the trigeminal nerve in addition to somatosensory connections for jaw opening and closing.

REVIEW:

Midbrain neurons projecting to spinal cord and hindbrain for motor control



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.

The midbrain was the connecting link between the primitive forebrain and motor systems

- **It controlled the three types of body movement**, prior to the refinements made possible by neocortex.
  - *Via* its projections to the hindbrain & spinal cord
- **It also controlled the visceral nervous system and associated motivational states** (*via* limbic midbrain areas)
  - With inputs from both below & above
  - Outputs to ANS and to somatic motor pattern networks
  - Modulatory projections to forebrain and other structures
  - Control of motivational states—an important component of Fixed Action Patterns (inherited instincts)
    - Higher control of the repertoire of fixed motor patterns organized by hindbrain & spinal cord
    - Examples: predatory attack, defensive aggression, courtship movements

The three major types of body movement,
existing prior to refinements made possible by neocortex
-- further discussion --

1) Locomotion

- Approach and Avoidance
- Foraging/exploring/seeking: basic for all drives

1) Orienting of head and body: important for accomplishing the goals of the above
2) Grasping: with mouth; with limbs (reaching and the control of distal muscles); important for consummation

REVIEW:

Approach & Avoidance: Evolution of head receptors in forward locomoting, bilaterally symmetric chordates

- The elicitation of approach and escape/ avoidance movements are basic functions of both surface and distance receptors.
- Head receptors evolved with these functions playing crucial roles.
  - This has shaped the chordate neural tube.

What are the sensory systems involved?

Question 6: What two sensory modalities most strongly shaped the evolution of the forebrain?

Head receptors and approach/avoidance

Inputs via forebrain cranial nerves

- **Olfaction**: Odors of objects or places that incite fear or entice approach required links to locomotor control
  – *Via* striatum to hypothalamus and more directly to midbrain (for locomotor control and for modulation of orienting mechanisms)
  – *Via* medial pallium (which evolved into hippocampal formation), which projected to ventral striatum as well as to hypothalamus & "limbic" parts of the midbrain

- **Vision**: The other modality that strongly shaped the early evolution of forebrain
  – Several links to locomotor controls (*via* subthalamus, pretectum, midbrain tectum)
  – Evolution of plastic links *via* pathways to the striatum and medial pallium, as for olfaction

Head receptors and approach/avoidance,
inputs from below the midbrain

- **Gustatory** inputs, *via* pathways from hindbrain, played an important role in learning which sights and smells to approach and which to avoid.
- **Somatosensory** inputs from head
  - Entering through the hindbrain, they no doubt played a critical role very early in brain evolution.
- **Auditory inputs**: likewise

Questions, textbook chapter 14

3) Locomotion is often initiated because of activity generated in what diencephalic structure?

Hypothalamus -- next slide

8) Where are the innate circuits underlying the locomotor patterns we call “gaits”? Discuss the pathways whereby a locomotor gait is initiated.

Primarily in the spinal cord's pattern generator circuits involving networks with interconnections via propriospinal fibers. Also involves hindbrain circuits.

Initiation from limbic structures of forebrain, via midbrain locomotor area

Locomotion is initiated not only by inputs from outside: Foraging activity can be initiated from hypothalamus

- Foraging drives can initiate and modulate locomotion.
  - Hypothalamic cell groups control cyclic behaviors, e.g., feeding, a preparation for which is the initiation of locomotion for foraging.
- Drive mechanisms have an endogenous buildup of the level of neuronal activity.
  - Such activity represents a motivational state, and corresponds to the "action specific potential" of ethologist Konrad Lorenz)
  - When it rises to a threshold, it initiates movement.
- **Next: Larry Swanson's conceptualization of the motor-system hierarchy, and how it works for locomotion.**

The Motor System Hierarchy

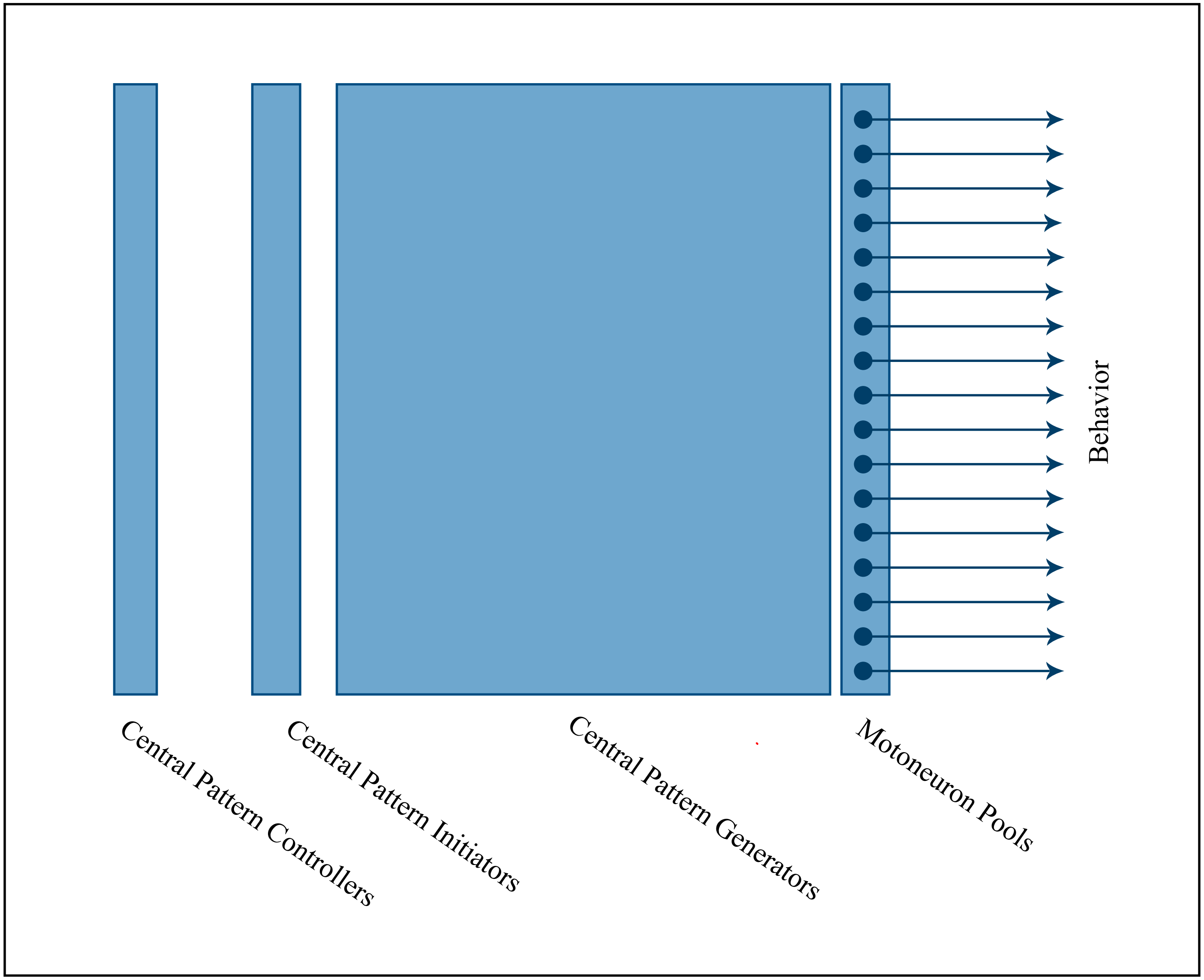


Image by MIT OpenCourseWare.

Hierarchic control of locomotor behavior

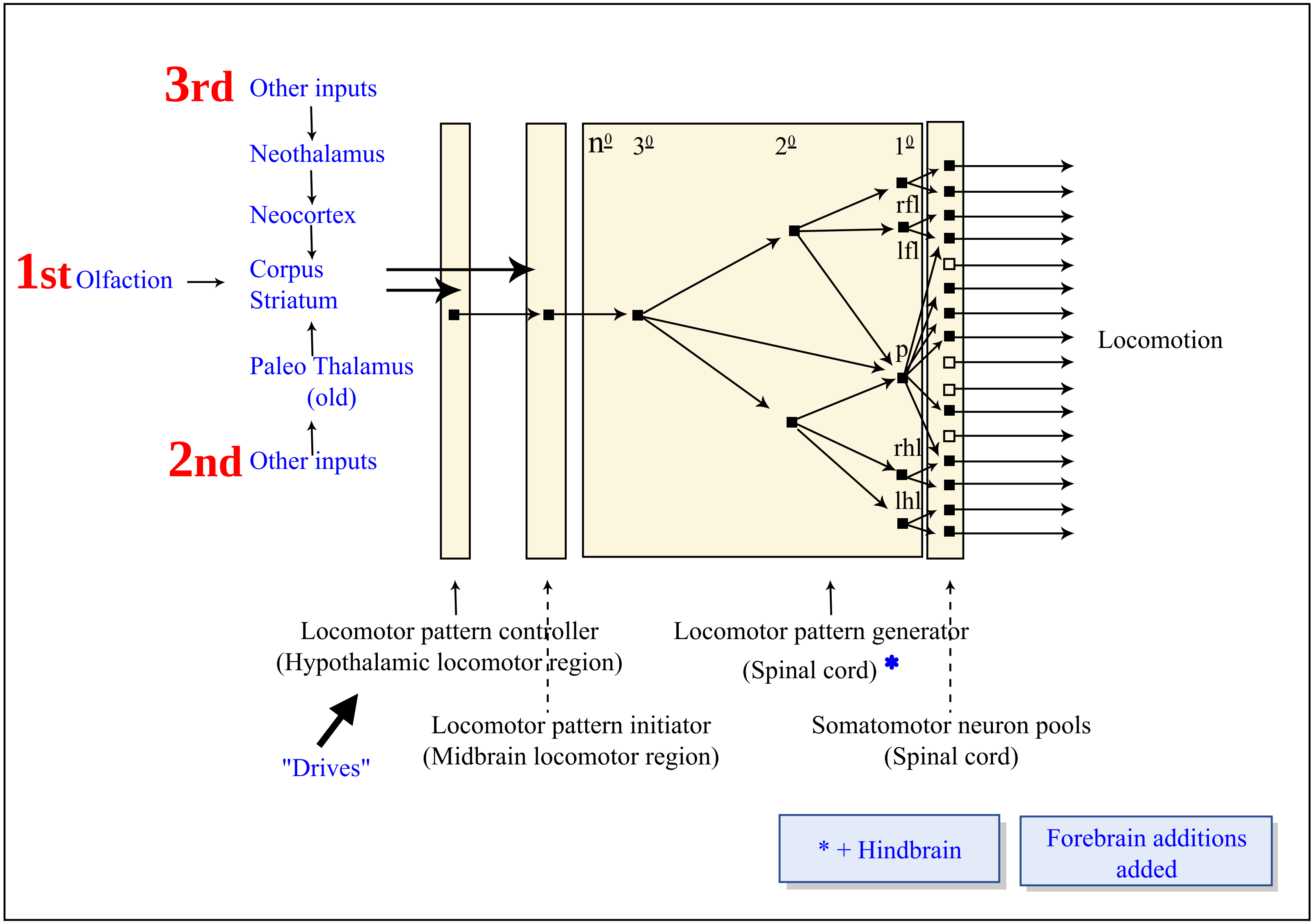


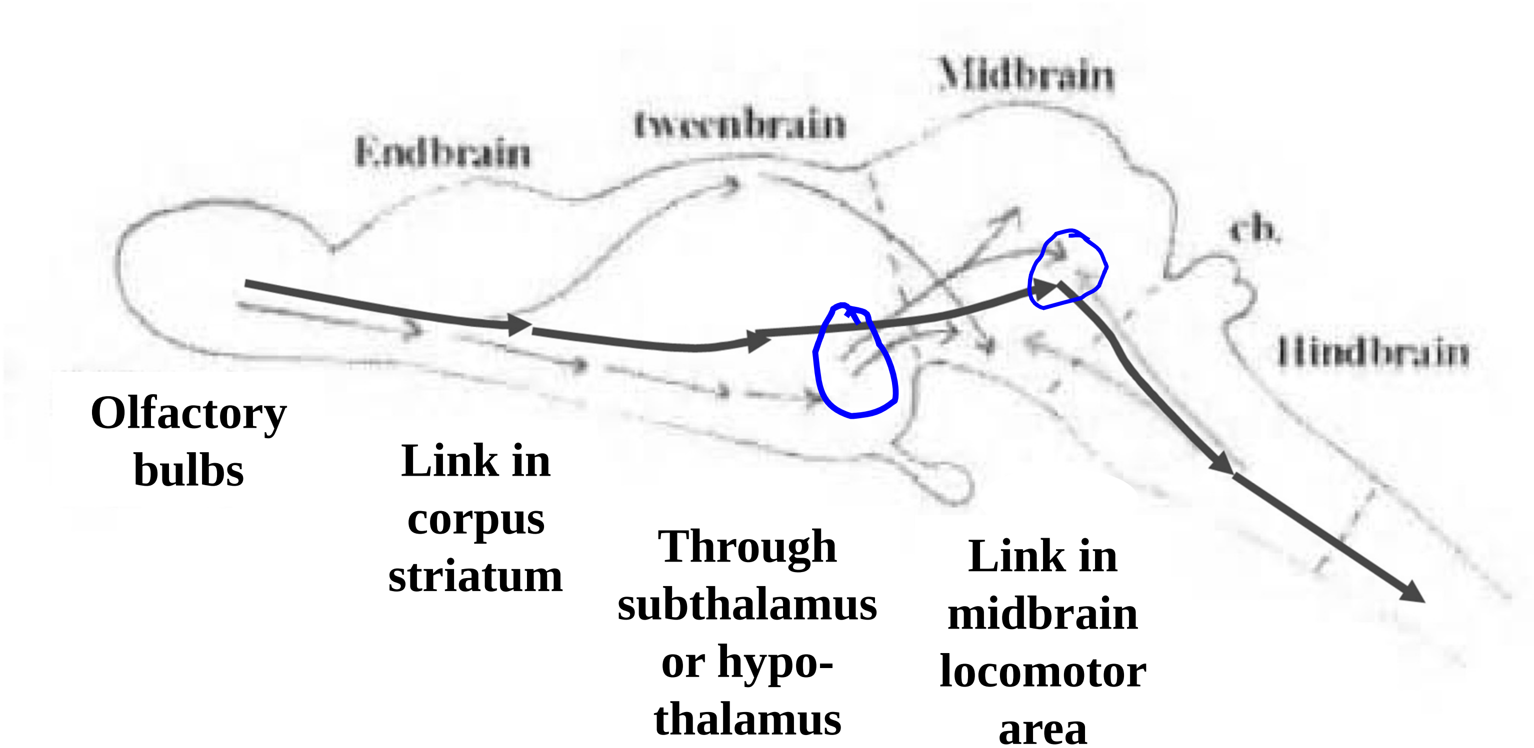
Image by MIT OpenCourseWare.

Modified from Swanson (2003): Forebrain contributions added.

Brain locations of locomotion pattern controllers and initiators

- Caudal Hypothalamic-subthalamic locomotor area (controller) (HLA)
  - Inputs from ventral striatum, which receives olfactory inputs
  - Some inputs from olfactory system bypass the striatum
- Midbrain locomotor area (MLA), which is an initiator/ controller of the more caudal locomotor pattern generators
  - Location: Caudal tectum level, below inferior colliculus in the reticular formation
  - Inputs from more rostral locomotion controllers (subthal/hypothal) and from striatum directly
    - Inputs from brainstem as well

Postulated pathway for control of approach and avoidance actions by olfaction in early chordates

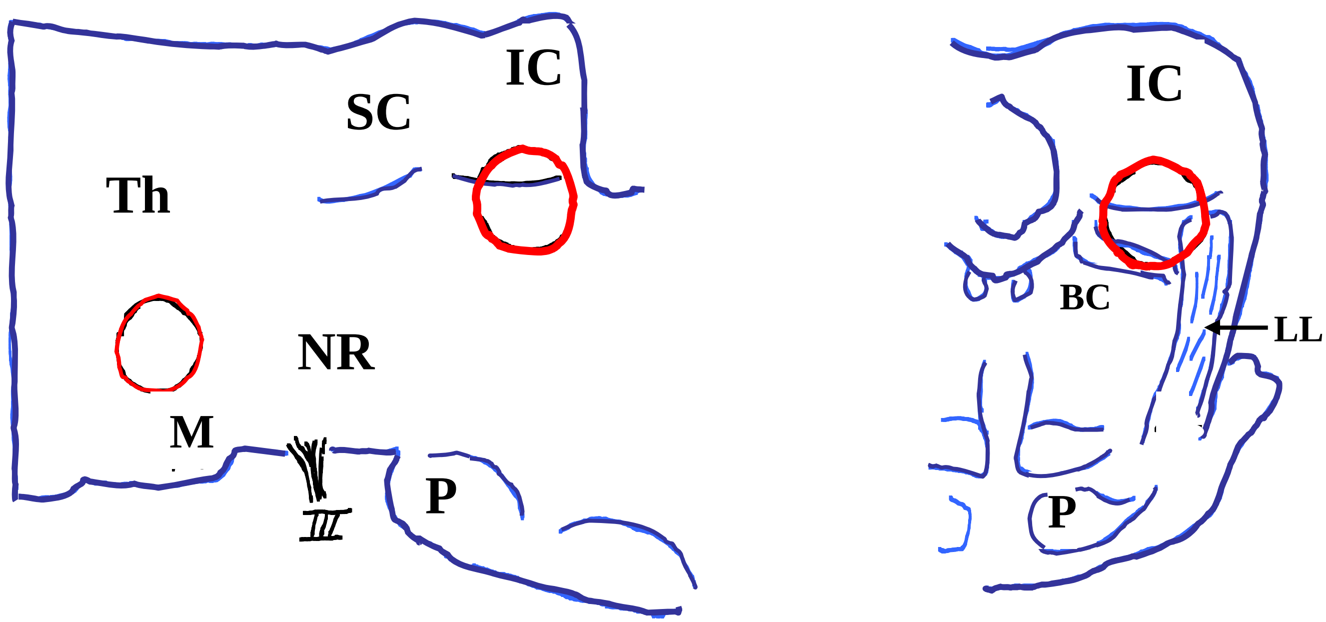


Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN: 9780262026734.

Question 7: Discuss the type of connections that the early forebrain must have used to influence the general-purpose movements referred to in questions one and two.

Illustrated are the most primitive of such connections.

Midbrain Locomotor Region or Area (MLA): Localization in cat by electrical stimulation studies



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 14-1 Based on figure by GN Orlovskii (1970), *Biofizika*, *15*: 171-177.

Questions, textbook chapter 14

9) Maintaining balance of the body during standing or locomotion depends on reticulospinal pathways from the hindbrain, and on two other descending pathways. What are they?

Descending pathways to spinal cord from vestibular nuclei and from cerebellum (from the medially located nucleus fastigious)

Locomotor pattern generation: adjustments in hindbrain & cord

- Locomotion depends on the spinal cord's propriospinal system (location of pattern generators, illustrated earlier)
- Its execution is strongly influenced by activity in hindbrain structures (to be reviewed next).
  - **Vestibular** nuclei
  - **Cerebellum**, part of which is closely connected to the vestibular nuclei
- Its execution is modulated by reflex inputs coming into **cord** through the dorsal roots, especially from the feet.

Vestibular Nuclei and Vestibular Nerve – part of the 8th cranial nerve

- Location in the alar plate of hindbrain
- The large cells of the lateral vestibular nucleus (Deiter's Nucleus) have direct projections to the spinal cord *via* descending axons of the vestibulospinal tract
- The Medial Longitudinal Fasciculus (*mlf*) of the brainstem interconnects the vestibular nuclei and the oculomotor nuclei – for stabilization of eye position during head movements.

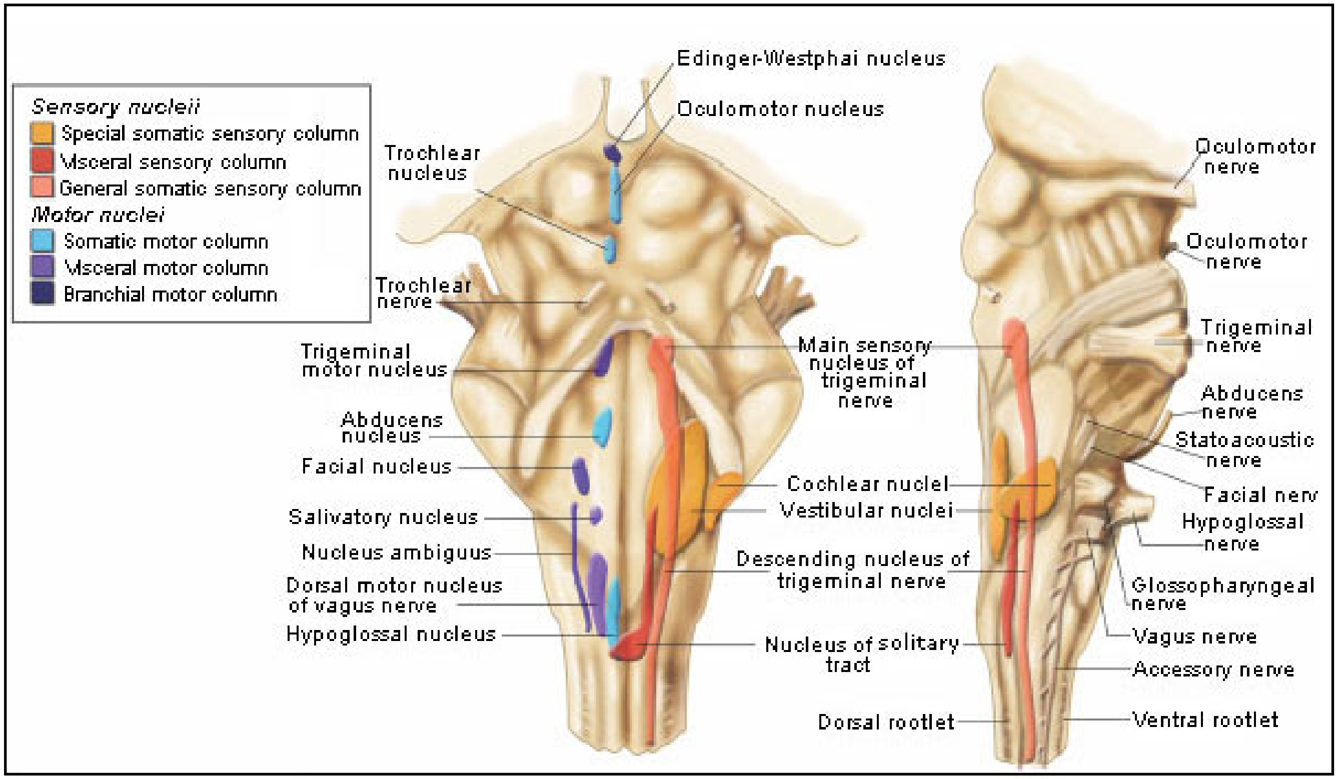


Image by MIT OpenCourseWare.

Brainstem Nuclei: secondary sensory and columns

Vestibular Nuclei: medial, lateral, superior, descending

The Vestibulo-cerebellum: *probably the most ancient part*

- ILLUSTRATIONS
  - The **flocculus** and **nodulus**, with direct input from vestibular nerve
  - **Fastigial nucleus**, the medial-most of the three deep nuclei of the cerebellum, with direct projections to the spinal cord (**fastigiospinal tract**)

Main cerebellar subdivisions

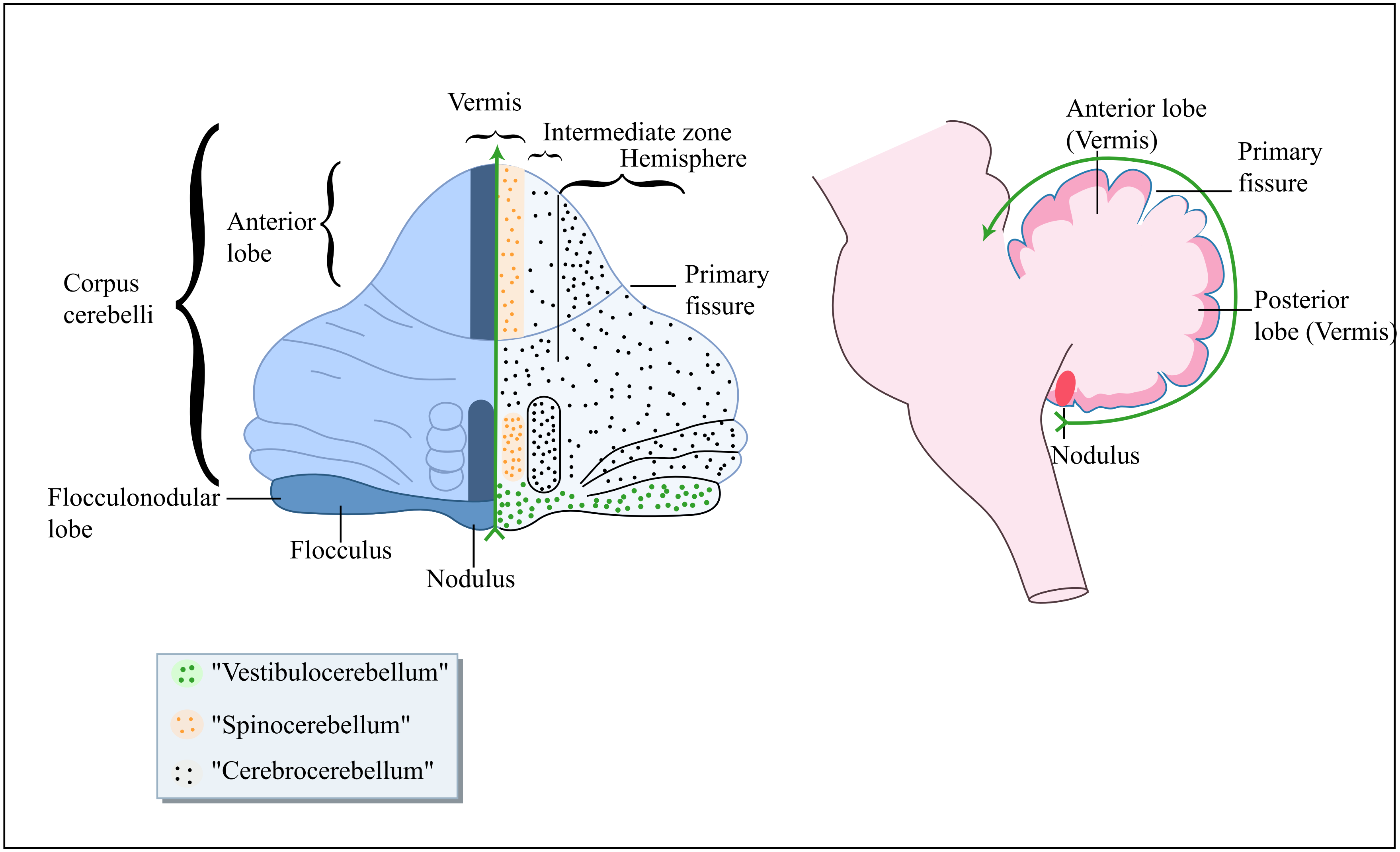


Image by MIT OpenCourseWare.

Questions, textbook chapter 14

10) What primary sensory neurons project directly to the cerebellar cortex?

Vestibular nerve to cerebellum:

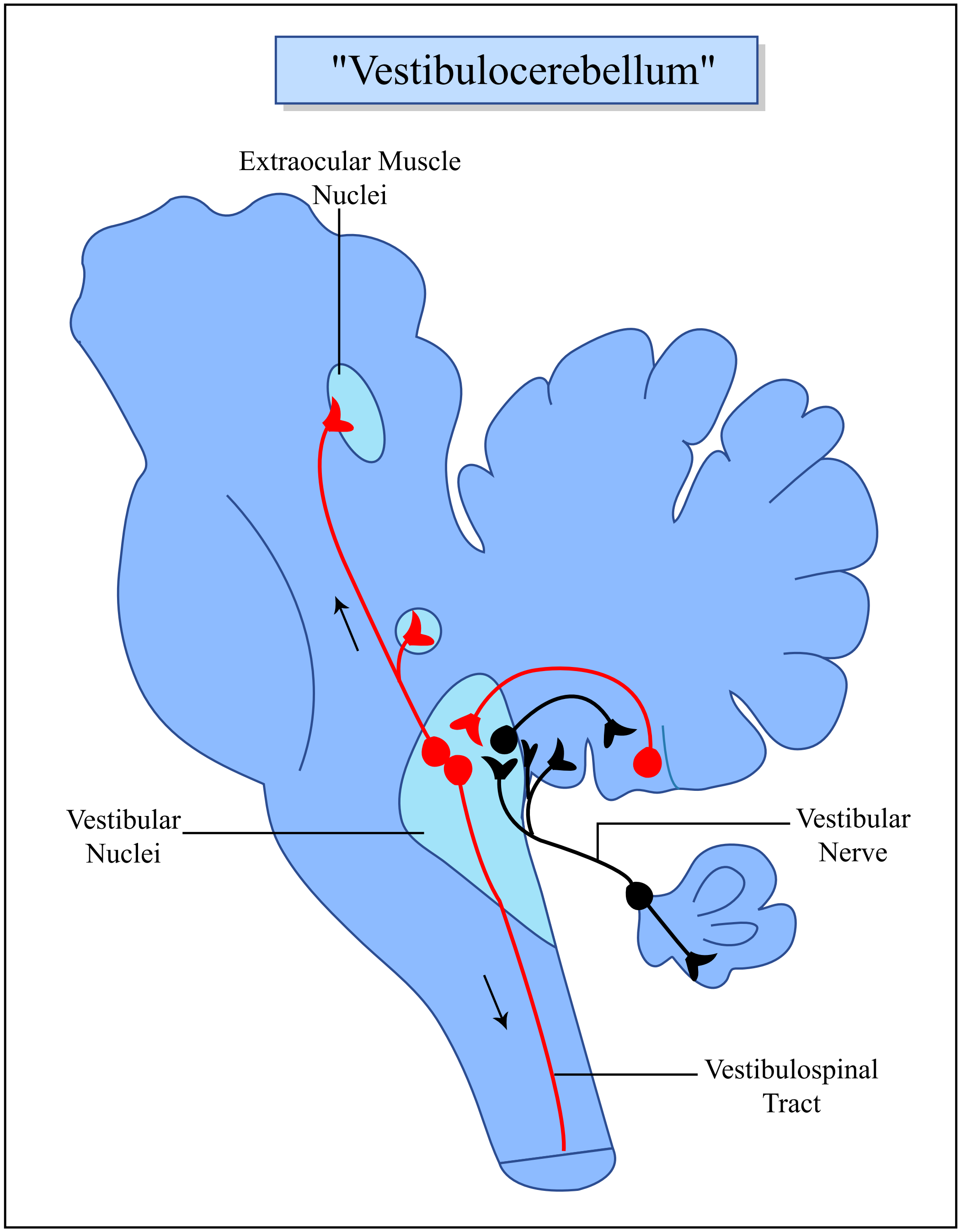


Image by MIT OpenCourseWare.

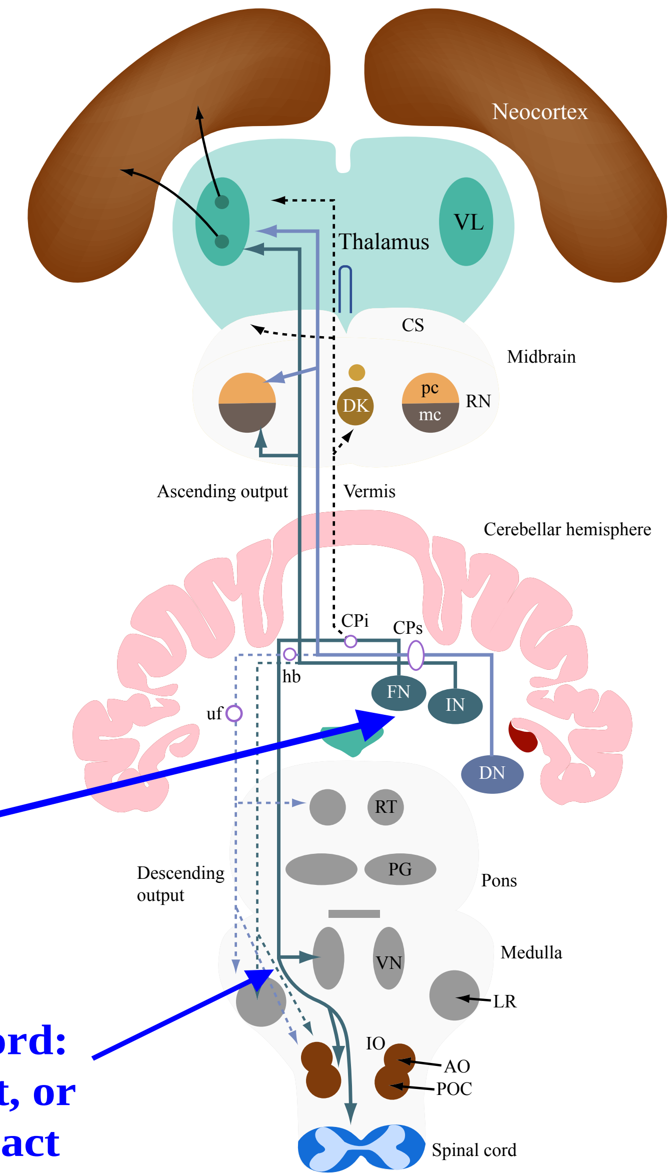
Note:

1) **Primary sensory neurons project to cerebellar cortex**
2) **Cb cortex projects to vestibular nuclei, bypassing deep Cb nuclei** (unlike other parts of the Cb cortex)
3) **Vestibular nucleus projects to spinal cord and to motor neurons controlling eye muscles**

Greater detail from Altman & Bayer

One of the major controllers of axial muscles (influencing body posture and balance)

Abbreviations	
AO	Anterior olivary complex
CPi	Cerebellar peduncle, inferior
CPs	Cerebellar peduncle, superior
CS	Superior colliculus
DK	Nucleus of darkschewitsch
DN	Dentate nucleus
FN	Fastigial nucleus
hb	Hook bundle
IN	Interpositus nucleus
IO	Inferior olive
LR	Lateral reticular nucleus
mc	Magnocellular
pc	Parvicellular
PG	Pontine gray nucleus
POC	Posterior olivary complex
RN	Red nucleus
RT	Pontine reticuloteg-mental nucleus
uf	Uncinate fasciculus
VL	Ventrolateral (motor) thalamus
VN	Vestibular nuclei



Fastigial nucleus

(medial-most deep cerebellar nucleus)

Axons to spinal cord: fastigiospinal tract, or cerebellospinal tract

Efferents of the Deep Nuclei
The major efferent targets of the cerebellar deep nuclei. The output from the fastigial nucleus is mainly descending the outflow from the interpositus and dentate nuclei is mainly ascending. Ipsilateral projections are not shown. for details, see text

Image by MIT OpenCourseWare.

End session 15

Three major types of body movement,
prior to refinements made possible by neocortex

1) Locomotion
   - Avoidance/escape or approach
   - Explore/forage/seek: basic for all drives

2) **Orienting of head and body**: important for accomplishing the goals of the above

3) Grasping
   - with mouth
   - with limbs (reaching and the control of distal muscles); important for consummation