

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?

REVIEW:

Progressive
determination of
cellular identity
during brain
development

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Kempermann, Gerd, and Fred H. Gage. "New Nerve Cells
for the Adult Brain." *Scientific American* 280 (1999): 48-67.

*From Kempermann and Gage,
1999*

From Kempermann and Gage article:

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Kempermann, Gerd, and Fred H. Gage. "New Nerve Cells
for the Adult Brain." *Scientific American* 280 (1999): 48-67.

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**Human
hippocampal
formation: stem
cells in dentate
gyrus give rise
to new neurons
(granule cells).**

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Kempermann, Gerd, and Fred H. Gage. "New Nerve Cells
for the Adult Brain." *Scientific American* 280 (1999): 48-67.

Proof of neuron formation in mature human brain (*Kempermann '99*): Labeling with BrdU injected to assess tumor growth

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Kempermann, Gerd, and Fred H. Gage. "New Nerve Cells
for the Adult Brain." *Scientific American* 280 (1999): 48-67.

Enriched environments stimulate dentate gyrus neurogenesis *(Kempermann '99)*

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Kempermann, Gerd, and Fred H. Gage. "New Nerve Cells
for the Adult Brain." *Scientific American* 280 (1999): 48-67.

Question: How do we know that the effect is due to the sensory enrichment? **General activity alone can increase the neurogenesis.**

Next: an experiment with implantation of stem cells into the basal forebrain and septal area of rats

Published by Laurie Doering & Evan Snyder, 2000

Experimental implantation of stem cells into the basal forebrain and septal area of rats:

Position in the hemispheres

(top) Medial view of hemisphere

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

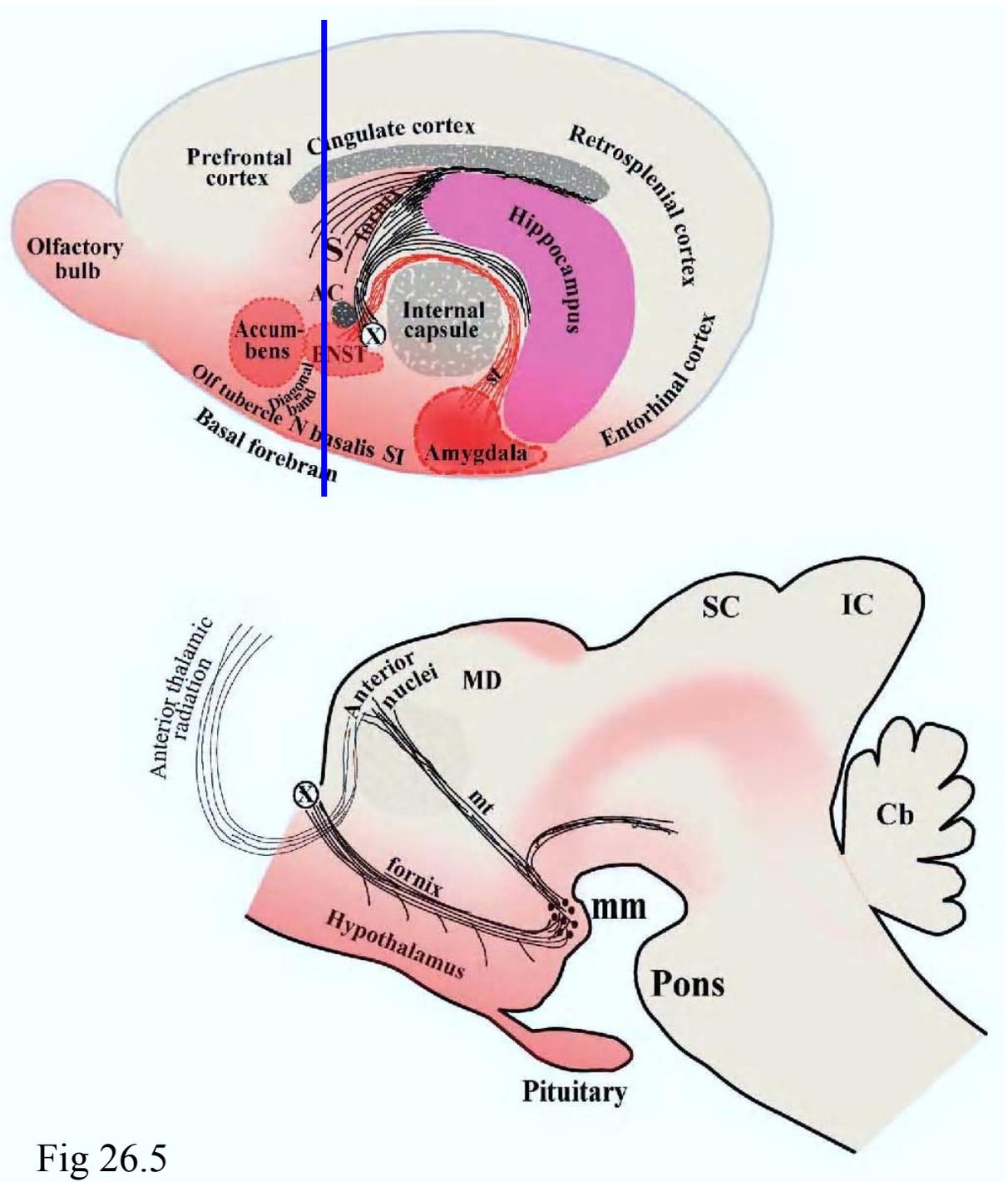


Fig 26.5

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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.

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Doering, Laurie C., and Evan Y. Snyder. "Cholinergic Expression by a Neural Stem Cell Line Grafted to the Adult Medial Septum / Diagonal Band Complex." *Journal of Neuroscience Research* 61, no. 6 (2000): 597-604.

Implanted stem cells surviving after 4-9 months in adult rat brain.

Fig 31-2

*Laurie Doering &
Evan Snyder, 2000:*

C17.2 cells
differentiate into
astrocytes (GFAP+)
and neurons
(neurofilament+),
seen 4-9 mo. after
implantation in
adult rat basal
forebrain

Figure removed due to copyright restrictions. Please see course textbook or:
Doering, Laurie C., and Evan Y. Snyder. "Cholinergic Expression by a Neural Stem Cell Line Grafted to the
Adult Medial Septum / Diagonal Band Complex." *Journal of Neuroscience Research* 61, no. 6 (2000): 597-604.

*Laurie Doering &
Evan Snyder, 2000:*

Some of the
implanted cells
express proteins
showing that they are
cholinergic.

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Doering, Laurie C., and Evan Y. Snyder. "Cholinergic Expression by a Neural Stem CellLine Grafted to the
Adult Medial Septum / Diagonal Band Complex." *Journal of Neuroscience Research* 61, no. 6 (2000): 597-604.

This is enhanced by prior
lesions of fornix (axons
from hippocampus)

Stem cell method treats Parkinson's symptoms in rats

- A team including MIT researchers (Rudolf Jaenisch and associates) has demonstrated for the first time that artificially created stem cells can be used to treat symptoms of Parkinson's disease in rats.
- The work, reported first in the online Early Edition of the Proceedings of the National Academy of Sciences (April 7, 2008), could lead to successful treatments for human patients of Parkinson's, the degenerative neurological disorder. However, the researchers pointed out that hurdles associated with reprogramming cells must first be cleared.

Another approach:

“Neurons derived from reprogrammed
fibroblasts functionally integrate into the
fetal brain and improve symptoms of rats
with Parkinson’s disease”

M Wernig, J-P Zhao, J Pruszak, E Hedlund, D Fu, F
Soldner, V Broccoli, M Constantine-Paton, O
Isacson, and R Jaenisch

PNAS, 2008

Also in 2008:

- “Highly efficient and large-scale generation of functional dopamine neurons from human embryonic stem cells”
- Myung Soo Cho et al, PNAS, 2008. [16 authors]

Brain structure and its origins

MIT 9.14 Class 35

G. E. Schneider

2014

**Evolution and functions of endbrain structures, with
a focus on neocortex**

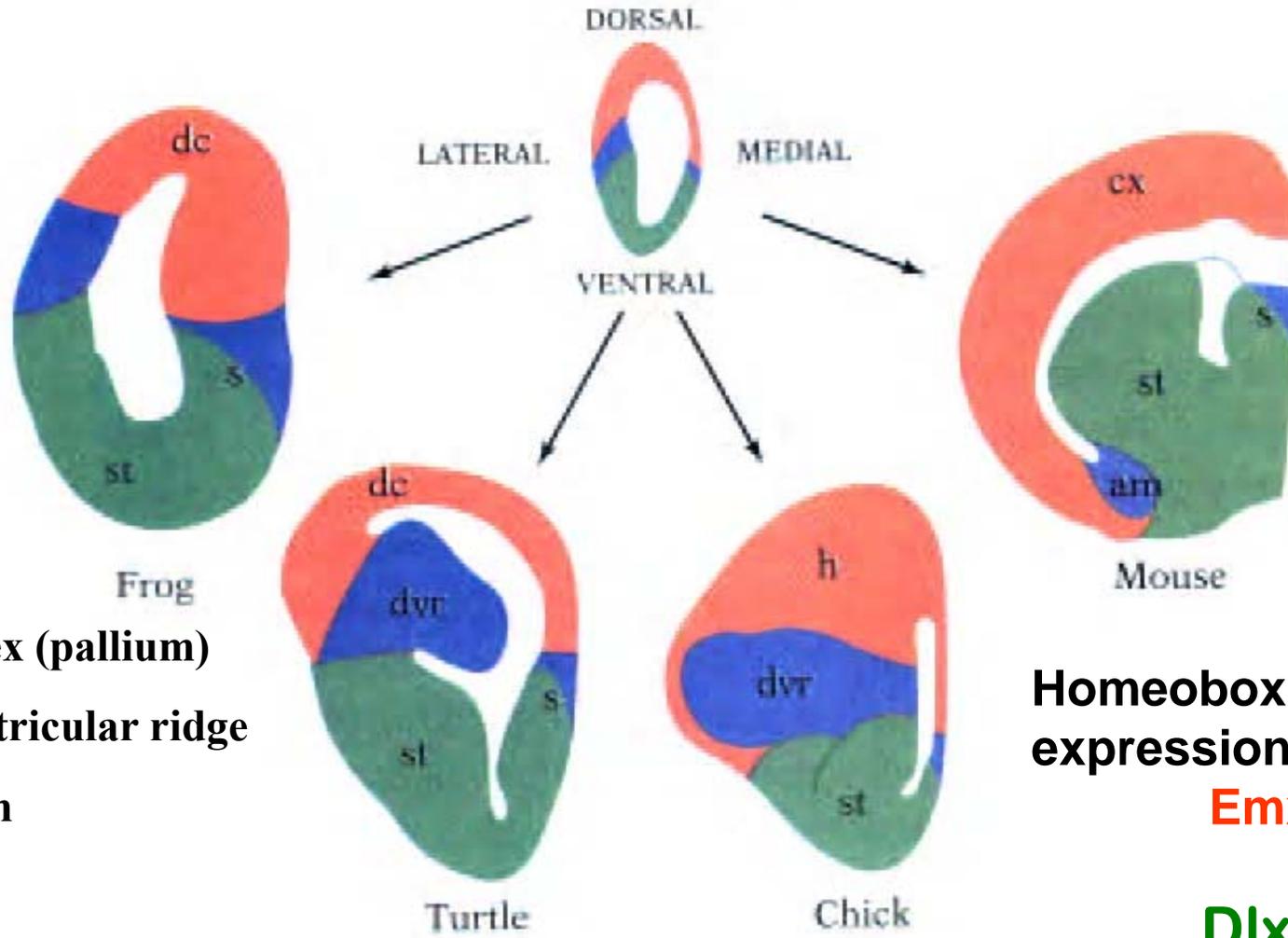
Chapter 32 issues and questions

Topics

- **Class 37**
 - **Evolution and functions of endbrain structures**
(introduction & review of previous material)
- **Class 36**
 - Cell types and their connections *introduced in class 36*
 - Regions of the expanding neocortex
 - Major fiber routes in and out of endbrain
- **Class 37**
 - Thalamocortical connections
 - Association cortex and transcortical connections
 - Thalamic evolution
- **Class 38**
 - Cortical development
 - Cortical plasticity with effects of activity

REVIEW:

Archetypal embryonic stage



cx = neocortex

dc = dorsal cortex (pallium)

dvr = dorsal ventricular ridge

h = hyperpallium

s = septum

st = striatum

Homeobox gene expression:

Emx-1

Dlx-1

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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.

Evolution of telencephalon based on expression patterns of regulatory genes during development

Fig 12-2

from a number of studies

Conclusions concerning the evolution of the endbrain

- The neocortex of mammals evolved from the dorsal pallium of ancestral vertebrates.
 - So did the dorsal cortex of amphibians and reptiles
 - So did the hyperpallium of birds (the Wulst)
- The claustrum and portions of the amygdala in mammals appear to have evolved from the same part of the ancestral neural tube as the dorsal ventricular ridge structures of non-mammals.

The recent data on gene expression are still incomplete.
Therefore:

- The full story of neocortical evolution is still unfolding, and will have many complexities.
- In this class we focus on the real driver of evolution: functional adaptations. **and the connections that support them.**

Questions, chapter 32

- 1) What sensory modality and what projections of this modality underlie the two major types of learning which were so important in evolution of the forebrain? Contrast the two types of learning.

Olfaction

- Object recognition, learning to approach or avoid these objects → habit formation
- place recognition: learning of good and bad places

The primitive functions of endbrain: Identification of **Objects and Places**, originally by olfaction, and later by other senses

- Compare with the midbrain's functions: *(review)*
 - Innate recognition of objects with triggering of innate responses that use information about locations around head/eyes
 - Simple forms of plasticity: sensitization and habituation
- The endbrain's appearance brought more than olfaction: It also brought new kinds of plasticity.
 - Alteration of sensorimotor connections resulting from feedback from the consequences of behavior (reinforcement learning)
 - Consequences that were helpful or hurtful could alter connections that had been active just before the effects were experienced
 - Retention of place information

The primitive functions of endbrain: Identification of **Object** and **Place**

1. **Objects, with innate & learned discrimination of good or bad** (+/- valences, the “affective tags”)
 - Ancient inputs:
 - Pheromones (vomeronasal system)
 - Olfaction
 - Taste *via* ascending projections from hindbrain
 - Later, visual, auditory, somatosensory inputs became major participants
 - Ancient outputs:
 - To hypothalamic & midbrain structures for motivational control
 - To ventral striatum for eliciting approach or avoidance, or for modulation of orienting, *via* midbrain.

These functions and connections are like those of the mammalian amygdala and ventral striatum.

The primitive functions of endbrain: Identification of **Object** and **Place**

2. **Places**, for anticipation of odors reaching nostrils and of possible actions needed: Evolution of place cells in medial pallium

- Ancient inputs:
 - Olfactory *via* olfactory bulbs & olfactory cortex
 - Later, a greater involvement of non-olfactory inputs
- Ancient outputs:
 - To hypothalamic structures for motivational control
 - To ventral striatum for influencing locomotion and orienting.

The medial pallium, important for these functions, evolved into the hippocampal formation.

Invasion of non-olfactory inputs, for advantages in identification of object and place

- To **striatum**, leading to evolution of **dorsal striatum**
 - Inputs reached paleothalamus from visual, auditory & somatosensory pathways; these reticular-formation-like neurons had axons projecting to corpus striatum as well as other areas.
 - The evolutionary elaboration of these thalamic structures was not great, because the striatal afferents from dorsal pallium became dominant.
- To **dorsal pallium (cortex)**, initially multimodal as in lamprey & hagfish
 - In ancient vertebrates, this region evolved connections that resemble connections of limbic and paralimbic cortex in mammals—e.g., parahippocampal areas. (Same in modern reptiles.)
 - Evolution and differentiation of this cortex took different courses in different groups of vertebrates.

Questions, chapter 32

2) From what part of the primitive pallium of pre-mammalian reptiles did neocortex evolve? What part of the mammalian cortex does this pallial region in modern reptiles most closely resemble?

- dorsal pallium / cortex
- para hippocampal areas

3) What structure in the bird endbrain evolved in a way that resembles the way that neocortex evolved in mammals?

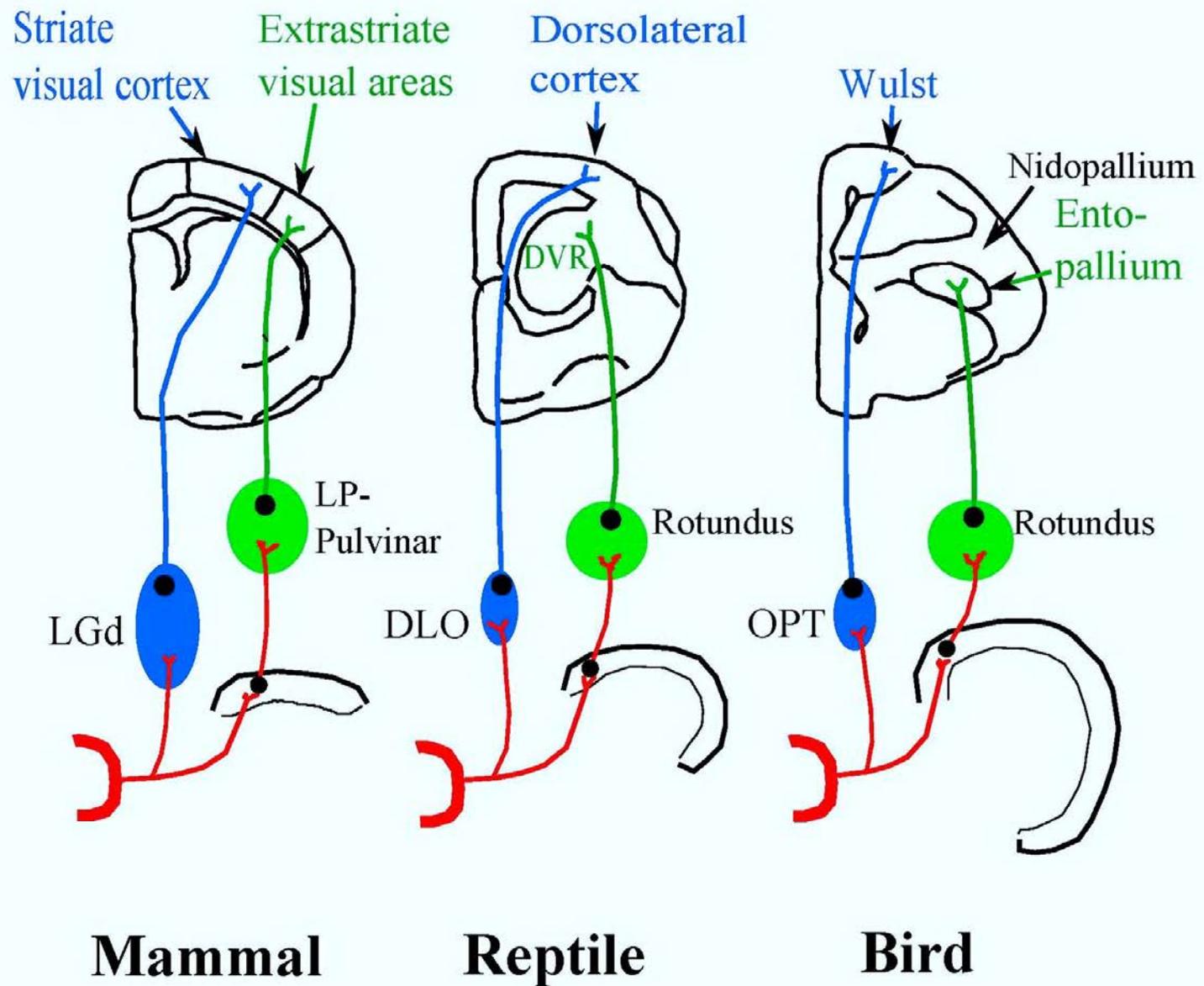
next → the Wulst

Expansions of the dorsal pallium

- Unimodal areas evolved within the multimodal sheet of neurons
- **Neocortex** appeared in part of the dorsal pallium with the evolution of mammals from mammal-like reptiles
 - Differentiation of thicker cortex by addition of superficial layers
 - Appearance of new interneurons by migrations from developing striatum
- Evolution of **Wulst (hyperpallium)** in another offshoot of reptiles: the birds

In mammals: **Why neocortex?** **Why not Wulst?**

- Allman describes the avian Wulst as much more “efficient” than mammalian neocortex. (Next slides)
- Then why is neocortex so successful, and so dominant, in mammals? Suggestions:
 - ***Benefits***
 - *Genetic efficiency: Single gene alterations can lead to major changes in area or thickness*
 - *By altering duration of symmetric and asymmetric cell division*
 - *Efficient local circuits, with multiplication of interconnected cortical areas to achieve complexity of information analysis*
 - ***Costs: Increased quantity of axons***
 - *This can be minimized by “small world architecture”*



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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.

Two major routes from retina to endbrain have evolved in the major groups of vertebrates

Fig 22-2

Owl wulst and owl monkey neocortex

(Allman, 2000, p 115)

Figure removed due to copyright restrictions. Please see figure on p. 115:
Allman, John Morgan. *Evolving Brains. Scientific American Library*: Distributed
by W. H. Freeman and Co., 1999. ISBN: 0716750767.

**Human neocortex:
3 cytoarchitectural
methods:**

**The dominant cell type
is the pyramidal cell.**

**Is there a consistent
pattern of connections
of these neocortical
cells?**

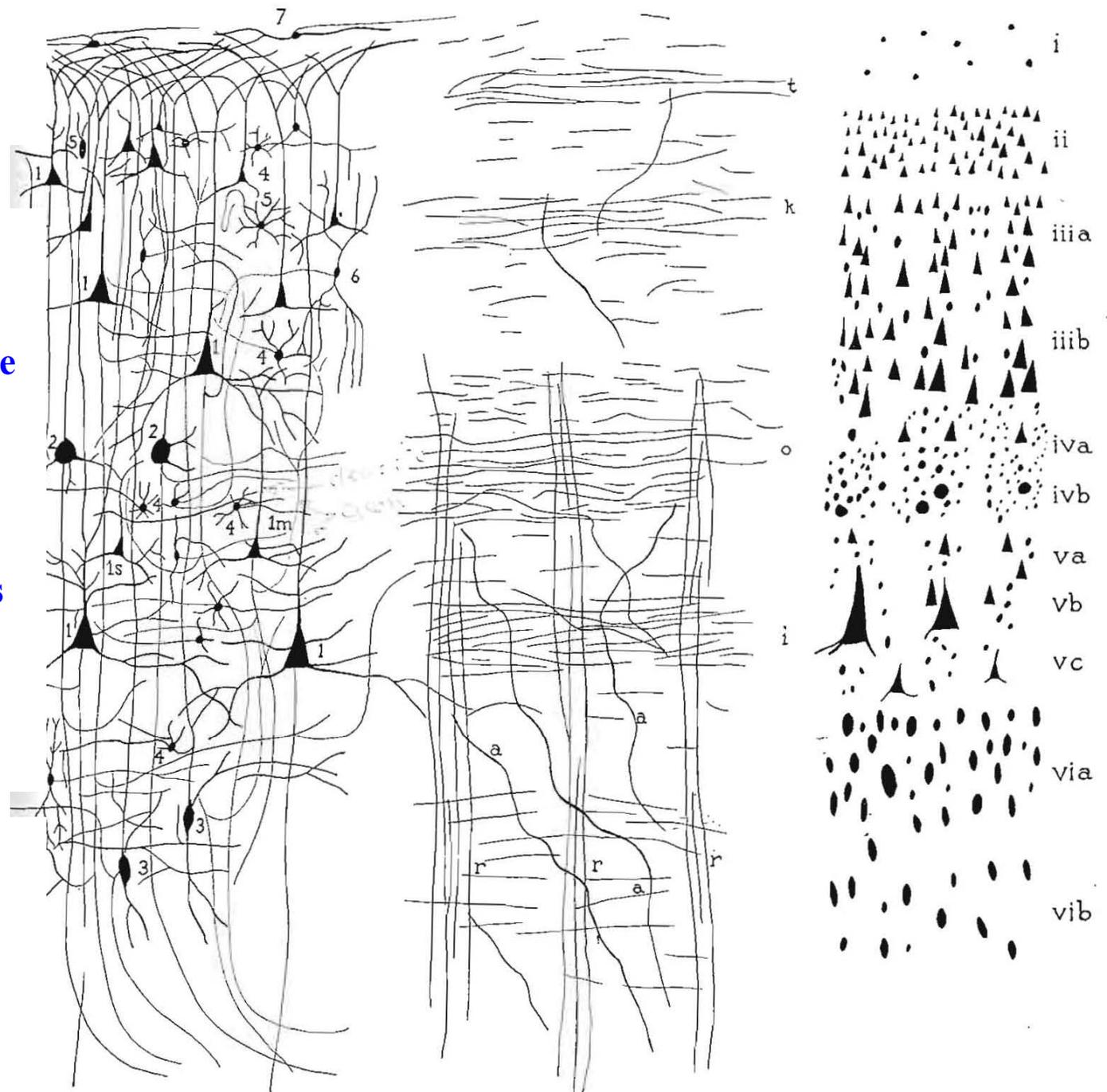


Fig 32-1a

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Poliakov, G. L. "On the Structural Mechanisms of Functional States in Neurons of the Cerebral Cortex." in *Brain Reflexes*. Vol. 22. Edited by E. A. Asratian. Elsevier, 1968.

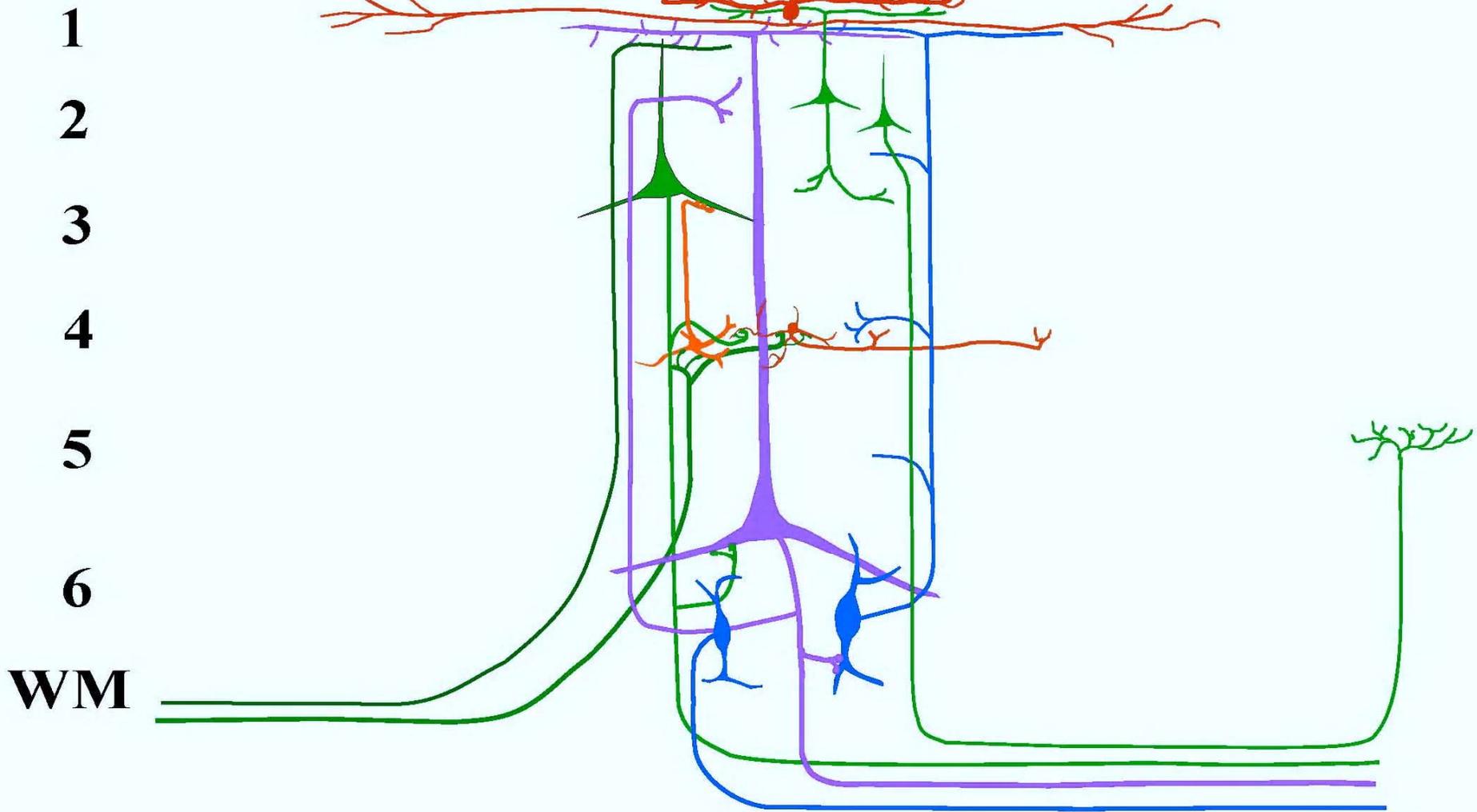
Drawings from Golgi-stained human neocortex by Poliakov

Fig 32-1b

Questions, chapter 32

- 4) Describe three different types of axon projections in the neocortex that begin and end within the cortex.

see the next slide →



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Sketch of a column of cells in the neocortex. Note the different types of axons: afferent, efferent, association

Fig 32-2

Figure removed due to copyright restrictions.

Drawing from ~~Golgi-stained~~ section — injected with HRP.
(Figure from NRP publication)

Figure removed due to copyright restrictions.

Drawing from ~~Golgi-stained~~ section
(Figure from NRP publication, work by Gilbert & Wiesel)

Why neocortex?

The basic sensorimotor functions

1. Sensory analyzers for complex, high-resolution imaging (**sensory acuity**)
2. Movement generators with high dexterity (**motor acuity**)

Neocortex was better than striatum for evolution of higher acuity: Acuity is correlated with the area of neocortex devoted to a given part of a sensory surface. Motor acuity appears to be similarly related to neocortical area.

Cf. the acuity of midbrain vision.

Questions, chapter 32

- 4) The neurologist/neuroanatomist Marek Marsel Mesulam has pictured the paralimbic cortical areas as divided into two main regions related to the two major types of learning referred to in question 1. What did he call these two regions?

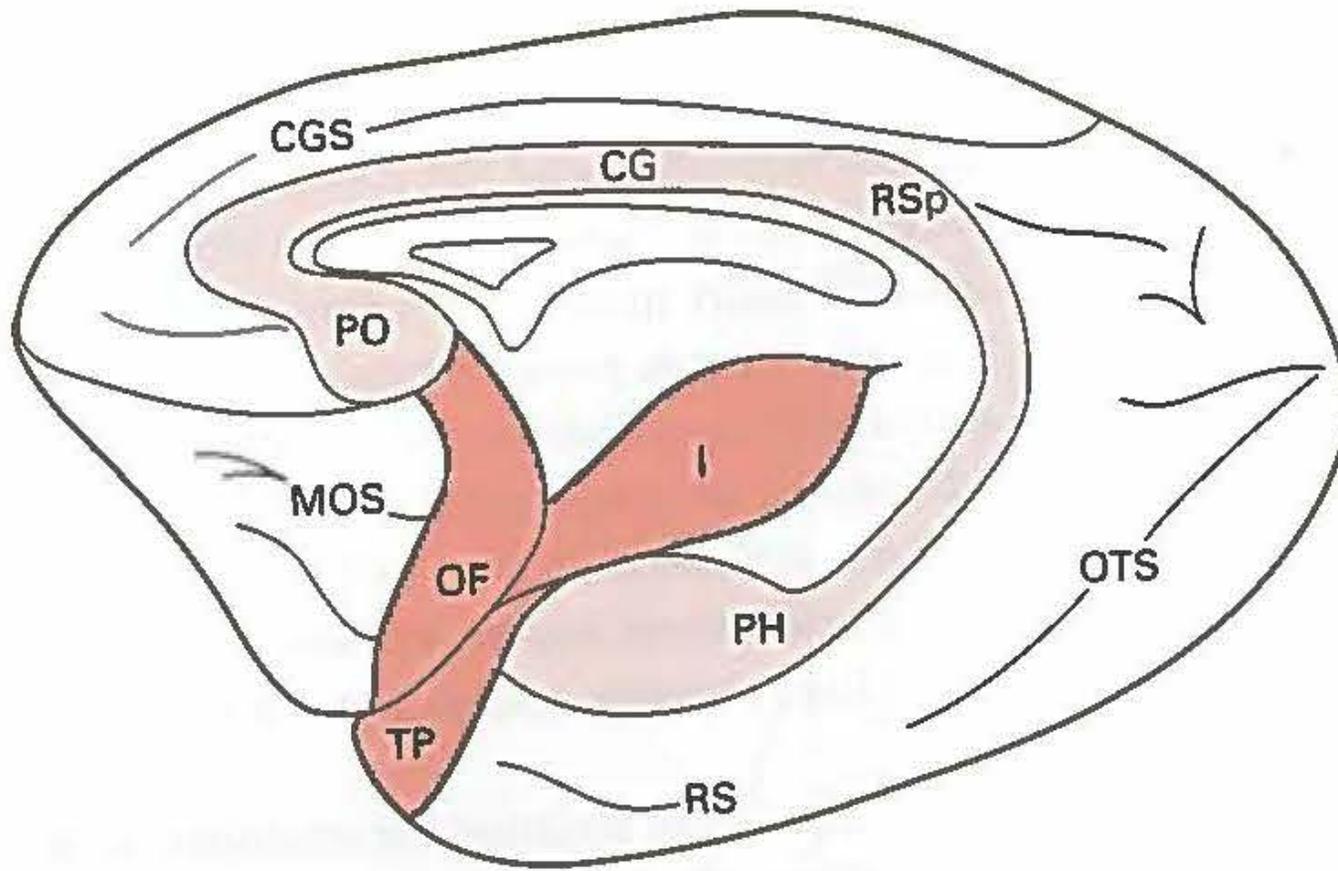
Why neocortex?

Two types of functional regions or connections

- For **place** sense: Hippocampocentric regions with inputs from all modalities
 - Enabled anticipation of inputs during movement from place to place
- For **object** sense:
 - Olfactocentric regions with inputs from olfactory and taste systems
 - Visual, somatosensory and auditory inputs became more central to object perception, with formation of images retained in memory.
 - Anticipation of inputs, when movement of an object occurred, was facilitated.

Cf. Mesulam's **grouping of the paralimbic areas:**

The girdle of paralimbic areas: olfactocentric & hippocampocentric



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Why neocortex? The basic functional regions

For both location sense and object sense, inputs from visual and auditory systems were of major importance. In some species, especially those with long vibrissae, somatosensory inputs were important for place as well as for object sense.

The somatosensory system played another major role:

- For more **dexterous motor control**:
 - Elaboration of somatosensory cortex led to multiple cortical areas representing the body surface.
 - Each region had outputs that influenced movement but **one region evolved into the primary motor cortex**.
 - Learning and planning of movements was facilitated.

Thus, there evolved the major types of functions of the neocortical mantle:

■ Location sense

- This set the stage for more and more anticipation of inputs

■ Object sense

- This also set the stage for more and more anticipation of inputs, involving both social and non-social objects

■ Functions of the prefrontal elaborations of motor cortex:

- Cortical elaboration of complex movement abilities
- More and more **planning** for future actions became possible:
 - Initially the immediate future, later the more distant future as well

Questions, chapter 32

- 6) Discussion question: How does the hippocampal system facilitate the ability to anticipate the stimuli that an animal or person is about to encounter? What neocortical areas are primarily involved?

- 7) Contrast the anticipatory activity of the neocortical areas rostral to the primary motor cortex with the anticipatory activity of the multimodal association areas of the parietal and temporal lobes.

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9.14 Brain Structure and Its Origins

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