Human neocortical anatomy in Moscow

- Three types of cortex described by Polyakov (*illustrated by A. Luria, fig. 15*).
  - *Polyakov, G.I. (1966) Modern data on the structural organization of the cerebral cortex. Ch. I, sec. 2 (pp. 39-69) in Luria, A. R., Higher cortical functions in man. New York, Basic Books.* The Russian anatomist uses some terms not common in Western neuroscience, but some of the data collected and figures are unique.
- Polyakov's **primary** fields of the nuclear zones are equivalent to Mesulam's *idiotypic* cortex. His **secondary** and **tertiary** fields are in equivalent in part to Mesulam's *unimodal* and *heteromodal association* areas.
- Species comparisons: See next slide

Figure removed due to copyright restrictions. Please see course textbook or:
Poliakov, G. I. "*Neuron Structure of the Brain*." Translated from the Russian by MaClean, Paul D. Harvard University Press, 1972.

Critique: The maps can imply that hedgehog and rat have no heteromodal cells in neocortex. But their cortex has many such cells. There has been **less parcellation.**

Fig 33-17 Polyakov's three neocortical fields

Three types of cortex, like Mesulam, but the "most advanced" type is larger than for Mesulam's heteromodal areas.

Information about neocortical association areas from studies of development

Illustrated on following slides

- Postnatal growth of different areas of human brain (Poliakov)
- Growth of association layer 3 in selected areas of human brain (Poliakov)
- Myelinogenesis in human neocortex (Cecile & Oscar Vogt; Paul Flechsig)
- Growth-associated protein in adult brain and in development (Larry Benowitz)

Postnatal growth of different territories, human neocortex

(*From Polyakov, in Luria '66, fig. 17)*

Figure removed due to copyright restrictions.

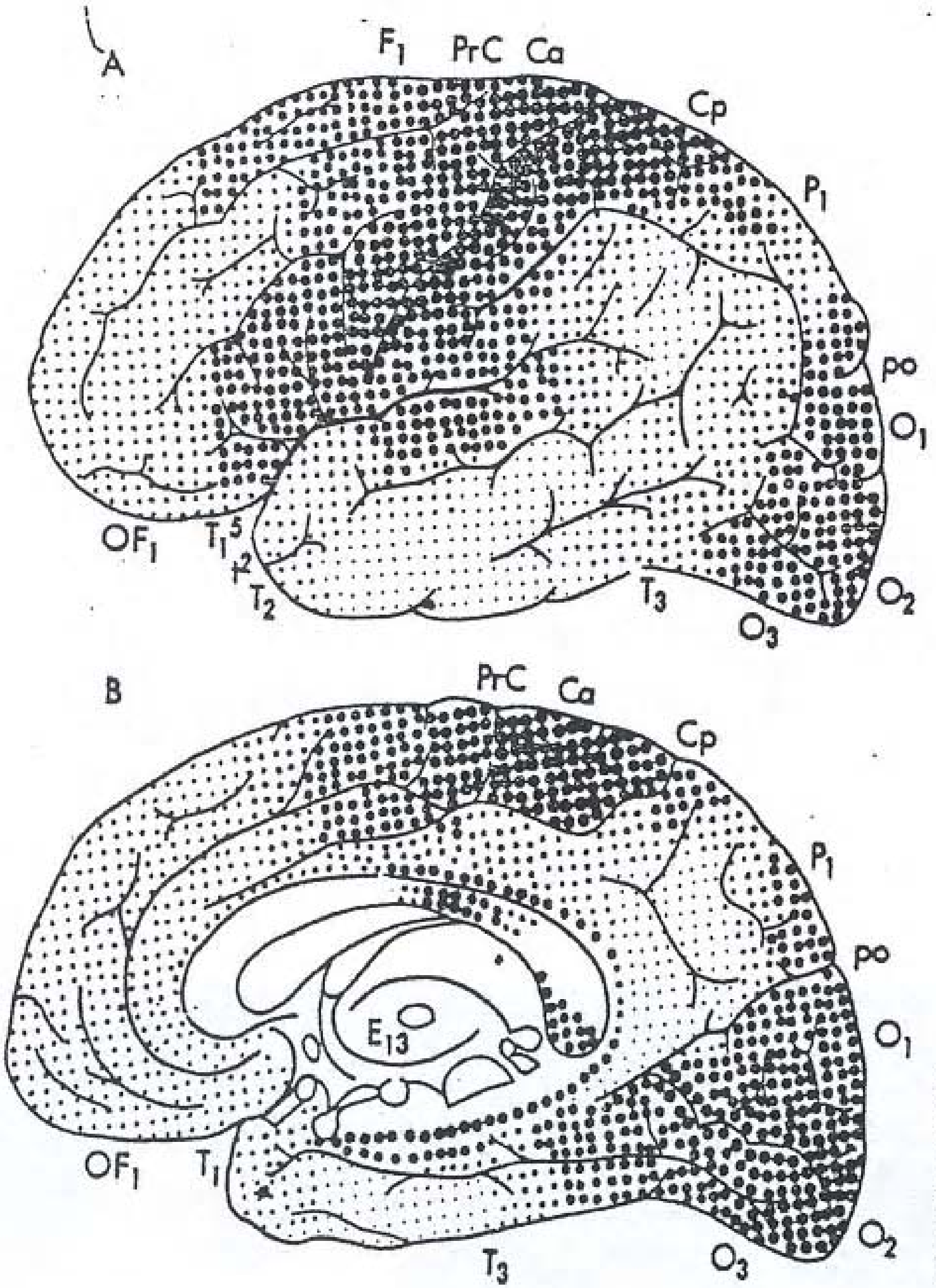


FIGURE 18 Myelogenetic chart. (*a*) Lateral surface; (*b*) medial surface. The large dots indicate the cortical portions that mature first; the small dots indicate those that mature last. (*From C. and O. Vogt, 1919–1920.*)

Myelogenesis *(C. and O. Vogt, 1919-1920):*

Areas of earlier and later maturation

Unimodal areas are earliest, multimodal areas are last in acquiring myelin.

Myelogenesis

Paul Flechsig (1920)

The order of appearance of myelin in the various cortical areas, as redrawn in a review by von Bonin (1950)

The numbers are not Brodmann areas. 1 is the earliest to acquire myelin, 45 is the last.

Figure removed due to copyright restrictions. Please see course textbook or: Von Bonin, Gerhardt. *Essay on the Cerebral Cortex*. no. 59. Thomas, 1950.

Fig 33-18

Growth of neocortical association layer 3

(Poliakov, in A. Luria (1962, 1966, 1980)

Figure removed due to copyright restrictions.

Larry Benowitz' studies of the growth-associated protein, GAP-43

- Present throughout growing axons during the developmental period (studies of rat brain development)

  and hamster

- Present in adult human neocortex, concentrated in association layers 2-3
  - This is the region where changes in dendrites of inhibitory interneurons occur in adult mice (imaging of live mouse brains by Elly Nedivi and collaborators).

(Note: I have data showing that the GAP-43 is also present in the local interneurons of the adult thalamus.)

Hemispheric specializations
(very briefly)

- What do the terms "dominant hemisphere" and "non-dominant hemisphere" mean?
- Are the two hemispheres structurally different?

yes, first found in Boston by behavioral neurologist Norman Geschwind and Albert Galaburda.

Questions, chapter 33

11) What are the two major ideas concerning the evolution of the thalamus summarized at the end of the chapter?

Ideas on thalamic evolution

- First, recall the ideas on the beginnings of the vertebrate endbrain.
- Then, we can suggest **two ideas** on how the thalamus changed as the endbrain expanded in evolution.
  - Support from findings of comparative neuroanatomy
  - Support from data on topographic organization
  - Support from studies of development and plasticity of axon systems.

X

Evolution of corpus striatum and telencephalic pallium: *a story*

1. Beginnings: a link between olfactory inputs and motor control: The link becomes “Ventral striatum”. It was a <u>modifiable</u> link (capable of experience-induced change).

2. Non-olfactory inputs invade the striatal integrating mechanisms (via paleothalamic structures).

3. Early expansions of endbrain: striatal and pallial.

4. Pre-mammalian & then mammalian expansions of cortex and striatum: For the striatum, the earlier outputs and inputs remain as connections with neocortex expand.

Figure 1. Postulated beginnings in primitive chordates

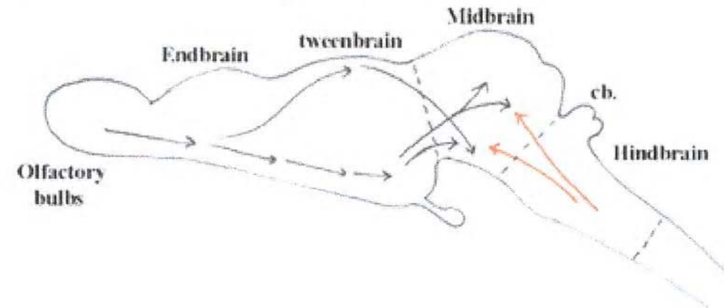


Figure 2. **Other inputs reached the striatum**

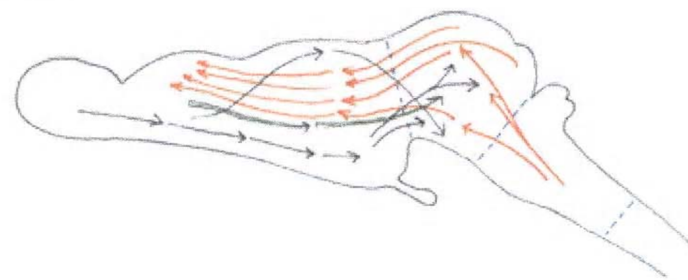


Figure 3. Early expansion of striatal and adjacent " limbic" areas

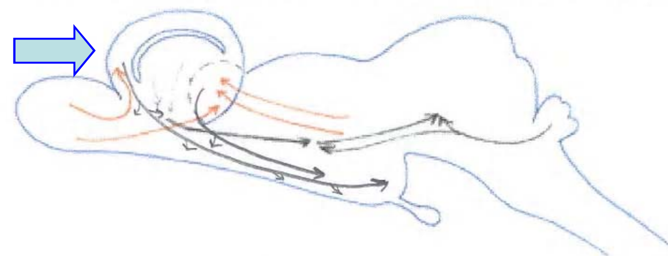
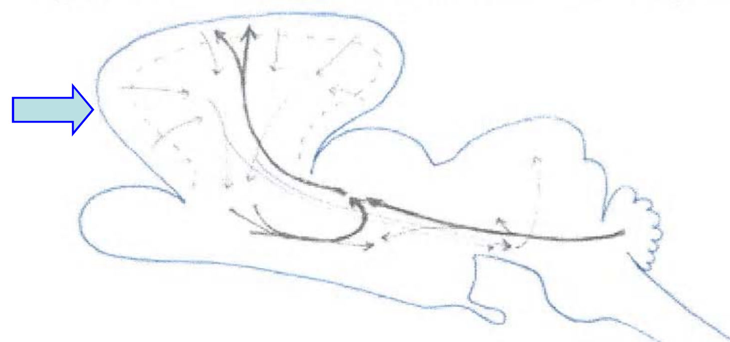


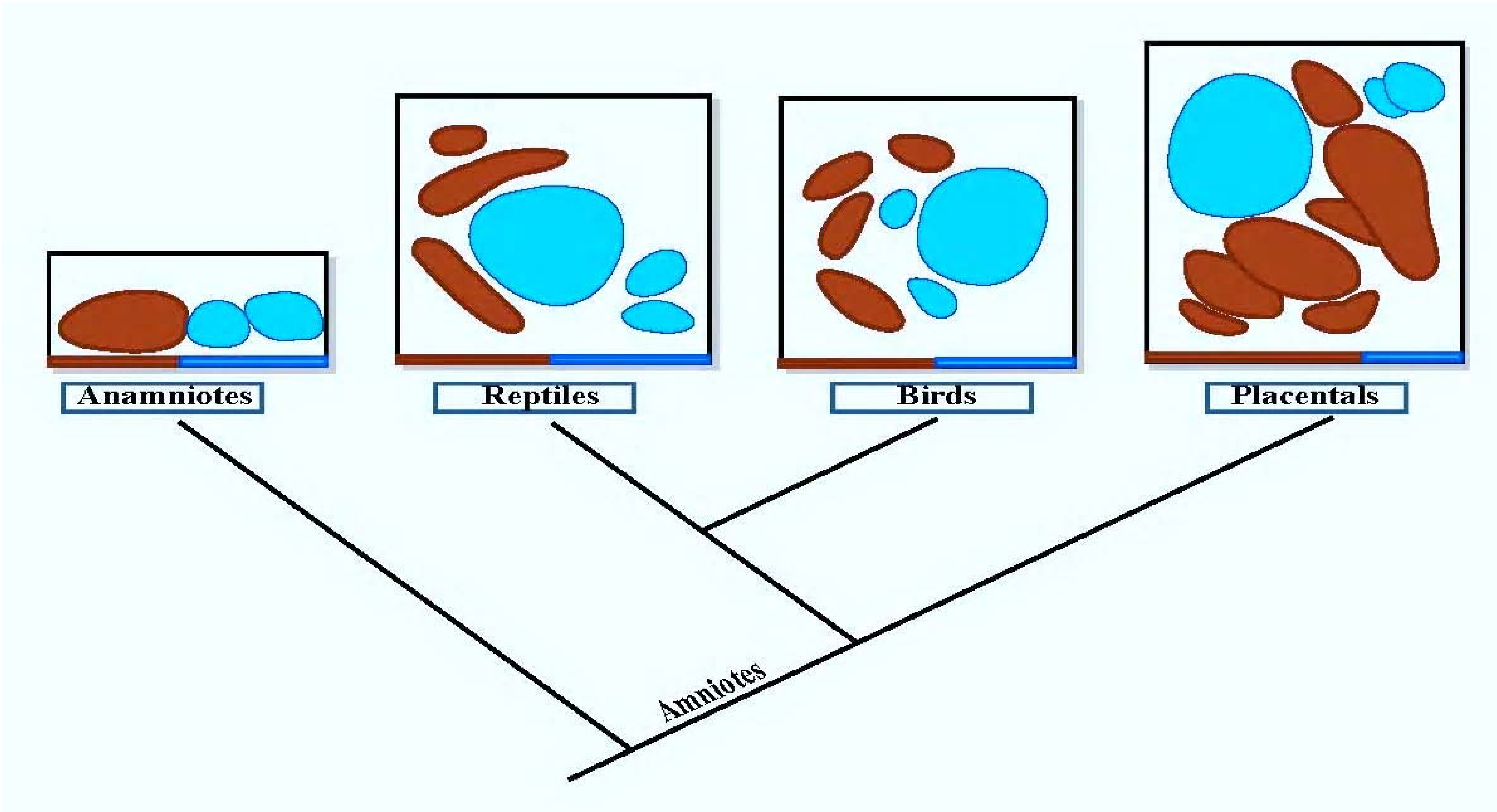
Figure 4. Pre-mammalian, and then mammalian expansions



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

Idea 1

- Earliest thalamus was multimodal and projected to primitive striatum and pallium.
- Within the primitive multimodal thalamus, unimodal regions formed by functional segregation (parcellation).
  - Distinct territories corresponded to axonal entry positions. This organization is preserved in the thalamic outputs to the cortex.
- Some multimodal cells remained.



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

Segregation of distinct cell groups in the dorsal thalamus in major vertebrate groups

Fig 32-5

Idea 2

- Gating, or modulation, of thalamic information destined for the endbrain was important early in forebrain evolution.
- This resulted in thalamus becoming a nearly "obligatory way station" for information passing to the endbrain.
- Modulatory projections come from hindbrain, midbrain and hypothalamus.
- Those from hindbrain and midbrain not only terminated in 'tweenbrain including the thalamus (5HT, NE): they also went directly to the endbrain (5HT, NE and DA containing axons).

Brain Structure and Its Origins

9.14 MIT 2014

G. E. Schneider

Class 38

Neocortex 4:

Development and plasticity

Conclusions about neocortex

Before we go through the final slides for the class, we report one important recent discovery reported in the Feb 27th issue of *Cell*.

"Neurogenesis in the striatum of the adult human brain."

Using histological and carbon-14 dating, investigators obtained evidence that the rostral migratory stream in the adult brain, which can be followed into the olfactory bulbs in other mammals, is diverted into the dorsal striatum in the human brain. The newly generated cells become interneurons.

Thus, in each of the two major forebrain systems for learning (hippocampus and striatum) there is adult turnover of neurons.

Development of the CNS: 4 major events

1. Neurulation, formation of neural tube
2. Proliferation
3. Migration
4. Differentiation, with growth of axons and dendrites

We have discussed all of these events previously. Today we will focus on unique aspects of proliferation and migration in the neocortex.

Questions, chapter 34

1) What is the subpial granular layer? When and where and in what animals is it found?

   In humans and other large mammals, a transient layer of dividing cells just below the pia, similar to a layer found in the developing cerebellar cortex.

2) What is the difference between symmetric and asymmetric cell division, and what are the consequences for development?

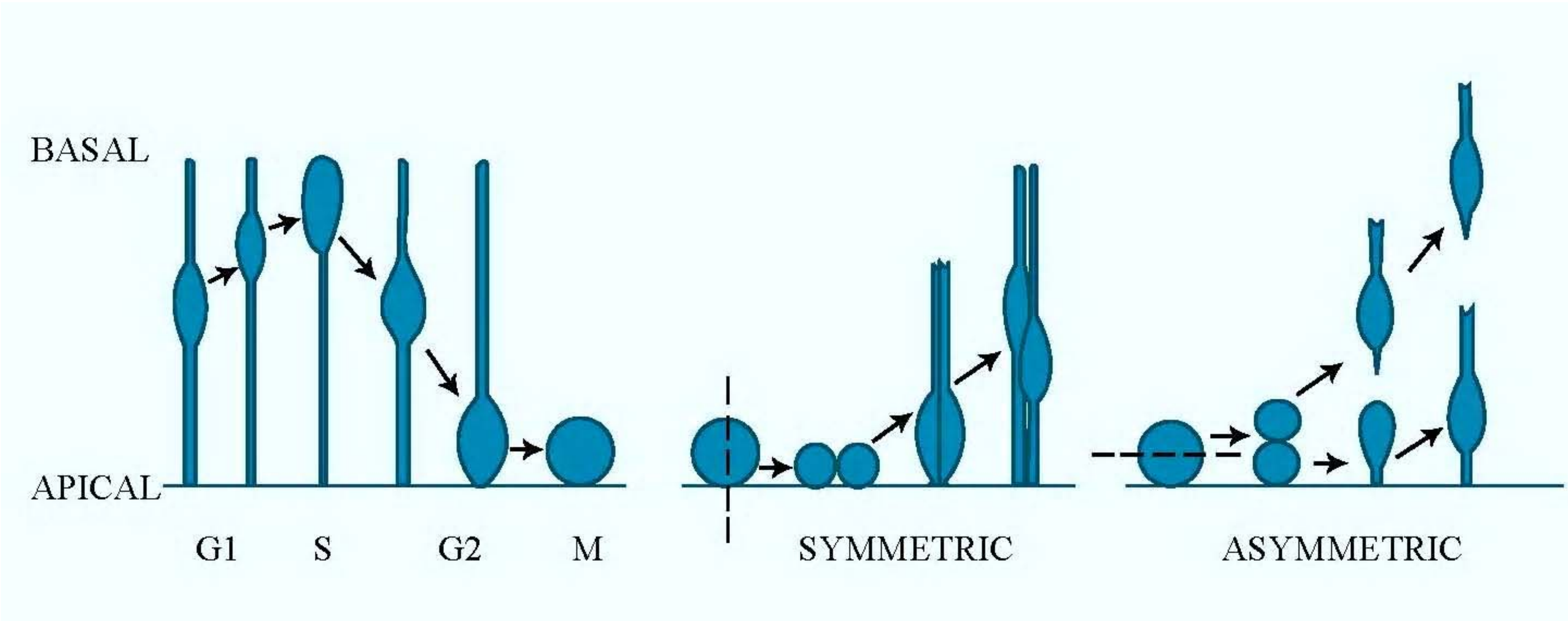
   fig 8.7 (next slide)

3) Explain the importance of evolutionary changes in the periods of symmetric and asymmetric cell division in neocortical development, as postulated by Pasco Rakic.

   see following →

REVIEW:

Neurogenesis: Cell proliferation (by mitosis)



Cell cycle **Two types of cell division**

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 8-7

Mitoses adjacent to the ventricle

- Symmetric cell division:
  - two daughter cells remain in proliferative state.
- Asymmetric cell division:
  - one daughter cell becomes post-mitotic and migrates away from ventricular layer.

- What causes the difference in cell fates?
  - The distribution of proteins Numb & Notch: Numb moves toward the ventricular side of the cell.
  - Numb without Notch causes cell to remain mitotic.
- What are the consequences for neocortical structure and size? (Next slide)

Modes of cell division & duration of corticogenesis

Neocortical area depends on duration of **symmetric** cell division.

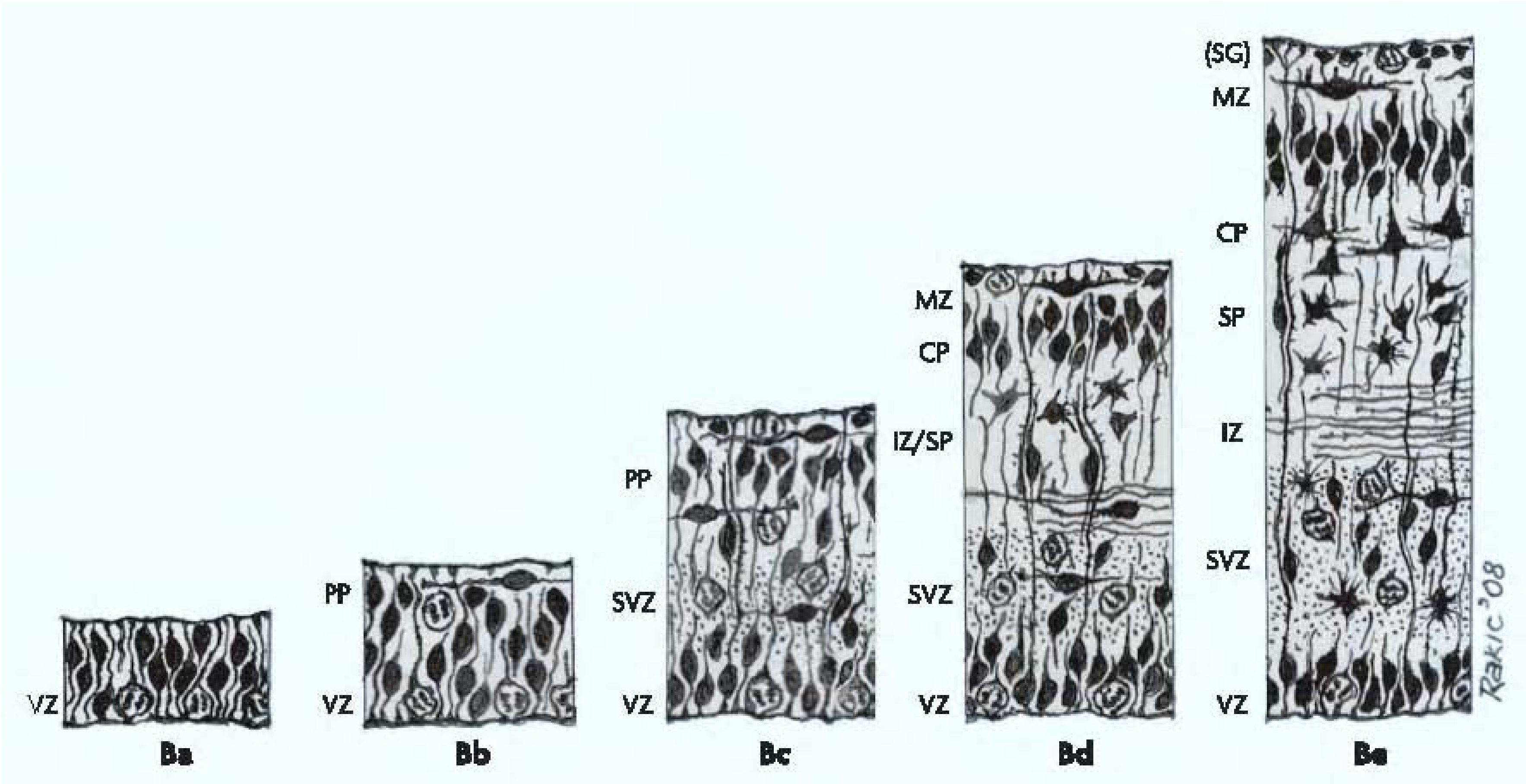
Monkey (< E40)
vs human (< E43)

Duration of **asymmetric** cell division → neocortical thickness. In monkey this period is many days shorter than in humans.

(P. Rakic, TINS, '95)

Fig 34-2

Figure removed due to copyright restrictions. Please see course textbook or: Rakic, Pasko. "A Small Step for the Cell, a Giant Leap for Mankind: A Hypothesis of Neocortical Expansion During Evolution." *Trends in Neurosciences* 18, no. 9 (1995): 383-8.



Early stages in the development of the primate neocortex

Fig 34-1a

Postnatal differentiation of visual cortex in hamster

Figure removed due to copyright restrictions. Please see course textbook or:
Naegele, Janice R., Sonal Jhaveri, et al. "Sharpening of Topographical Projections and Maturation of Geniculocortical Axon Arbors in the Hamster." *Journal of Comparative Neurology* 277, no. 4 (1988): 593-607.

Fig 34-1b

Questions, chapter 34

5) How do neurons that begin their migration from the ventricular zone in the neocortex reach their final destinations? What is meant by an "inside-out" pattern of migration?

REVIEW

Migration: Three types

1. Nuclear translocation *(D. Kent Morest, U. Conn.)*
2. Guidance by radial glia cells *(Pasco Rakic, Yale)*
3. Tangential migration: movement of whole cells along adhesive pathways

In the neocortex, a major type of migration is #2. However, type #3 also occurs for inhibitory interneurons that migrate from the medial ganglionic eminence and the caudal ganglionic eminence.

Figures removed due to copyright restrictions. Please see course textbook or:
Rakic, Pasko. "Mode of Cell Migration to the Superficial Layers of Fetal Monkey Neocortex." *Journal of Comparative Neurology* 145, no. 1 (1972): 61-83.

Fig 34-6

Figure removed due to copyright restrictions. Please see course textbook or:
Pasko Rakic. "Development Events Leading to Lamina and Areal Organization of the Neocortex." In *The Organization of the Cerebral Cortex: Proceedings of a Neurosciences Research Program Colloquium (on Cerebral Cortex) at the Marine Biological Laboratory, Woods Hole, Mass. 1979.* Edited by FO Schmidt. MIT Press, 1981.

Cortical Layer Birthdates

Method: ^{3}H-thymidine autoradiography.

Evidence for "inside-out" pattern of neurogenesis, confirming results from studies of mice and rats.

Fig 34-5

Questions, chapter 34

6) Besides the ventricular zone, two other proliferative regions are the sources of other neurons that migrate into the developing cortical plate. Where are these two regions located, and what kind of neurons do these other cells become? (See p 230-231, 597, 607-608, 646-647, 651.)

   Mostly from the medial ganglionic eminence and from the caudal ganglionic eminence. Cells become GABA-ergic (inhibitory) short-axon interneurons.

4) Explain how Finlay and Darlington plotted the sizes of various brain structures in primates and other mammals, showing a kind of concerted evolution. What did their graphs show about the relative size of neocortex compared with other structures? →

Re: the topic of question 4

How much does the neocortex grow in various mammalian species?

Does the rest of the brain grow proportionately?

Finlay & Darlington's argument for *concerted evolution*

Simians
Prosimians
Insectivores
Bats

Figure removed due to copyright restrictions. Please see course textbook or:
Finlay, Barbara L., and Richard B. Darlington. "Linked Regularities in the Development and Evolution of Mammalian Brains." *Science* 268, no. 5217 (1995): 1578-84.

Size of brain subdivisions plotted as a function of total brain size (log-log plot)

Fig 34-3

Figure removed due to copyright restrictions. Please see course textbook or:
Finlay, Barbara L., and Richard B. Darlington. "Linked Regularities in the Development and Evolution of Mammalian Brains." *Science* 268, no. 5217 (1995): 1578-84.41

Finlay and Darlington: principal components analysis of data on size of brain structures:

- **Blue bars**: factor 1 accounts for over 96% of total variance (data from 11 structures), and is most highly correlated with neocortex and least with olfactory bulb.
- **Orange bars**: factor 2 accounts for 3% of total variance, and is most highly correlated with olfactory bulb, next with limbic system structures.

Thus, there appears to have been more "mosaic evolution" in the olfactory and limbic system structures.

However, this analysis would miss mosaic evolution in individual portions of the neocortex.

How does the cortex gets specified into different areas? Two major hypotheses have been found to describe two different factors that we have come to expect in studies of development:

1) **Nature (genetic factors)**
2) **Nurture (epigenetic factors)**

Two major hypotheses:

1. ***A genetically determined map of cortical areas*** *appears early during development, before the areas become structurally different. ("Protomap" hypothesis: Rakic)*

2. *The cortex begins as genetically uniform, then* ***epigenetic factors cause areas to become different.*** *Factors in the local environment shape the cortex, such as afferent axons and their activity. ("Protocortex": O'Leary, Finlay, others)*

There are findings supporting each hypothesis, so we can conclude that there is **genetic determination but also major epigenetic influences**—e.g., influences of connections formed.

Tests of the two factors

- Genetic determination from the ventricular layer
  - Support from findings of genetic differences between cortical areas. Data have been increasing.
  - Early example: Levitt's LAMP (Limbic Associated Membrane Protein)
    - Transplant limbic to SS cortex: fate defined by LAMP.
    - Result depends on age at transplantation (before or after E12)
  - For more recent data in support of this hypothesis, see article in 2006 in the journal *Cerebral Cortex*: http://cercor.oxfordjournals.org/cgi/content/full/16/1/124
- Support for epigenetic factors in the tissue environment: studies of transplants of V1 to S1 (*O'Leary et al.*)
- Another epigenetic factor: the role of activity (next slides)

Role of activity in the development and plasticity of cortical connections

– **Synaptic activity shapes the construction of some cortical circuits**
  - Some of the molecular mechanisms involved in activity-dependent development of the neocortex are known.
– **Re-wiring the cortex: The role of patterned activity**
  - Development
  - Adult plasticity
– **The visual system has been a good model** for studying the effects of development.

Questions about developing visual system:

Projections in the visual system in many species become highly organized before birth: Does sensory experience play any role in the development of this system?

Is there activity in sensory pathways before there is sensory input? **(See the next slide.)**

Questions on chapter 34:

7) Describe an example of how neuronal activity can affect the development of axonal connections even prenatally or before the eyes open, before there is any visual experience.

Figure removed due to copyright restrictions. Please see course textbook or:
Meister, Markus, R. O. Wong, et al. "Synchronous Bursts of Action Potentials in Ganglion Cells of the Developing Mammalian Retina." *Science* 252, no. 5008 (1991): 939-43.

Electrical activity before experience: waves of spontaneous activity in retina

prenatal cat

From Meister M, Wong ROL, Baylor DA, Shatz CJ (1991)

Fig 34-7

Electrophysiological studies indicate that this kind of very early organized activity shapes the precision of termination of the retinofugal axons, visible in the terminal arbors. How could it do this?
(We will see a picture of some of the evidence in what follows.)

NEXT: Neuronal activity shapes binocular responsiveness of neocortical neurons.

- ***What is the ocular dominance of a cell in primary visual cortex?***
- ***What is an ocular dominance column?***

Ocular dominance in unit recordings

Sum of 1-5 is always 100%

Figure removed due to copyright restrictions.

What is the meaning of the following terms: "critical period", "binocular competition"?

We can understand these terms with the help of neuroanatomical figures

Figure removed due to copyright restrictions. Please see course textbook or: Goodman, Corey S., and Carla J. Shatz. "Developmental Mechanisms that Generate Precise Patterns of Neuronal Connectivity." *Cell* 72 (1993): 77-98.

From chapter 13

Figure removed due to copyright restrictions.

Fig 13-9b Thalamocortical axons in primary visual cortex of cat, layer 4. At top, axon in 17-day kitten. Below, axon from normal adult cat.

Figure removed due to copyright restrictions.Please see course textbook or:
Antonini, Antonella, and Michael P. Stryker. "Rapid Remodeling of Axonal Arbors in the Visual Cortex." *Science* 260, no. 5115 (1993): 1819-21.

Arbors of thalamocortical axons in visual cortex.

ND=non-deprived; D=deprived. Numbers indicate cortical layers.

Fig 34-8

How does activity have these effects on the anatomical connections?

- Changes are found at the level of terminal arbors **and** at the level of synaptic details
- Activity promotes the vigor of axonal growth.
  - It can cause the release of neurotrophins, which further influence growth.
- Hebb's postulate to explain learning in terms of changes in synaptic strength can be used to explain how precision in topographic connections develops from a less precise earlier organization.
  - "Cells that fire together wire together" by effects of correlated pre- and post-synaptic activity.
  - Molecular mechanisms underlying the synaptic changes have been discovered, and continue to be discovered.

Three additional experimental paradigms

that show large effects of activity in shaping the connections of the neocortex:

1. **Re-wiring sensory pathways by early lesions**
2. Altered neocortical connection patterns after early sensory deprivation, as in blind animals or persons.
3. Alteration of receptive fields by repetitive stimulation in adult somatosensory cortex

A novel paradigm for studying the developmental shaping of a visual cortex: Early lesions of SC and of auditory pathways to the MGB in ferrets (see also figure 13-13)

Sur, Mriganka, Alessandra Angelucci, et al. "Rewiring Cortex: The Role of Patterned Activity in Development and Plasticity of Neocortical Circuits." *Journal of Neurobiology* 41, no. 1 (1999): 33-43.

M. Sur et al., J. Neurobiol. '99, Fig 1

An organized visual cortex has appeared where the auditory cortex would be in the normal ferret.

From M.Sur *et al., J Neurobiol.* '99

The re-wired cortex has orientation tuning in a pattern that resembles that in visual cortex.

This must be an effect of organized activity patterns during development.

From M. Sur *et al.*,
J Neurobiol '99, Fig. 3

Fig 34-10

Questions on chapter 34:

8) What evidence has been found in mammals for brain changes after blinding? Are the changes/anomalies necessarily structural in nature?

Three additional experimental paradigms

that show large effects of activity in shaping the connections of the neocortex:

1. Re-wiring sensory pathways by early lesions
2. **Altered neocortical connection patterns after early sensory deprivation, as in blind animals or persons.**
3. Alteration of receptive fields by repetitive stimulation in adult somatosensory cortex

Figure removed due to copyright restrictions. Please see course textbook or:
Karlen, Sarah J., and Leah Krubitzer. "Effects of Bilateral Enucleation on the Size of Visual and Nonvisual Areas of the Brain." *Cerebral Cortex* 19, no. 6 (2009): 1360-71.

Effects of early bilateral eye removal in short-tailed opossums

A possible mechanism explaining the increased number of bimodal cells: normally sparse connections have become stronger.

Sparse connections may be too weak in their effects to cause firing of action potentials, and therefore they would be missed in unit recording studies.

Fig 34-11

Questions on chapter 34:

9) Describe experiments with mature monkeys in which changes in the primary somatosensory cortex were found. Describe the behavioral task and the nature of the changes found.

Three additional experimental paradigms

that show large effects of activity in shaping the connections of the neocortex:

1. Re-wiring sensory pathways by early lesions
2. Altered neocortical connection patterns after early sensory deprivation, as in blind animals or persons.
3. **Alteration of receptive fields by repetitive stimulation in <u>adult</u> somatosensory cortex**

Somatosensory cortex plasticity in adults: Remodeling of hand representation is determined by timing of tactile stimulation

- Subjects: Owl Monkeys
- Procedure
  1) Monkeys learn to position hand reliably and repeatedly— see next slides.
  2) 4-6 weeks of training, several hundred trials per day
  3) Electrophysiological mapping of neuronal responses in layer 3 of area 3b (primary somatosensory cortex)
- Result: Reorganized cortical maps had **multiple-digit receptive fields** and continuous zones
- Such changes were not found in receptive fields of thalamic neurons

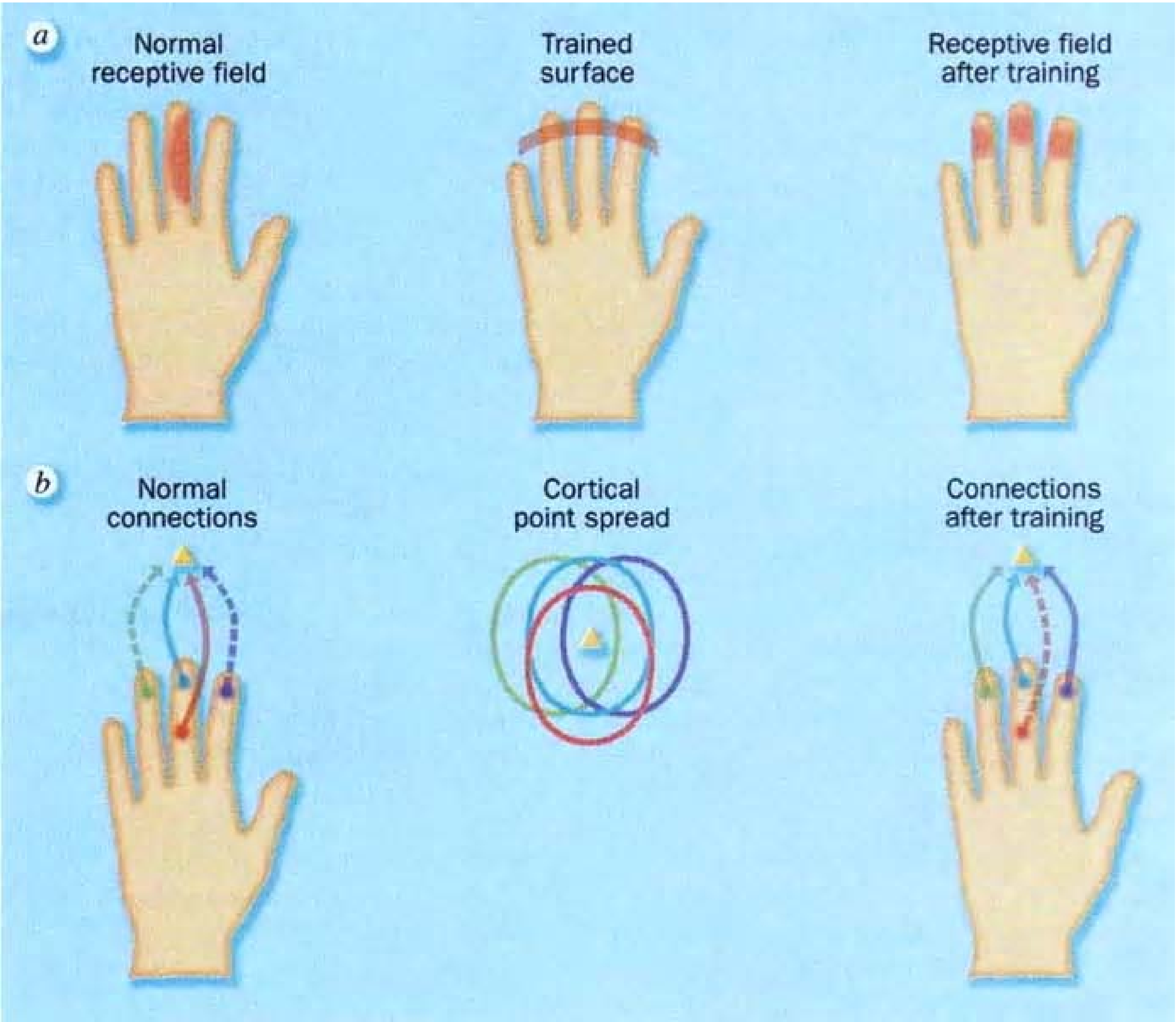
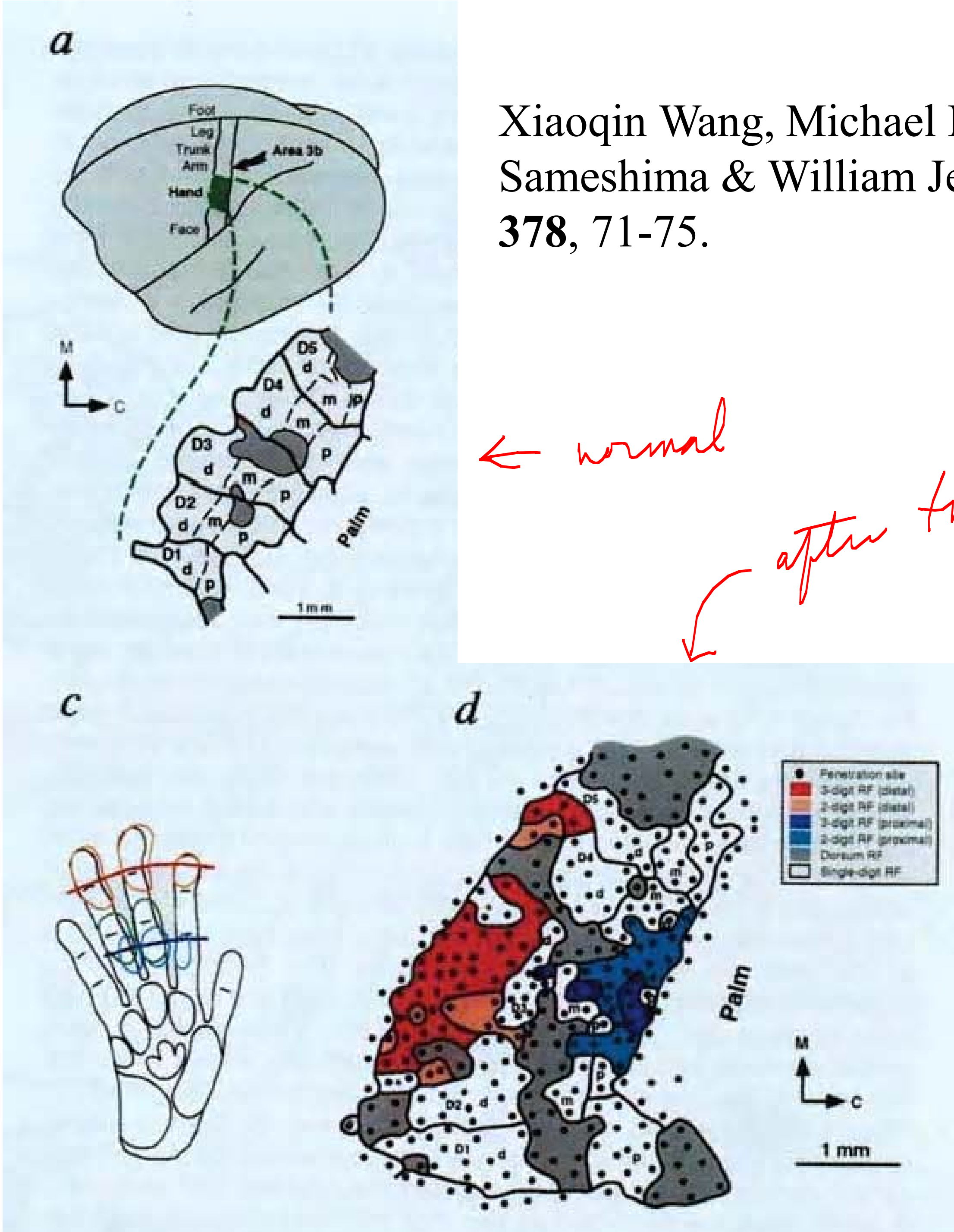

a
Normal
receptive field
Trained
surface
Receptive field
after training
b
Normal
connections
Cortical
point spread
Connections
after training

Fig 34-12

Xiaoqin Wang, Michael Merzenich, Koichi Sameshima & William Jenkins, *Nature* 1995, **378**, 71-75.



Red and blue colors indicate multi-digit receptive fields, not found before the training.

Fig 34-13

What is changing in these monkeys?

- The mechanism is not certain. The change is not in the thalamus
- The speed at which changes have been found indicate fairly rapid changes in synaptic connections or in synaptic strength.
- It appears that new connections are either grown rapidly or that previously inactive connections become active.
- The latter hypothesis is called the "silent synapse" hypothesis. There is electrophysiological evidence that such inactive connections exist and can become active.
- The first hypothesis is very unlikely because new axons would have to grow over distances that are very unlikely in accounting for such rapid change.

Questions on chapter 34:

10) The important role of the hippocampus in the formation of now spatial or declarative memories has been made clear by effects of lesions. Where are the engrams underlying the long-term storage of these memories? Where are the cells that show an anatomical plasticity that is likely to be involved in the formation of such long-term memories?

Probably in parietal multi-sensory areas. Cells are probably the GABA-ergic interneurons of layers 2 and 3.

11) What are two major types of transcortical inputs to the prefrontal areas that shape the planning of movements in the immediate future?

From posterior neocortical multimodal areas; from limbic and paralimbic areas, e.g., the nearby cingulate cortex and the amygdala.

What is, anatomically, "plastic" in the normal mature neocortex?

- Suggestions by Cajal, Altman, and others: the small, short-axon interneurons change their connections in neocortex during learning. (*Cf* the hippocampus.)
- These neurons have been the most difficult to study with neuroanatomical methods, but recent genetic labeling methods are changing this.
- Evidence that many such short-axon neurons express GAP-43 in the adult mammal; in humans, levels are highest in association layers of multimodal association cortex.
- Visualization of dendrites of GABA-ergic interneurons in superficial layers of mouse neocortex shows rapid structural changes (Nedivi & collaborators at MIT).

Other brain regions where there is adult plasticity:

- Corpus striatum
  - Habit formation: Associative learning of the type studied in conditioning studies (procedural learning)
- Cerebellum
  - Motor learning of various types
- Hippocampal formation
  - Cells respond to specific places after time spent in a particular environment
- Short-term habituation & sensitization
  - Habituation in deep layers of the superior colliculus *via* presynaptic changes
  - Similar changes in other sensory regions
- Persistent electrical activity after excitation in prefrontal cortex and in superior colliculus: a likely basis for working memory.

Only in recent years have researchers been finding that changes in synaptic strength during learning are often accompanied by anatomical changes.

The learning and memory capacity of the neocortex and closely connected forebrain structures is certainly a great marvel. **However, do not conclude that everything is so plastic. Remember**:

- The major patterns and organization of CNS pathways and connections are inherited.
- They have resulted from a very long period of evolution and from genetically directed development.
- Everything is not connected to everything else!
- Connections matter. They determine function.

Conclusions about the neocortex:

Its evolution added **high acuity** to visual and somatosensory perception and sophisticated discrimination of temporally patterned inputs in audition. This perceptual ability controlled movements *via* various outputs:

--Orienting *via* midbrain tectum and connected structures
--Approach & avoidance *via* corpus striatum, amygdala, locomotor areas

It also added **better information on spatial locations of the organism** in the environment *via* connections to the hippocampal formation.

The roles of learning became greatly expanded with the evolution of reward pathways and plasticity in various forebrain connections.

The **evolution of motor cortex** added precision in control of movements, and **led to the evolution of anticipatory movements and planning** in the frontal lobe.

Conclusions about the neocortex, continued:

In posterior parts of the hemisphere, memory functions led to abilities to anticipate sensory inputs rather than just responding to their occurence.

Transcortical connections evolved, and some of these connected the anticipatory and planning activities of the frontal lobe with the predictive activities of the sensory systems of the parietal and temporal lobes.

The concluding slides summarize this view of the greatest innovations of the neocortex, and mention some of the greatest challenges for future research. (I'm sure that there are many more.)

The greatest innovations of the neocortex, and some of the greatest challenges for future research

- Posterior (postcentral) portions of the hemisphere
  - High-resolution sensory information relayed to structures generating innate and learned habits
  - Object perception with anticipation of inputs in the immediate future.
    - How are temporal patterns in auditory and somatosensory objects analysed and integrated?
    - How do the objects represented in multiple modalities form single objects? (What binds them together?)
  - Space sense with memory of locations in the environment
    - How are entire scenes represented?
    - How are representations of many different local environments retained and activated when needed?
  - Together, these abilities generate images that constitute an internal model used in the planning of actions.
    - These images include temporally patterned activity. How do cortical circuits represent the temporal patterns?

Neocortical innovations and challenges, continued:

- Anterior (frontal, precentral) portions of the hemisphere
  - High-resolution movement generation *via* direct projections to brainstem and spinal cord
  - Generation of organized movement patterns that fit the images represented in the more caudal hemisphere
    - These patterns include temporal patterns. How do cortical circuits represent the temporal patterns?
  - Planning of movements in the immediate future, with choices influenced by two kinds of connections:
    - Connections from posterior hemisphere carrying predictive coding of anticipated sensory inputs.
    - Connections with paralimbic cortex with information about motivational state
  - Planning of actions to occur in the more distant future:
    - The planning of actions includes generation of broad temporal patterns: How do cortical circuits generate these patterns?

Neocortical innovations and challenges, continued:

- Brain state changes can alter the processes of both posterior and anterior portions of neocortex.
  - How do brain state changes alter the representations of plans or cause shifts in priorities?
  - Brain state changes must also alter the activation of specific images and movements (*i.e.*, remembered objects and learned movements).
- These alterations are not well studied.

The study of brain structure and its origins lays the groundwork for understanding the mechanisms underlying behavior and mental abilities.

The field of neuroscience has scarcely begun to explore some of the abilities just reviewed. Some of you, I hope, will be doing further exploration in this area.

As you proceed, remember the dictum of von Gudden: “First anatomy, then physiology. But if first physiology, then not without anatomy!”

(“Physiology” is to be understood broadly, to include all studies of function.)