

Introduction to Neuroscience: Systems Neuroscience

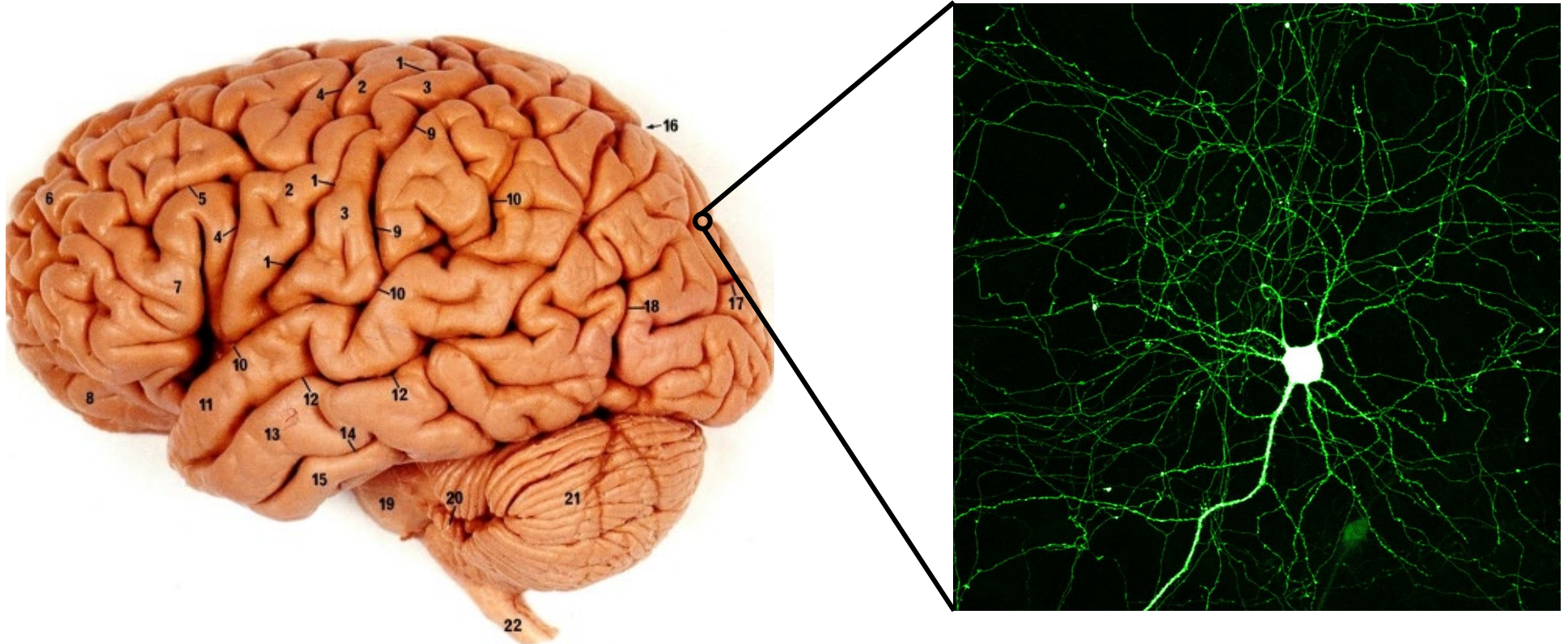
Lecture #1

Nachum Ulanovsky, Rony Paz, Michal Rivlin, Rafi Malach, Noam Sobel,
Ilan Lampl, Ehud Ahissar, Shabtai Barash, Yadin Dudai, Takashi
Kawashima, Ofer Yizhar

Weizmann Institute of Science

2022-2023, 1st semester

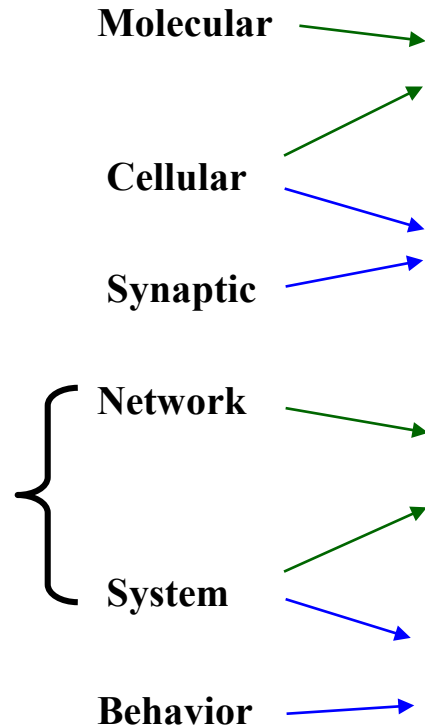
The brain underlies everything that makes us Human – it's the hub of our sensations, memories, emotions, behaviors, consciousness...



The current course will focus on the function of networks and systems in the brain.

Core courses in Brain Sciences at the Weizmann Institute

Levels of Analysis of the Nervous System



Four Core Courses in Neuroscience

**Introduction to Neuroscience:
Molecular Neuroscience - Genes to Behavior**

**Introduction to Neuroscience:
Cellular and Synaptic Physiology**

**Introduction to Neuroscience:
Systems Neuroscience**

**Introduction to Neuroscience:
Behavioral Neuroscience**

Course syllabus (by week)

1. Overview of brain systems and general principles of their functional organization: From cortical maps and subcortical loops to the micro-structure of brain circuits and their interconnections. (**Ulanovsky**)
2. Moving: Movement generation — Peripheral and central processes. (**Paz**)
3. Seeing: Peripheral visual processes. (**Rivlin**)
4. Seeing: Central visual processes. (**Malach**)
5. Smelling: Peripheral and central processes. (**Sobel**)
6. Hearing (and balance): Peripheral and central processes. (**Ulanovsky**)
7. Mechanisms of stimulus feature selectivity in sensory systems. (**Lampl**)

Course syllabus (by week)

8. Touching: Peripheral and central processes. (**Ahissar**)
9. Active sensing: Closing motor-sensory loops. (**Ahissar**)
10. Looking and seeing: Mind-body interactions between periphery, brainstem and cortex. (**Barash**)
11. Remembering: Overview of memory systems. (**Dudai**)
12. Learning: Basal ganglia. (**Rivlin**)
13. Integrating: The hippocampus in spatial navigation and memory consolidation. (**Ulanovsky**)
14. Modulating: Neuromodulatory systems of the brain. (**Kawashima**)
15. Integrating: The prefrontal cortex. (**Yizhar**)

Formalities

- **Course Website** (*will include ALL the presentations and updated lecture dates*):
www.weizmann.ac.il/brain-sciences/labs/ulanovsky/courses
Or: Google "Nachum Ulanovsky" → go to "Courses" tab.
- **Grading:** Final exam - Open material.
- **Bibliography:**
 - Purves *et al.*, Neuroscience, 6rd edition (2017).
 - Kandel *et al.*, Principles of Neural Science, 6th edition (2021).
- **Book Chapters to read:** Will be posted on course website before each lecture. Some of these chapters are **compulsory** for the exam (indicated near them). Other chapters are not for the exam – but we DO expect you to read them, especially those of you who don't have any background in Neuroscience!
- **Level of course:** Each lecture: Starting basic → Going advanced.

Formalities

- For questions about the course, feel free to contact me anytime at:

Nachum Ulanovsky (*coordinator of this course*)

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Email: nachum.ulanovsky@weizmann.ac.il

Outline of today's Introductory lecture

- Basic overview of neurons and synapses
- Getting oriented in the brain
- Functional organization of the brain
- Methodologies used in Systems Neuroscience: Brief Overview
- Basic functional properties of neurons, circuits, and systems

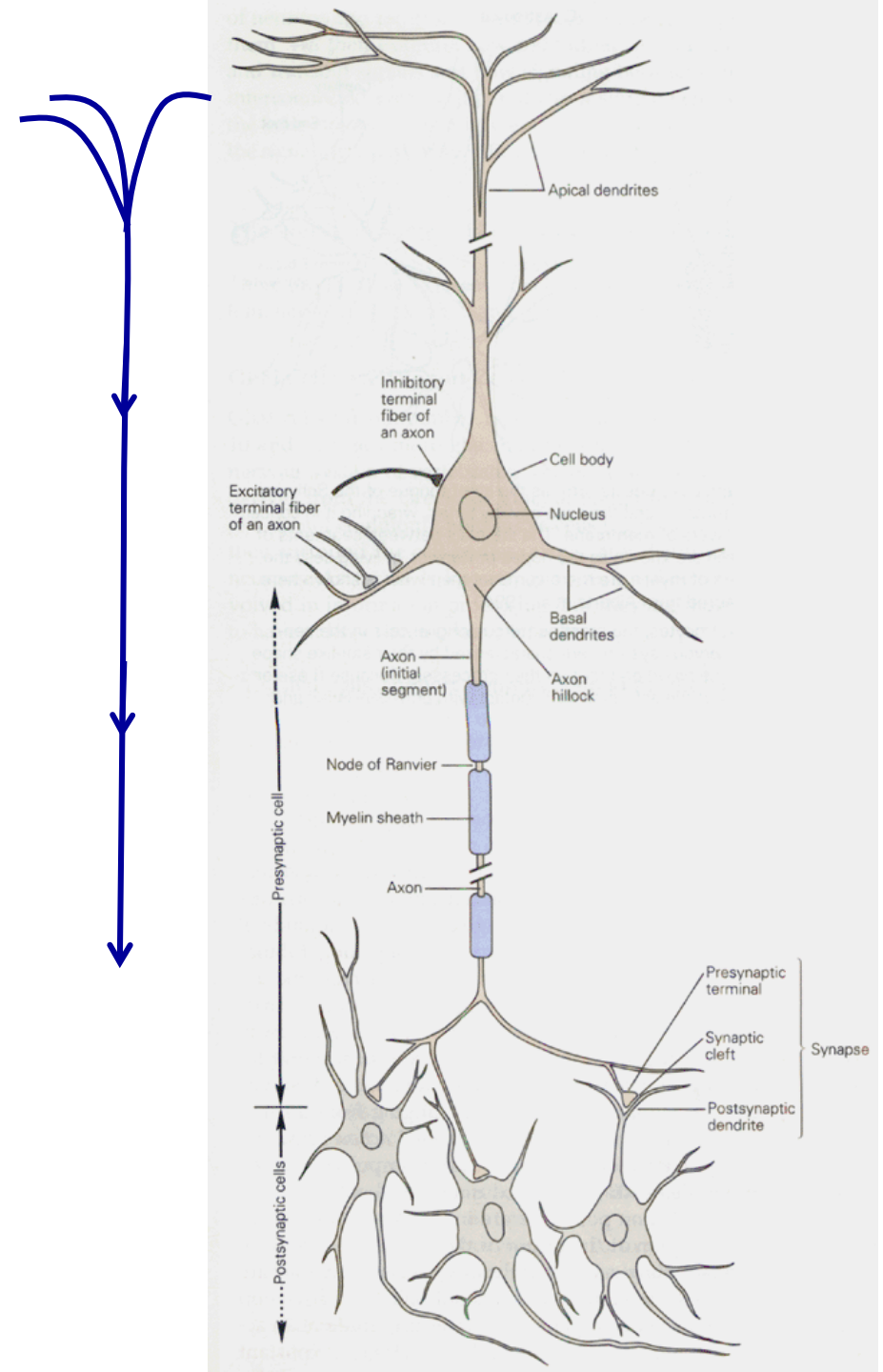
Today's lecture provides an introduction to subsequent lectures.

Outline of today's Introductory lecture

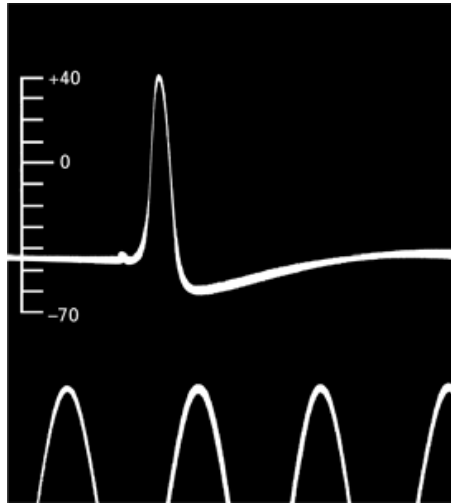
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The neuron (nerve cell)

To a first approximation,
electrical signals flow in neurons
in a uni-directional fashion:
dendrites → soma → axon.



Neurons communicate with action potentials (spikes) *(with some exceptions in invertebrate brains)*

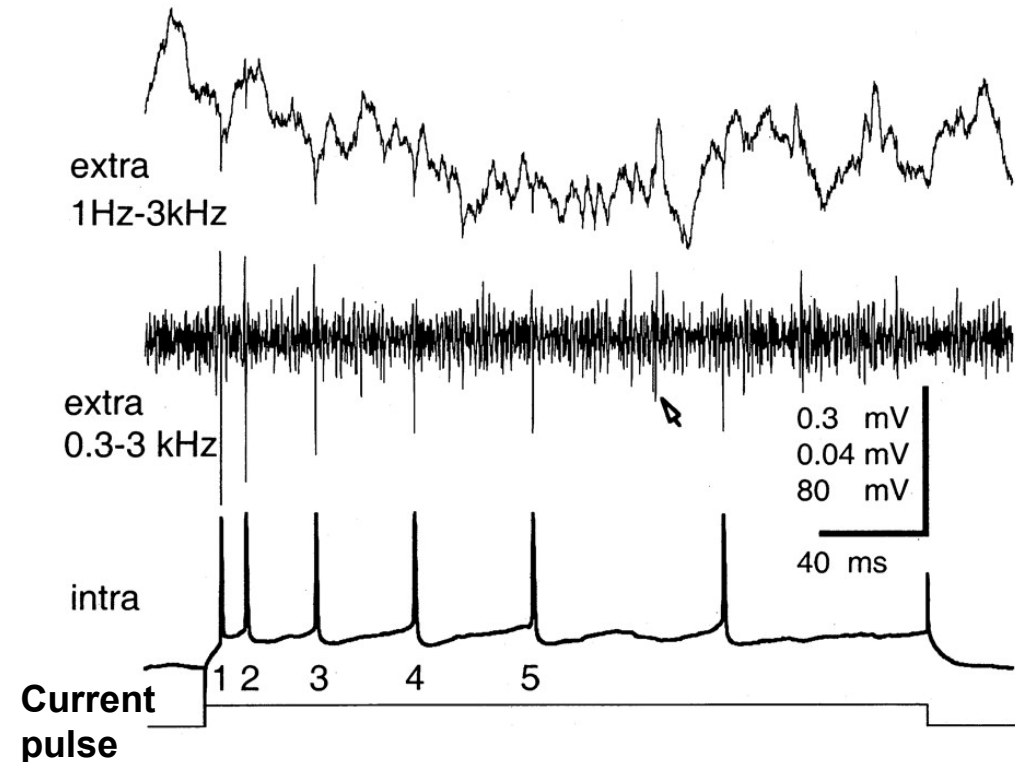


First published action potential (Hodgkin & Huxley 1939)

500 Hz sine wave (time marker)

Some basic terms:

- Action potential (spike)
- Resting membrane potential
- Depolarization
- Hyperpolarization
- Intracellular recordings vs. Extracellular recordings

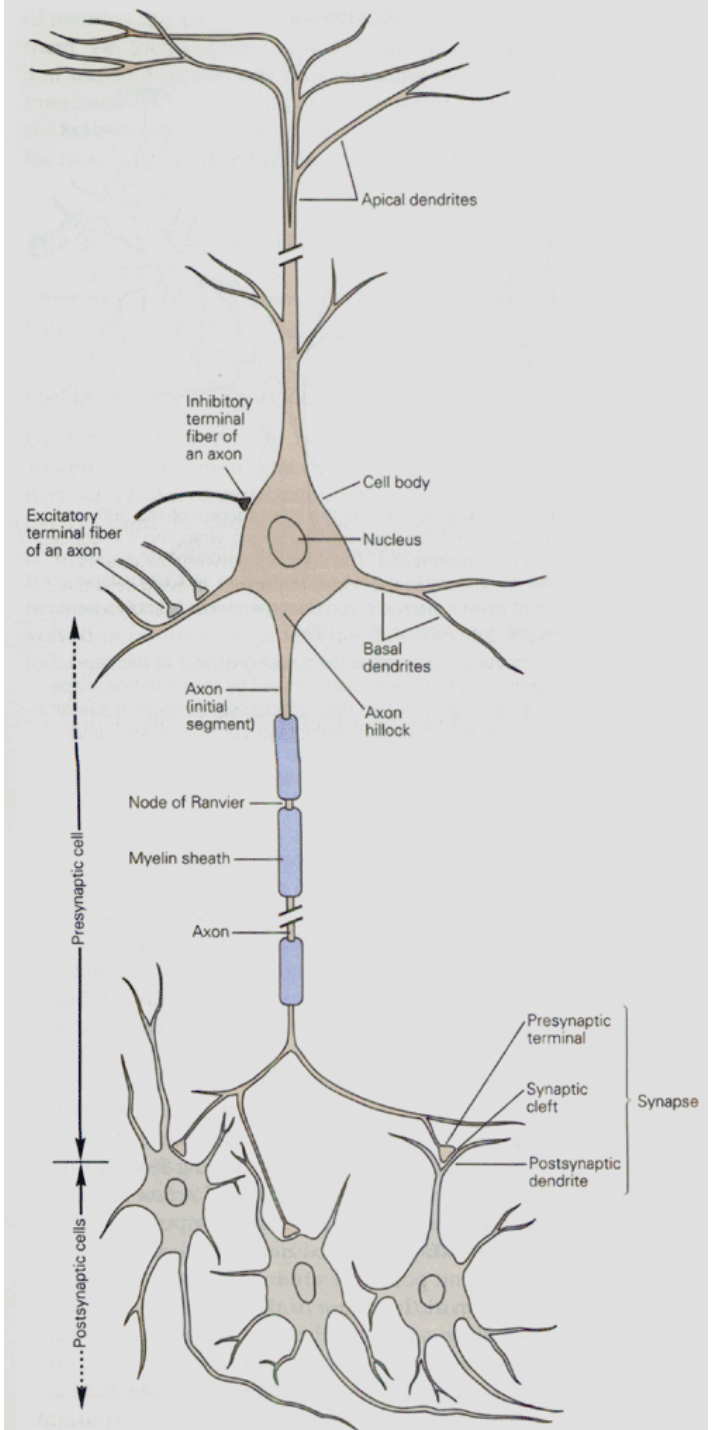


Henze et al. (2000)

The structure of a neuron

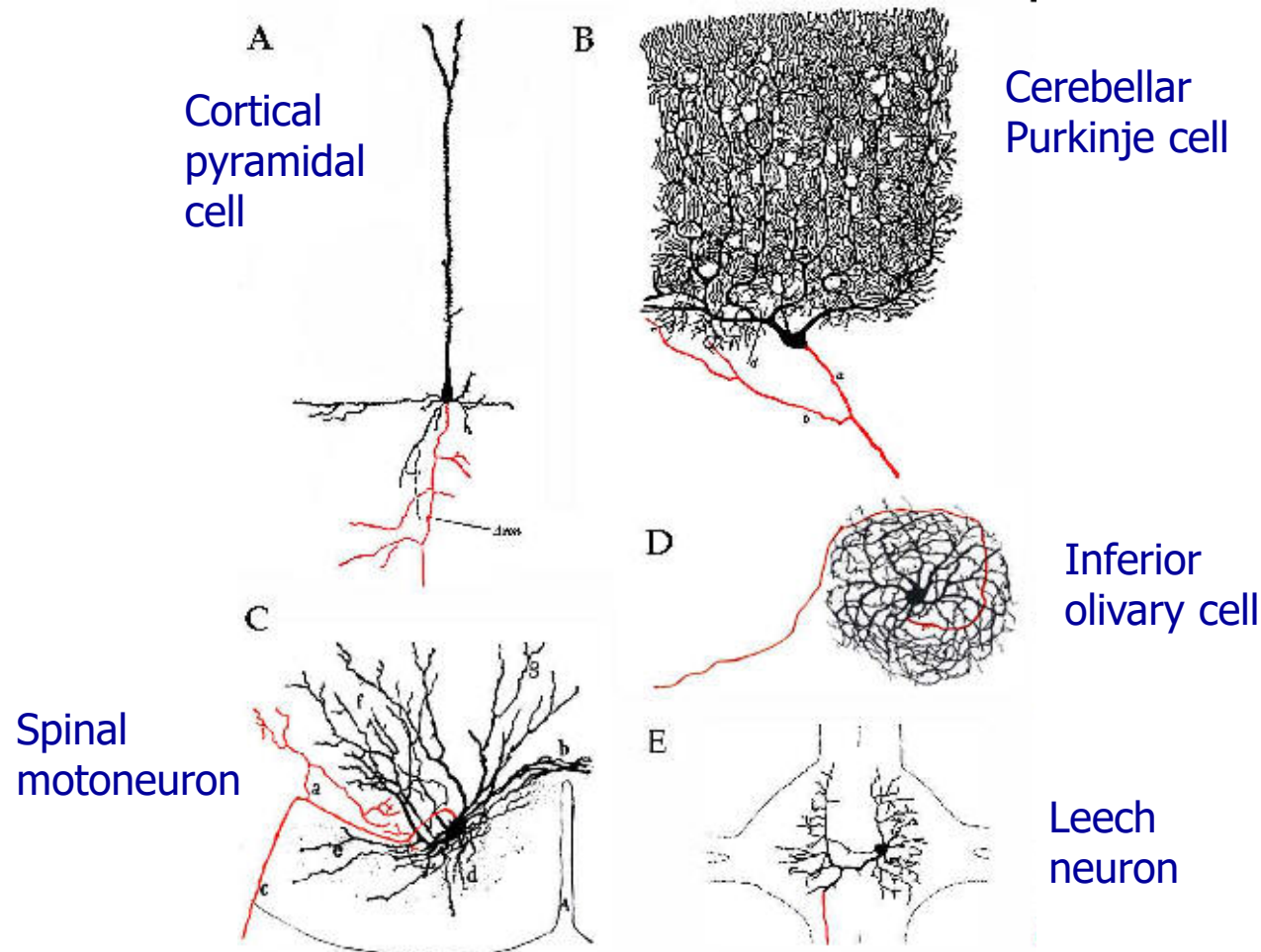
Some basic terms:

- Membrane
- Cell body (soma)
- Dendrite
- Dendritic tree
- Axon
- Synapse
- Anterograde, Retrograde

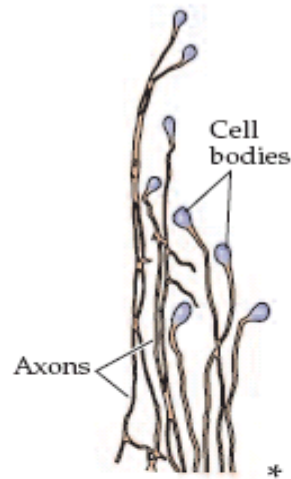


Neurons come in different shapes and sizes.

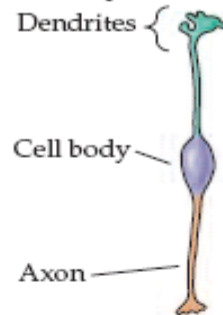
Heterogeneity of neuronal morphology is likely related to the different functions of different neurons.



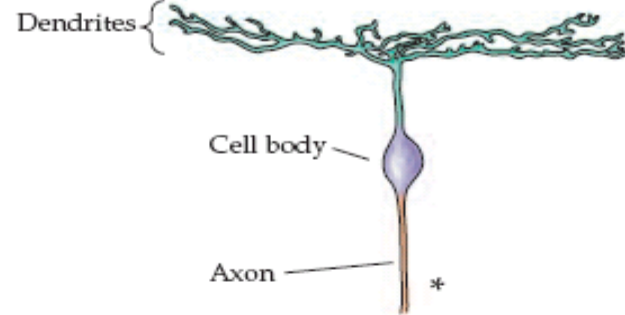
(A) Neurons in mesencephalic nucleus of cranial nerve V



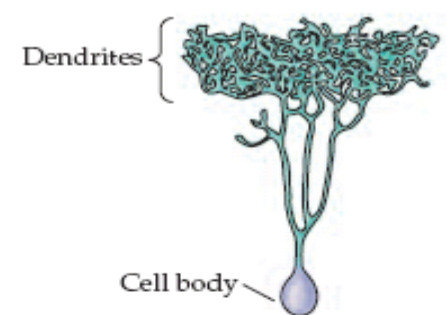
(B) Retinal bipolar cell



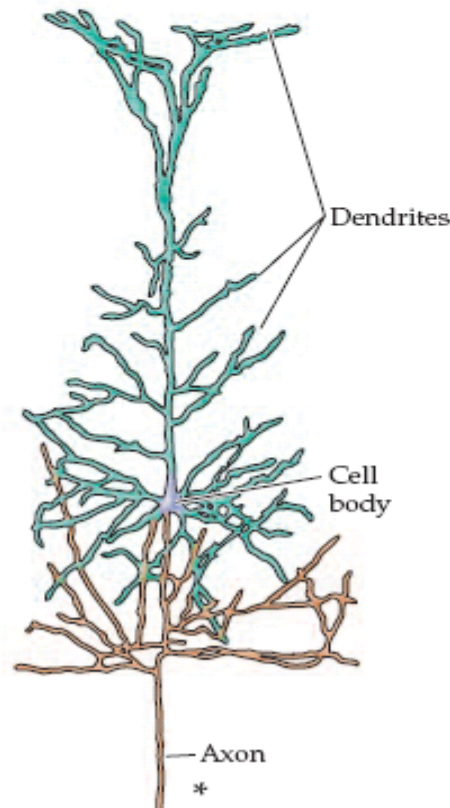
(C) Retinal ganglion cell



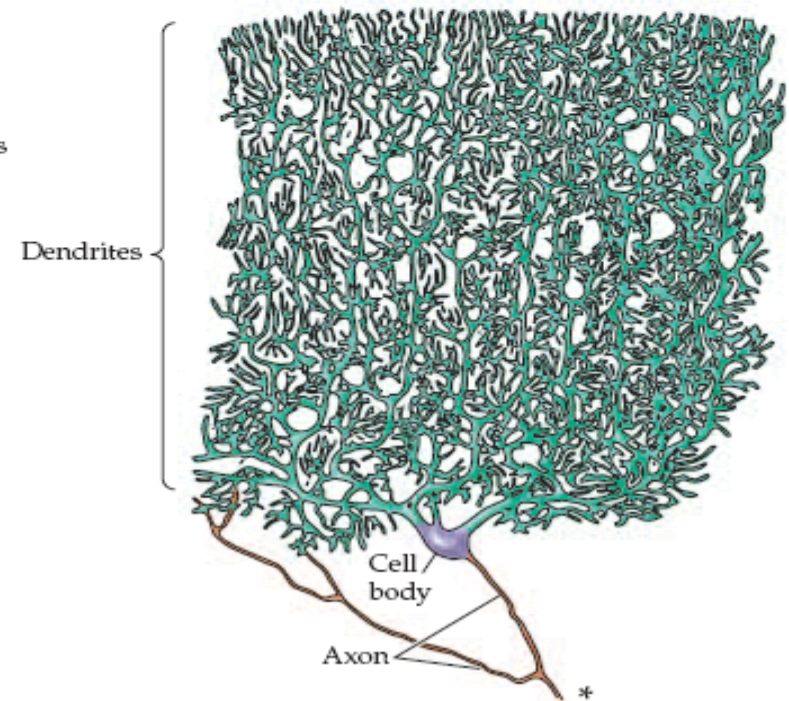
(D) Retinal amacrine cell



(E) Cortical pyramidal cell



(F) Cerebellar Purkinje cells



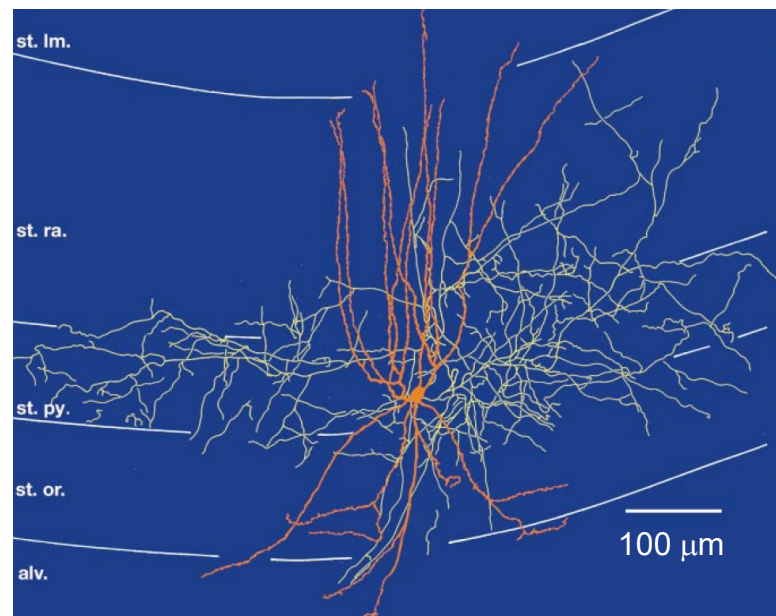
Some basic terms:

- Pyramidal cell
- Purkinje cell
- Bipolar cell
- Axon collateral
- Autapse (auto-synapse)

Some basic terms:

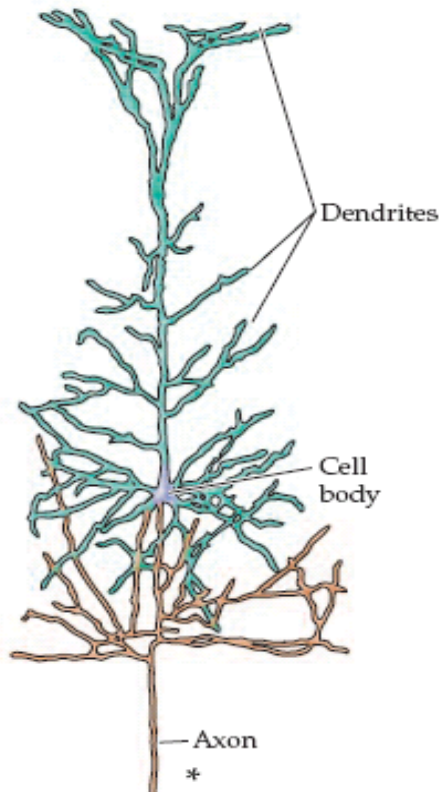
- Projection neuron (principal cell) – sends a long-range axon outside the local brain area (e.g., cortical and hippocampal pyramidal cells; cerebellar Purkinje cells, ...)
- Interneuron – a neuron that sends only *local* axons, i.e. does not project out of the local brain area (many many types of interneurons are known; usually inhibitory).

Caveat: Some interneurons do project long distances – locally, or even to other brain regions !

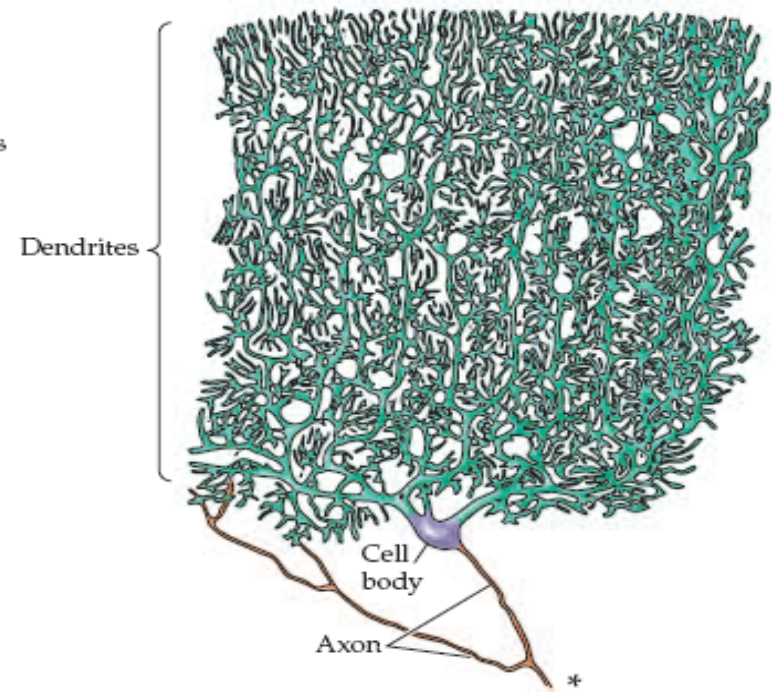


Hippocampal CA1 basket cell, showing soma & dendrites (red), axon (yellow) (Klausberger et al., *Nature* 2003)

(E) Cortical pyramidal cell



(F) Cerebellar Purkinje cells



Glia (glial cells, neuroglia)

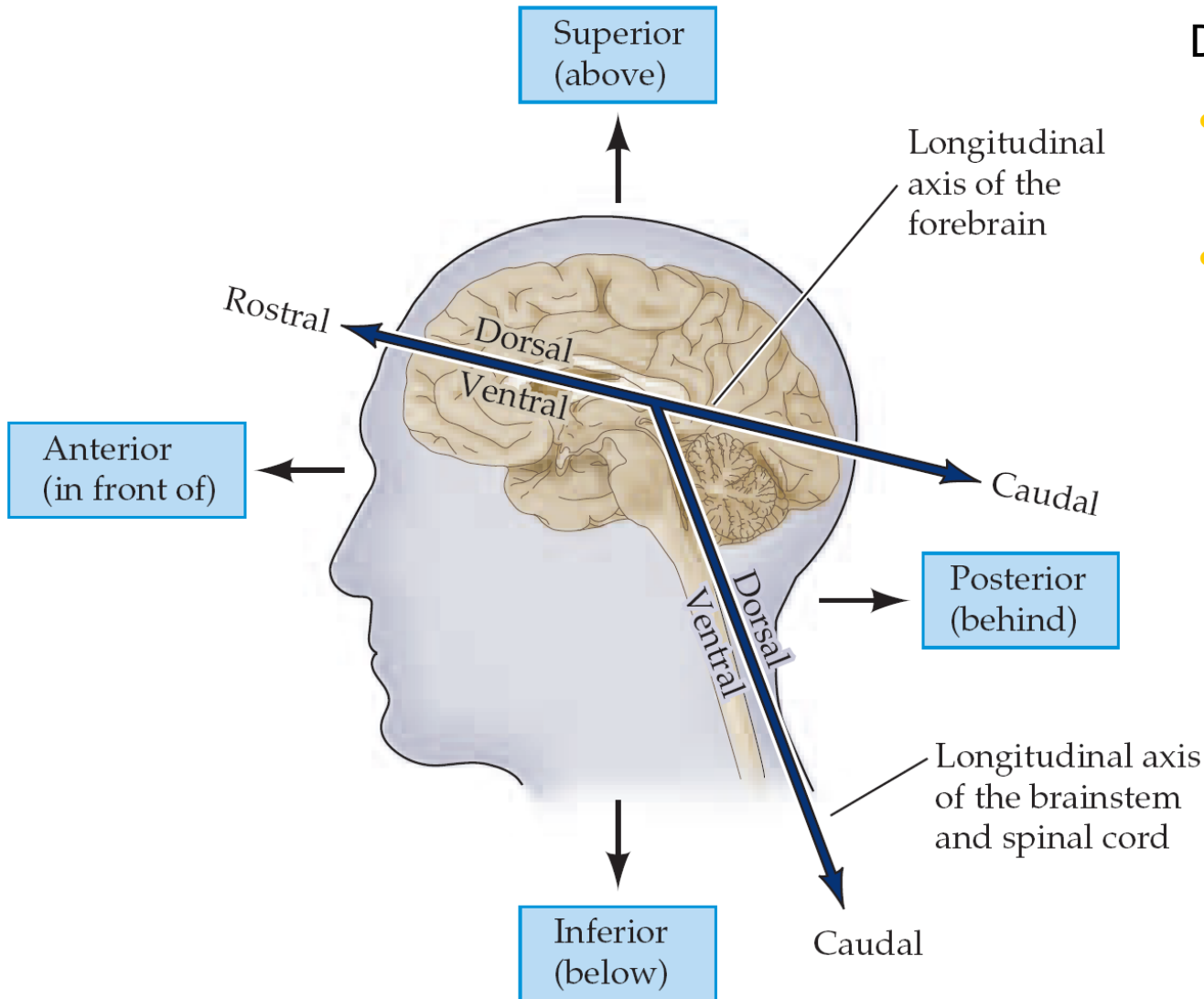
- **Microglia:** immune system cells in the CNS (central nervous system)
- **Macroglia:**
 - **Oligodendrocytes** (in CNS) and **Schwann cells** (in PNS) form the *Myelin Sheath* (insulation of axons) → faster action potential propagation
 - **Astrocytes** – (1) bring nutrients to neurons, (2) form the BBB (blood-brain barrier), (3) maintain extracellular potassium (K^+) concentration, (4) uptake neurotransmitters.
 - A few other types of macroglia.
- Recent years provide increasing evidence that glia can directly modulate the function of neurons.

Glia are discussed in a few other courses. In this course we will discuss only the function of neurons.

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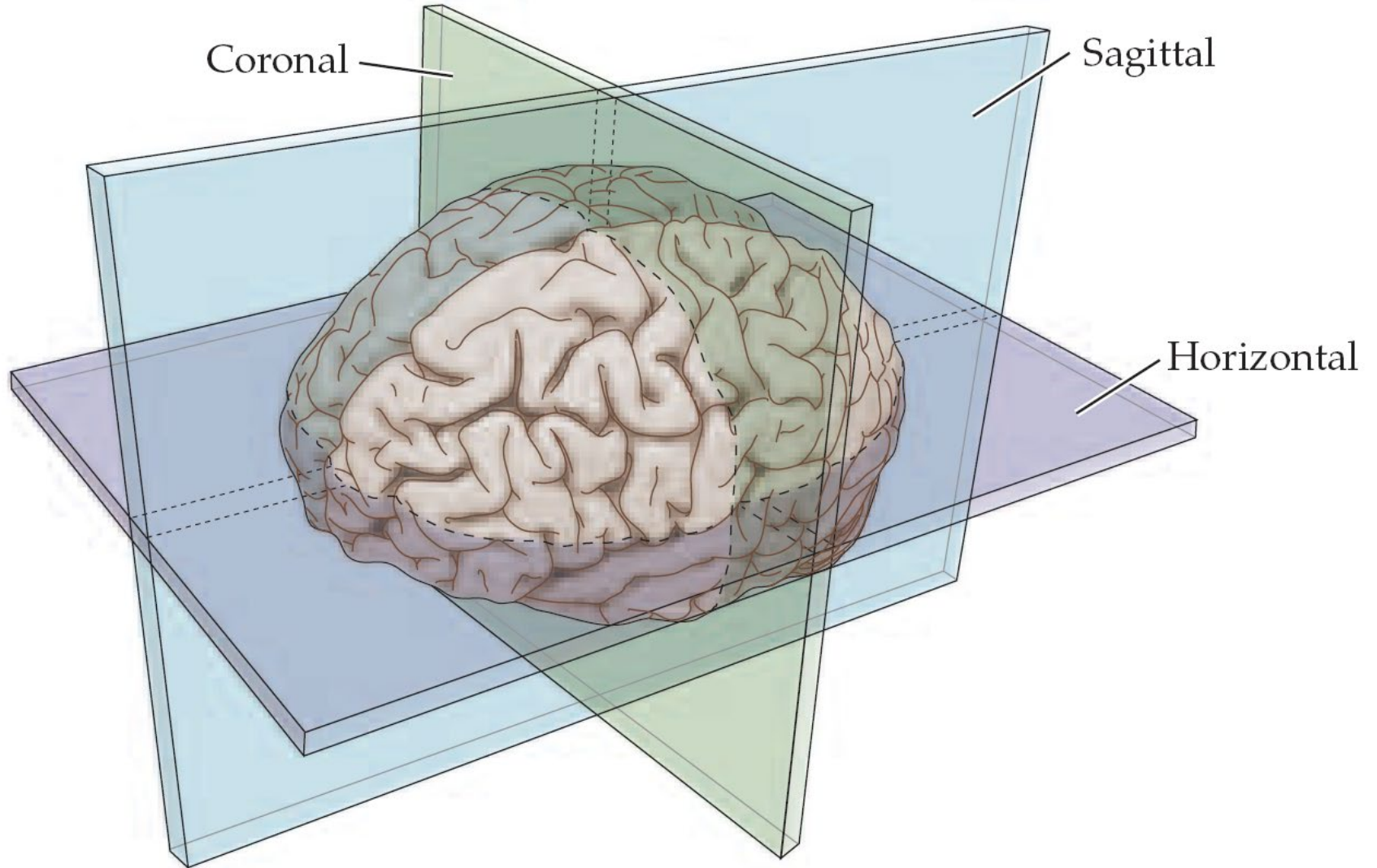
Getting oriented in the brain – directions



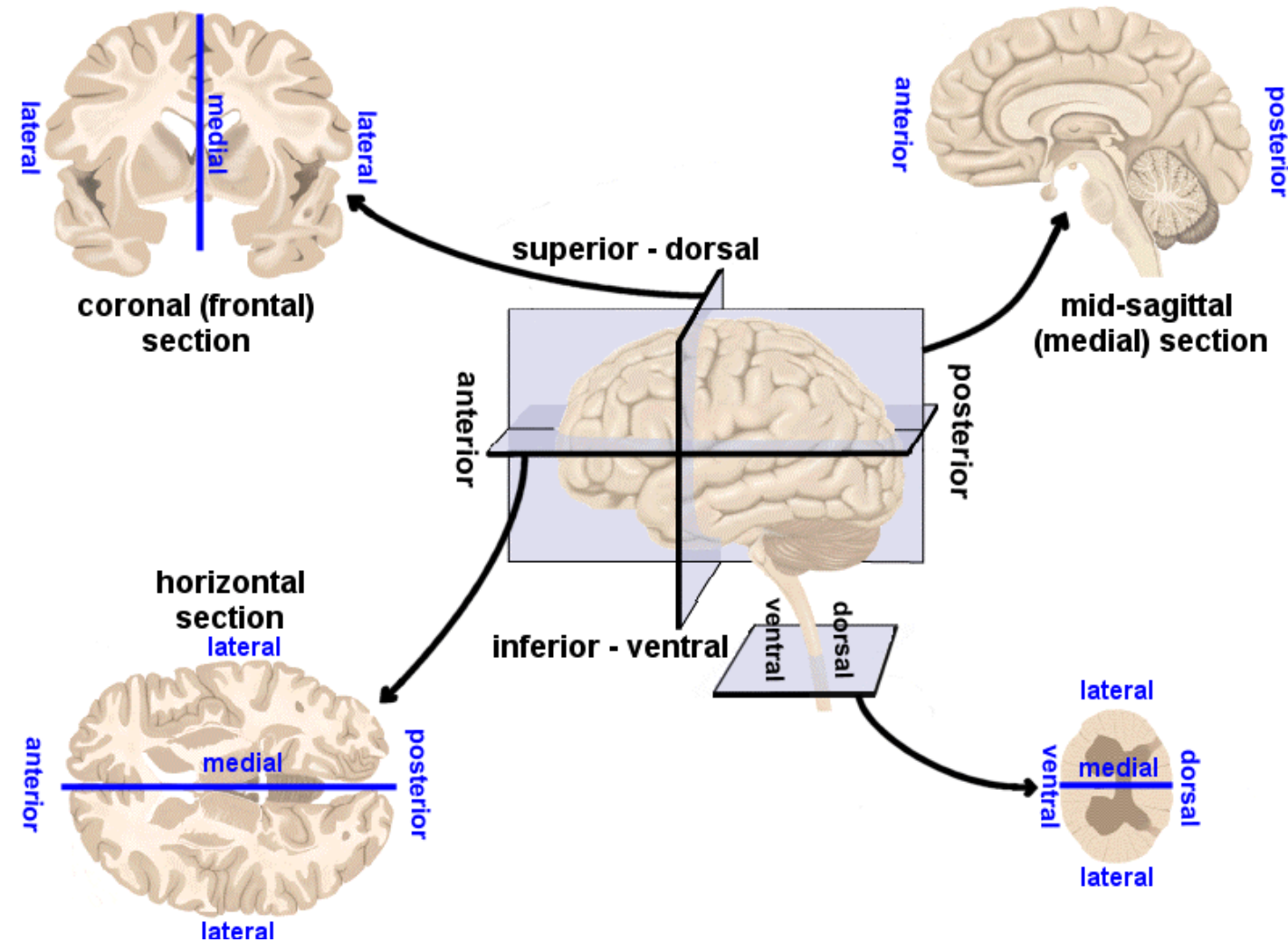
Directions in the brain:

- Anterior/Posterior/Superior/Inferior – *absolute* directions
- Rostral/Caudal/Dorsal/Ventral – directions *relative* to the long axis of the brain/spinal cord

Getting oriented in the brain – planes of section



Getting oriented in the brain



Directions in the brain:

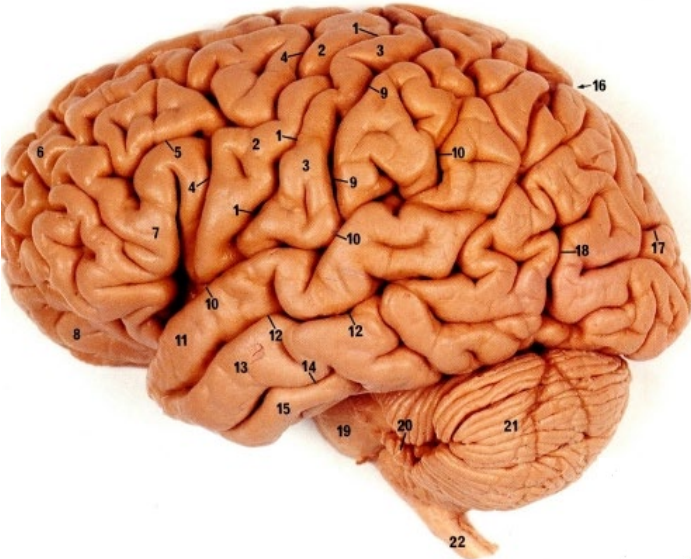
- Dorsal/Ventral
- Lateral/Medial
- Anterior/Posterior
- Rostral/Caudal
- "dlPFC" vs. "vmPFC"

These topics are expanded in the courses "Neuroanatomy" and "Neuroanatomy laboratory" (every year)

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The vertebrate brain



Beaver brain



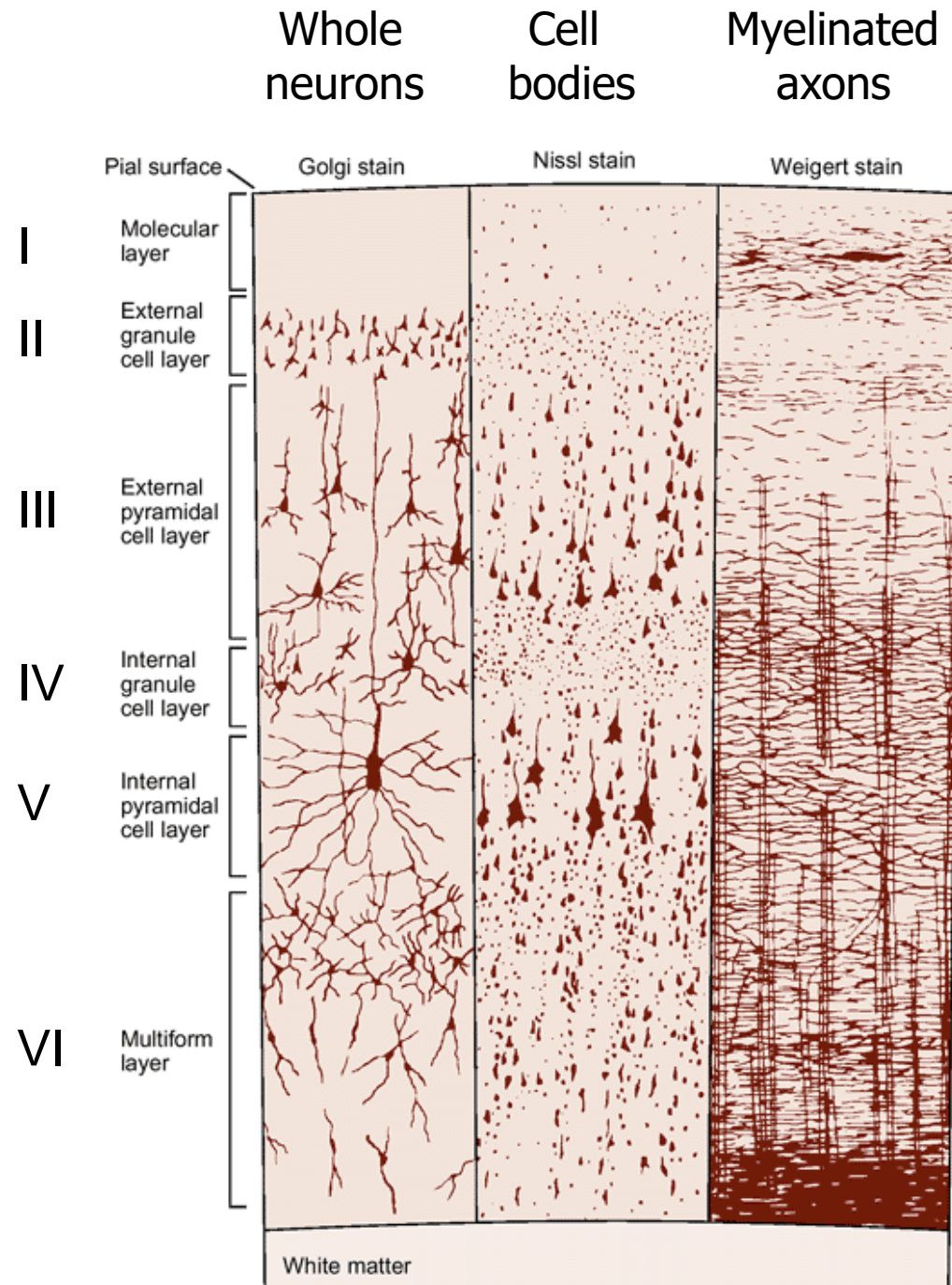
Some basic terms:

- Cortex (*6-layer cortex: only in mammals*)
- Gray matter / white matter
- Sulcus, Gyrus
- Corpus callosum
- Hippocampus
- Cerebellum
- Nucleus

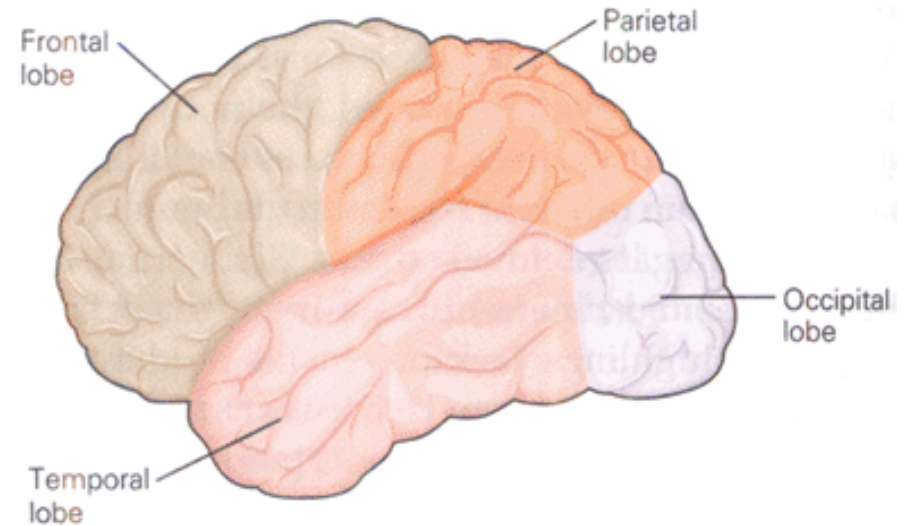
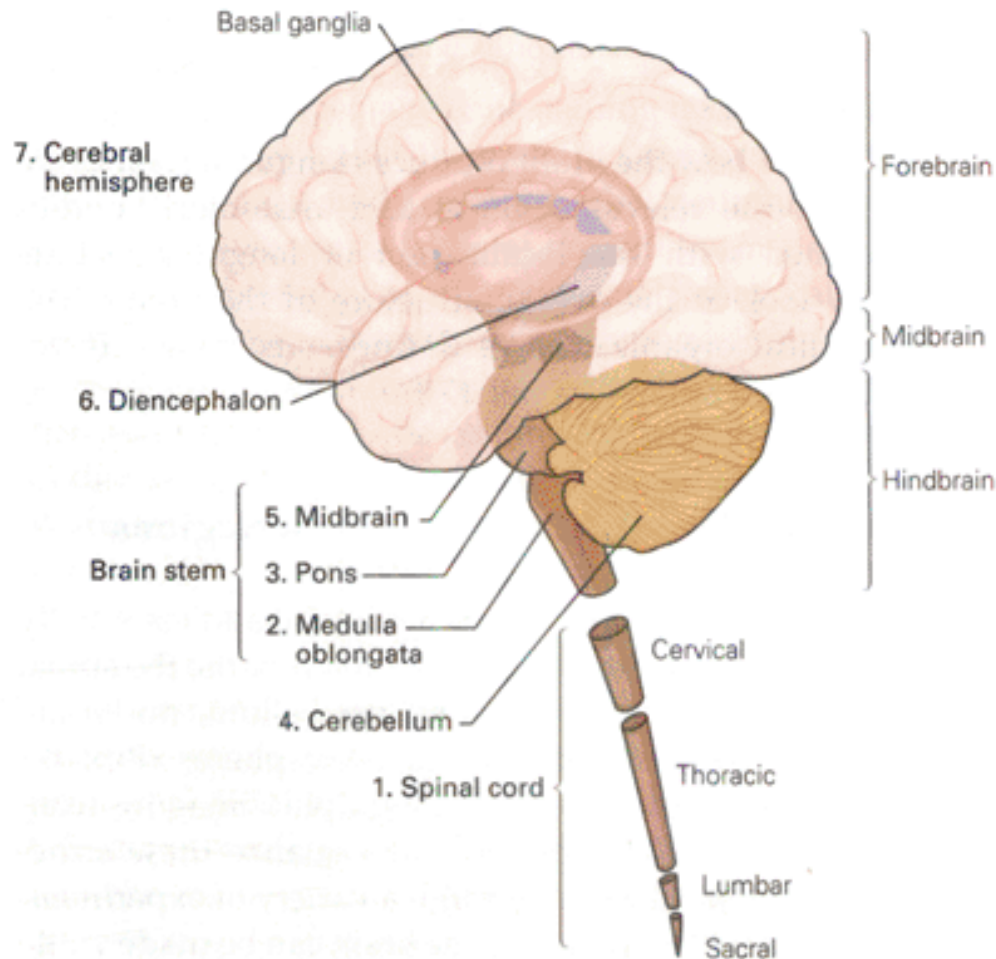
*These topics are expanded in the course
“Neuroanatomy” (every year)*

The cerebral cortex is organized in layers. Typically 6 layers.

- Input/output of the cerebral cortex is layer-specific.
- Functional properties of individual neurons are sometimes also layer-specific.

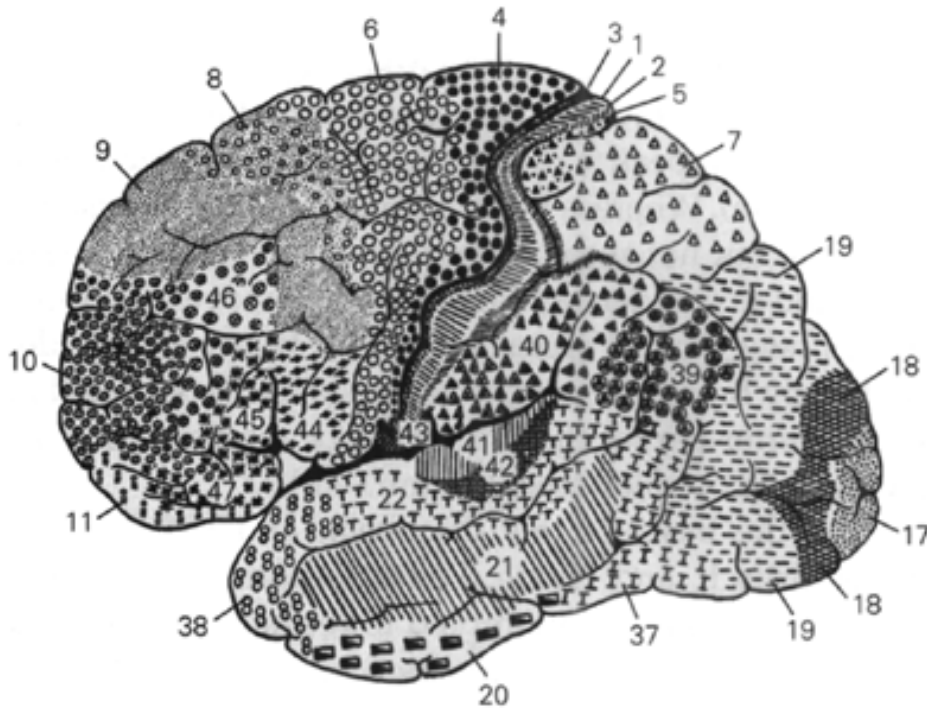


Brain areas differ in structure

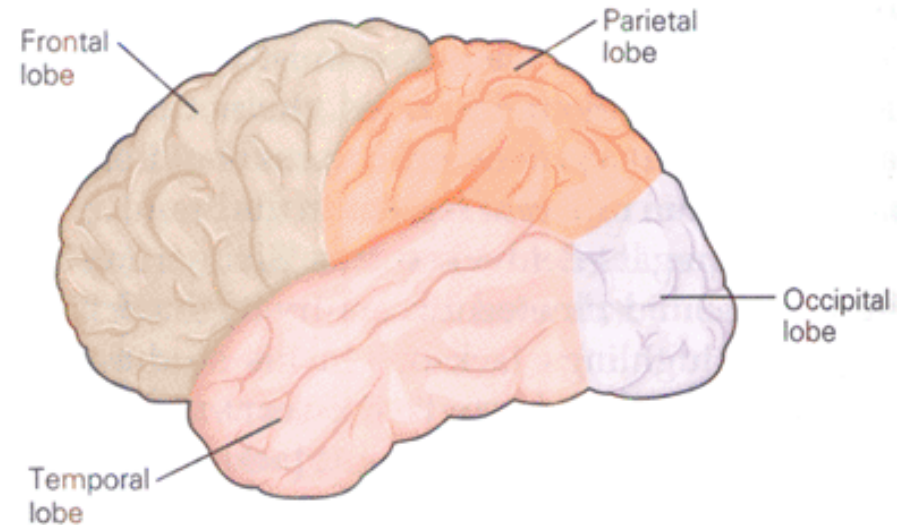


The cerebral cortex can be divided into 4 lobes (division is based on *structure*): Occipital, Parietal, Temporal, and Frontal lobe

Brain areas differ in structure

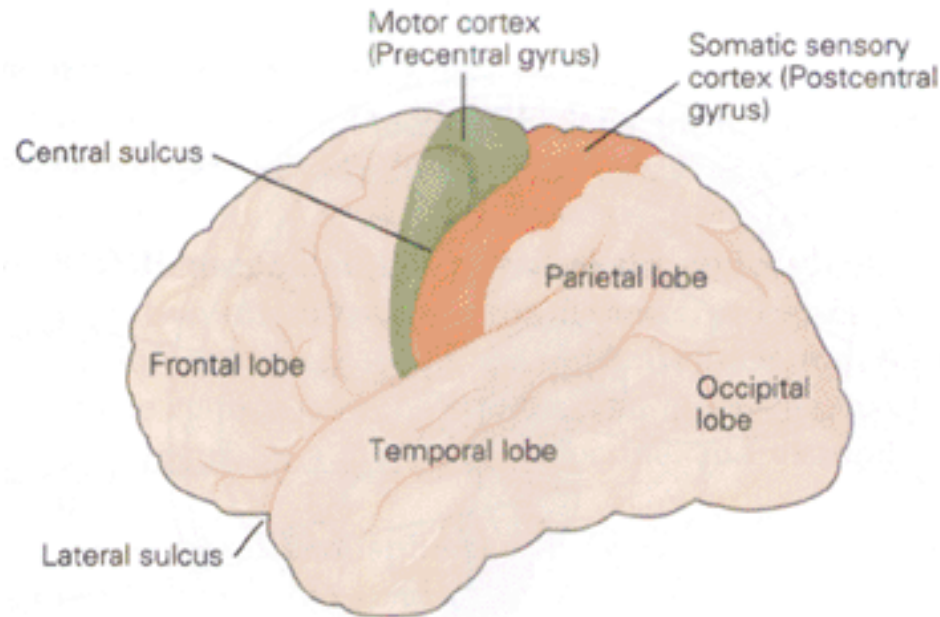


The cerebral cortex can be further divided into many areas, based on structure: Here shown are the 52 areas of Brodmann (1909).

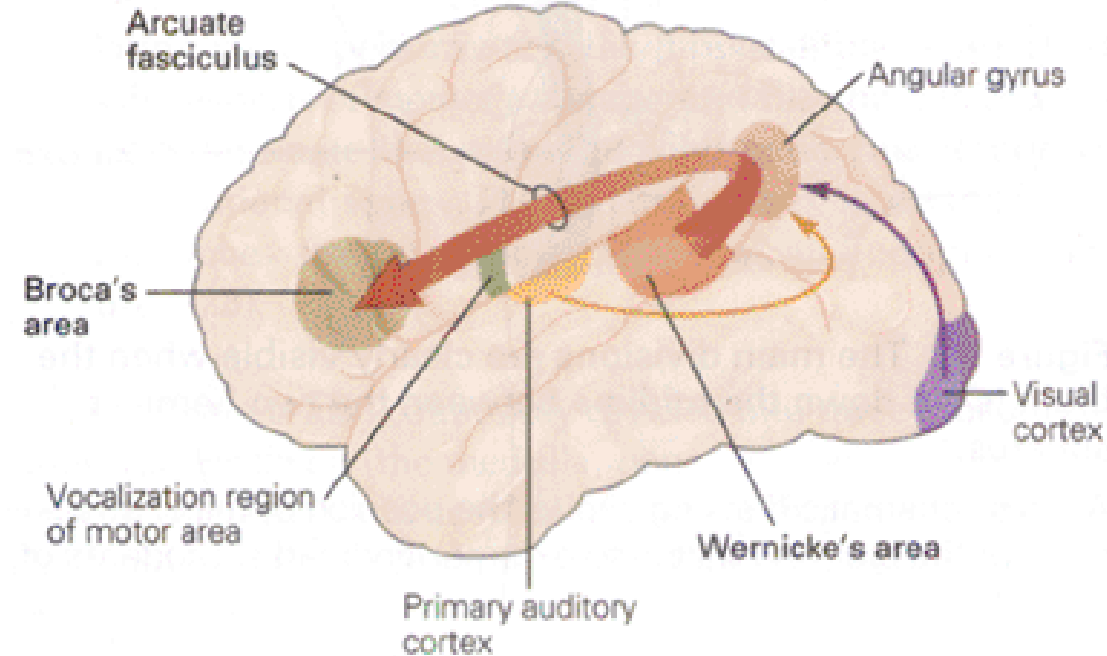


The cerebral cortex can be divided into 4 lobes (division is based on *structure*): Occipital, Parietal, Temporal, and Frontal lobe

Brain areas differ in structure – and have different functions



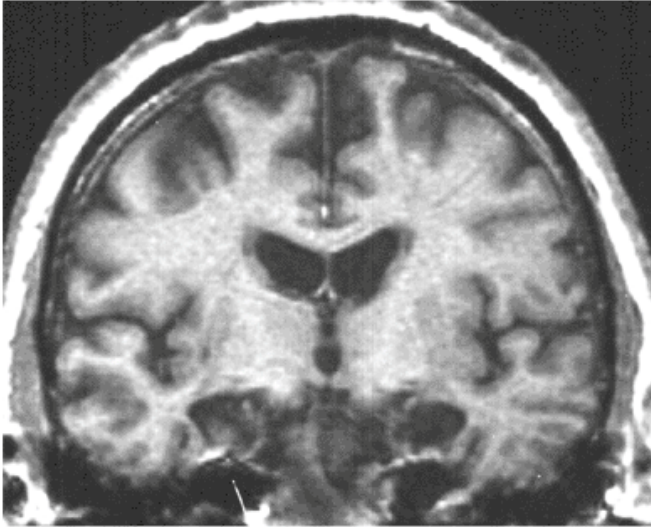
Motor cortex and somatosensory cortex are located on different gyri, and are separated by the central sulcus



Language-related areas

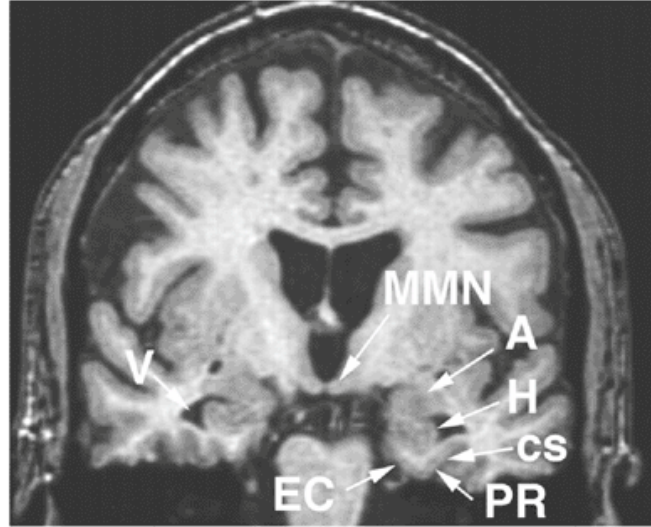
Brain areas differ in structure – and have different functions

B₁ H.M.



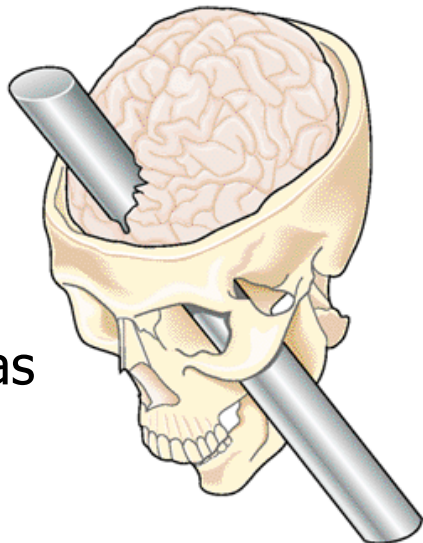
Patient H.M.

B₂ Control



Control brain

c



Phineas
Gage

Function of a brain area can be (partially) revealed by lesions:

- A rod that passed through the frontal lobes in Phineas Gage caused major personality changes – but memory was not affected.
- Bilateral removal of the hippocampus and surrounding areas in patient H.M. (Henry Molaison) has led to severe anterograde amnesia (inability to remember new events/facts).
- World Wars and advances in Neuroscience.

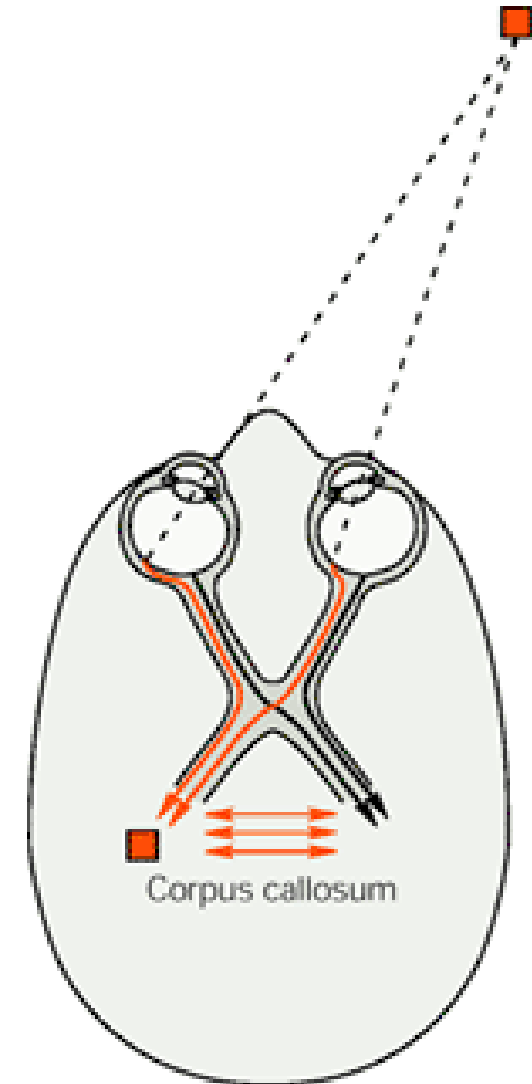
Functional systems on one side of the brain control the other side of the body

For example: Left Motor Cortex controls the right part of the body, while Right Motor Cortex controls the left part of the body.

Sensory areas of the brain are also primarily *contralateral*.

TWO COMMENTS:

- * Symmetric brain areas in both hemispheres are interconnected via the **corpus callosum** and additional **commisures**: Thus, under normal conditions, information reaches *both* sides of the brain.
- * In split-brain patients, Roger Sperry described asymmetries in some high cognitive tasks (language – left hemisphere, visuospatial – right hemisphere).

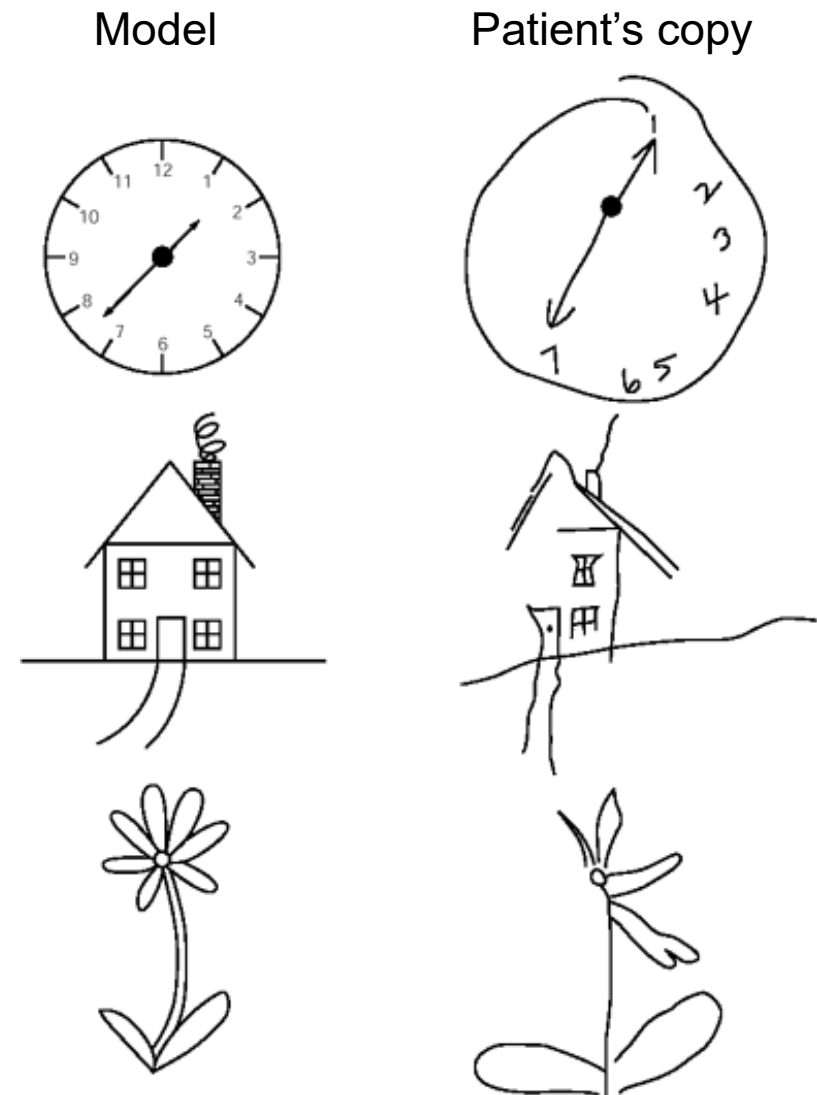


Functional systems on one side of the brain control the other side of the body

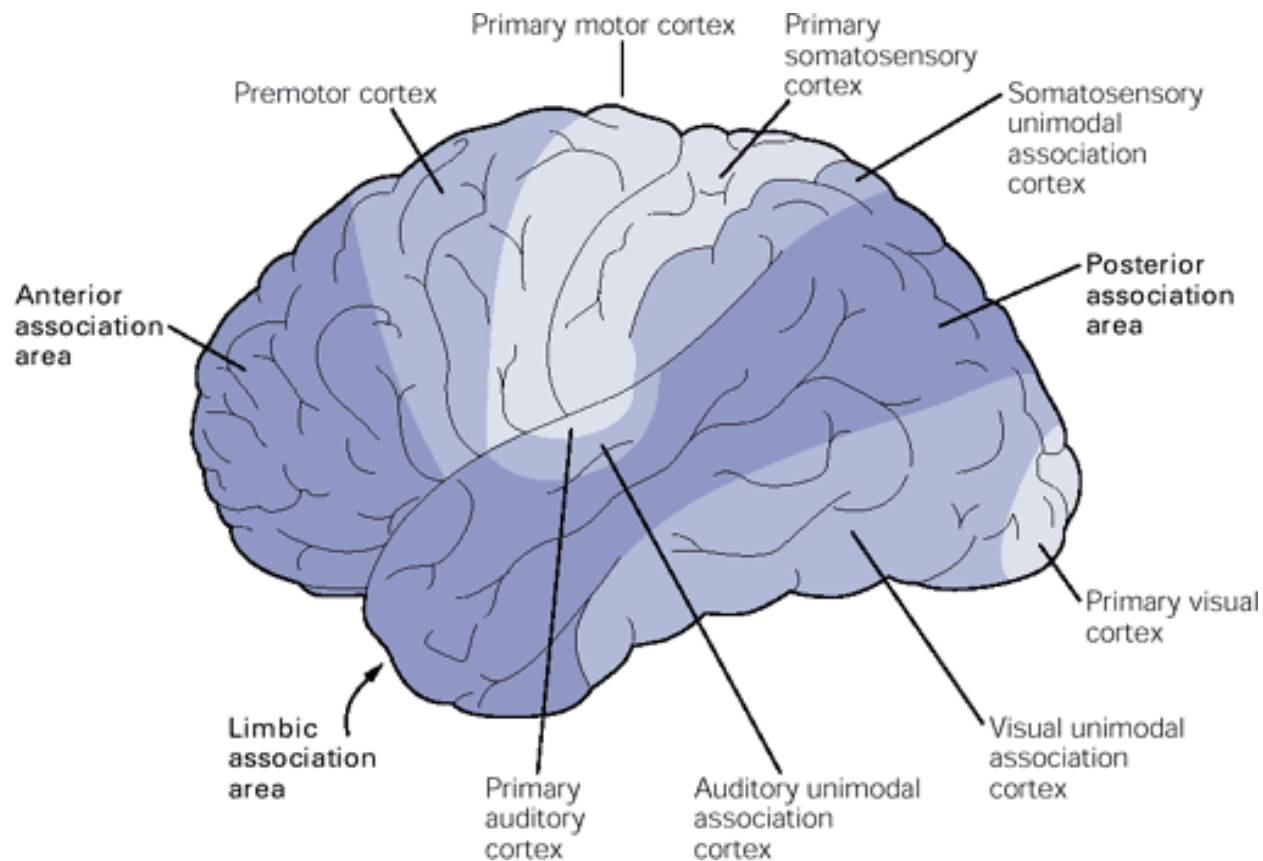
The principle of contralateral control holds also for some higher brain areas:
For example, attempt to copy the model drawing revealed severe unilateral neglect, in a patient with lesions in the *right* posterior parietal cortex.

* Similar results for *imagining* (experiment on Duomo square in Milano).

- Function is specific to brain areas and also to hemisphere.
- Asymmetry: Unilateral neglect primarily follows right-hemispheric lesions.



The cerebral cortex is often schematically sub-divided to:
(1) Sensory areas, (2) Motor areas, (3) Association areas

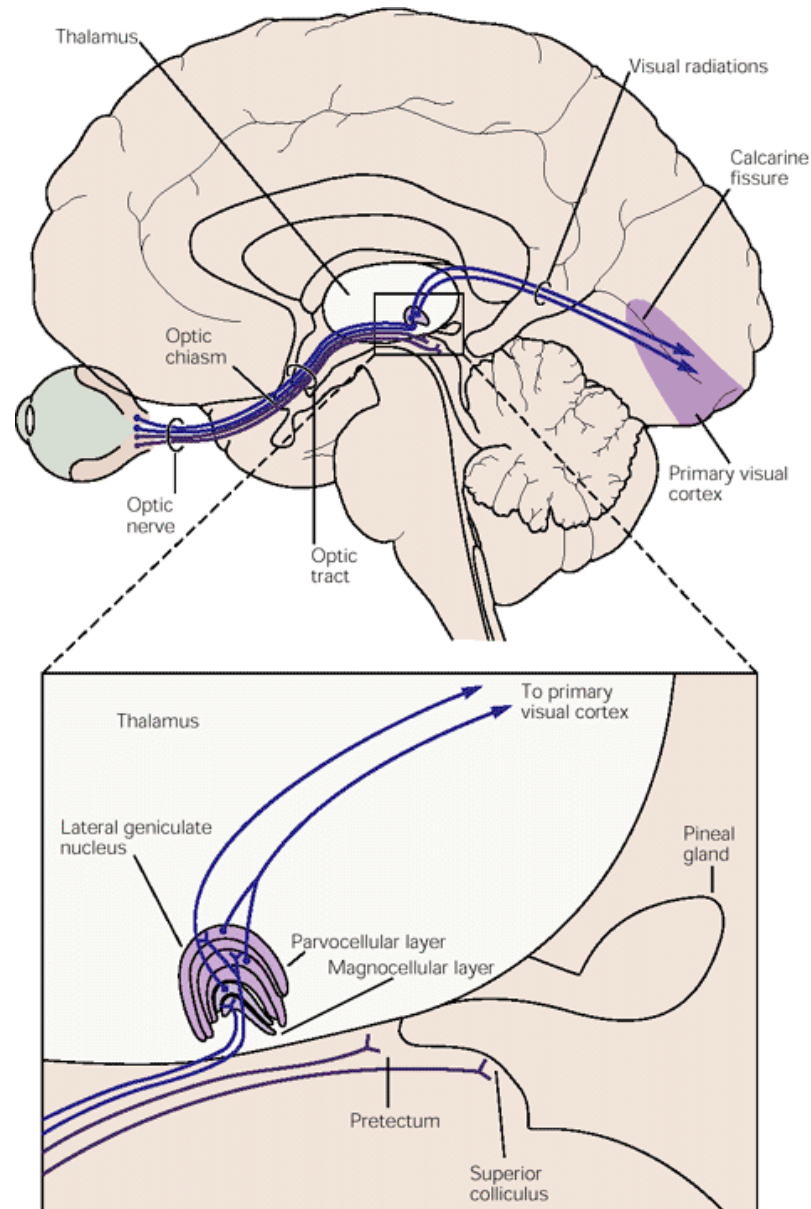


Sensory and motor areas are hierarchically organized.

Connections are often reciprocal (feedforward + feedback).

Example:

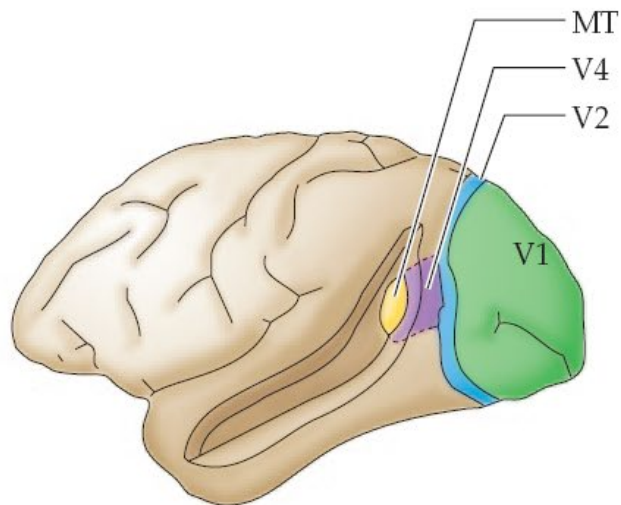
Ascending visual pathway



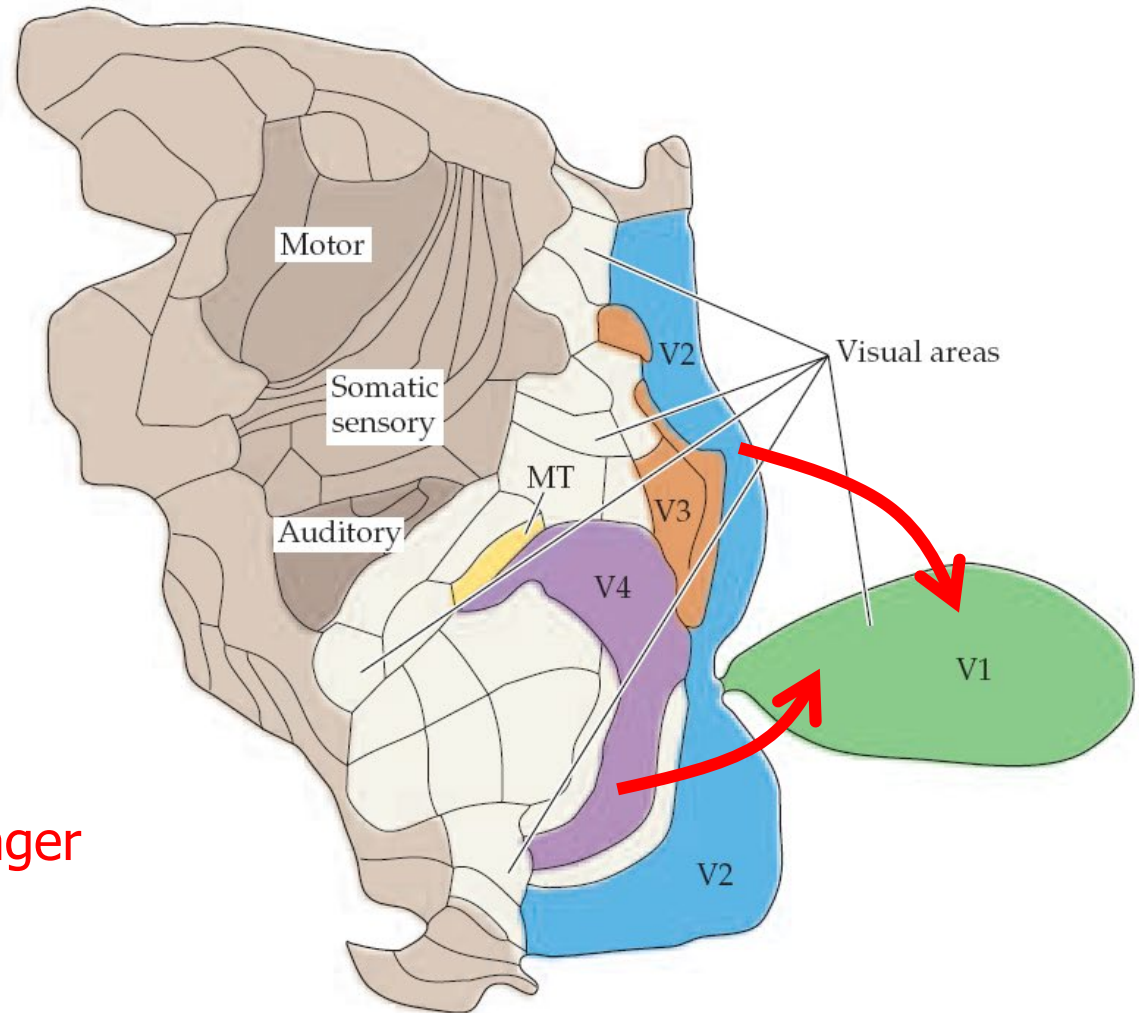
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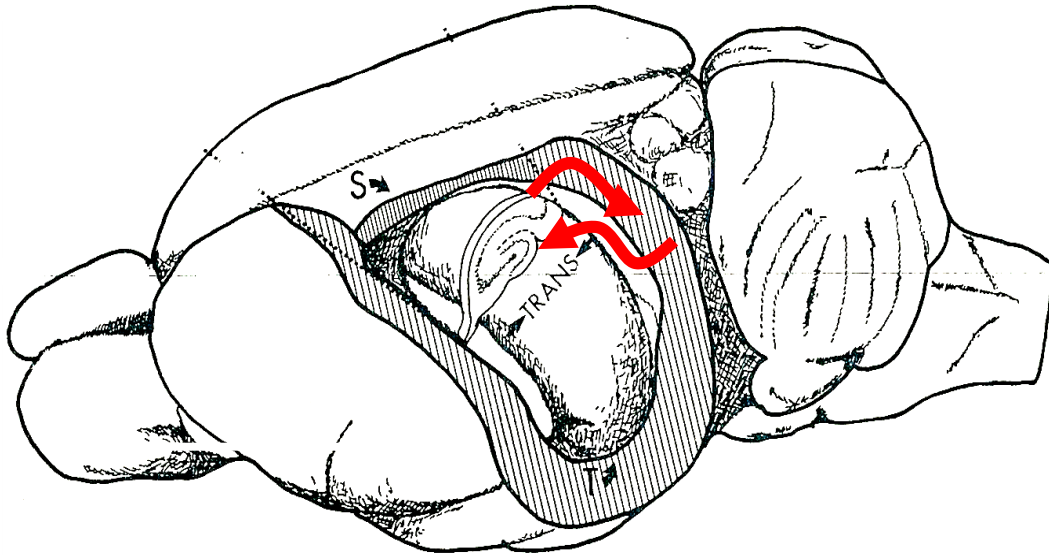
Ascending visual pathway



Feedback projections are often stronger
than feedforward projections.



Another principle of brain connectivity: The great subcortical loops



Example:

- Information flows from the neocortex to the hippocampus and back to the neocortex: A cortico-hippocampal-cortical loop
- This loop is involved in memory consolidation.

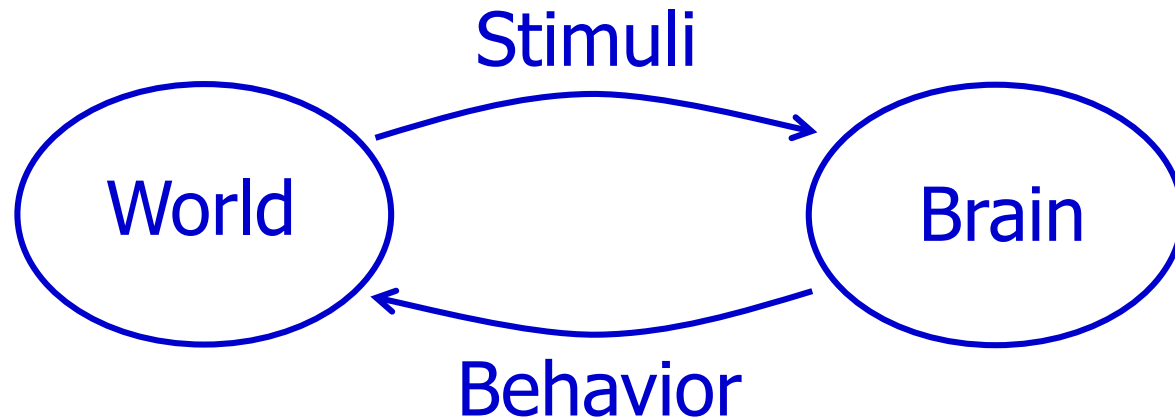
Other important subcortical loops go from the cortex – through the cerebellum, the basal ganglia, or the amygdala – back to cortex.

We will learn in detail about most of these subcortical loops later in this course, or in other courses.

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Three basic approaches for studying the brain

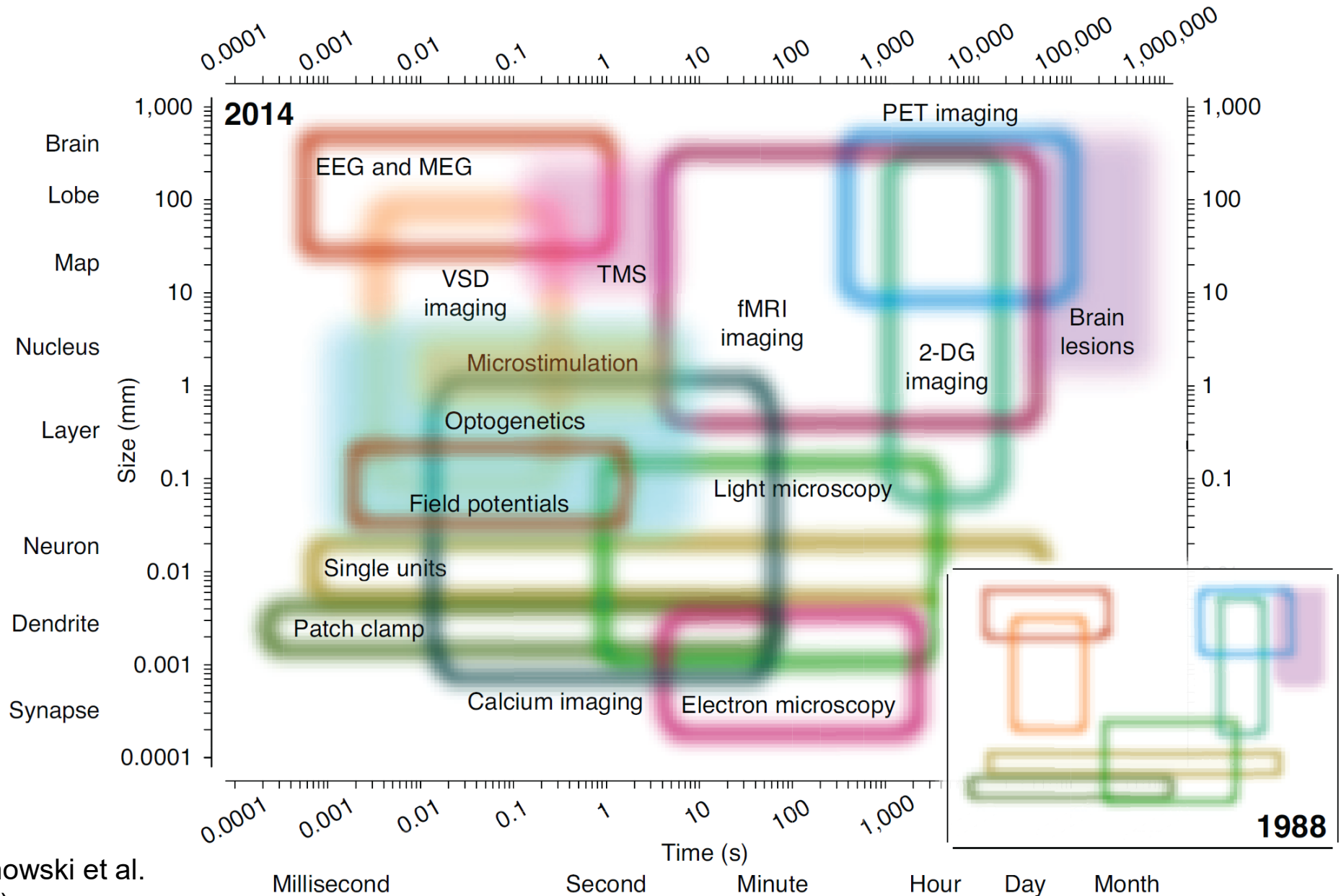


- Approach 1: Manipulate Stimuli → Measure Δ Brain activity
- Approach 2: Manipulate Behavior → Measure Δ Brain activity
- Approach 3: Manipulate Brain → Measure Δ Behavior or Δ perception of Stimuli

Methodologies that we need:

- Measuring Brain activity → electrophysiology, imaging
- Manipulating Brain activity → optogenetics, chemogenetics, pharmacology, lesions
- Measuring Behavior → Great advances in recent years: Underappreciated !

Spatial and temporal resolutions of different methods



(Sejnowski et al.
2014)

Most of the findings you will hear about in this course were achieved by electrophysiology + pharmacology/lesions

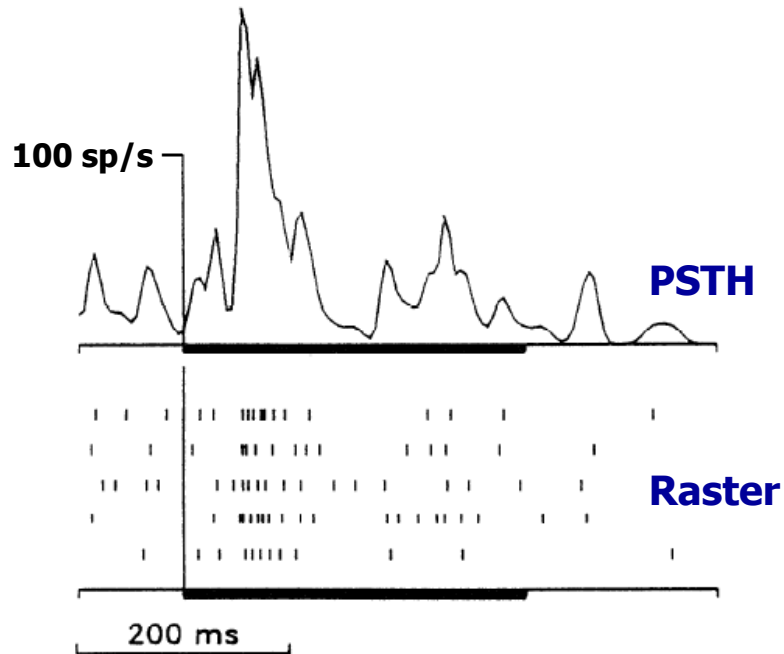


Methodological topics are expanded in the courses “Methods in Neuroscience - Theoretical” (frontal lectures) and “Methods in Neuroscience – Practical” (summer Lab)

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Sensory neurons respond to stimuli with changes in firing-rate

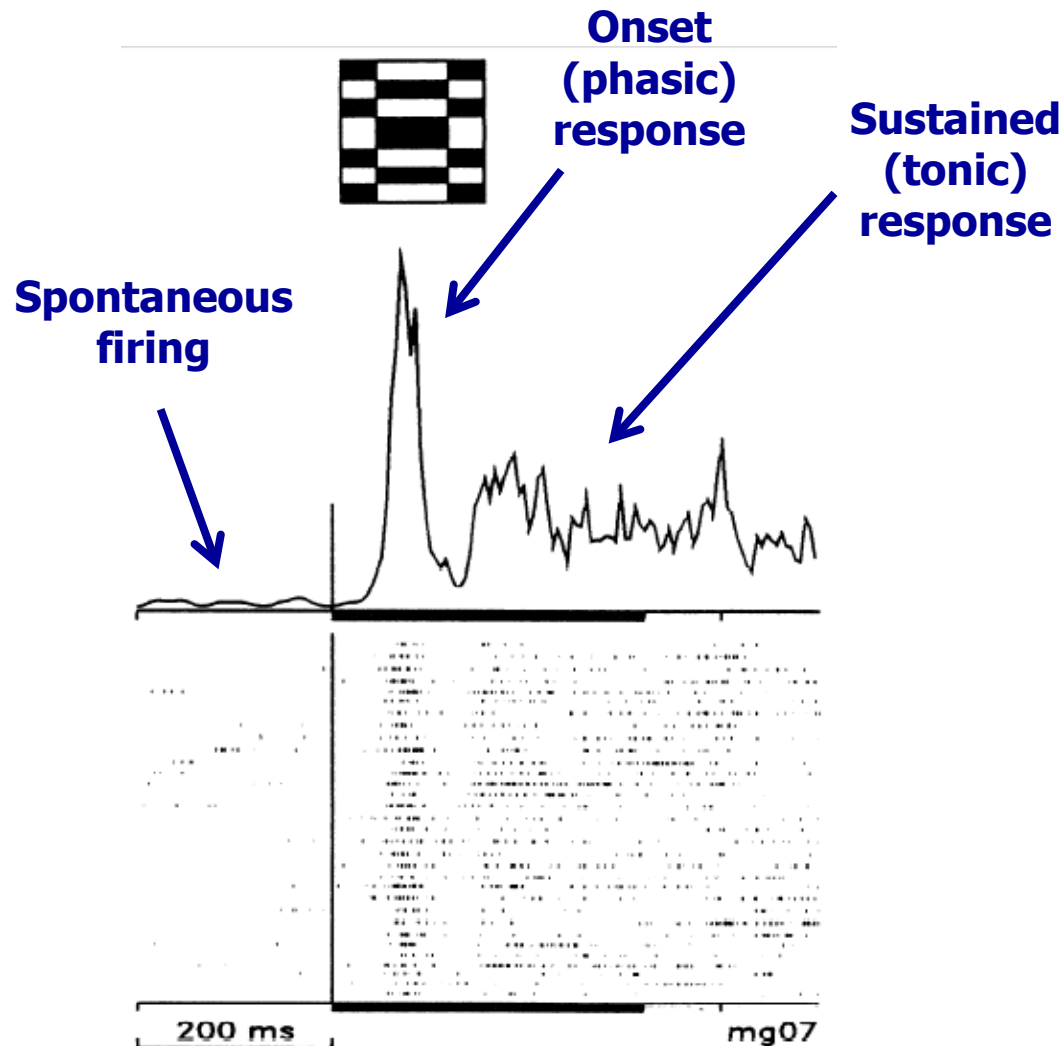


Richmond et al. (1990)
Responses of a V1 neuron
to complex visual patterns

Some basic terms:

- Trial (of an experiment)
- Raster display of spikes
- Peri-stimulus time histogram (PSTH)

Sensory neurons respond to stimuli with changes in firing-rate



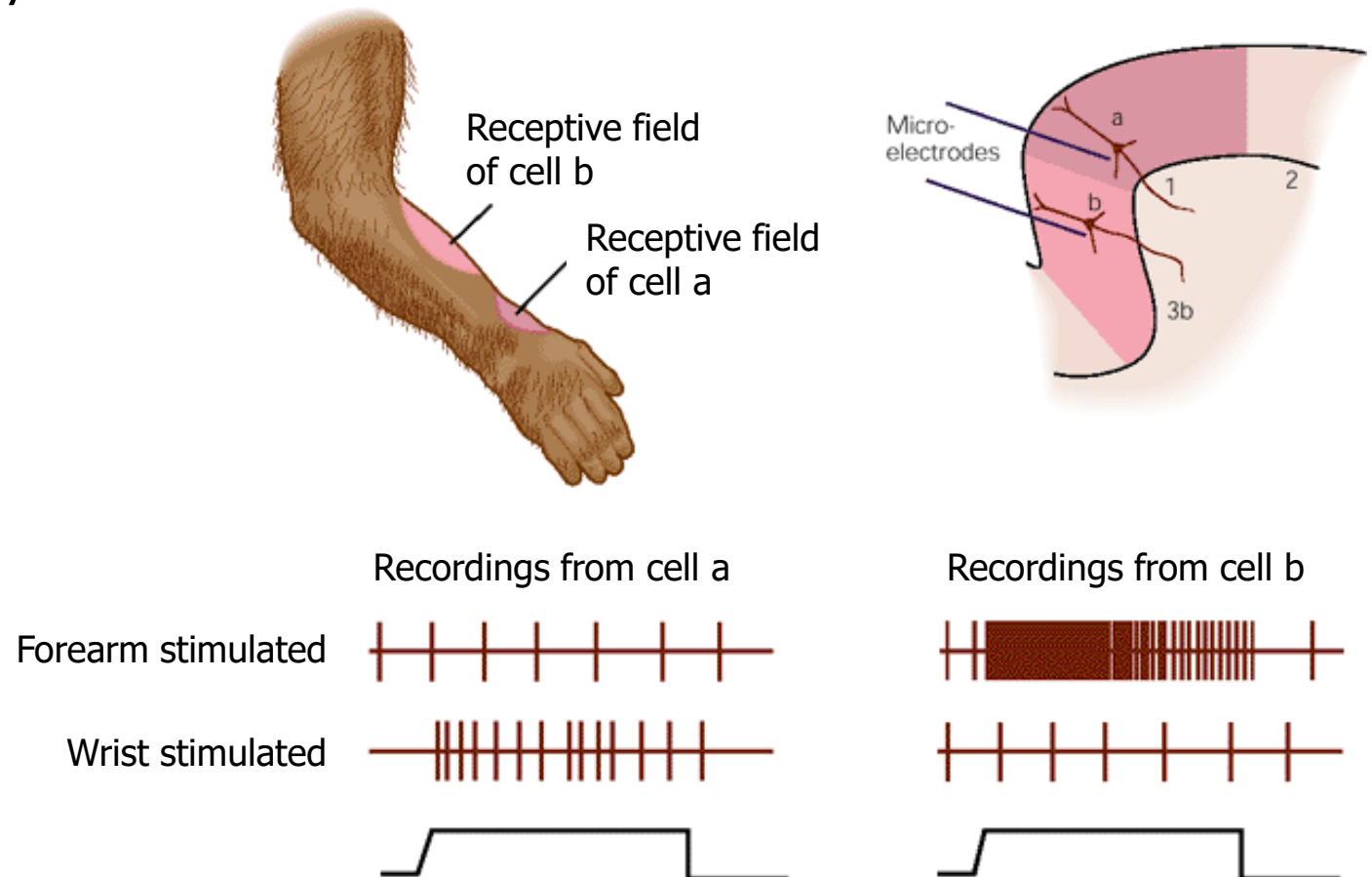
Some basic terms:

- Spontaneous firing
- Onset (phasic) response
- Sustained (tonic) response

Receptive Fields

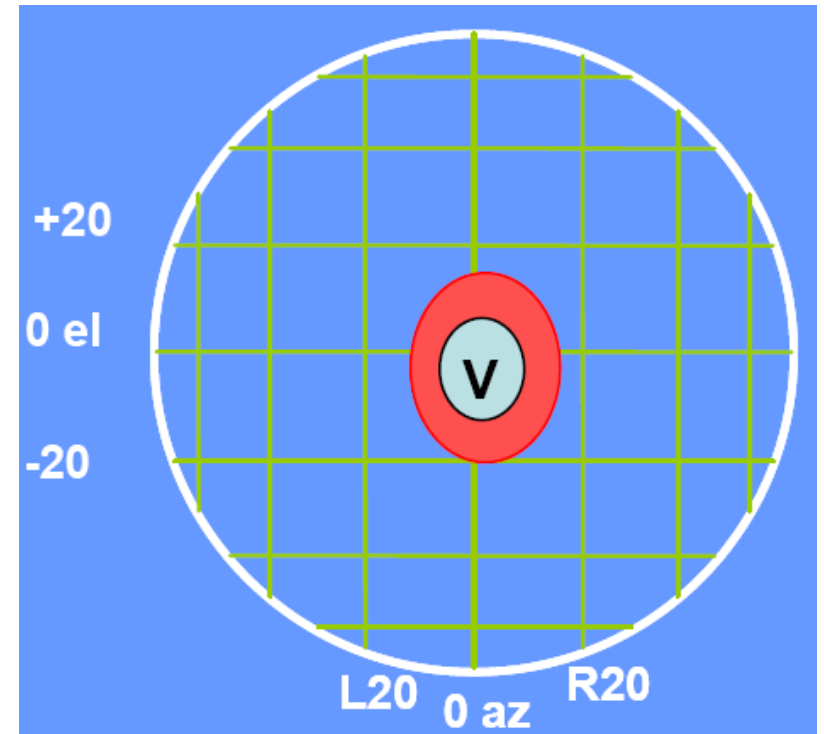
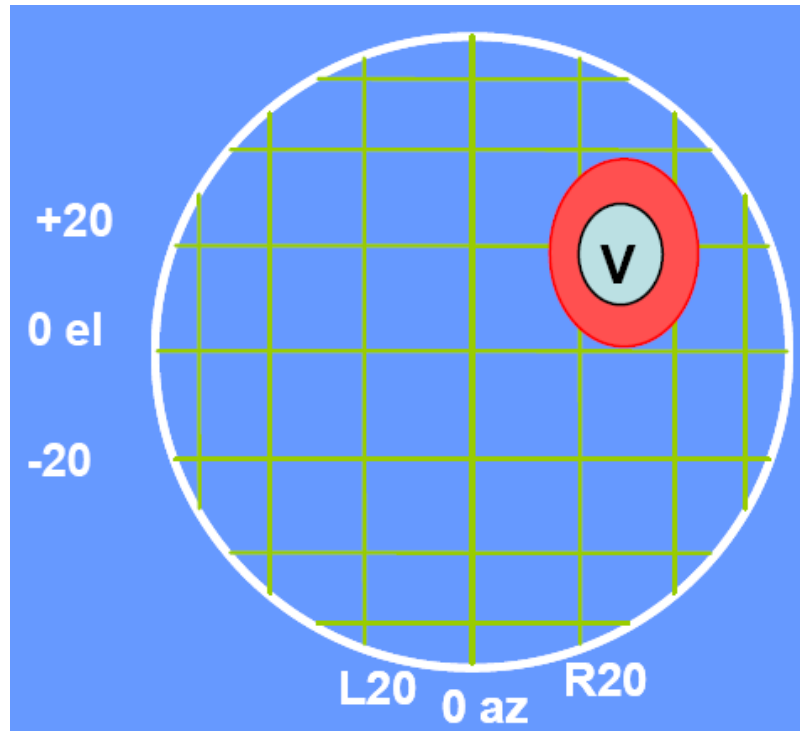
Sensory neurons usually respond only to stimuli coming from a portion of space, the “receptive field”.

Examples of Somatosensory receptive fields for 2 neurons in the monkey primary somatosensory cortex:



Receptive Fields

Examples of Visual receptive fields for 2 neurons in the barn owl's Optic Tectum (the bird homologue of the mammalian Superior Colliculus):



(Thanks to Yoram Gutfreund)

Receptive Fields – some properties

- Receptive field size may vary between adjacent neurons
- Receptive field size generally gets larger along ascending sensory pathways:
Small receptive fields early in pathway, large receptive fields in high cortical areas
- The receptive field is NOT the key computational property of the neuron; instead, the receptive field can be thought as a “permissive property”:

if

Stimulus is within the receptive field of the neuron

then

Do whatever (complex) computation the neuron is supposed to do

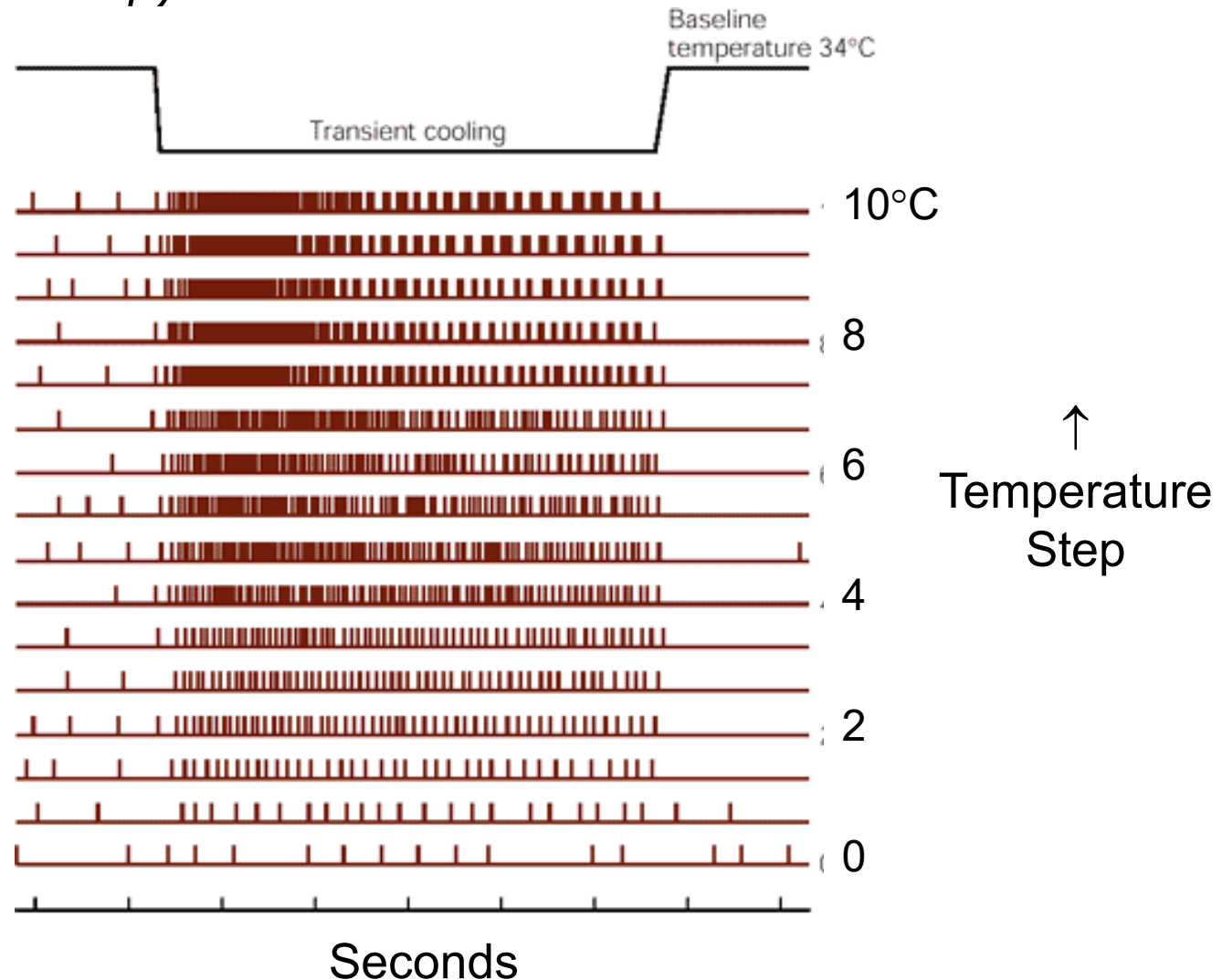
else

Do nothing

end

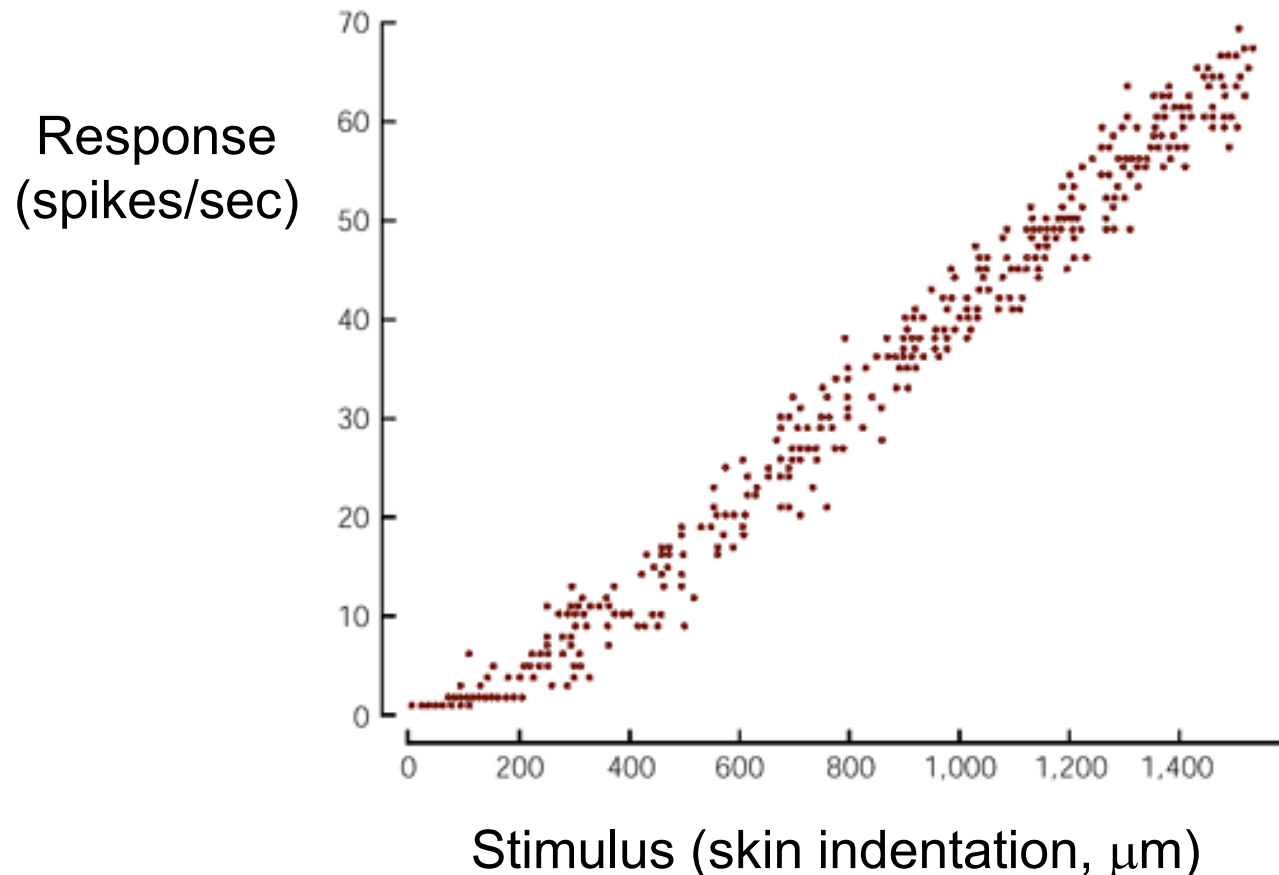
Stimulus intensity is encoded by the firing-rate of sensory neurons

Example of a Cold Receptor, which increases its firing rate linearly with the stimulus (*stimulus = temperature-step*):



Stimulus intensity is encoded by the firing-rate of sensory neurons

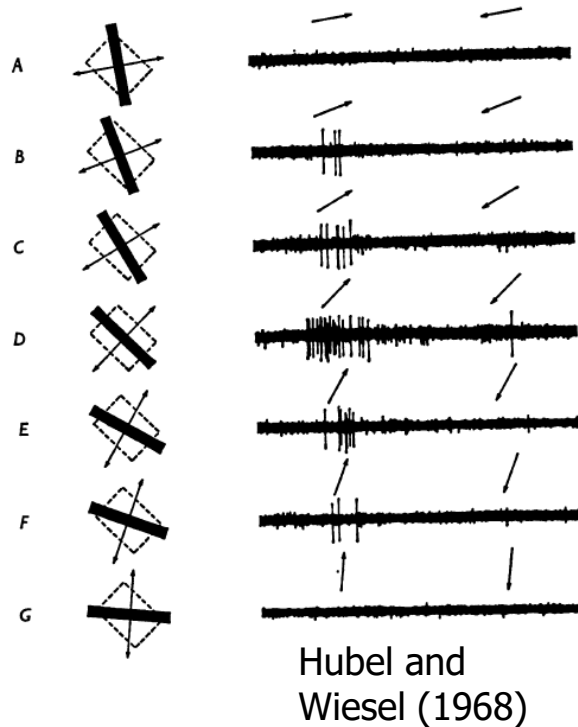
Example of a Somatosensory (Touch) Receptor, which increases its firing rate linearly with the stimulus:



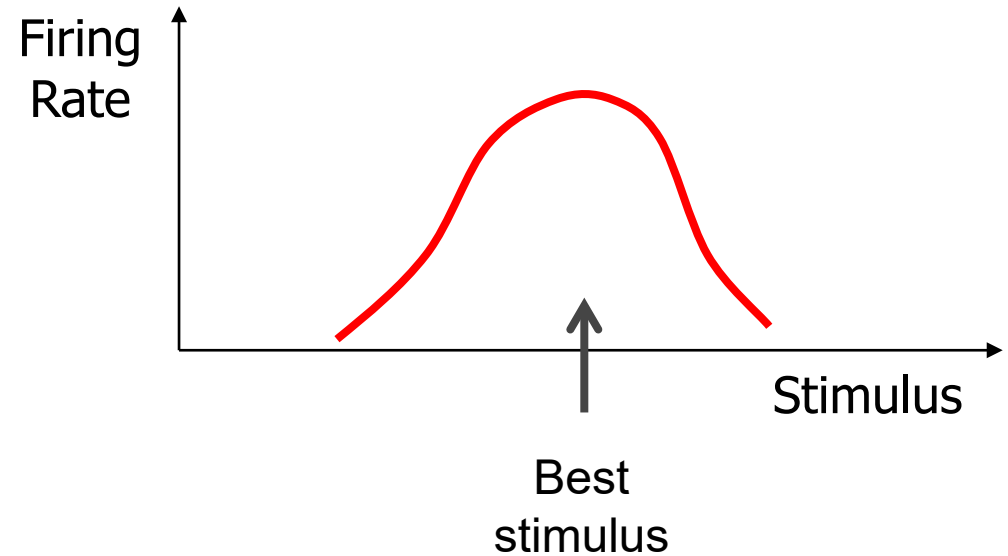
“Rule”: The relation between stimulus intensity and firing-rate is often monotonic (increasing) – although not necessarily linear.

Caveat: This is not *always* the case: e.g. in some auditory neurons, firing-rate increases at low sound intensities but then decreases at very high sound intensities.

The Tuning Curve and the Best Stimulus



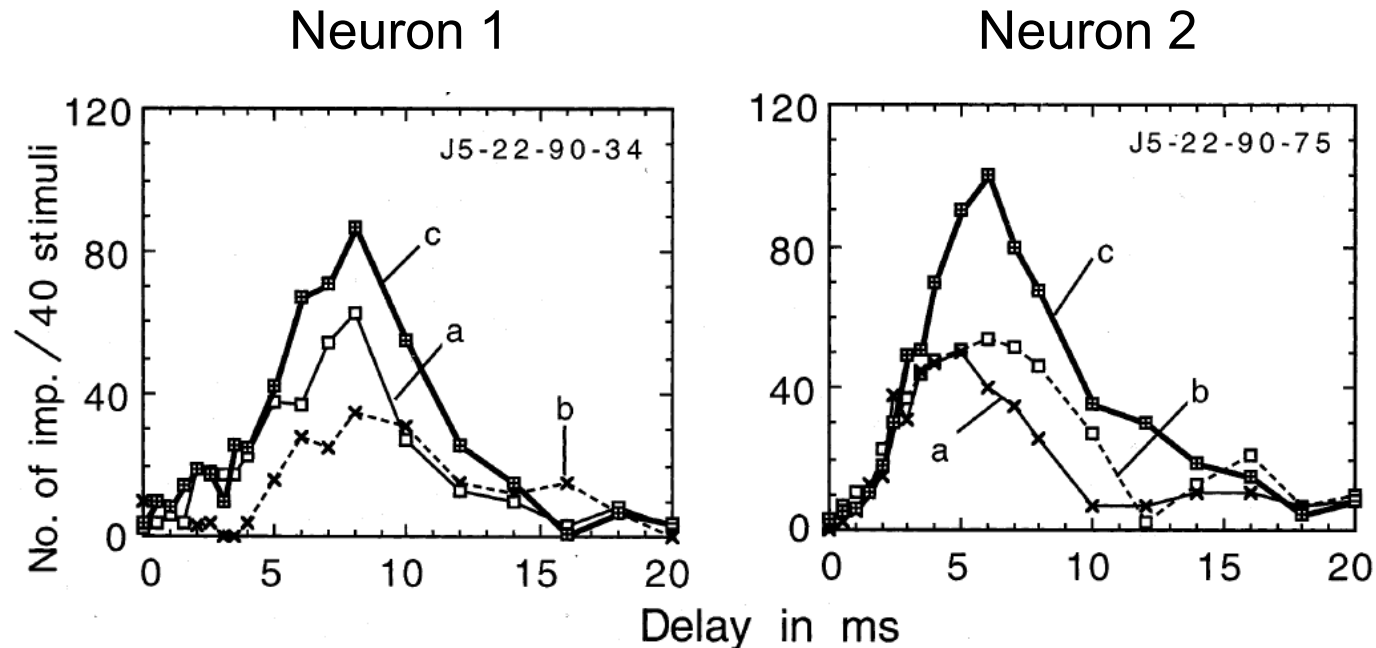
A neuron in V1 (primary visual cortex), presented with a moving bar within its receptive field, responds in a manner that is tuned to the orientation of the bar.



The general concepts of the tuning curve and the best stimulus (or “preferred stimulus”) in sensory neurons: Applies to many types of sensory neurons and many stimuli.

The Tuning Curve and the Best Stimulus

Another example for a tuning curve: Delay-Tuned neurons in bat auditory cortex
(the delay between the outgoing pulse and returning echo signals the *target range*)

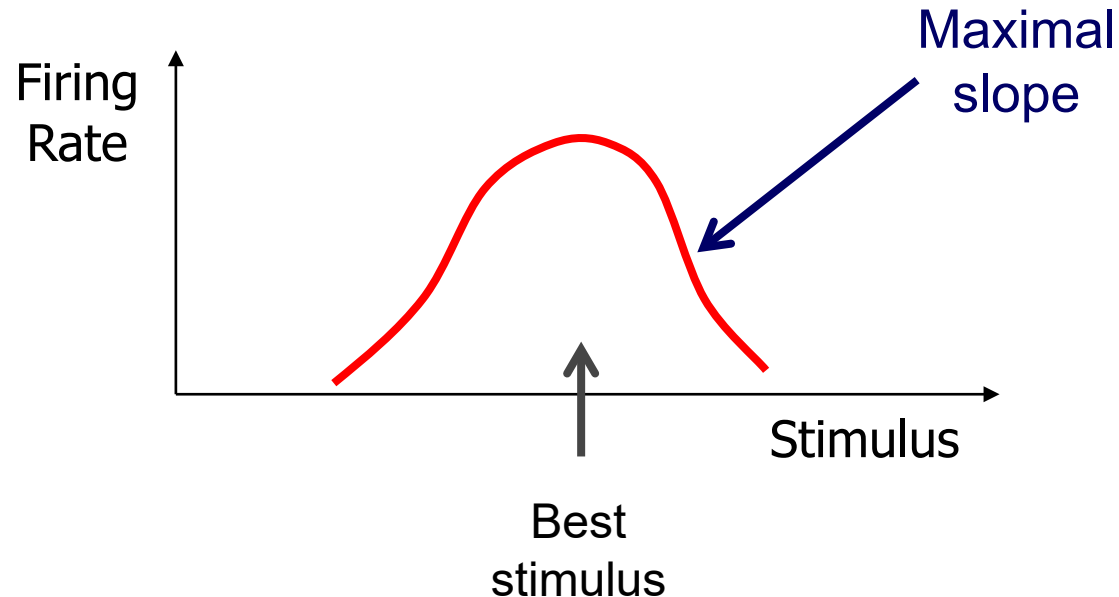


Caveats to the concepts of “Tuning Curve” and “Best Stimulus”

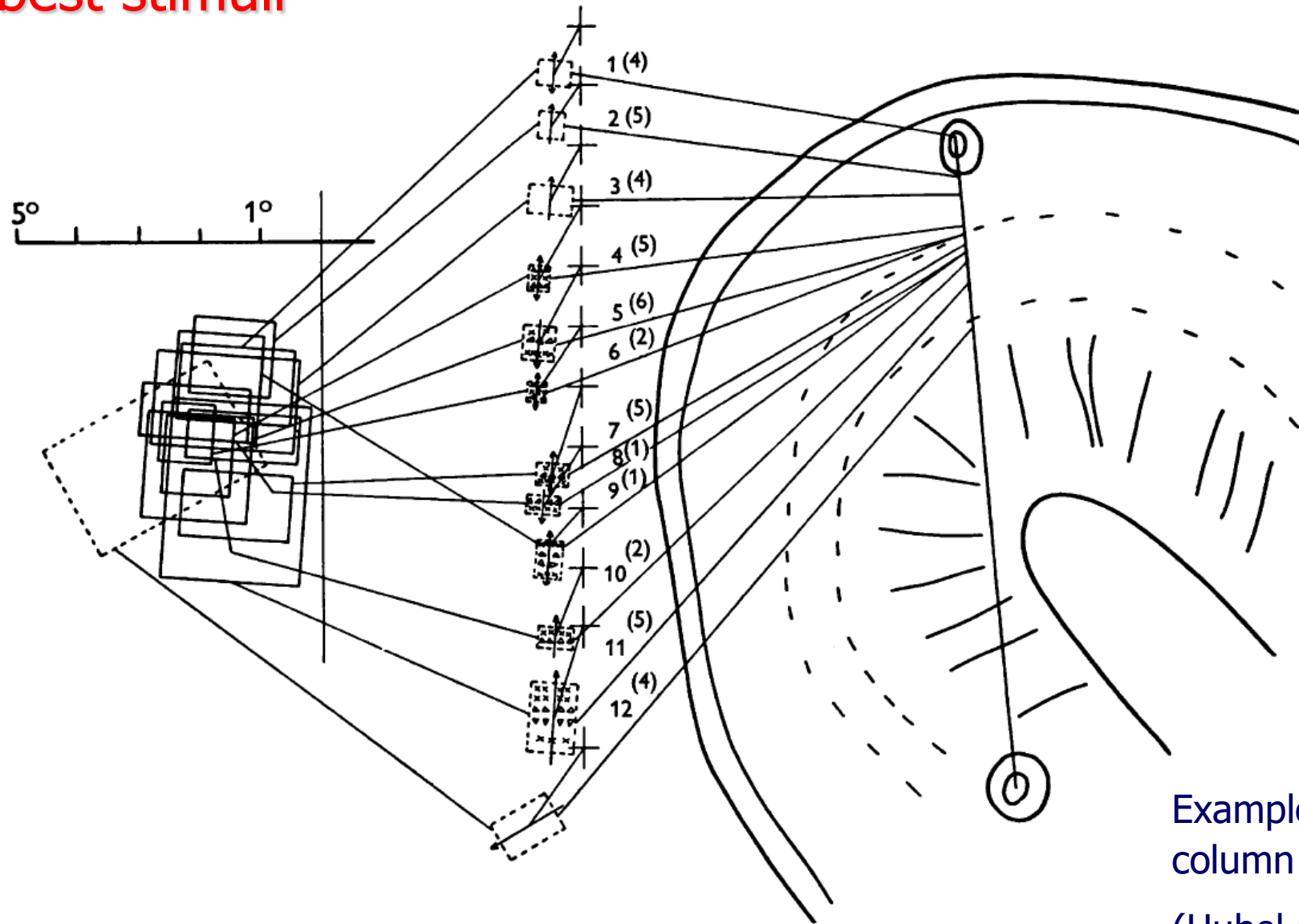
- Neurons are often tuned to many parameters simultaneously: **The tuning curve is multi-dimensional.** For example, a visual neuron that is sensitive to a moving-grating (set of parallel oriented bars) may be tuned to the orientation + spatial-frequency + temporal-frequency (velocity) + direction of the grating.
→ A technical (but important) corollary of this is that the “best stimulus” of a neuron may therefore be difficult, or even impossible to find, even if you try running your experiment following some gradient-ascent optimization algorithms. (“The curse of dimensionality”).
- “Tuning curve” definition relies on a physically-ordered stimulus space (which can be cyclical, like orientation; or can be linear, like the frequency of an auditory tone) – but **not all stimuli have an ordinal structure, and then it is impossible to define tuning curves.** Example: Odors.

Caveats to the concepts of "Tuning Curve" and "Best Stimulus"

- "Best stimulus" has a subtle implication that it is somehow better, or more important than other stimuli. But **the "best stimulus" is in fact the *worst* stimulus if you care about stimulus *discrimination* – for optimal discrimination, it is better to use the *maximal slope* of the tuning curve.**



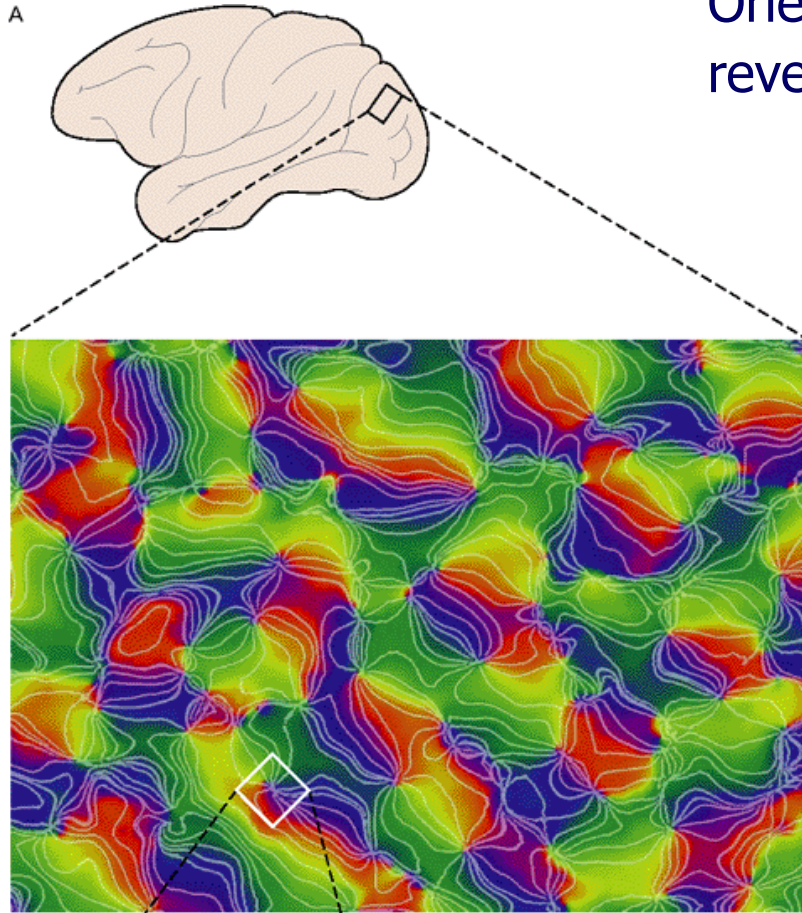
The cortical column: Nearby cortical neurons often have similar "best stimuli"



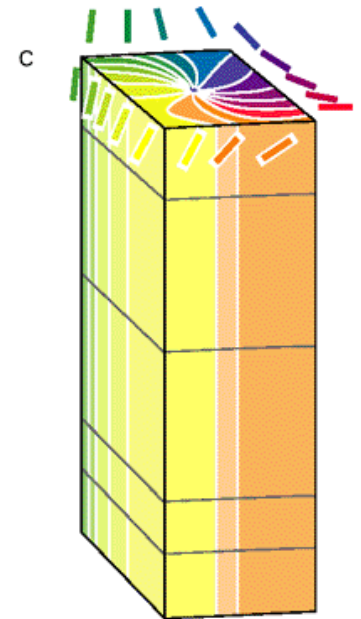
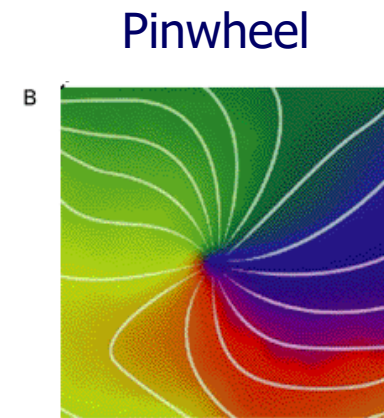
Example of orientation column in cat V1

(Hubel and Wiesel 1962)

The cortical column: Nearby cortical neurons often have similar "best stimuli"

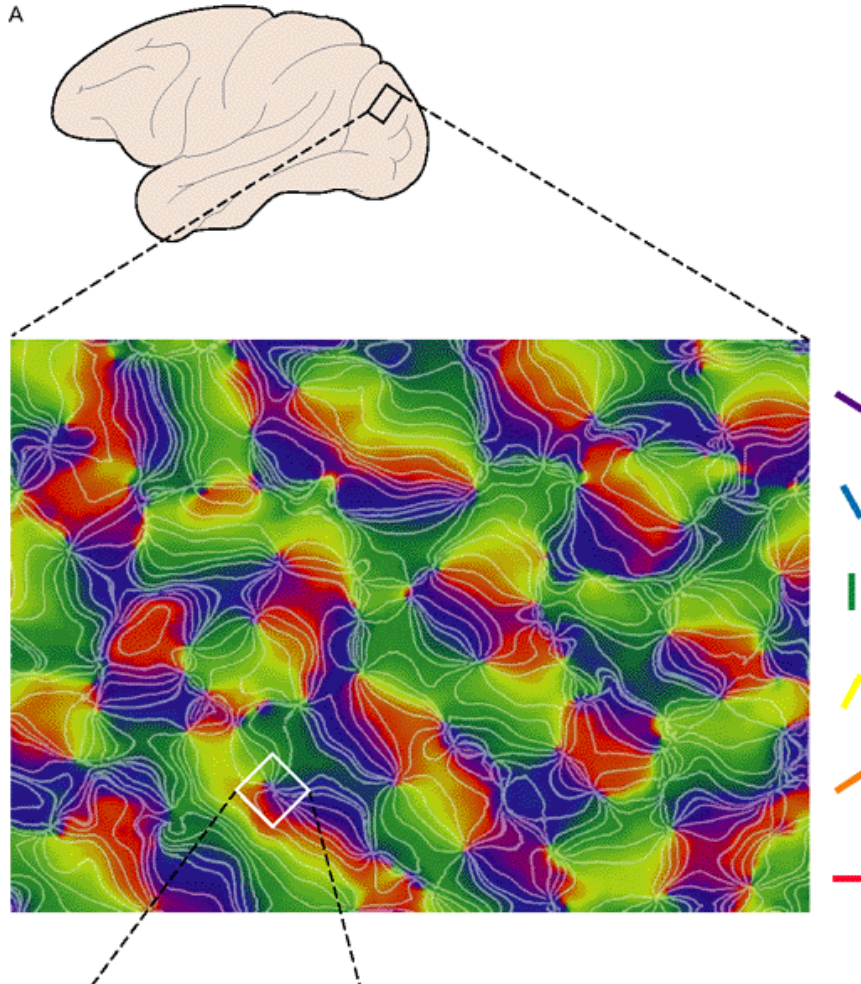


Orientation columns in V1 of the monkey, revealed by optical imaging



Best stimuli are independent of cortical depth

The cortical column: Nearby cortical neurons often have similar “best stimuli”

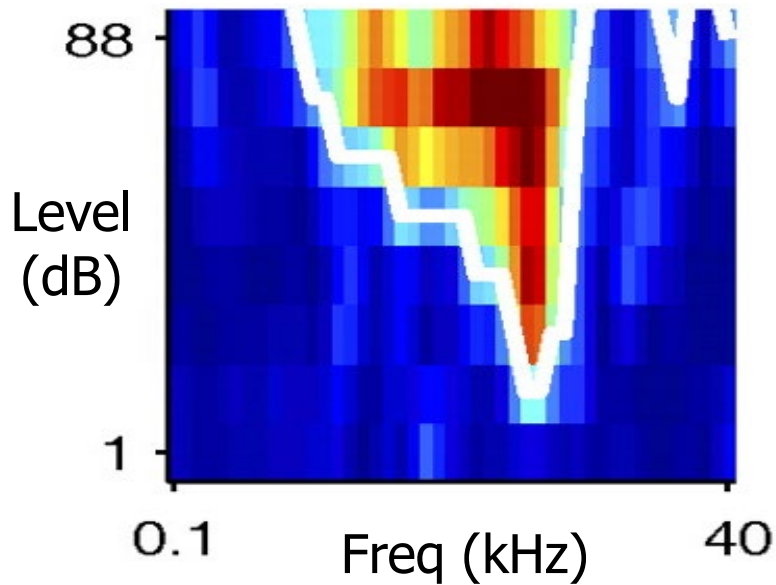


- Cortical Columns with similar functional properties are sometimes inter-connected anatomically in a very specific way (*will be discussed later in this course by Rafi Malach*)

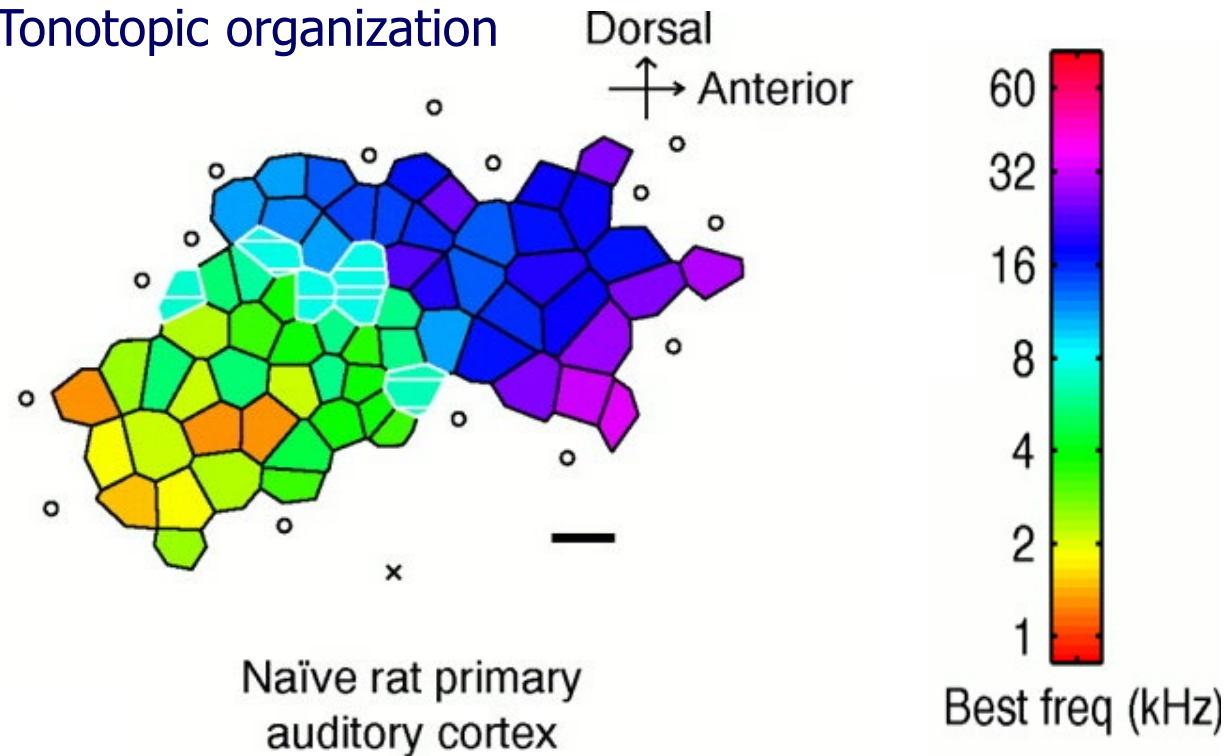
Cortical maps: Columns are often arranged in an orderly way

Tonotopic frequency organization of primary auditory cortex (A1): An example of a topographic organization. This organization is inherited from the periphery (cochlea).

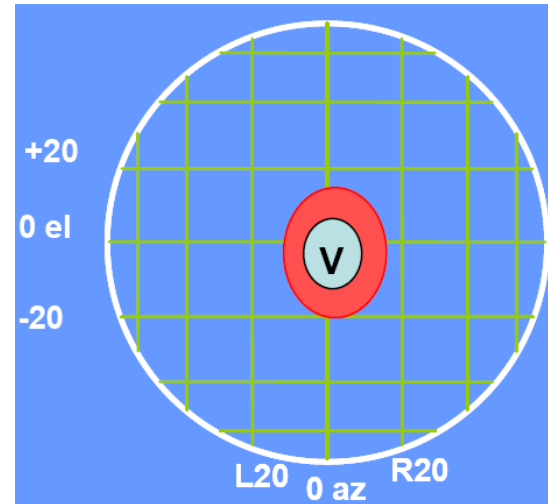
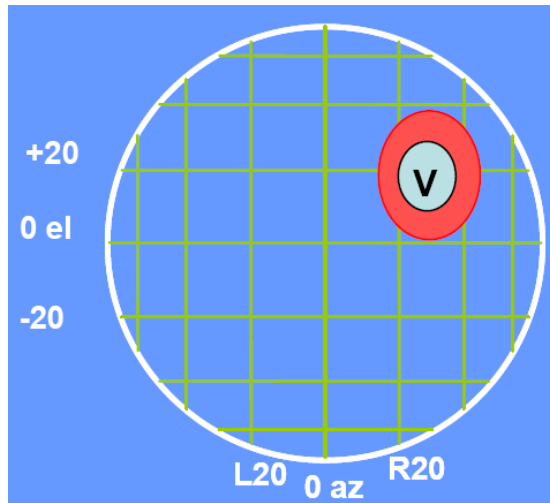
Frequency tuning curve



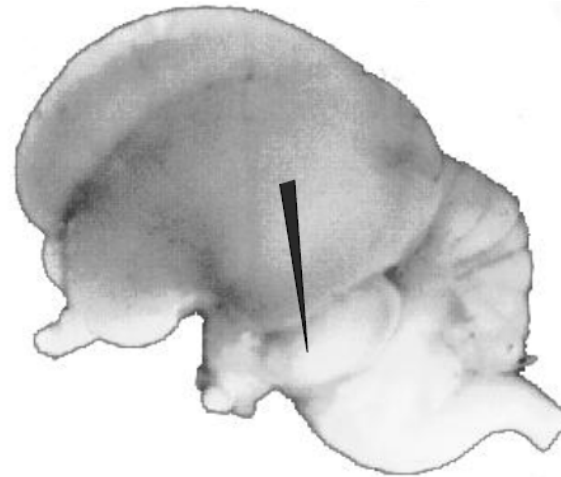
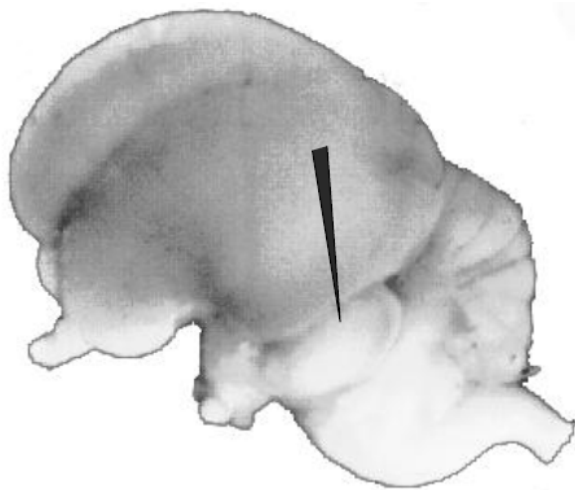
Tonotopic organization



Cortical maps: Columns are often arranged in an orderly way

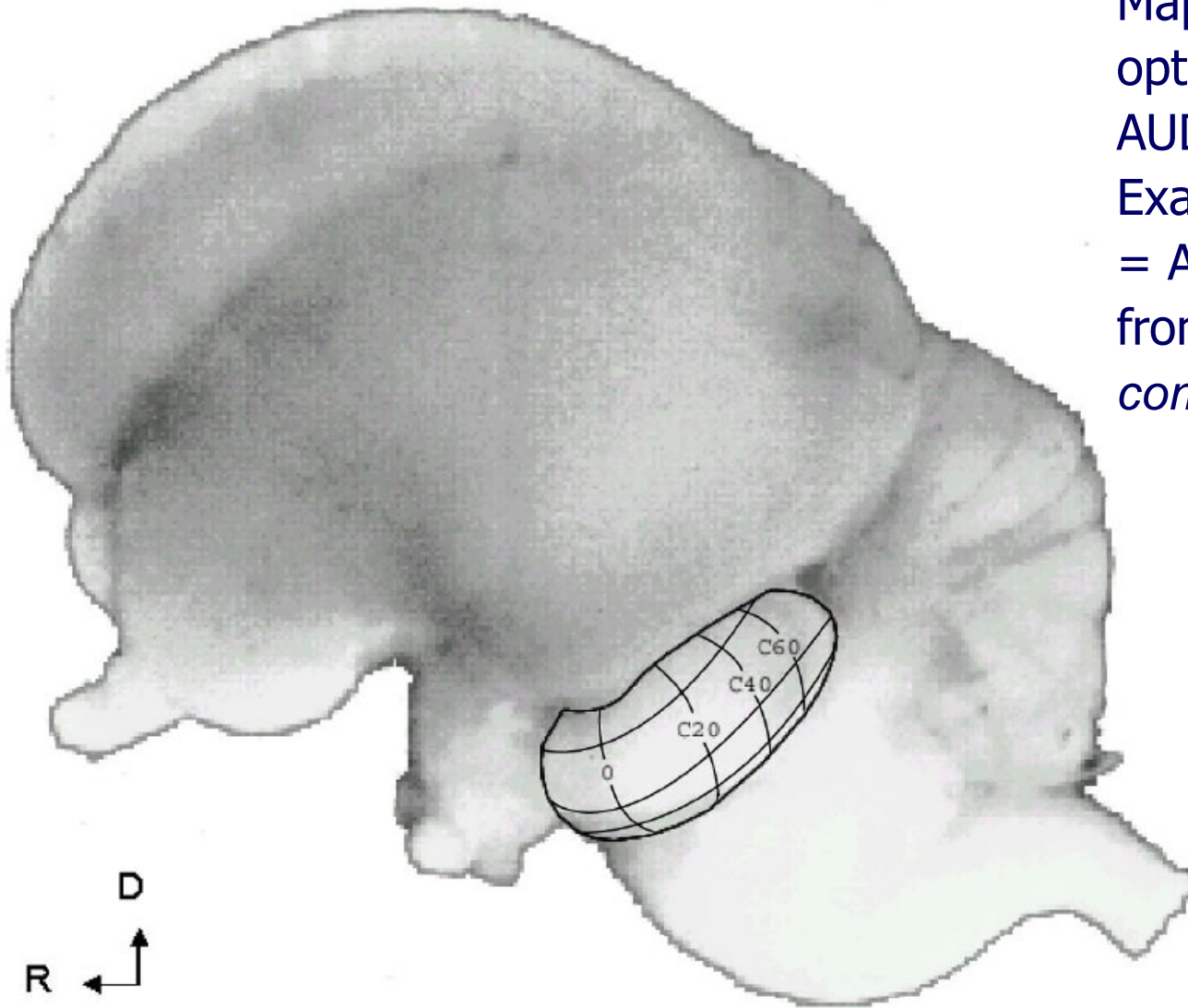


Going back to the receptive fields of the 2 neurons from the barn owl's optic tectum: they were recorded in 2 different locations



(Thanks to Yoram Gutfreund)

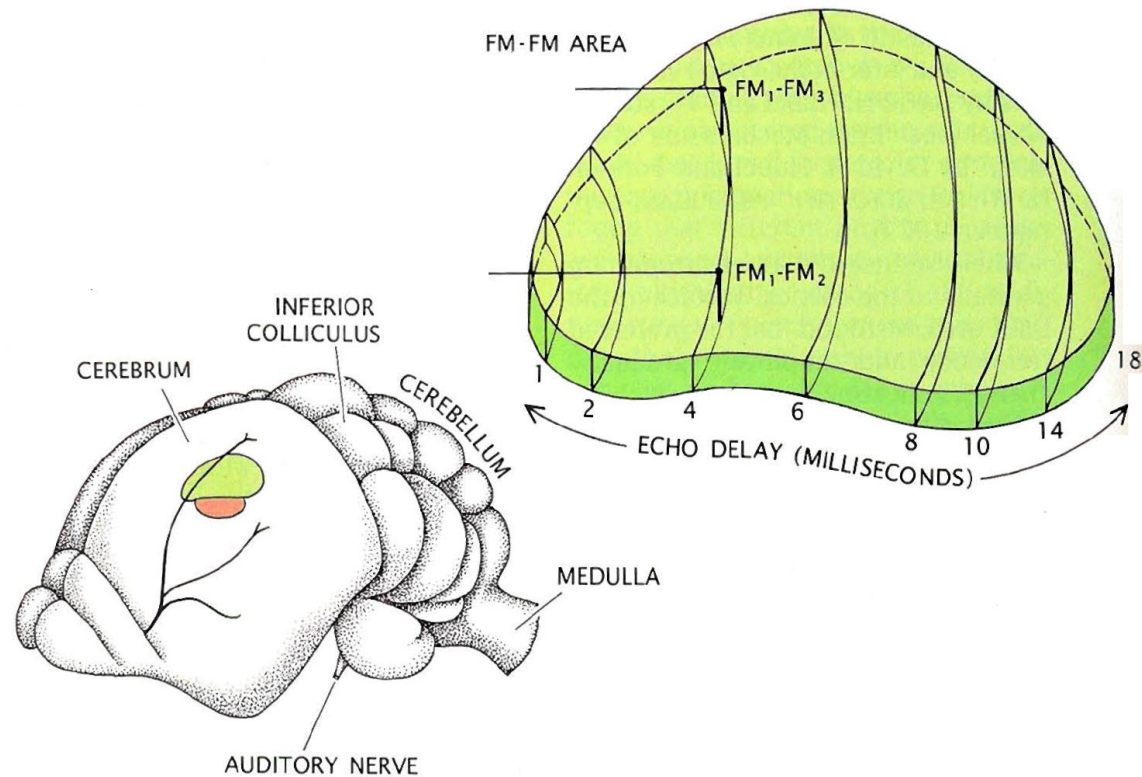
Cortical maps: Columns are often arranged in an orderly way



Map of space in the barn owl's optic tectum: Exists also for AUDITORY receptive fields – Example of a computational map = A map that is NOT inherited from the periphery, but has to be *computed* by the brain.

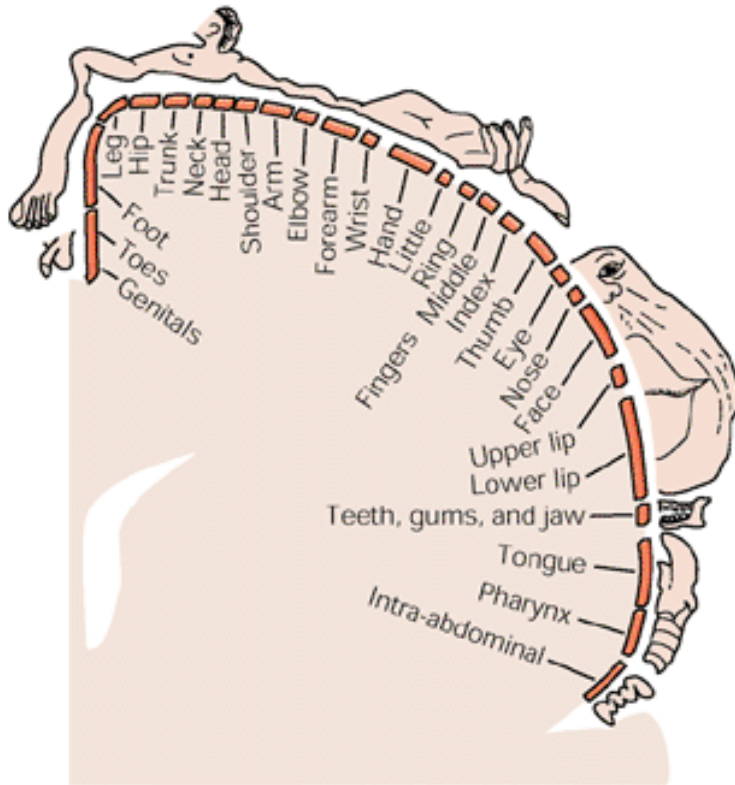
Cortical maps: Columns are often arranged in an orderly way

Another example of a computational map = map of target delay (range) in the mustached bat auditory cortex



The homunculus

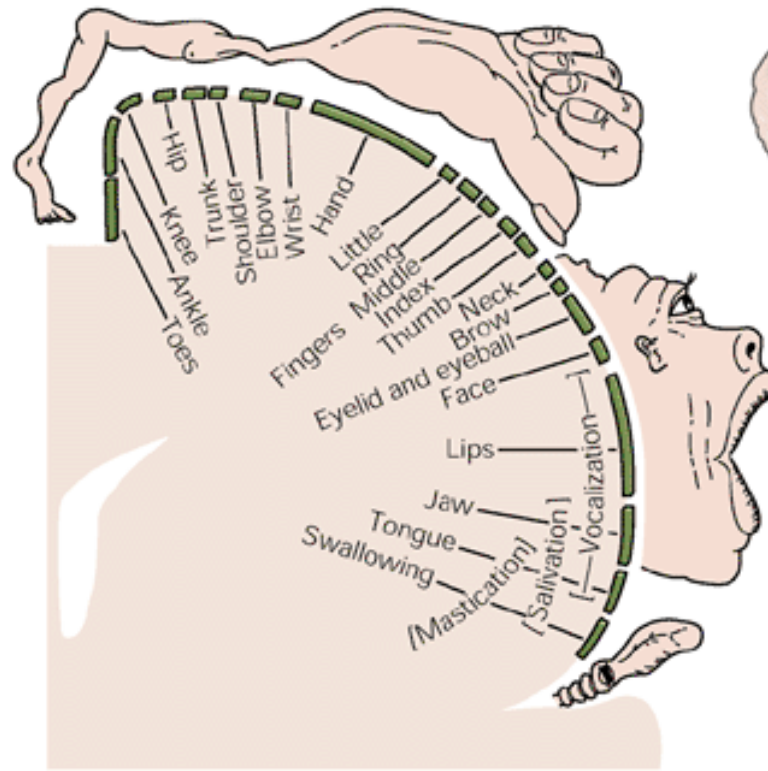
A. Sensory homunculus



Medial

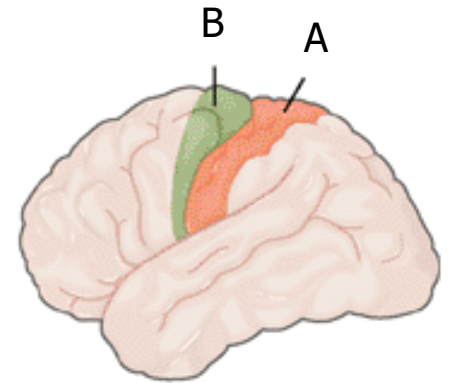
Lateral

B. Motor homunculus



Medial

Lateral



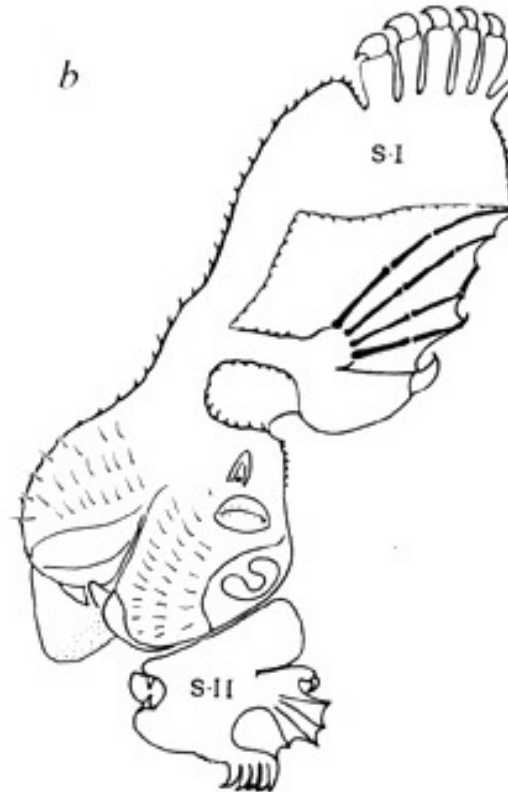
- The homunculi were discovered by Wilder Penfield, by stimulating the cortex in human patients undergoing brain surgery.

Analogous to the homunculus were found in numerous species

Rat-unculus



Bat-unculus



- Note that there are multiple maps of the body (S-I, S-II...).

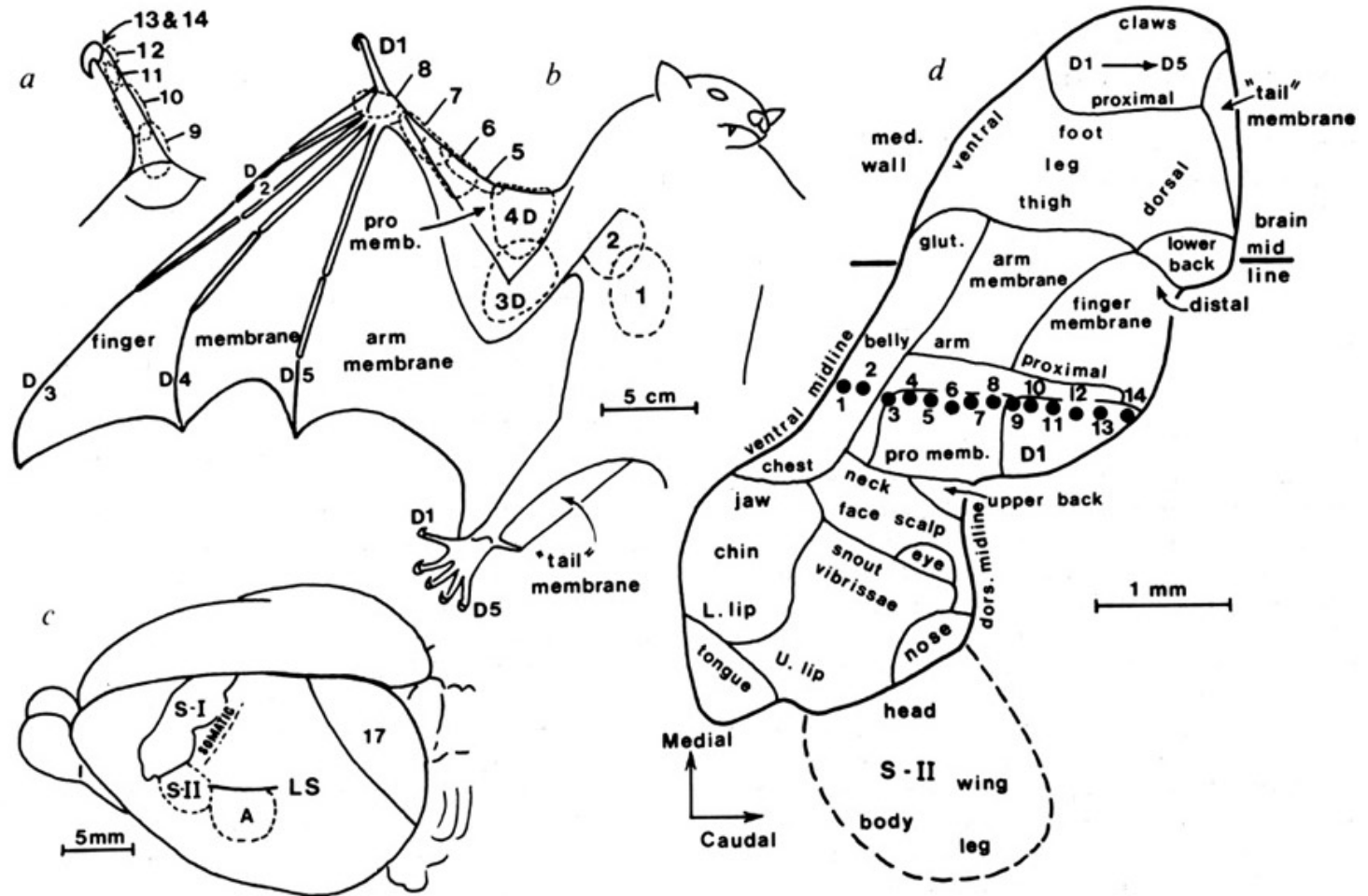
This multiplicity of maps generally applies to other senses as well.

(Calford, Pettigrew et al. *Nature* 1985)

Analogs to the homunculus were found in numerous species

Batunculus

(Calford, Pettigrew
et al. *Nature* 1985)



- Large chunks of cortex are devoted to body parts that are important for the animal species (e.g. face and fingers in humans ; face, wings and thumb in bats).

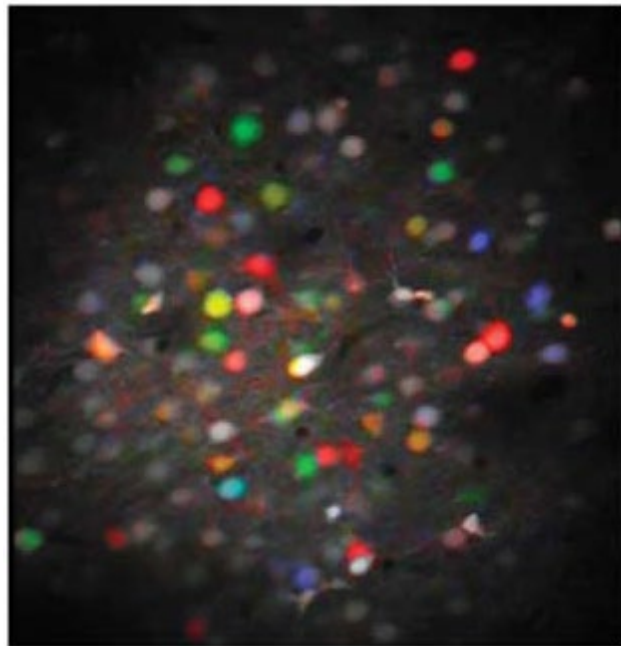
Caveats to the concept of “map”

- Not all brain regions have columns or maps. *Example:* Hippocampus (no columns – nearby neurons have different place coding).
- Even in cortex, there are stimulus properties that are arranged in columns (nearby neurons do similar things) but *not* in maps (no large-scale organization of the columns). *Example:* Excitatory-Inhibitory columns in auditory cortex.
- In principle: Topographical organization may not be important – because it can be scrambled, while still maintaining the same network architecture (interconnections), which is the truly important network property.

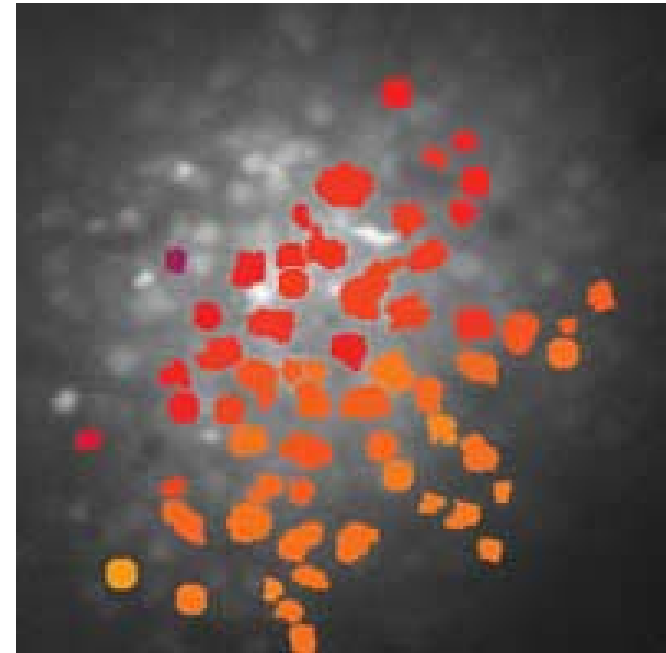
Caveats to the concept of "map"

- Even stimuli that are organized in columns and maps in one animal species, can have *no* columnar or map organization in another species. *Example*: Orientation selectivity in V1, measured with 2-photon imaging (Ohki, Reid et al., Nature 2005).

Rat V1



Cat V1



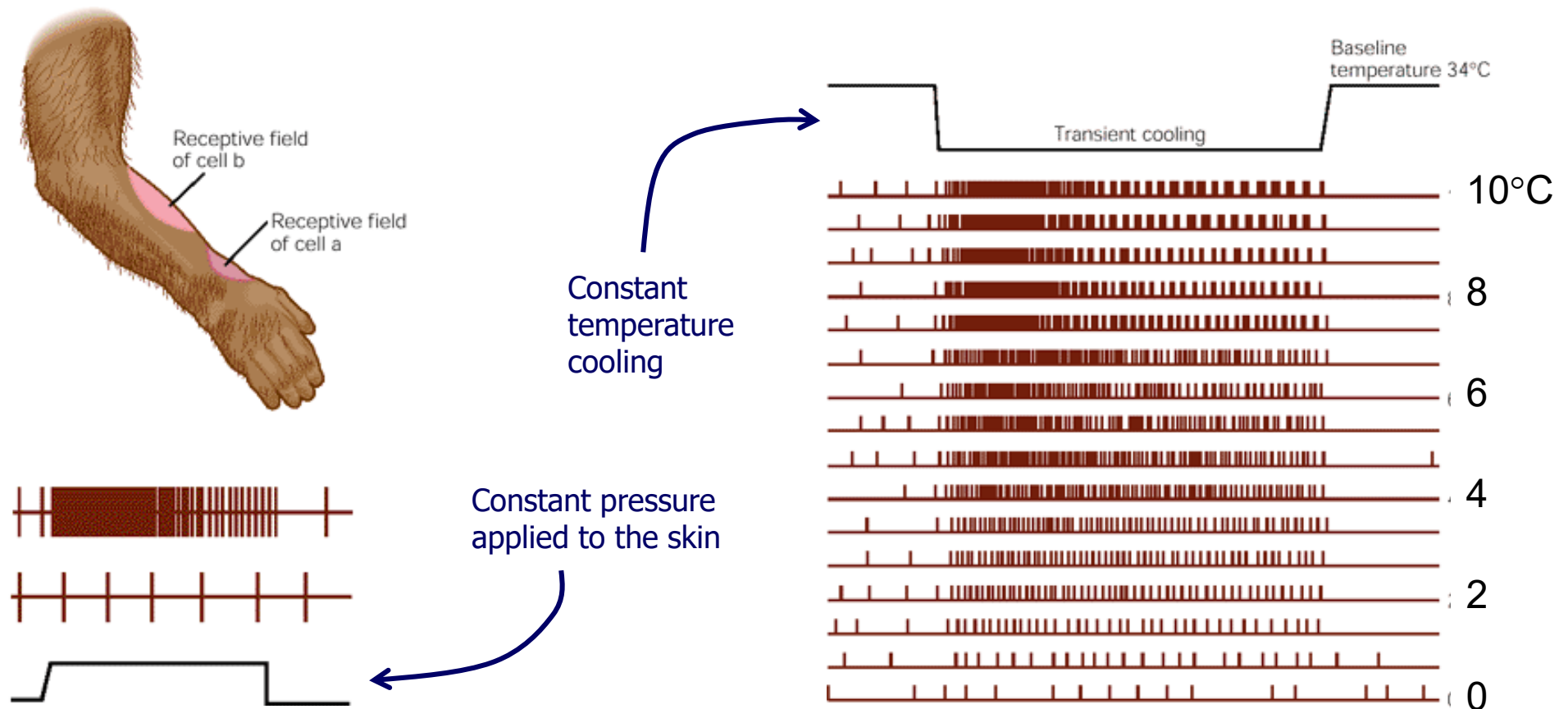
Both images are
~300 μm across

'Salt-and-pepper' organization

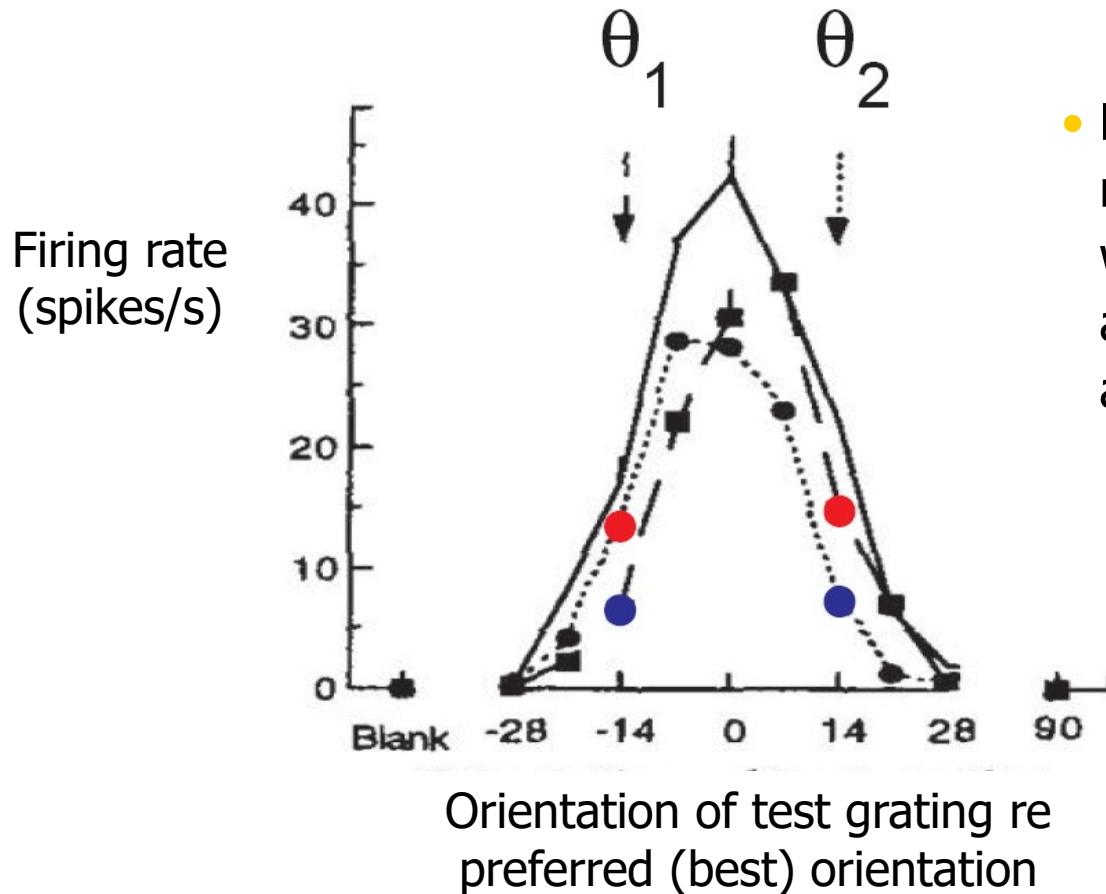
Map organization

Spatial organization is not everything: Temporal dynamics is also very important

- Many neurons exhibit firing-rate adaptation: Gradual *decrease* in the neuron's firing rate during the presentation of a *constant* stimulus.



Adaptation is not always just “fatigue”: It can be stimulus-specific adaptation (habituation)



- Example of an orientation-tuned neuron in V1, which was presented with high-contrast “adapting stimulus” at two orientations: The tuning-curve adapted in a stimulus-specific way.

(Muller et al., *Science* 1999)

Adaptation is not always just “fatigue”: It can be stimulus-specific adaptation (habituation)

- Neural responses depend on stimulus history.
- As a consequence, neural responses may depend on stimulus probability:

f1 f1 f1 f1 f2 f1 f1 f1 f1 f2 f1 f1 f1 versus f2 f2 f2 f2 f1 f2 f2 f2 f2 f1 f2 f2 f2

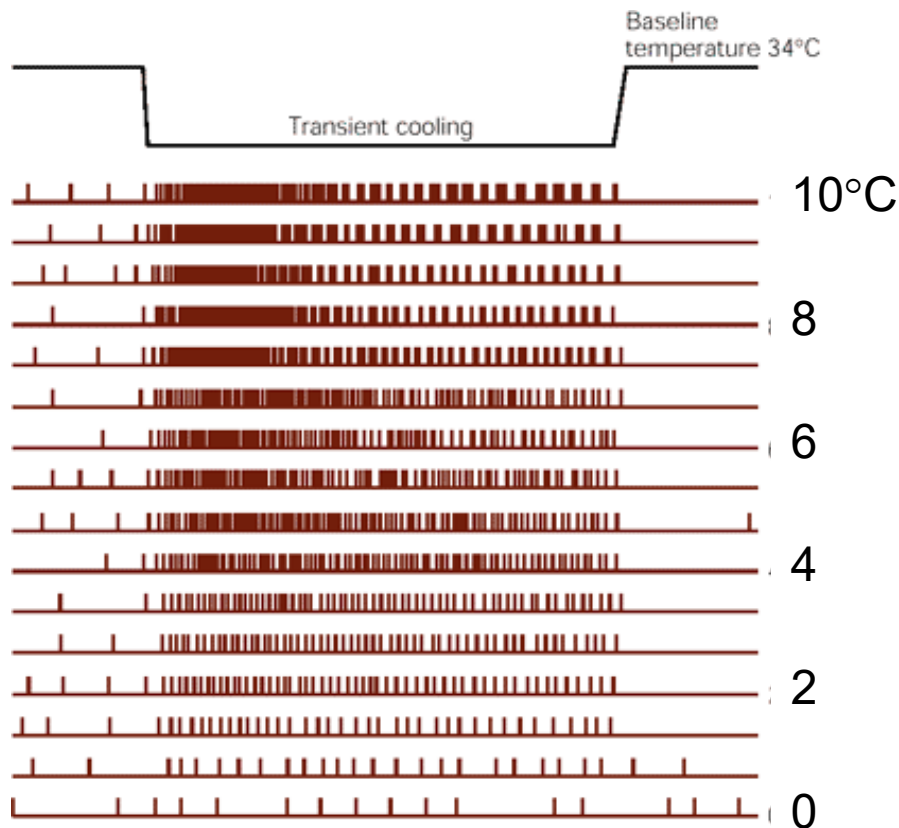
Responses to the same physical stimulus differ depending on its probability – sensory neurons can perform *novelty detection* (Ulanovsky et al., *Nature Neurosci* 2003)

Why is adaptation useful?

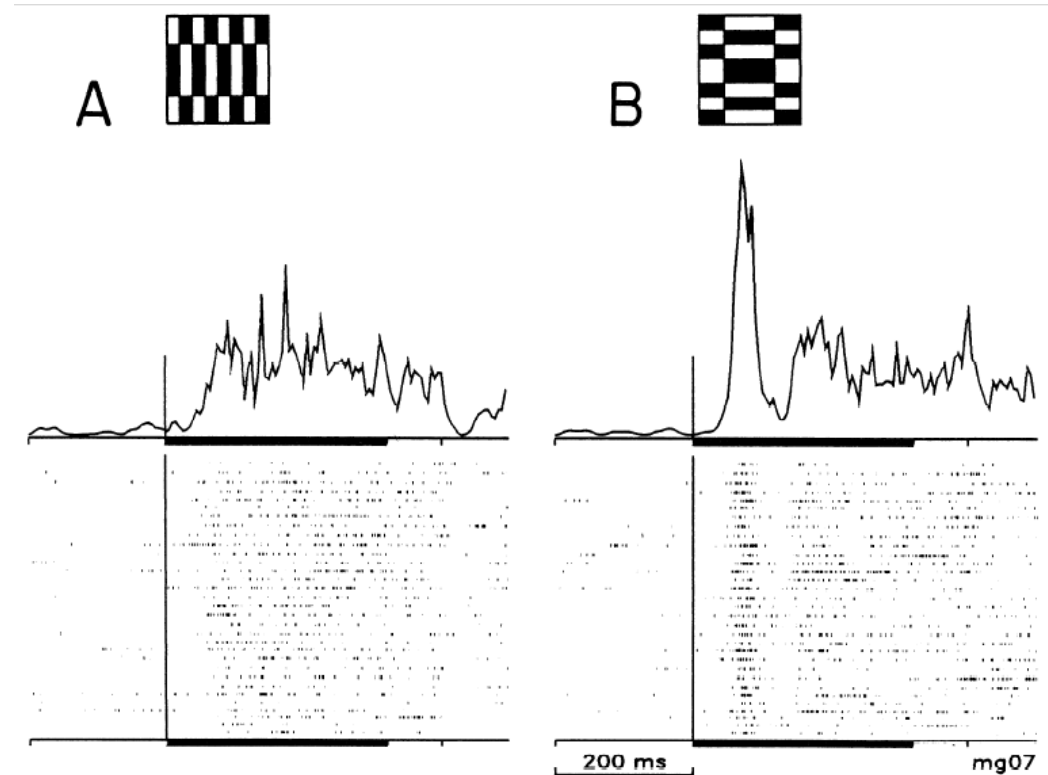
- Economy of spikes: saves energy (spike generation is energetically very costly)
- Stimulus-specific adaptation forms a transient “sensory memory” trace
- Stimulus-specific adaptation can increase the discriminability of incoming stimuli (increases the slope of the tuning curve)
- Adaptation to stimulus statistics optimizes neural coding (beyond this lecture’s scope)

Neural Coding: the ultimate frontier of neural dynamics

Rate Coding: Example of a cold-receptor that encodes temperature cooling by changes in its firing rate



Temporal Coding: Example of one V1 neuron that responds with the same firing-rate, but with different temporal patterns to two stimuli



Richmond et al. (1990)

Neural Coding: the ultimate frontier of neural dynamics

- **Rate coding:** Stimulus identity is encoded by the neuron's firing-rate. In rate coding, temporal dynamics of the neuron's firing is deemed irrelevant.
- **Temporal coding:** Stimulus identity is encoded by fine temporal dynamics of the neuron's response, or even by the precise timing of spikes at the millisecond level.
- **Labeled-line coding:** Stimulus identity is encoded by the identity of the active neuron (active / non-active).
- **Oscillation coding:** Example of temporal coding, where information is carried by neural oscillations, or by the firing phase of neurons relative to ongoing oscillations.
- **Population coding:** Stimulus identity is encoded by groups of neurons.
- **Synchrony coding:** Example of population temporal coding, where information is carried by synchronization between groups of neurons (cell assemblies), even without changes in firing-rate or temporal dynamics of individual neurons.

These coding schemes are not necessarily mutually exclusive !

Neural Coding topics will be further discussed in some parts of this course, as well as in courses in Theoretical Neuroscience.

Further Reading

- Kandel 6th edition, chapter 4 (posted on course website) – more on basic organizational principles of the brain. **Compulsory** reading for the exam !