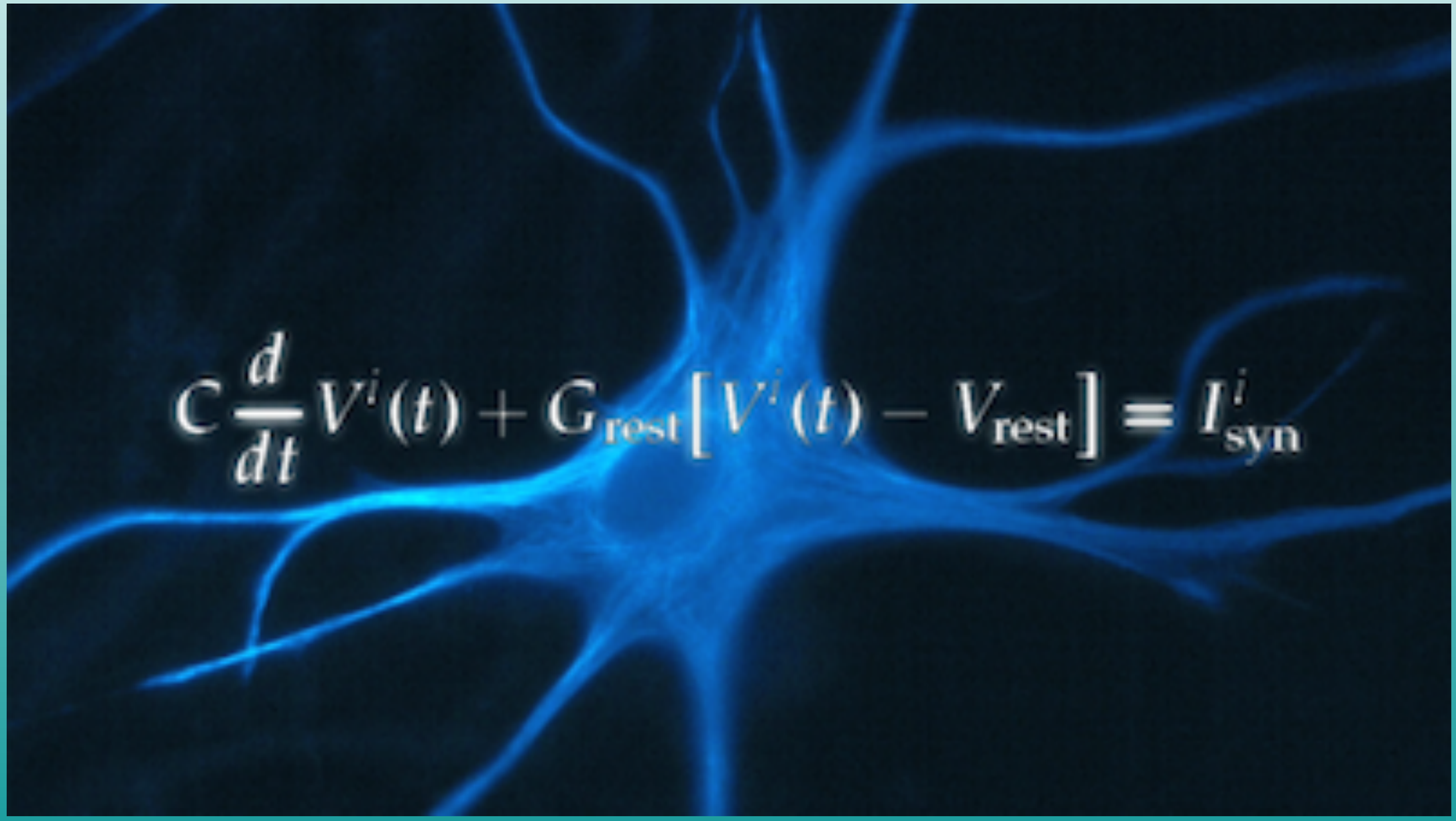
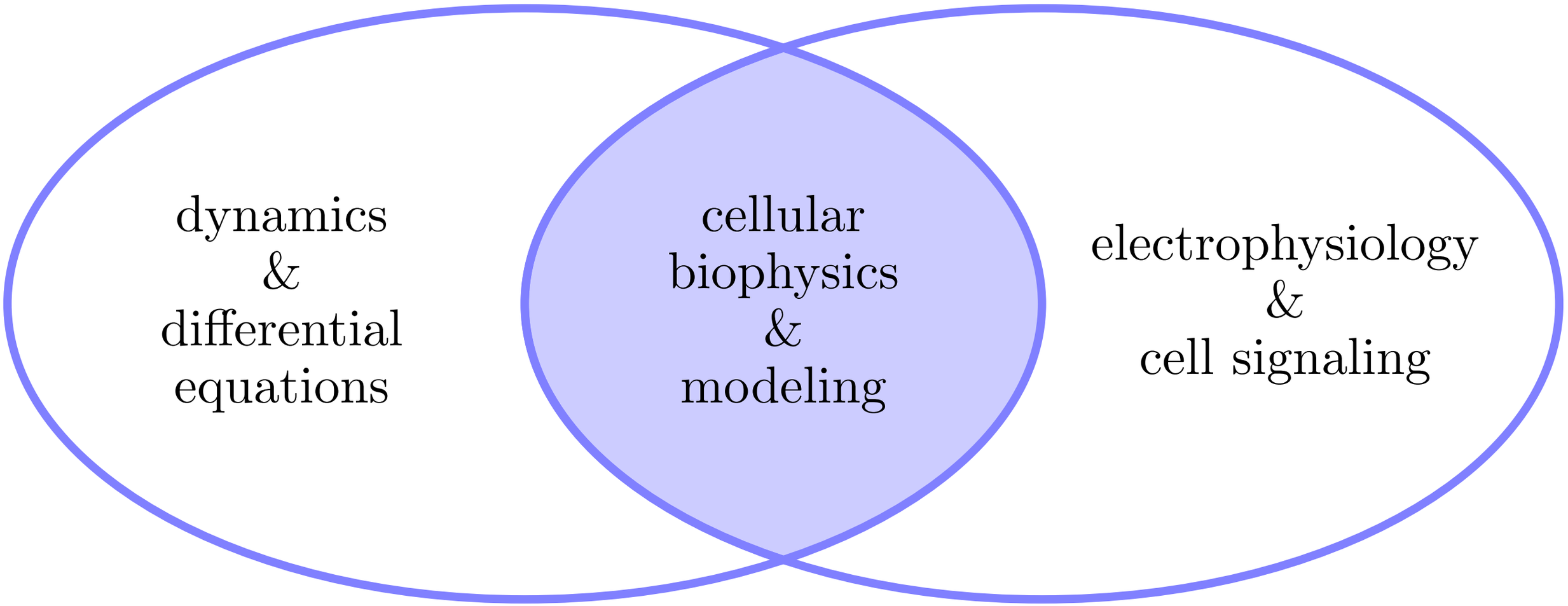
Cellular Biophysics & Modeling - APSC 351

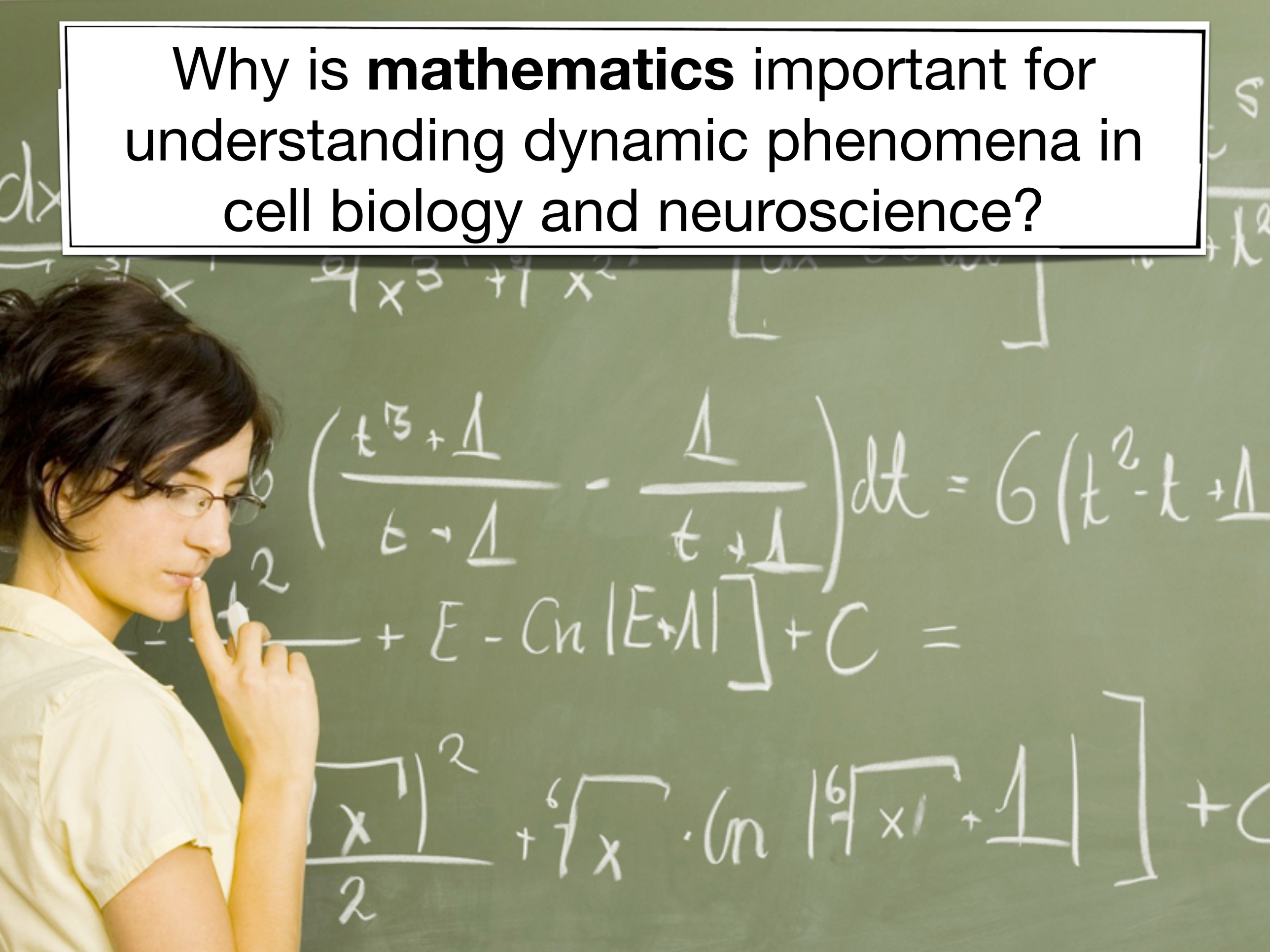


mathematics

neuroscience



Why is **mathematics** important for understanding dynamic phenomena in cell biology and neuroscience?



Dynamical phenomena can only be understood using mathematical and computational techniques

(2c) $\frac{dy}{dt} = y(y-1)(5-y)$ $\quad 0 = y_{ss}(y_{ss}-1)(5-y_{ss})$

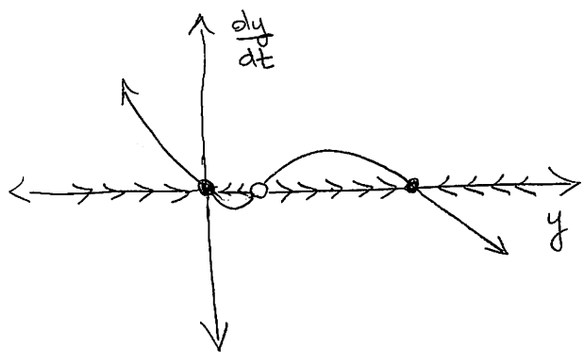
$f(y) = y(y-1)(5-y)$ $\quad y_{ss} \in \{0, 1, 5\}$

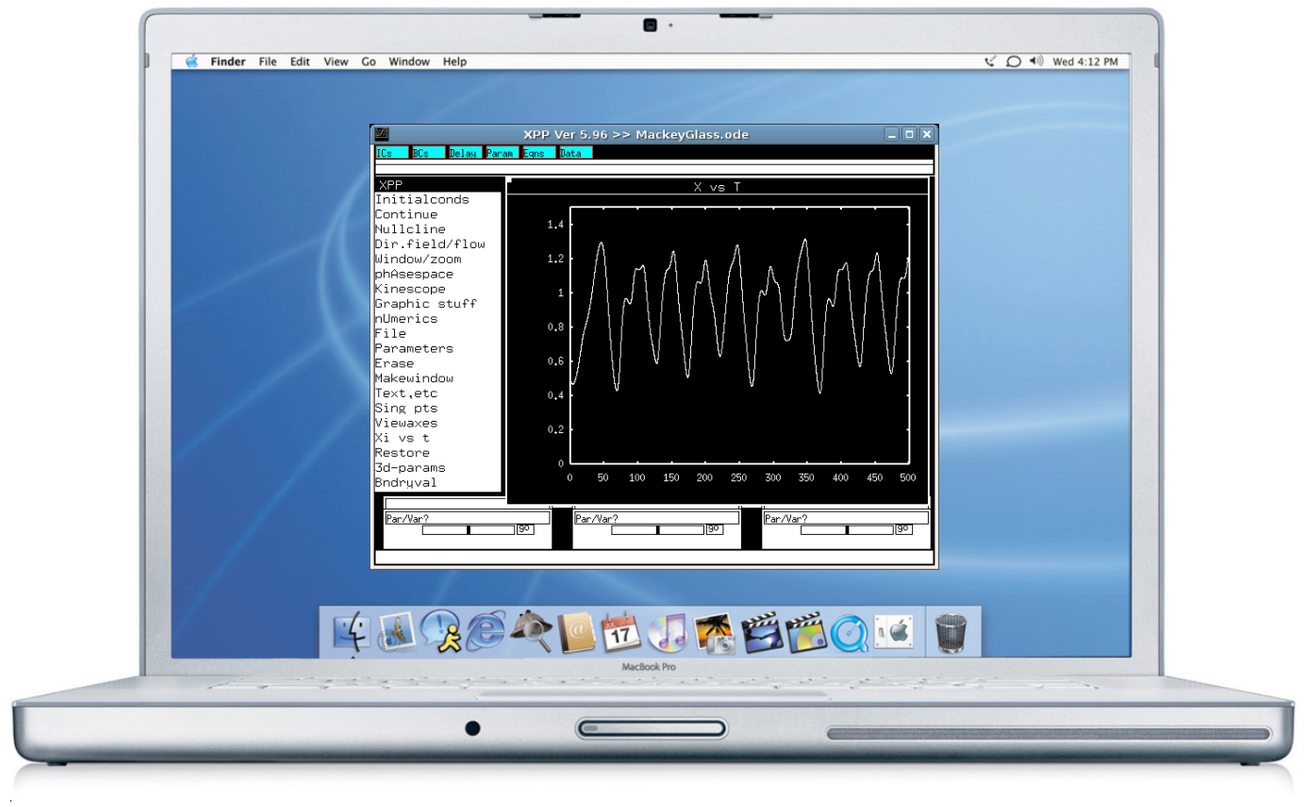
$f'(y) = (y-1)(5-y) + y(5-y) - y(y-1)$

$y_{ss}=0$ is stable because $f'(0)<0$

$y_{ss}=1$ is unstable because $f'(1)>0$

$y_{ss}=5$ is stable because $f'(5)<0$





All you need to know is calculus! I will teach you <u>nonlinear dynamics</u> in this <u>cell biophysical context</u>

Emphasis on intuitive graphical techniques

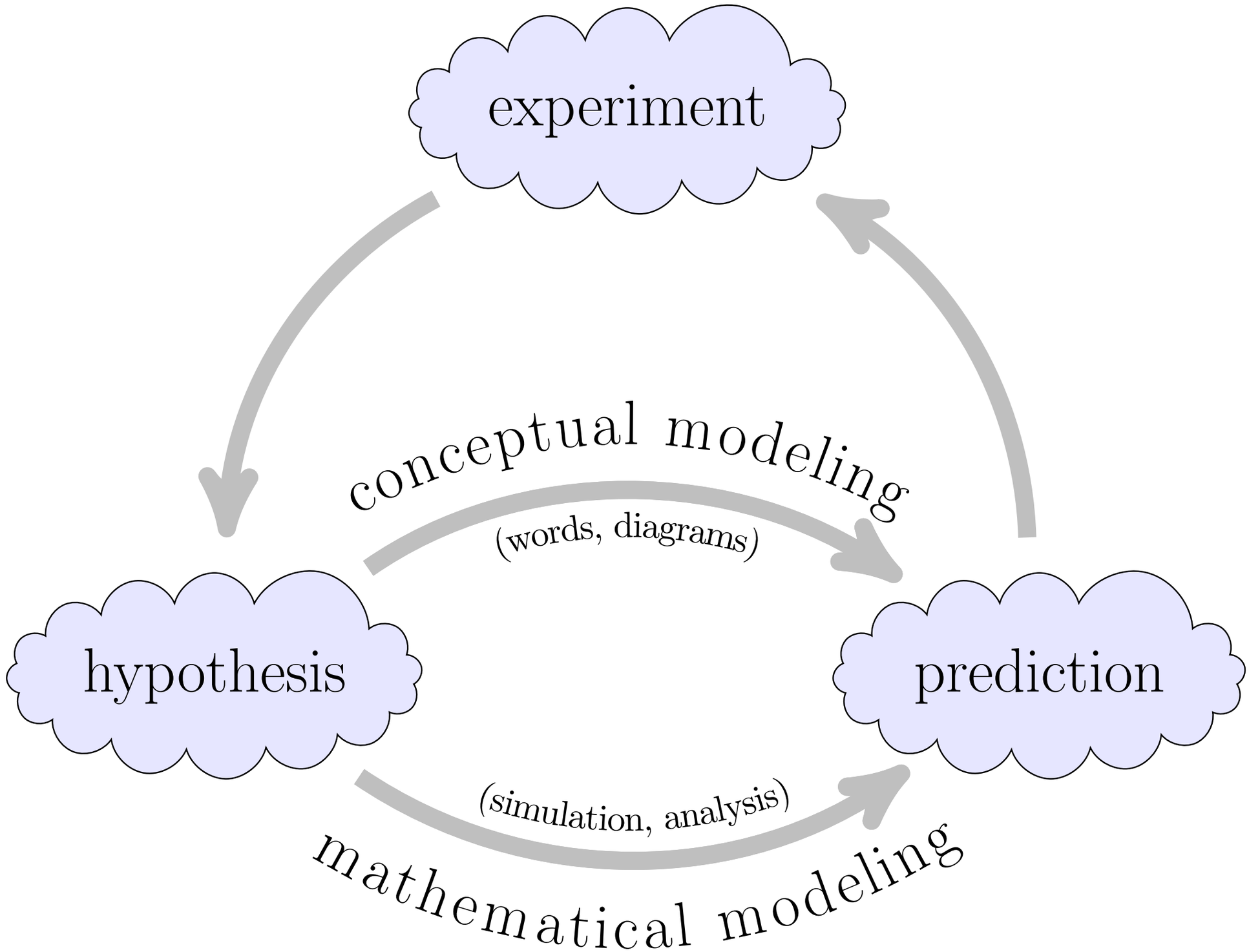


Figure 1.3 The cycle of experiment, hypothesis and prediction in the biological sciences. Moving from hypothesis to prediction requires either conceptual or mathematical modeling.

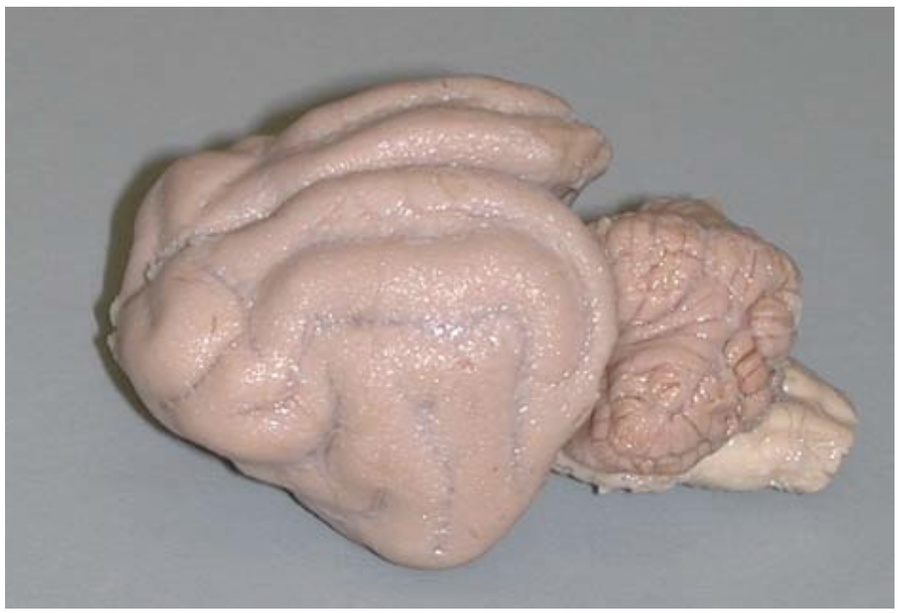
What is the basic plan of the brain?

Ask 10 of the world's leading neuroscientists how the brain works—how it thinks, feels, perceives, and acts as a unified whole—and you will get 10 different answers, unless they are very narrowly framed around the biophysics and chemistry of nerve impulse conduction and synaptic transmission.

Larry W. Swanson
Brain Architecture

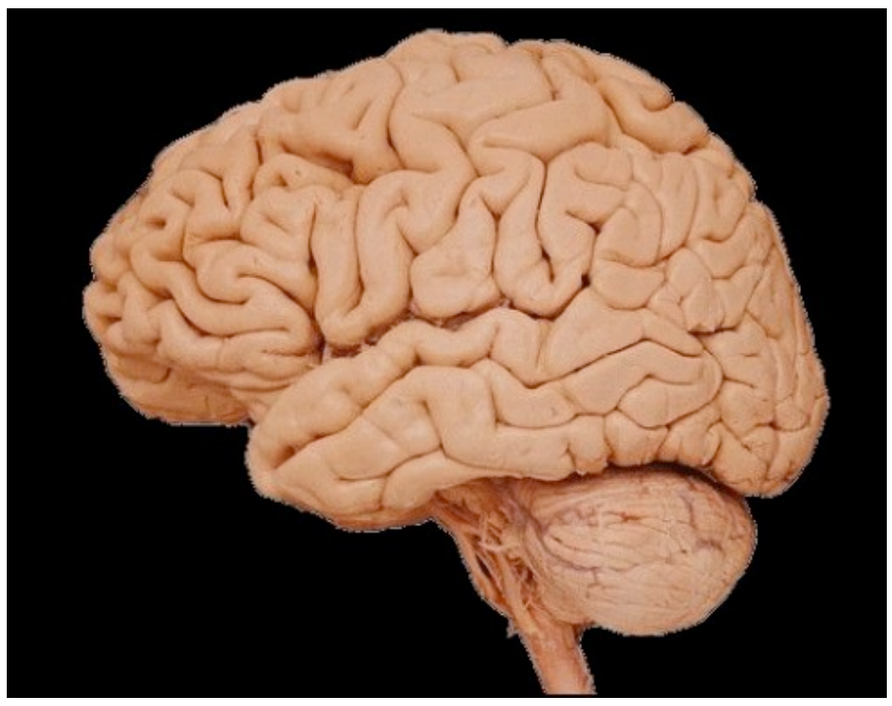
comparative gross neuroanatomy

frog



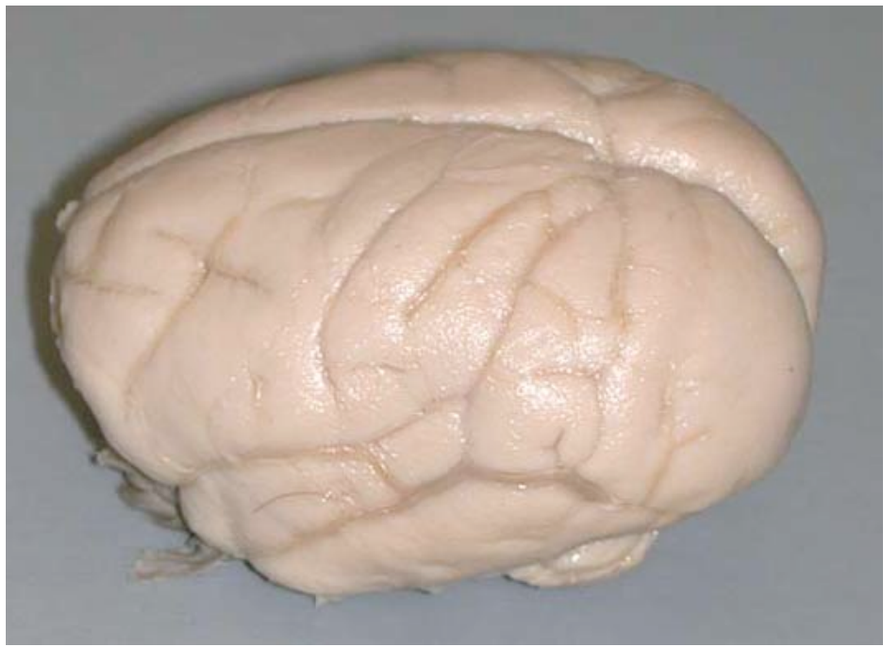
cat

rat



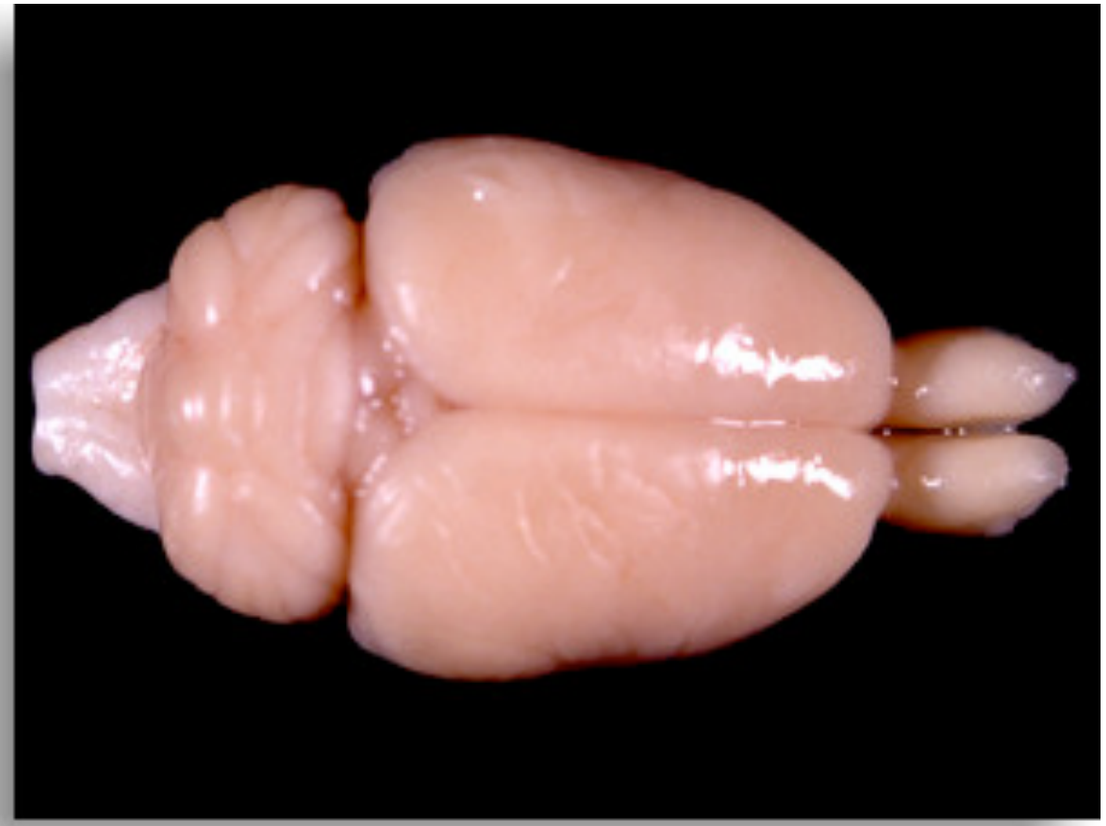
human

monkey

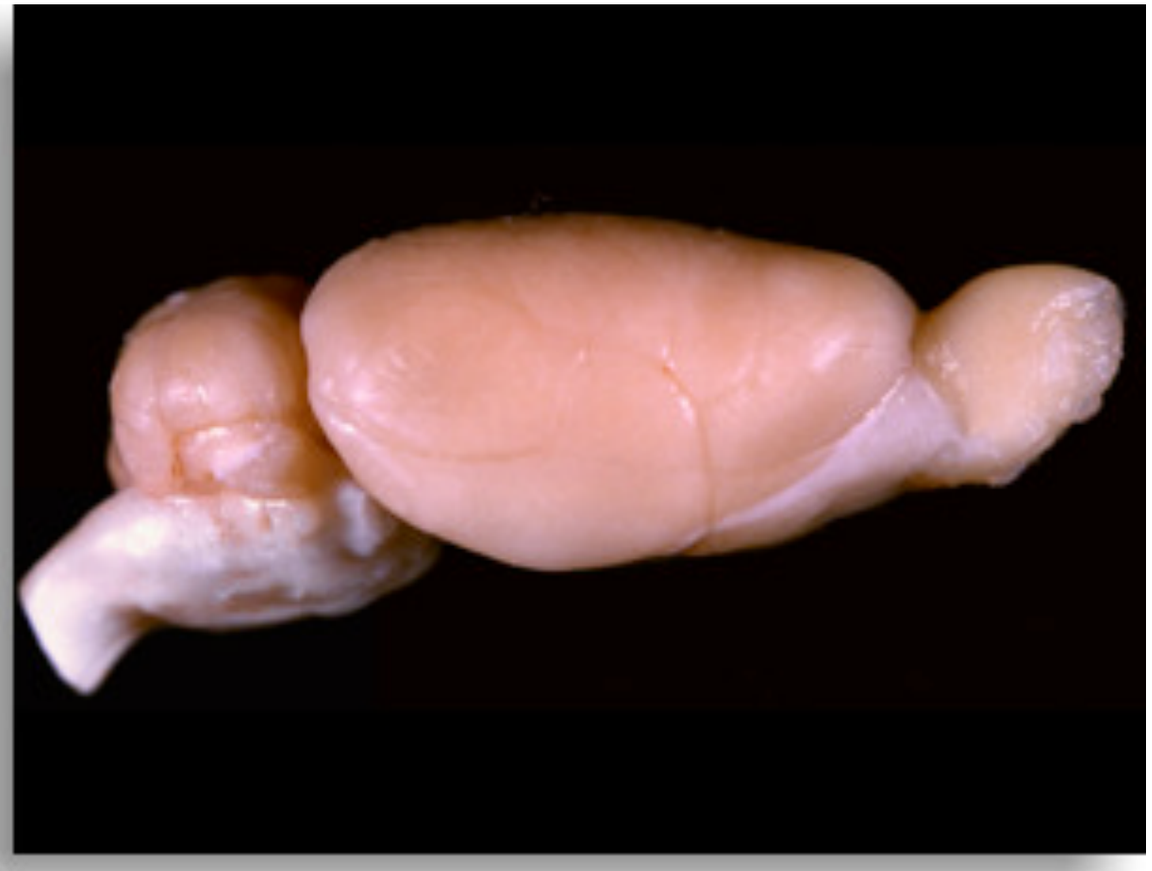


http://serendip.brynmawr.edu/bb/kinser/Home1.html

whole rat brain

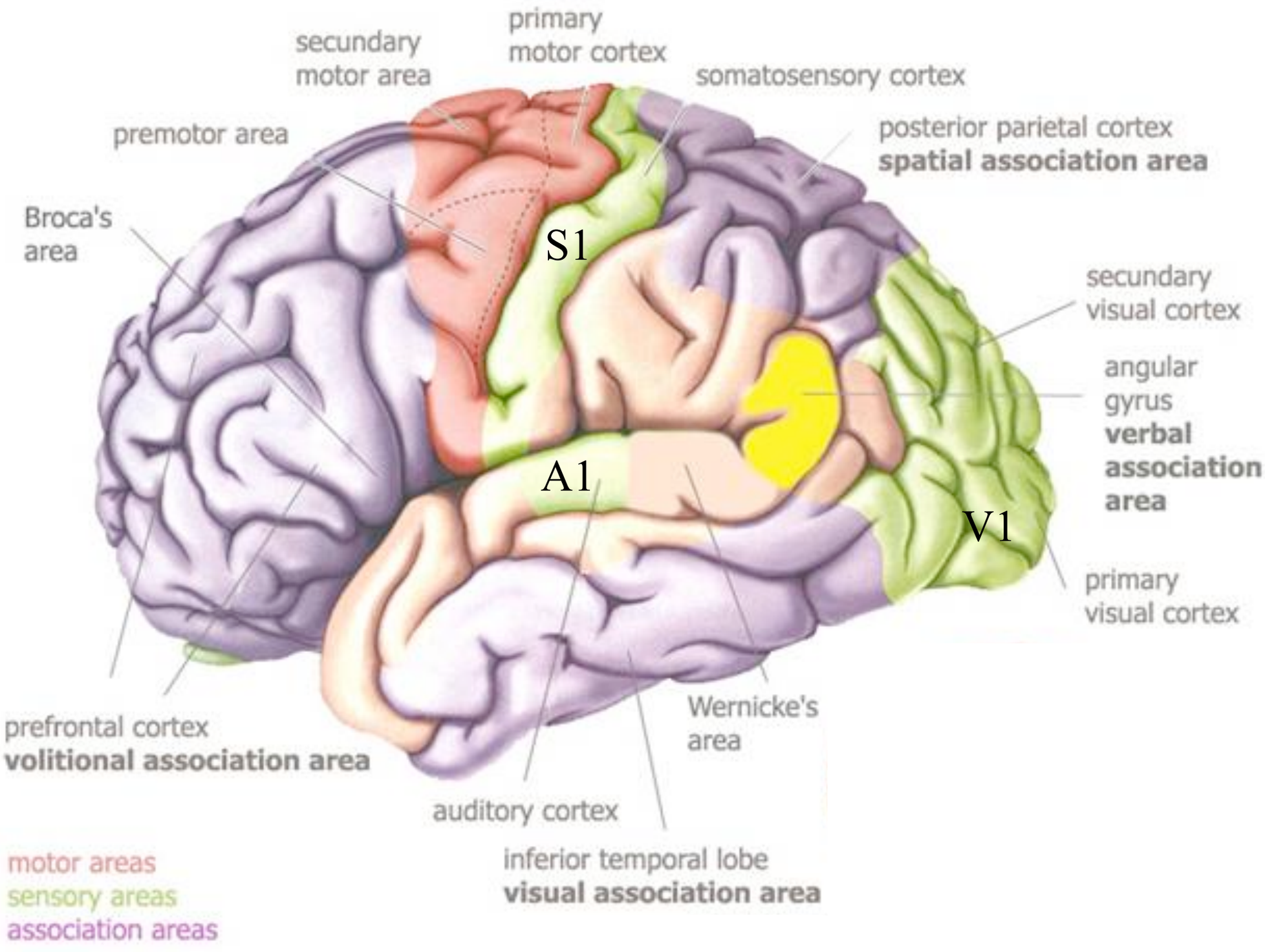


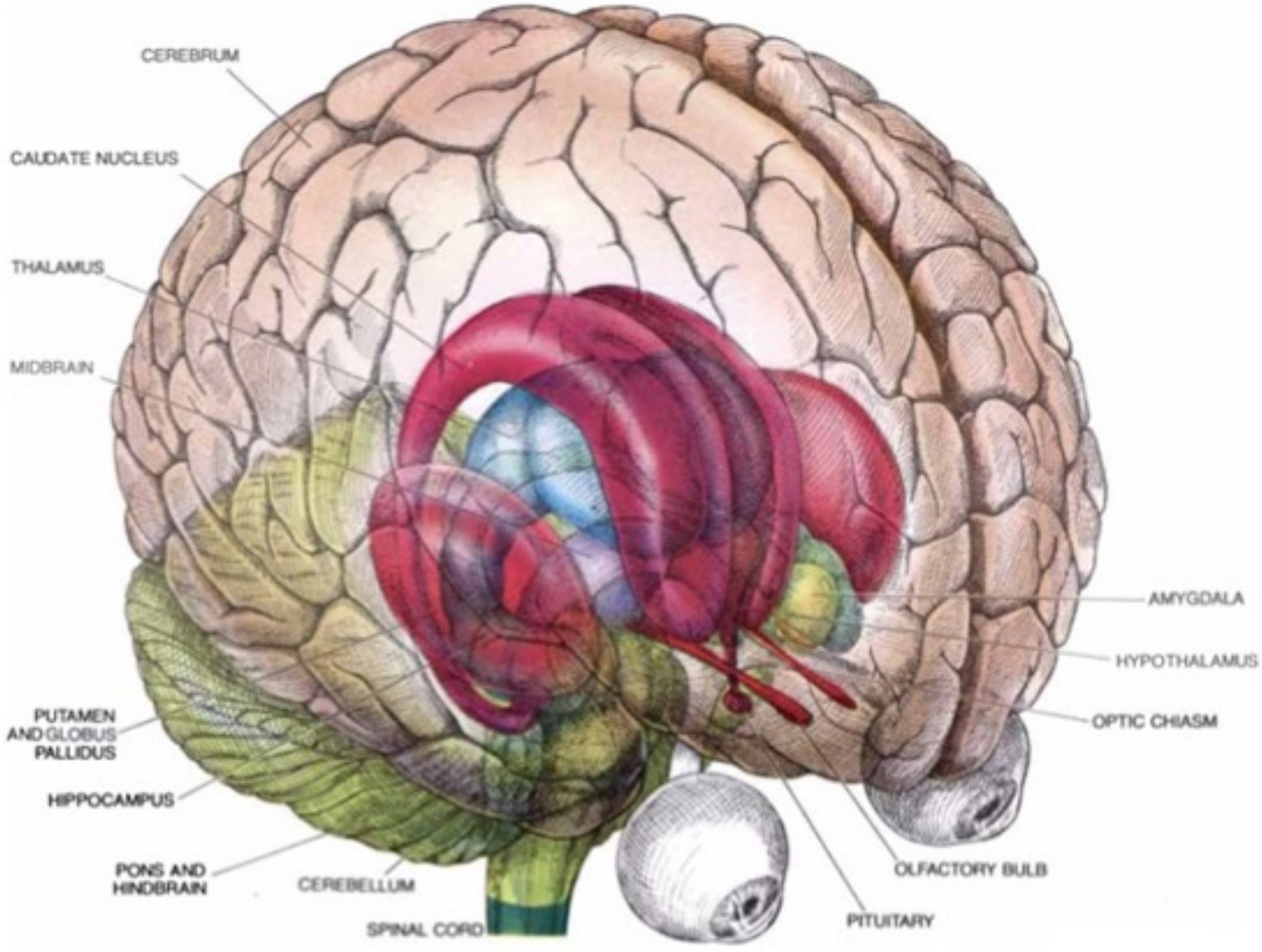
top view

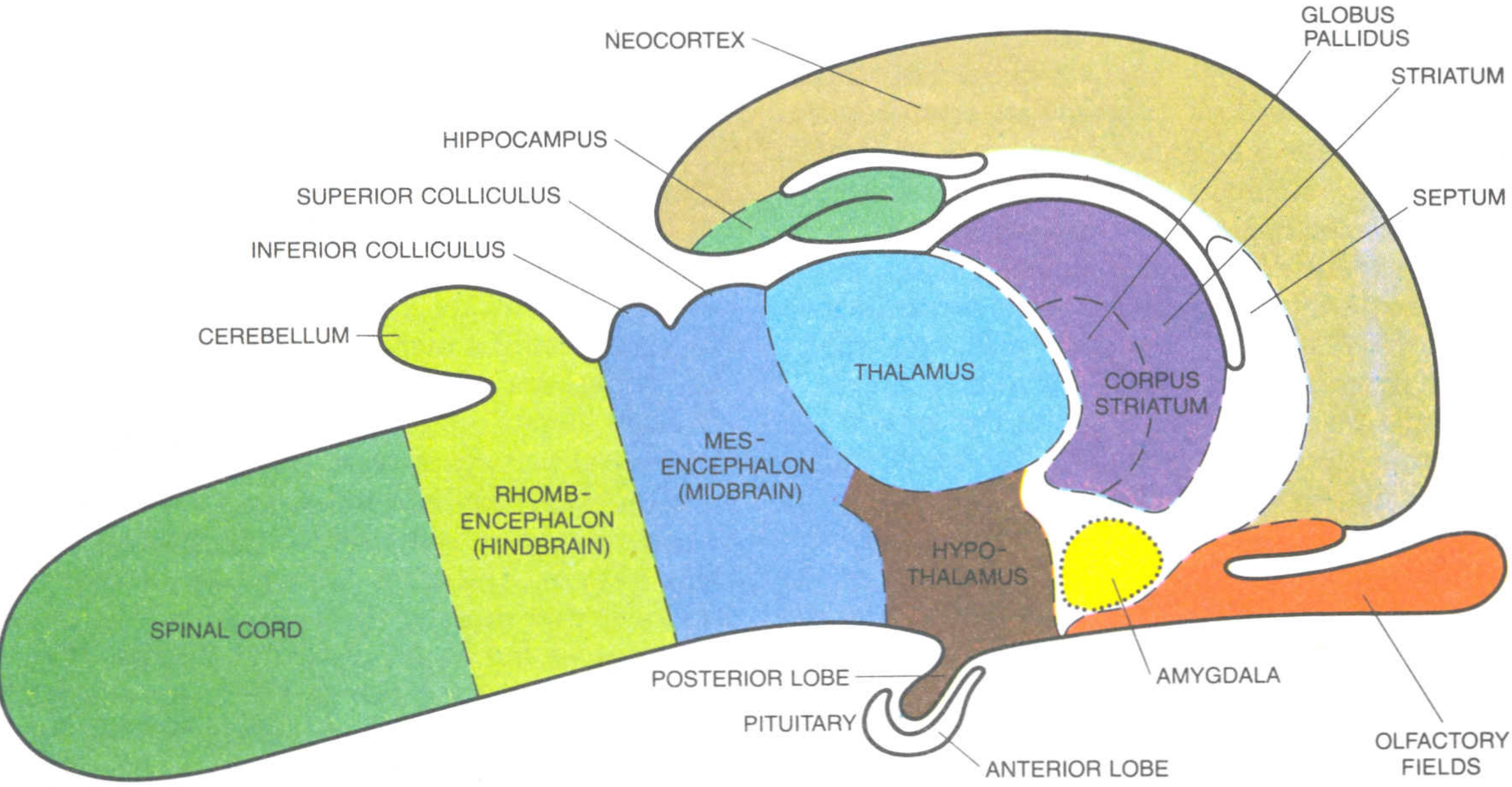


side view

http://www.apuche.org/OIA/

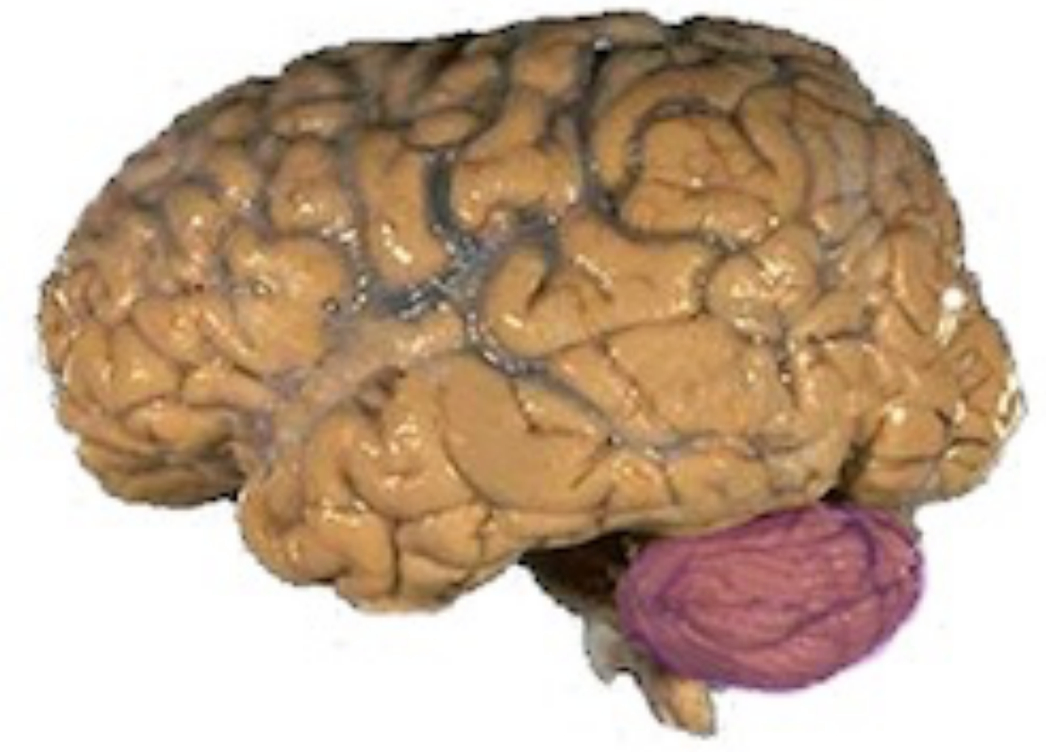

secundary
motor area
primary
motor cortex
somatosensory cortex
premotor area
posterior parietal cortex
spatial association area
Broca's
area
S1
secundary
visual cortex
angular
gyrus
verbal
association
area
A1
V1
primary
visual cortex
Wernicke's
area
prefrontal cortex
volitional association area
auditory cortex
inferior temporal lobe
visual association area
motor areas
sensory areas
association areas


CEREBRUM
CAUDATE NUCLEUS
THALAMUS
MIDBRAIN
PUTAMEN AND GLOBUS PALLIDUS
HIPPOCAMPUS
PONS AND HINDBRAIN
CEREBELLUM
SPINAL CORD
AMYGDALA
HYPOTHALAMUS
OPTIC CHIASM
OLFACTORY BULB
PITUITARY


NEOCORTEX
GLOBUS PALLIDUS
STRIATUM
HIPPOCAMPUS
SEPTUM
SUPERIOR COLLICULUS
INFERIOR COLLICULUS
CEREBELLUM
THALAMUS
CORPUS STRIATUM
MES-ENCEPHALON (MIDBRAIN)
RHOMB-ENCEPHALON (HINDBRAIN)
HYPO-THALAMUS
SPINAL CORD
POSTERIOR LOBE
AMYGDALA
PITUITARY
OLFACTORY FIELDS
ANTERIOR LOBE

How many neurons are there in the brain?

200 – 400 billion stars
in Milky Way galaxy



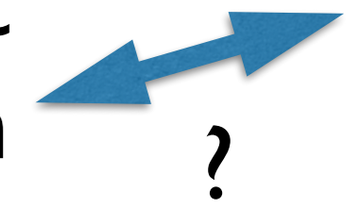
10 – 100 billion neurons
in human brain

The iPhone 15 Pro contains 19 billion transistors

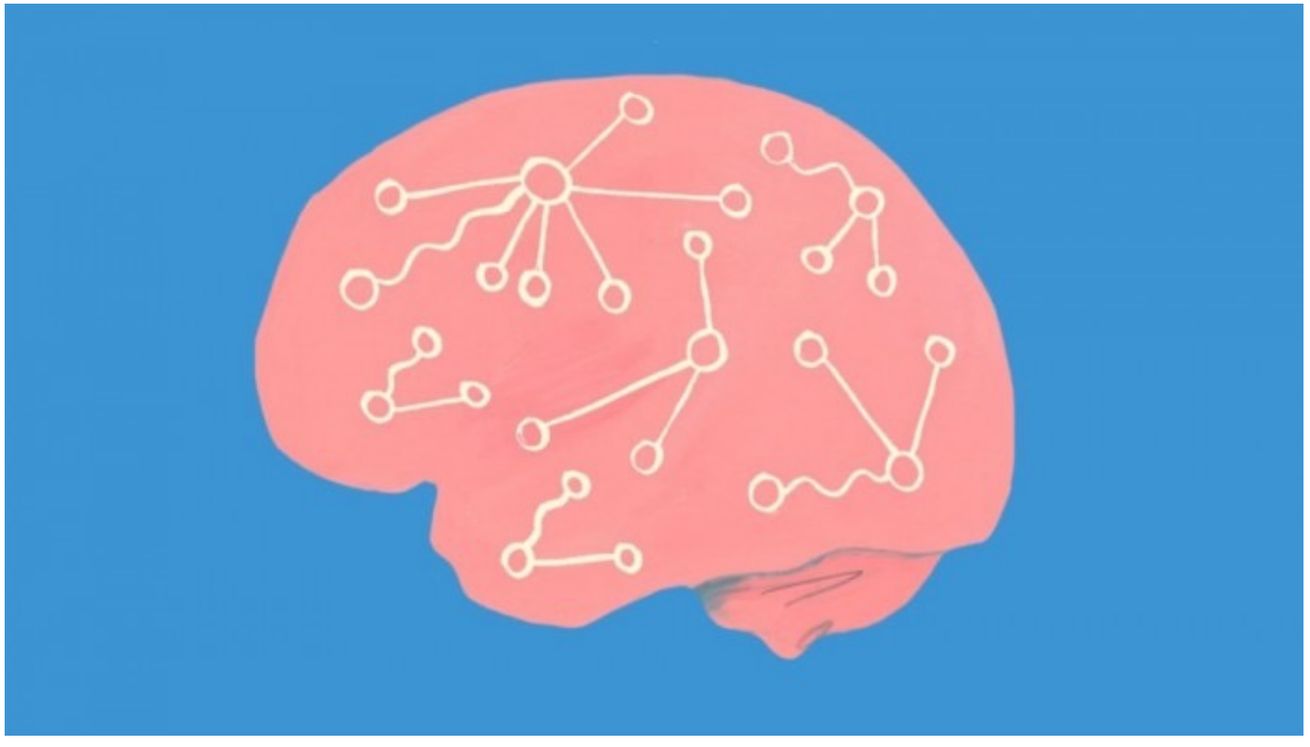
Why are we comparing neurons with transistors???

network
computer
central processing unit
integrated circuit
transistor

brain
microcircuit
neuron
synapse
signaling complex
ion channel
protein phosphorylation

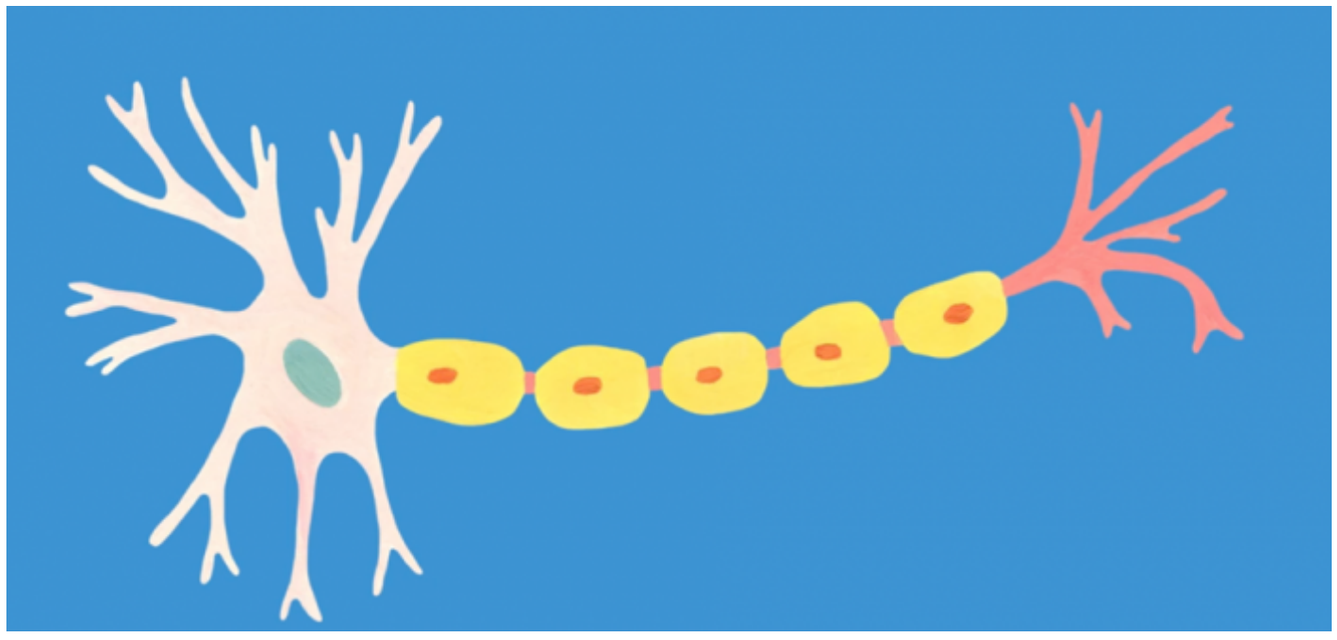


?



The **neuron doctrine** is the working hypothesis that has become the basis of modern neuroscience.

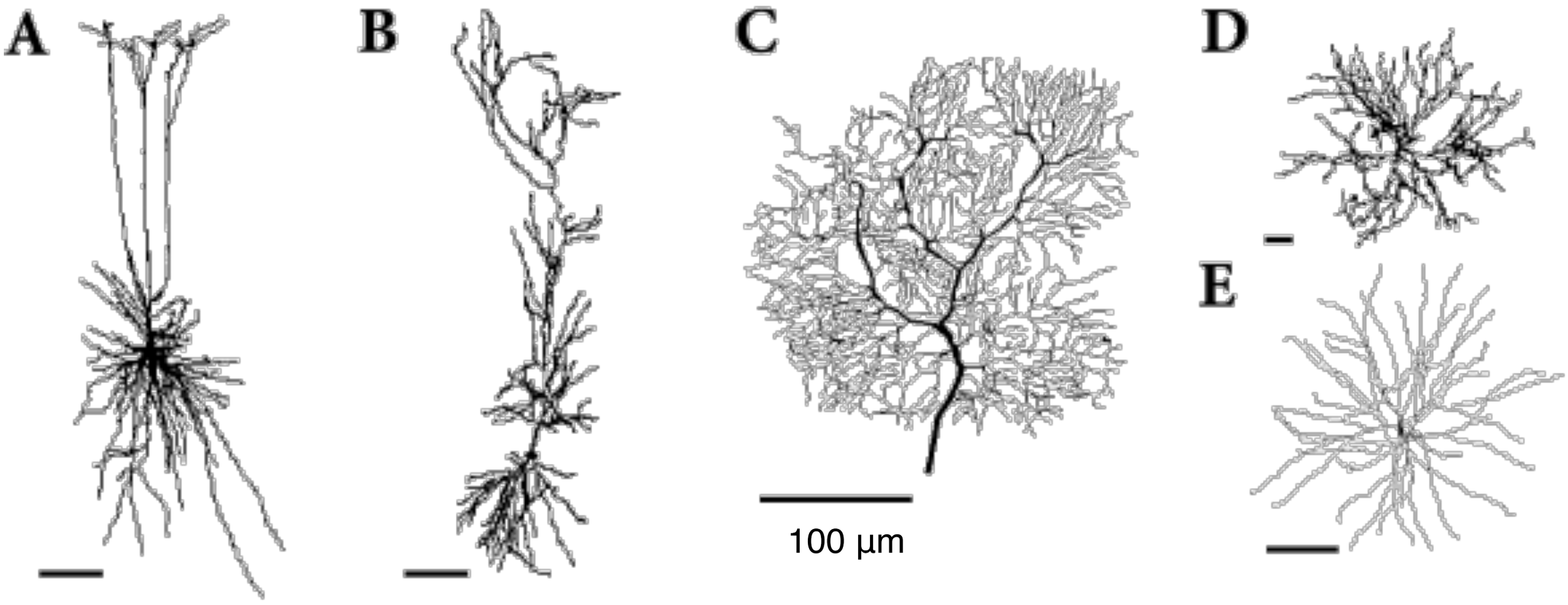
(1) the neuron is an independent cellular unit



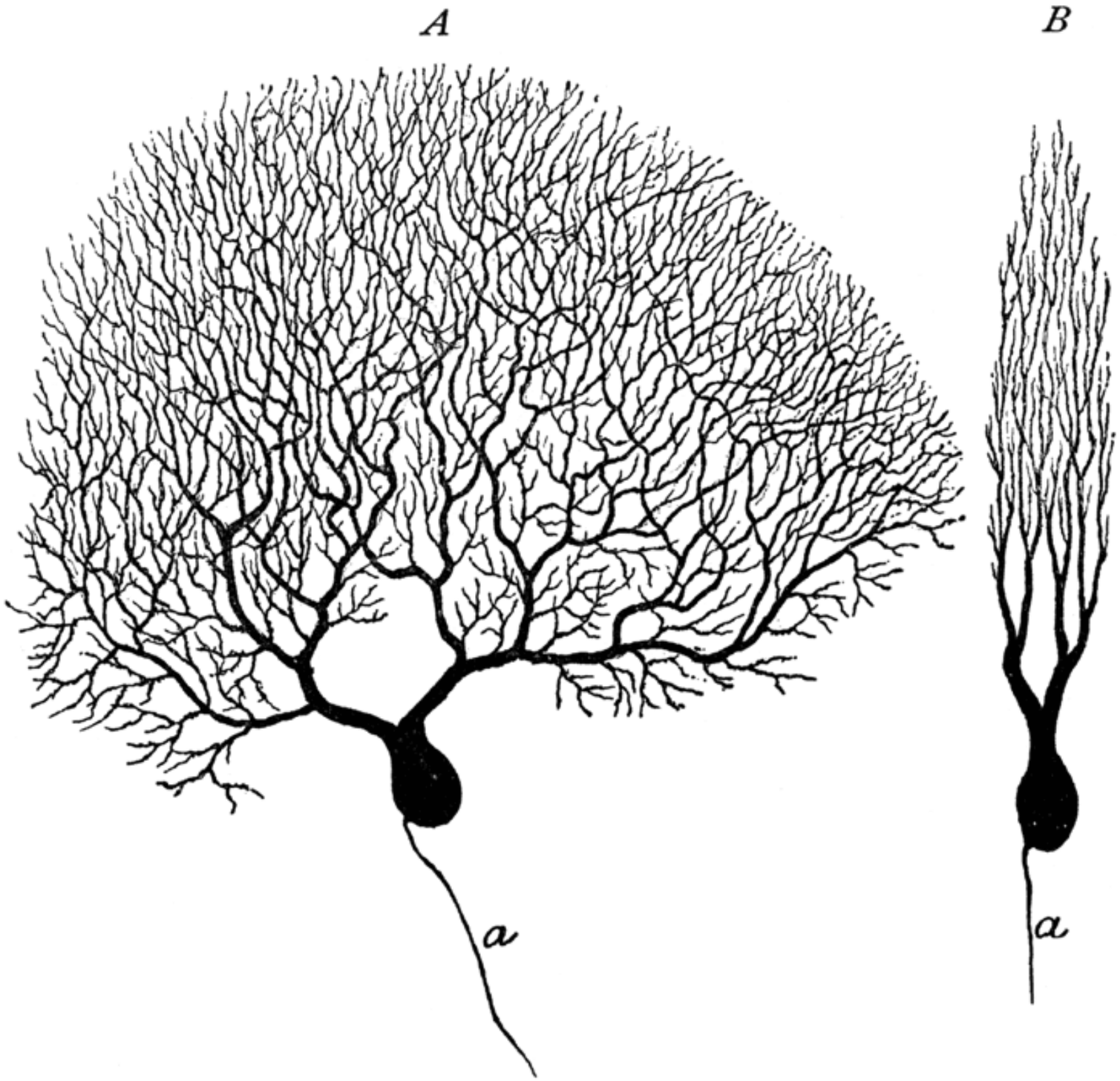
(2) neurons are polarized to mediate input/output functions

How many **types** of neurons per brain?

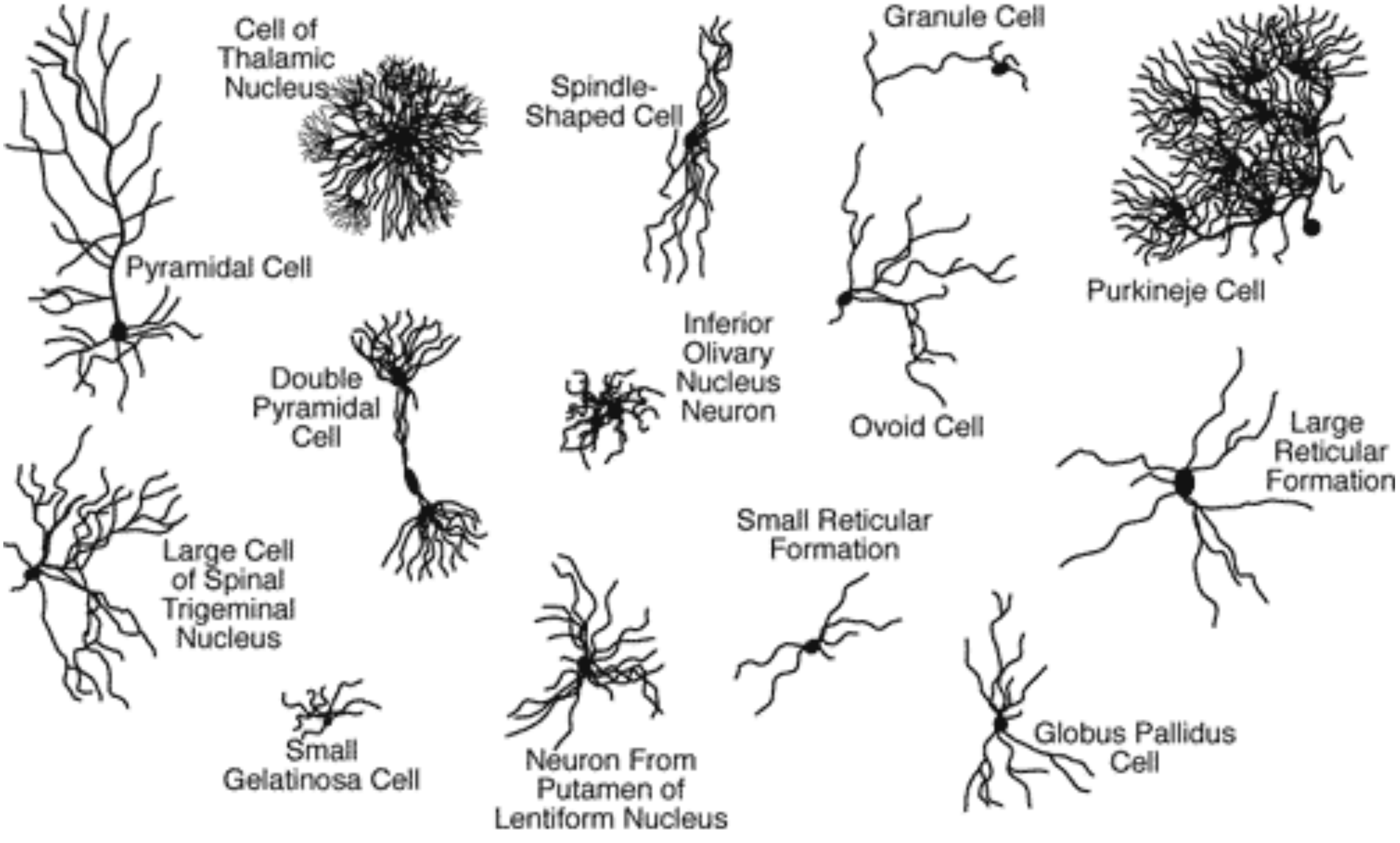
morphology of various types of neurons



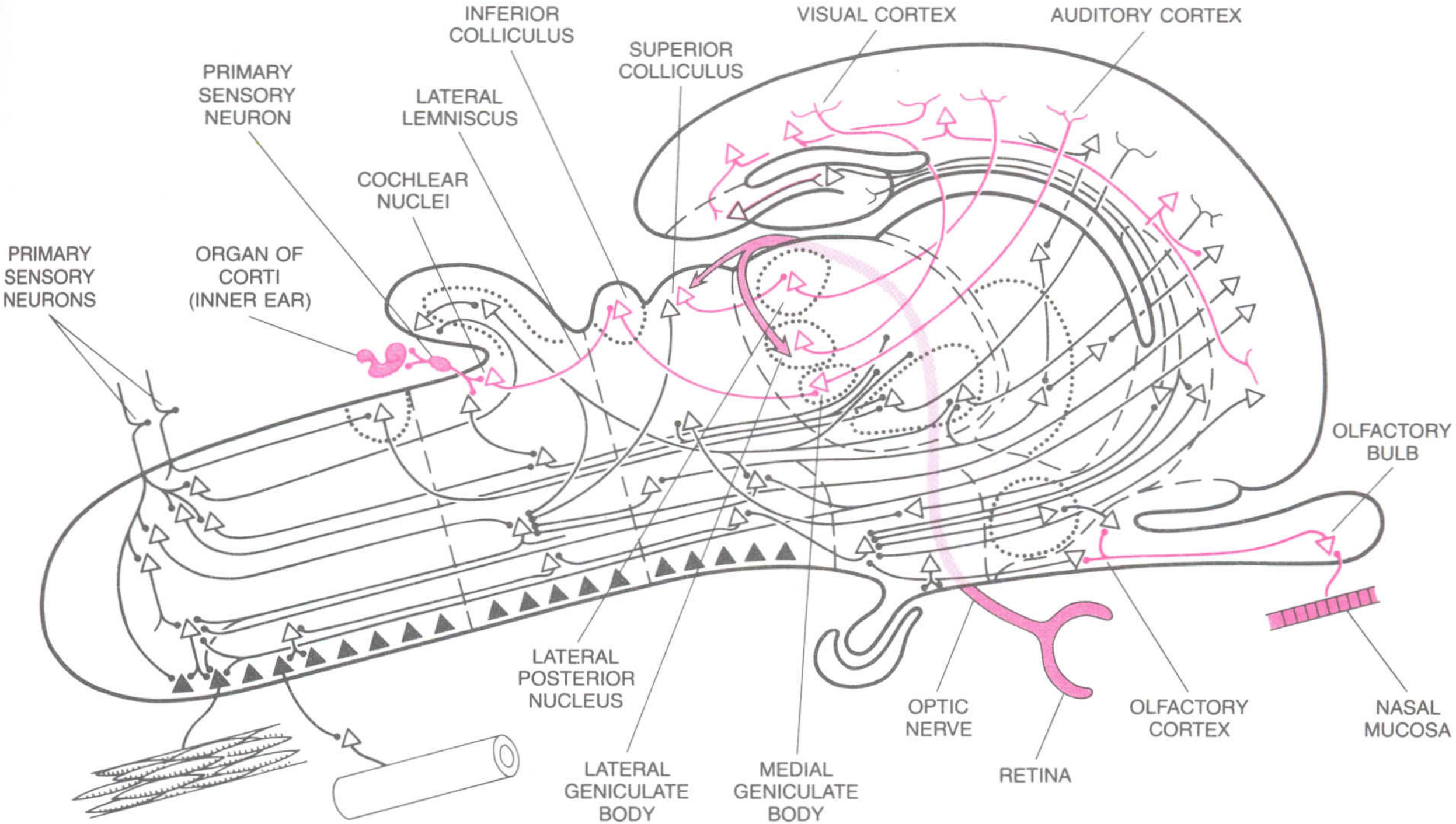
A. Pyramidal neuron from a deep cortical layer. B. Pyramidal neuron from the CA1 of the hippocampus. C. Purkinje cell from the cerebellum. D. Motoneuron from the spinal cord (axon not reconstructed). E. Stellate neuron from the neocortex. http://NeuroMorpho.org. Scale bars represents 100 µm.

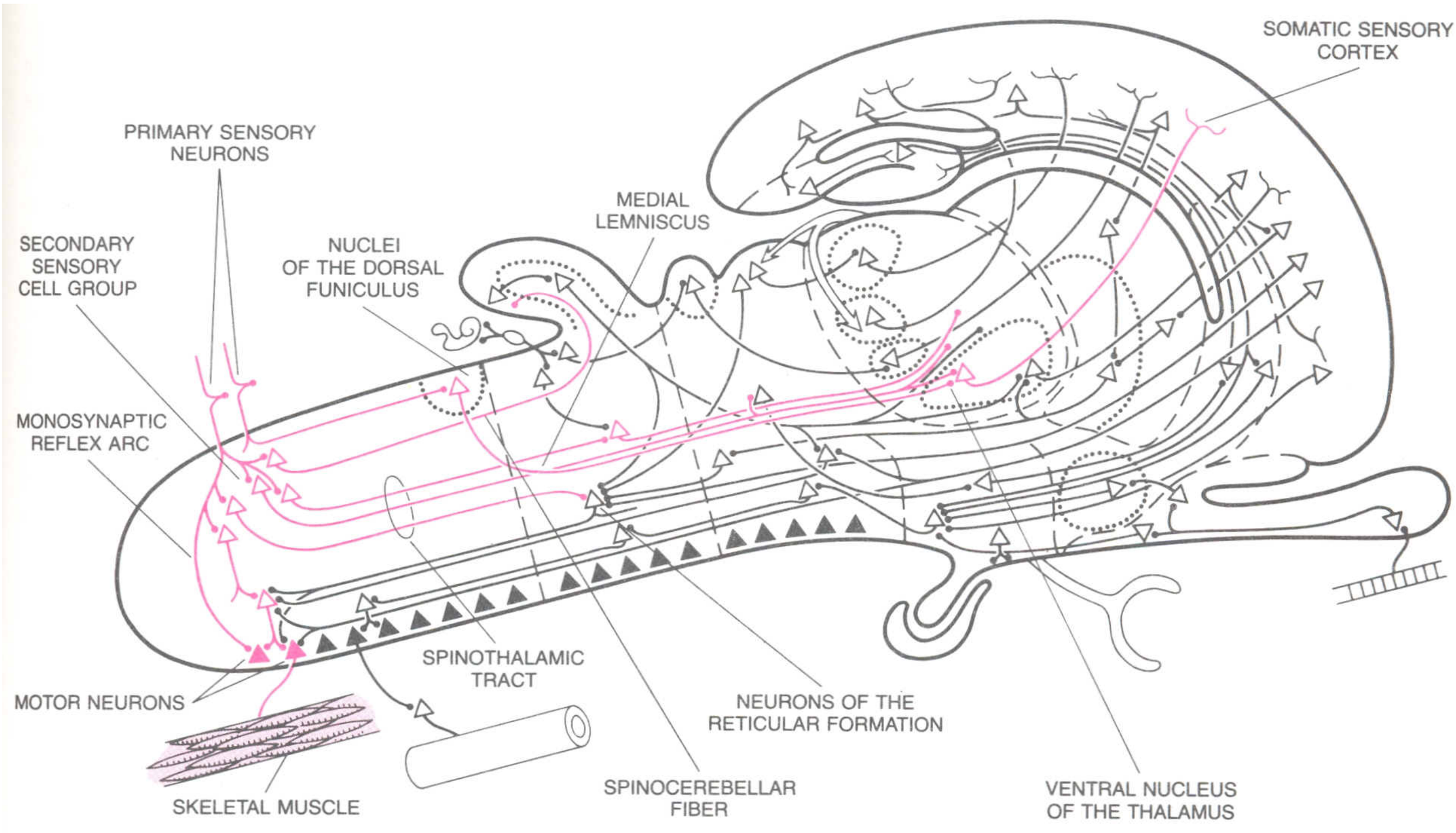


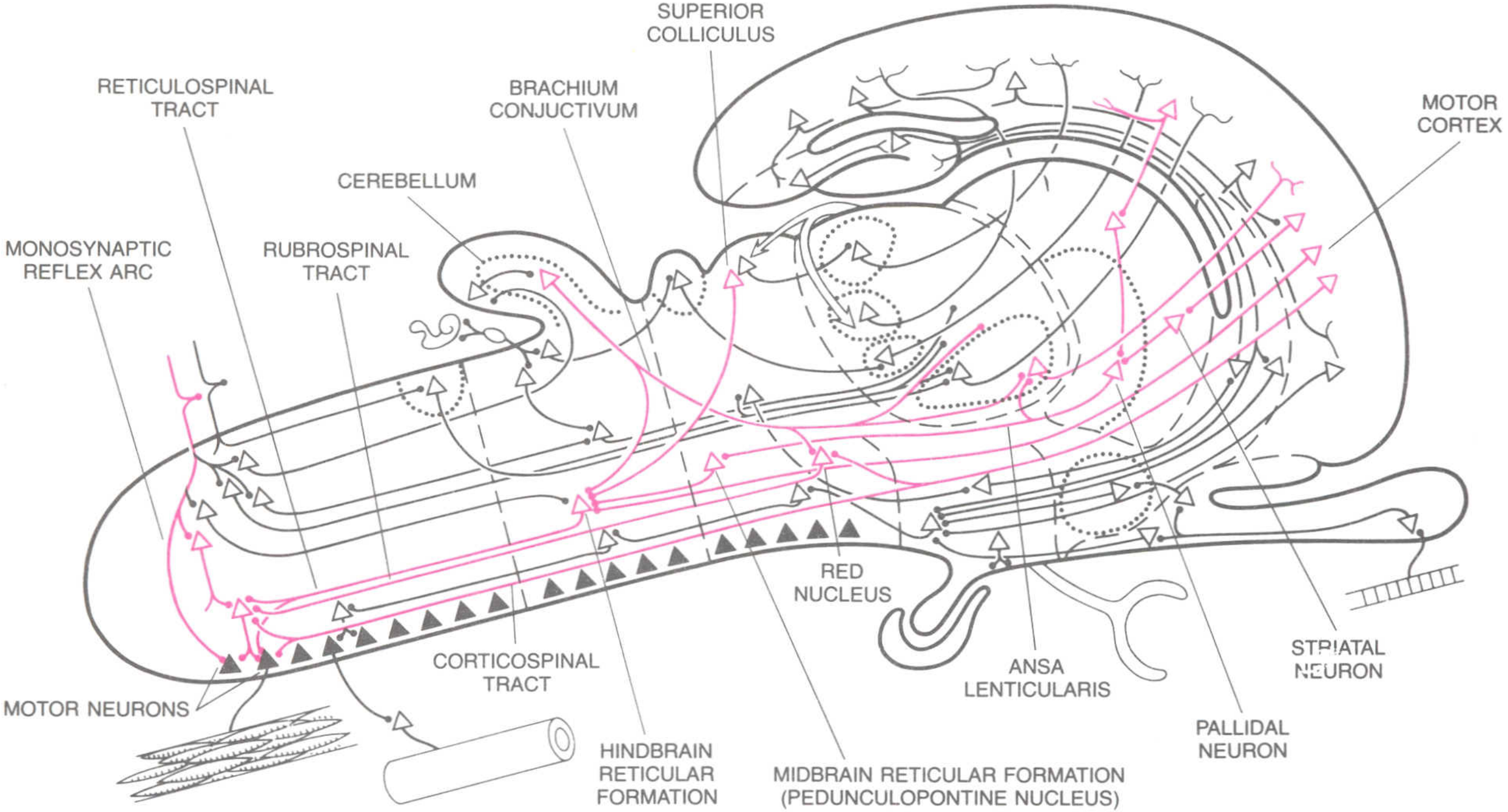
Purkinje neuron of the cerebellum - two different orientations


Cell of Thalamic Nucleus
Pyramidal Cell
Double Pyramidal Cell
Large Cell of Spinal Trigeminal Nucleus
Small Gelatinosa Cell
Spindle-Shaped Cell
Inferior Olivary Nucleus Neuron
Neuron From Putamen of Lentiform Nucleus
Granule Cell
Ovoid Cell
Small Reticular Formation
Purkineje Cell
Large Reticular Formation
Globus Pallidus Cell

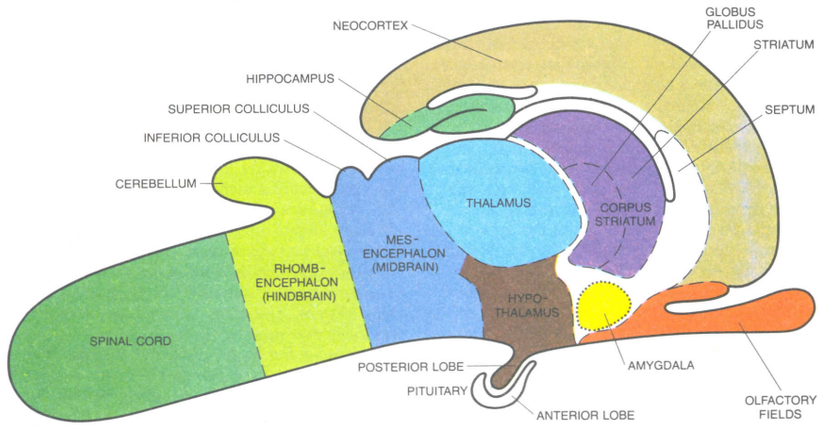
How are these neurons wired up?


INFERIOR COLLICULUS
VISUAL CORTEX
AUDITORY CORTEX
SUPERIOR COLLICULUS
PRIMARY SENSORY NEURON
LATERAL LEMNISCUS
COCHLEAR NUCLEI
PRIMARY SENSORY NEURONS
ORGAN OF CORTI (INNER EAR)
OLFACTORY BULB
LATERAL POSTERIOR NUCLEUS
OPTIC NERVE
OLFACTORY CORTEX
NASAL MUCOSA
LATERAL GENICULATE BODY
MEDIAL GENICULATE BODY
RETINA


SOMATIC SENSORY CORTEX
PRIMARY SENSORY NEURONS
MEDIAL LEMNISCUS
SECONDARY SENSORY CELL GROUP
NUCLEI OF THE DORSAL FUNICULUS
MONOSYNAPTIC REFLEX ARC
SPINOTHALAMIC TRACT
MOTOR NEURONS
NEURONS OF THE RETICULAR FORMATION
SKELETAL MUSCLE
SPINOCEREBELLAR FIBER
VENTRAL NUCLEUS OF THE THALAMUS


SUPERIOR COLLICULUS
RETICULOSPINAL TRACT
BRACHIUM CONJUCTIVUM
MOTOR CORTEX
CEREBELLUM
MONOSYNAPTIC REFLEX ARC
RUBROSPINAL TRACT
RED NUCLEUS
CORTICOSPINAL TRACT
ANSA LENTICULARIS
STRIATAL NEURON
MOTOR NEURONS
PALLIDAL NEURON
HINDBRAIN RETICULAR FORMATION
MIDBRAIN RETICULAR FORMATION (PEDUNCULOPONTINE NUCLEUS)

The Organization of the Brain



The brain and spinal cord of mammals, including man, consist of some billions of neurons, and a single neuron may connect with thousands of others. How is this enormous three-dimensional network organized?

• • •

Walle J. H. Nauta and Michael Feirtag

September, 1979

Why read primary scientific literature?

J Neurophysiol 103: 3472–3489, 2010.

Characterization of Voltage-Gated K^+ Currents Contributing to Subthreshold Membrane Potential Oscillations in Hippocampal CA1 Interneurons

2010; doi:10.1152/jn.00848.2009. CA1 inhibitory interneurons at the stratum lacunosum-moleculare and radiatum junction (LM/RAD-INs) display subthreshold membrane potential oscillations (MPOs) involving voltage-dependent Na^+ and A-type K^+ currents. LM/RAD-INs also express other voltage-gated K^+ currents, although their properties and role in MPOs remain unclear. Here, we characterized these voltage-gated K^+ currents and investigated their role in MPOs. Using outside-out patch recordings from LM/RAD-IN somata, we distinguished four voltage-gated K^+ currents based on their pharmacology and activation/inactivation properties: a fast delayed rectifier current (I_{Kfast}), a slow delayed rectifier current (I_{Kslow}), a rapidly inactivating A-type current (I_A), and a slowly inactivating current (I_D). Their relative contribution to the total K^+ current was $I_A > I_{Kfast} > I_{Kslow} = I_D$. The presence of I_D and the relative contributions of K^+ currents in LM/RAD-INs are different from those of other CA1 interneurons, suggesting the presence of differential complement of K^+ currents in subgroups of interneurons. We next determined whether these K^+ currents were sufficient for MPO generation using a single-compartment model of LM/RAD-INs. The model captured the subthreshold voltage dependence of MPOs. Moreover, all K^+ currents were active at subthreshold potentials but I_D, I_A, and the persistent sodium current (I_{NaP}) were most active near threshold. Using impedance analysis, we found that I_A and I_{NaP} contribute to MPO generation by modulating peak spectral frequency during MPOs and governing the voltage range over which MPOs occur. Our findings uncover a differential expression of a complement of K^+ channels that underlies intrinsic rhythmic activity in inhibitory interneurons.

By the end of the semester you will totally get this.

High Frequency Stimulation of the Subthalamic Nucleus Eliminates Pathological Thalamic Rhythmicity in a Computational Model

Abstract. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) has recently been recognized as an important form of intervention for alleviating motor symptoms associated with Parkinson's disease, but the mechanism underlying its effectiveness remains unknown. Using a computational model, this paper considers the hypothesis that DBS works by replacing pathologically rhythmic basal ganglia output with tonic, high frequency firing. In our simulations of parkinsonian conditions, rhythmic inhibition from GPi to the thalamus compromises the ability of thalamocortical relay (TC) cells to respond to depolarizing inputs, such as sensorimotor signals. High frequency stimulation of STN regularizes GPi firing, and this restores TC responsiveness, despite the increased frequency and amplitude of GPi inhibition to thalamus that result. We provide a mathematical phase plane analysis of the mechanisms that determine TC relay capabilities in normal, parkinsonian, and DBS states in a reduced model. This analysis highlights the differences in deinactivation of the low-threshold calcium T-current that we observe in TC cells in these different conditions. Alternative scenarios involving convergence of thalamic signals in the cortex are also discussed, and predictions associated with these results, including the occurrence of rhythmic rebound bursts in certain TC cells in parkinsonian states and their drastic reduction by DBS, are stated. These results demonstrate how DBS could work by increasing firing rates of target cells, rather than shutting them down.

Keywords: deep brain stimulation, basal ganglia, Parkinson's disease

JONATHAN E. RUBIN

DAVID TERMAN

Journal of Computational Neuroscience 16, 211–235, 2004

By the end of the semester you will totally get this.

BK_{Ca}-Cav Channel Complexes Mediate Rapid and Localized Ca^{2+}-Activated K^+ Signaling

Henrike Berkefeld,[1]* Claudia A. Sailer,[1,3]* Wolfgang Bildl,[1,2] Volker Rohde,[2] Jörg-Oliver Thumfart,[1] Silke Eble,[1] Norbert Klugbauer,[4] Ellen Reisinger,[1] Josef Bischofberger,[1] Dominik Oliver,[1] Hans-Günther Knaus,[3] Uwe Schulte,[2]† Bernd Fakler[1]†

Large-conductance calcium- and voltage-activated potassium channels (BK_{Ca}) are dually activated by membrane depolarization and elevation of cytosolic calcium ions (Ca^{2+}). Under normal cellular conditions, BK_{Ca} channel activation requires Ca^{2+} concentrations that typically occur in close proximity to Ca^{2+} sources. We show that BK_{Ca} channels affinity-purified from rat brain are assembled into macromolecular complexes with the voltage-gated calcium channels Cav1.2 (L-type), Cav2.1 (P/Q-type), and Cav2.2 (N-type). Heterologously expressed BK_{Ca}-Cav complexes reconstitute a functional "Ca^{2+} nanodomain" where Ca^{2+} influx through the Cav channel activates BK_{Ca} in the physiological voltage range with submillisecond kinetics. Complex formation with distinct Cav channels enables BK_{Ca}-mediated membrane hyperpolarization that controls neuronal firing pattern and release of hormones and transmitters in the central nervous system.

…and this…

Persistent Sodium Current, Membrane Properties and Bursting Behavior of Pre-Bötzinger Complex Inspiratory Neurons In Vitro

…and this…

Del Negro, Christopher A., Naohiro Koshiya, Robert J. Butera, Jr., and Jeffrey C. Smith. Persistent sodium current, membrane properties and bursting behavior of pre-Bötzinger complex inspiratory neurons in vitro. *J Neurophysiol* 88: 2242–2250, 2002; 10.1152/jn.00081.2002. We measured persistent Na^+ current and membrane properties of bursting-pacemaker and nonbursting inspiratory neurons of the neonatal rat pre-Bötzinger complex (pre-BötC) in brain stem slice preparations with a rhythmically active respiratory network in vitro. In whole-cell recordings, slow voltage ramps ($\leq$100 mV/s) inactivated the fast, spike-generating Na^+ current and yielded N-shaped current-voltage relationships with nonmonotonic, negative-slope regions between -60 and -35 mV when the voltage-sensitive component was isolated. The underlying current was a TTX-sensitive persistent Na^+ current (I_{NaP}) since the inward current was present at slow voltage ramp speeds (3.3–100 mV/s) and the current was blocked by 1 μM TTX. We measured the biophysical properties of I_{NaP} after subtracting the voltage-insensitive "leak" current (I_{Leak}) in the presence of Cd^{2+} and in some cases tetraethylammonium (TEA). Peak I_{NaP} ranged from -50 to -200 pA at a membrane potential of -30 mV. Decreasing the speed of the voltage ramp caused time-dependent I_{NaP} inactivation, but this current was present at ramp speeds as low as 3.3 mV/s. I_{NaP} activated at -60 mV and obtained half-maximal activation near -40 mV. The subthreshold voltage dependence and slow inactivation kinetics of I_{NaP}, which closely resemble those of I_{NaP} mathematically modeled as a burst-generation mechanism in pacemaker neurons of the pre-BötC, suggest that I_{NaP} predominantly influences bursting dynamics of pre-BötC inspiratory pacemaker neurons in vitro. We also found that the ratio of persistent Na^+ conductance to leak conductance (g_{NaP}/g_{Leak}) can distinguish the phenotypic subpopulations of bursting pacemaker and nonbursting inspiratory neurons: pacemaker neurons showed $g_{NaP}/g_{Leak} > g_{NaP}/g_{Leak}$ in nonpacemaker cells ($P < 0.0002$). We conclude that I_{NaP} is ubiquitously expressed by pre-BötC inspiratory neurons and that bursting pacemaker behavior within the heterogeneous population of inspiratory neurons is achieved with specific ratios of these two conductances, g_{NaP} and g_{Leak}.

Administrative Stuff

Syllabus, calendar, exam schedule, readings, assignments, and announcements are on the course blog

password for specific resources: **1693**

Two midterm exams at 20% each. Final exam 40%
Homework and participation 20%.

Attendance is required.

Do homework!
Collaborate!

NEUROSCIENCE
Exploring the Brain
Third Edition
Mark F. Bear
Barry W. Connors
Michael A. Paradiso
Lippincott Williams & Wilkins
a Wolters Kluwer business