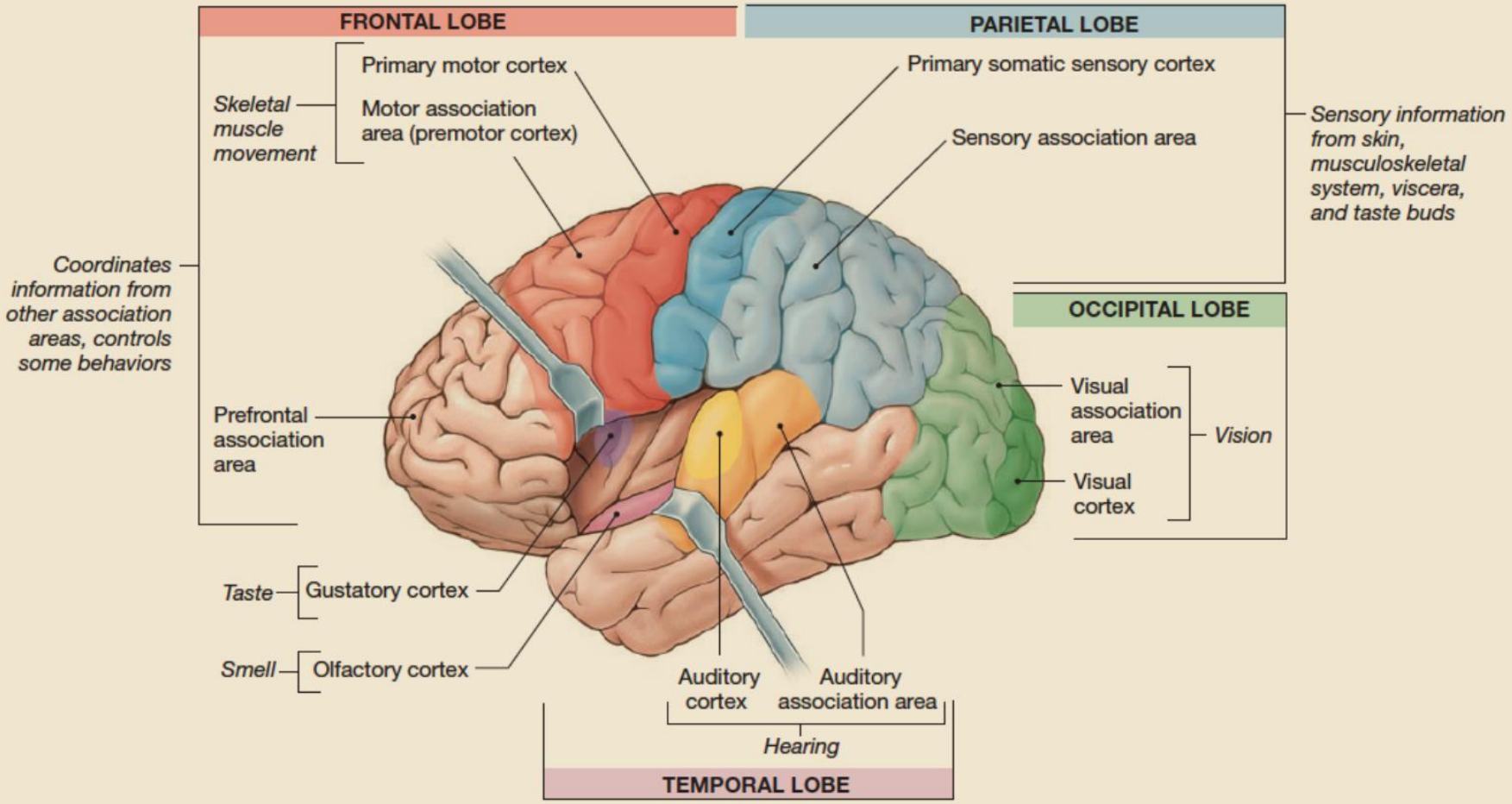
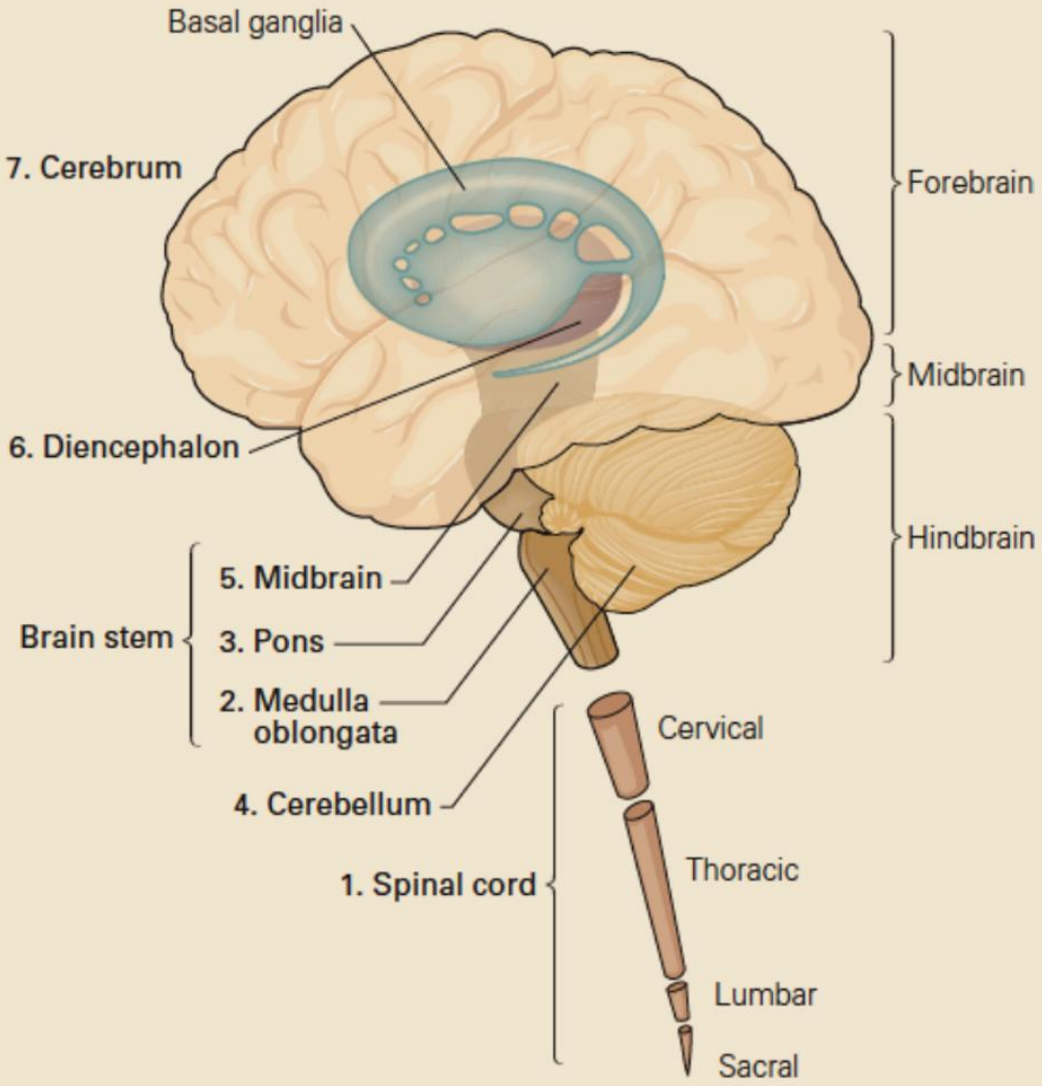
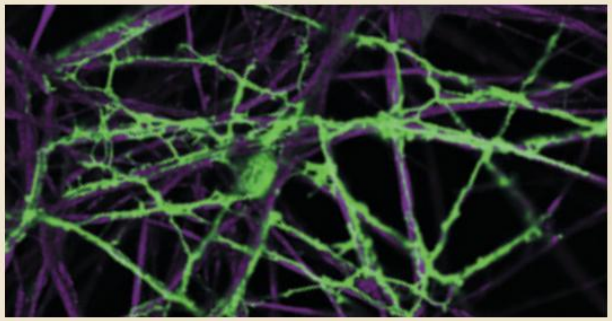
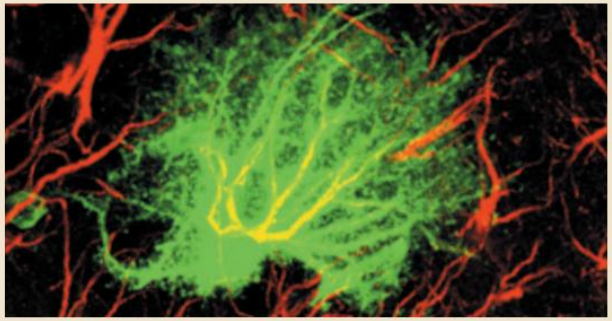

FRONTAL LOBE
PARIETAL LOBE
OCCIPITAL LOBE
TEMPORAL LOBE
Primary motor cortex
Motor association area (premotor cortex)
Skeletal muscle movement
Coordinates information from other association areas, controls some behaviors
Prefrontal association area
Primary somatic sensory cortex
Sensory association area
Sensory information from skin, musculoskeletal system, viscera, and taste buds
Visual association area
Visual cortex
Vision
Taste
Gustatory cortex
Smell
Olfactory cortex
Auditory cortex
Auditory association area
Hearing


Basal ganglia
7. Cerebrum
6. Diencephalon
5. Midbrain
3. Pons
2. Medulla oblongata
4. Cerebellum
1. Spinal cord
Brain stem
Cervical
Thoracic
Lumbar
Sacral
Forebrain
Midbrain
Hindbrain



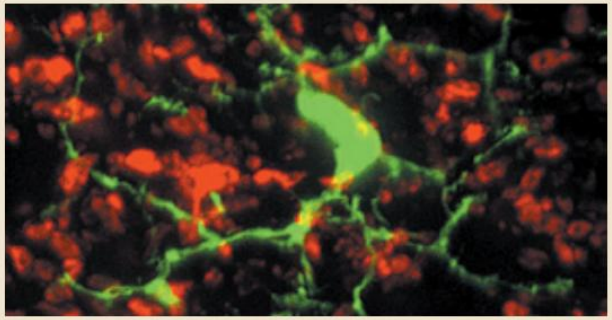
Oligodendrocytes (green)

- Form myelin electrical insulation, increasing conduction velocity by at least 50 times.
- Provide vital metabolic support for axons (purple).
- Involved in multiple sclerosis, amyotrophic lateral sclerosis and the inhibition of repair after spinal-cord injury.



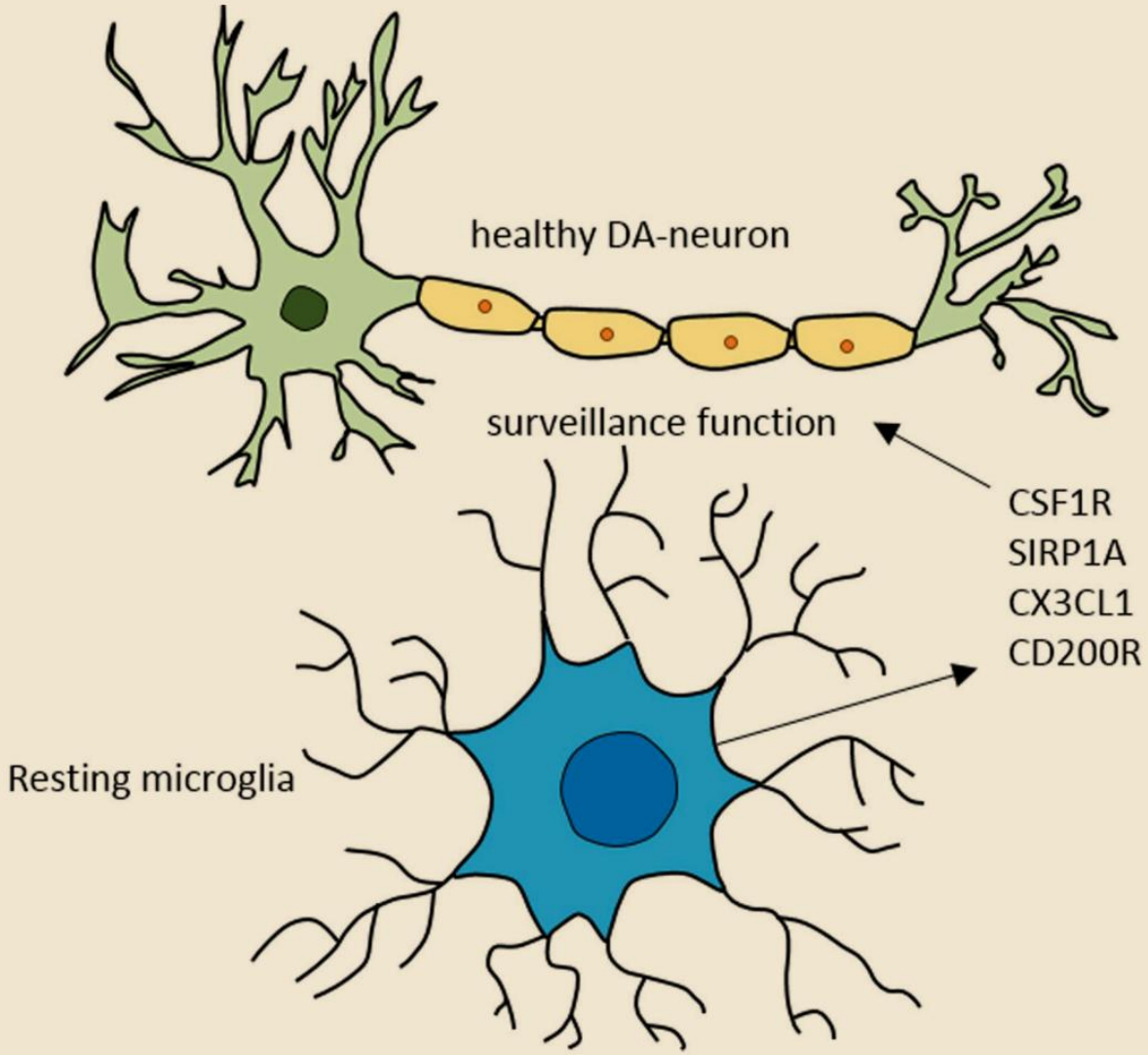
Astrocytes (red and green)

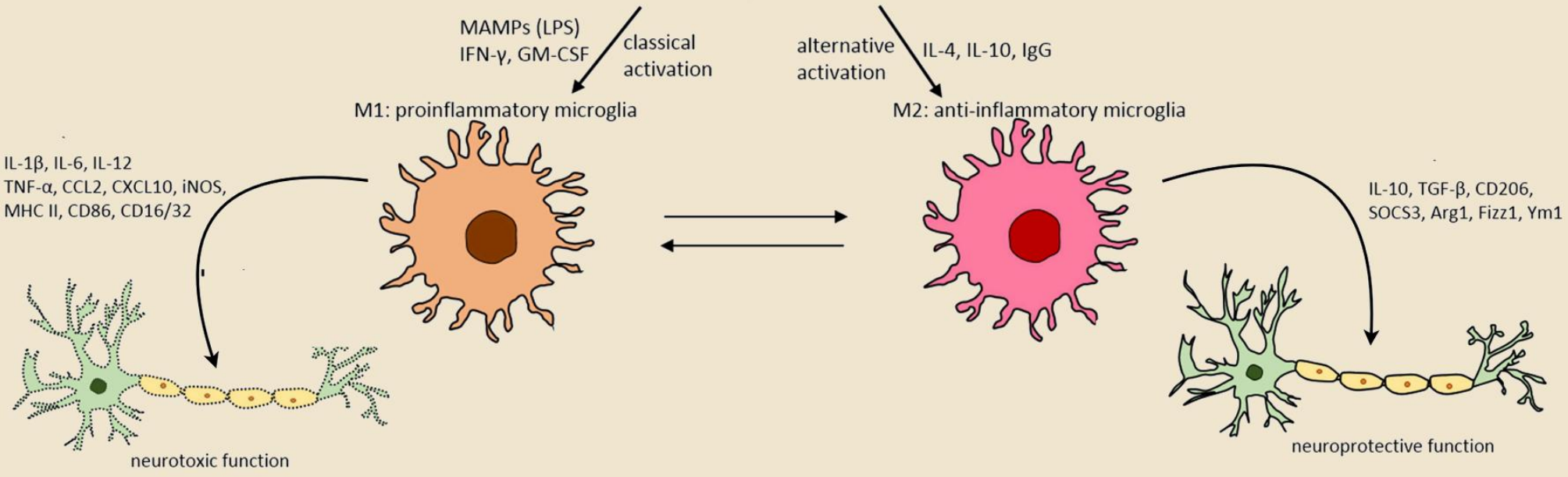
- Ensheath synapses, regulate neuronal excitability and synaptic transmission.
- Respond to injury by secreting extracellular matrix proteins.
- Implicated in neurogenesis, cell migration, and many neurological and psychiatric disorders.

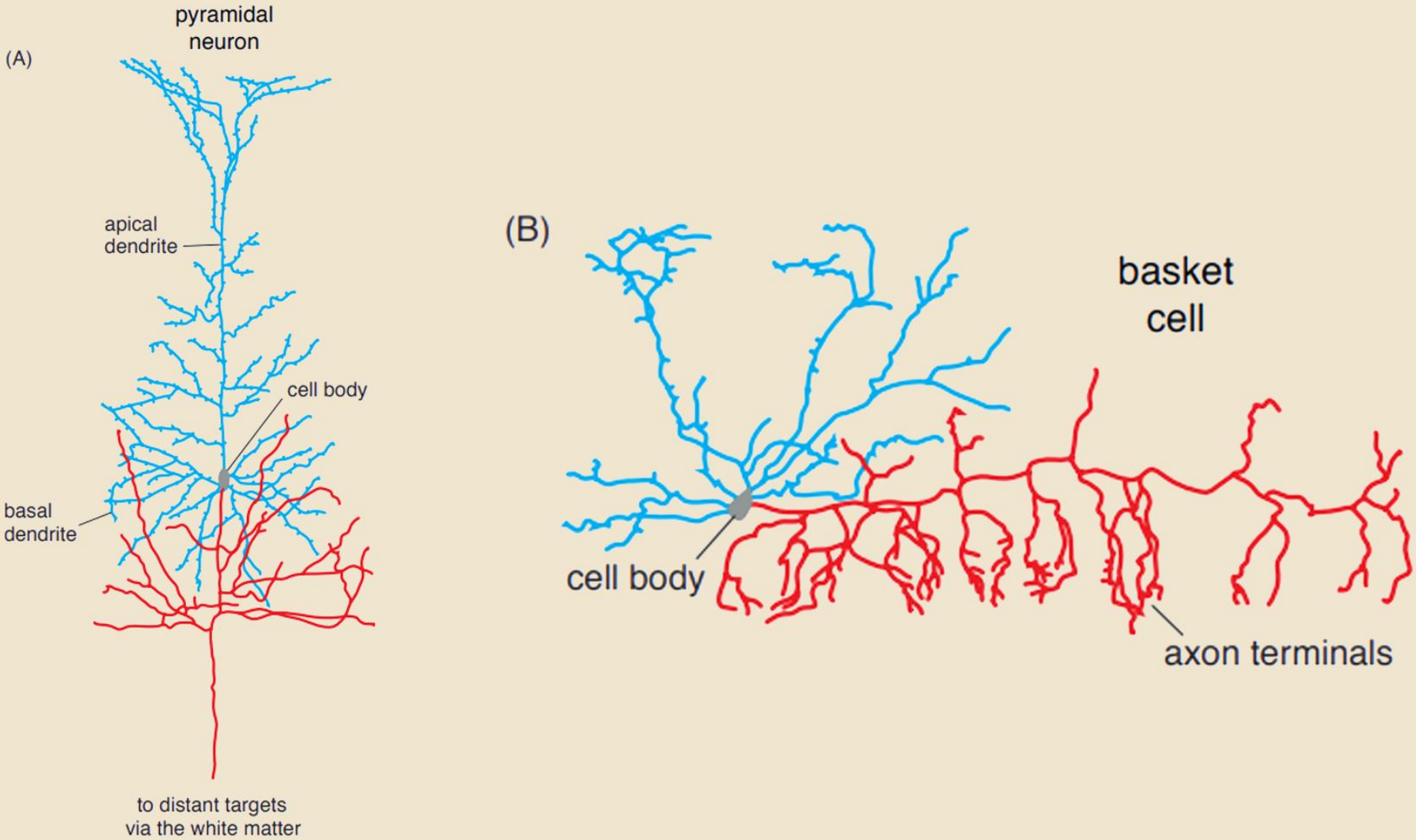


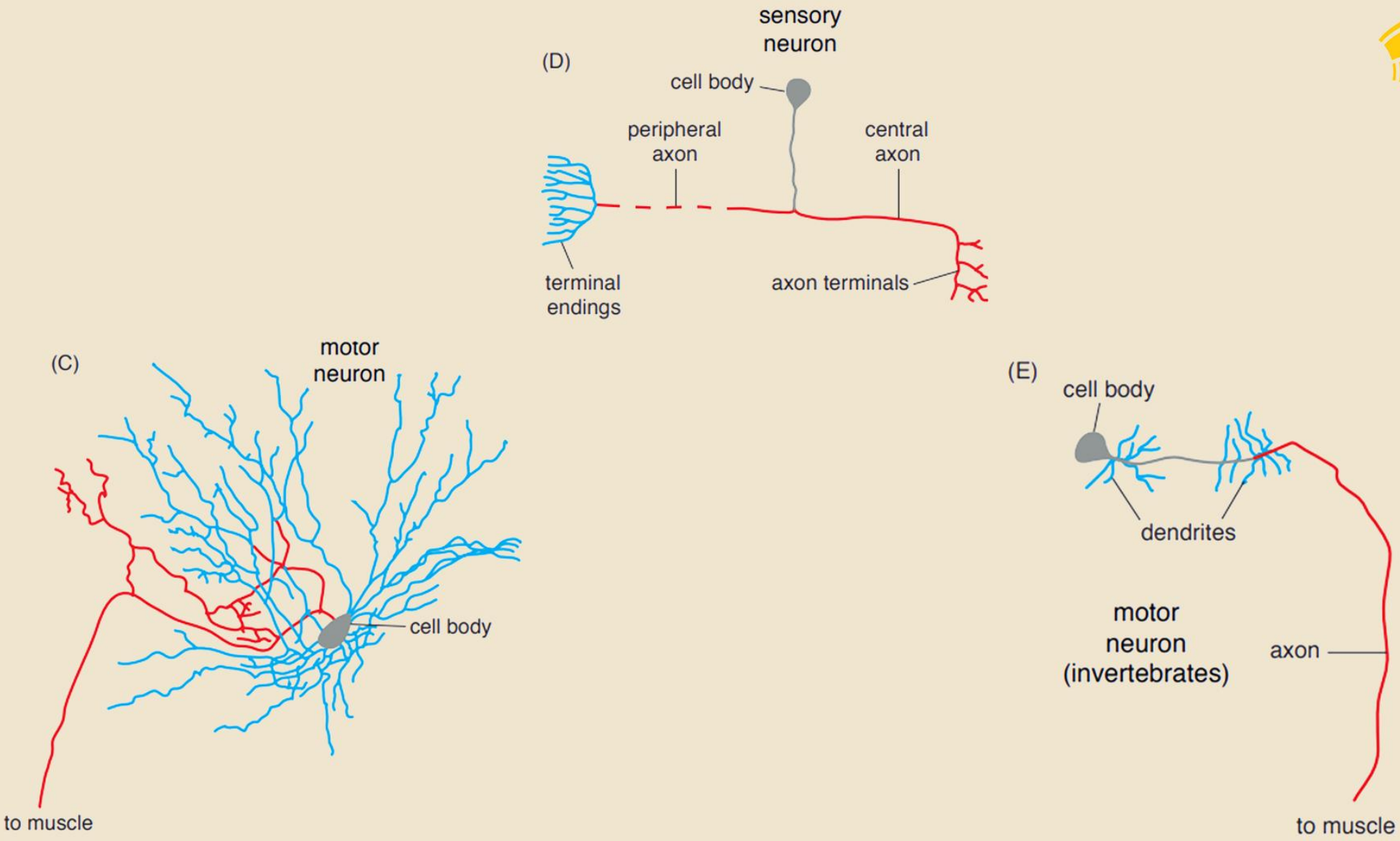
Microglia (green)

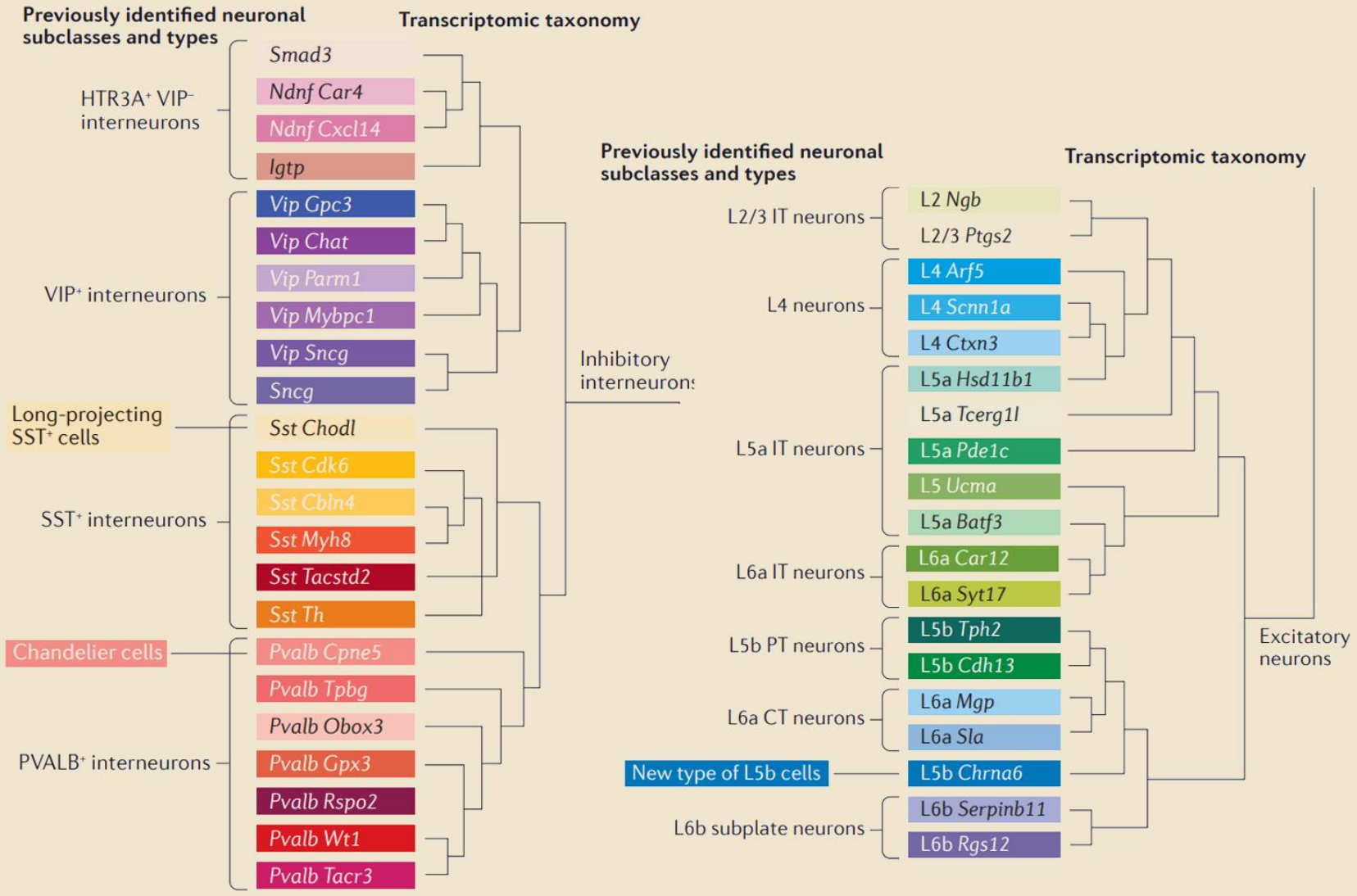
- Highly motile and responsive to nervous-system injury and infection.
- Monitor electrical activity in neurons and prune synaptic connections (red).
- Involved in almost all nervous-system diseases and in certain psychiatric conditions.

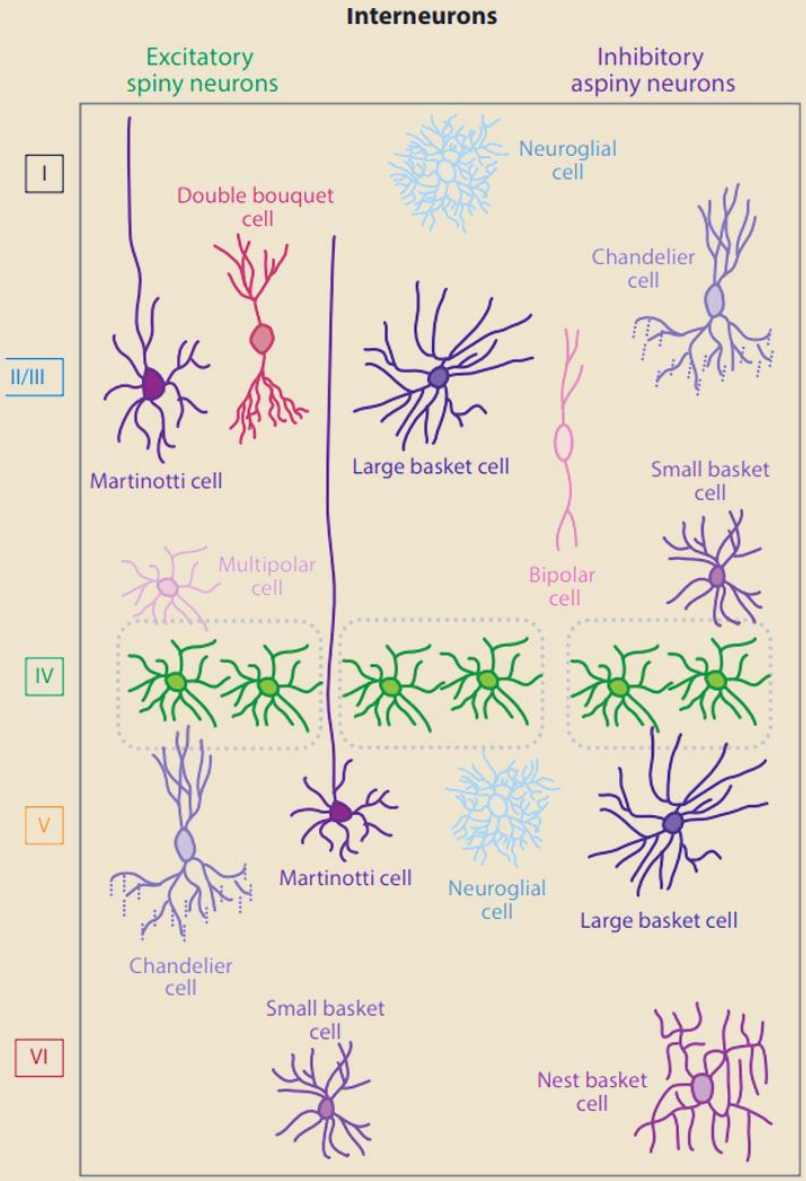

healthy DA-neuron
surveillance function
CSF1R
SIRP1A
CX3CL1
CD200R
Resting microglia


MAMPs (LPS)
IFN-γ, GM-CSF
classical activation
alternative activation
IL-4, IL-10, IgG
M1: proinflammatory microglia
M2: anti-inflammatory microglia
IL-1β, IL-6, IL-12
TNF-α, CCL2, CXCL10, iNOS,
MHC II, CD86, CD16/32
IL-10, TGF-β, CD206,
SOCS3, Arg1, Fizz1, Ym1
neurotoxic function
neuroprotective function


(A)
pyramidal neuron
apical dendrite
cell body
basal dendrite
to distant targets via the white matter
(B)
basket cell
cell body
axon terminals


(D)
sensory neuron
cell body
peripheral axon
central axon
terminal endings
axon terminals
(C)
motor neuron
cell body
to muscle
(E)
cell body
dendrites
motor neuron (invertebrates)
axon
to muscle

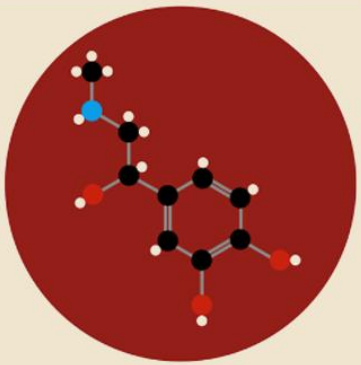

Previously identified neuronal subclasses and types
Transcriptomic taxonomy
HTR3A+ VIP− interneurons
Smad3
Ndnf Car4
Ndnf Cxcl14
Igtp
VIP+ interneurons
Vip Gpc3
Vip Chat
Vip Parm1
Vip Mybpc1
Vip Sncg
Sncg
Long-projecting SST+ cells
Sst Chodl
SST+ interneurons
Sst Cdk6
Sst Cbln4
Sst Myh8
Sst Tacstd2
Sst Th
Chandelier cells
Pvalb Cpne5
PVALB+ interneurons
Pvalb Tpbg
Pvalb Obox3
Pvalb Gpx3
Pvalb Rspo2
Pvalb Wt1
Pvalb Tacr3
Inhibitory interneurons
Previously identified neuronal subclasses and types
Transcriptomic taxonomy
L2/3 IT neurons
L2 Ngb
L2/3 Ptgs2
L4 neurons
L4 Arf5
L4 Scnn1a
L4 Ctxn3
L5a IT neurons
L5a Hsd11b1
L5a Tcerg1l
L5a Pde1c
L5 Ucma
L5a Batf3
L6a IT neurons
L6a Car12
L6a Syt17
L5b PT neurons
L5b Tph2
L5b Cdh13
L6a CT neurons
L6a Mgp
L6a Sla
New type of L5b cells
L5b Chrna6
L6b subplate neurons
L6b Serpinb11
L6b Rgs12
Excitatory neurons


Interneurons
Excitatory spiny neurons
Inhibitory aspiny neurons
I
II/III
IV
V
VI
Neuroglial cell
Double bouquet cell
Chandelier cell
Martinotti cell
Large basket cell
Small basket cell
Multipolar cell
Bipolar cell
Martinotti cell
Neuroglial cell
Large basket cell
Chandelier cell
Small basket cell
Nest basket cell

neurotransmitters

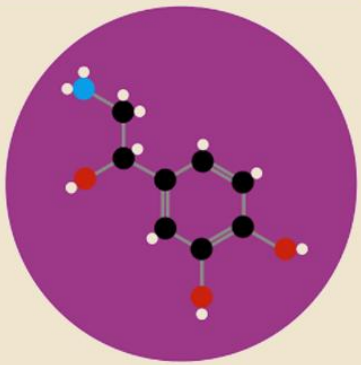
ADRENALINE $C_9H_{13}NO_3$

THE FIGHT OR FLIGHT NEUROTRANSMITTER



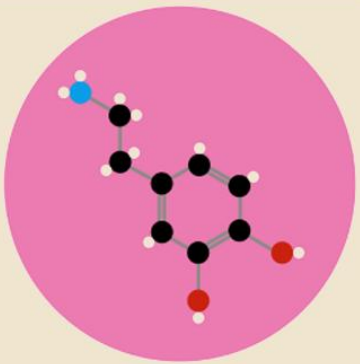
NORADRENALINE $C_8H_{11}NO_3$

THE CONCENTRATION NEUROTRANSMITTER



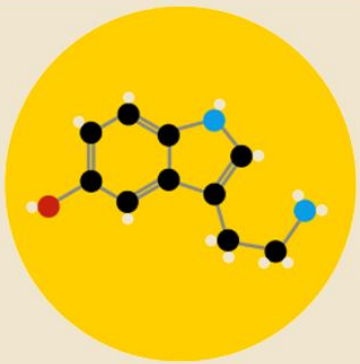
DOPAMINE $C_8H_{11}NO_2$

THE PLEASURE NEUROTRANSMITTER



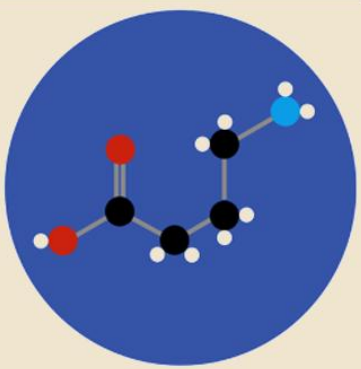
SEROTONIN $C_{10}H_{12}N_2O$

THE MOOD NEUROTRANSMITTER



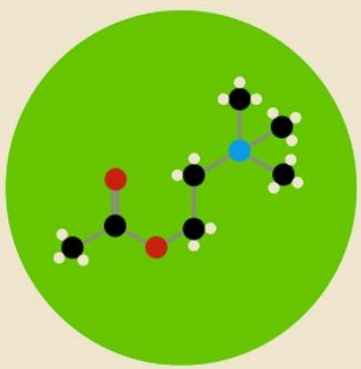
γ-AMINOBUTYRIC ACID $C_4H_9NO_2$

THE CALMING NEUROTRANSMITTER



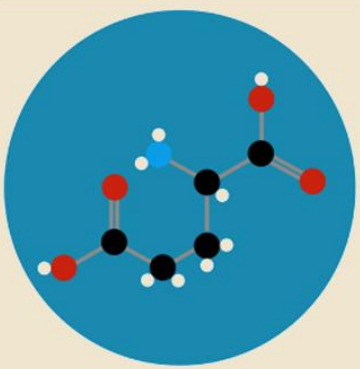
ACETYLCHOLINE $C_7H_{16}NO_2^+$

THE LEARNING NEUROTRANSMITTER



GLUTAMATE $C_5H_9NO_4$

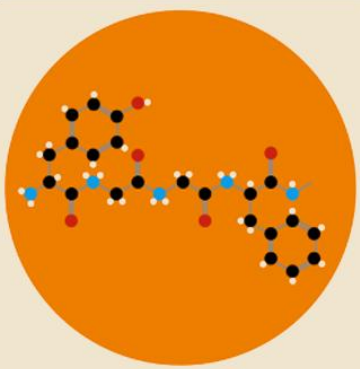
THE MEMORY NEUROTRANSMITTER

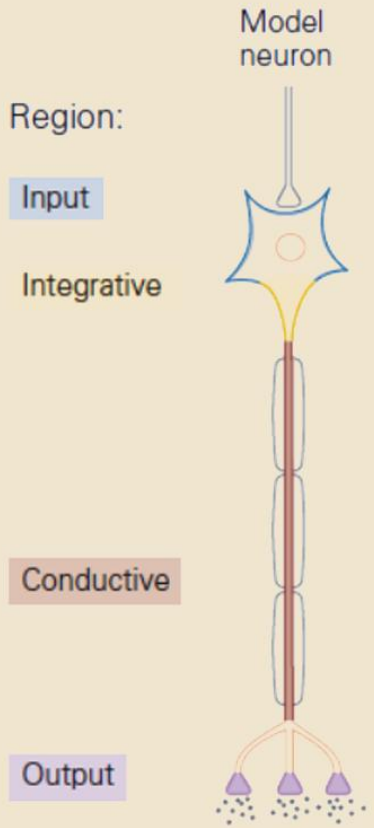


ENDORPHINS

THE EUPHORIA NEUROTRANSMITTERS

20+ TYPES IN THE HUMAN BODY





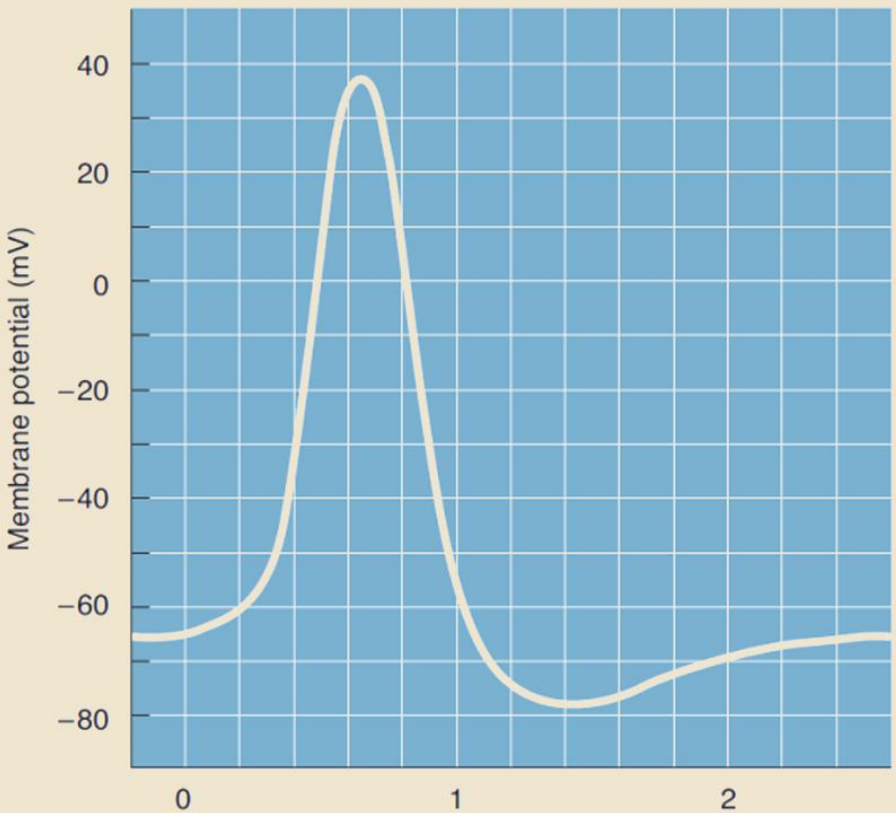
The action potential is a rapid and transient nerve impulse, with the feature of an “all or nothing” phenomenon

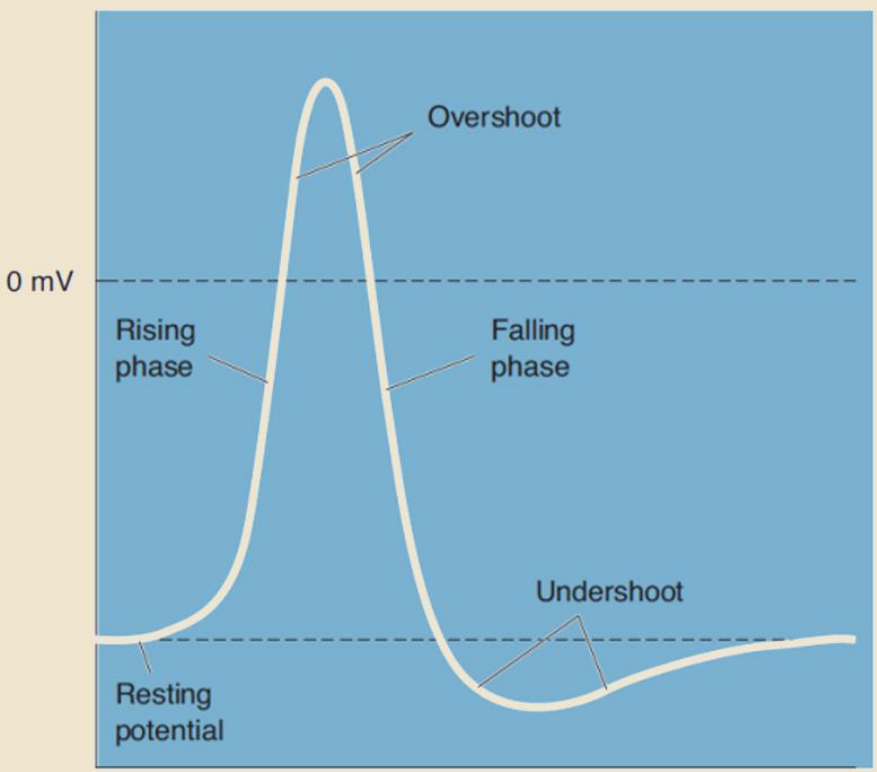
Amplitude of about 100 mV (millivolts)

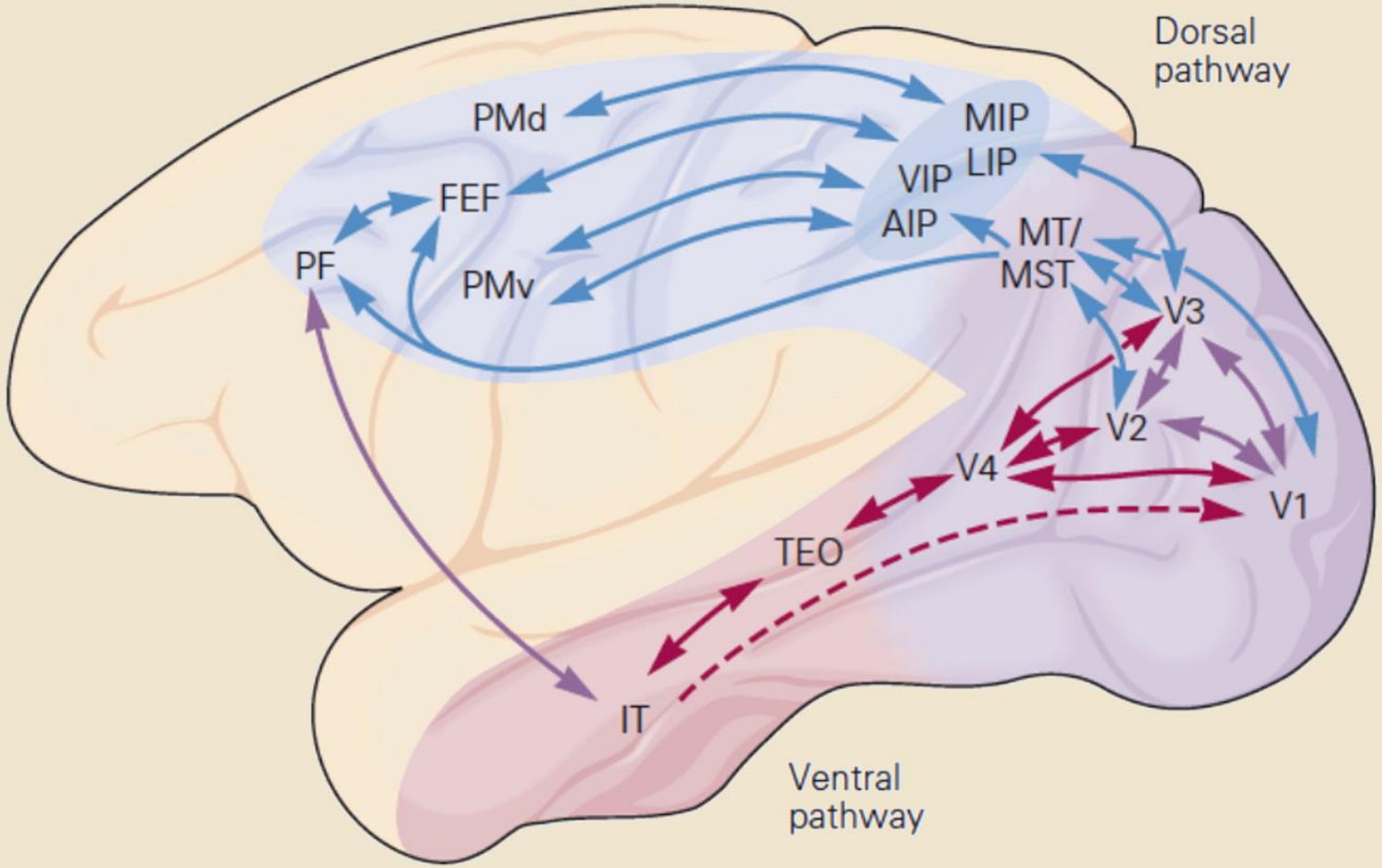
Duration of about 1 ms (milliseconds)

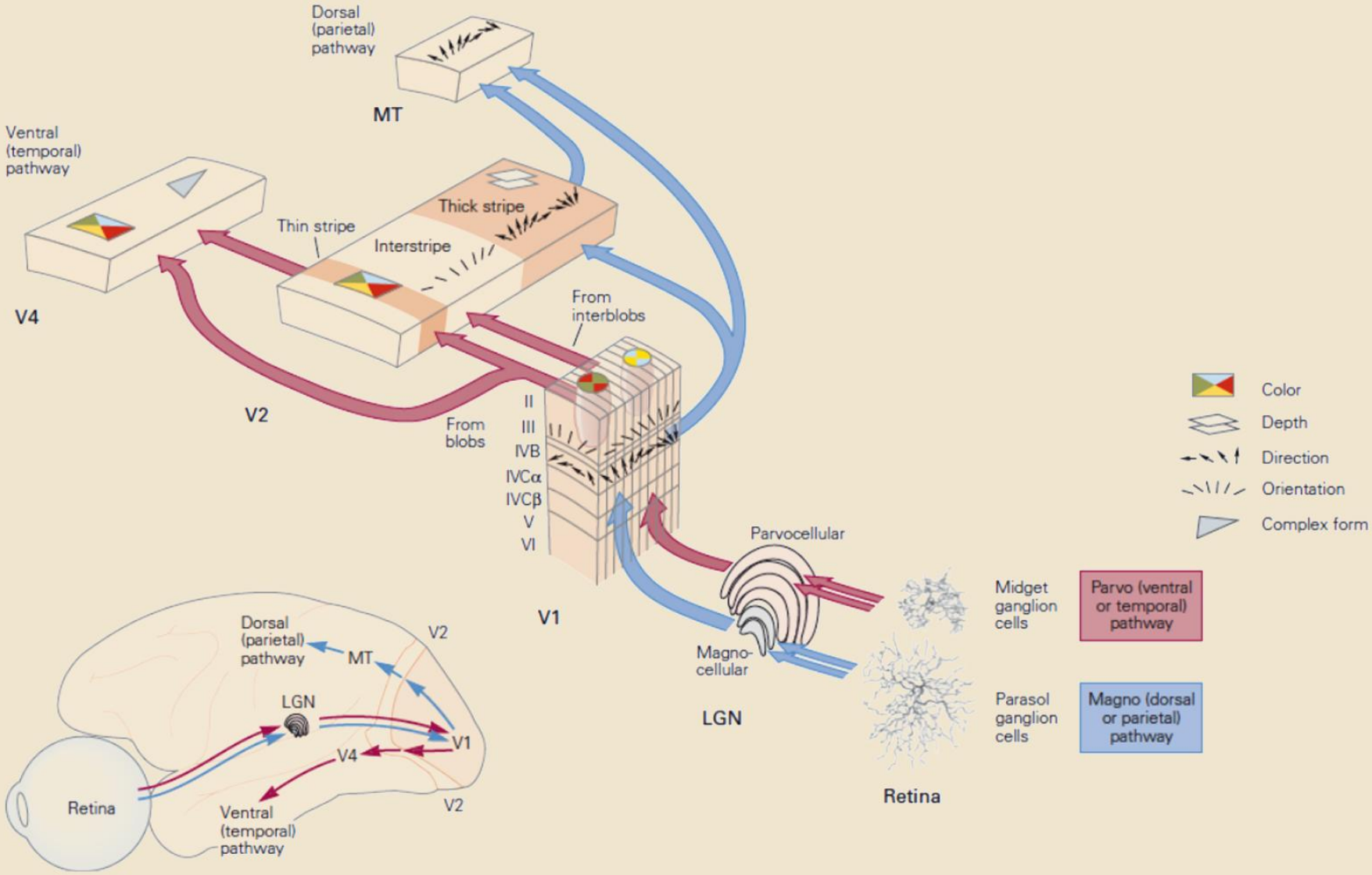
It starts from the axon hillock

It is conducted along the axon


Membrane potential (mV)
40
20
0
−20
−40
−60
−80
0
1
2


0 mV
Overshoot
Rising phase
Falling phase
Undershoot
Resting potential


Dorsal
pathway
PMd
MIP
LIP
VIP
AIP
FEF
PF
PMv
MT/
MST
V3
V2
V4
V1
TEO
IT
Ventral
pathway


Dorsal (parietal) pathway
MT
Ventral (temporal) pathway
Thick stripe
Thin stripe
Interstripe
V4
From interblobs
V2
From blobs
II
III
IVB
IVCα
IVCβ
V
VI
V1
Parvocellular
Magno-cellular
LGN
Retina
Color
Depth
Direction
Orientation
Complex form
Midget ganglion cells
Parvo (ventral or temporal) pathway
Parasol ganglion cells
Magno (dorsal or parietal) pathway
Dorsal (parietal) pathway
MT
V2
LGN
V1
V4
Retina
V2
Ventral (temporal) pathway

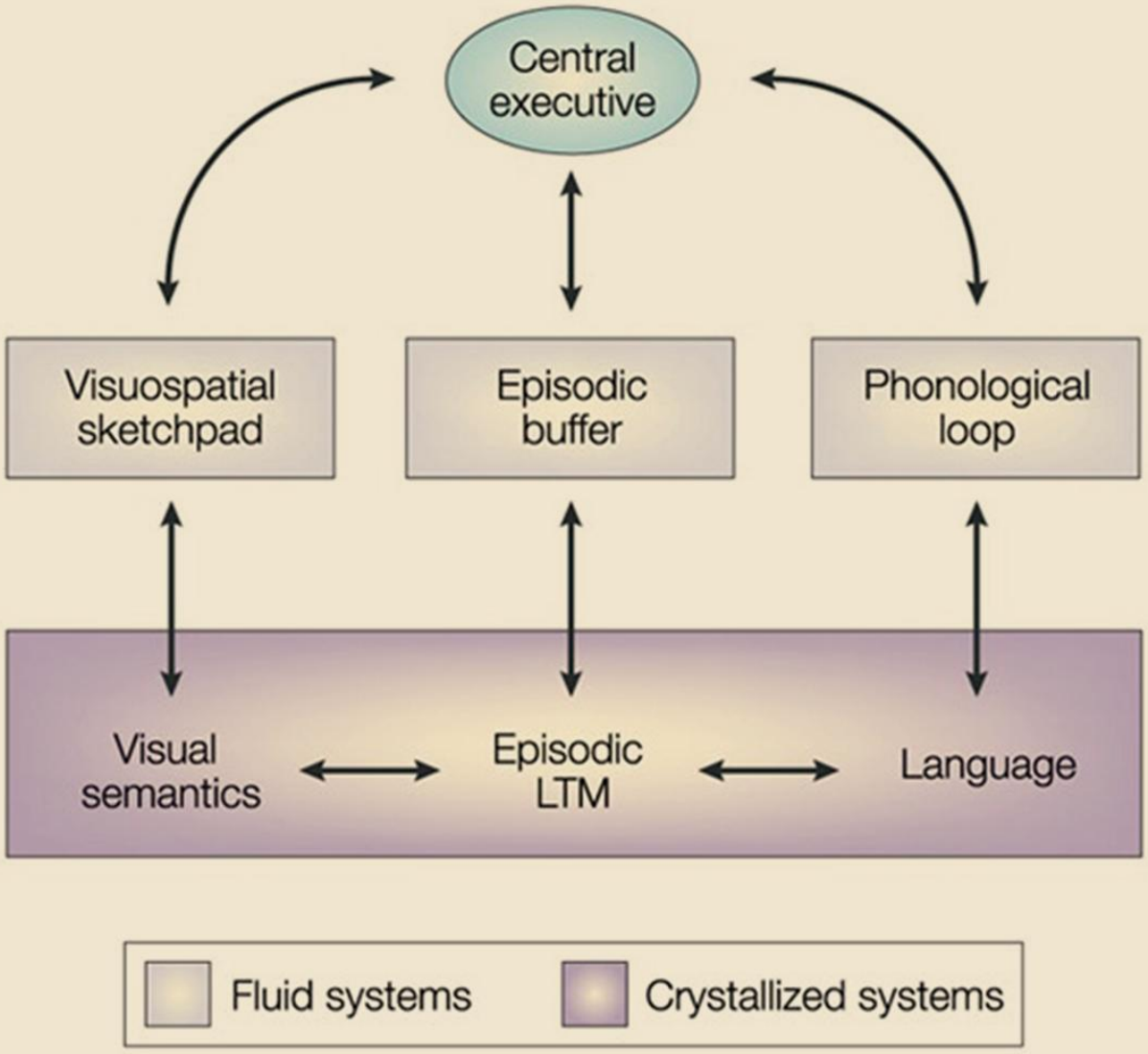
- **Ventral pathway**

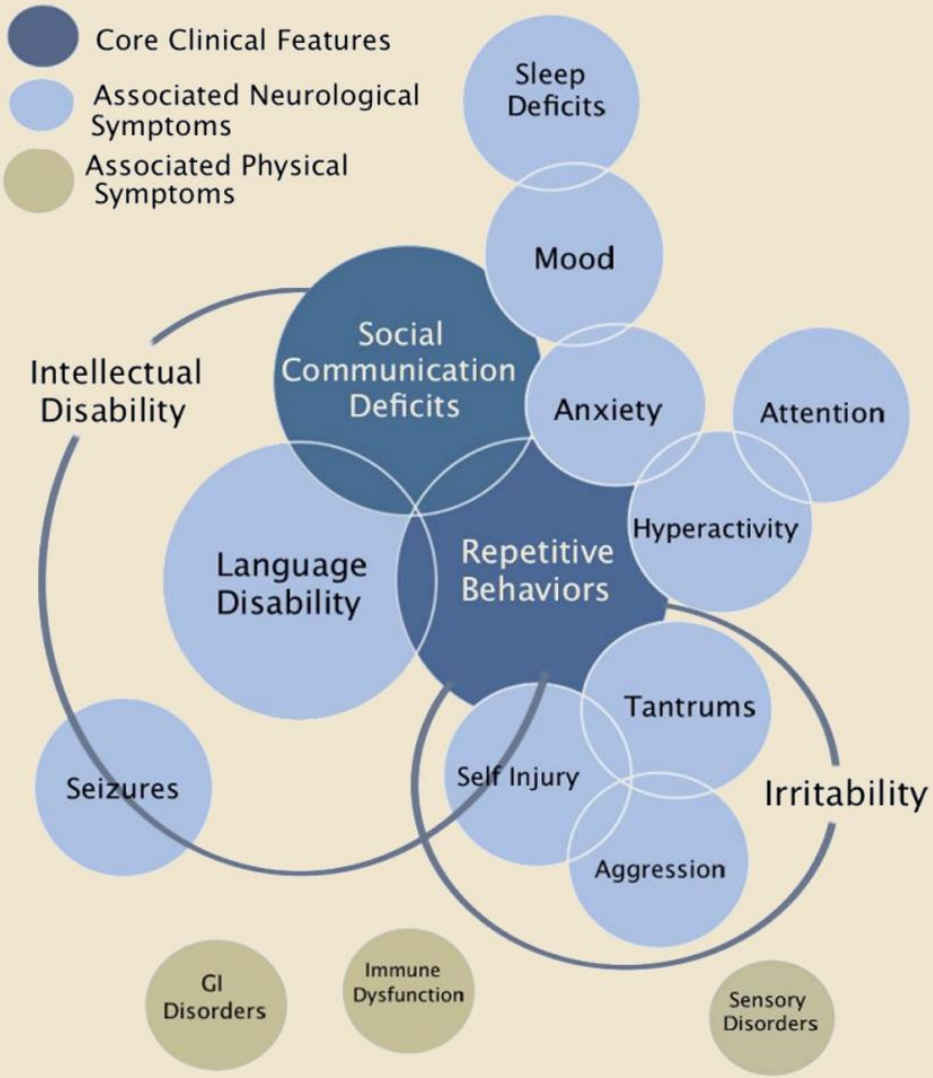
(V1-V4 to temporal lobe and hippocampus)
object recognition

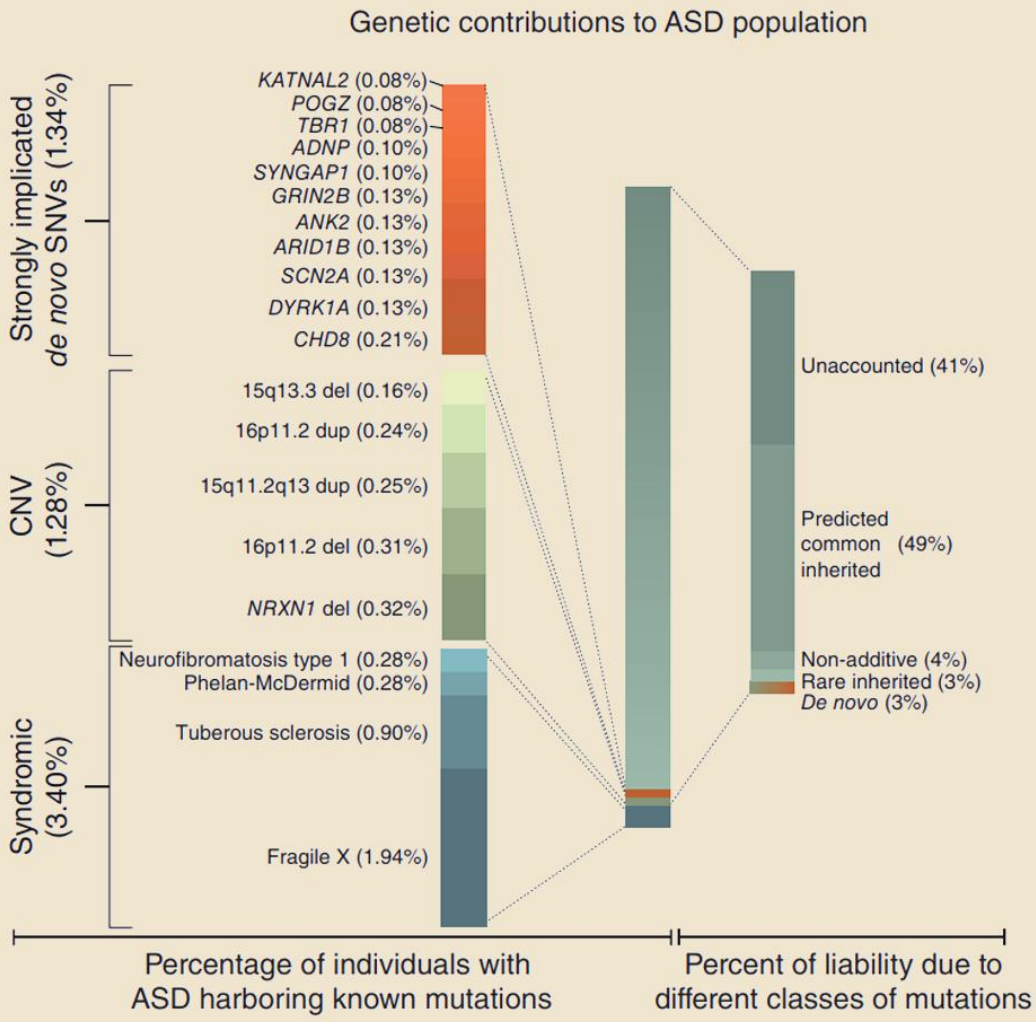
- **Dorsal pathway**

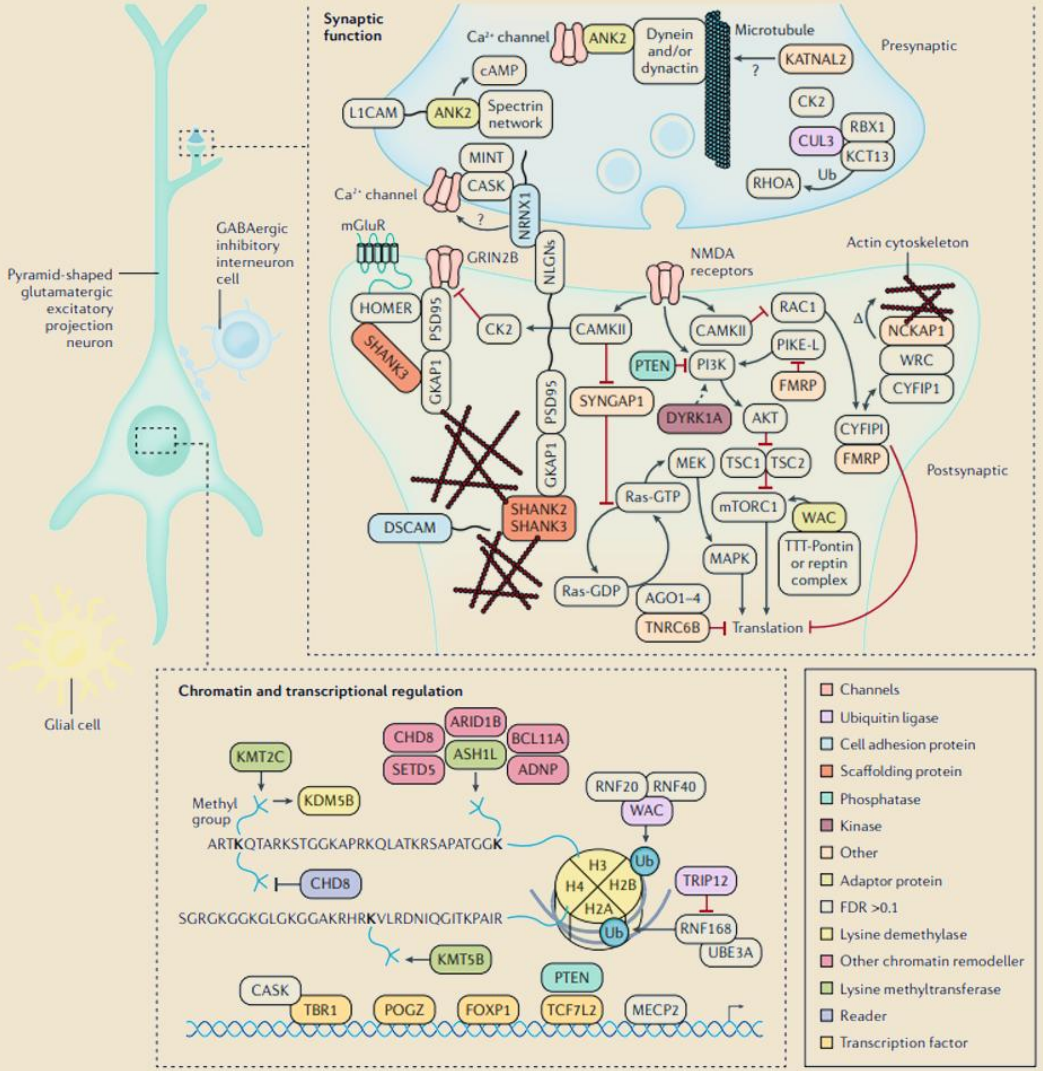
(V1-V3 to premotor area and prefrontal cortex)
action-related visual processing

Dorsal pathway (magnocellular pathway):
depth, motion, contrast, luminance
Ventral pathway (parvocellular pathway):
color, shape
The properties of **dorsal** and **ventral** pathways are determined by the properties of **M-cells**, **P-cells** and their respective target cells in LGN and visual cortical areas)

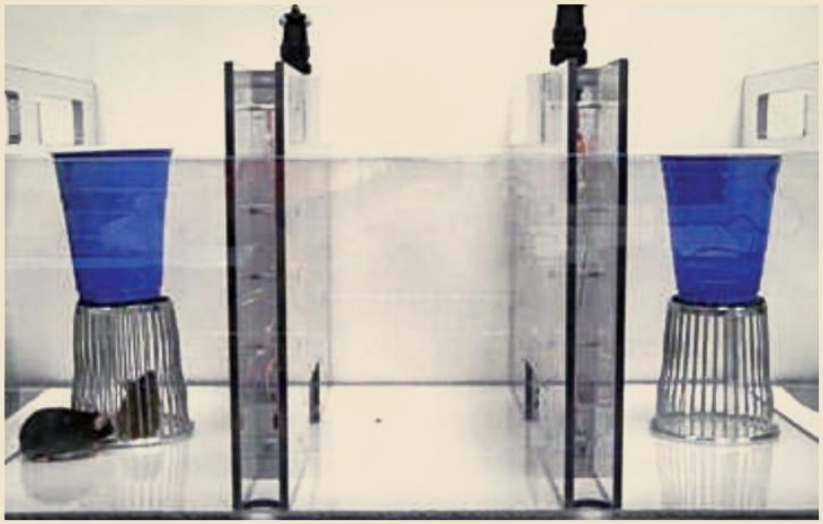

Central executive
Visuospatial sketchpad
Episodic buffer
Phonological loop
Visual semantics
Episodic LTM
Language
Fluid systems
Crystallized systems


Core Clinical Features
Associated Neurological Symptoms
Associated Physical Symptoms
Sleep Deficits
Mood
Social Communication Deficits
Anxiety
Attention
Intellectual Disability
Hyperactivity
Language Disability
Repetitive Behaviors
Tantrums
Seizures
Self Injury
Irritability
Aggression
GI Disorders
Immune Dysfunction
Sensory Disorders


Genetic contributions to ASD population
Strongly implicated
de novo SNVs (1.34%)
KATNAL2 (0.08%)
POGZ (0.08%)
TBR1 (0.08%)
ADNP (0.10%)
SYNGAP1 (0.10%)
GRIN2B (0.13%)
ANK2 (0.13%)
ARID1B (0.13%)
SCN2A (0.13%)
DYRK1A (0.13%)
CHD8 (0.21%)
CNV
(1.28%)
15q13.3 del (0.16%)
16p11.2 dup (0.24%)
15q11.2q13 dup (0.25%)
16p11.2 del (0.31%)
NRXN1 del (0.32%)
Syndromic
(3.40%)
Neurofibromatosis type 1 (0.28%)
Phelan-McDermid (0.28%)
Tuberous sclerosis (0.90%)
Fragile X (1.94%)
Unaccounted (41%)
Predicted
common (49%)
inherited
Non-additive (4%)
Rare inherited (3%)
De novo (3%)
Percentage of individuals with
ASD harboring known mutations
Percent of liability due to
different classes of mutations

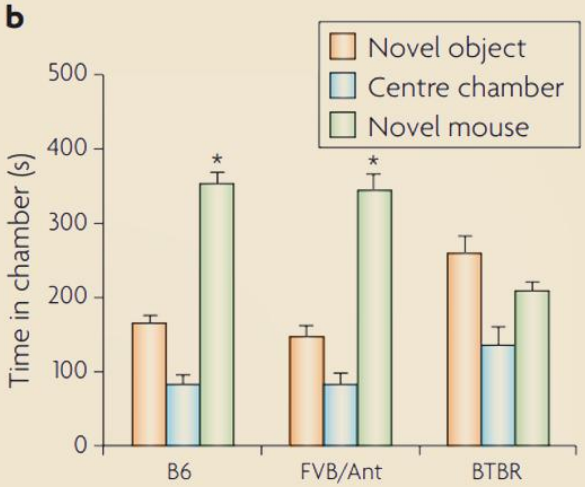

Synaptic function
Presynaptic
Postsynaptic
Pyramid-shaped glutamatergic excitatory projection neuron
GABAergic inhibitory interneuron cell
Glial cell
Ca²⁺ channel
ANK2
Dynein and/or dynactin
Microtubule
KATNAL2
cAMP
L1CAM
Spectrin network
CK2
RBX1
CUL3
KCT13
RHOA
Ub
MINT
CASK
NRNX1
mGluR
GRIN2B
NLGNs
NMDA receptors
Actin cytoskeleton
HOMER
PSD95
SHANK3
GKAP1
CAMKII
RAC1
NCKAP1
WRC
CYFIP1
PIKE-L
FMRP
PTEN
PI3K
SYNGAP1
DYRK1A
AKT
MEK
TSC1
TSC2
Ras-GTP
mTORC1
WAC
TTT-Pontin or reptin complex
MAPK
DSCAM
SHANK2
SHANK3
Ras-GDP
AGO1–4
TNRC6B
Translation
Chromatin and transcriptional regulation
KMT2C
CHD8
ARID1B
BCL11A
SETD5
ASH1L
ADNP
RNF20
RNF40
WAC
Methyl group
KDM5B
ARTKQTARKSTGGKAPRKQLATKRSAPATGGK
H3
H4
H2B
H2A
Ub
TRIP12
RNF168
UBE3A
SGRGKGGKGLGKGGAKRHRKVLRDNIQGITKPAIR
KMT5B
PTEN
CASK
TBR1
POGZ
FOXP1
TCF7L2
MECP2
Channels
Ubiquitin ligase
Cell adhesion protein
Scaffolding protein
Phosphatase
Kinase
Other
Adaptor protein
FDR >0.1
Lysine demethylase
Other chromatin remodeller
Lysine methyltransferase
Reader
Transcription factor

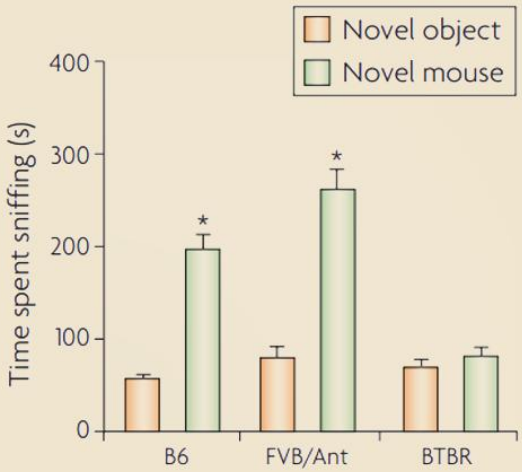
a

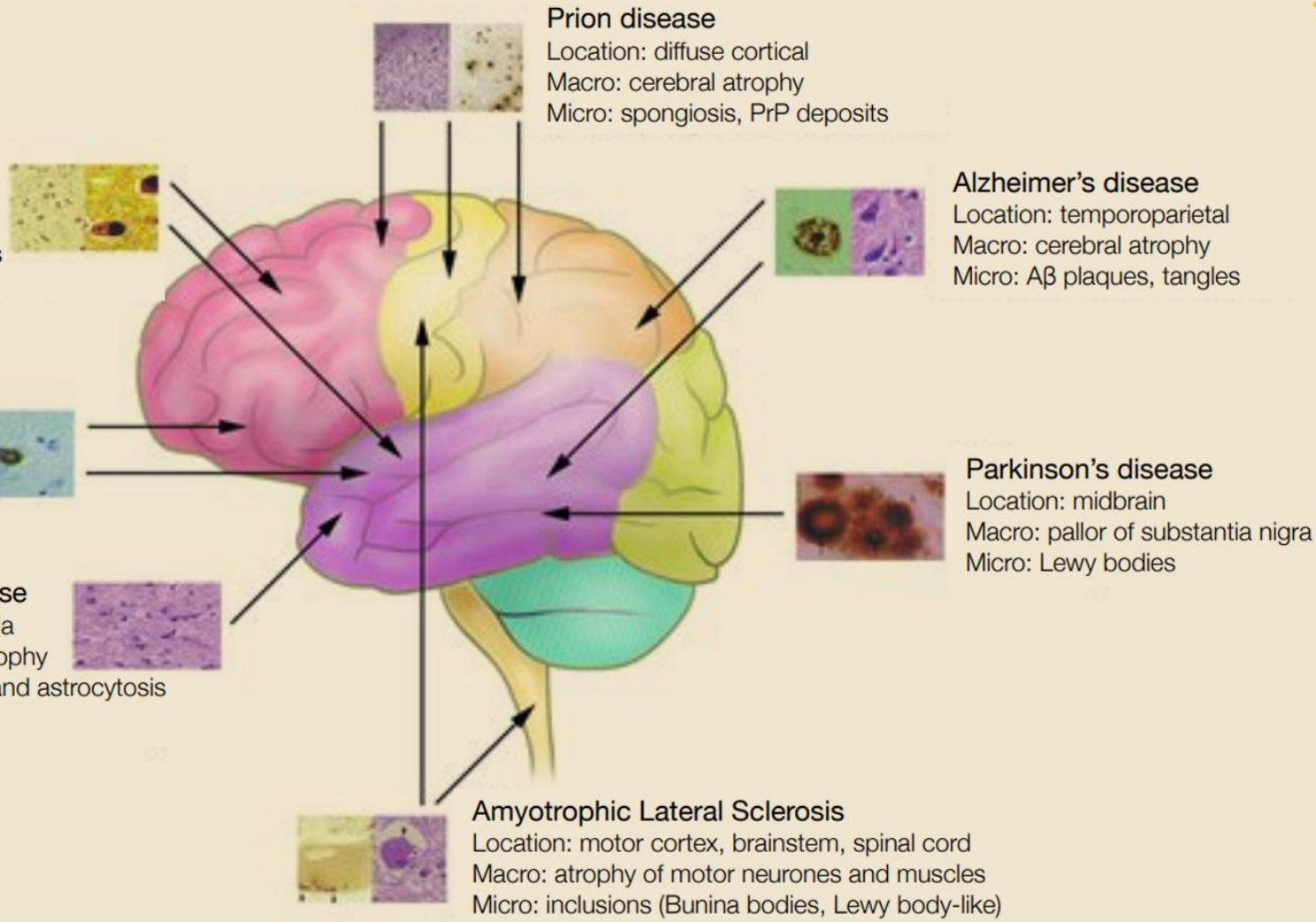


three-chambered social approach test

b







Prion disease
Location: diffuse cortical
Macro: cerebral atrophy
Micro: spongiosis, PrP deposits

Frontotemporal dementia
Location: frontotemporal
Macro: cerebral atrophy
Micro: tau deposits, Pick bodies

Alzheimer's disease
Location: temporoparietal
Macro: cerebral atrophy
Micro: Aβ plaques, tangles

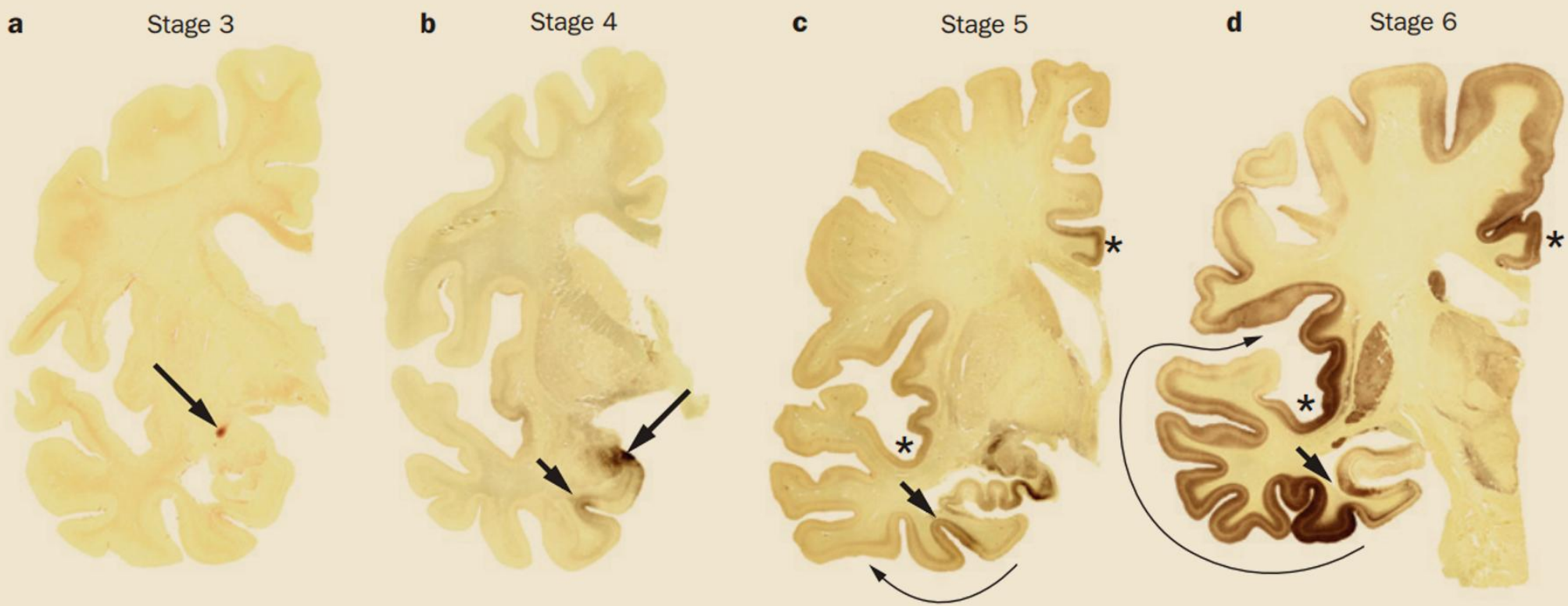
Dementia with Lewy bodies
Location: frontotemporal
Macro: cerebral atrophy
Micro: Lewy bodies

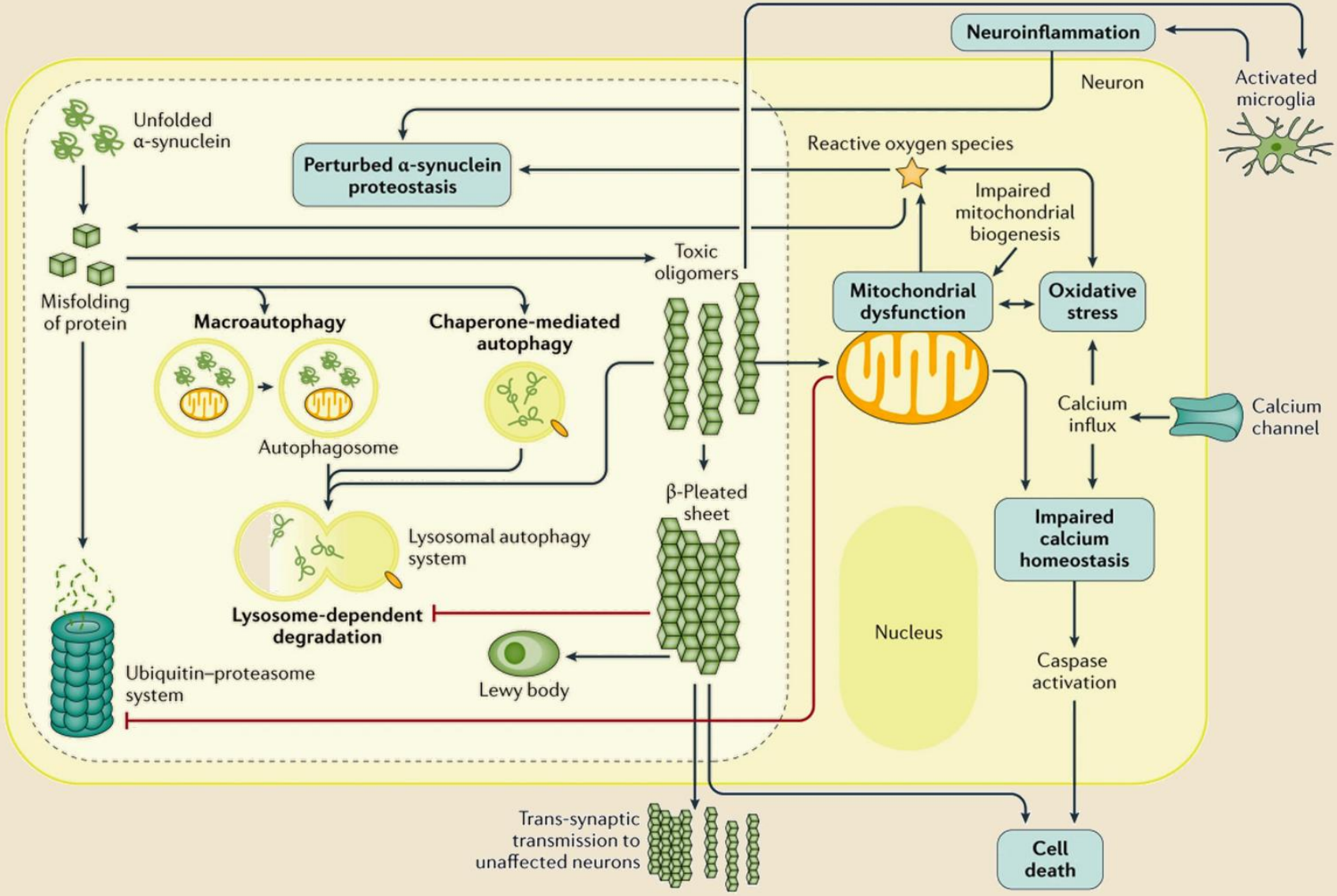
Parkinson's disease
Location: midbrain
Macro: pallor of substantia nigra
Micro: Lewy bodies

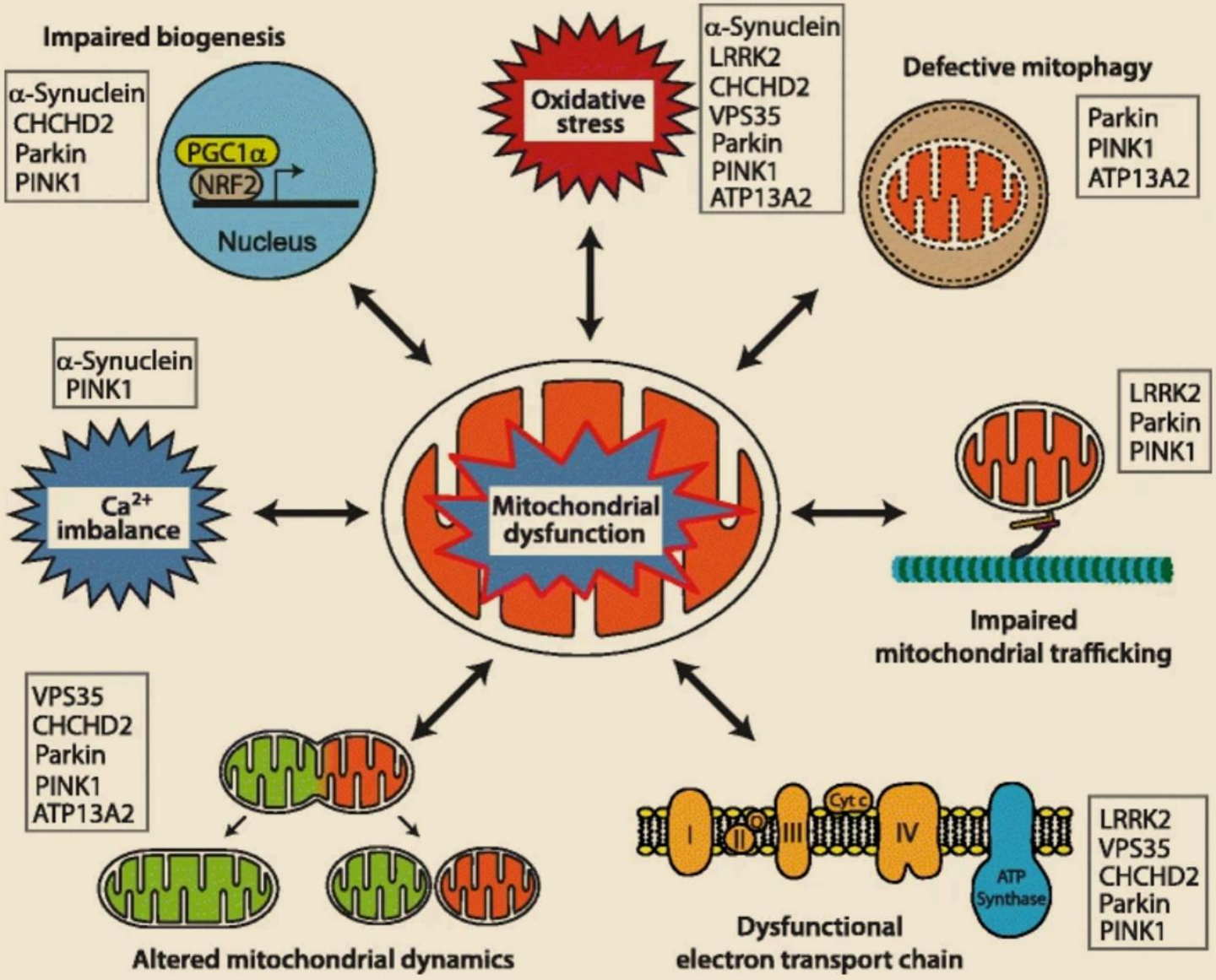
Huntington's disease
Location: basal ganglia
Macro: neostriatal atrophy
Micro: neuronal loss and astrocytosis

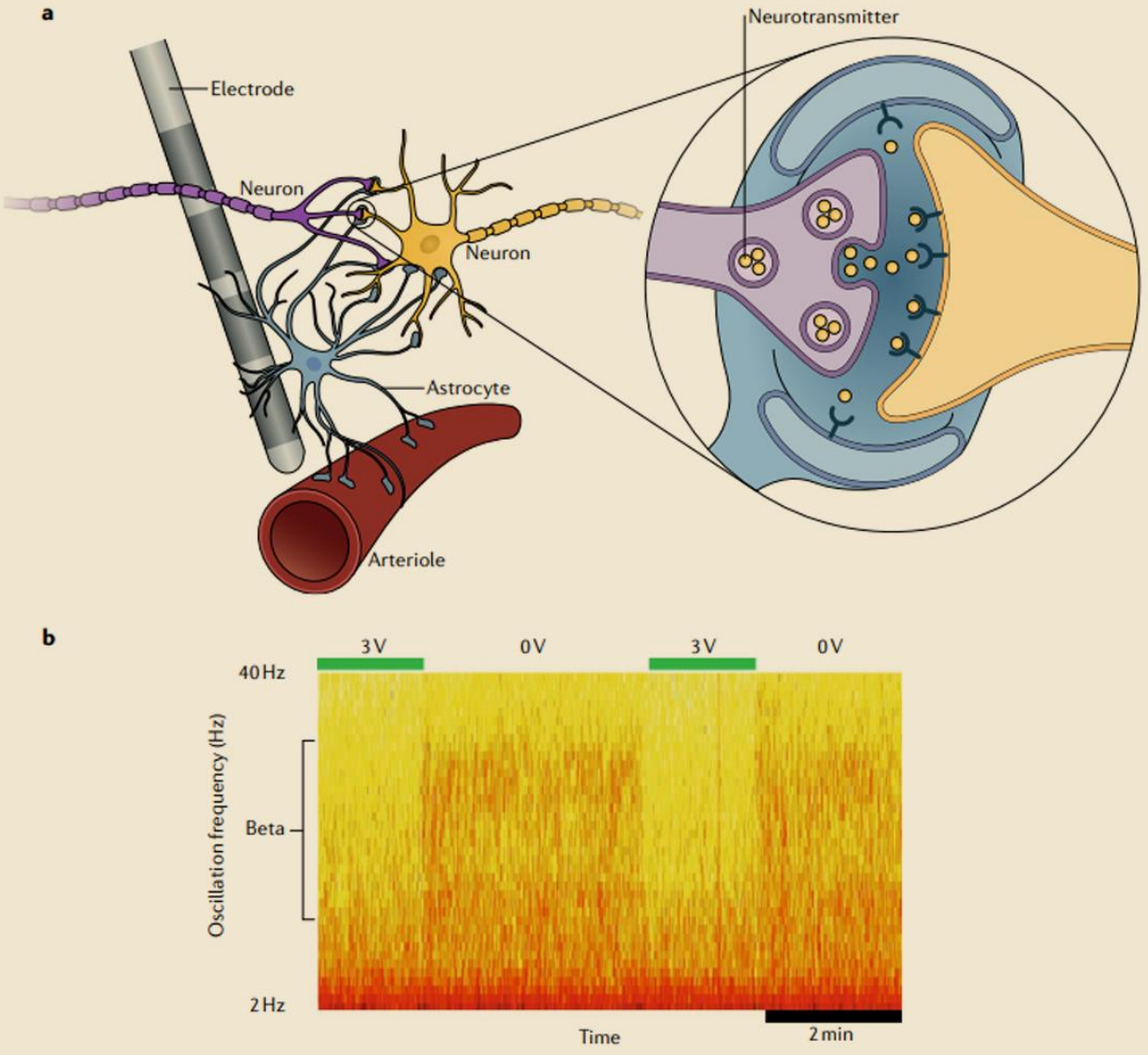
Amyotrophic Lateral Sclerosis
Location: motor cortex, brainstem, spinal cord
Macro: atrophy of motor neurones and muscles
Micro: inclusions (Bunina bodies, Lewy body-like)

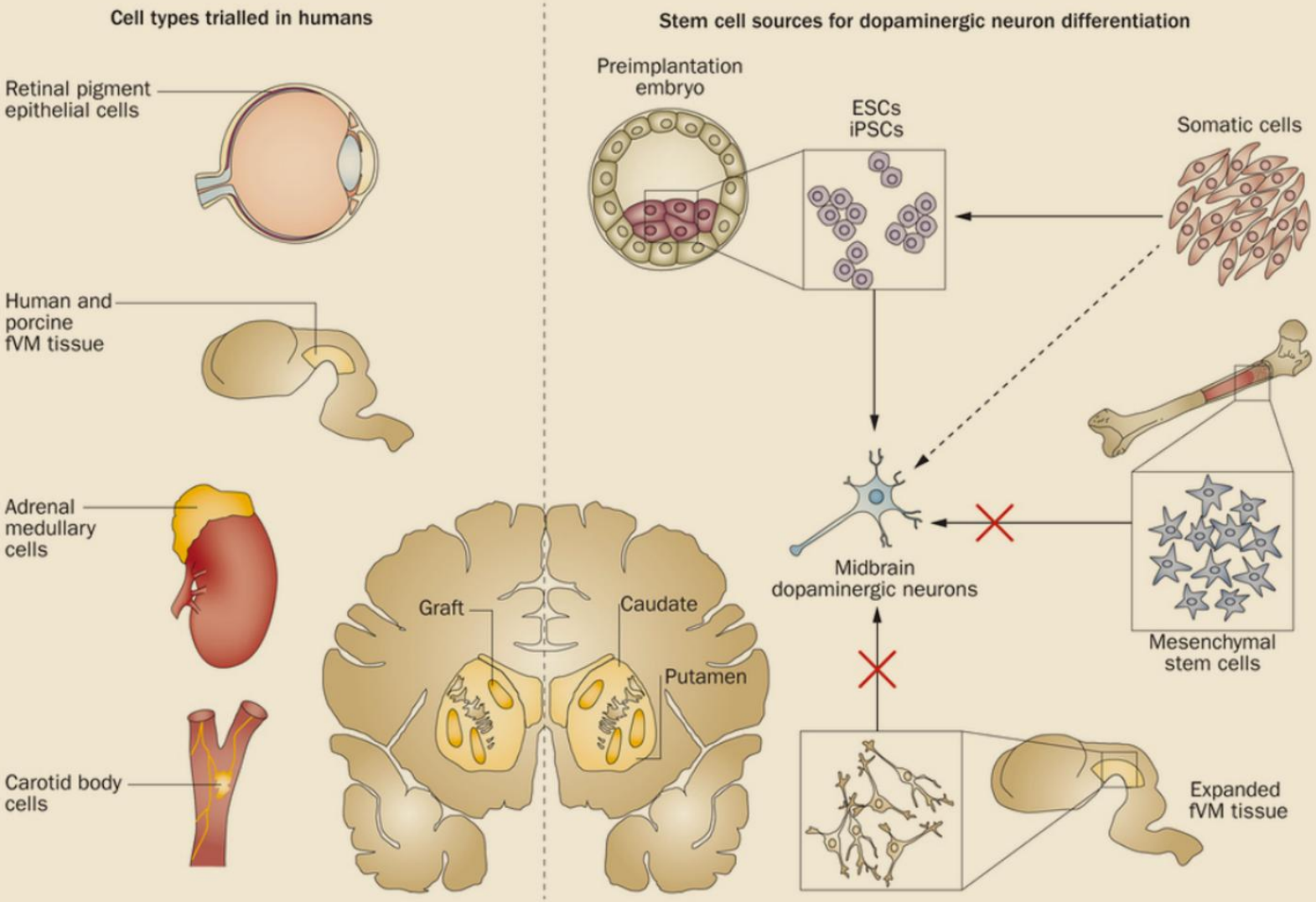
PARKINSON'S DISEASE(DEGENERATIVE STAGES)




Neuroinflammation
Activated microglia
Neuron
Unfolded α-synuclein
Perturbed α-synuclein proteostasis
Reactive oxygen species
Impaired mitochondrial biogenesis
Toxic oligomers
Misfolding of protein
Macroautophagy
Chaperone-mediated autophagy
Mitochondrial dysfunction
Oxidative stress
Autophagosome
Calcium influx
Calcium channel
β-Pleated sheet
Lysosomal autophagy system
Impaired calcium homeostasis
Lysosome-dependent degradation
Nucleus
Ubiquitin–proteasome system
Lewy body
Caspase activation
Trans-synaptic transmission to unaffected neurons
Cell death


Impaired biogenesis
α-Synuclein
CHCHD2
Parkin
PINK1
PGC1α
NRF2
Nucleus
Oxidative stress
α-Synuclein
LRRK2
CHCHD2
VPS35
Parkin
PINK1
ATP13A2
Defective mitophagy
Parkin
PINK1
ATP13A2
α-Synuclein
PINK1
Ca2+ imbalance
Mitochondrial dysfunction
LRRK2
Parkin
PINK1
Impaired mitochondrial trafficking
VPS35
CHCHD2
Parkin
PINK1
ATP13A2
Altered mitochondrial dynamics
Cyt c
I
II
III
IV
ATP Synthase
Dysfunctional electron transport chain
LRRK2
VPS35
CHCHD2
Parkin
PINK1


a
Neurotransmitter
Electrode
Neuron
Neuron
Astrocyte
Arteriole
b
3 V
0 V
3 V
0 V
40 Hz
Oscillation frequency (Hz)
Beta
2 Hz
Time
2 min


Cell types trialled in humans
Retinal pigment epithelial cells
Human and porcine fVM tissue
Adrenal medullary cells
Carotid body cells
Graft
Caudate
Putamen
Stem cell sources for dopaminergic neuron differentiation
Preimplantation embryo
ESCs iPSCs
Somatic cells
Midbrain dopaminergic neurons
Mesenchymal stem cells
Expanded fVM tissue

nature biotechnology

Optogenetics enables functional analysis of human embryonic stem cell–derived grafts in a Parkinson's disease model

Julius A Steinbeck[1,2], Se Joon Choi[3], Ana Mrejeru[3], Yosif Ganat[1,2], Karl Deisseroth[4–6], David Sulzer[3,7,8], Eugene V Mosharov[3] & Lorenz Studer[1,2]