SINDROME LONG COVID

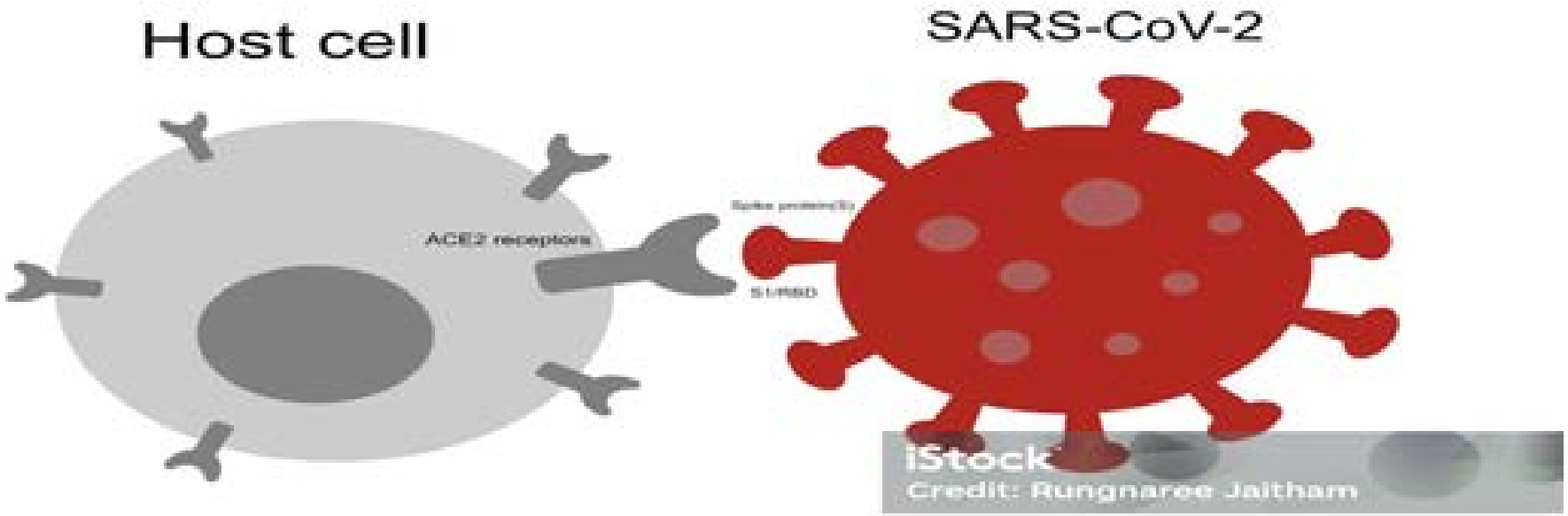
COMPLICANZE

NEUROLOGICHE

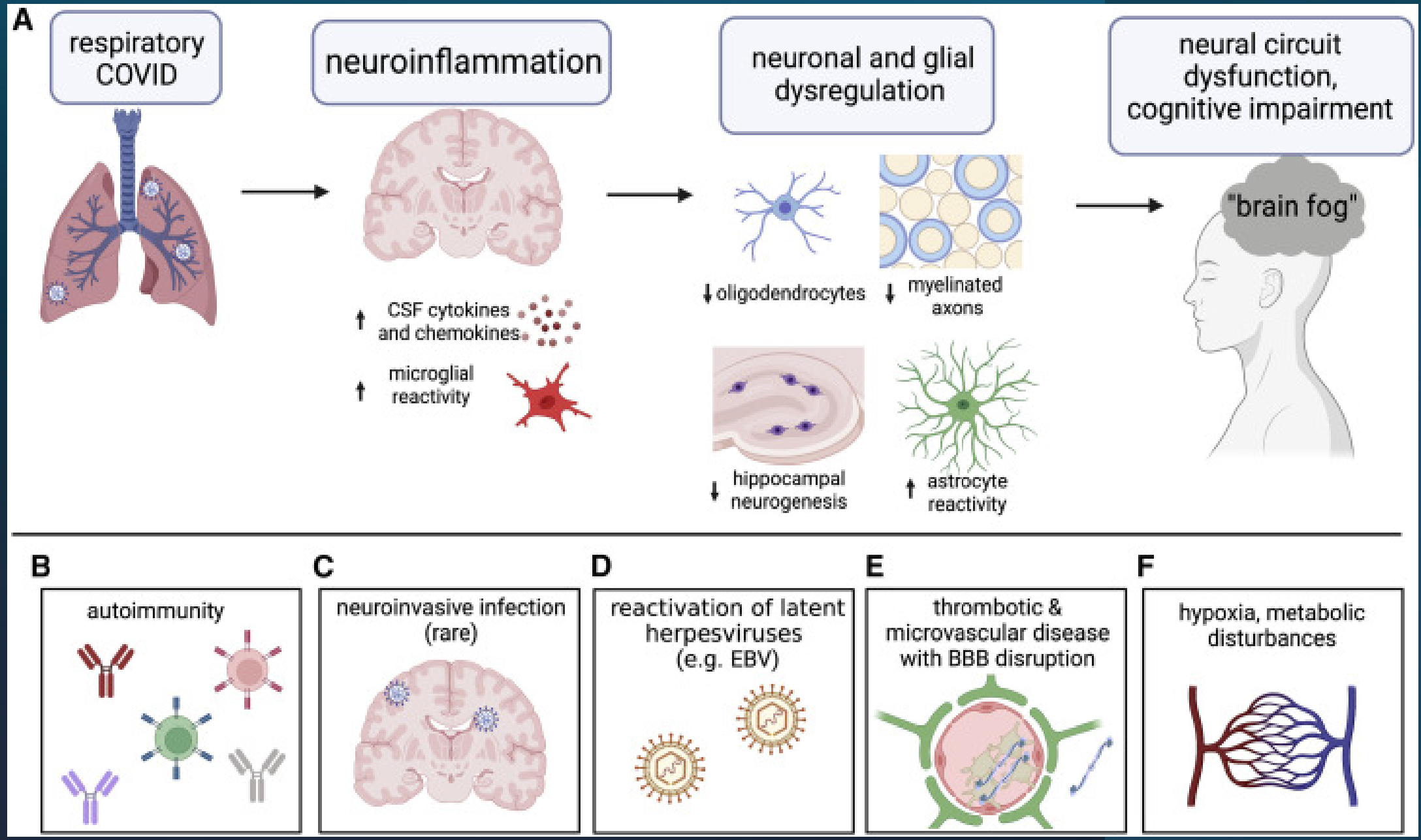
COMPLICANZE NEUROLOGICHE

LO STATO DI ENDEMIA DI VARIANTI DEL COVID IL NUOVO COVID E LE CAMPAGNE DI VACCINAZIONE INDEBOLISCONO IL NOSTRO SISTEMA IMMUNITARIO E SI FANNO SEMPRE PIU’ PRESENTI E PERICOLOSE LE COMPLICANZE NEUROLOGICHE ANCHE UN COVID LIEVE LASCIA PROBLMI NEUROLOGI

MODALITA’ DI INGRESSO DEL VIRUS NELLA CELLULA


Host cell
SARS-CoV-2
ACE2 receptors
S1/RBD
iStock
Credit: Rungnaree Jaitham

MODALITA’ DI TRASMISSIONE DELLA INFEZIONE DA CORONAVIRUS


A
respiratory COVID
neuroinflammation
neuronal and glial dysregulation
neural circuit dysfunction, cognitive impairment
CSF cytokines and chemokines
microglial reactivity
oligodendrocytes
myelinated axons
"brain fog"
hippocampal neurogenesis
astrocyte reactivity
B
autoimmunity
C
neuroinvasive infection (rare)
D
reactivation of latent herpesviruses (e.g. EBV)
E
thrombotic & microvascular disease with BBB disruption
F
hypoxia, metabolic disturbances

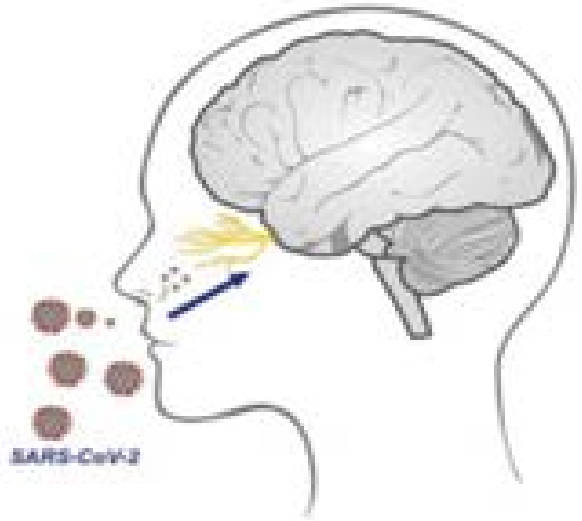

Adobe Stock | #1457995617

NEUROINVASIONE ED EMATOINVASIONE DEL CORONAVIRUS

1) Neuroinvasive via retrograde axonal transport

2) Hematogenous neuroinvasive route

A Transcribrial neuroinvasive route

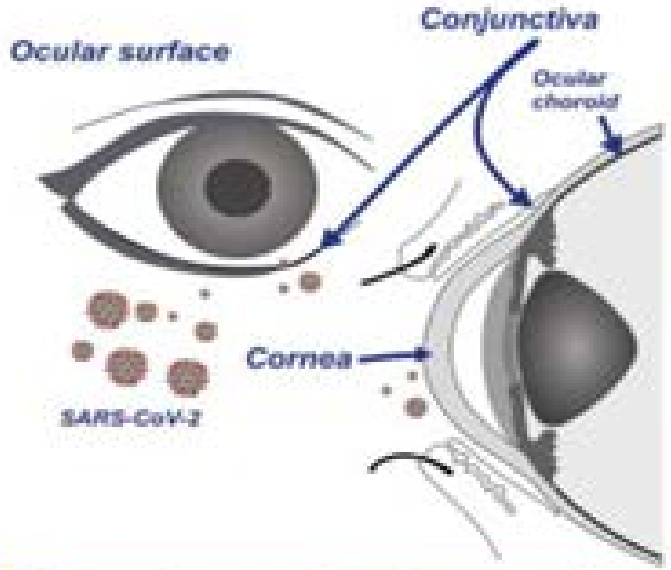


SARS-CoV-2 could reach the CNS via cranial nerves:

- *olfactory nerve*
- *trigeminal nerve*
- *vagus nerve*

ACE2 expression found in olfactory bulb and olfactory neuroepithelium

B Ocular surface route

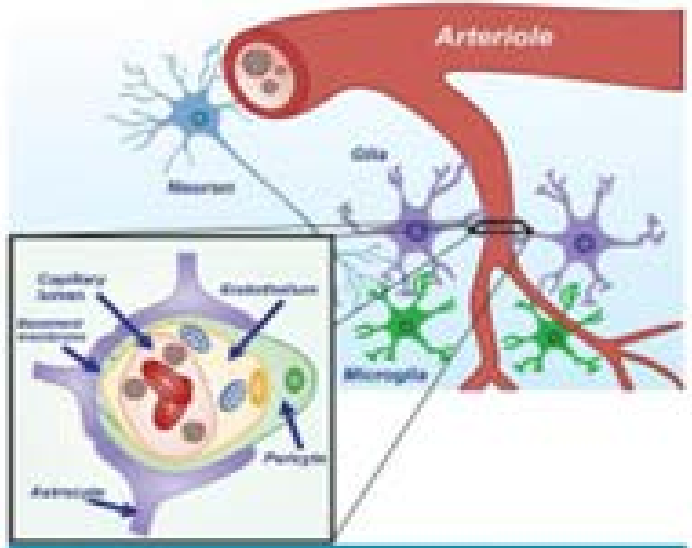


The ocular surface is susceptible to viral infections

ACE2 expression found in:

- *trabecular meshwork*
- *ocular choroid cells*
- *optic nerve*
- *geniculocalcarine tract*

C Virus across the BBB



Possible mechanism of hematogenous route:

- *Transcellular migration*
- *Paracellular migration*
- *The "Trojan horse" strategy*

ACE2 and TMPRSS2 expression found in endothelian cells

AUTOPSIA POLMONE E CERVELLO BAMBNO DI 14 ANNI

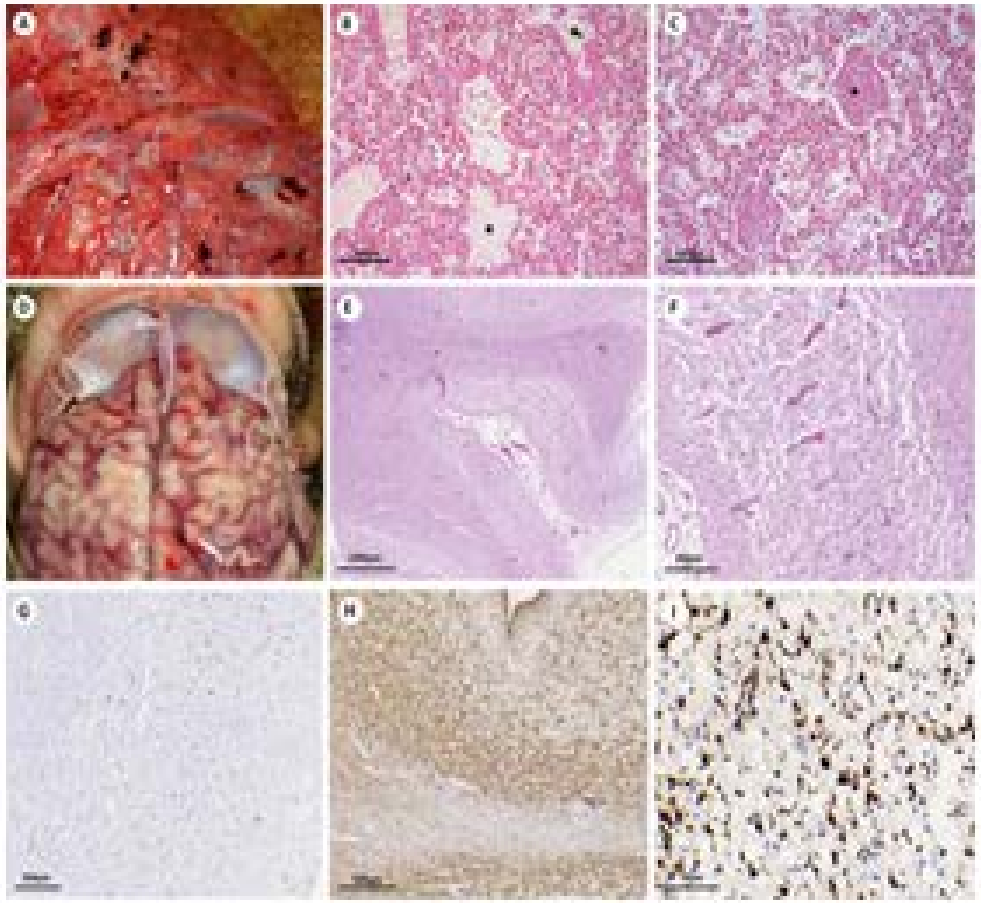
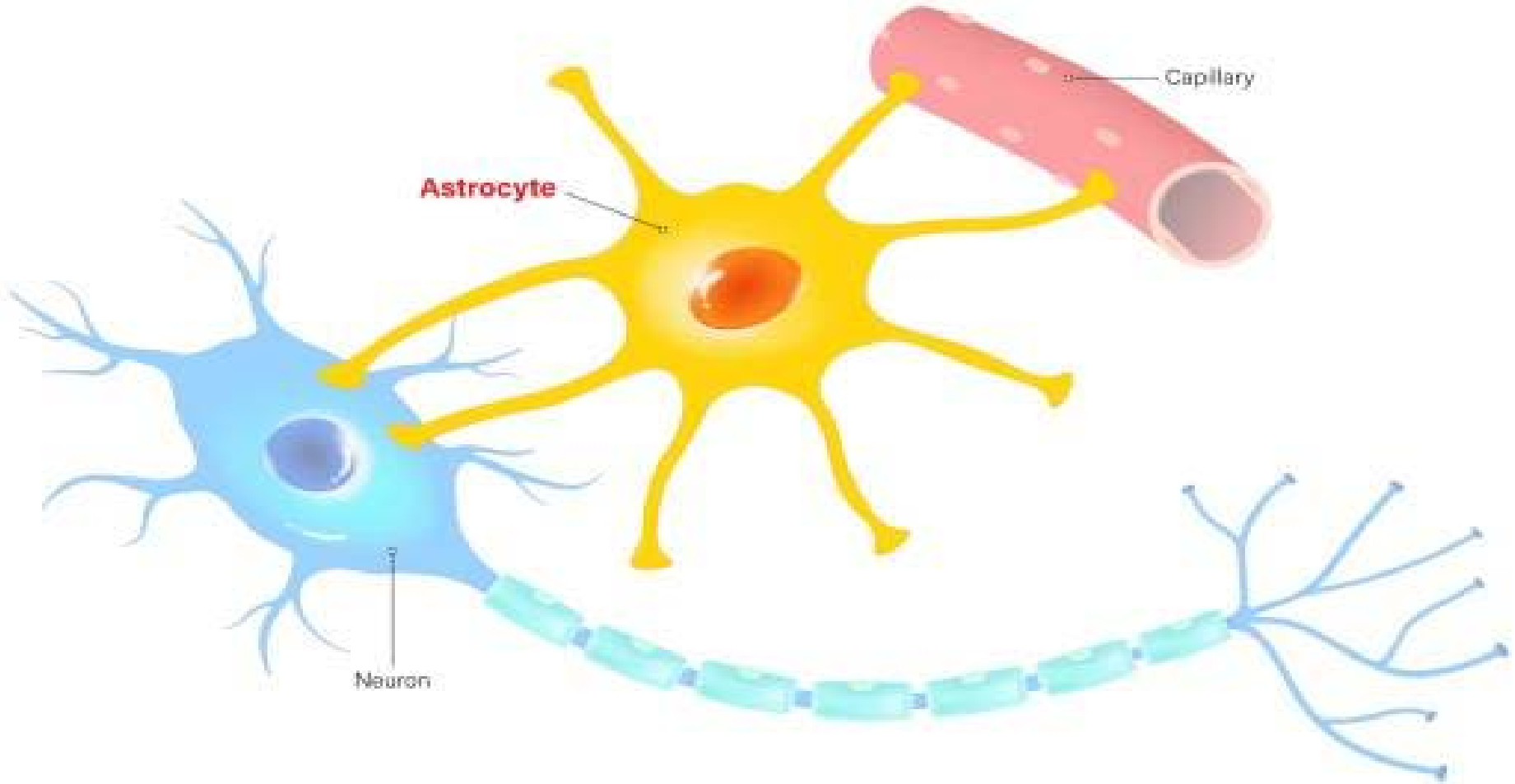
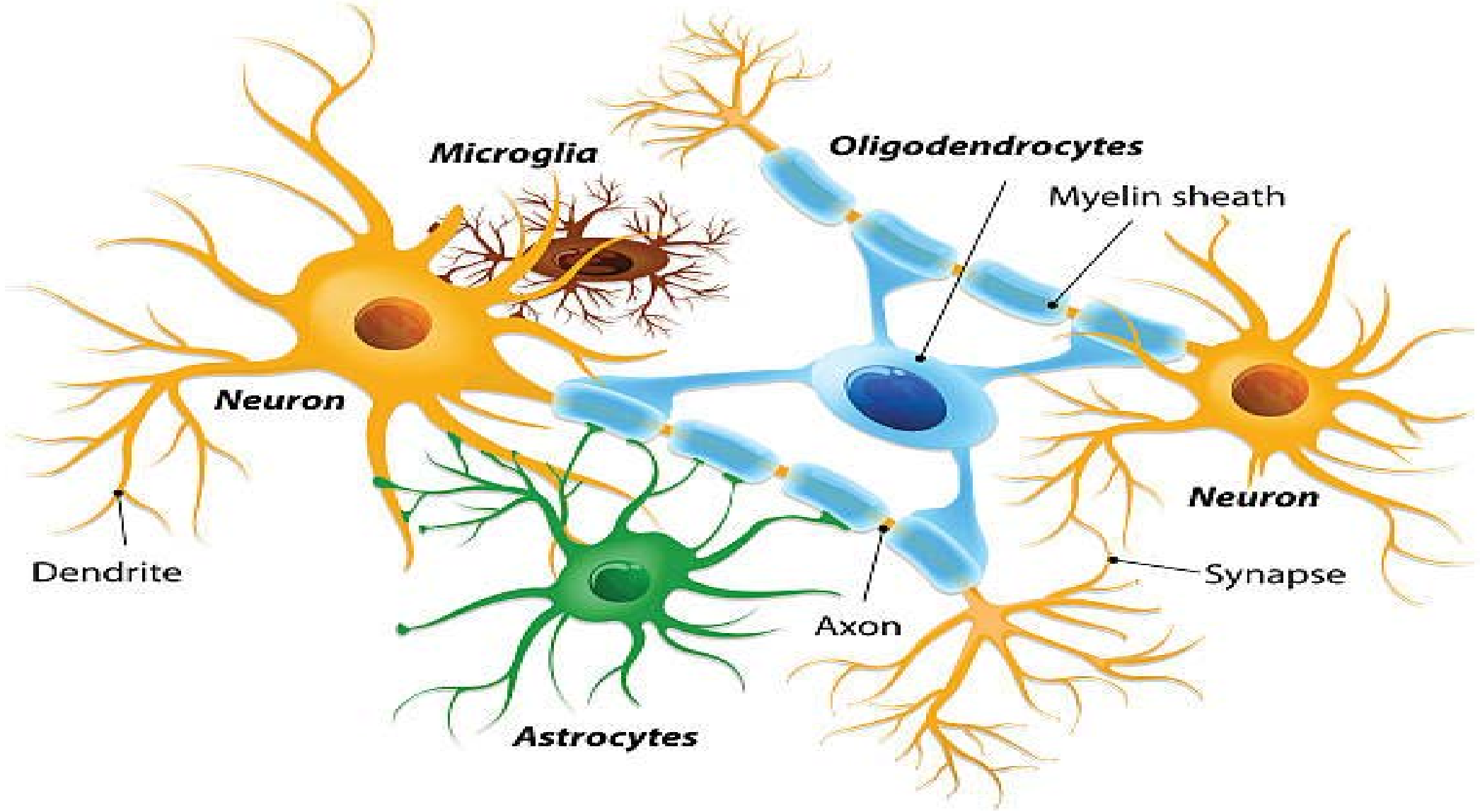


IMMAGINE DEI TIPI DI CELLULE COINVOLTE NEL PROCESSO DI NEUROINFIAMMAZIONE



Astrocyte

NEURONS AND NEUROGLIAL CELLS



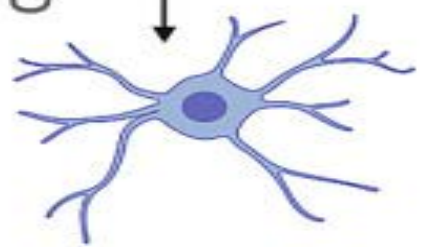
IMMAGINI DELLE CONSEGUENZE DELLA NEUROINFIAMMAZIONE

astrocyte reactivity

impaired support of synapses

killing of susceptible neurons

killing of oligodendrocytes

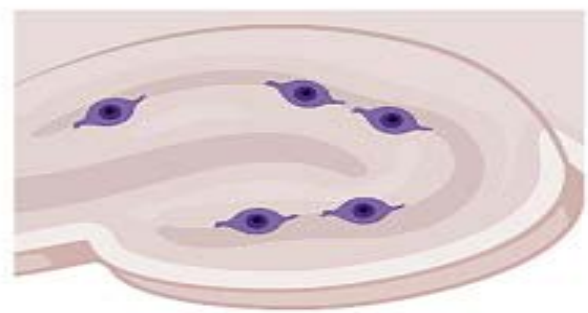


↓ oligodendrocytes

↓ myelinated axons

↓ myelin plasticity

↑ synapse pruning, altered synaptic function



↓ hippocampal neurogenesis

DIDASCALIA DELLE FIGURE PRECEDENTI

LA **MICROGLIA REATTIVA (ROSSO)INDUCE UNA DISREGOLAZIONE CELLULARE CHE COLPISCE NEURONI E OLIGODENDROCITI COME RIDUZIONE DEGLI OLIGODENDROCITI (BLU) E DEGLI ASSONI MILEINIZZATI EVIDENZIANDO L'OMEOSTASI DELLA MIELINA (BLU) INTERROTTA**

LA MICROGLIA REATTIVA PUO' INDURRE UNA REATTIVITA' NEUROTOSSICA DEGLI ASTROCITI .

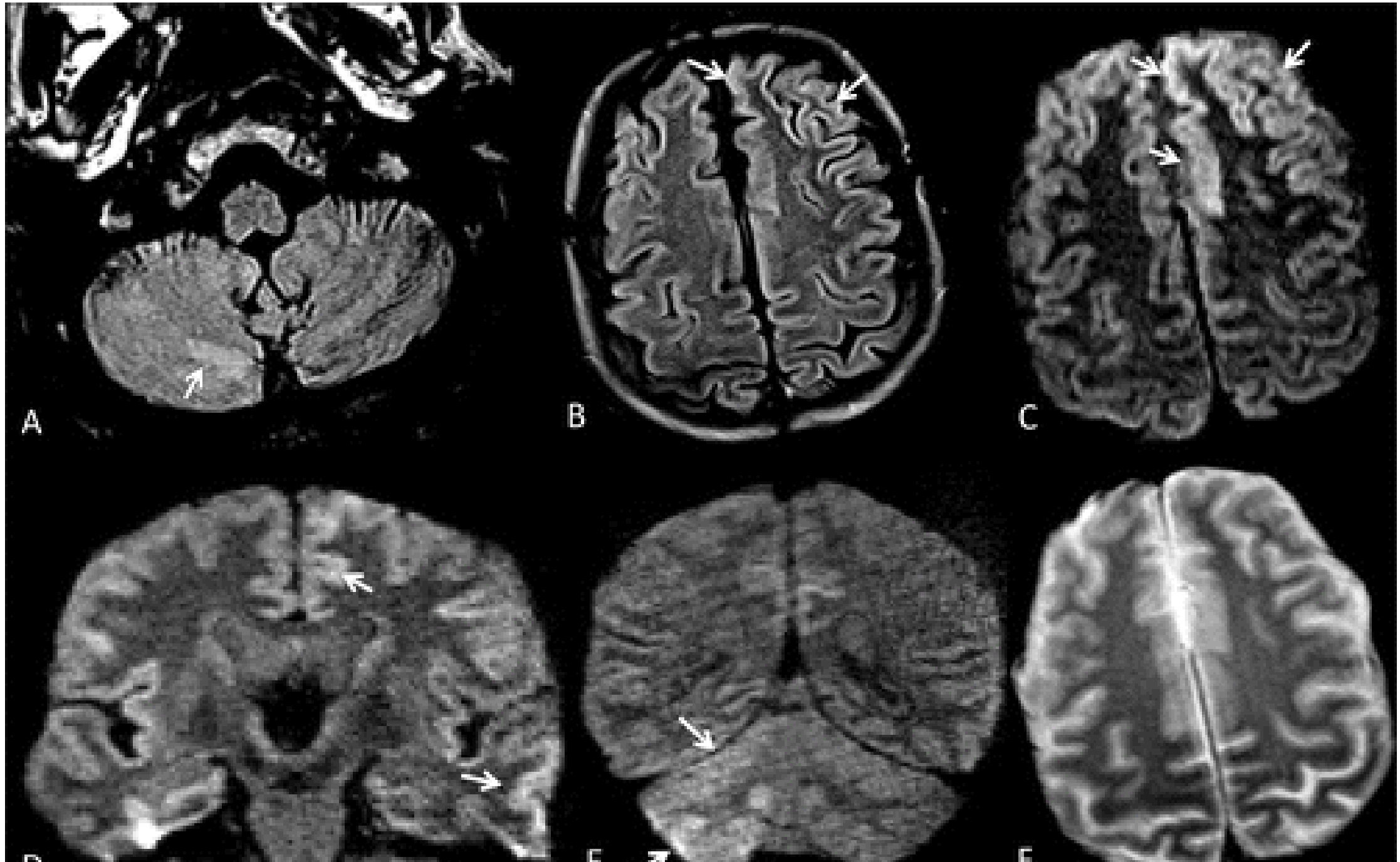
GLI ASTROCITI REATTIVI NEUROTOSSSICI (VERDE) UCIDONO GLI OLIGODENDROCITI E I NEURONI (LAVANDA)

VENGONO POTATE LE SINAPSI O ALTERARE LA ECCITABILITA' NEURONALE

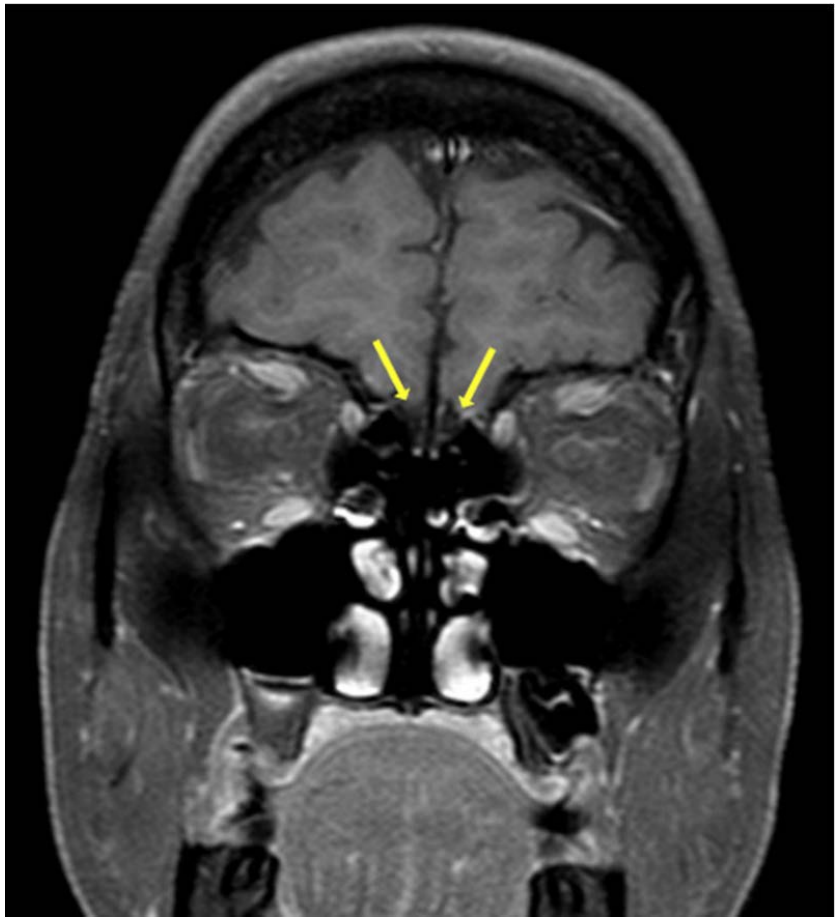
LE INTERLEUCHINE DERIVATE DALLA MICRIGLIA INFIAMMATA COMPROMETTONO LA NEUROGENESI IPPOCAMPALE

TAC DELLA ENCEFALOPATIA ACUTA

NOTARE LA DIMINUZONE DELLA SOSTANZA GRIGIA

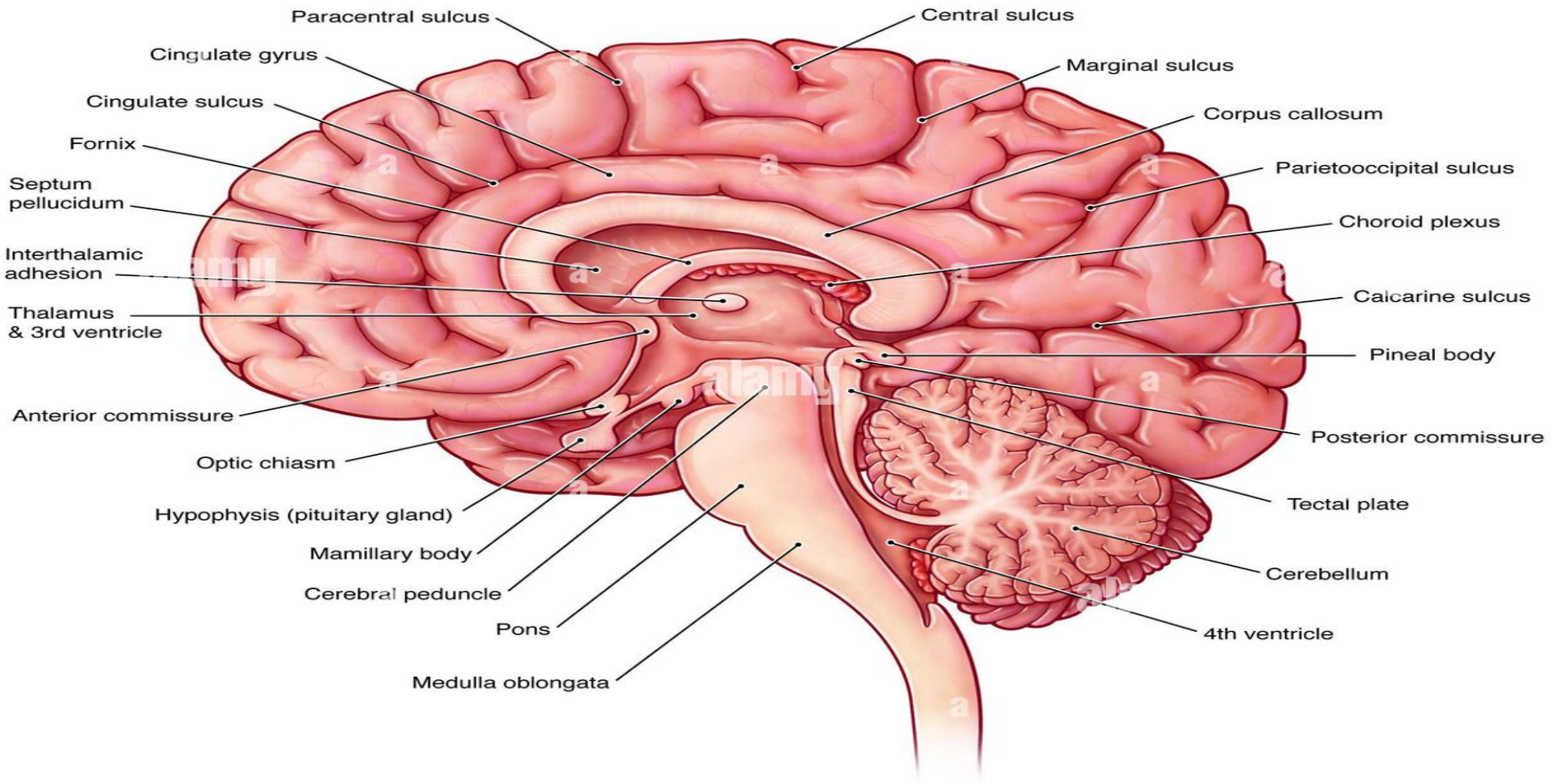

A
B
C

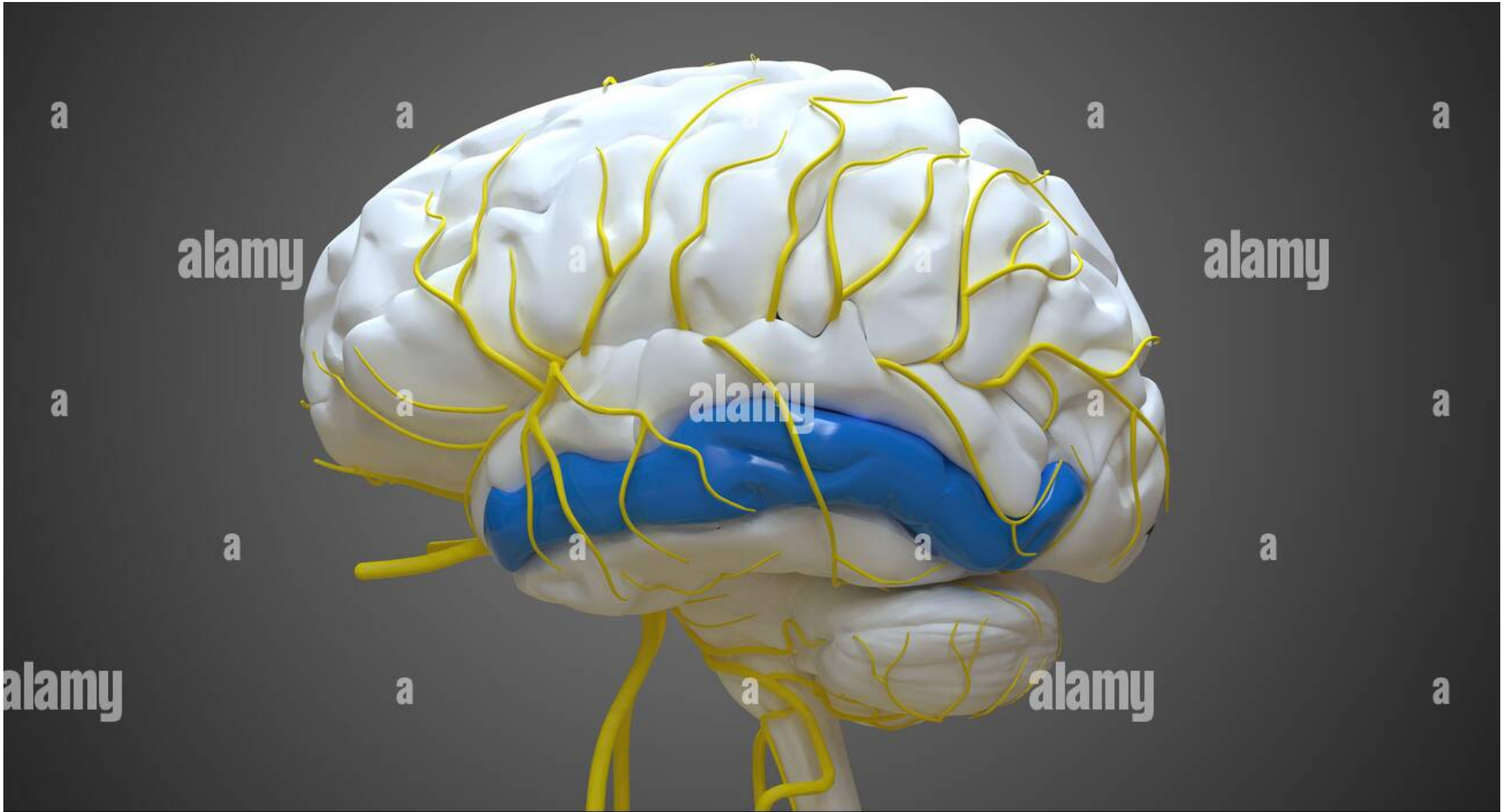
DANNO BULBI OLFATTIVI BILATERALI



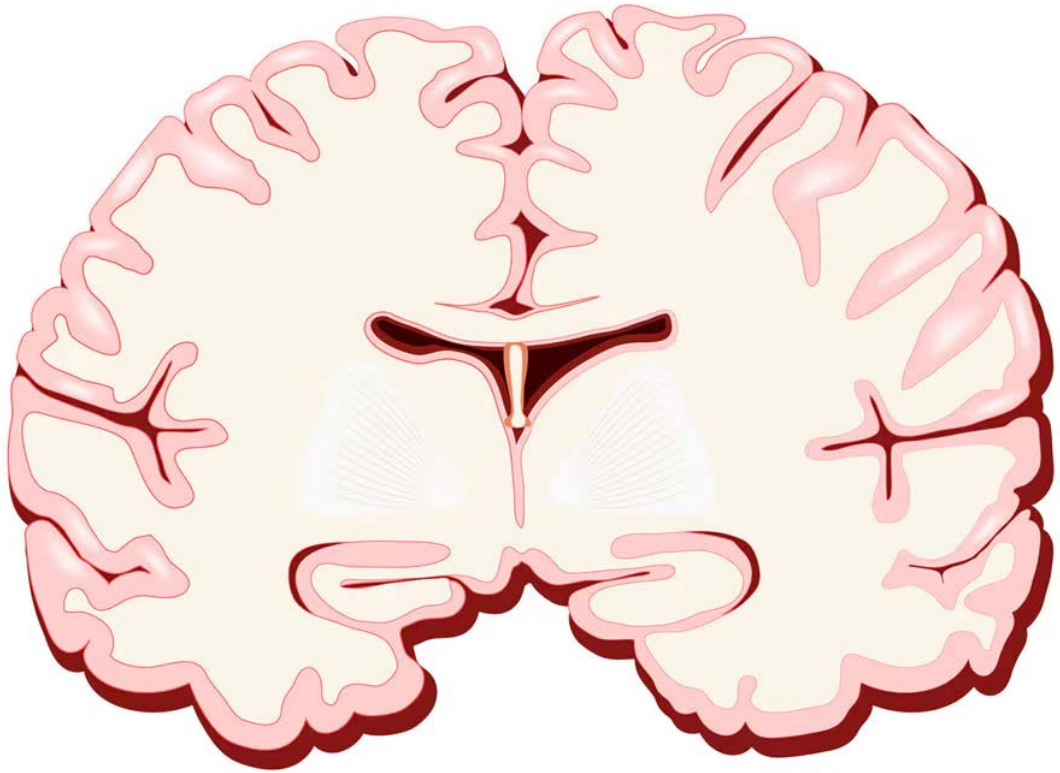
IL PLESSO COROIDEO E’ LA PORTA DI INGRESSO AL CERVELLO

PLESSO COROIDEO

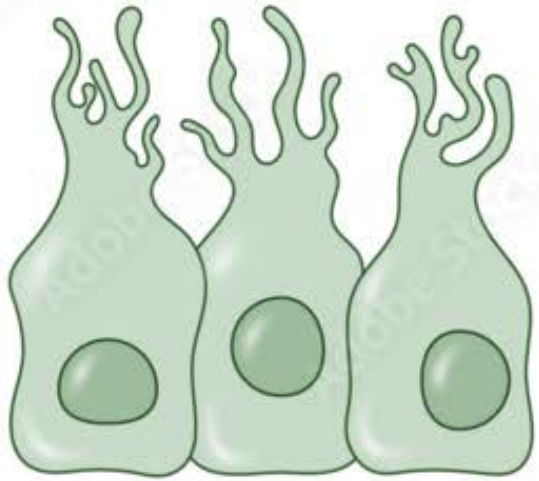



alamy
Image ID: 2G54YJN
www.alamy.com

SOSTANZA BIANCA

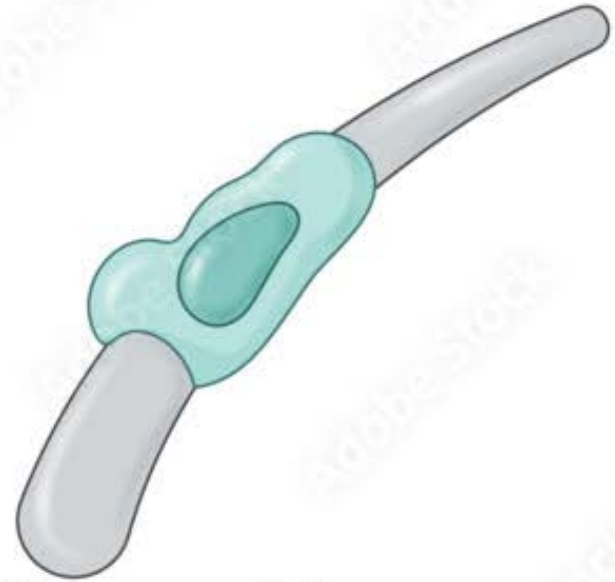


MICROGLIA



Ependymal Cell

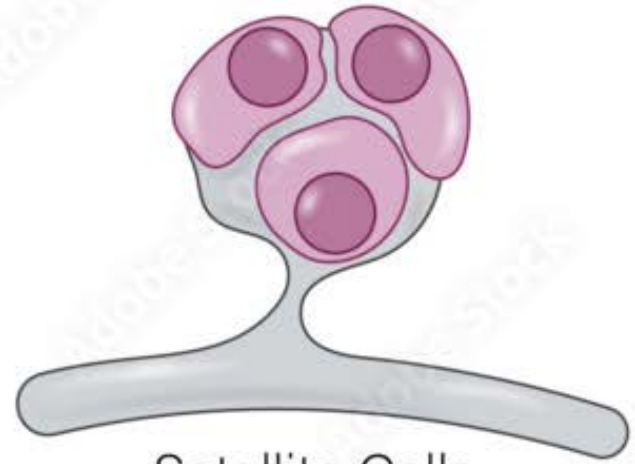
Microglia



Schwann Cell

Astrocytes

Oligodendrites

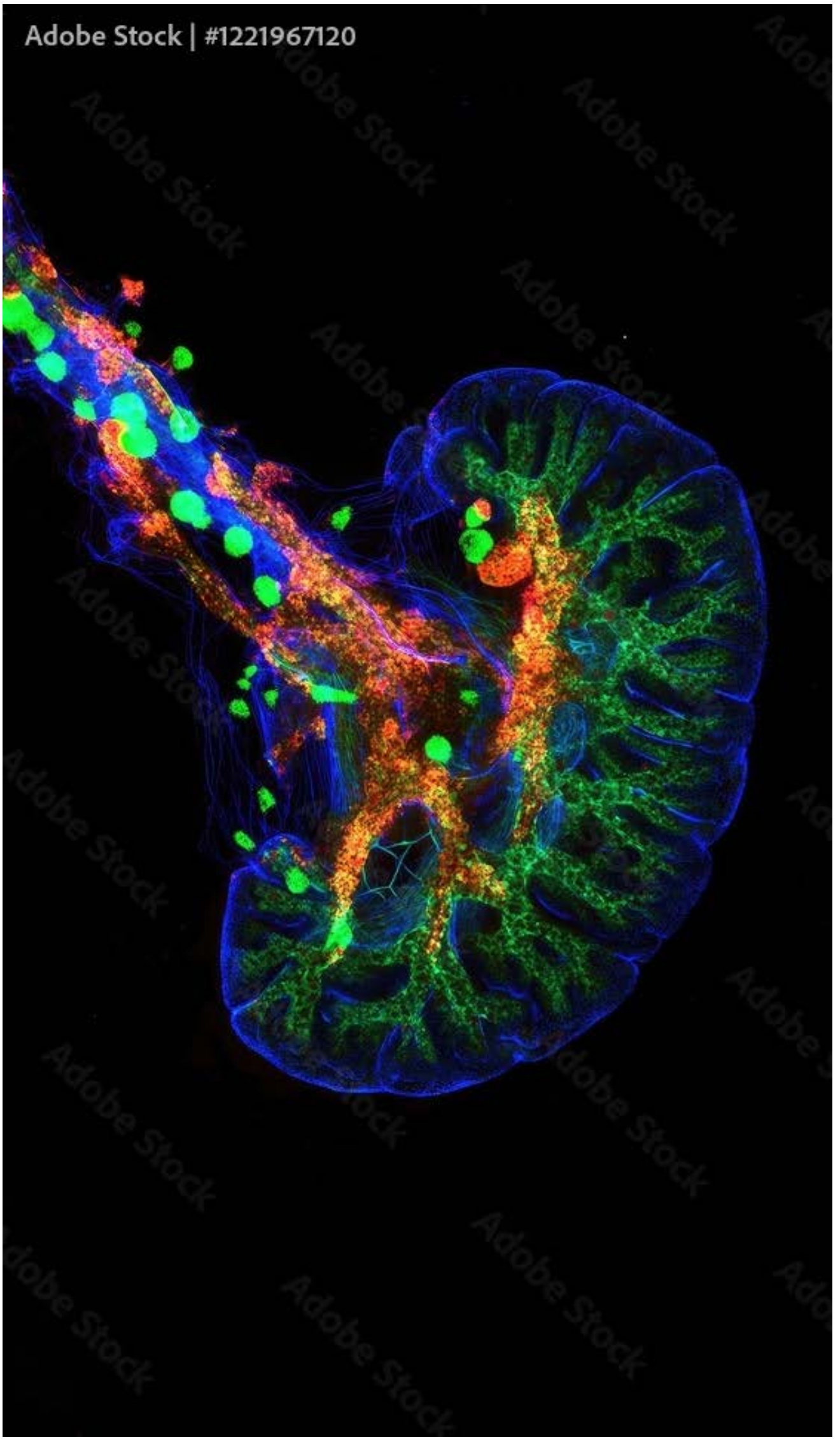


Satellite Cells


Adobe Stock | #1513779496


Adobe Stock | #1249875943


Adobe Stock | #1059087714

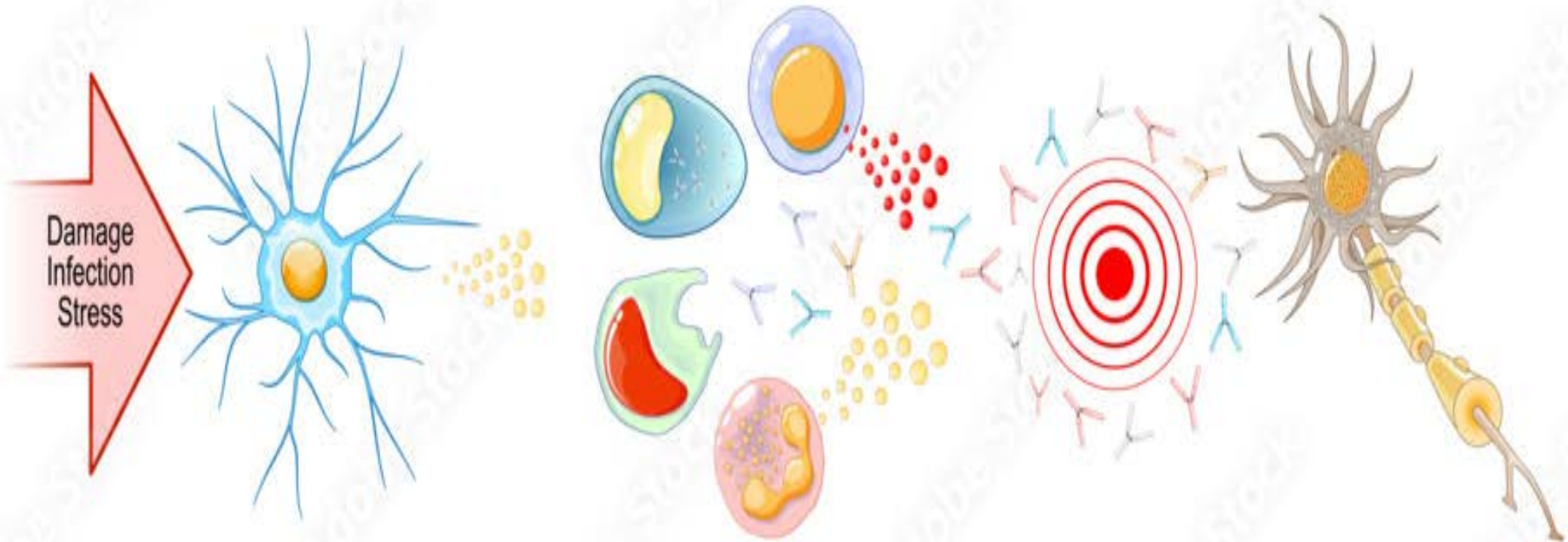

Adobe Stock | #1221967120

INVECCHIAMENTO CEREBRALE

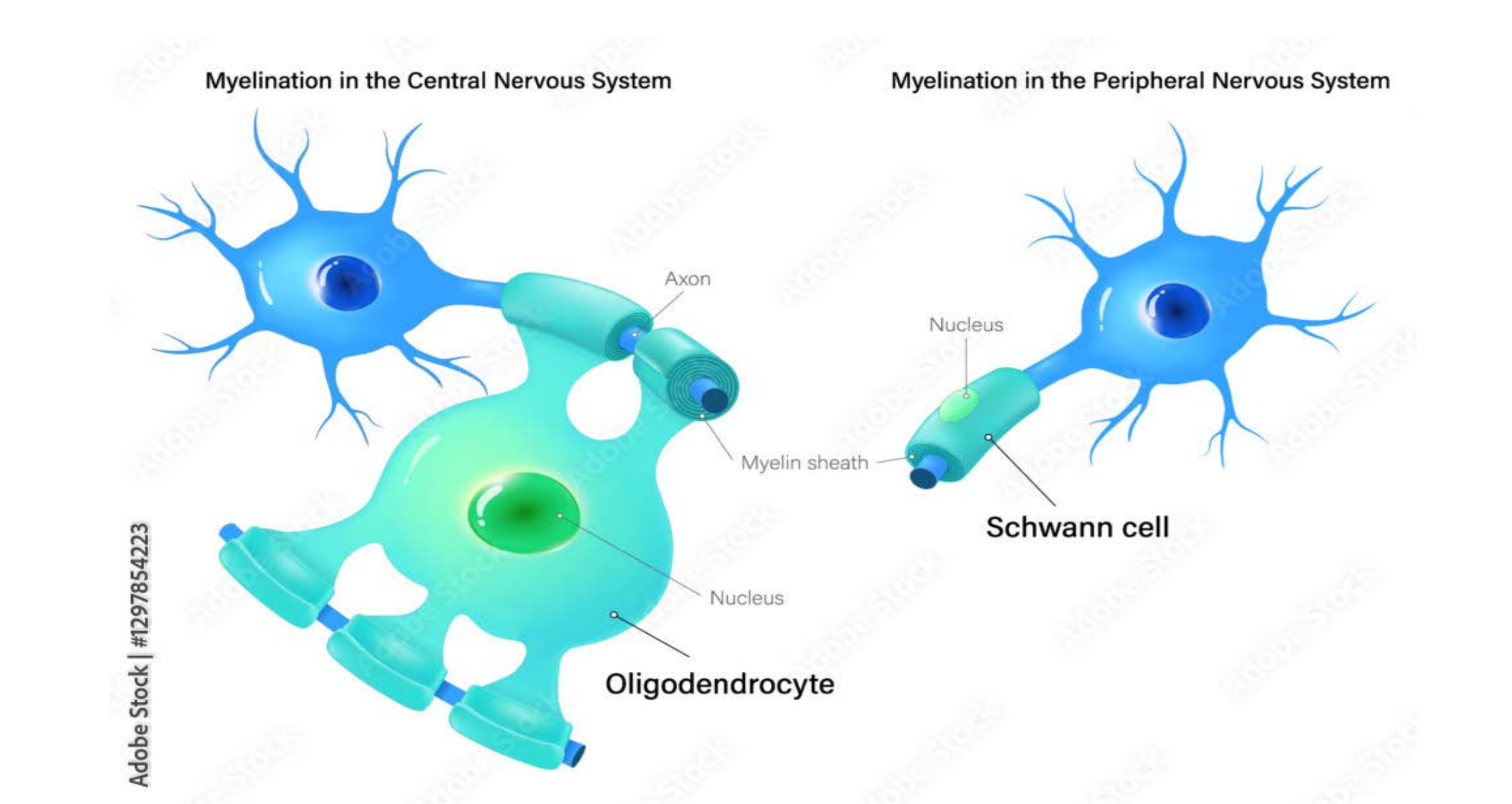

Adobe Stock | #1309115176

NEUROINFIAMMAZIONE

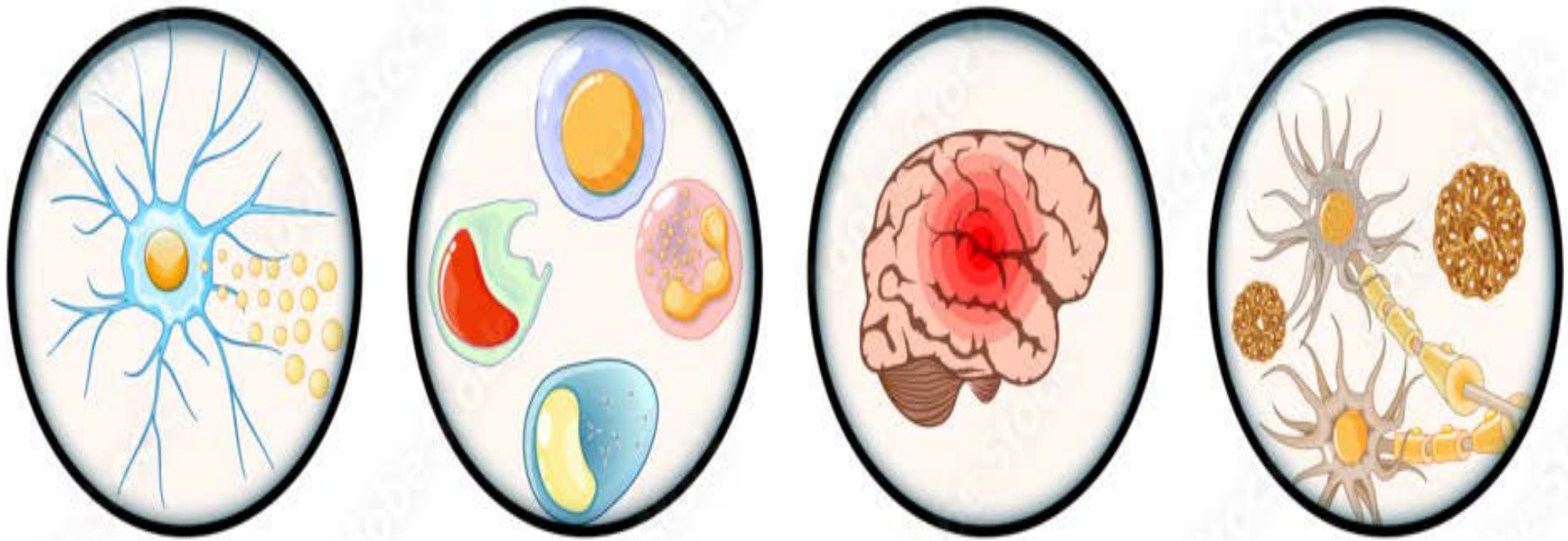
NEUROINFLAMMATION



1. Microglia activation (release of pro-inflammatory cytokines)
2. Recruitment of peripheral immune cells
3. Chronic inflammation
4. Neuronal damage and death

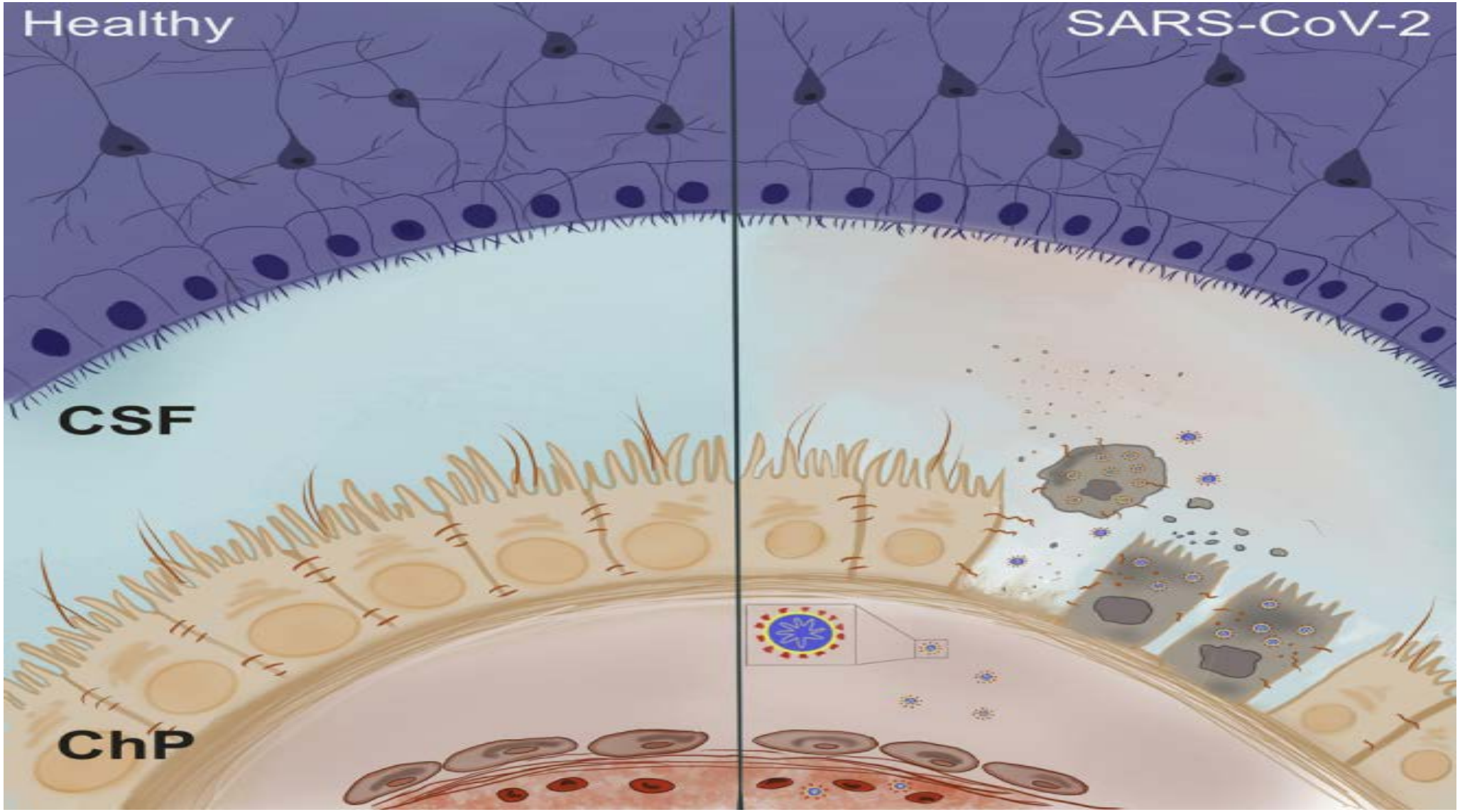

Myelination in the Central Nervous System
Axon
Myelin sheath
Nucleus
Oligodendrocyte
Myelination in the Peripheral Nervous System
Nucleus
Schwann cell
Adobe Stock | #1297854223

Neuroinflammation



INFEZIONE DIRETTA

INFEZIONE DIRETTA SNC

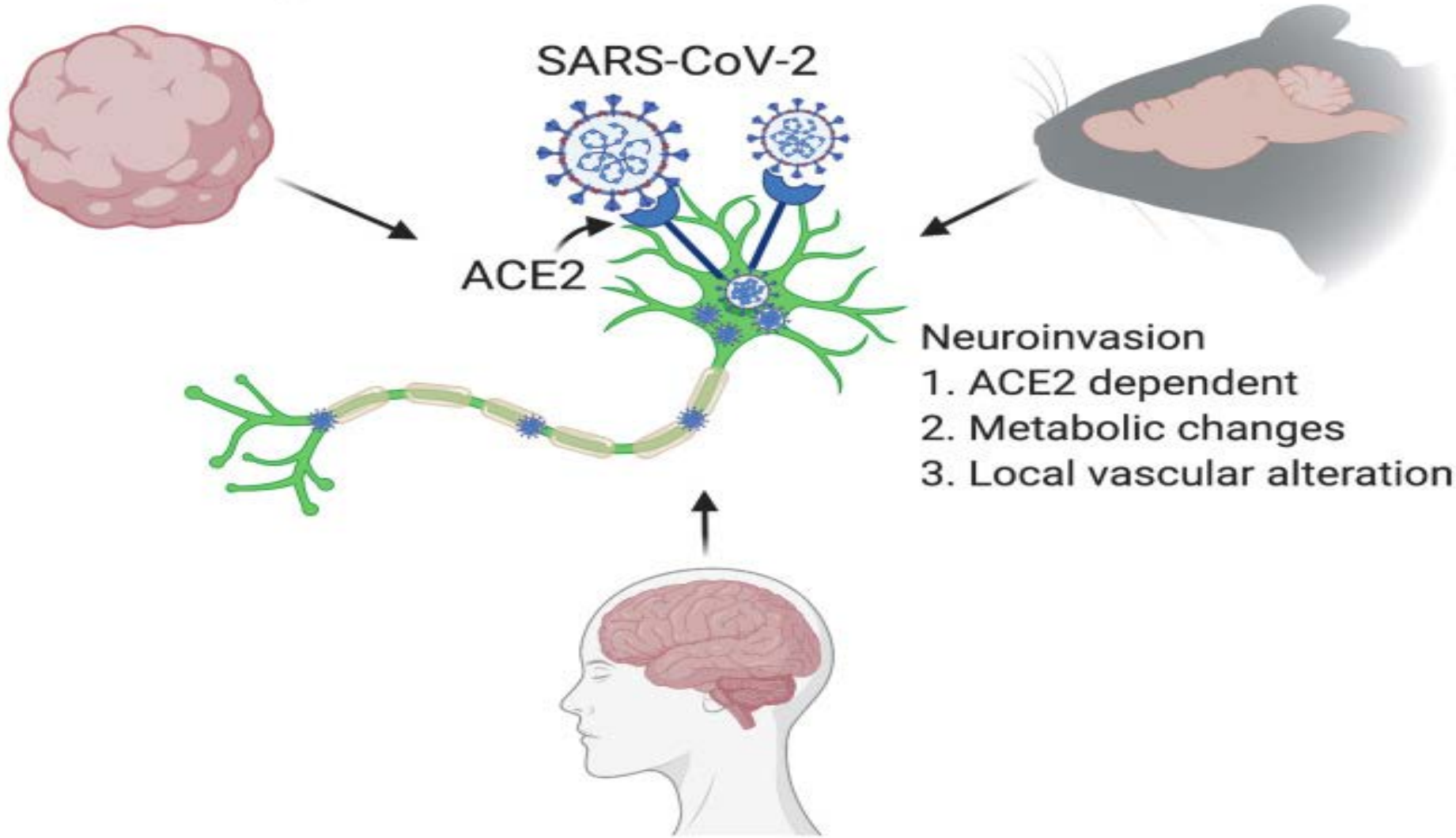


In vitro

Human brain organoids

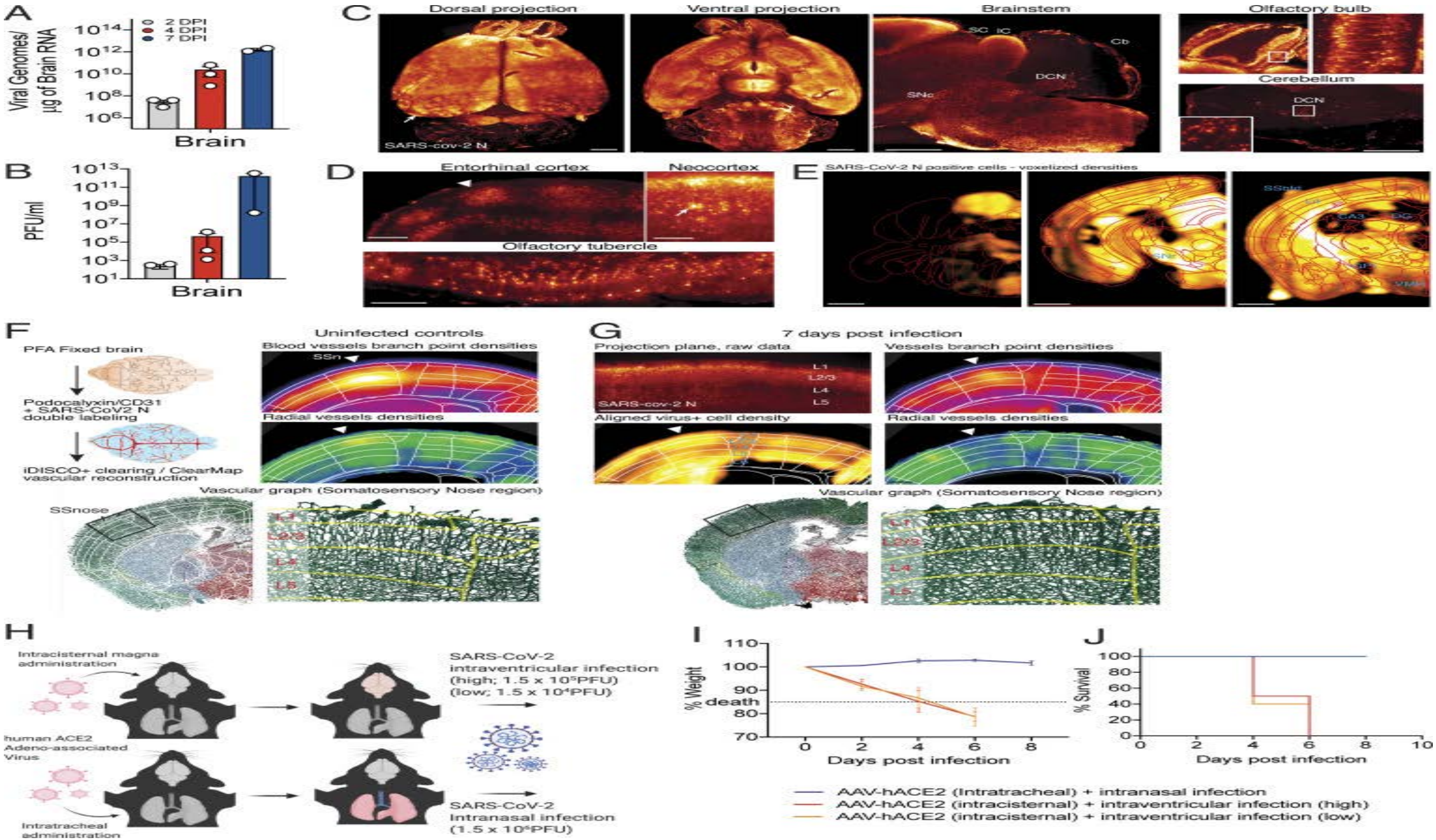
In vivo

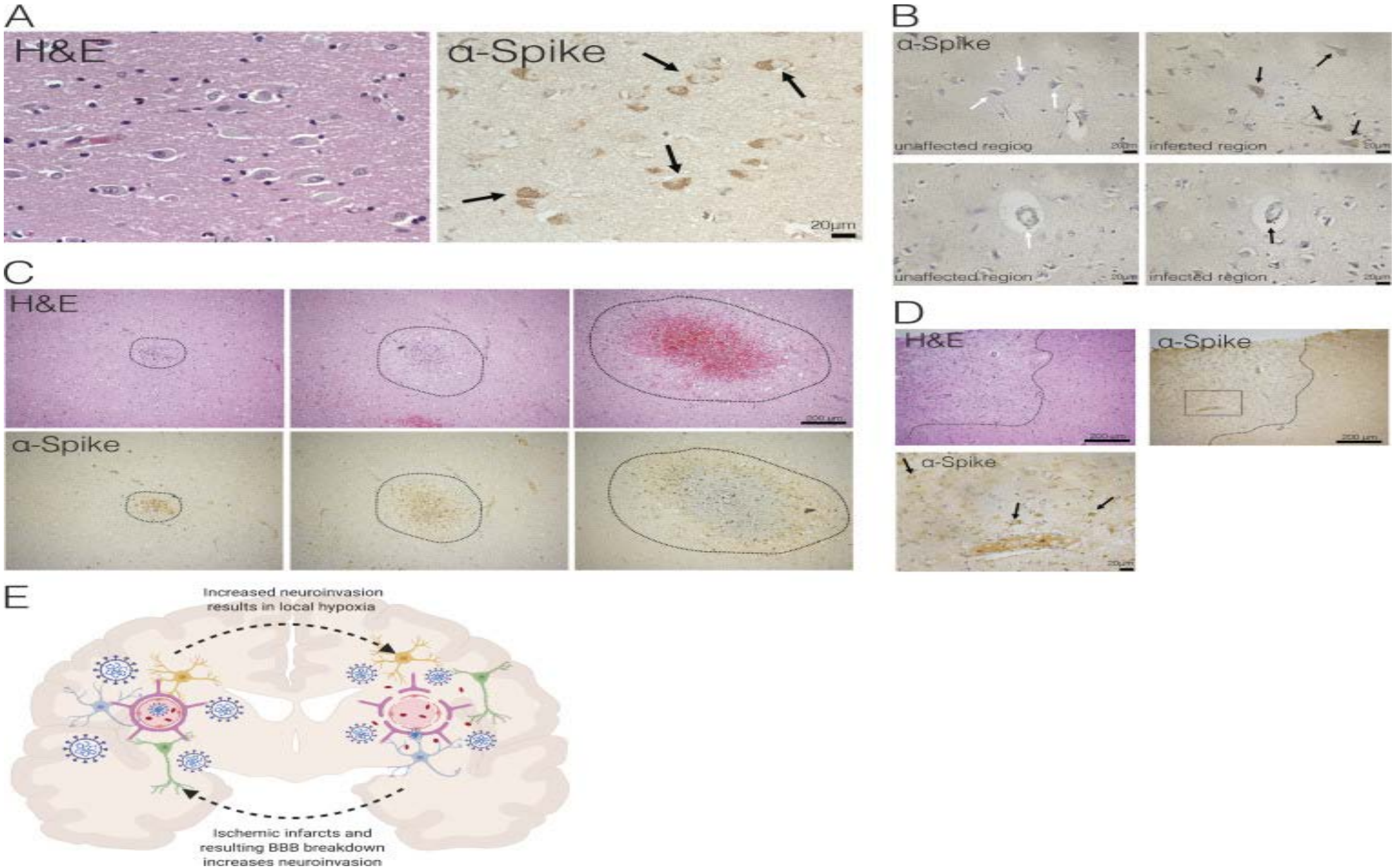
SARS-CoV-2 mouse model



Post mortem

COVID-19 patient brain samples

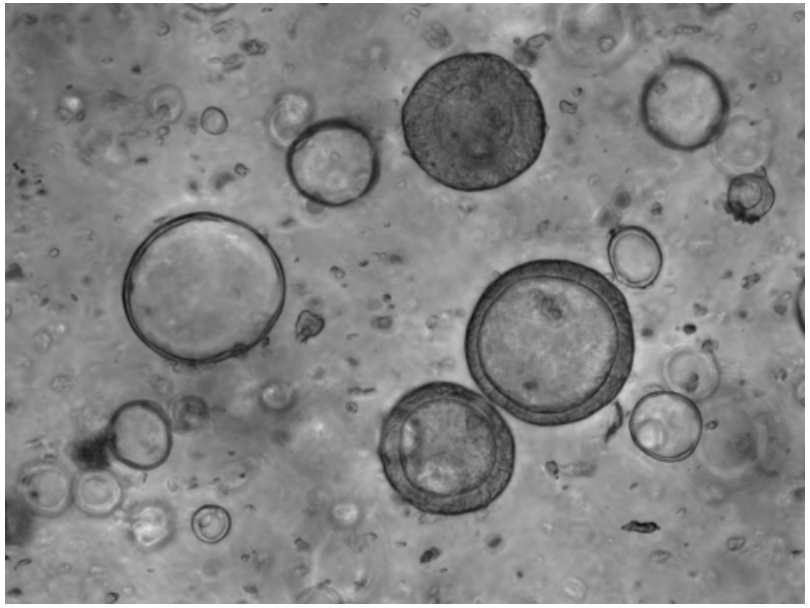

A
Viral Genomes/ µg of Brain RNA
2 DPI
4 DPI
7 DPI
Brain
B
PFU/ml
Brain
C
Dorsal projection
Ventral projection
Brainstem
Olfactory bulb
SARS-cov-2 N
SC
IC
Cb
DCN
SNc
Cerebellum
D
Entorhinal cortex
Neocortex
Olfactory tubercle
E
SARS-CoV-2 N positive cells – voxelized densities
F
Uninfected controls
PFA Fixed brain
Podocalyxin/CD31 + SARS-CoV2 N double labeling
iDISCO+ clearing / ClearMap vascular reconstruction
Blood vessels branch point densities
SSn
Radial vessels densities
Vascular graph (Somatosensory Nose region)
SSnose
L1
L2/3
L4
L5
G
7 days post infection
Projection plane, raw data
SARS-cov-2 N
Vessels branch point densities
Aligned virus+ cell density
Radial vessels densities
Vascular graph (Somatosensory Nose region)
H
Intracisternal magna administration
human ACE2 Adeno-associated Virus
Intratracheal administration
SARS-CoV-2 intraventricular infection (high; 1.5 x 10⁵PFU) (low; 1.5 x 10⁴PFU)
SARS-CoV-2 Intranasal infection (1.5 x 10⁶PFU)
I
% Weight
% death
Days post infection
J
% Survival
Days post infection
AAV-hACE2 (Intratracheal) + intranasal infection
AAV-hACE2 (intracisternal) + intraventricular infection (high)
AAV-hACE2 (intracisternal) + intraventricular infection (low)


A
H&E
α-Spike
20μm
B
α-Spike
unaffected regiog
infected region
unaffected region
infected region
C
H&E
α-Spike
D
H&E
α-Spike
α-Spike
E
Increased neuroinvasion
results in local hypoxia
Ischemic infarcts and
resulting BBB breakdown
increases neuroinvasion

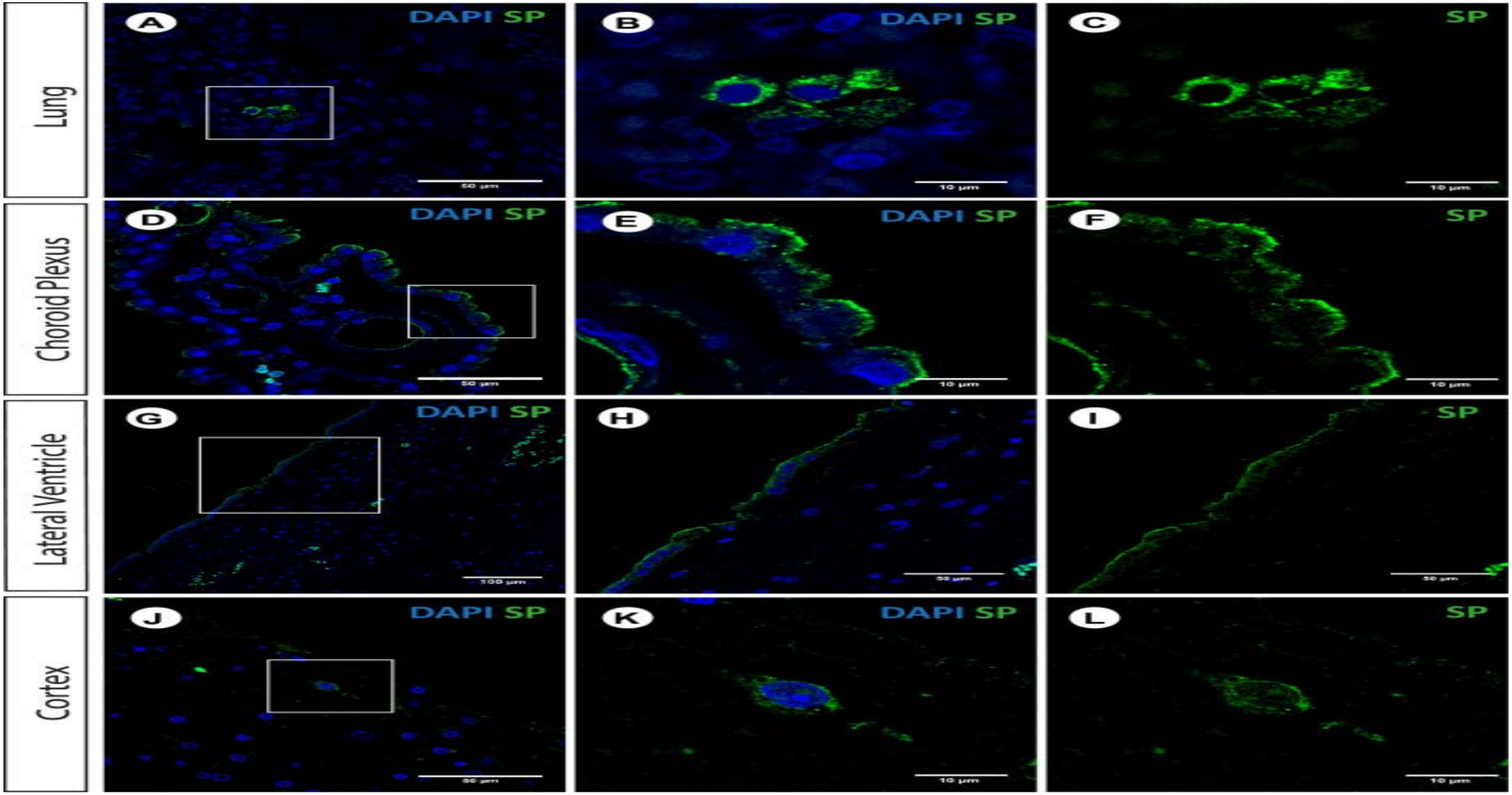
DEFINIZIONE DI ORGANOIDE

- Un Organoide è una versione semplificata e miniaturizzata di un organo prodotto in vitro in tre dimensioni che mostra caratteristiche microanatomiche realistiche. Vengono create a partire da poche cellule di tessuto, come cellule staminali embrionali o cellule staminali pluripotenti che si possono auto-organizzare in una coltura tridimensionale. La tecnica per la crescita degli organoidi si è rapidamente evoluta dal 2010 in poi ed è stata nominata da The Scientist come uno dei più grandi avanzamenti scientifici del

ORGANOIDE DI FEGATO

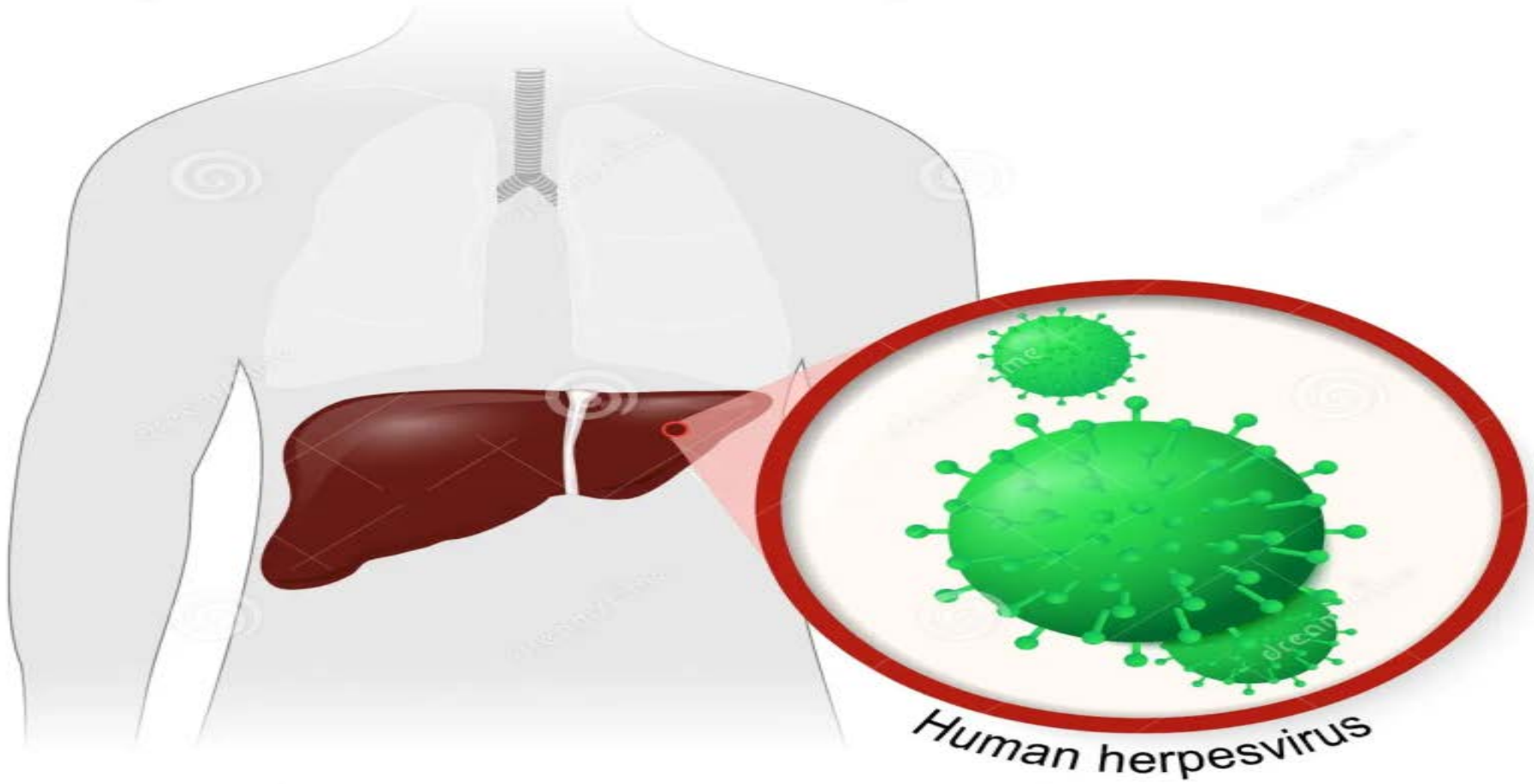


IMMUNOCOLORAZIONE



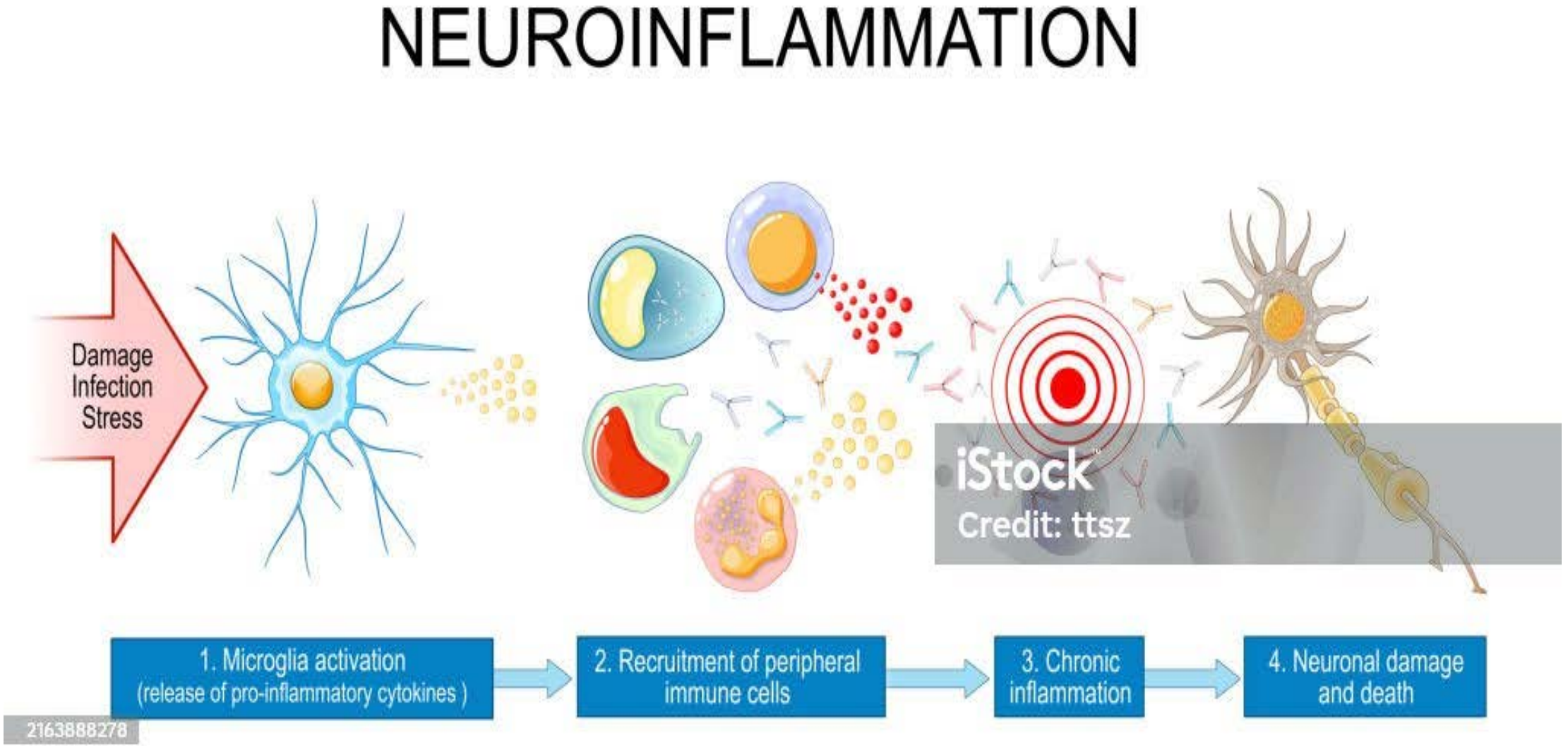
RIATTIVAZIONE DI VIRUS DI EPSTEIN BARR E HERPES ZOSTER

INFECTIOUS MONONUCLEOSIS



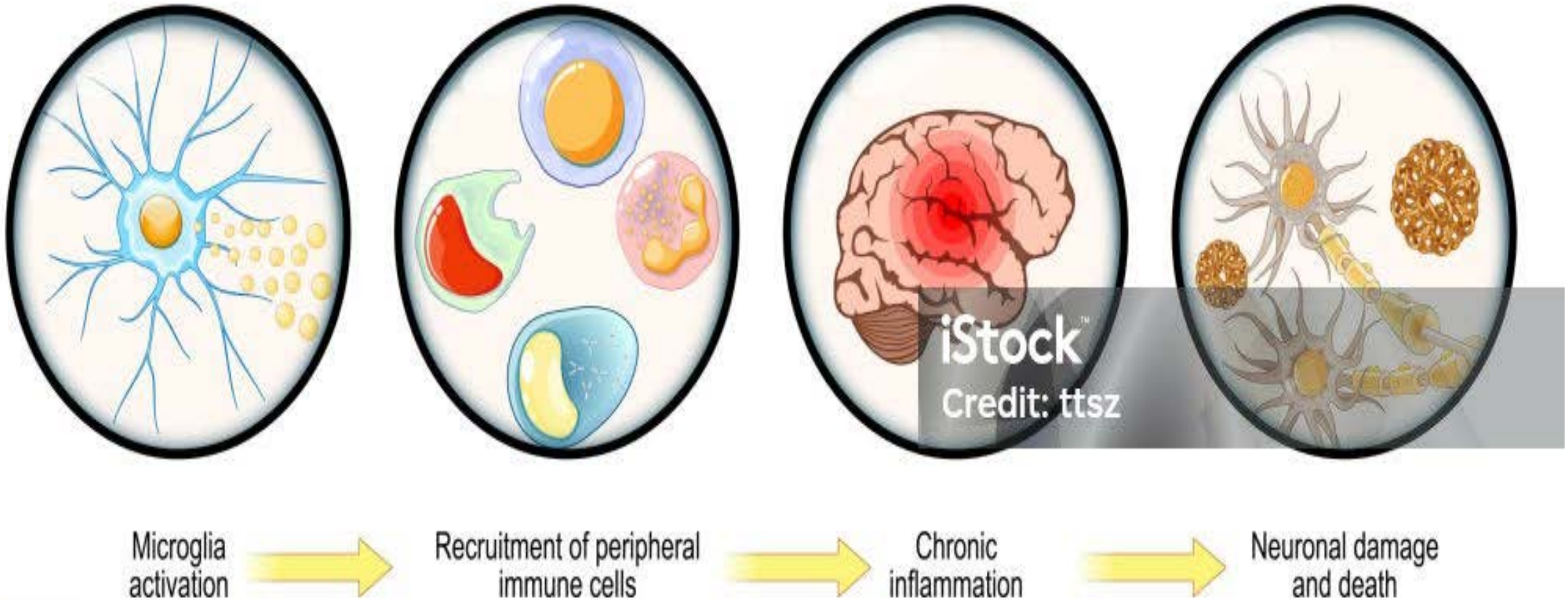

depositphotos

NEUROINFLAMMATION

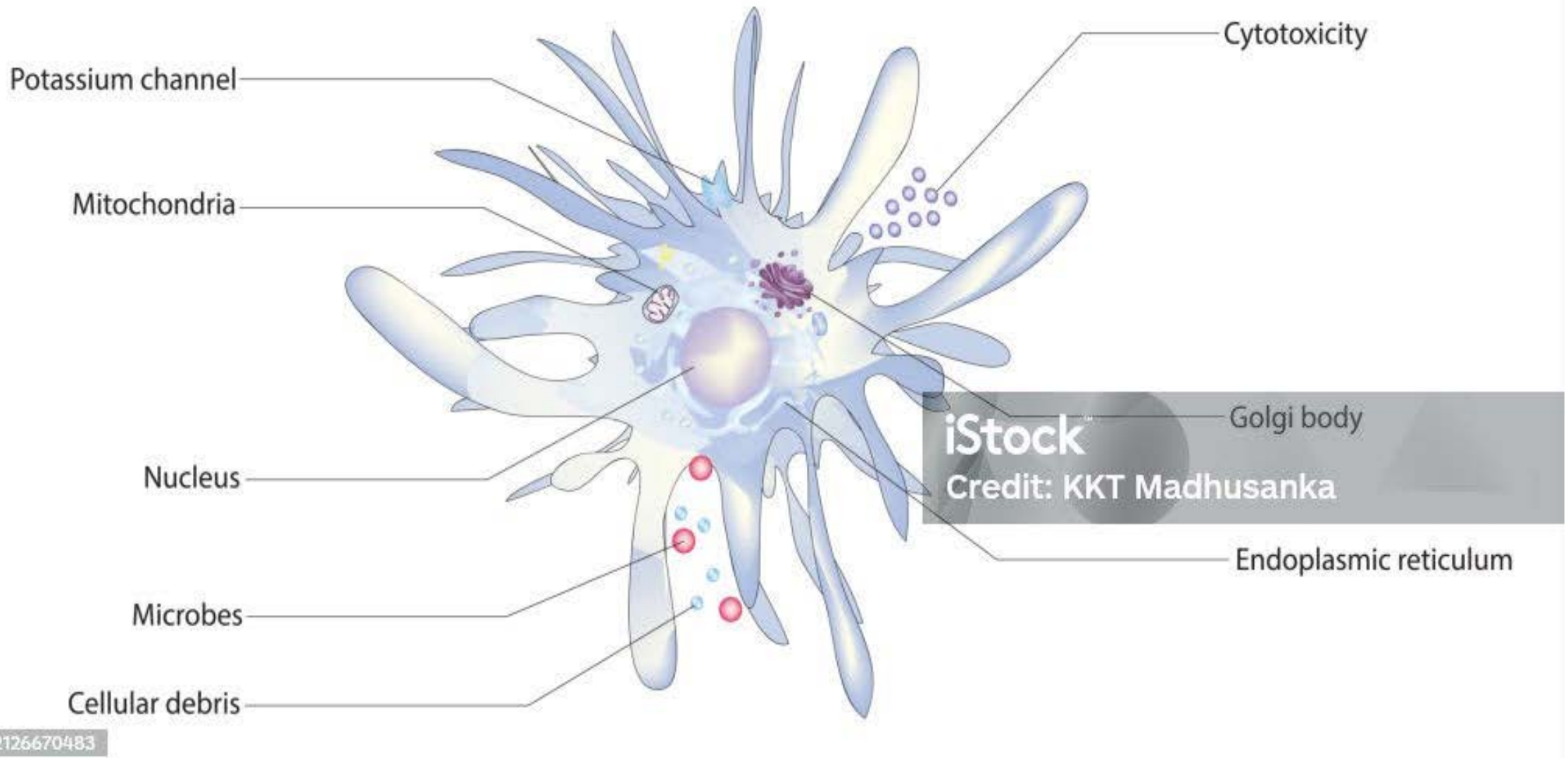


NEURONOFAGIA

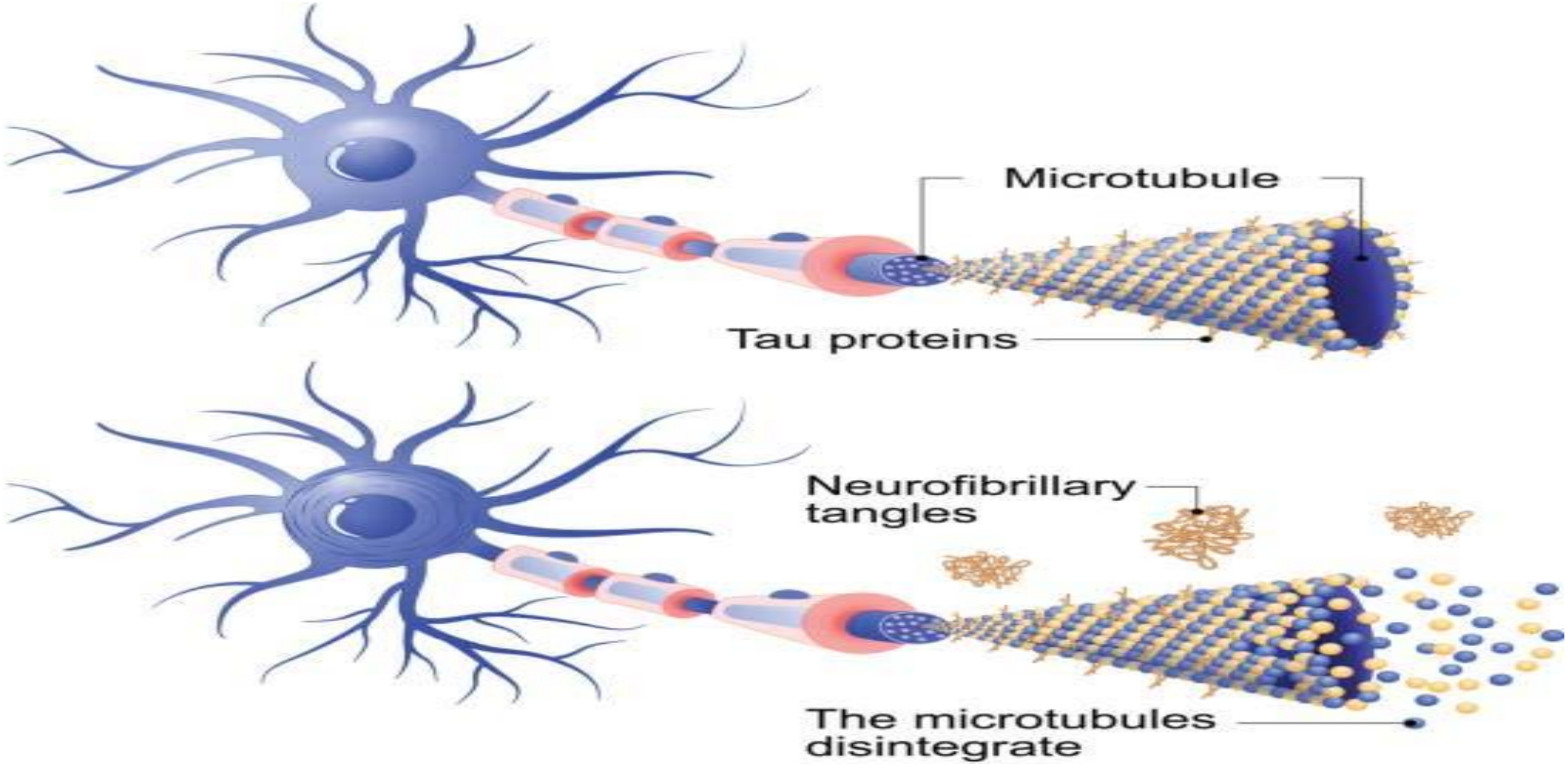
Neuroinflammation



Microglia

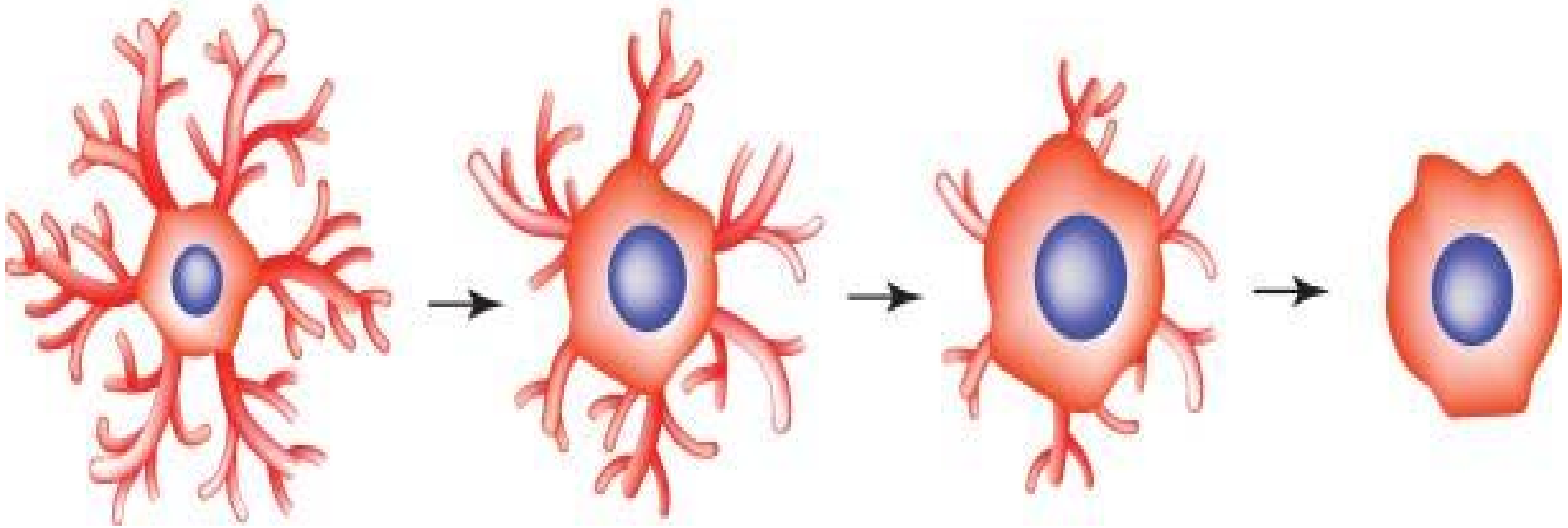


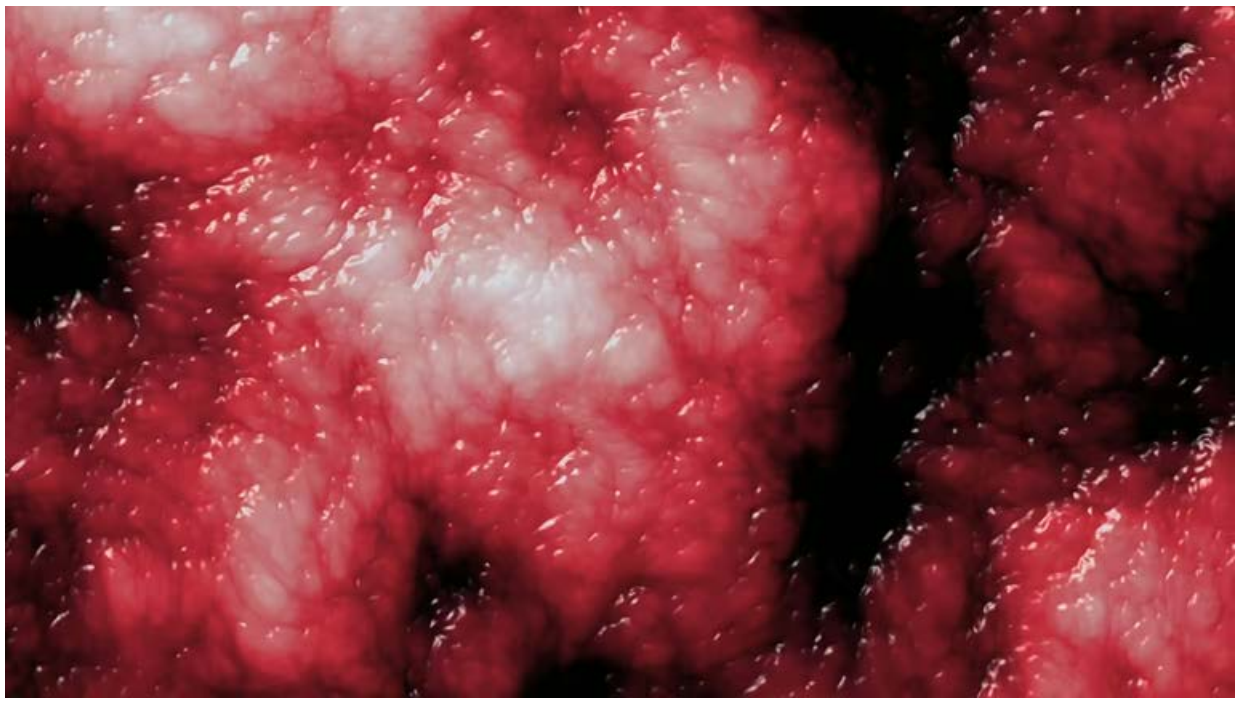
HEALTHY NEURON

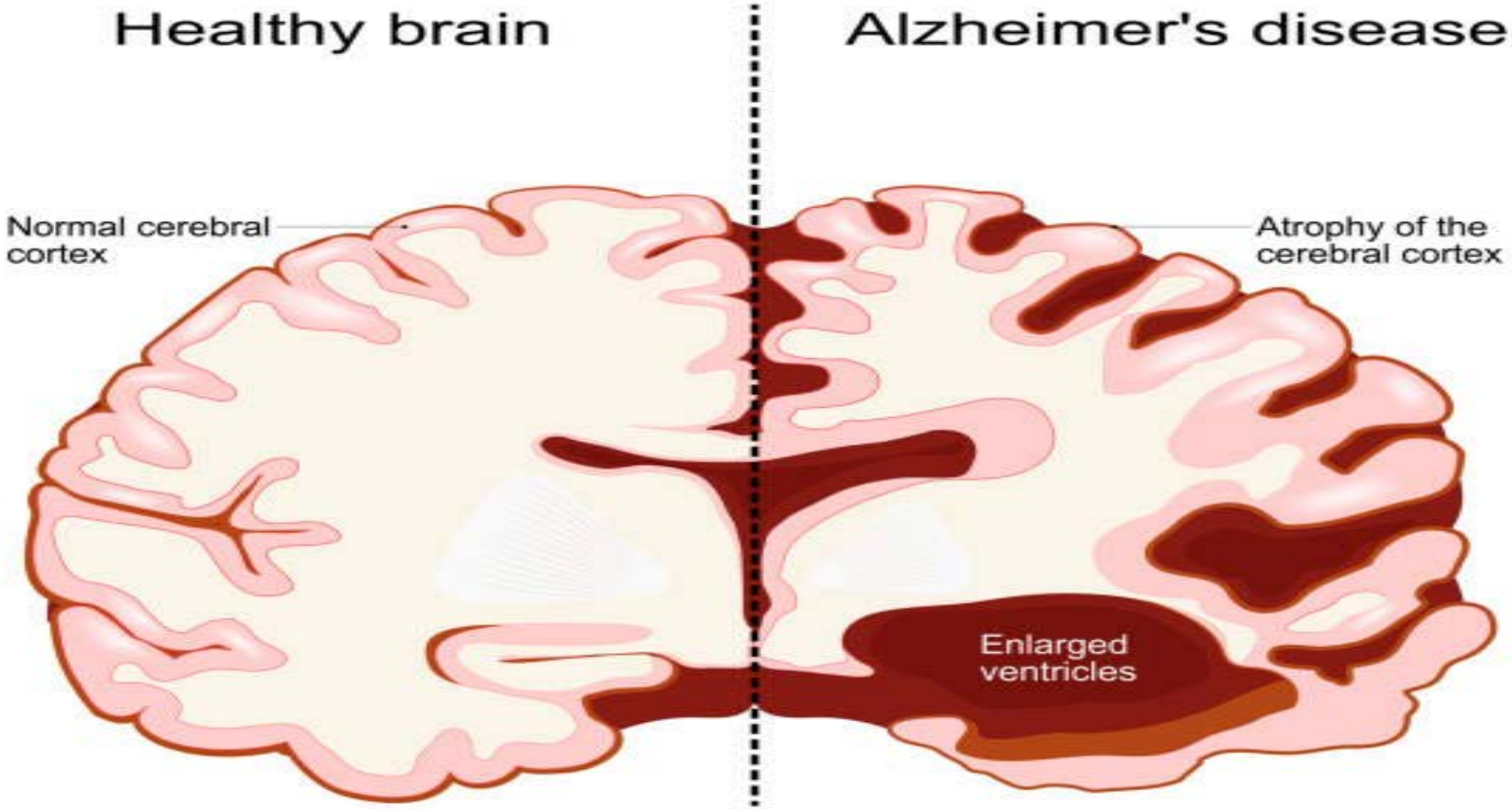


ALZHEIMER'S DISEASE

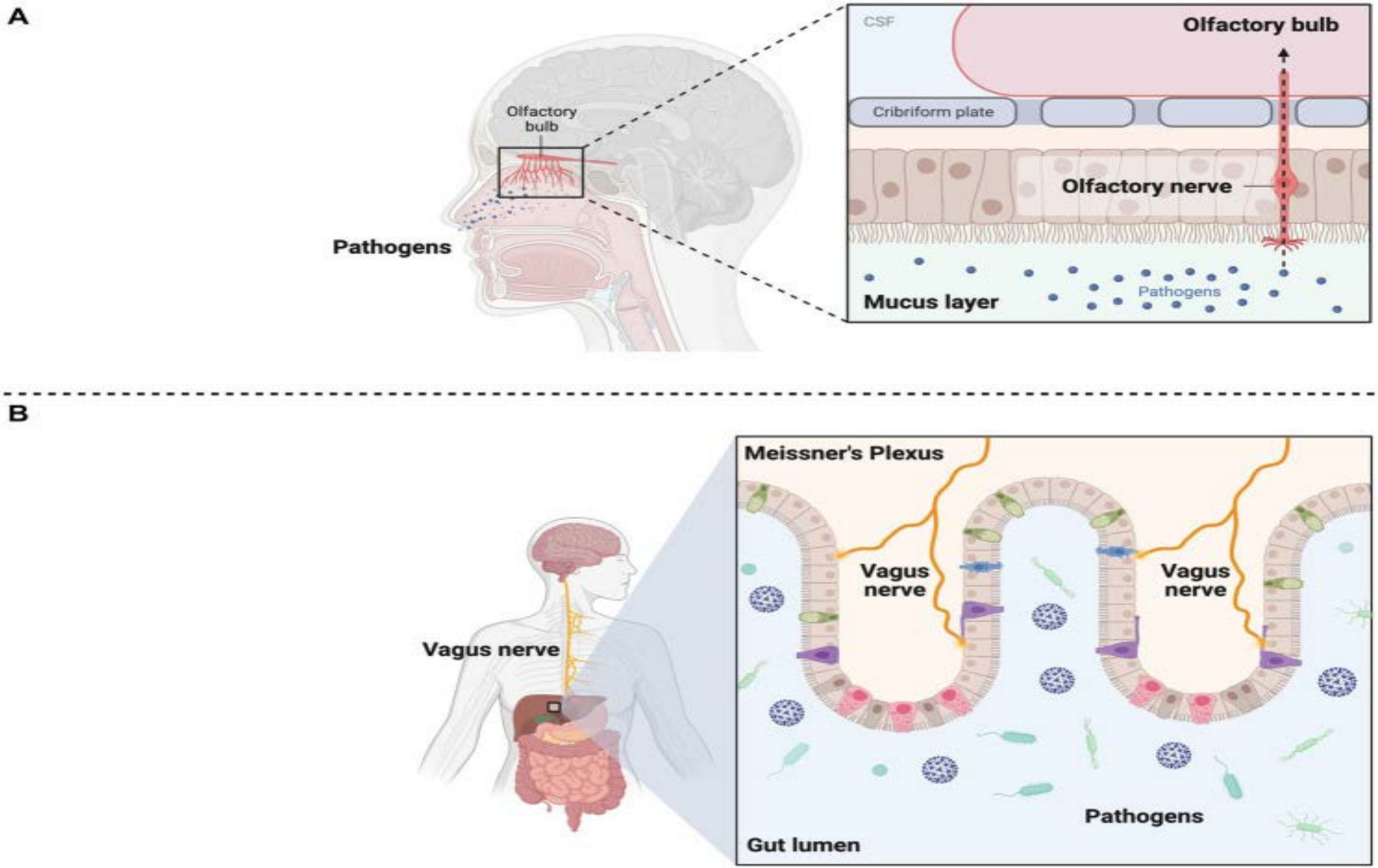
MICROGLIAL ACTIVATION






Healthy brain
Alzheimer's disease
Normal cerebral cortex
Atrophy of the cerebral cortex
Enlarged ventricles

PARKINSON


A
Olfactory bulb
Pathogens
CSF
Olfactory bulb
Cribriform plate
Olfactory nerve
Pathogens
Mucus layer
B
Vagus nerve
Meissner's Plexus
Vagus nerve
Vagus nerve
Pathogens
Gut lumen

SARS-CoV-2 infection

Cortical functioning

Prevalence of cognitive decline in up to 5%

Hit and run hypothesis

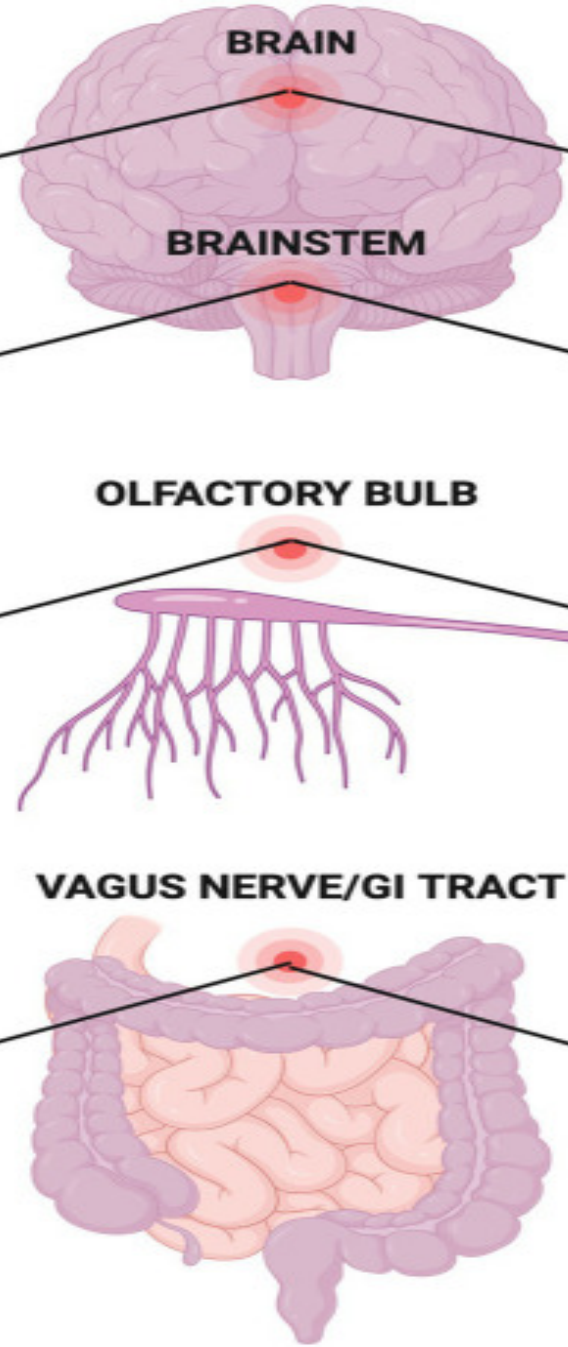
Putative inflammatory damage of dopaminergic neurons of the nistrostriatal pathway. Not demonstrated

Virus root entry

Hyposmia affects up to 65% of patients and it may persist in 10-20% of cases. Olfactory epithelium damage

Virus root entry

Constipation may persist in up to 80% of patients as a part of long-COVID syndrome



Parkinson's disease

Cortical functioning

Prevalence of cognitive decline in up to 15-45%

Nigrostriatal degeneration

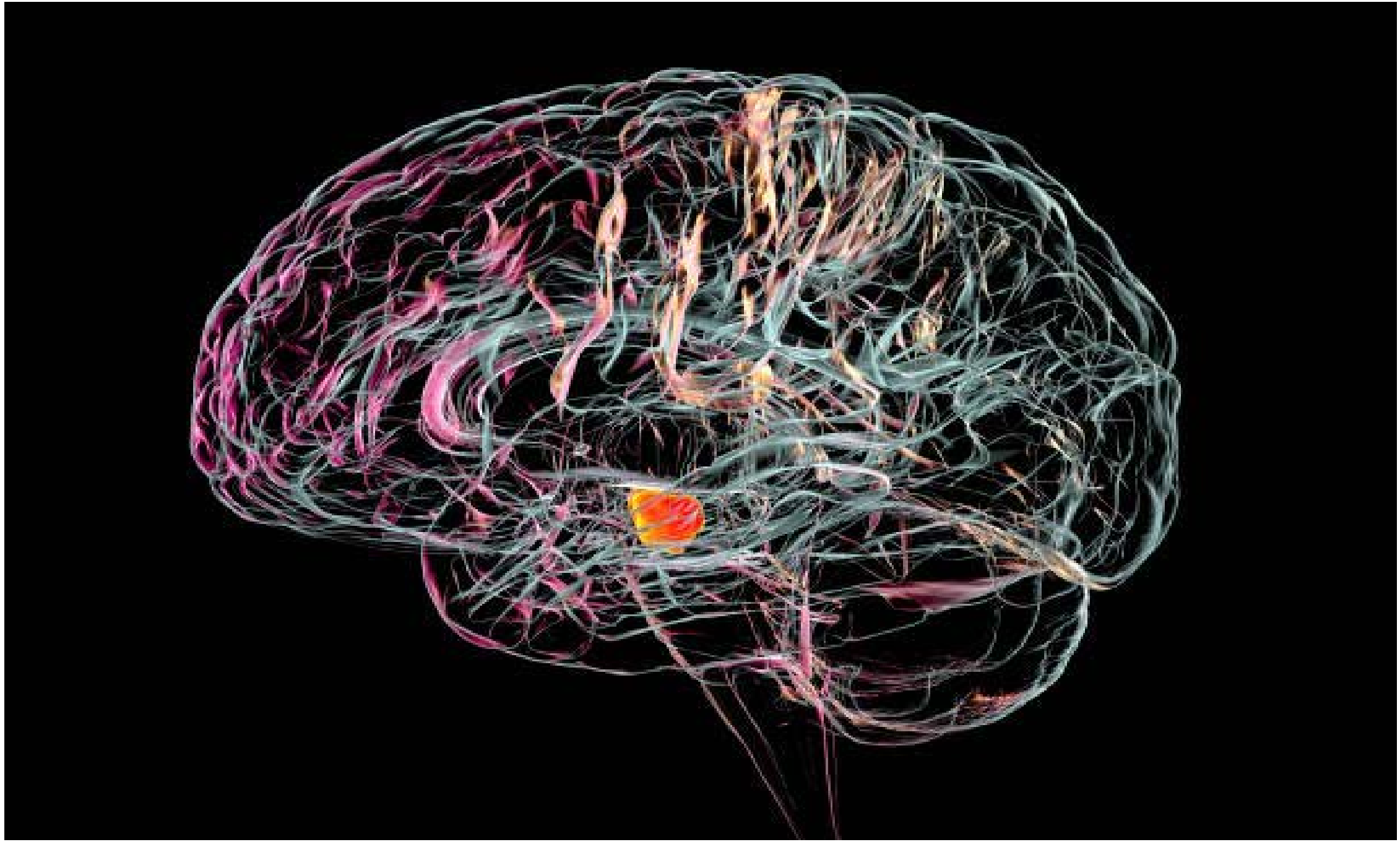
Progressive loss of dopaminergic neurons and LB accumulation

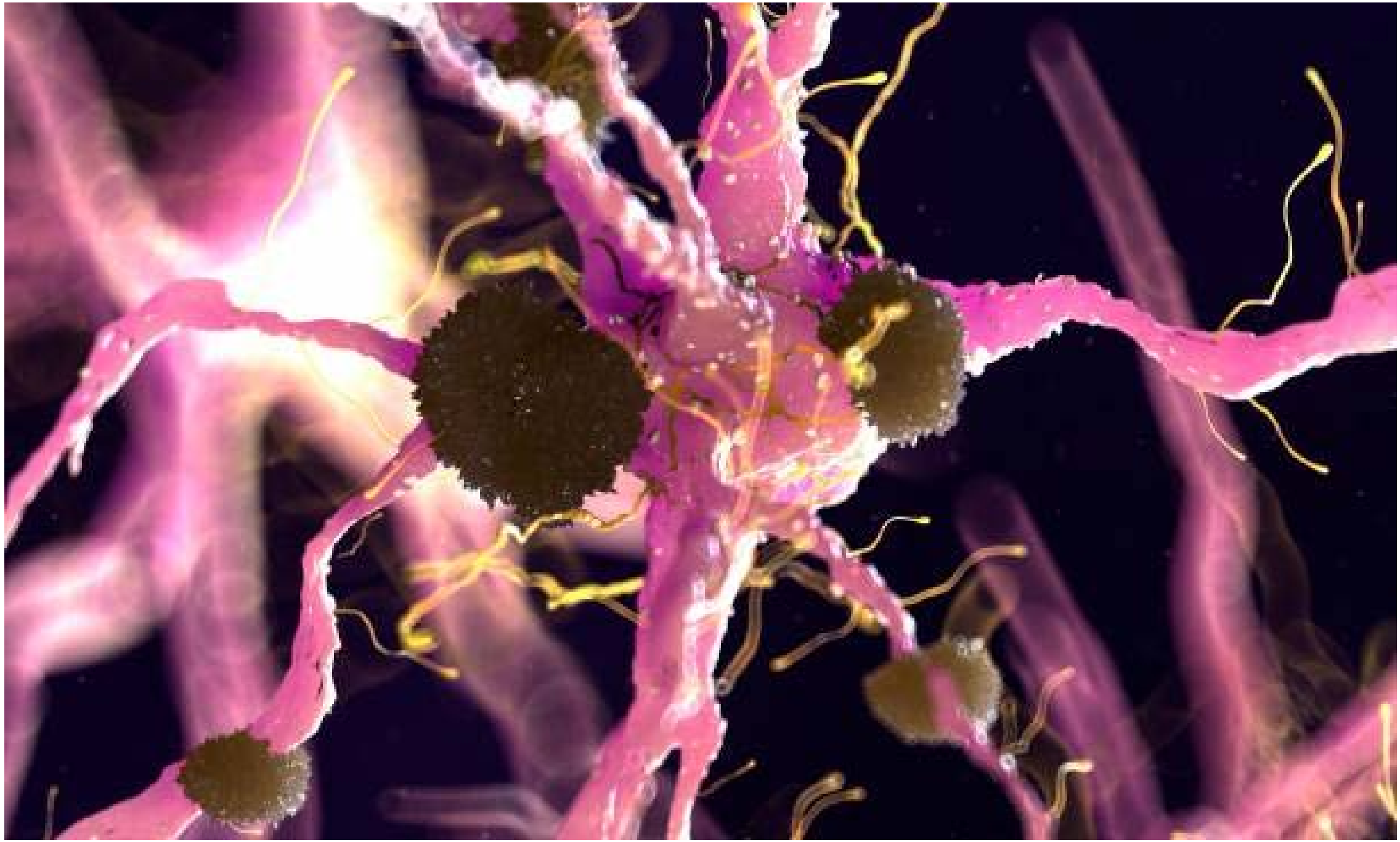
Neurons degeneration

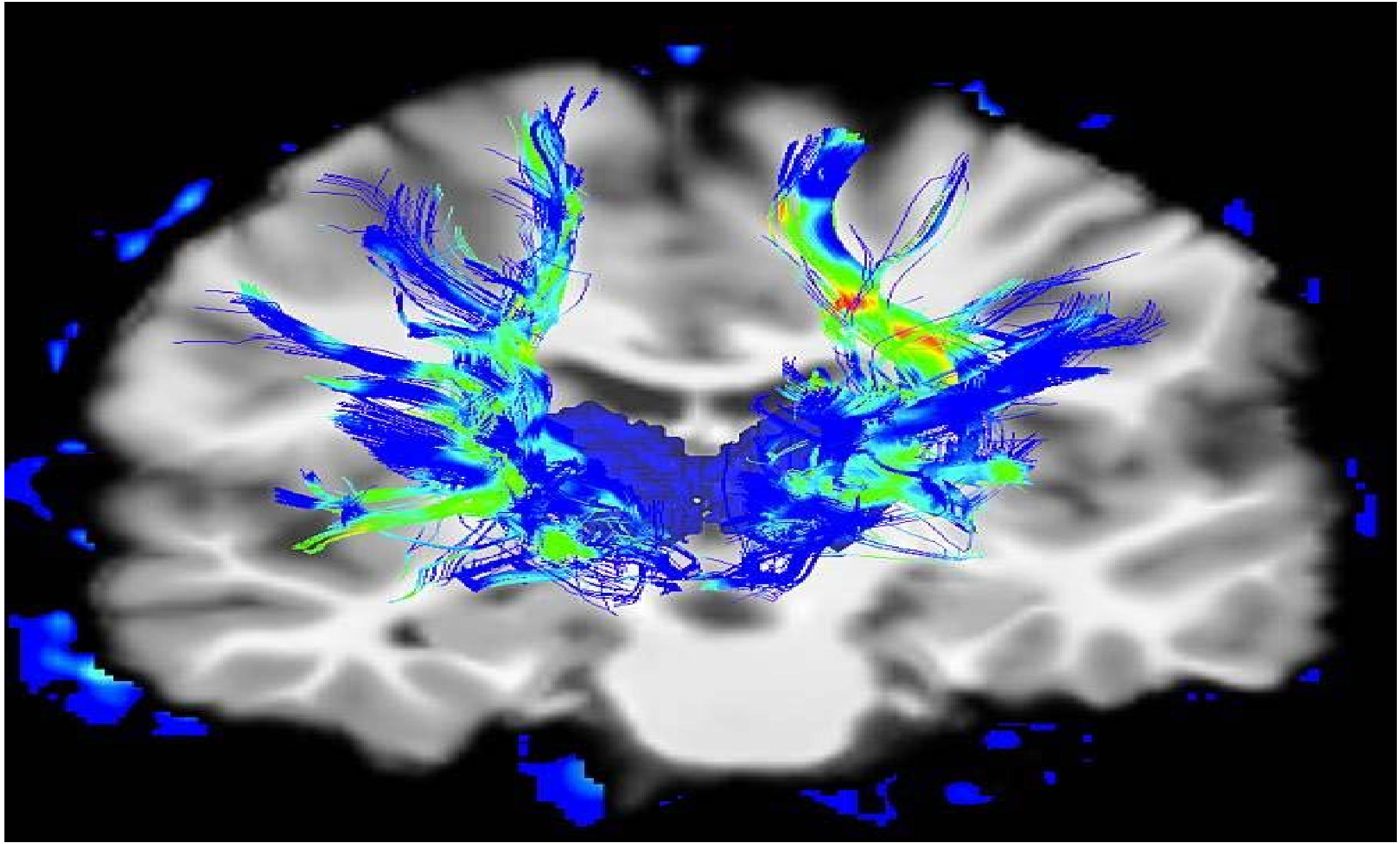
Hyposmia is found in up to 90% of patients. Progressive loss of olfactory neurons, LB deposition and amygdala degeneration

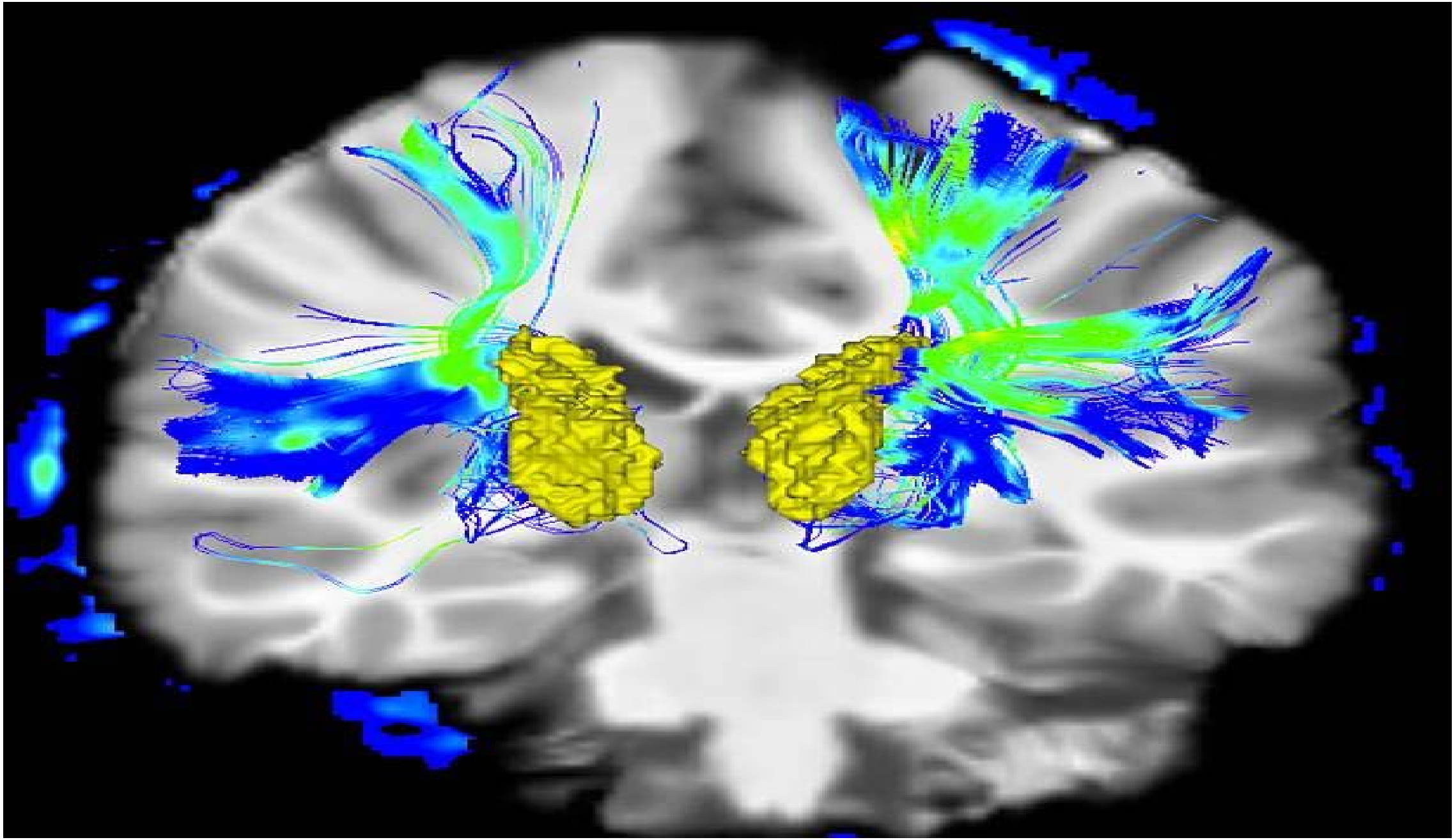
Progressive damage

Constipation is found in up to 60% of patients. Presence of LB in the esophagus, small intestine and the colon thorughout the Auerbach and Meissner plexuses

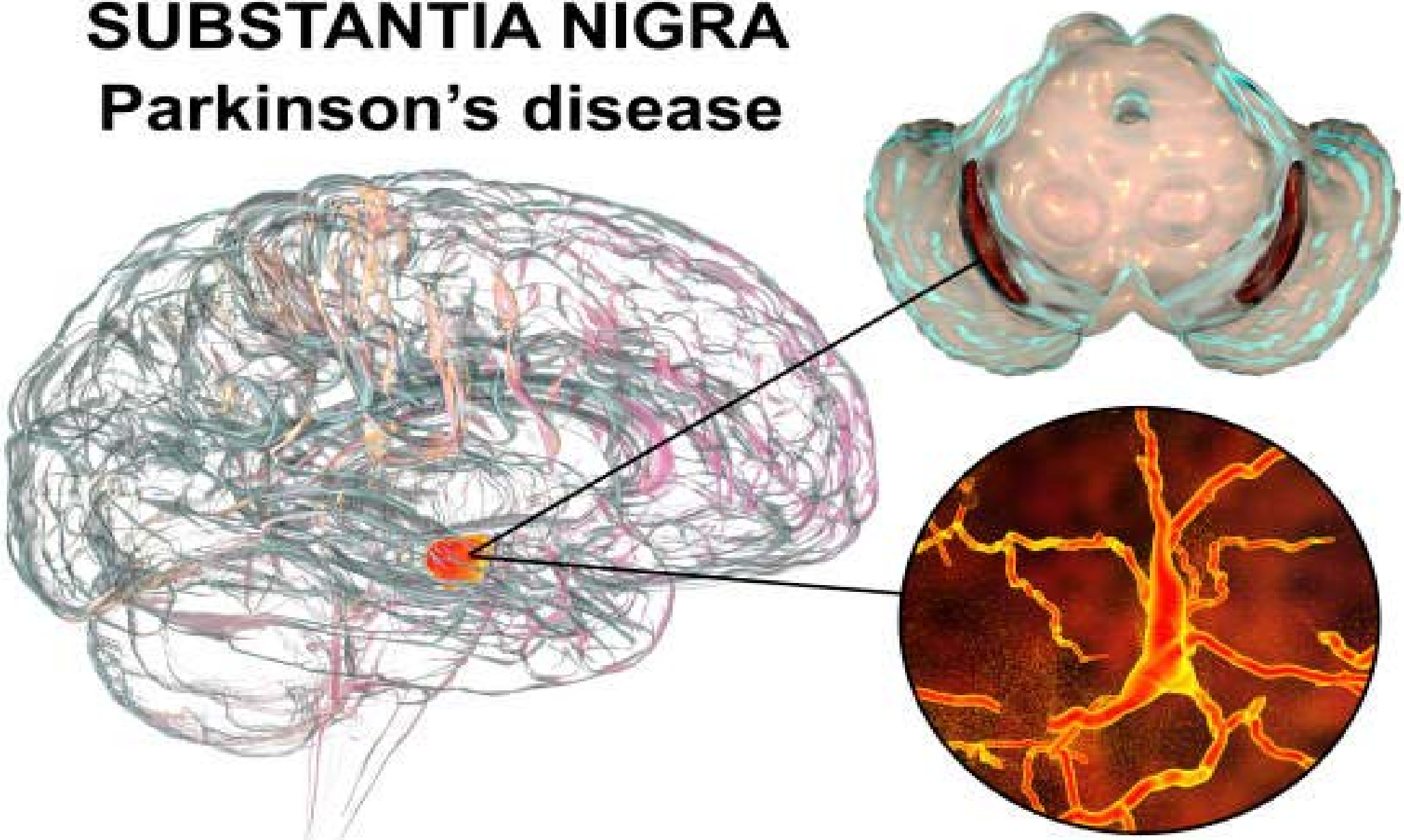


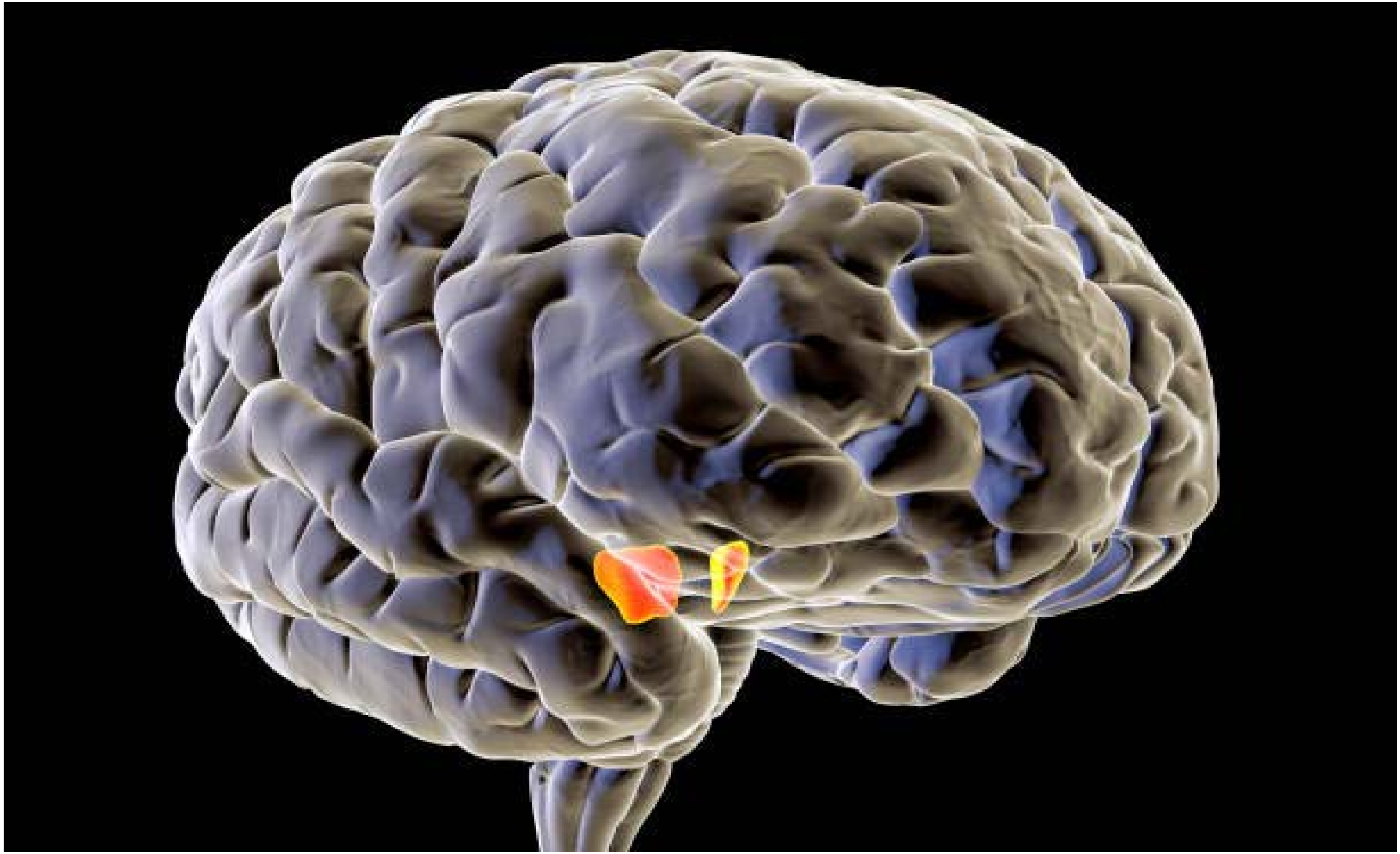


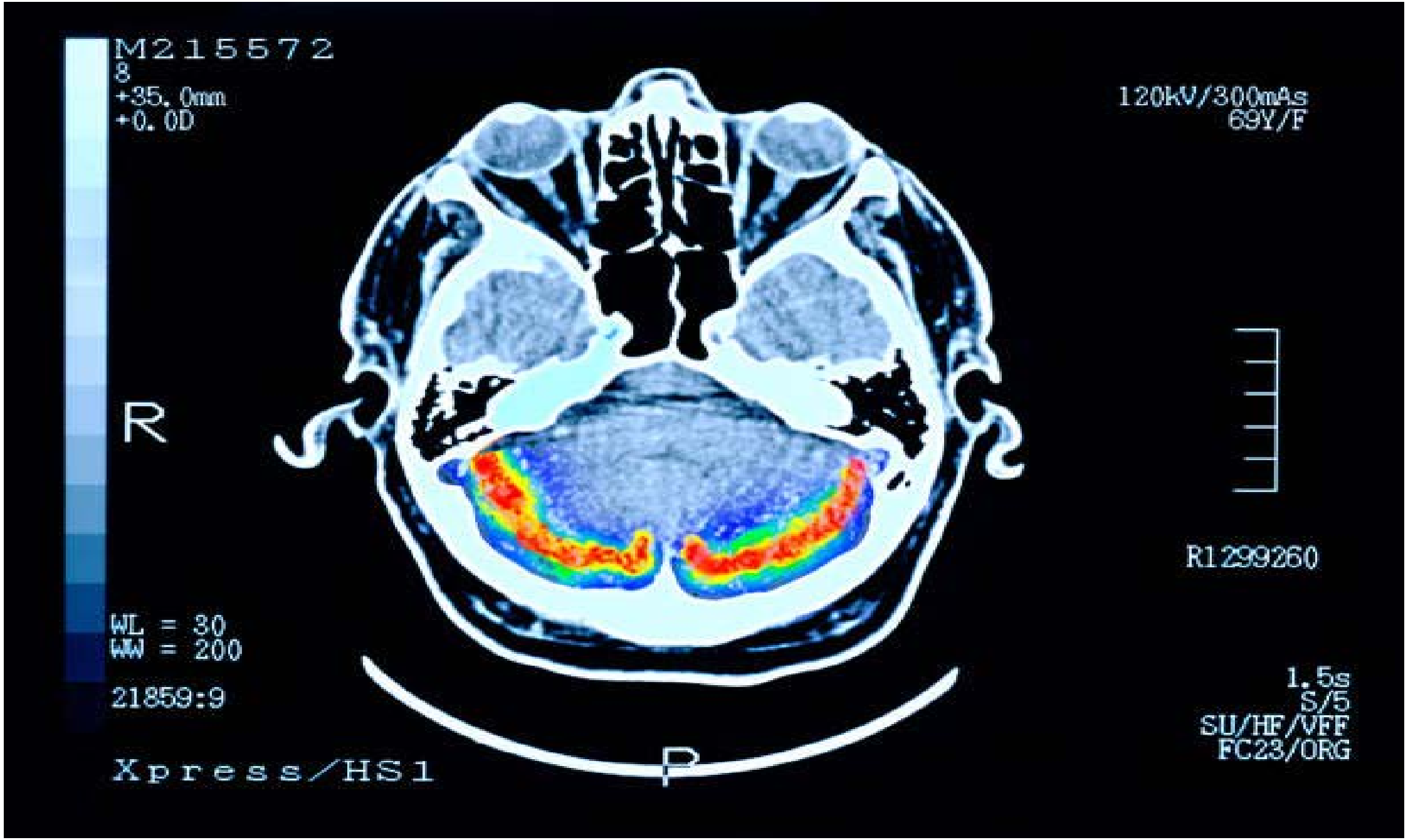


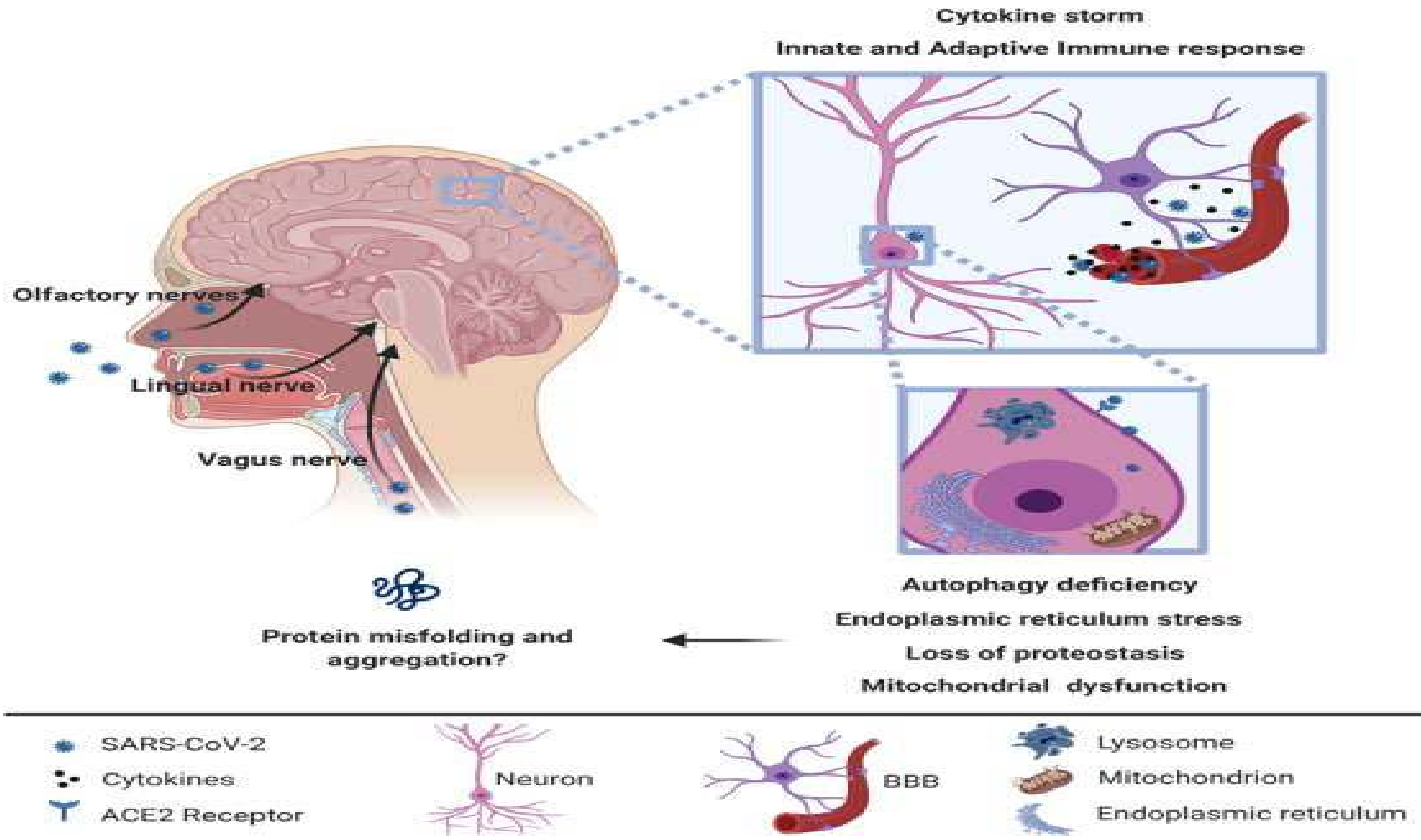


SUBSTANTIA NIGRA
Parkinson's disease

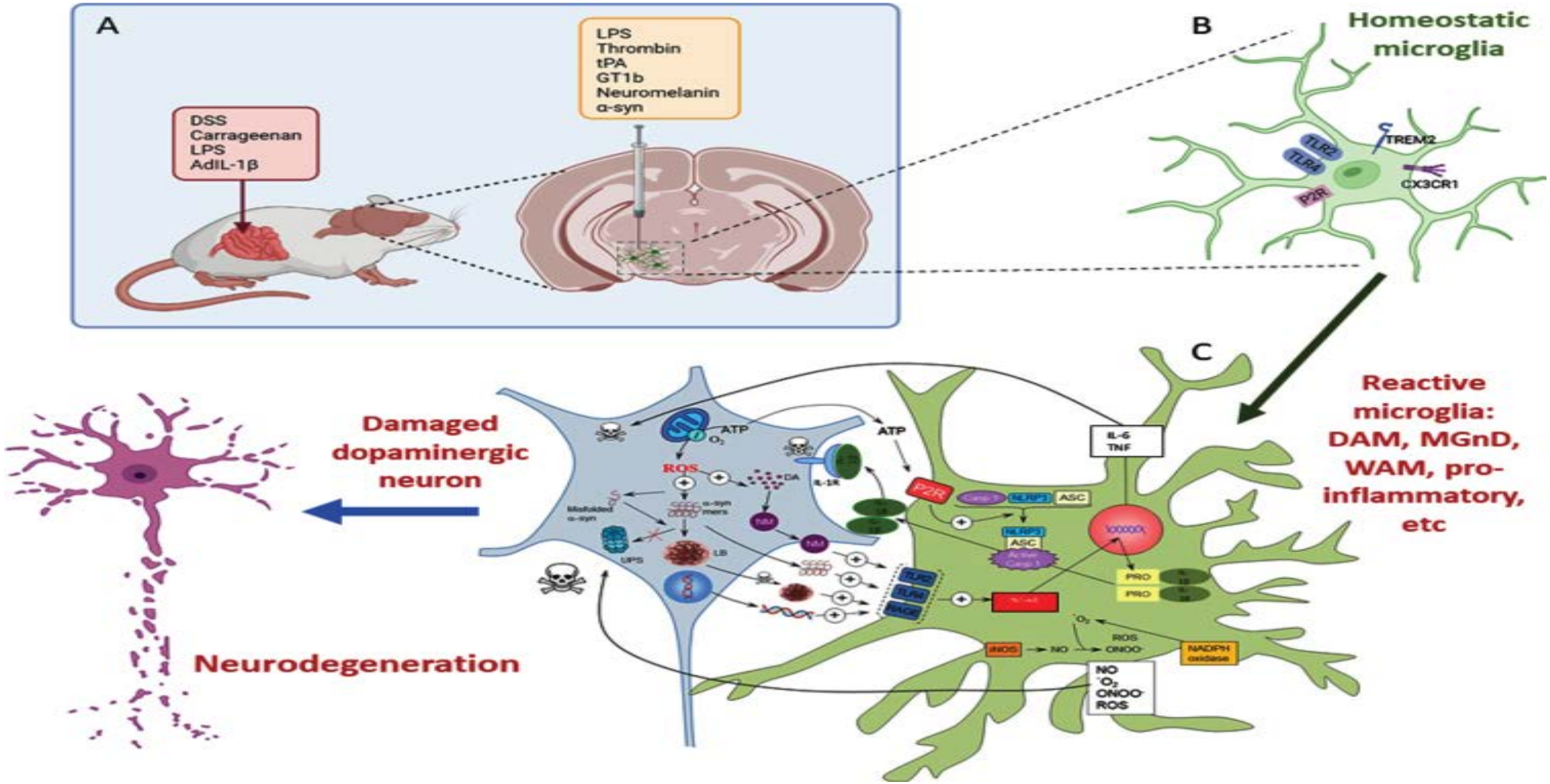




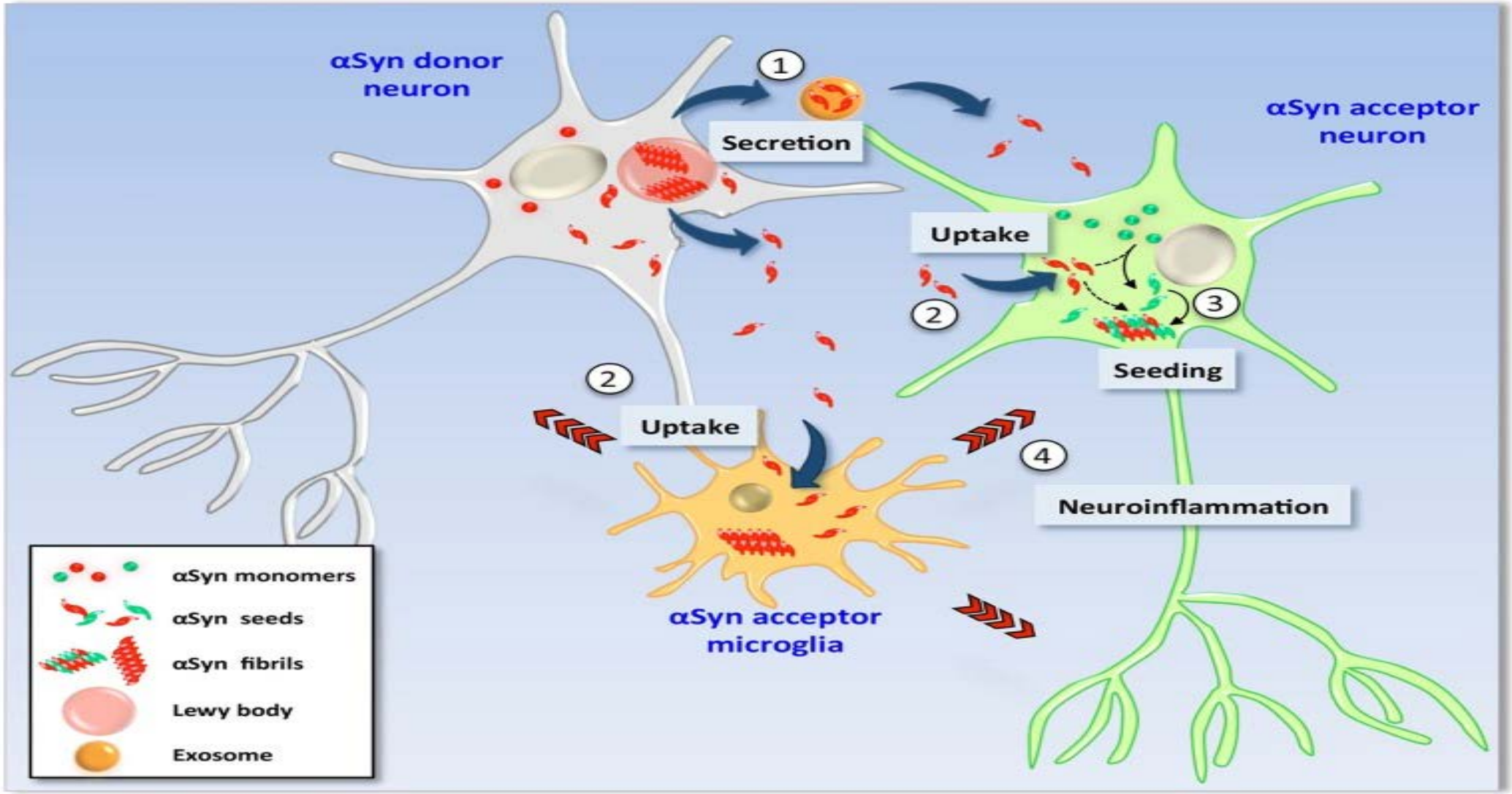

M215572
8
+35.0mm
+0.0D
120kV/300mAs
69Y/F
R
R1299260
WL = 30
WW = 200
21859:9
1.5s
S/5
SU/HF/VFF
FC23/ORG
Xpress/HS1
P


Cytokine storm
Innate and Adaptive Immune response
Olfactory nerves
Lingual nerve
Vagus nerve
Autophagy deficiency
Endoplasmic reticulum stress
Loss of proteostasis
Mitochondrial dysfunction
Protein misfolding and aggregation?
SARS-CoV-2
Cytokines
ACE2 Receptor
Neuron
BBB
Lysosome
Mitochondrion
Endoplasmic reticulum

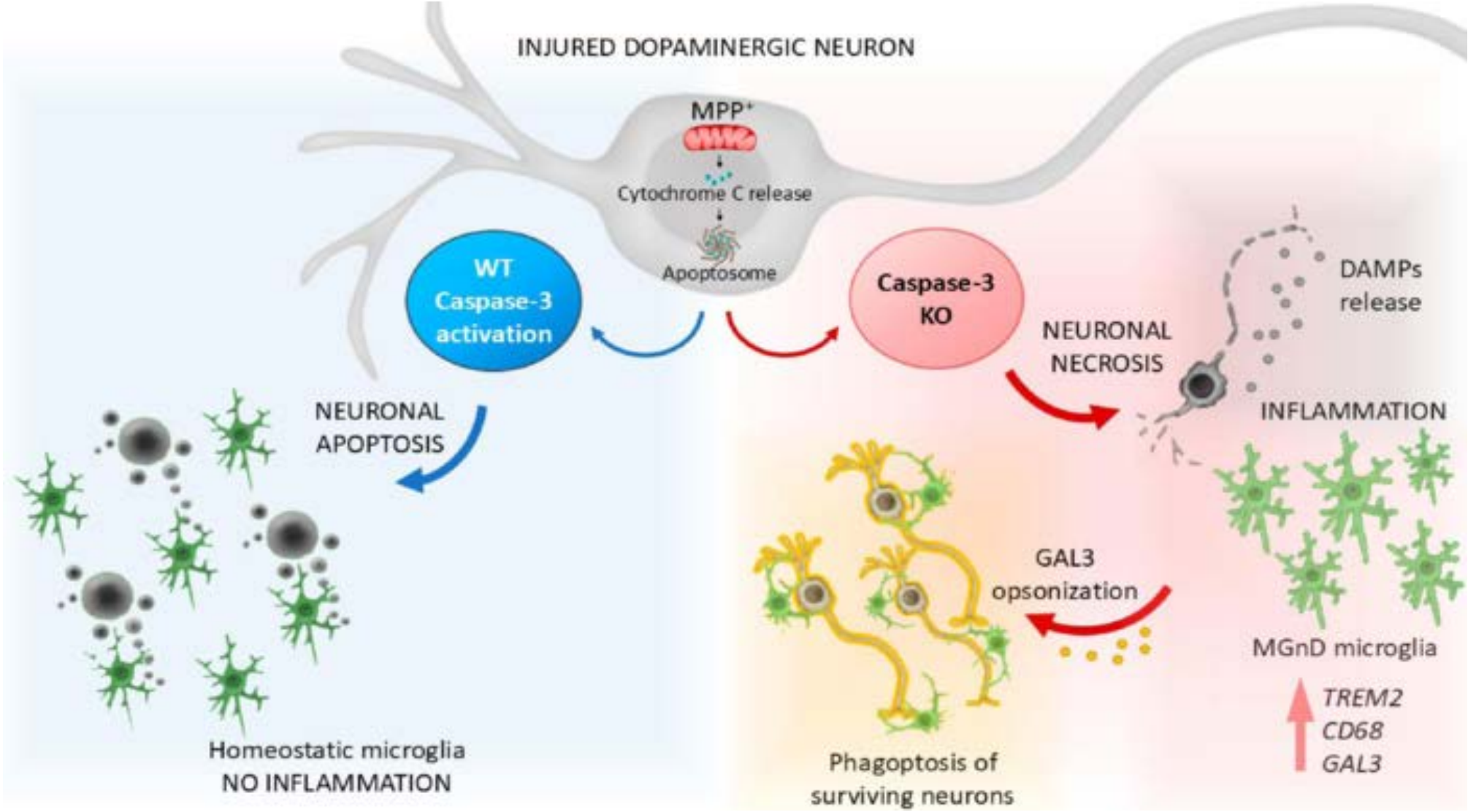
BIOLOGIA DEL PARKINSON



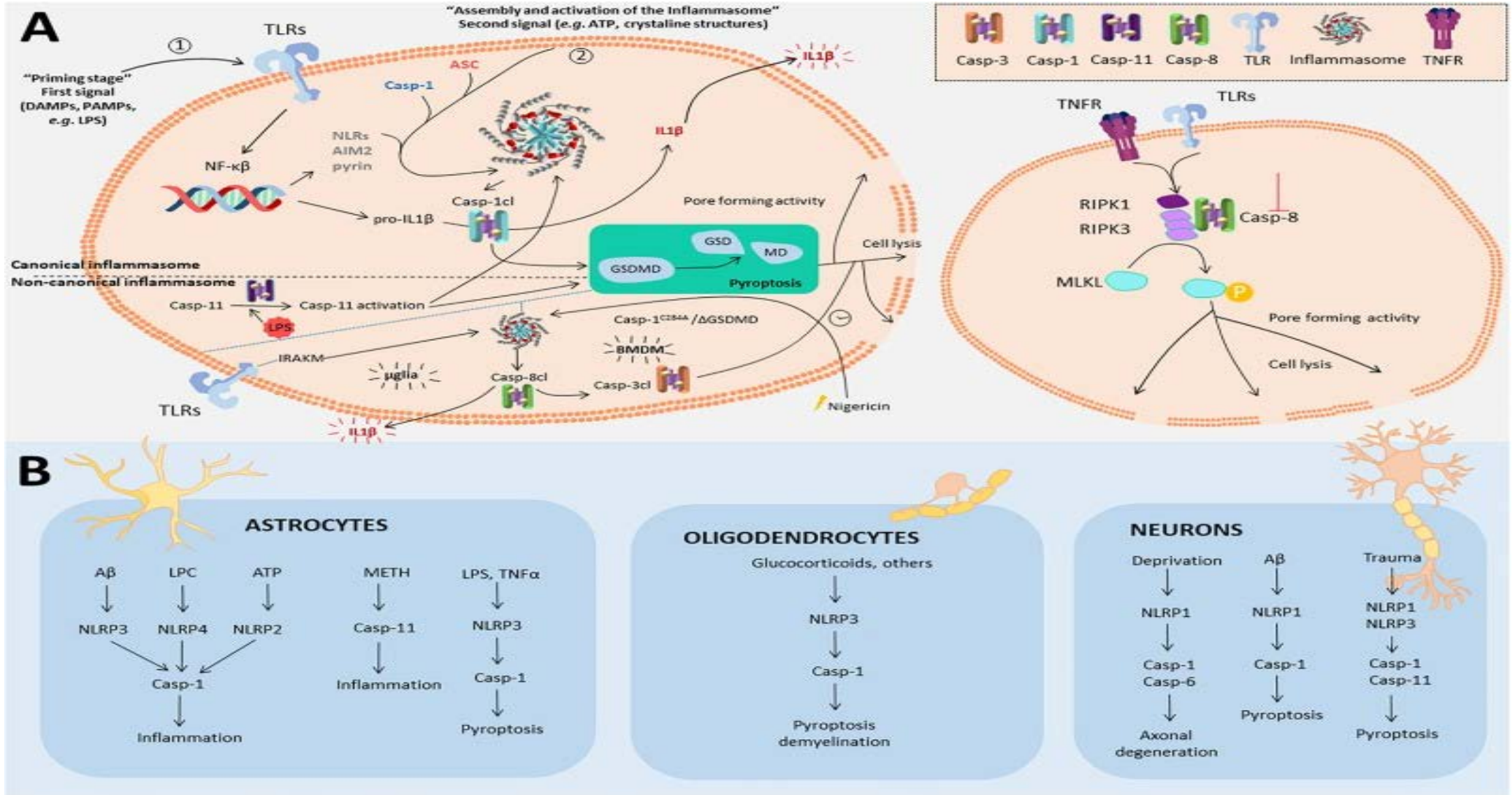
BIOLOGIA DEL PARKINSON RUOLO DELLA SINUCLEINA E DEI C DI LEWY



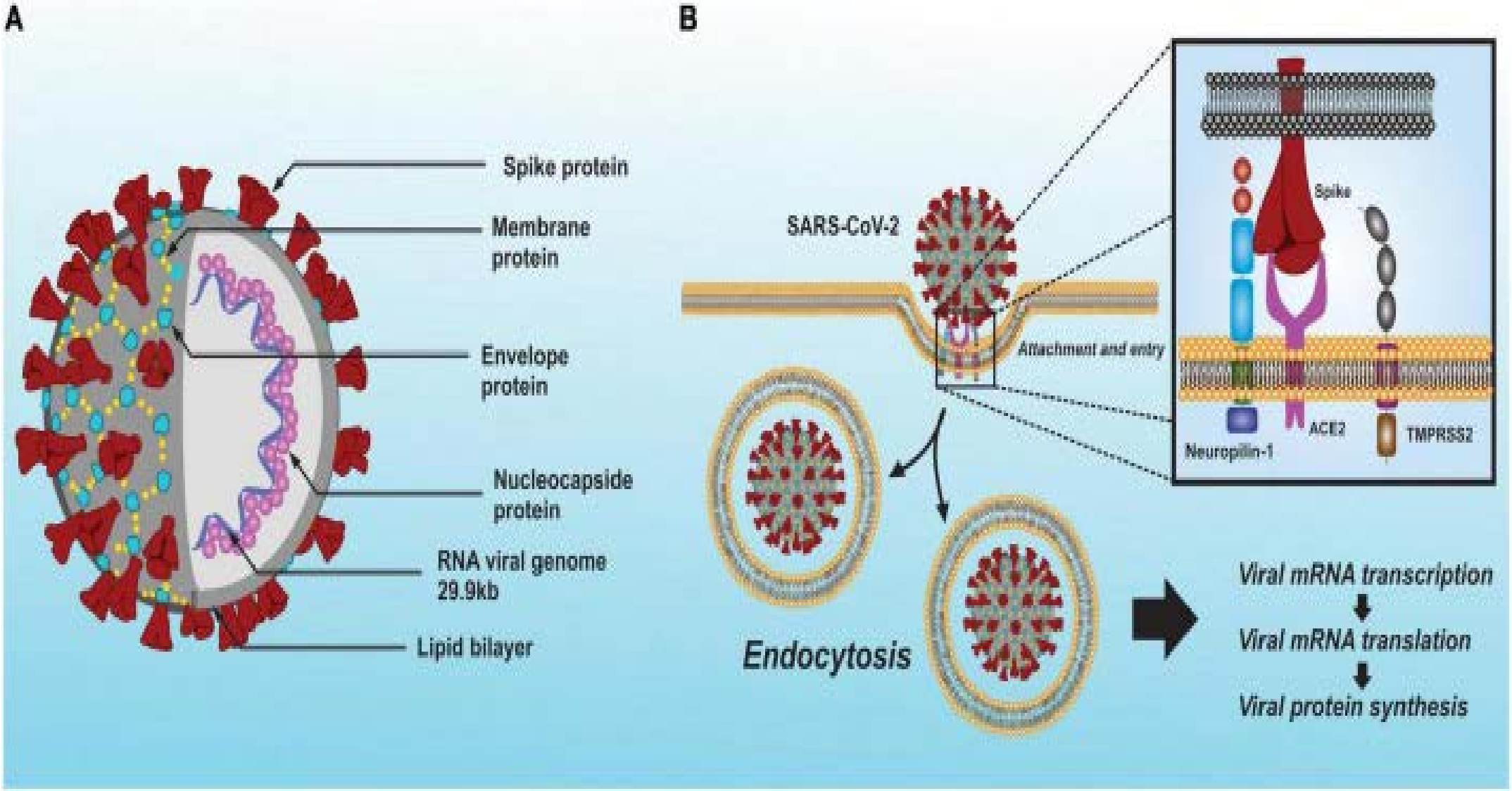
PARKINSON RUOLO DELLA CASPASI



CASPASI


A
"Assembly and activation of the Inflammasome"
Second signal (e.g. ATP, crystaline structures)
TLRs
"Priming stage"
First signal
(DAMPs, PAMPs,
e.g. LPS)
ASC
Casp-1
IL1β
NLRs
AIM2
pyrin
NF-κβ
pro-IL1β
Casp-1cl
Pore forming activity
GSD
MD
GSDMD
Pyroptosis
Cell lysis
Canonical inflammasome
Non-canonical inflammasome
Casp-11
Casp-11 activation
LPS
IRAKM
μglia
Casp-1C284A /ΔGSDMD
BMDM
Casp-8cl
Casp-3cl
Nigericin
Casp-3
Casp-1
Casp-11
Casp-8
TLR
Inflammasome
TNFR
TNFR
TLRs
RIPK1
RIPK3
Casp-8
MLKL
P
Pore forming activity
Cell lysis
B
ASTROCYTES
Aβ
LPC
ATP
NLRP3
NLRP4
NLRP2
Casp-1
Inflammation
METH
Casp-11
Inflammation
LPS, TNFα
NLRP3
Casp-1
Pyroptosis
OLIGODENDROCYTES
Glucocorticoids, others
NLRP3
Casp-1
Pyroptosis
demyelination
NEURONS
Deprivation
NLRP1
Casp-1
Casp-6
Axonal
degeneration
Aβ
NLRP1
Casp-1
Pyroptosis
Trauma
NLRP1
NLRP3
Casp-1
Casp-11
Pyroptosis

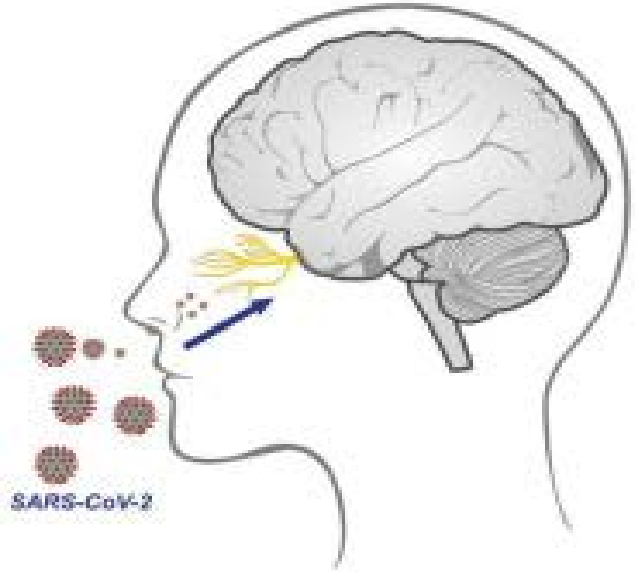
COVID - DANNO CEEREBRALE



1) Neuroinvasive via retrograde axonal transport

2) Hematogenous neuroinvasive route

A Transcribrial neuroinvasive route

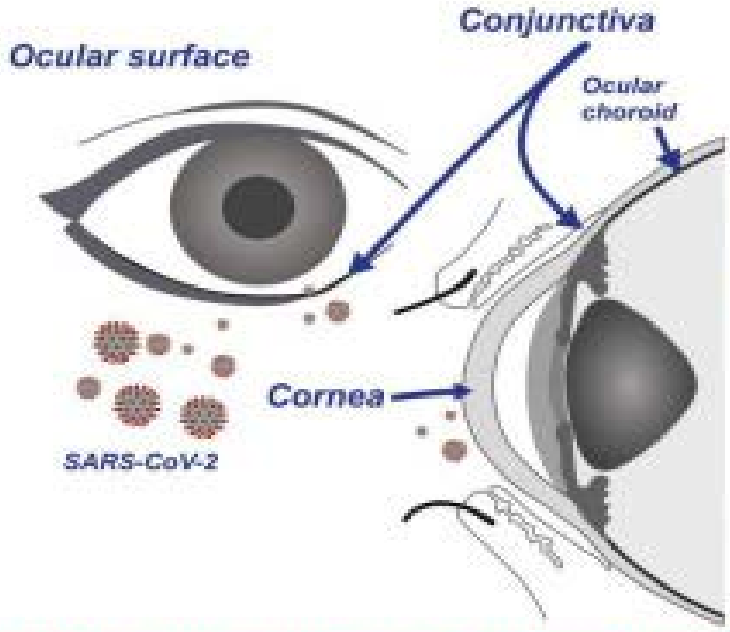


SARS-CoV-2 could reach the CNS via cranial nerves:

- *olfactory nerve*
- *trigeminal nerve*
- *vagus nerve*

ACE2 expression found in olfactory bulb and olfactory neuroepithelium

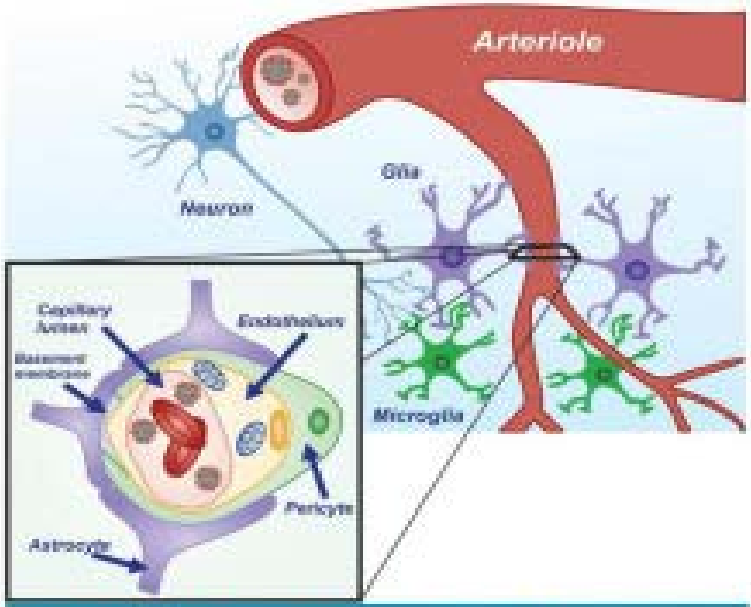
B Ocular surface route



The ocular surface is susceptible to viral infections

ACE2 expression found in:
- *trabecular meshwork*
- *ocular choroid cells*
- *optic nerve*
- *geniculocalcarine tract*

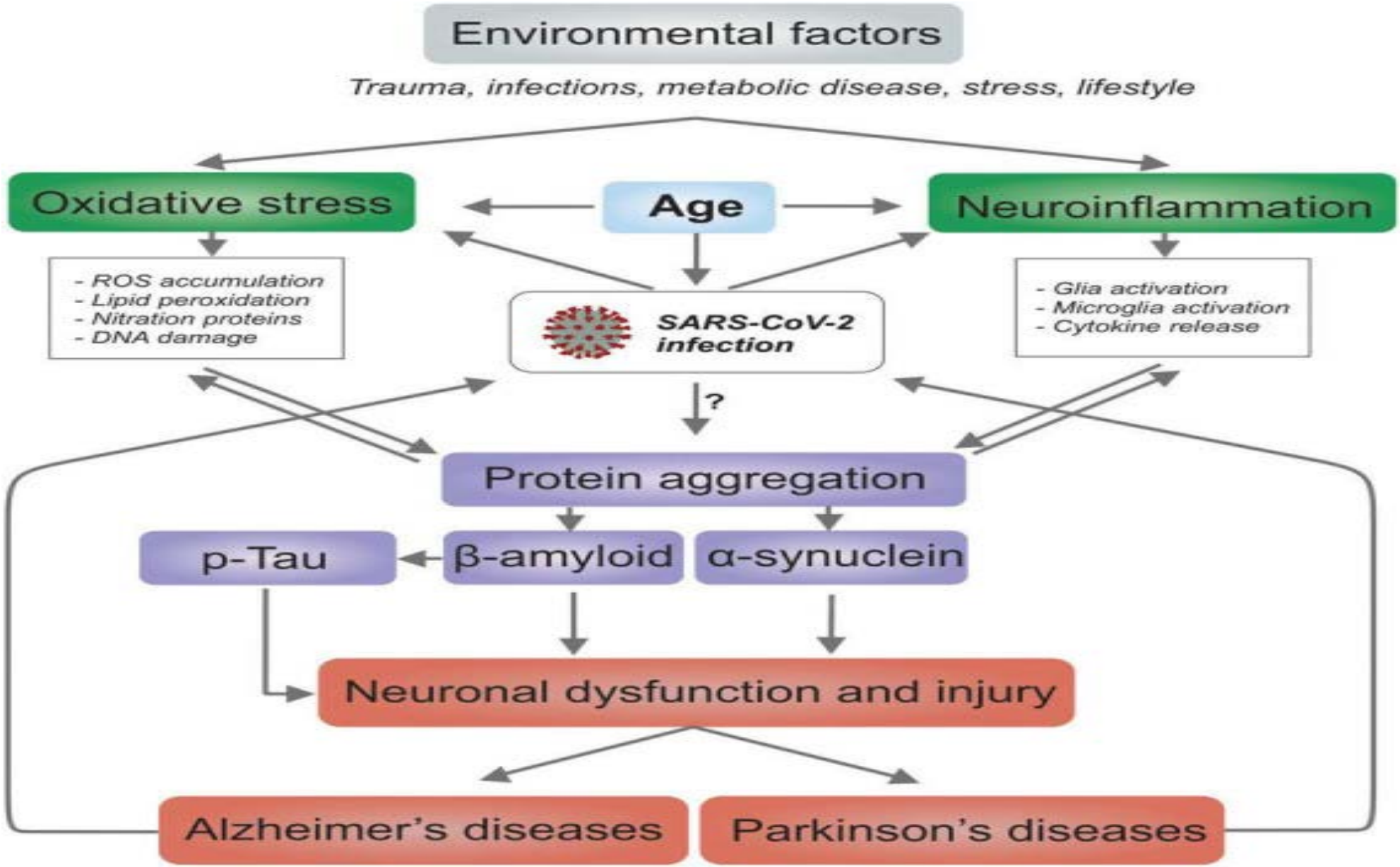
C Virus across the BBB



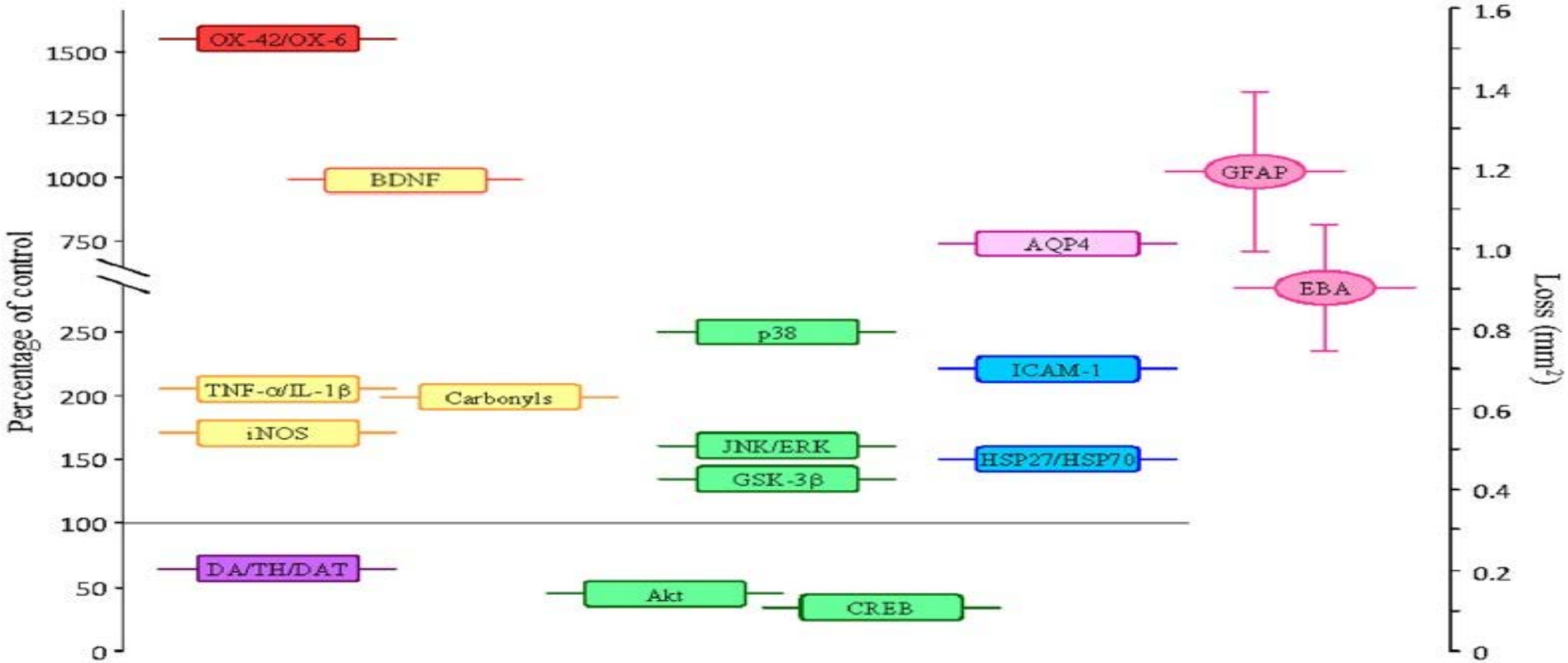
Possible mechanism of hematogenous route:

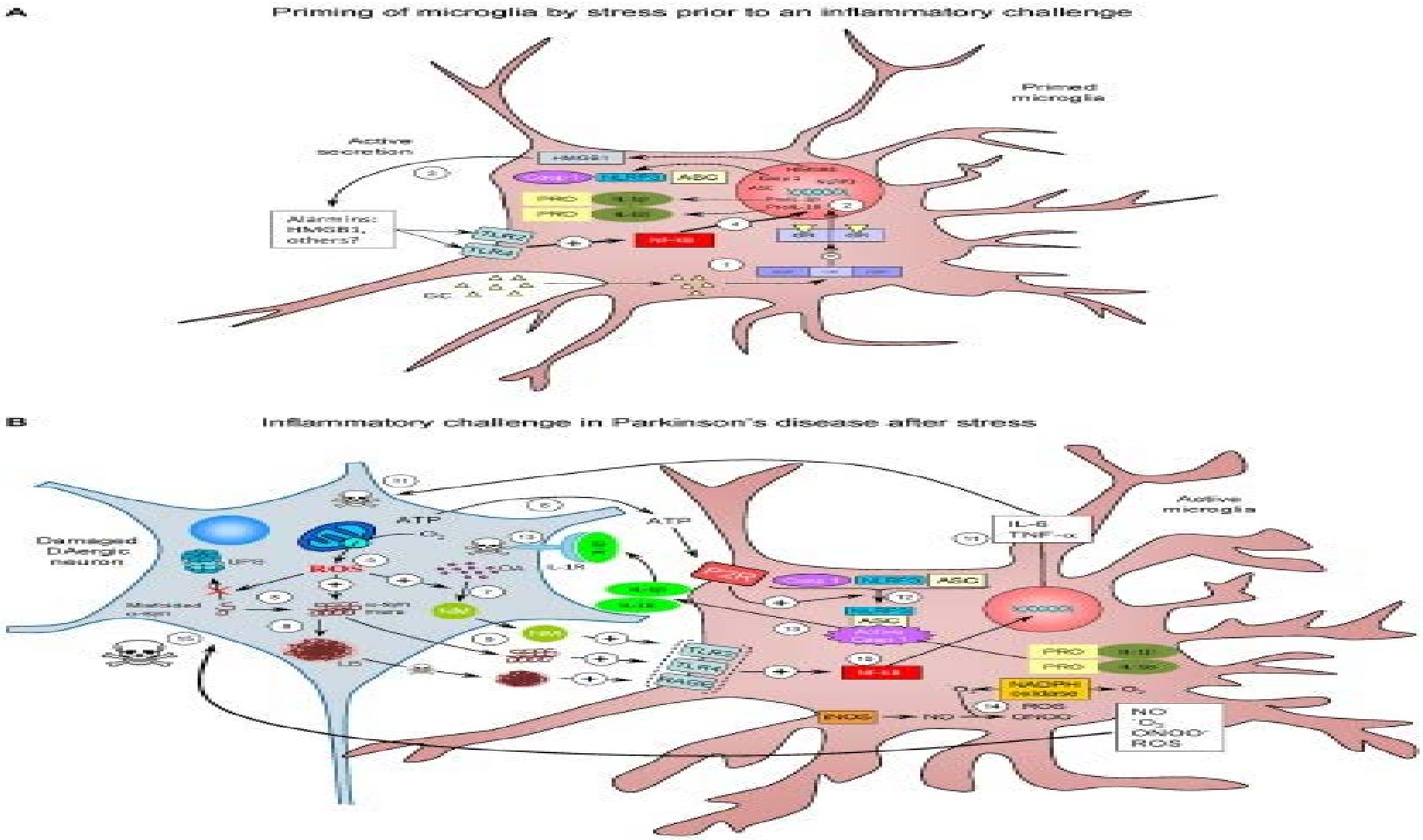
- *Transcellular migration*
- *Paracellular migration*
- *The "Trojan horse" strategy*

ACE2 and TMPRSS2 expression found in endothelian cells

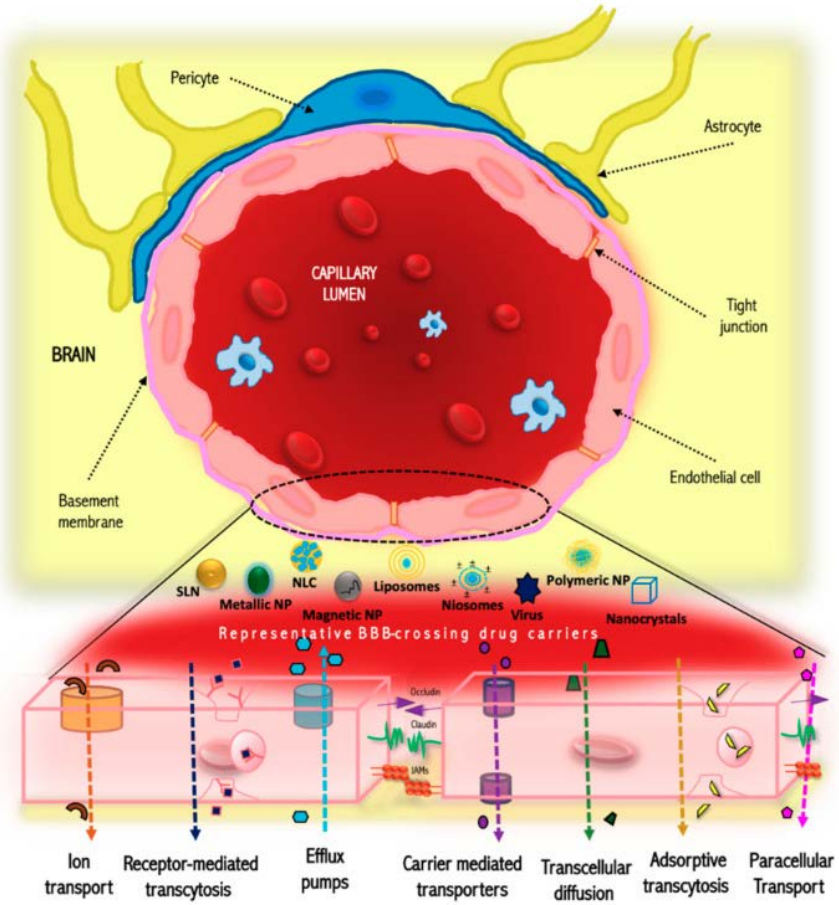

Environmental factors
Trauma, infections, metabolic disease, stress, lifestyle
Oxidative stress
Age
Neuroinflammation
- ROS accumulation
- Lipid peroxidation
- Nitration proteins
- DNA damage
SARS-CoV-2 infection
- Glia activation
- Microglia activation
- Cytokine release
?
Protein aggregation
p-Tau
β-amyloid
α-synuclein
Neuronal dysfunction and injury
Alzheimer's diseases
Parkinson's diseases

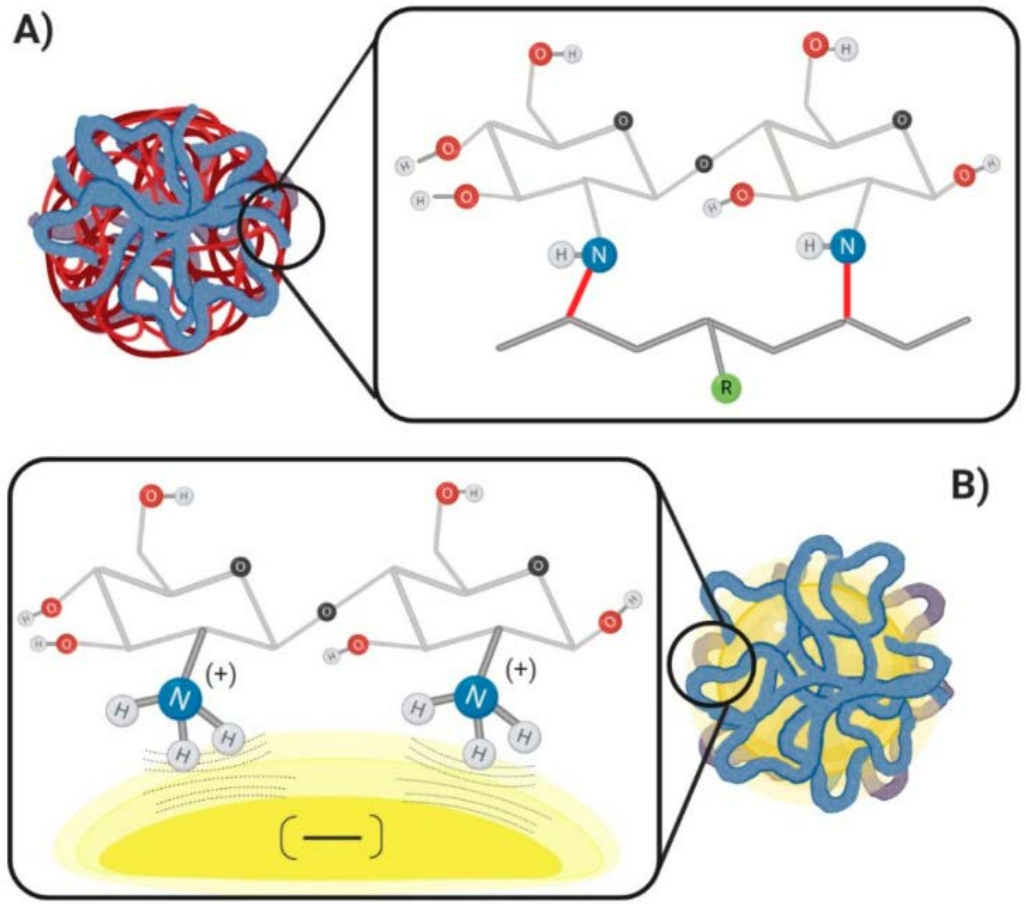
STRESS CRONICO E parkinson

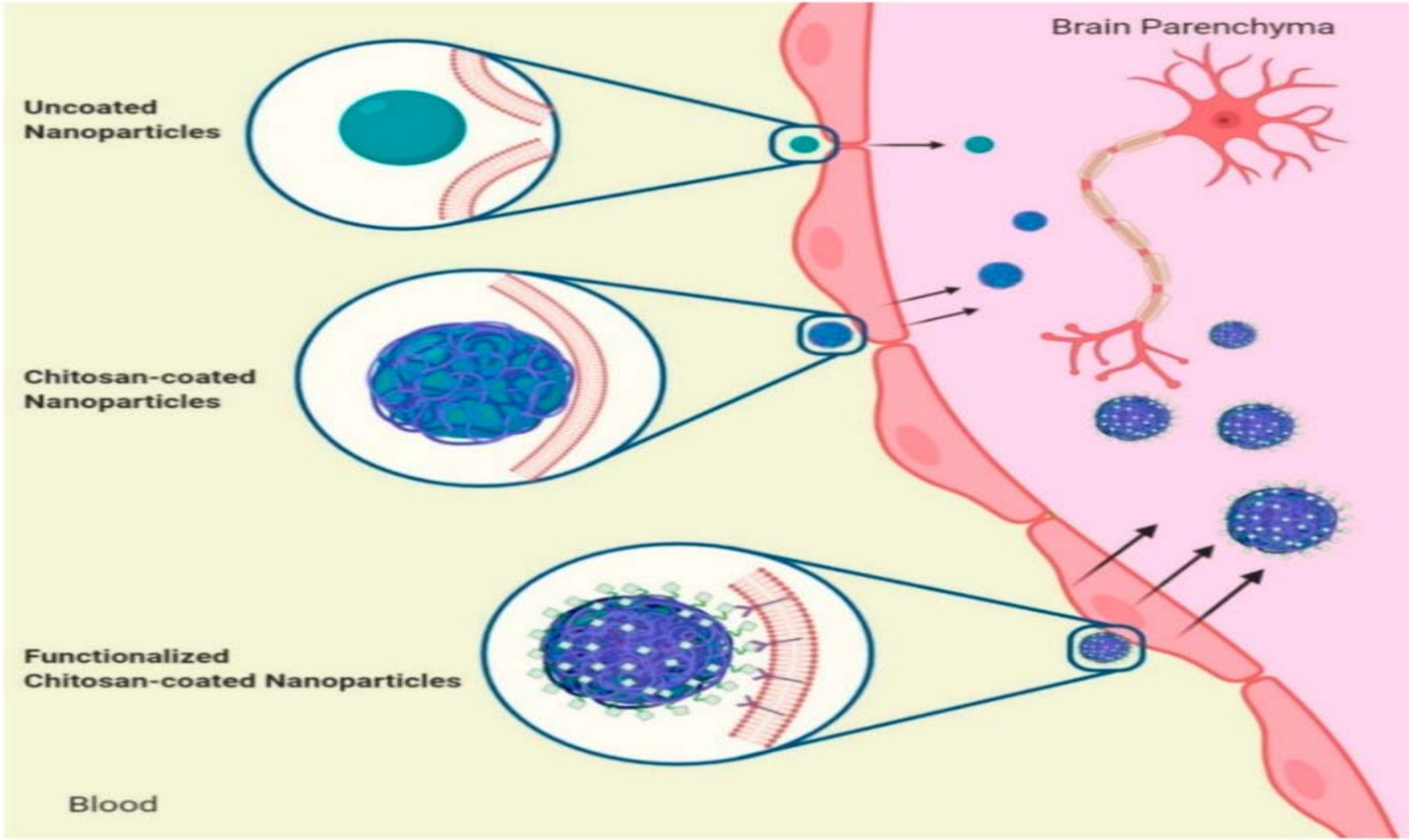



A
Priming of microglia by stress prior to an inflammatory challenge
Primed microglia
Active secretion
Alarmins: HMGB1, others?
HMGB1
ASC
PRO
IL-1β
IL-18
NF-κB
B
Inflammatory challenge in Parkinson's disease after stress
Damaged DAergic neuron
Active microglia
ATP
ROS
UPS
IL-1R
IL-6
TNF-α
NF-κB
ASC
PRO
IL-1β
IL-18
NADPH oxidase
iNOS
NO
O2
ONOO-
ROS

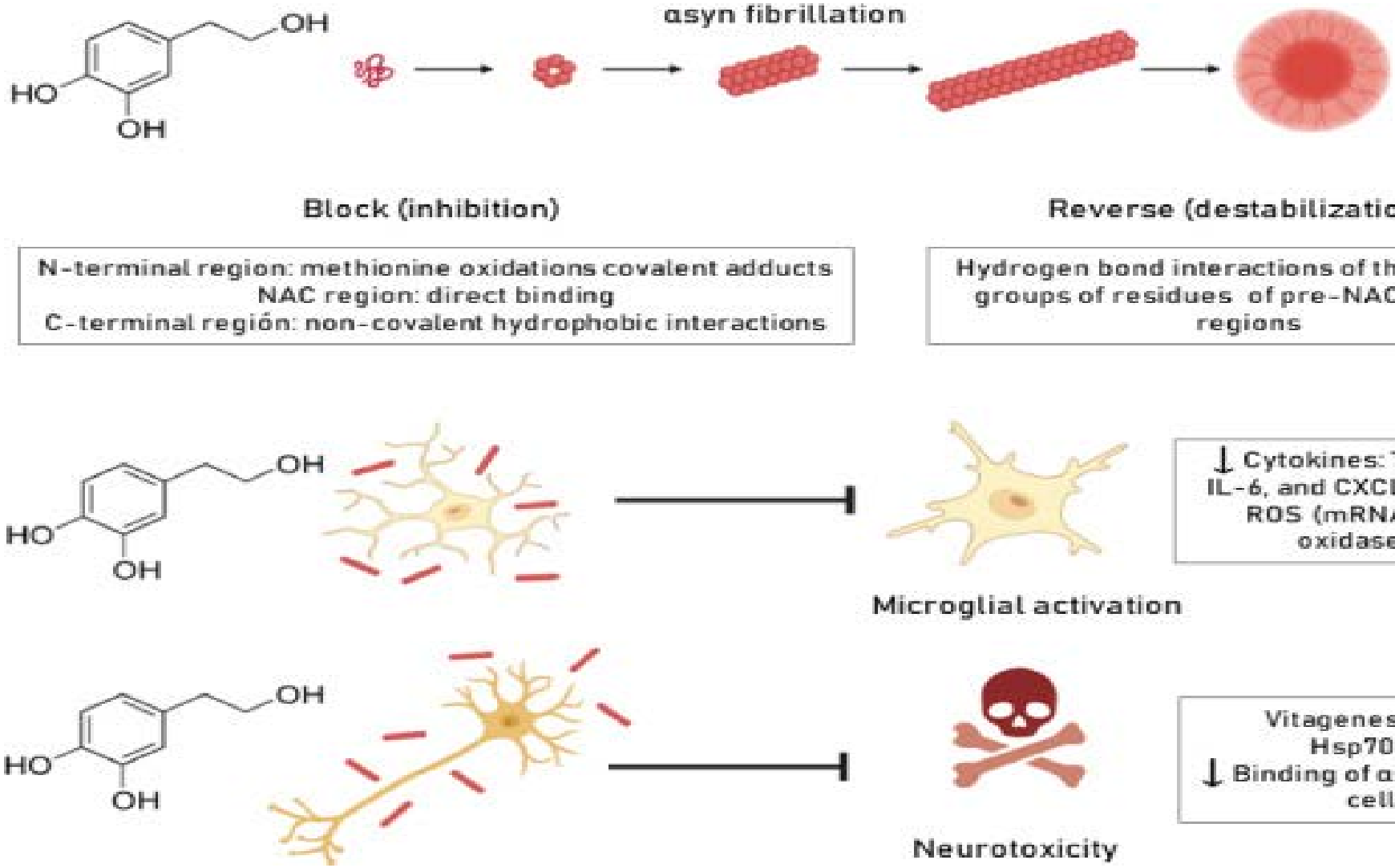
Nanoparticelle di chitosano

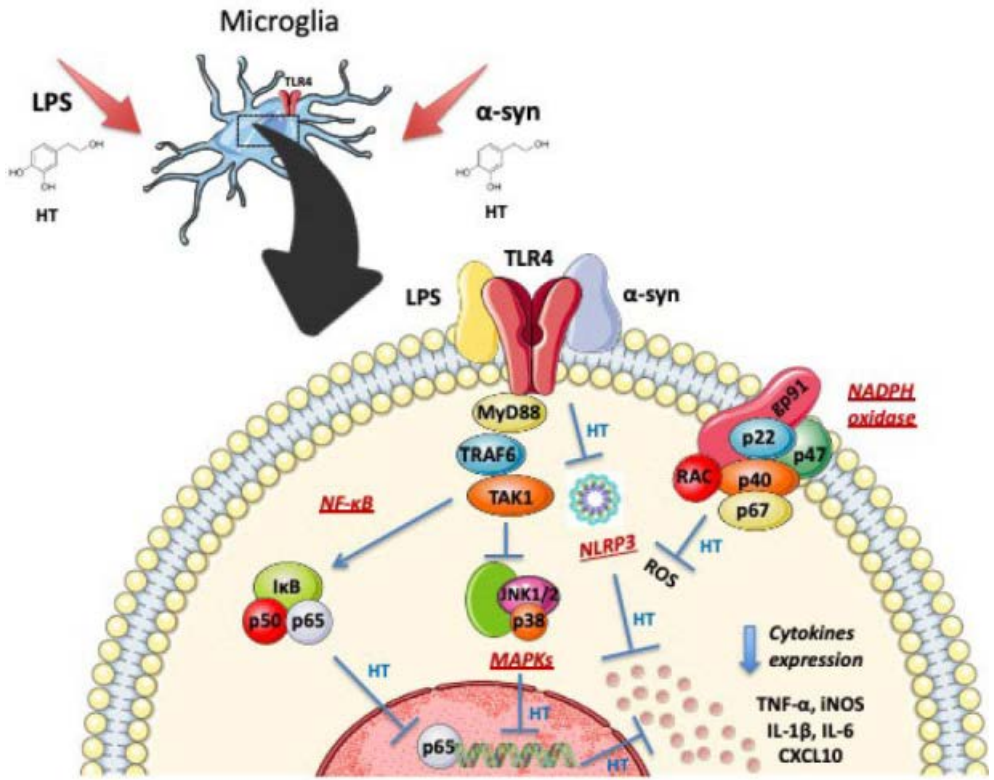



A)
B)
(+)
(+)

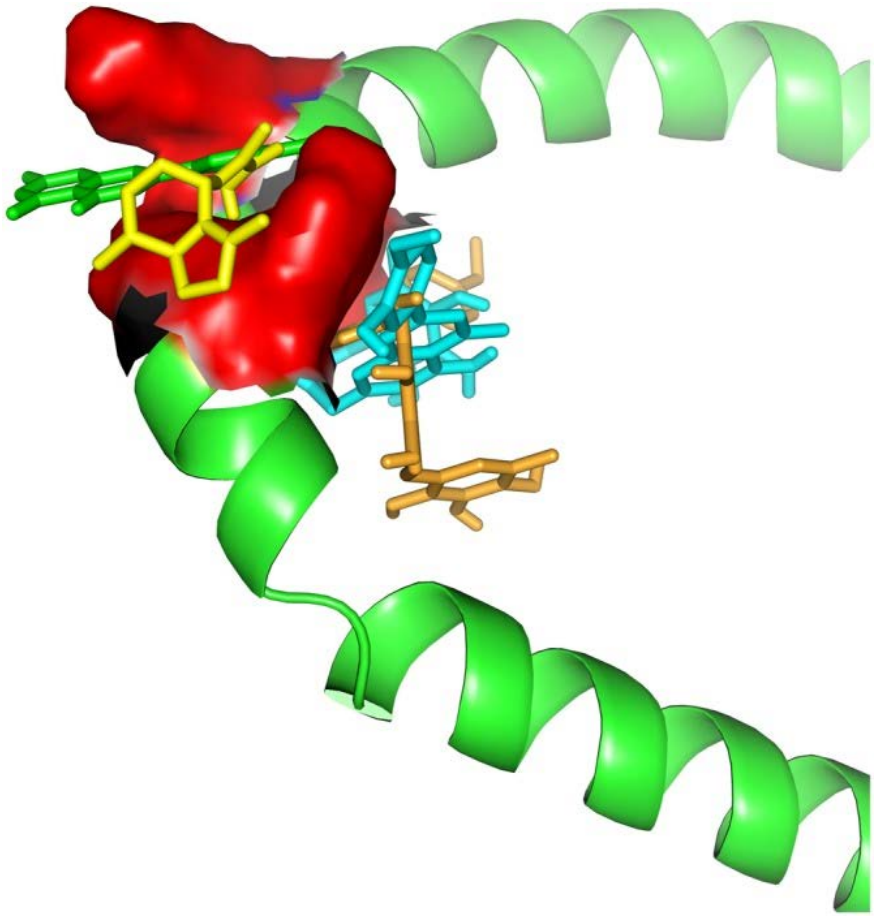

Brain Parenchyma
Uncoated
Nanoparticles
Chitosan-coated
Nanoparticles
Functionalized
Chitosan-coated Nanoparticles
Blood

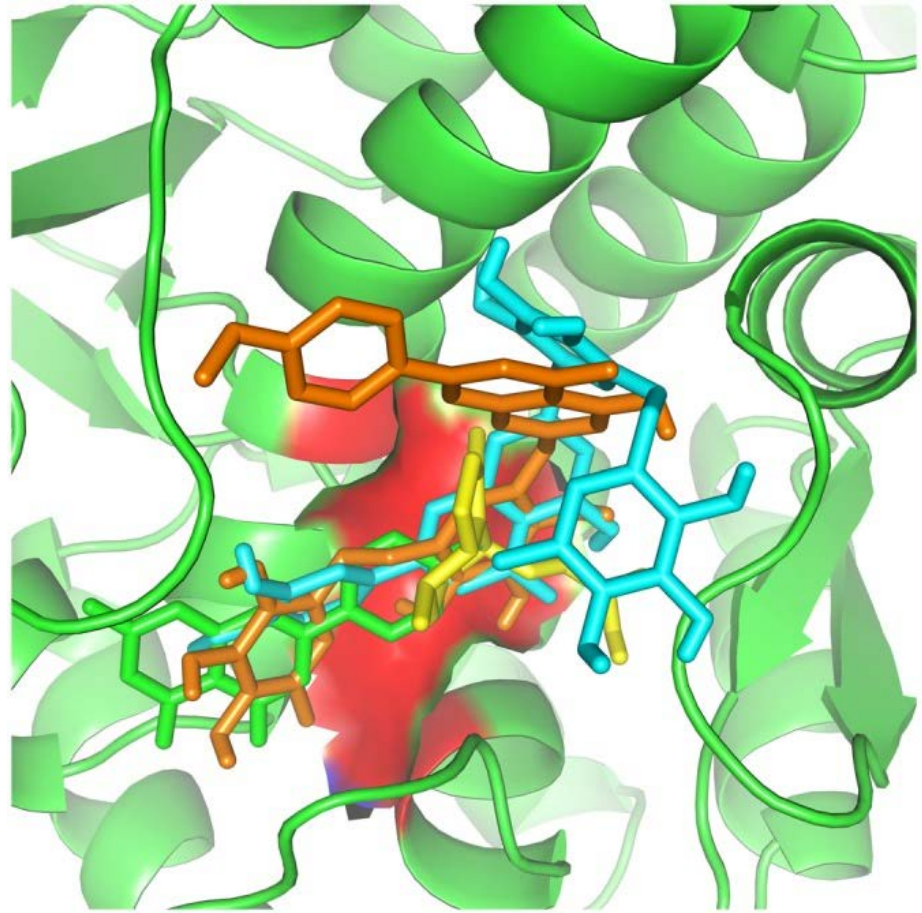
idrossitirosolo



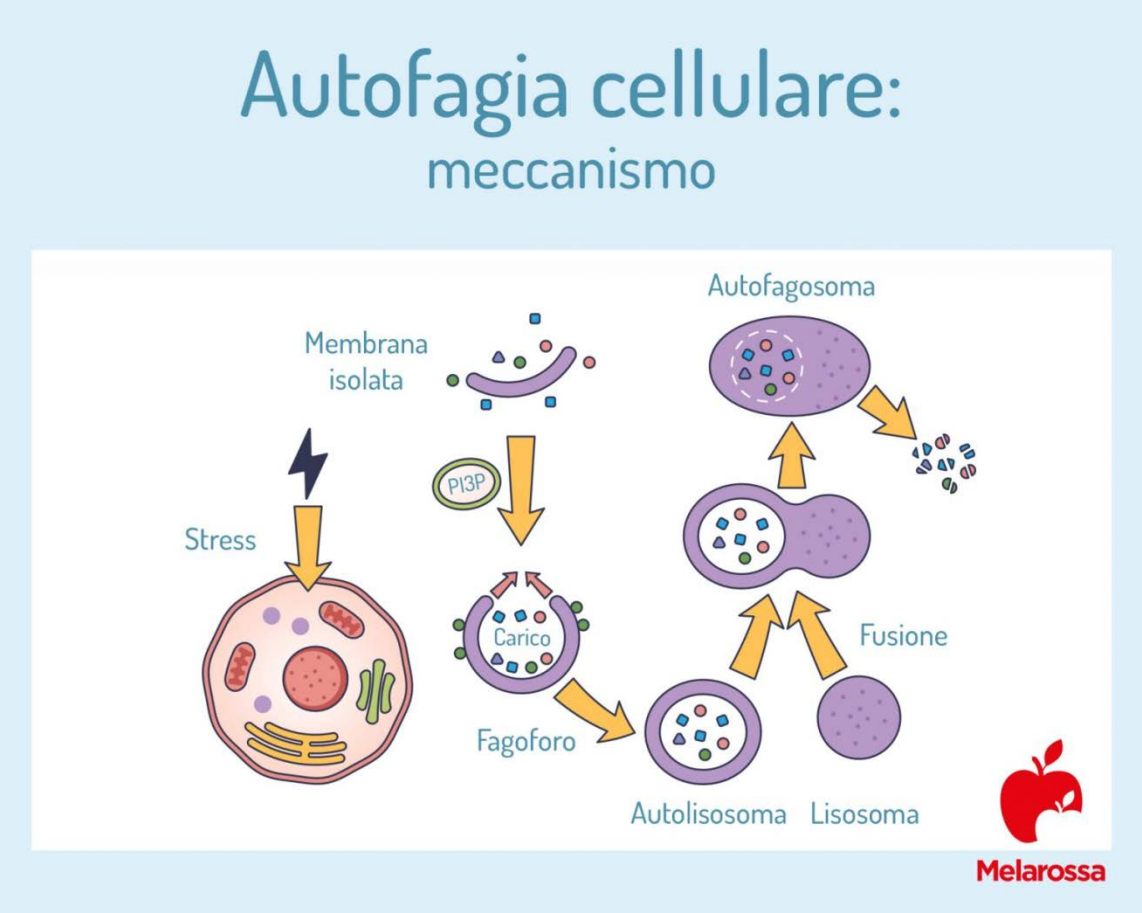

Microglia
TLR4
LPS
α-syn
HT
HT
TLR4
LPS
α-syn
MyD88
TRAF6
TAK1
HT
NF-κB
IκB
p50
p65
JNK1/2
p38
MAPKs
HT
HT
p65
HT
NLRP3
ROS
HT
HT
gp91
p22
p47
RAC
p40
p67
NADPH oxidase
Cytokines expression
TNF-α, iNOS
IL-1β, IL-6
CXCL10

Valeriana e parkimson





autofagia


Autofagia cellulare:
meccanismo
Autofagosoma
Membrana
isolata
PI3P
Stress
Carico
Fusione
Fagoforo
Autolisosoma
Lisosoma
Melarossa