Current concepts in immune-related CNS diseases

Degenerative CNS diseases

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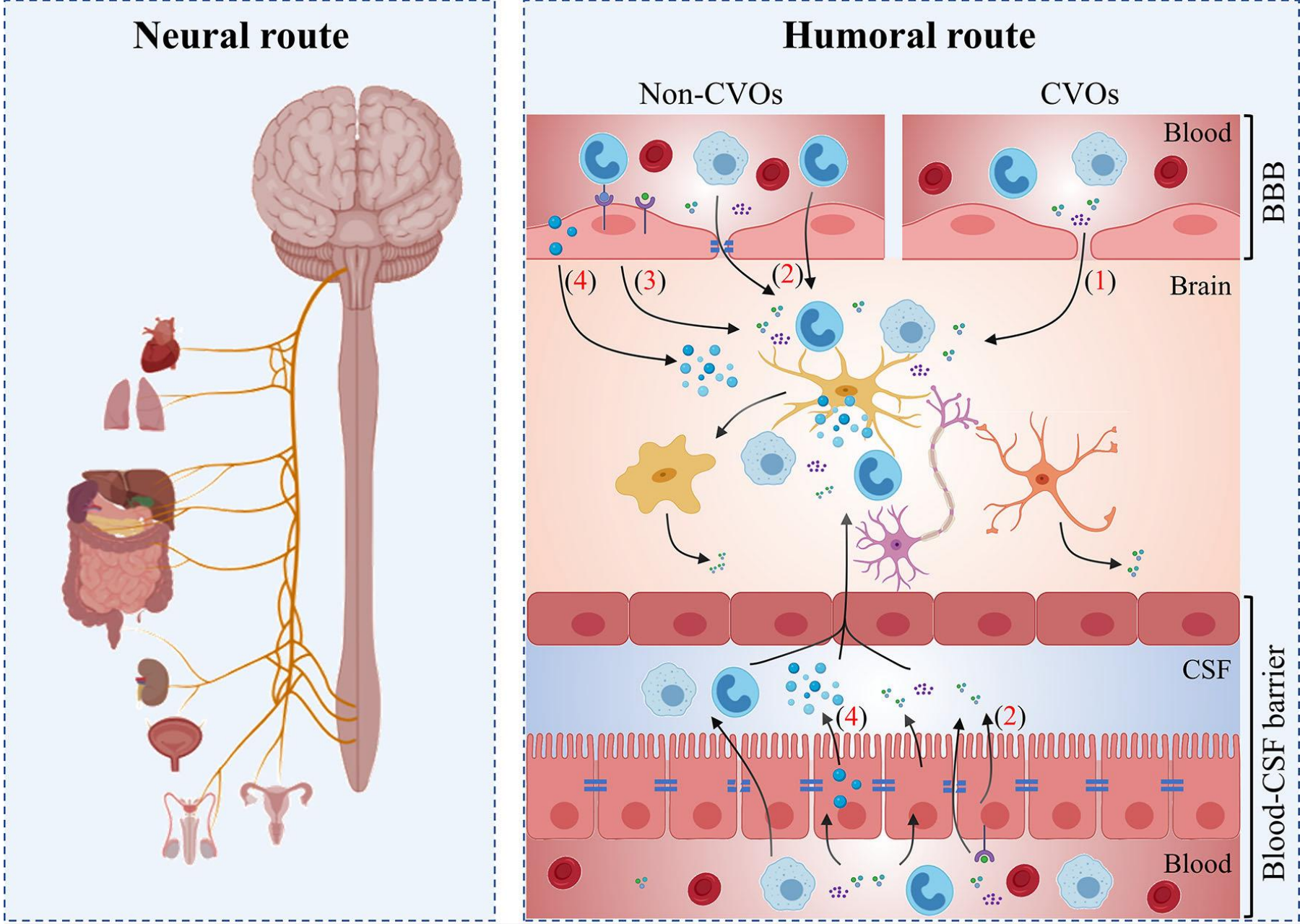
Lecture Outline

- ✓ Overview of the Periphery to Brain communication
- ✓ Background for Alzheimer’s disease
- ✓ Alzheimer’s disease & Systemic inflammation
- ✓ Background for Parkinson’s disease
- ✓ Parkinson’s disease & Systemic inflammation

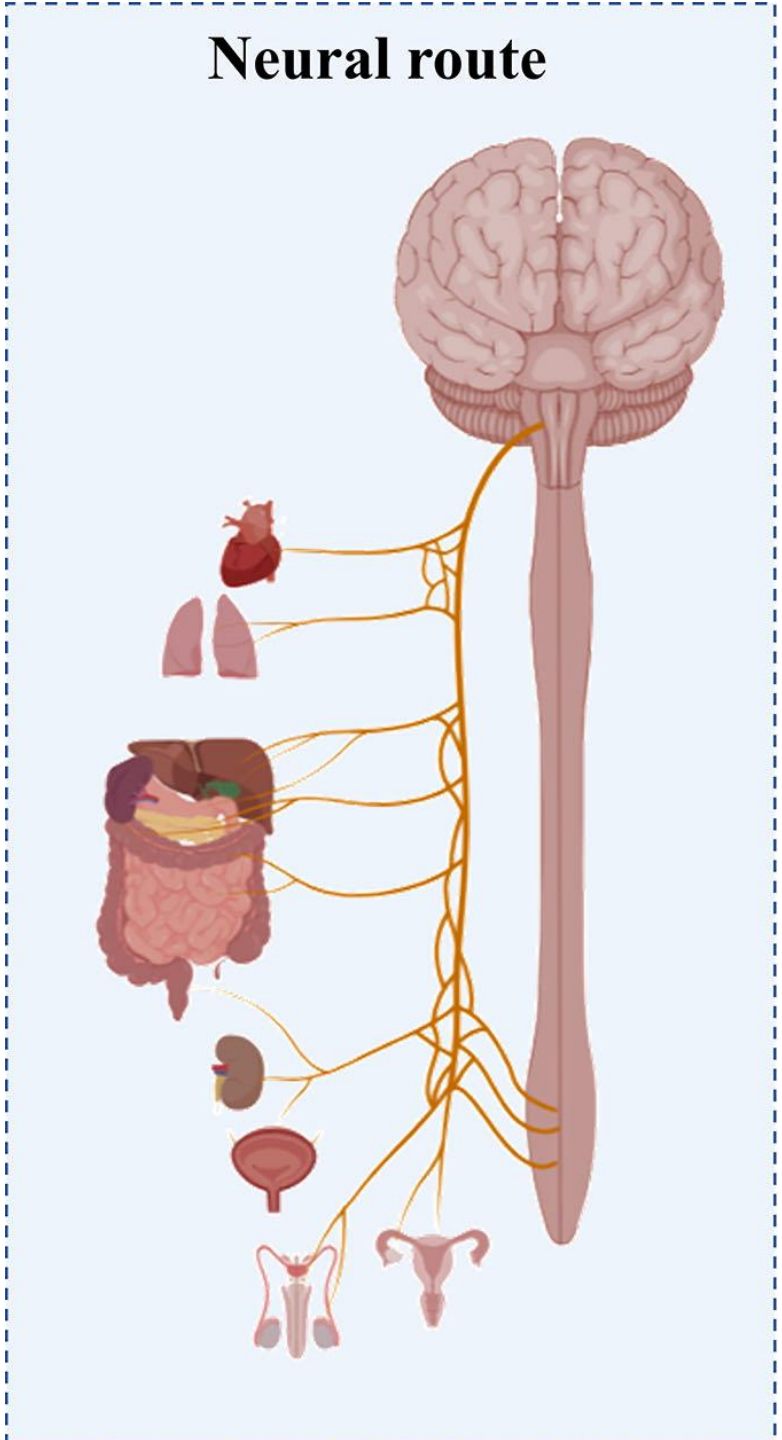
Periphery-to-brain communication pathways



Xie J et al (2022) Front. Immunol. 12:796867

Periphery-to-brain communication pathways

- ✓ Vagus Nerve
- ✓ Gut-brain axis

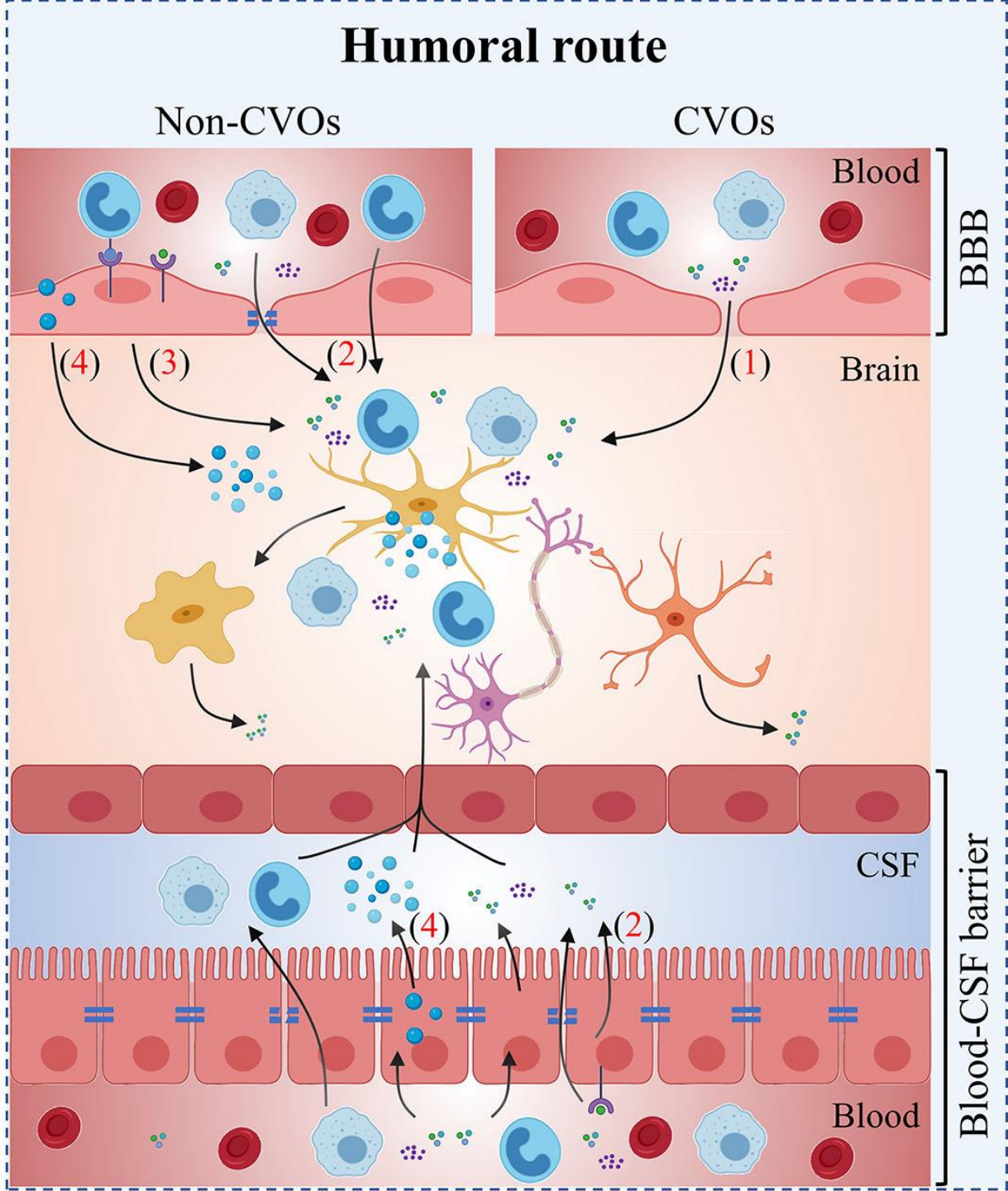


Xie J et al (2022) Front. Immunol. 12:796867

Periphery-to-brain communication pathways

- ✓ Blood-Brain Barrier
- ✓ Circumventricular organs
- ✓ Choroid plexus epithelium

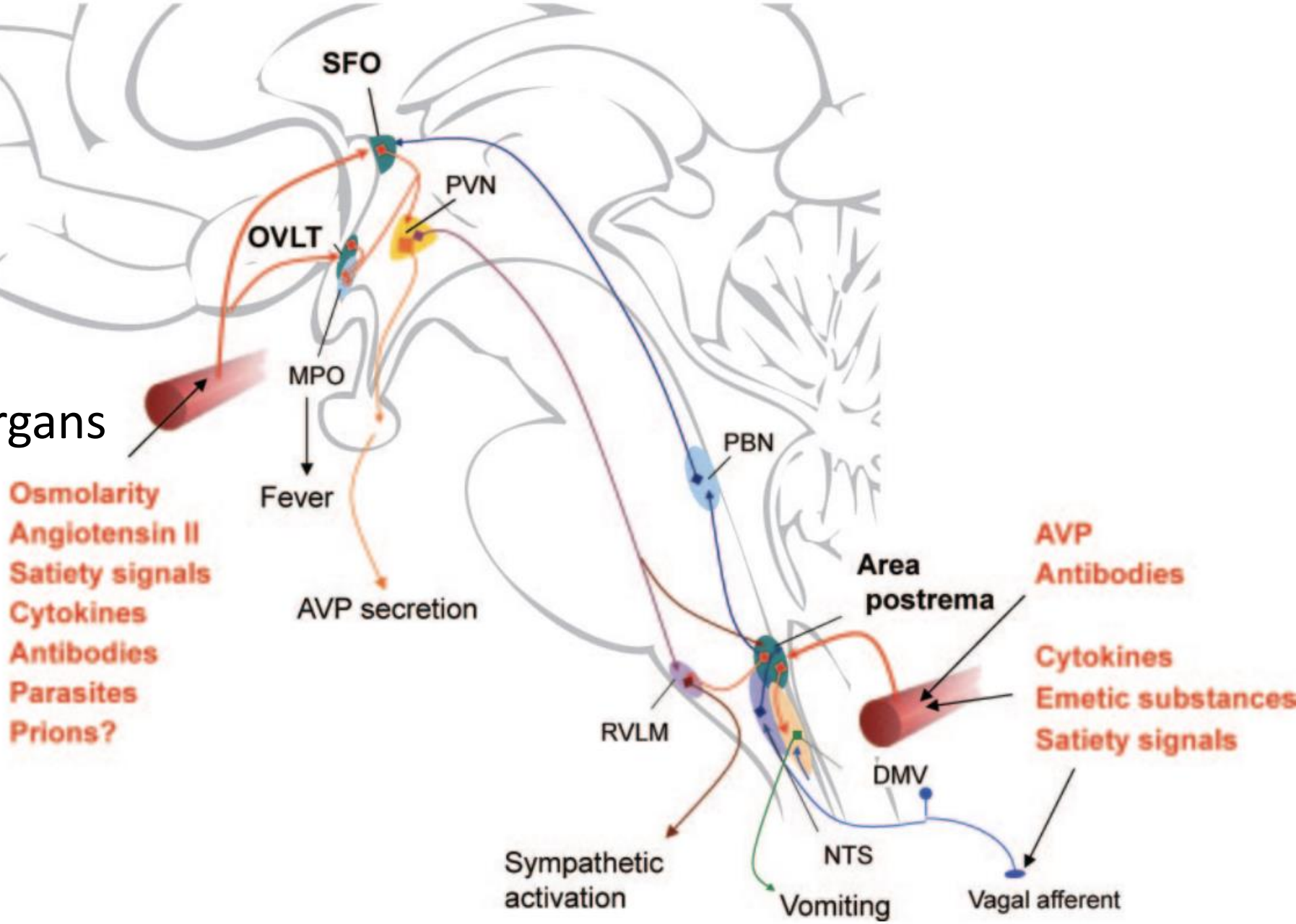
(blood-CSF barrier)



Xie J et al (2022) Front. Immunol. 12:796867

Periphery-to-brain communication pathways

- ✓ Circumventricular organs

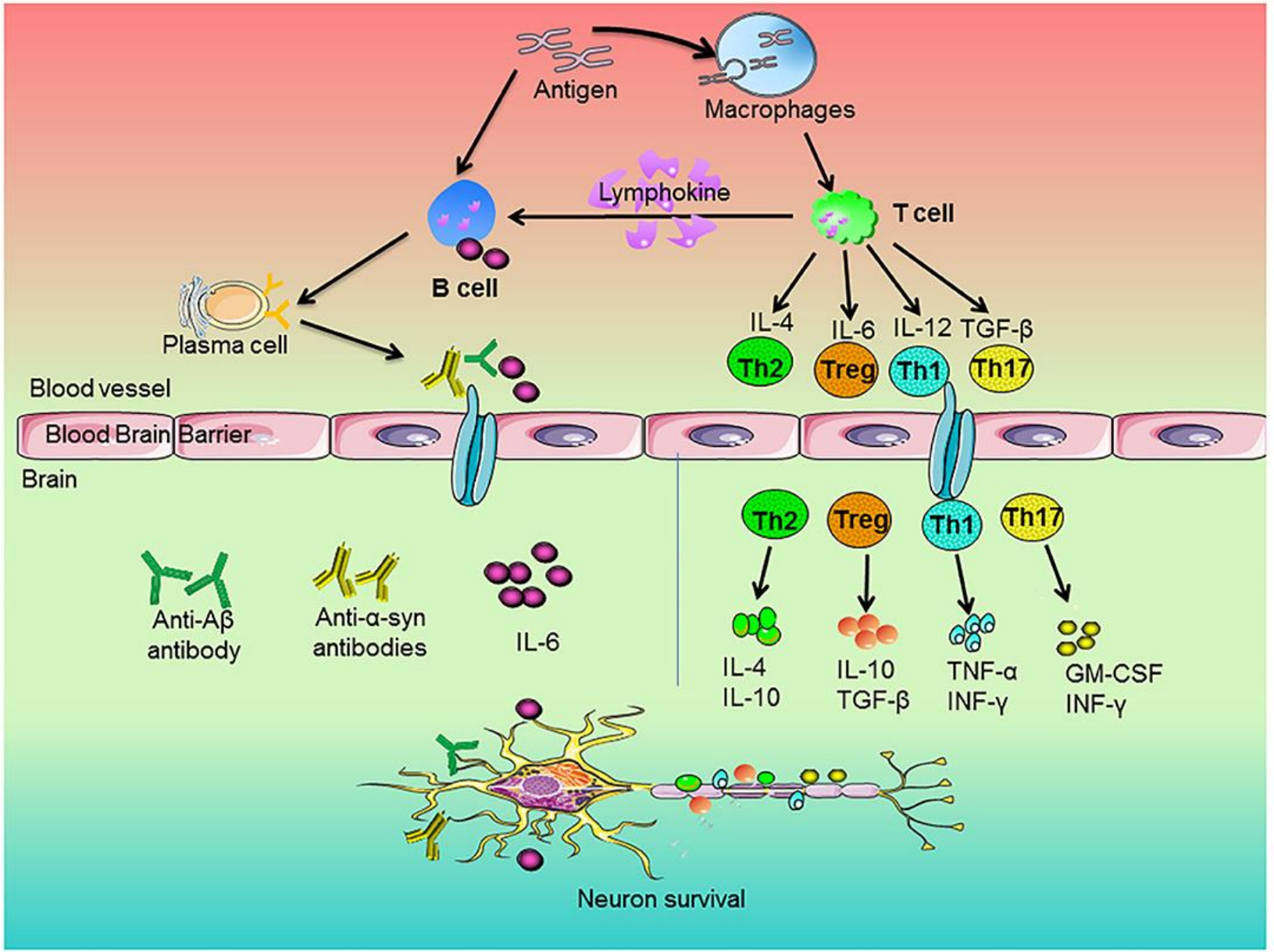


Benarroch EE. Neurology. 2011 Sep 20;77(12):1198-204

Periphery-to-brain communication pathways

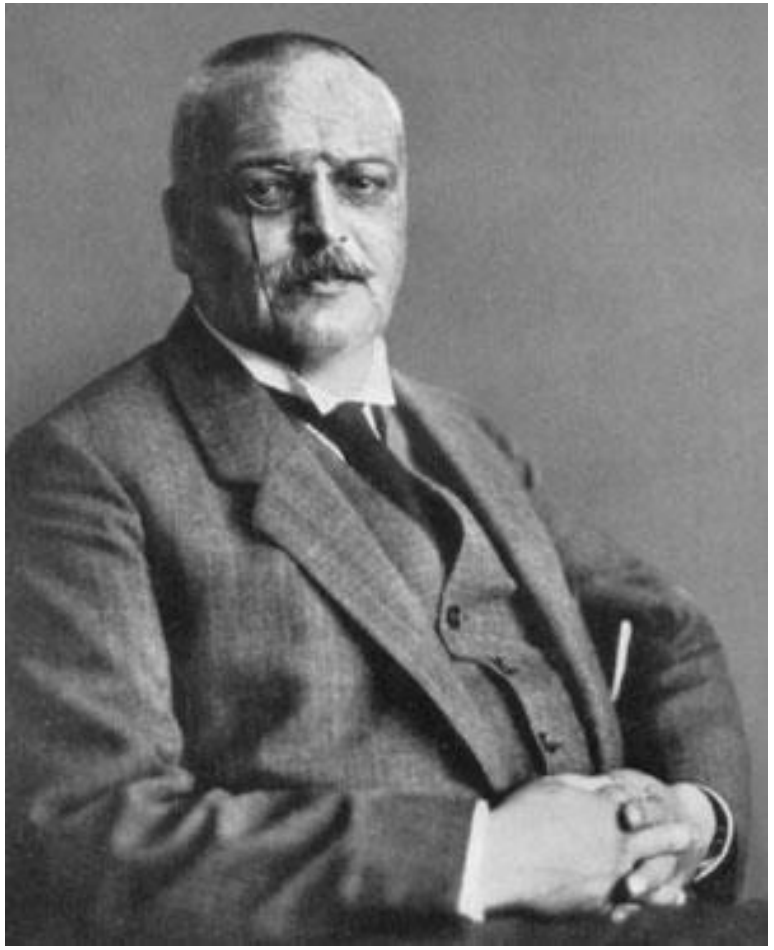
- ✓ Peripheral Immune Cells-

  Mediated Inflammation



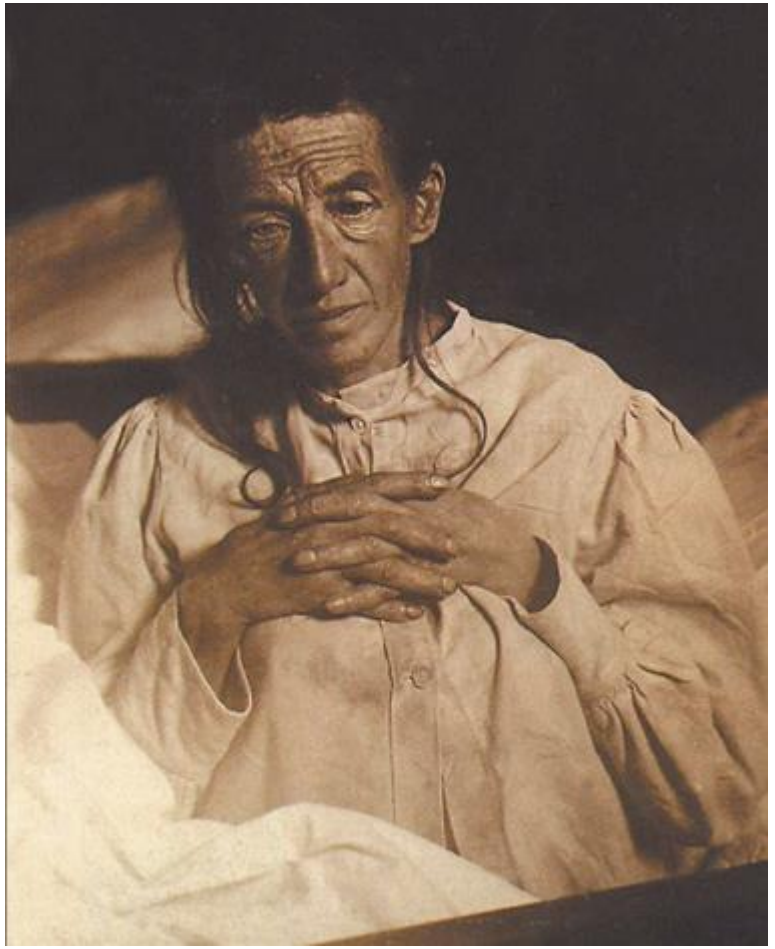
Qiuyu Yang et al Front. Immunol., 15 October 2020

Alzheimer’s Disease – Global facts

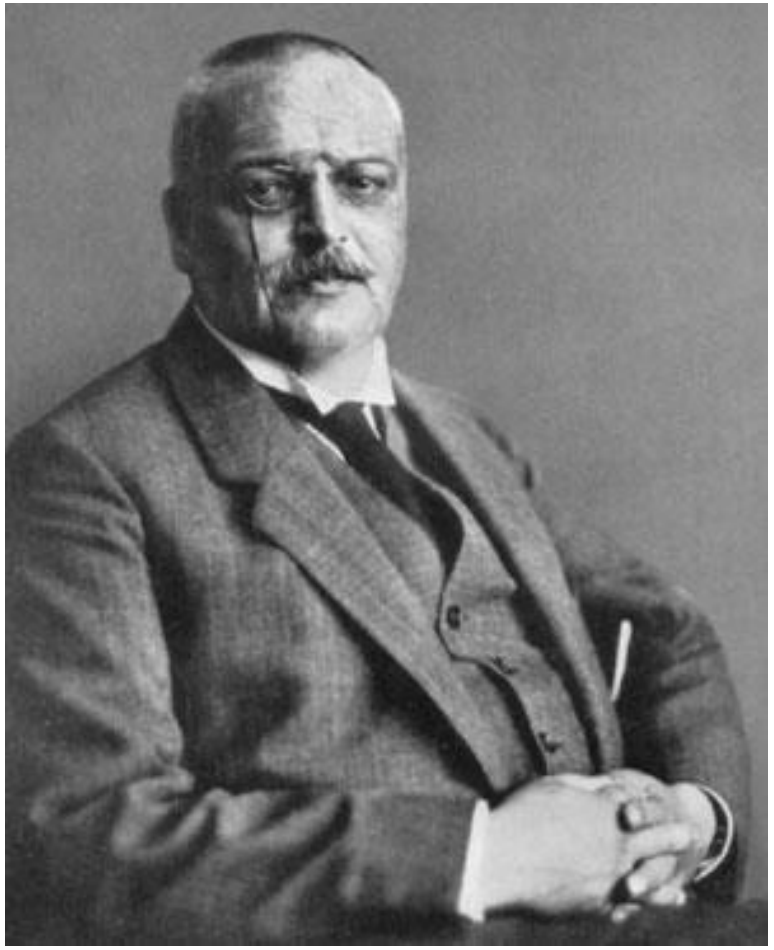


Dr. Alois Alzheimer
1864 - 1915

Auguste Deter
1849 - 1906



Alzheimer's Disease – Symptoms & Neuropathology



Dr. Alois Alzheimer
1864 - 1915

"presenile dementia"

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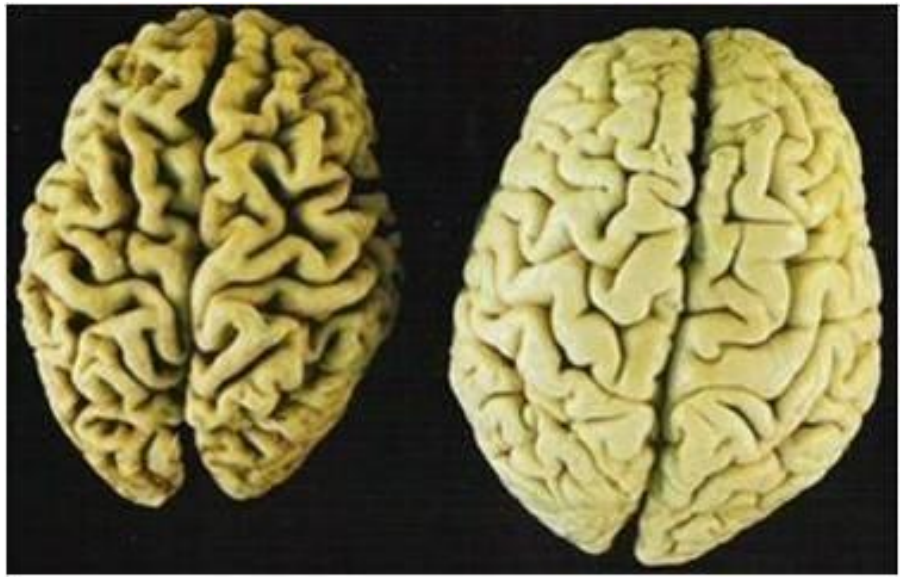
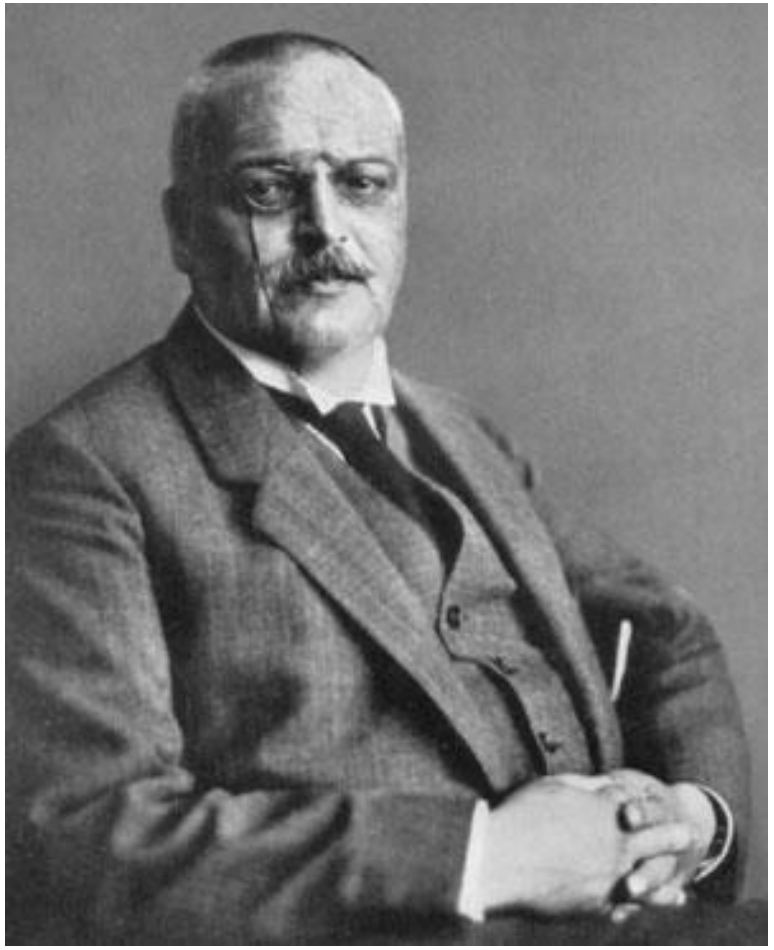


Alzheimer's Disease – Symptoms & Neuropathology



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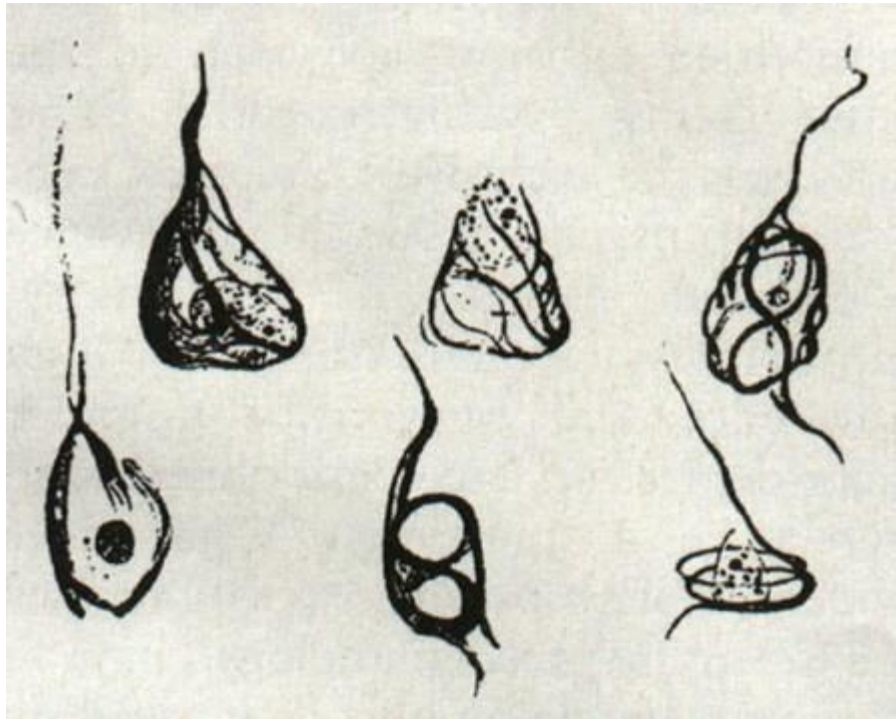

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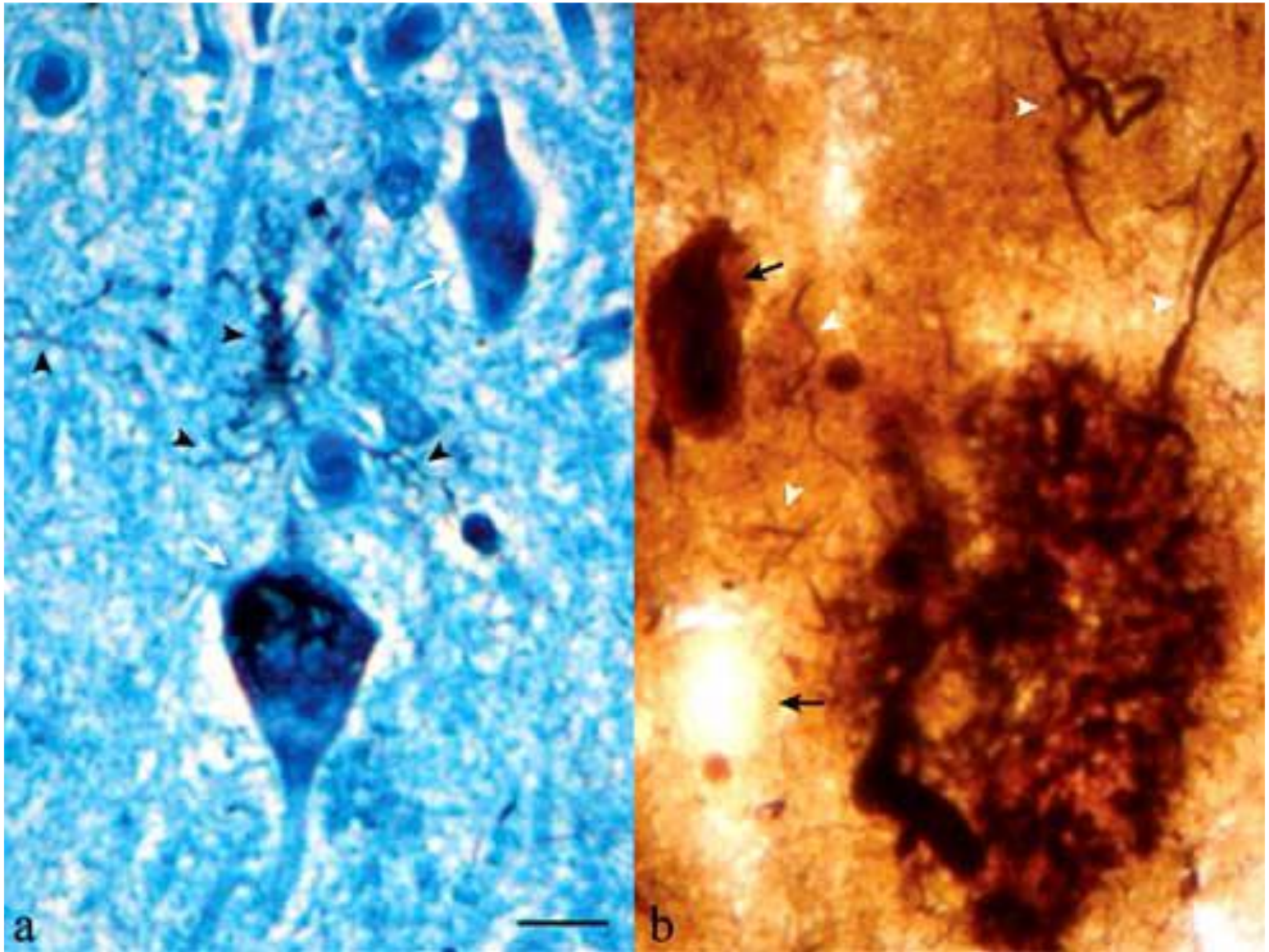
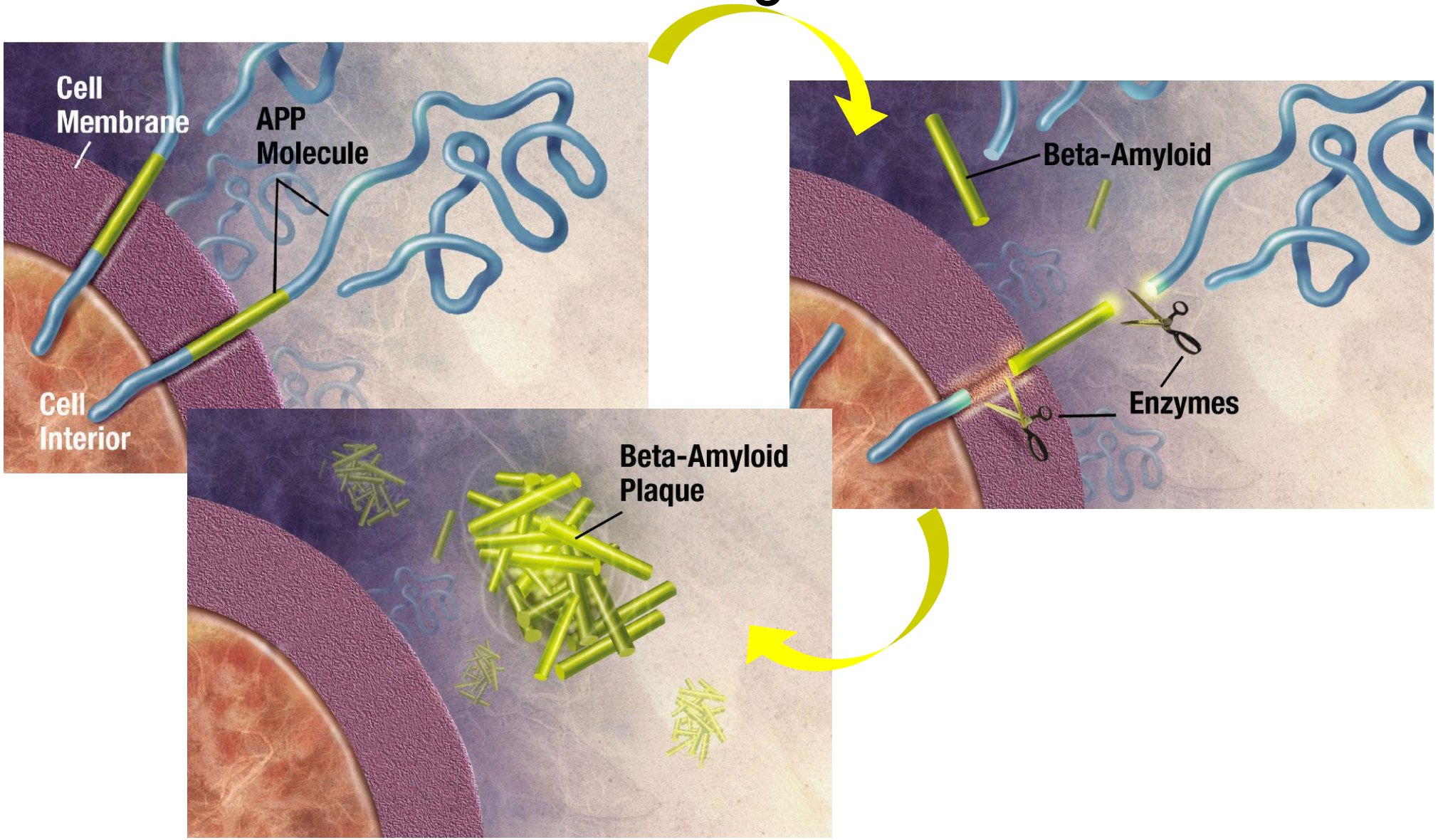
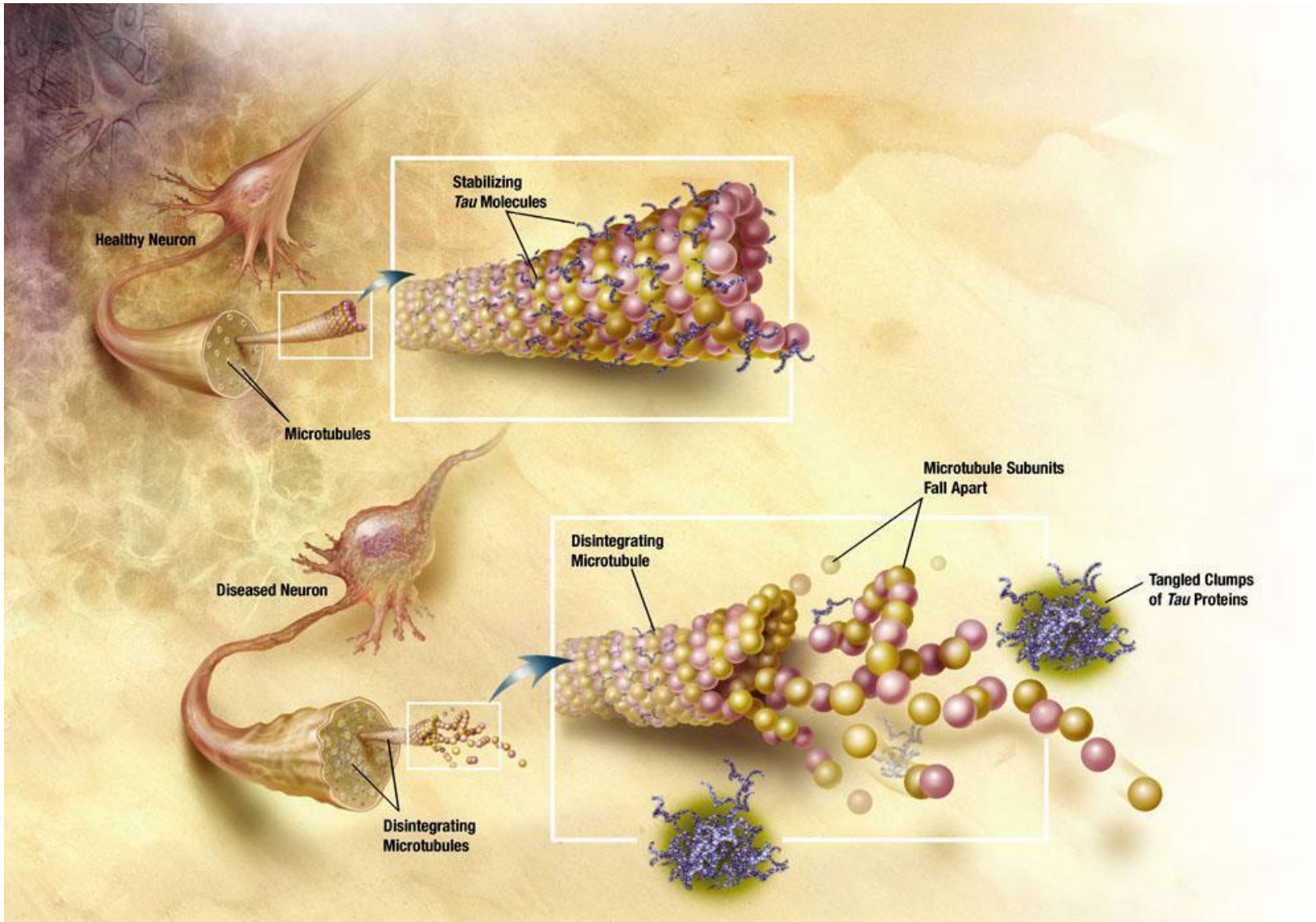


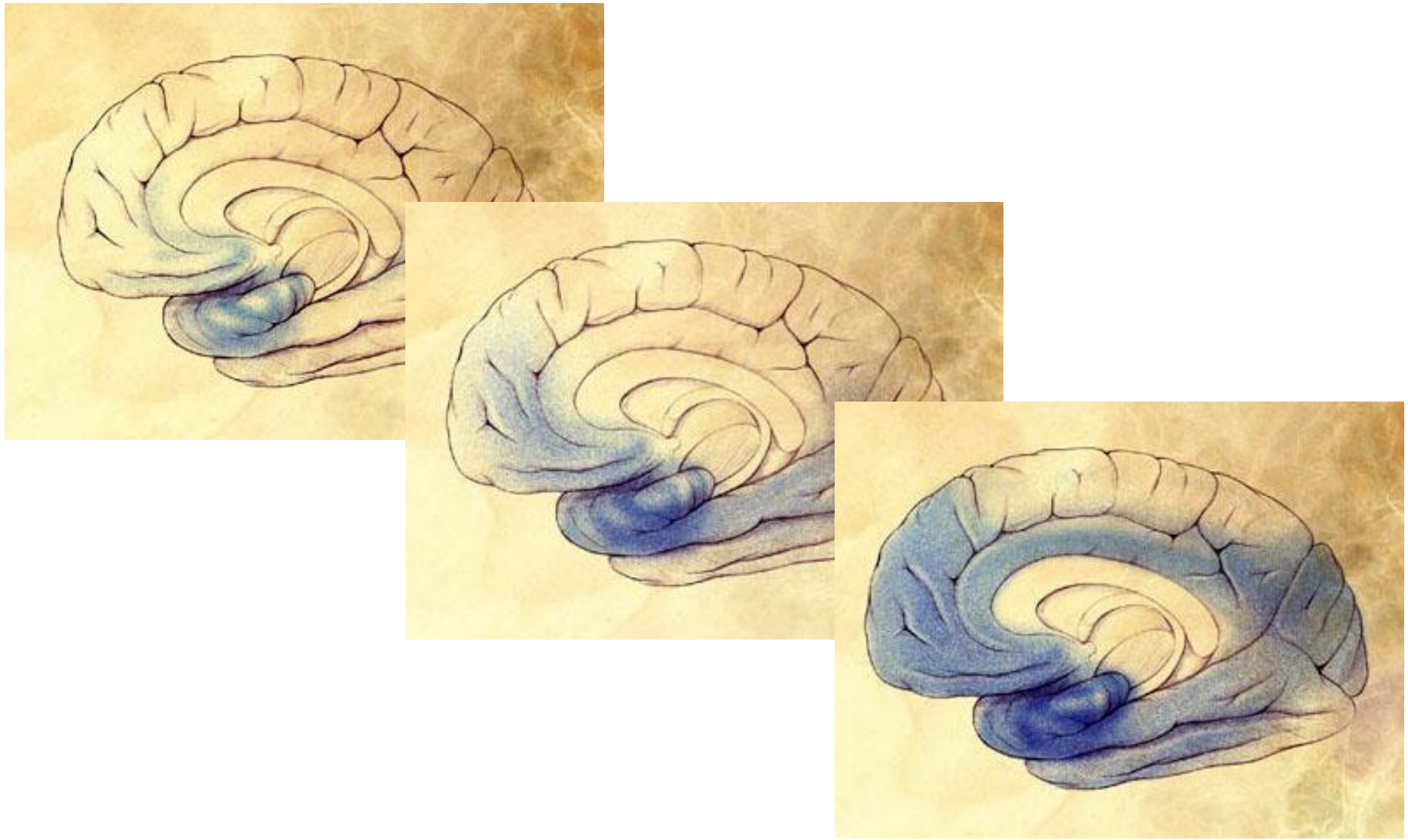
Alzheimer's Disease – Pathogenetic mechanisms



Alzheimer's Disease – Pathogenetic mechanisms



Alzheimer’s Disease – Pathogenetic mechanisms



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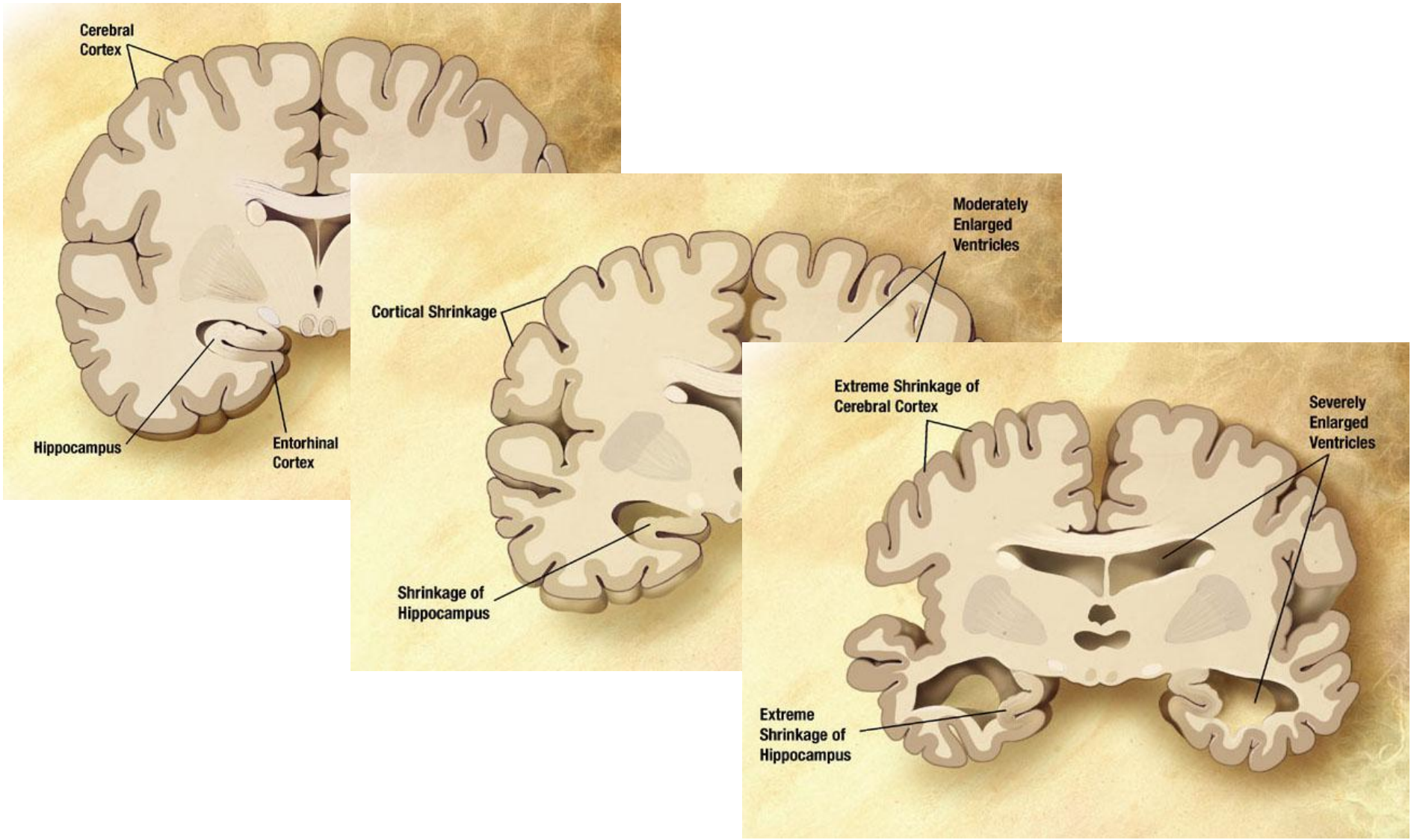
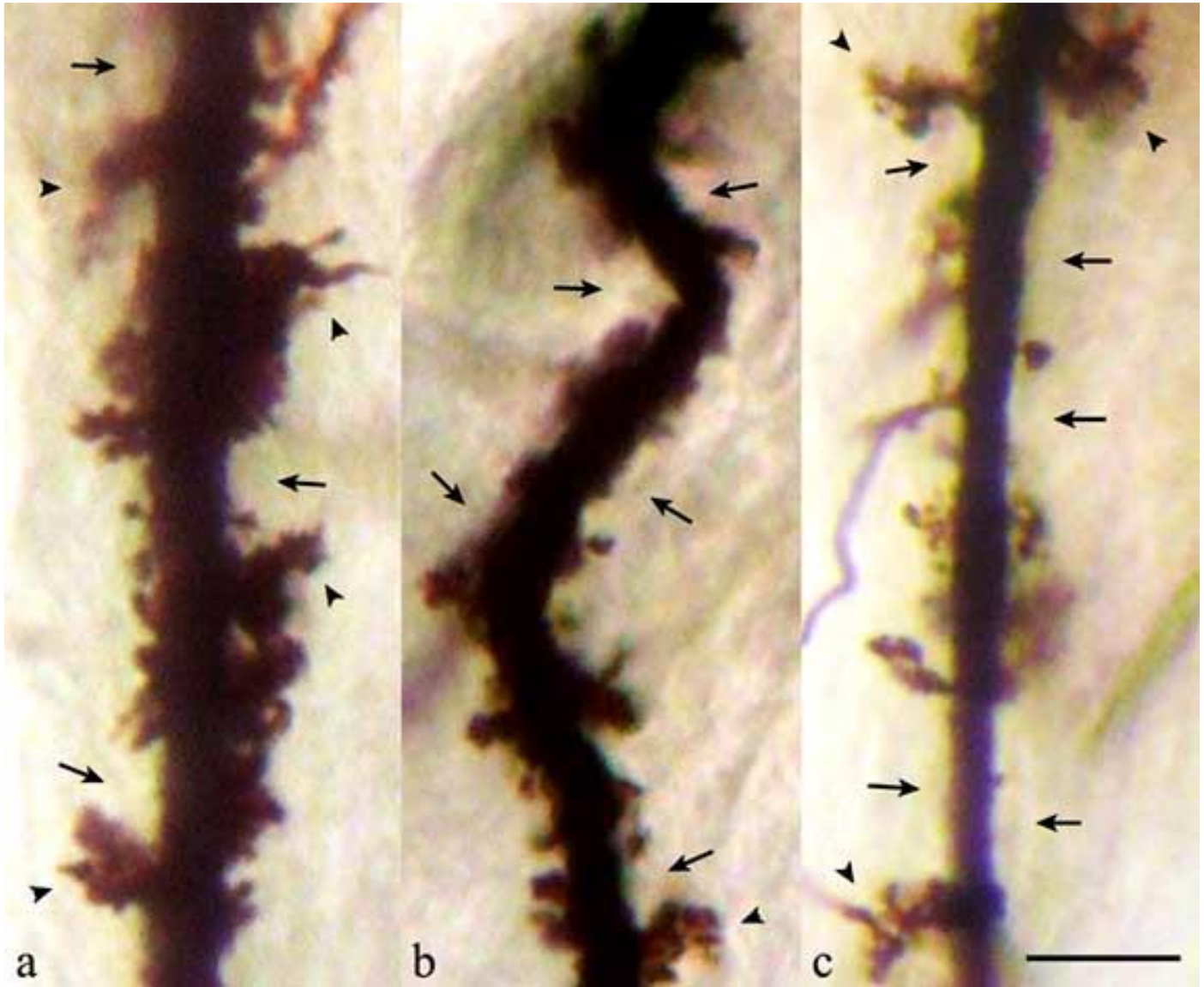


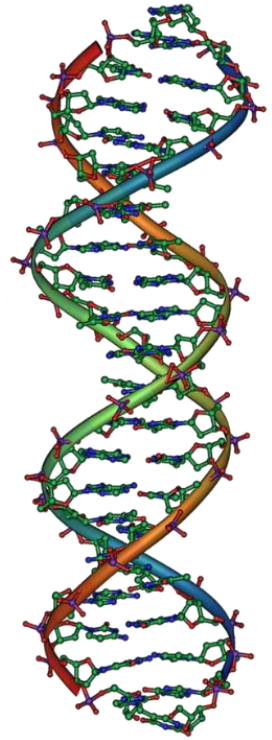
Alzheimer's Disease – Pathogenetic mechanisms



Alzheimer's Disease – Cause

Genetic Risk Factors

- Familial AD – early onset – APP, PS1, PS2 – (5-10%)
- Familial clustering – 20% of late-onset – APOE E4, MAPT, …
- Sporadic AD – late onset – >20 risk genes (GWAS)



Alzheimer's Disease – Cause

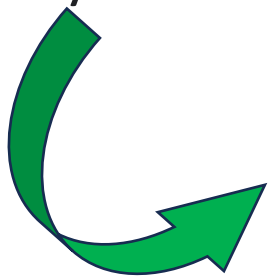
Non-Genetic Risk Factors

- Obesity – Diabetes Mellites – Insulin Resistance
- Cardiovascular disease – Hyperlipidemia – Hypertension
- Immune related factors
- Head trauma
- Oxidative stress
- … … … …

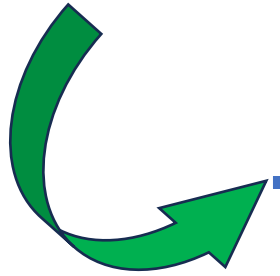
Alzheimer's Disease – Systemic Inflammation

Animal Models

Lipopolysaccharide immune response



Systemic inflammation

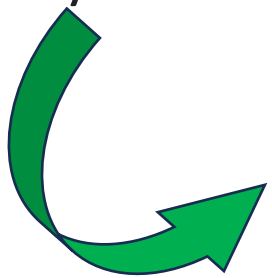


- temporal induction of neuronal death
- increased deposition of Aβ
- increased phospho-Tau levels

Alzheimer's Disease – Systemic Inflammation

Animal Models

Lipopolysaccharide immune response



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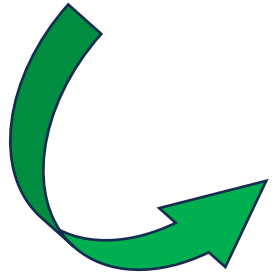


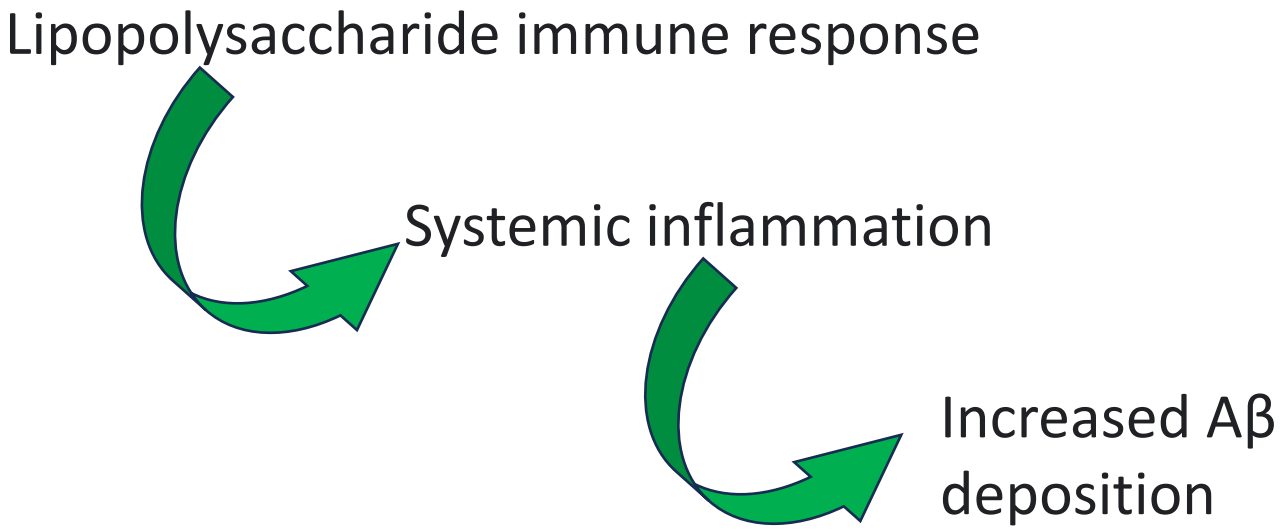
Microglia activation

- antimicrobial peptides
- anti-inflammatory cytokines (IL-10)
- transforming growth factor TGF-b
- prostaglandin E2 (PGE2)
- anti-nuclear factor-kappa B (NF-kB)
- mitogen-activated protein
- suppressor of cytokine signaling proteins

Alzheimer's Disease – Systemic Inflammation

Animal Models

Transgenic AD Models



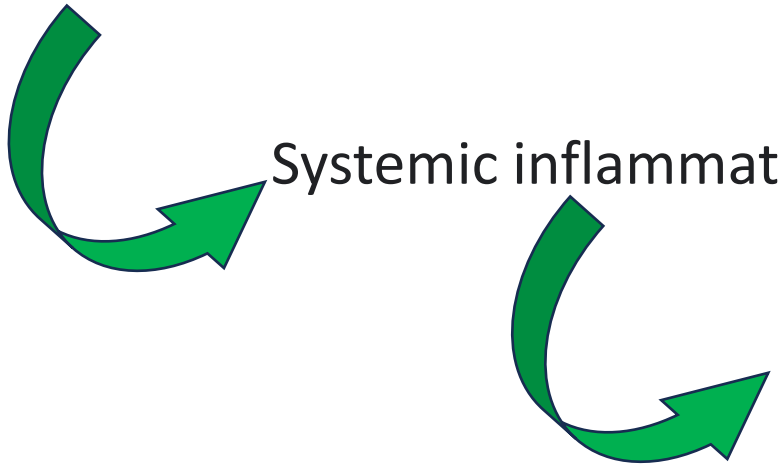
Controversial Results

Reduced Aβ burden upon systemic Lipopolysaccharide challenge !!!

Alzheimer's Disease – Systemic Inflammation

Animal Models

Helicobacter pylori & Porphyromonas gingivalis infection



Systemic inflammation

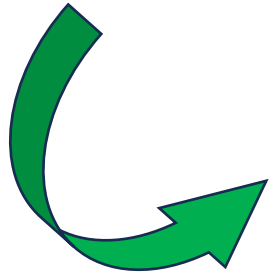
- exacerbated cognitive impairment
- increased Aβ deposits
- tau hyperphosphorylation
- activation of glycogen synthase kinase-3b

Alzheimer's Disease – Systemic Inflammation

Animal Models

Viruses & parasites
Surgical interventions &Head trauma
Atherosclerosis, obesity, & diabetes

Systemic inflammation



- exacerbated cognitive impairment
- increased Ab deposits
- tau hyperphosphorylation
- activation of glycogen synthase kinase-3b

Alzheimer's Disease – Systemic Inflammation

Clinical Studies

General

- patients with cognitive impairment and increased Aβ exhibit an increased systemic inflammatory response and increased microglial activation compared to healthy subjects
- persons with high Aβ loads but without dementia have lower level of pro-inflammatory cytokines than AD patients
- AD patients show a significant correlation between cognition and microglial activation but not with Aβ loads

Alzheimer's Disease – Systemic Inflammation

Clinical Studies

Infections

- AD patients show elevated levels of antibodies against periodontal bacteria
- AD and MCI patients have higher *anti-H. pylori* IgG titers in their blood and brain and indicate that AD patients have more gastric inflammation
- viral neurotropic pathogens such as HSV-1 have been repeatedly isolated from the brains of AD patients and HSV infection is associated with a higher risk for dementia in some studies

Alzheimer's Disease – Systemic Inflammation

Clinical Studies

Chronic Diseases

- Obesity
- Diabetes Mellites & Insulin Resistance
- Cardiovascular disease, Hyperlipidemia, & Hypertension

Controversial Results

Alzheimer's Disease – Systemic Inflammation

Systemic inflammation leads to neuroinflammation

peripheral immune cells infiltrate in the CNS

pro-inflammatory cytokines → neural and humoral pathways → increased **microglial** activation

increased **microglial** activation →

IL-1b
TNF
IL-6
nitric oxide (NO)
reactive oxygen species (ROS)

→

- neuronal cell death
- suppression of axonal transport
- suppression adult neurogenesis

Alzheimer's Disease – Systemic Inflammation

Systemic inflammation leads to neuroinflammation

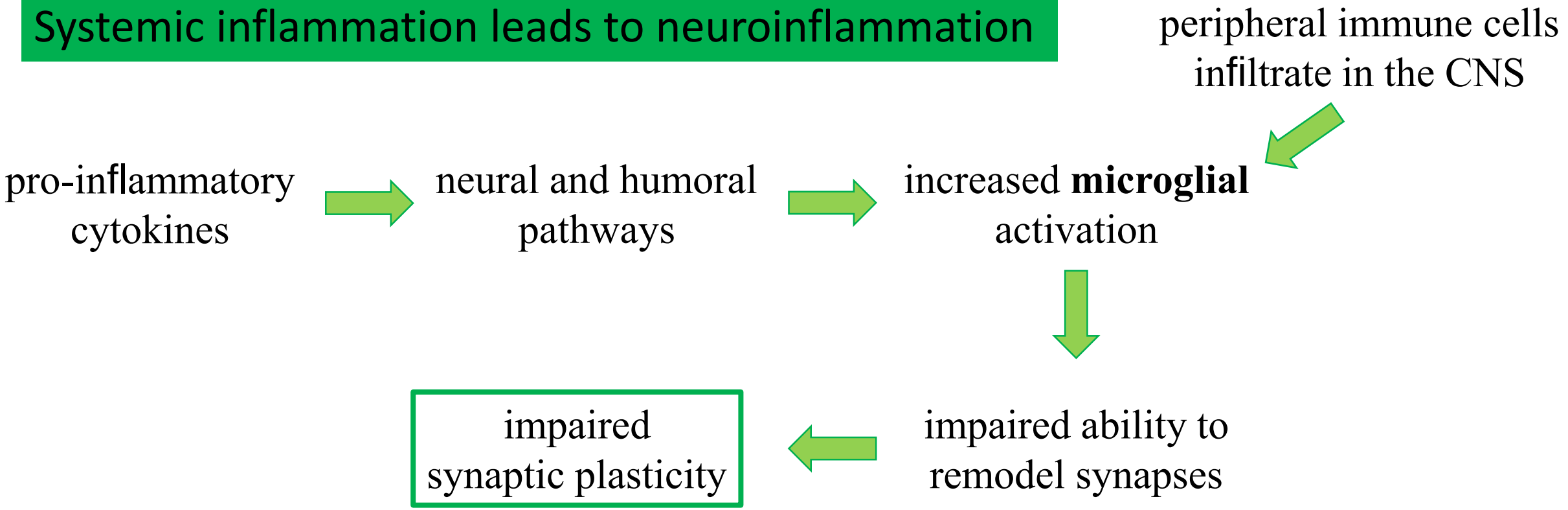
pro-inflammatory cytokines → neural and humoral pathways → increased **microglial** activation

peripheral immune cells infiltrate in the CNS → increased **microglial** activation

increased **microglial** activation → recognize misfolded and aggregated proteins such as Aβ

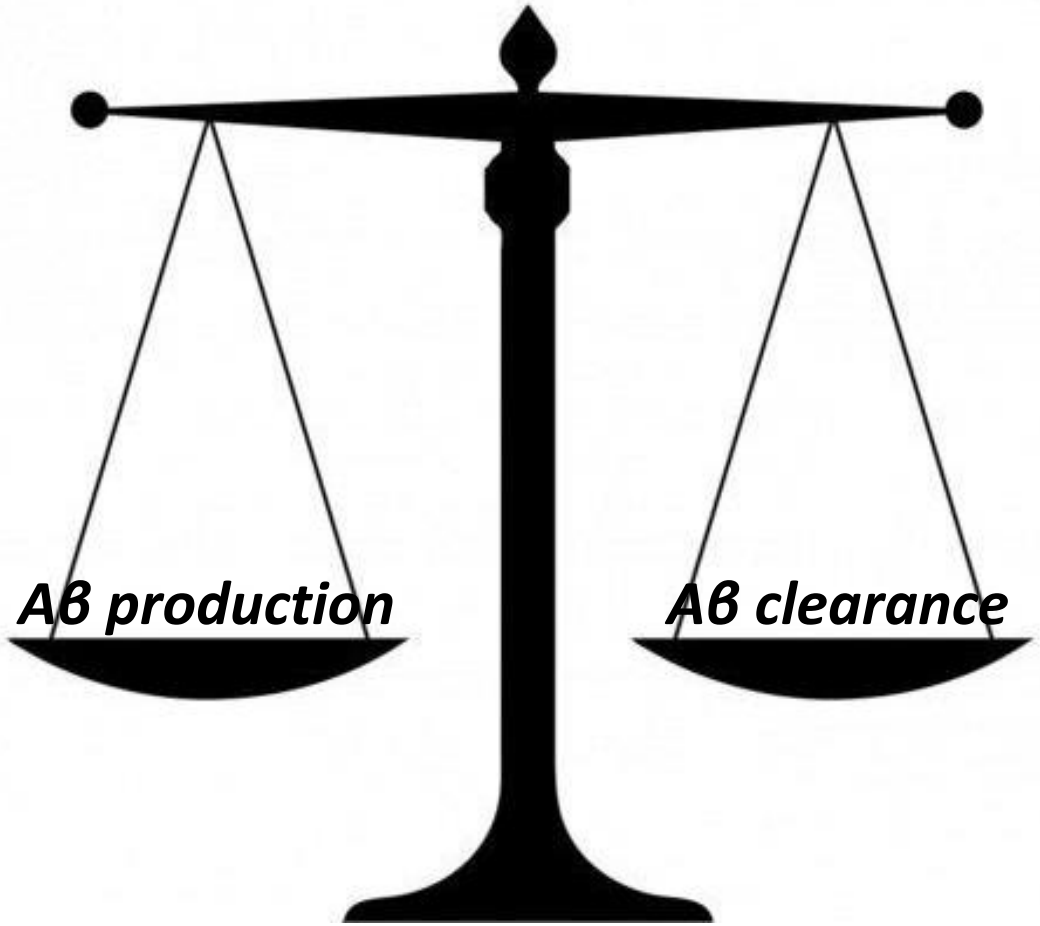
Alzheimer's Disease – Systemic Inflammation

Systemic inflammation leads to neuroinflammation



Alzheimer's Disease – Systemic Inflammation

Systemic Inflammation Impairs Aβ Clearance

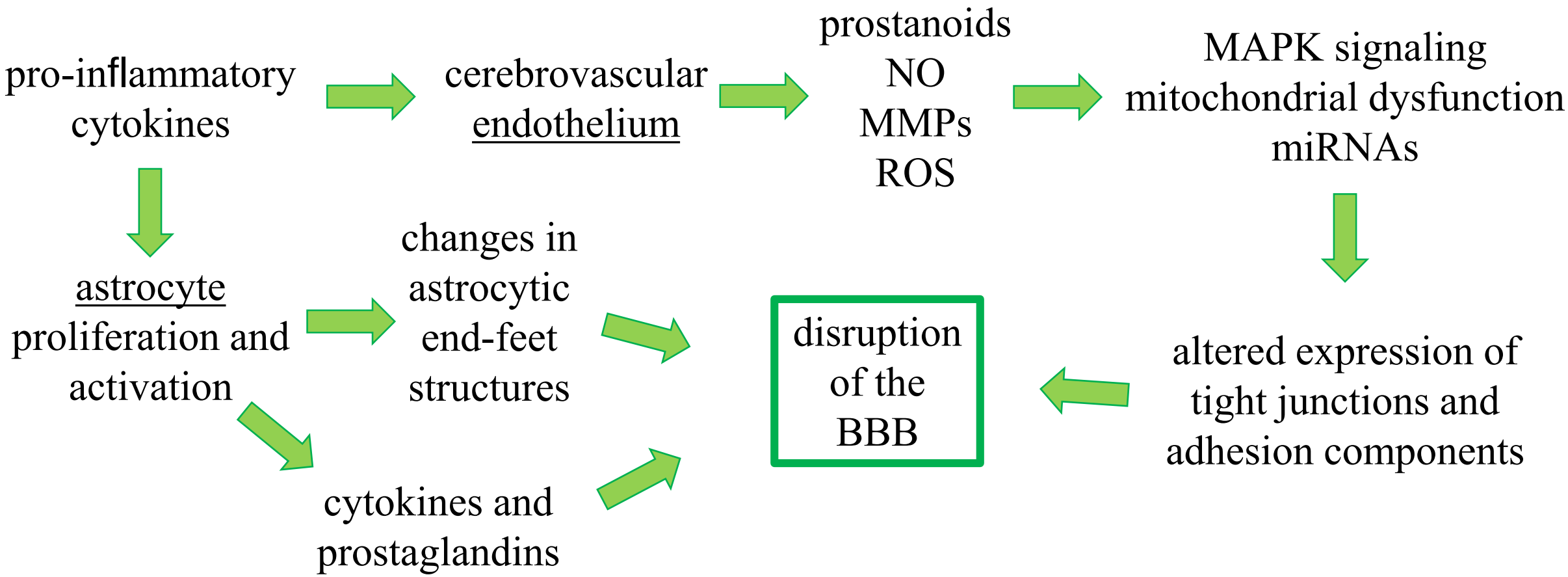


pro-inflammatory cytokines

impaired **microglial** phagocytosis of Aβ

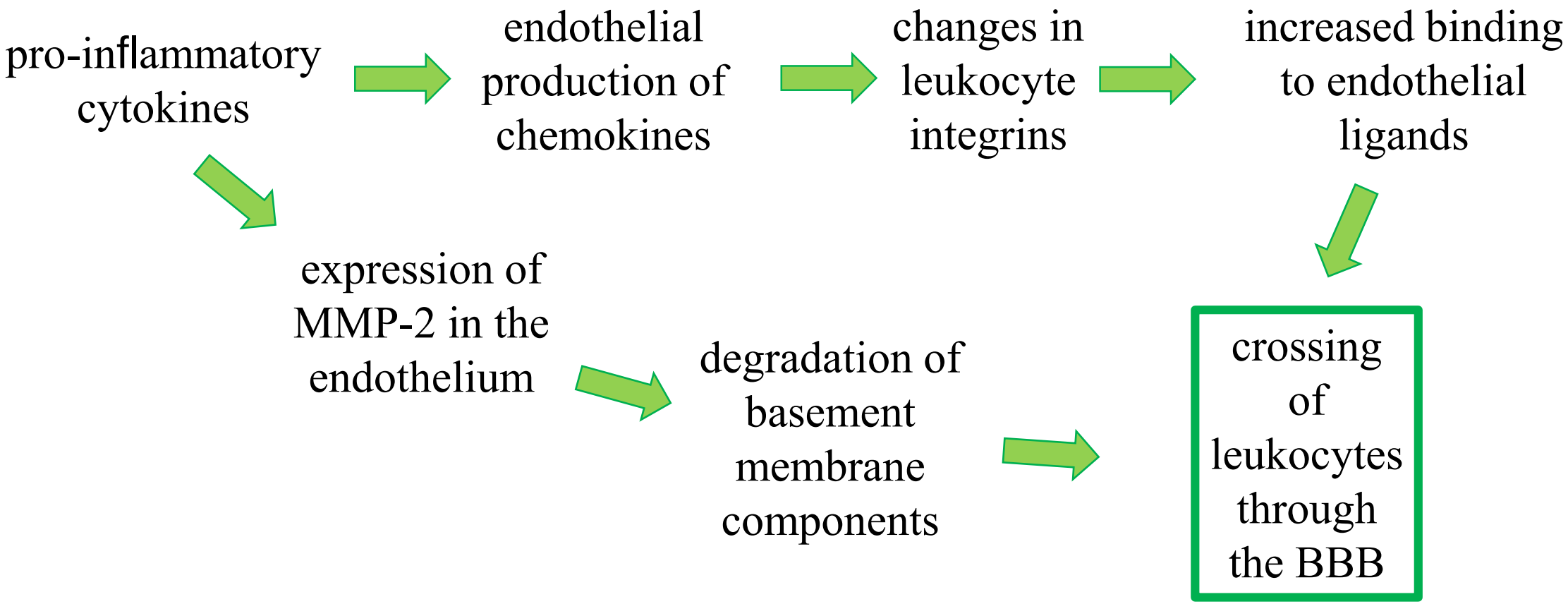
Alzheimer's Disease – Systemic Inflammation

Systemic Inflammation induces changes at the Brain Barriers



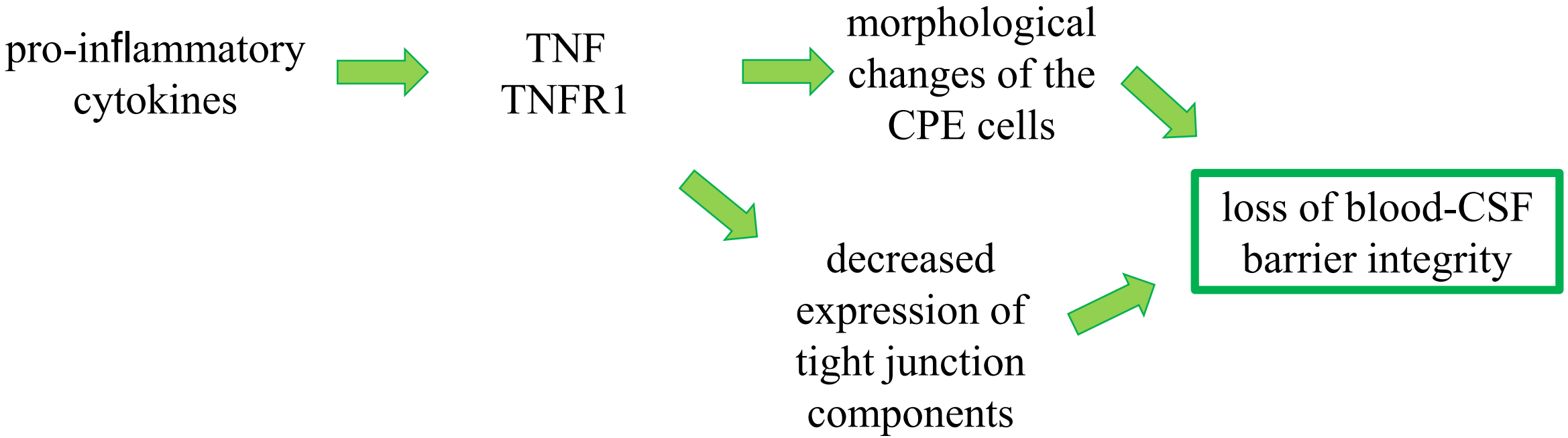
Alzheimer's Disease – Systemic Inflammation

Systemic Inflammation induces changes at the Brain Barriers



Alzheimer's Disease – Systemic Inflammation

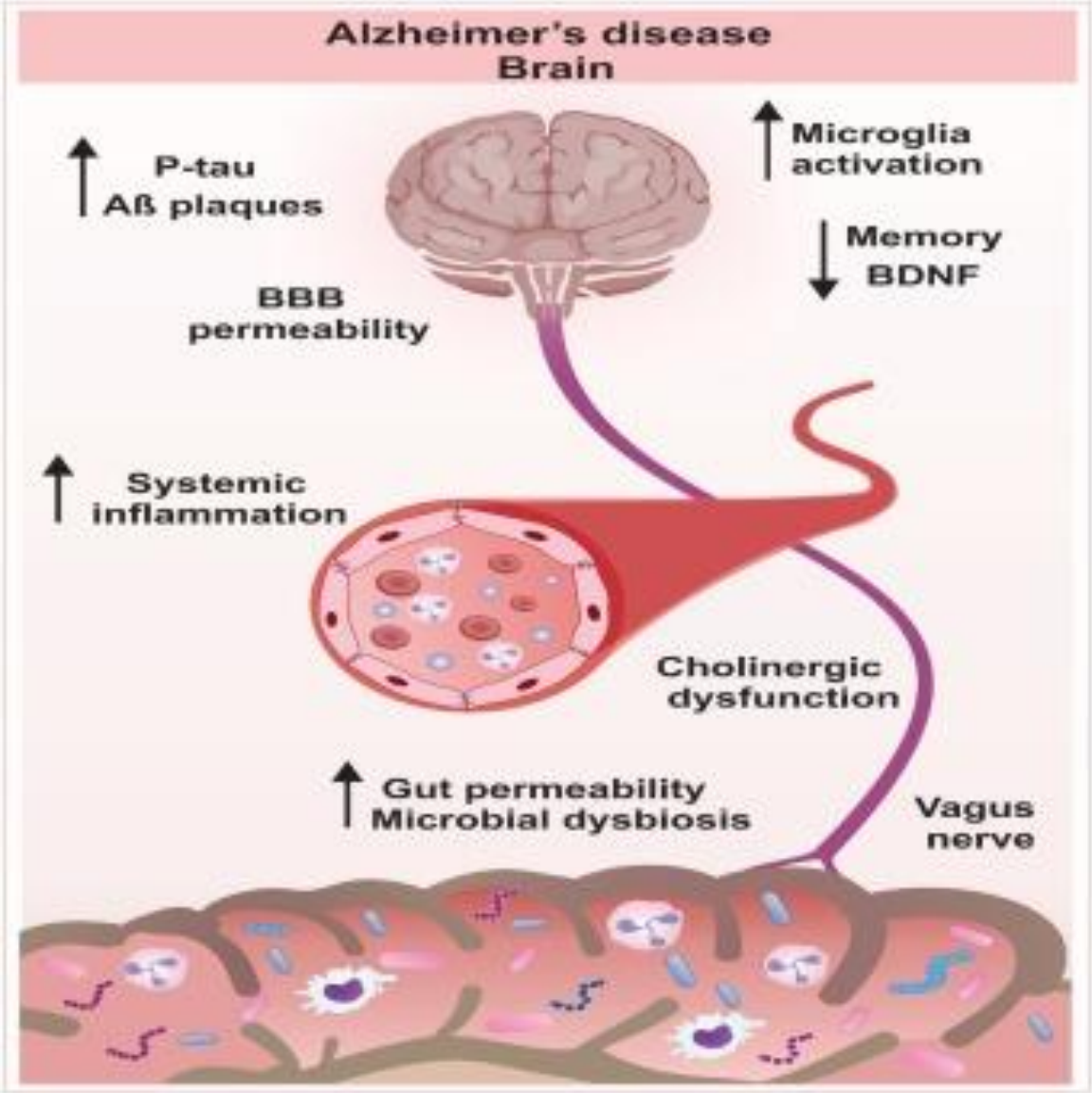
Systemic Inflammation induces changes at the Brain Barriers



Alzheimer's Disease – Systemic Inflammation

Gut – Brain axis

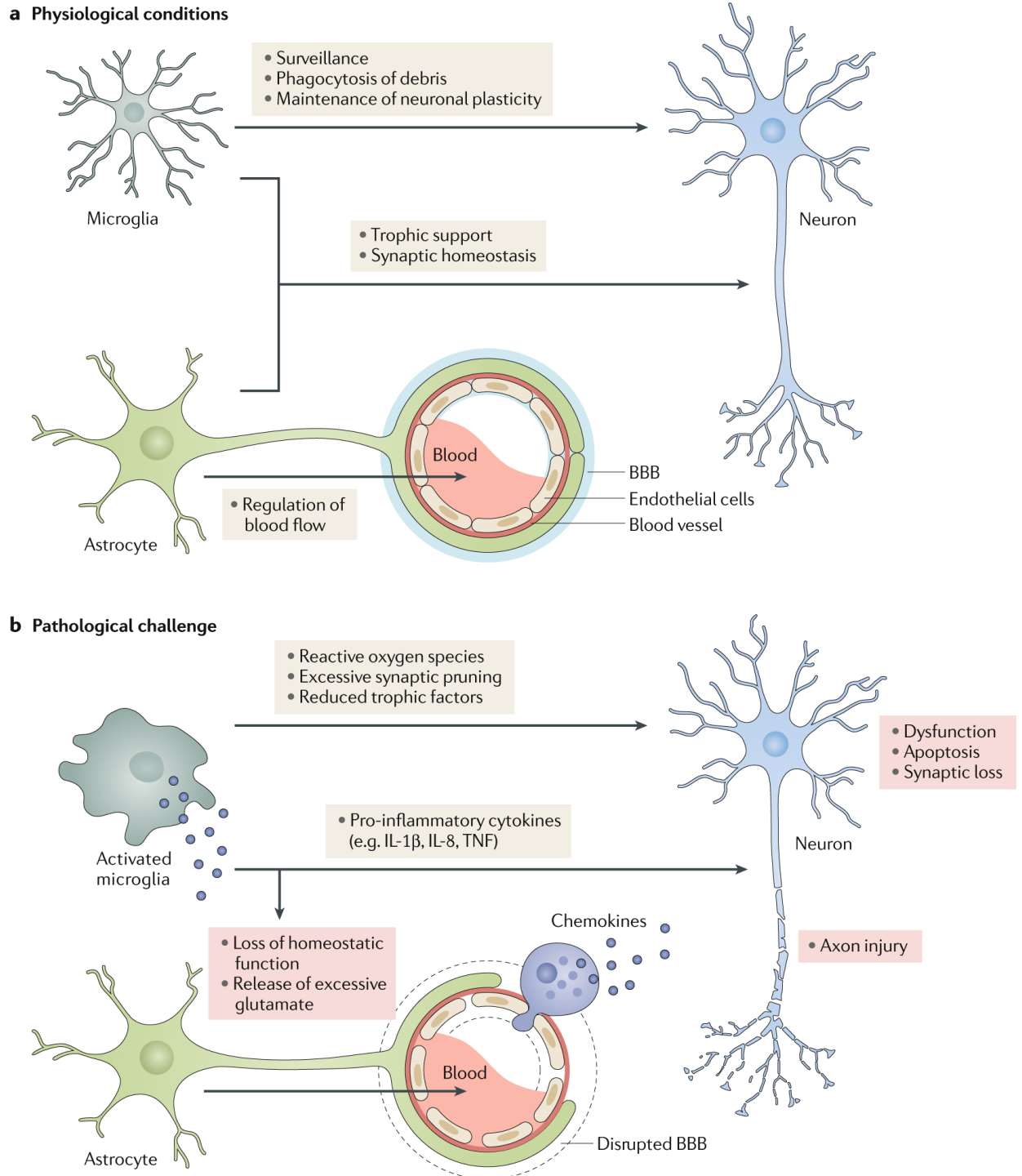
- vagal sensory inputs can modulate microglial state
- activated microglia produce pro-inflammatory molecules and cytokines
- influence on neuroinflammatory state
- vagal efferents sent an inhibitory feedback to the intestine to reduce further cytokine production



Doifode T et al. Pharmacol Res. 2021 Feb;164:105314

Alzheimer's Disease – Systemic Inflammation

- Activated microglia
- Activated astrocytes



Leng, F., Edison, P. Nat Rev Neurol 17, 157–172 (2021)

Parkinson's Disease – Global facts

James Parkinson (1755 – 1824)

Parkinson's home and office

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

153

Parkinson’s Disease – Global facts

- Parkinson’s Disease is a Progressive Neurodegenerative Disease

  - ✓ Insidious onset of symptoms
  - ✓ Progressively deteriorating course
  - ✓ Unknown etiology (genetic risk factors and environmental factors)
  - ✓ Loss of structure and function of neuronal circuits

Parkinson’s Disease – Symptoms

- ✓ Motor symptoms
- ✓ Non-motor symptoms

Parkinson's Disease – Symptoms

- ***Motor symptoms***

  <u>Cardinal features</u> include:

  ✓ Bradykinesia (slowness of movements)

  ✓ Rigidity (increased muscle tone)

  ✓ Resting tremor

  ✓ Postural instability

Parkinson's Disease – Symptoms

- ***Motor symptoms***

  <u>Secondary features</u> include:

  ✓ Hypomimia and glabellar reflexes

  ✓ Dysarthria, dysphagia, sialorrhea

  ✓ Micrographia

  ✓ Shuffling gait, festination, freezing

  ✓ Dystonia

Parkinson's Disease – Symptoms

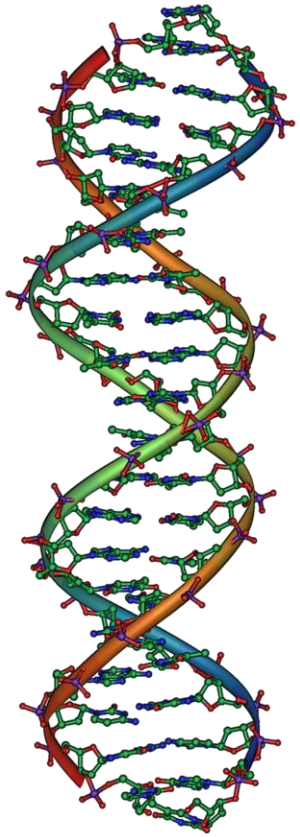
- ***Non-motor symptoms*** *include:*

  - ✓ Autonomic dysfunction
  - ✓ Gastroenterology symptoms
  - ✓ Cognitive dysfunction
  - ✓ Mood and behavioral abnormalities
  - ✓ Sleep disorders
  - ✓ Sensory abnormalities (anosmia, paresthesias, pain)

Parkinson’s Disease – Cause

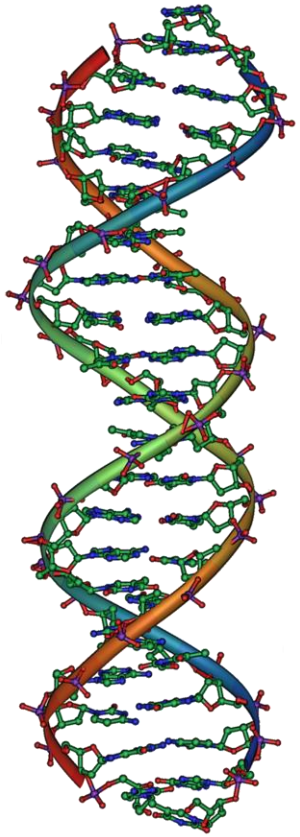
The exact cause of Parkinson's disease is currently unknown

- ✓ Environmental and behavioral factors
- ✓ Genetic factors



Parkinson's Disease – Cause

- ***Genetic factors***



Rare Familial Early Onset PD ***vs*** Common Sporadic Idiopathic PD

Monogenic Forms ***vs*** Complex Polygenic Forms

Parkinson's Disease – Cause

- ***Genetic factors***

  <u>Monogenic Forms</u>

  ✓ Autosomal Dominant or Recessive

  ✓ Loci involved in monogenic forms of PD (Park 1~19)

  ✓ Genes SNCA, PRKN, DJ-1, PINK1, LRRK2, VPS35 and GBA

  ✓ All known monogenic forms of PD explain only 30% of familial cases

Parkinson's Disease – Cause

- ***Genetic factors***

  Polygenic Forms

  ✓ Several susceptibility genes and numerous risk loci

  ✓ Genes SNCA, LRRK2, GBA and MAPT … … …

  ✓ Small proportion of the phenotypic variability has been explained by genetics

  ✓ Combination of many genetic and environmental factors lead to PD

Parkinson's Disease – Cause

- ***Environmental and behavioral factors***

  ✓ Several environmental and behavioral factors ***seem*** to modify the risk of developing PD (inconsistent data)

  ✓ *Increased risk*:

- Heavy Metals (e.g. Fe - Cu - Mn - Hg - Pb)
- Pesticides (e.g. MPTP, 2,4-D, paraquat, permethrin, dieldrin, diquat, maneb, mancozeb, rotenone)
- Illicit Substances (e.g. Amphetamine, Methamphetamine, Cocaine)

Parkinson's Disease – Cause

- ***Environmental and behavioral factors***

  ✓ Several environmental and behavioral factors ***seem*** to modify the risk of developing PD (inconsistent data)

  ✓ *Decreased risk*:

- Coffee
- Smoking
- Physical activity

Parkinson’s Disease – Pathogenetic mechanisms

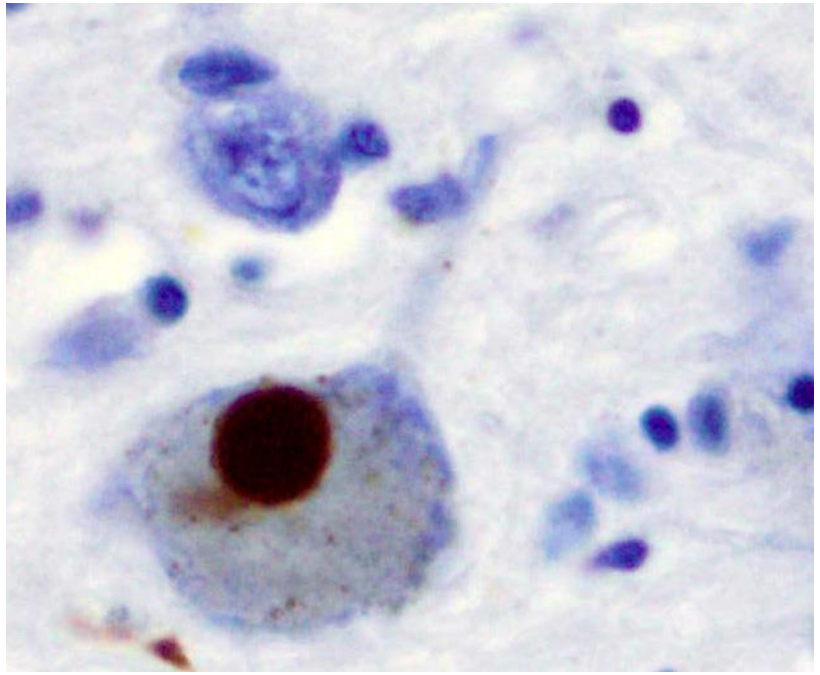
- **Gene-environment interactions** seems to be the underlying cause of idiopathic PD

- These interactions lead to the initiation and propagation of the **pathogenetic cascade**

Parkinson's Disease – Pathogenetic mechanisms

- ***Pathogenetic mechanisms*** *include:*

  - ✓ *Alpha-synuclein* aggregation → fibril formation
  - ✓ Dysfunctional autophagy/*lysosome* pathways
  - ✓ Defective intracellular *trafficking*
  - ✓ Dysregulation of *calcium* signaling
  - ✓ *Mitochondrial* dysfunction
  - ✓ Mitochondrial *oxidative* stress

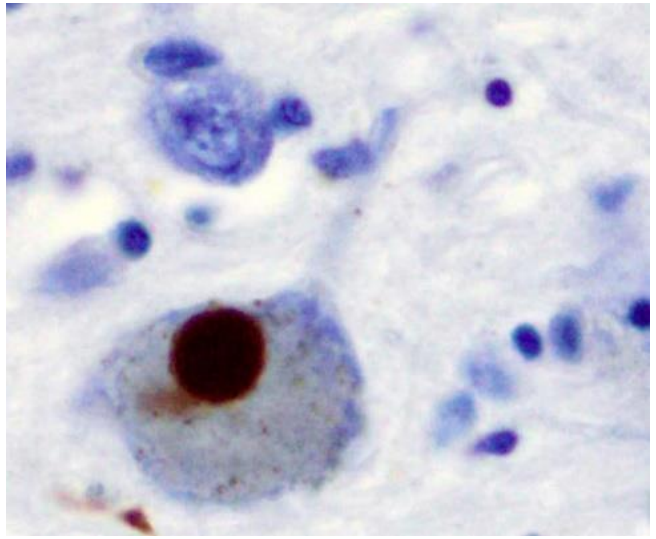


Parkinson's Disease – Pathogenetic mechanisms

- ***Pathogenetic mechanisms*** *lead to:*

  ✓ Protein aggregation → Lewy Body formation

  ✓ Neuronal degeneration and cell death



- Vulnerability of Dopaminergic Neurons in Substantia Nigra pars compacta (SNc)
- Pathology gradually spreads to the whole brain

Parkinson's Disease – Pathogenetic mechanisms

- ***Pathogenetic mechanisms*** *lead to:*

✓ Basal Ganglia Neural Networks

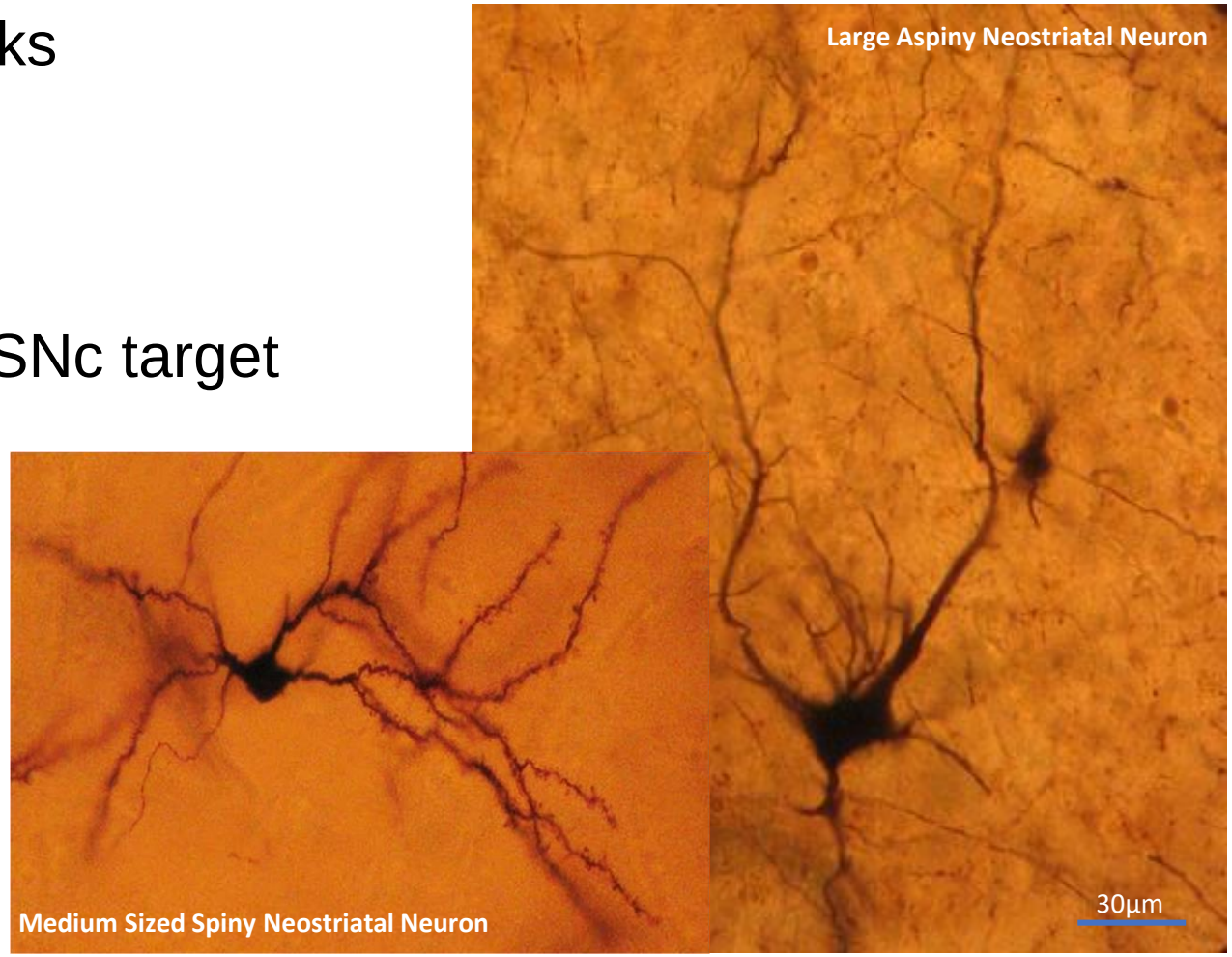
Breakdown

- Dopaminergic fibers from SNc target

mainly Neostriatum

✓ Development of

symptoms



Parkinson's Disease – Systemic Inflammation

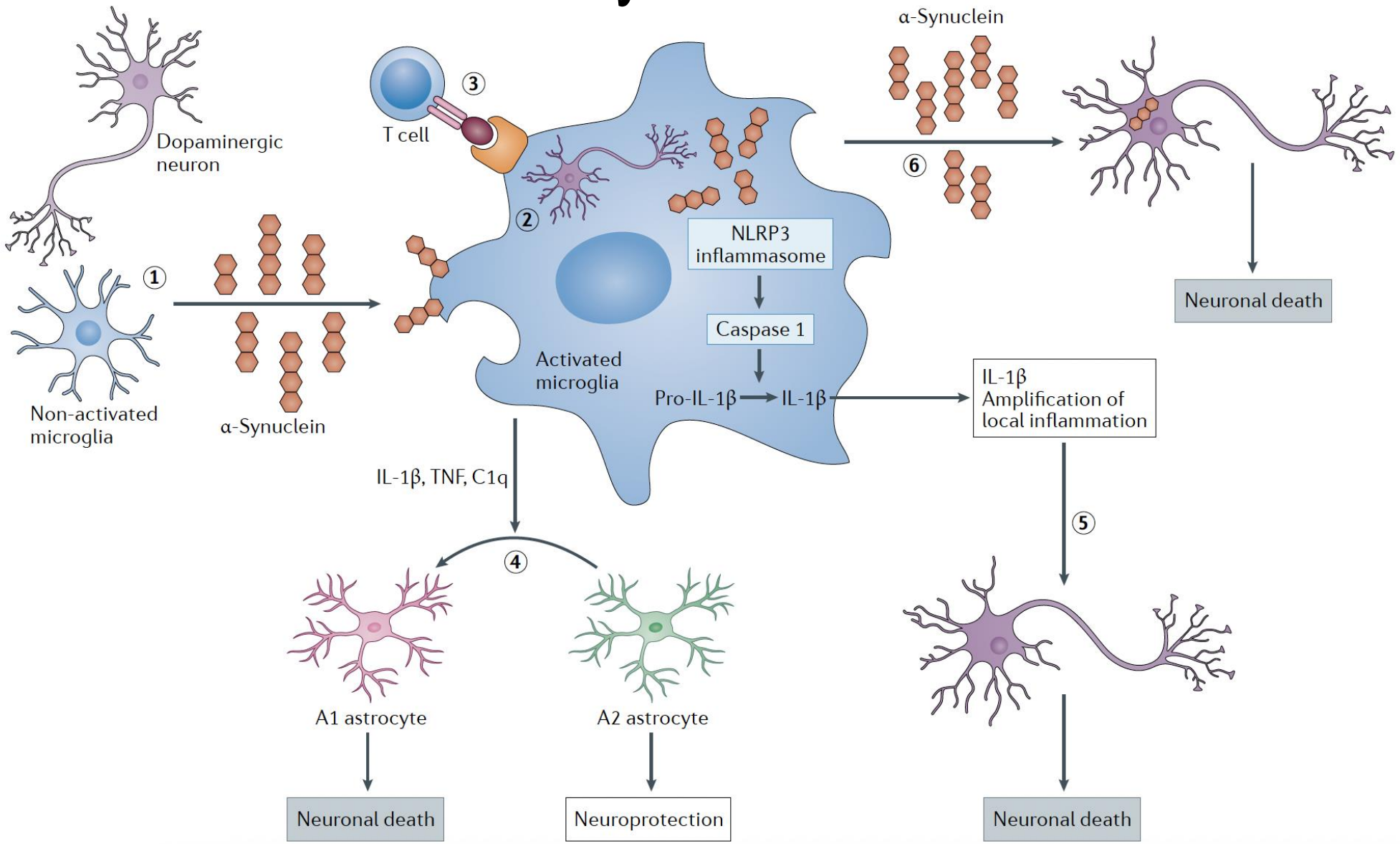
Controversial Results

- ✓ Association of PD with autoimmune diseases
- ✓ Autoantibodies against α-synuclein are present in the serum and CSF of patients with PD
- ✓ Radiolabeled translocator protein (TSPO) as the PET tracer has indicated that microglial activation is higher in patients with PD than in healthy controls

Parkinson's Disease – Systemic Inflammation

- ✓ α-synuclein can activate microglia via the Toll-like receptors 2 and 4 (TLR2 and TLR4)
- ✓ Activated microglia in turn exert toxic effects on dopaminergic neurons
- ✓ Activated microglia produce NO, TNF, and interferons
- ✓ Inflammasome → Caspase 1 → IL-1 → Amplification of Inflammation

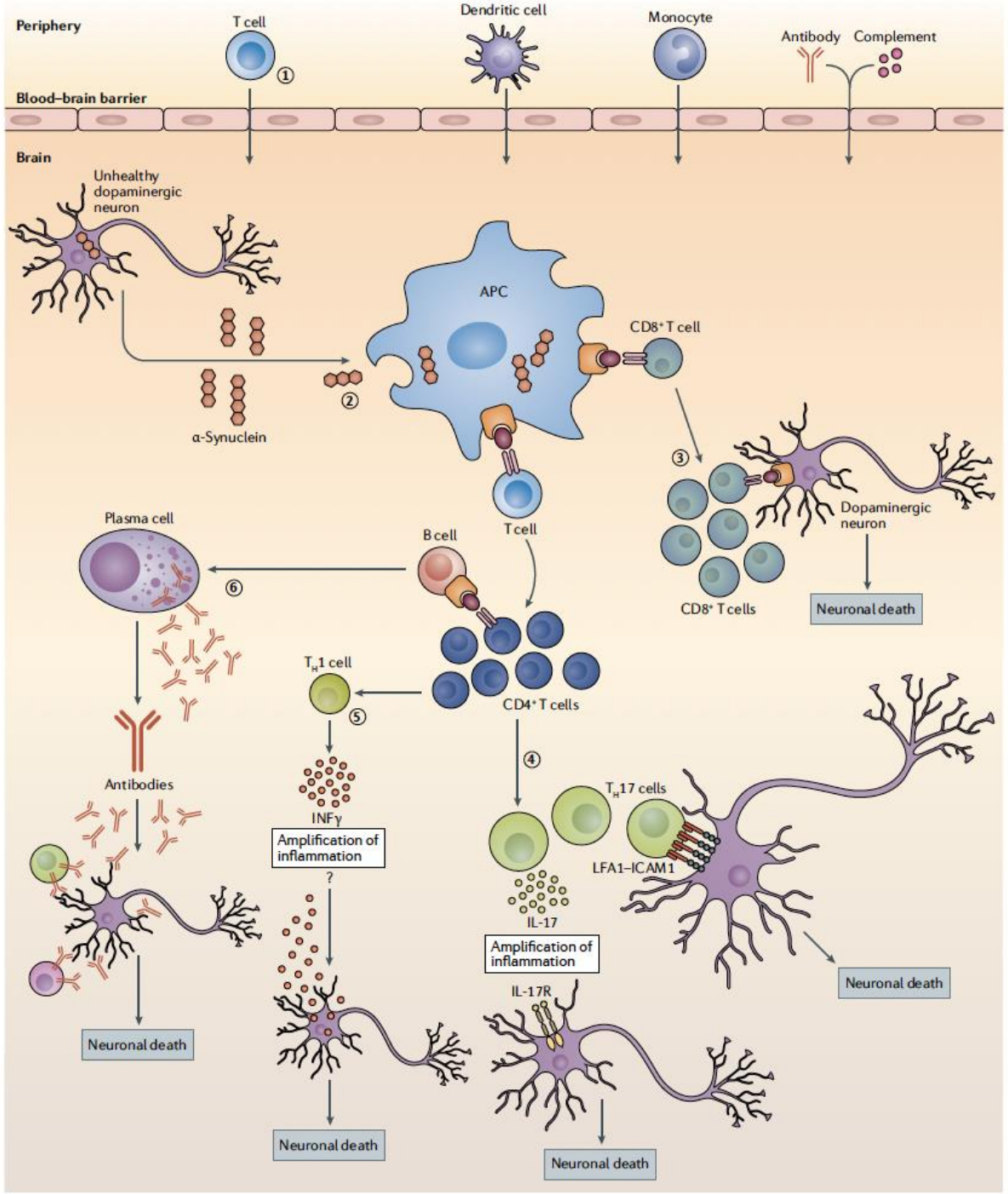
Parkinson's Disease – Systemic Inflammation



Tan, EK.et al. Nat Rev Neurol 16, 303–318 (2020)

Parkinson's Disease – Systemic Inflammation

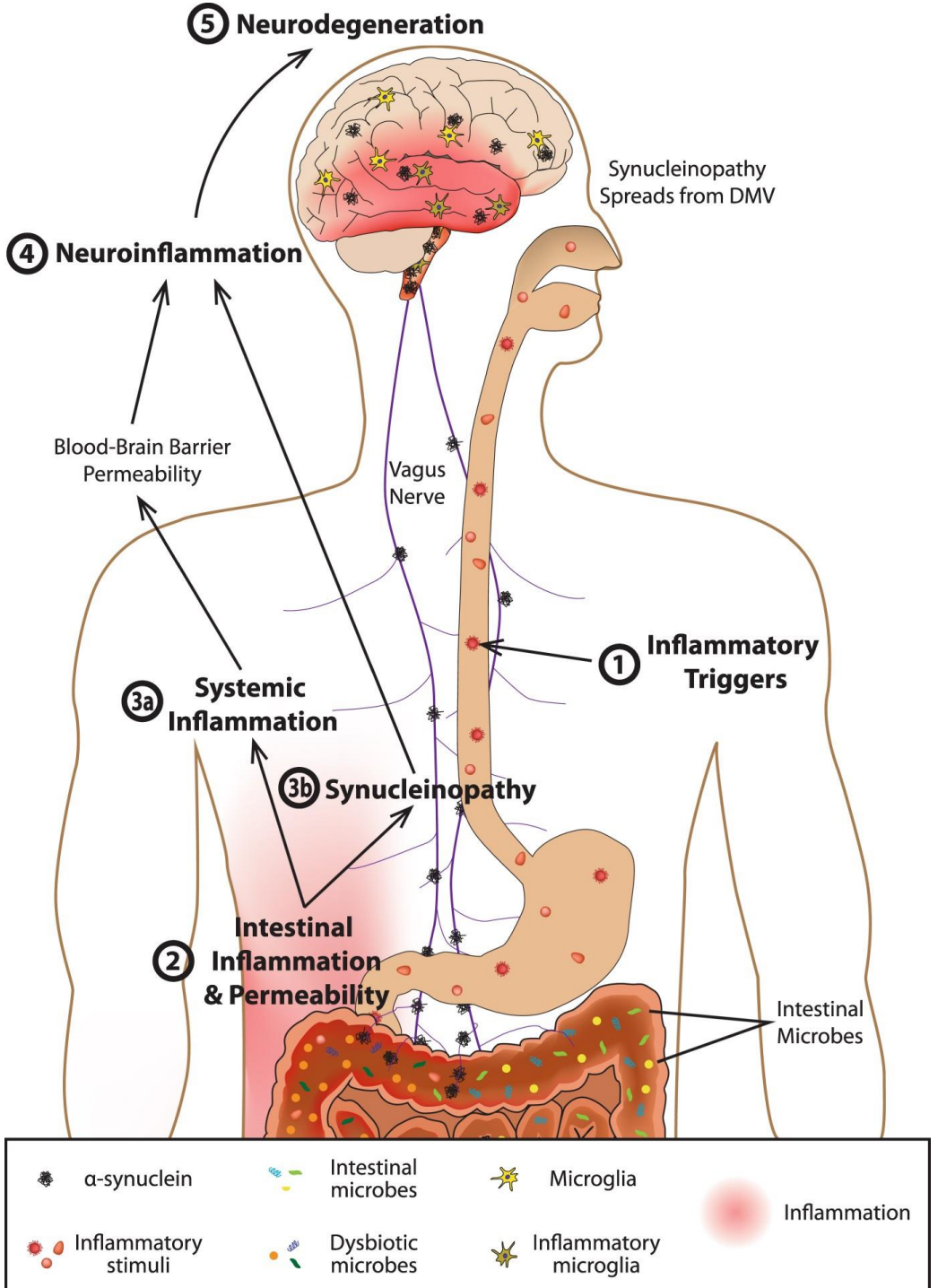
- Humoral immune responses
- Cellular immune responses



Tan, EK.et al. Nat Rev Neurol 16, 303–318 (2020)

Parkinson's Disease – Systemic Inflammation

- ✓ Gut – Brain axis



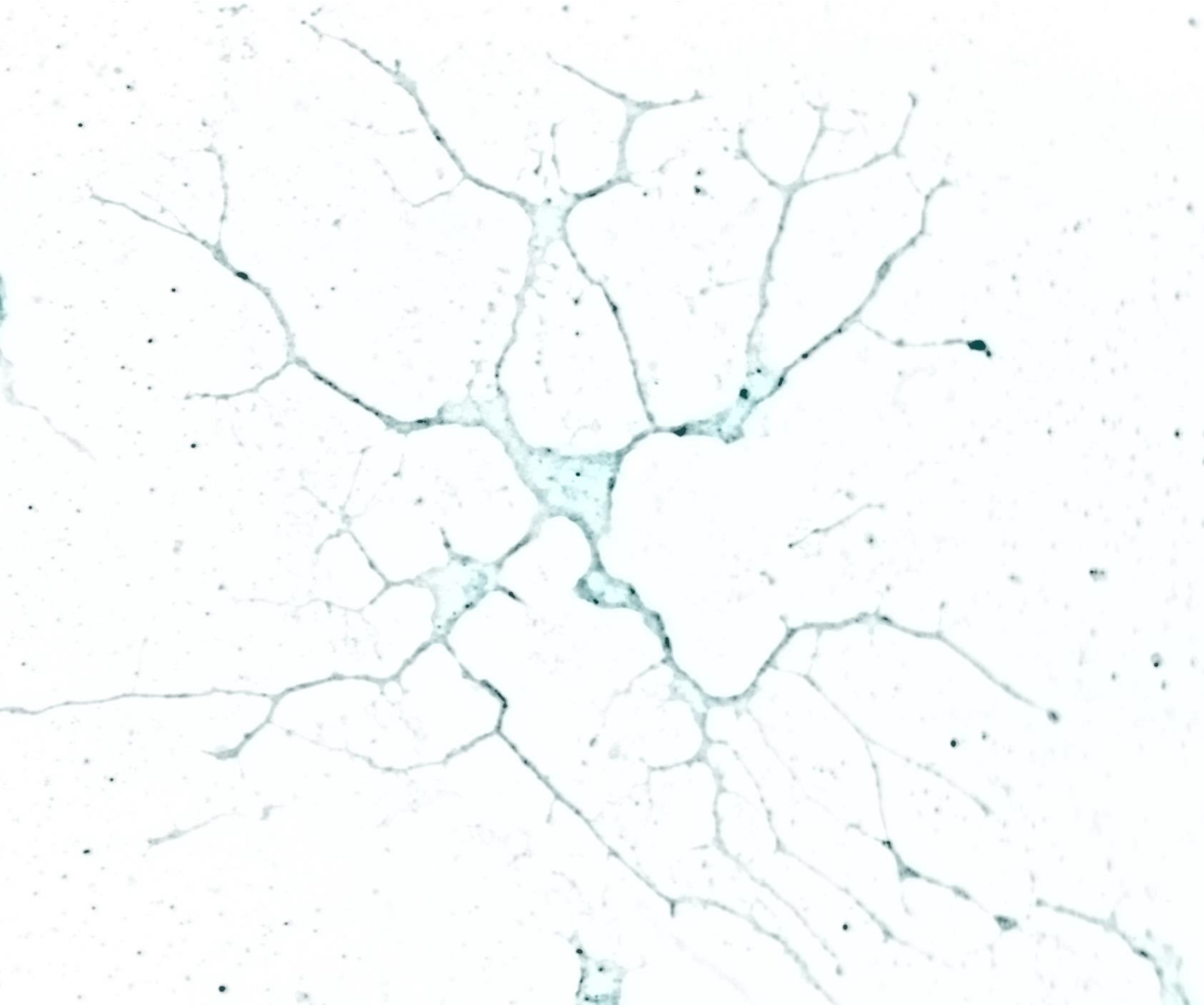
Houser, M.C., Tansey, M. npj Parkinson's Disease 3, 3 (2017)

Degenerative CNS diseases – Systemic Inflammation

- There is a clear link between systemic inflammation and neurodegenerative disorders
- The central role is attributed to microglia activation
- Key factors in these pathways have yet to be discovered
- Immunotherapeutic approaches have potential in neurodegenerative disorders

On going research
Faculty of Medicine, University of Ioannina

- Laboratory of Physiology & Department of Neurology
- Prospective observational study of disease progression in PD
- 40 patients follow up for 2-3 years
- Comparison between digital biomarkers, genetic markers, imaging, clinical evaluation, and inflammatory markers
- Foivos Kanellos, PhD Candidate
  Eleni Kosmidi, PhD Candidate



Thank you !!!