



# Neuroinflammation and Neurodegenerative Disorders

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# Neurodegenerative Disorders (NDDs)

- Broad category of illnesses marked by the gradual degradation of neurons, leading to cognitive deterioration, motor dysfunction, and other neurological symptoms.
  - **Alzheimer's Disease (AD):** Memory loss and cognitive decline driven by A $\beta$  plaques and tau tangles.
  - **Parkinson's Disease (PD):** Tremors and stiffness from dopamine-producing neuron degeneration.
  - **Huntington's Disease (HD):** Involuntary movements and cognitive decline.
  - **Amyotrophic Lateral Sclerosis (ALS):** Progressive muscle weakness and paralysis.

# Neurodegenerative Disorders (NDDs)

- Global Impact: Leading cause of physical and cognitive disability.
- Prevalence: Affects over 15% of the world population.
- General Causes of NDDs: complex interplay of genetic, environmental, and lifestyle factors.

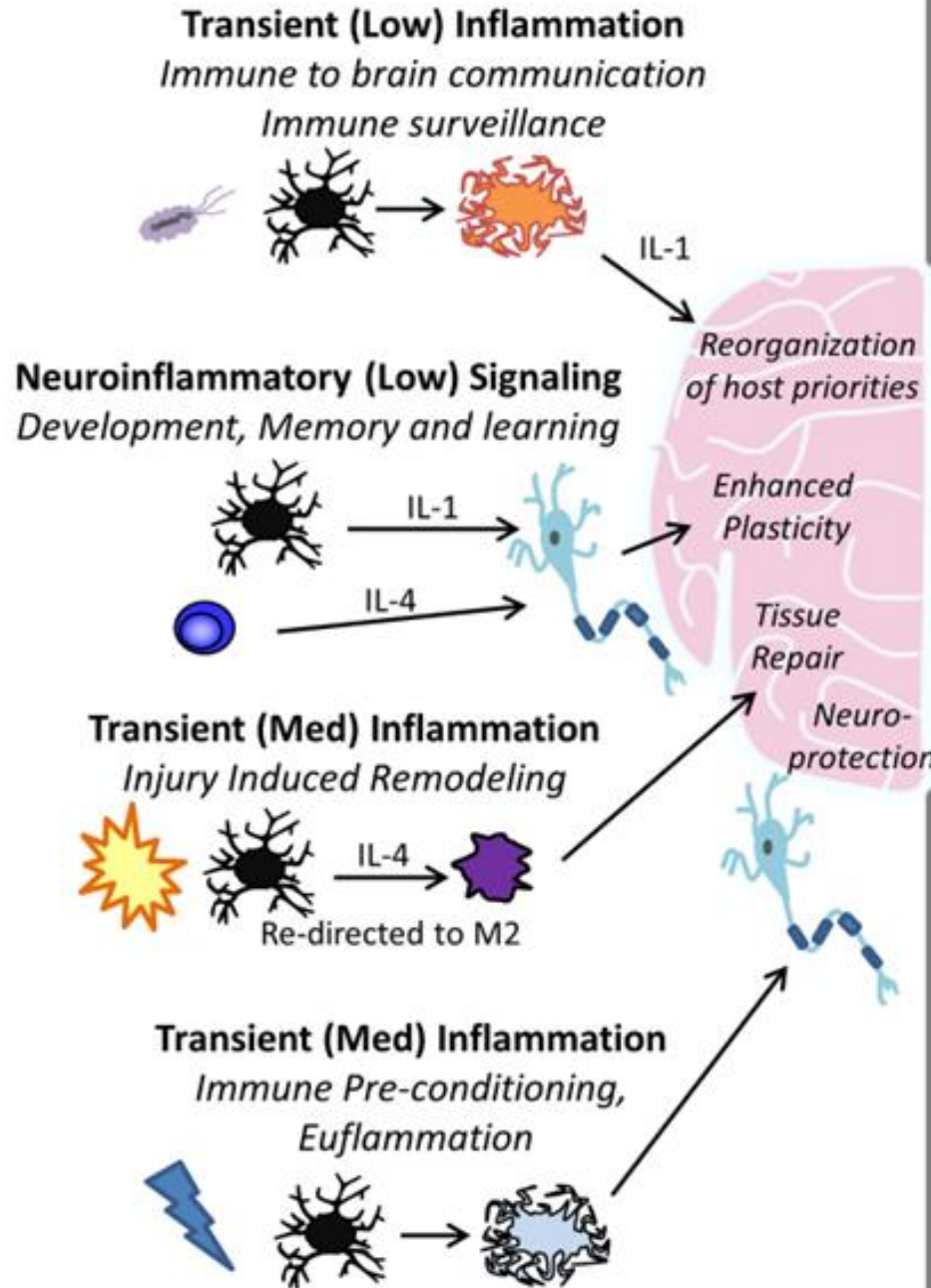
# Neurodegenerative Disorders (NDDs)

- Neuroinflammation is acknowledged to be a significant factor in the progression of neurological disorders, especially chronic NDDs.
- Chronic inflammation in the brain can contribute to the deterioration of neurons and intensify the symptoms associated with these conditions.
- There are many causes of neurodegeneration, but inflammation is a common attribute among all of them.

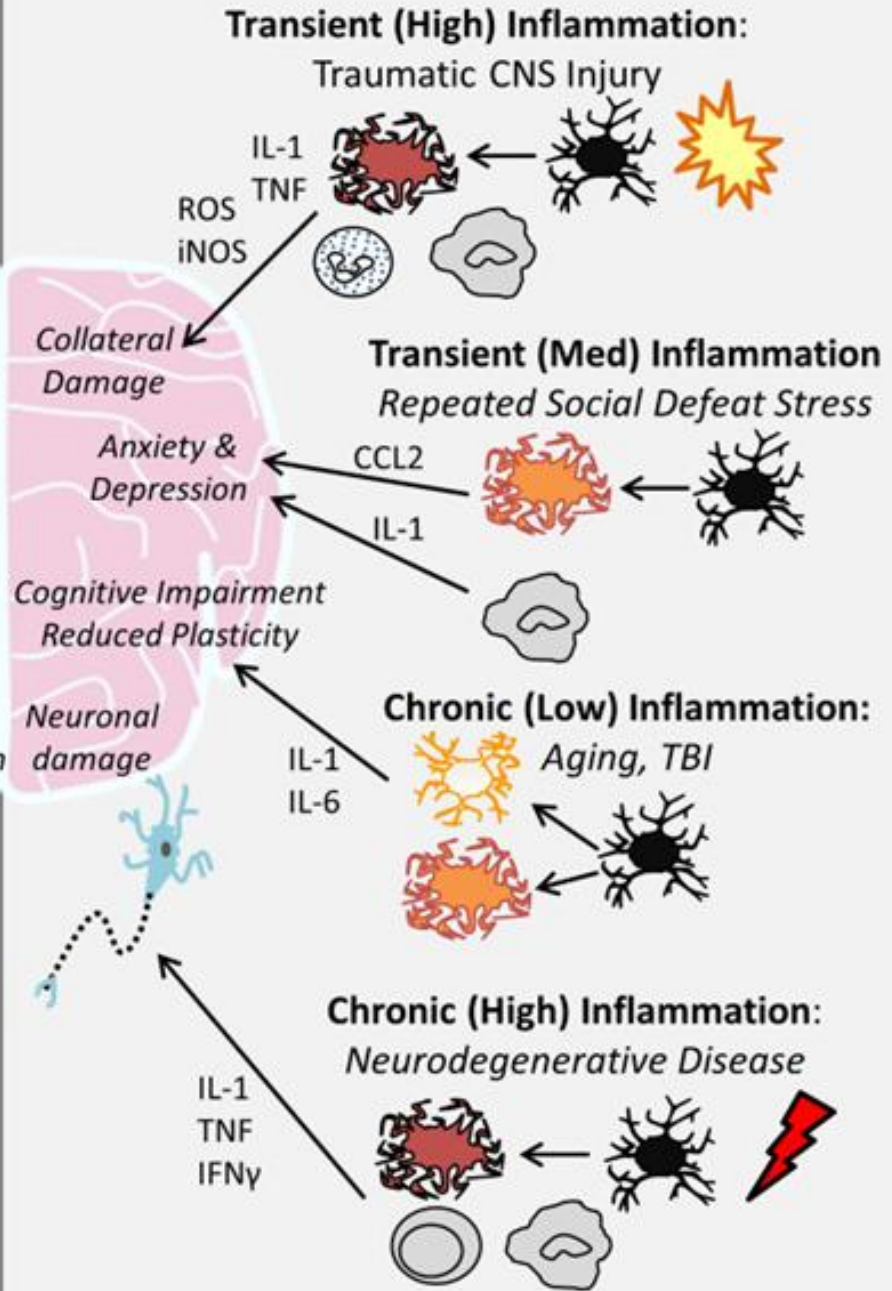
# Neuroinflammation

- Defined as an inflammatory response in the CNS, mediated by the production of cytokines, chemokines, and inflammatory enzymes, which are released by endothelial cells, immune cells from the peripheral system, and resident glial cells in the CNS, such as microglia and astrocytes.

## Positive Aspects of Neuroinflammation



## Negative Aspects of Neuroinflammation



# Neuroinflammation

- Although neuroinflammation has a protective role in defending the brain from harmful agents and assisting in tissue repair, it can become problematic when it is **prolonged or excessive**.
- Factors like genetic mutations, protein aggregation, infections, trauma, and certain drugs can all trigger sustained neuroinflammation, which in turn can hinder regeneration and contribute to neurodegenerative diseases.
- Stress increases pro-inflammatory cytokine production, fueling neuroinflammation. This can worsen conditions like depression, anxiety, and other mental health disorders, further impairing brain function.

# Causes of neuroinflammation

- **Infections and peripheral inflammation:** Viral infections in the CNS, as well as chronic conditions like joint pain or gut inflammation, are significant contributors to neuroinflammation.
- **Autoimmune disorders:** Autoimmune conditions, such as paraneoplastic limbic encephalitis (PLE), show how the immune system can mistakenly attack neural tissues. In cancers like small cell lung cancer, immune cross-reactions with onconeural antigens can damage neural tissue, triggering neuroinflammation.
- **Lifestyle factors:** **Poor diet** can disrupt gut microbiota, alter blood-brain barrier (BBB) permeability, and promote neuroinflammation. **Obesity, metabolic syndrome, and diabetes** accelerate neuronal metabolism, producing ROS that leads to oxidative stress and inflammation.

# Causes of neuroinflammation

- **Stress and sleep deprivation:** **Psychological stress** increases cytokines such as TNF- $\alpha$  and IL-1, contributing to neuroinflammation and conditions like depression and anxiety. Similarly, **sleep deprivation** has been linked to increased neuroinflammation.
- **CNS injuries:** **Brain and spinal cord injuries** lead to significant neuroinflammation, marked by glial activation (microglia and astrocytes), cytokine and chemokine production, immune cell infiltration, and increased BBB permeability. Both penetrating and non-penetrating injuries trigger an acute inflammatory response that is beneficial for repair but harmful if prolonged. Secondary and chronic inflammation after these injuries often leads to long-term complications.

# Neuroinflammation

- Neuroinflammation can even occur without underlying pathology, highlighting the need to better understand its mechanisms for prevention and treatment.

# Glia: central players in neuroinflammation

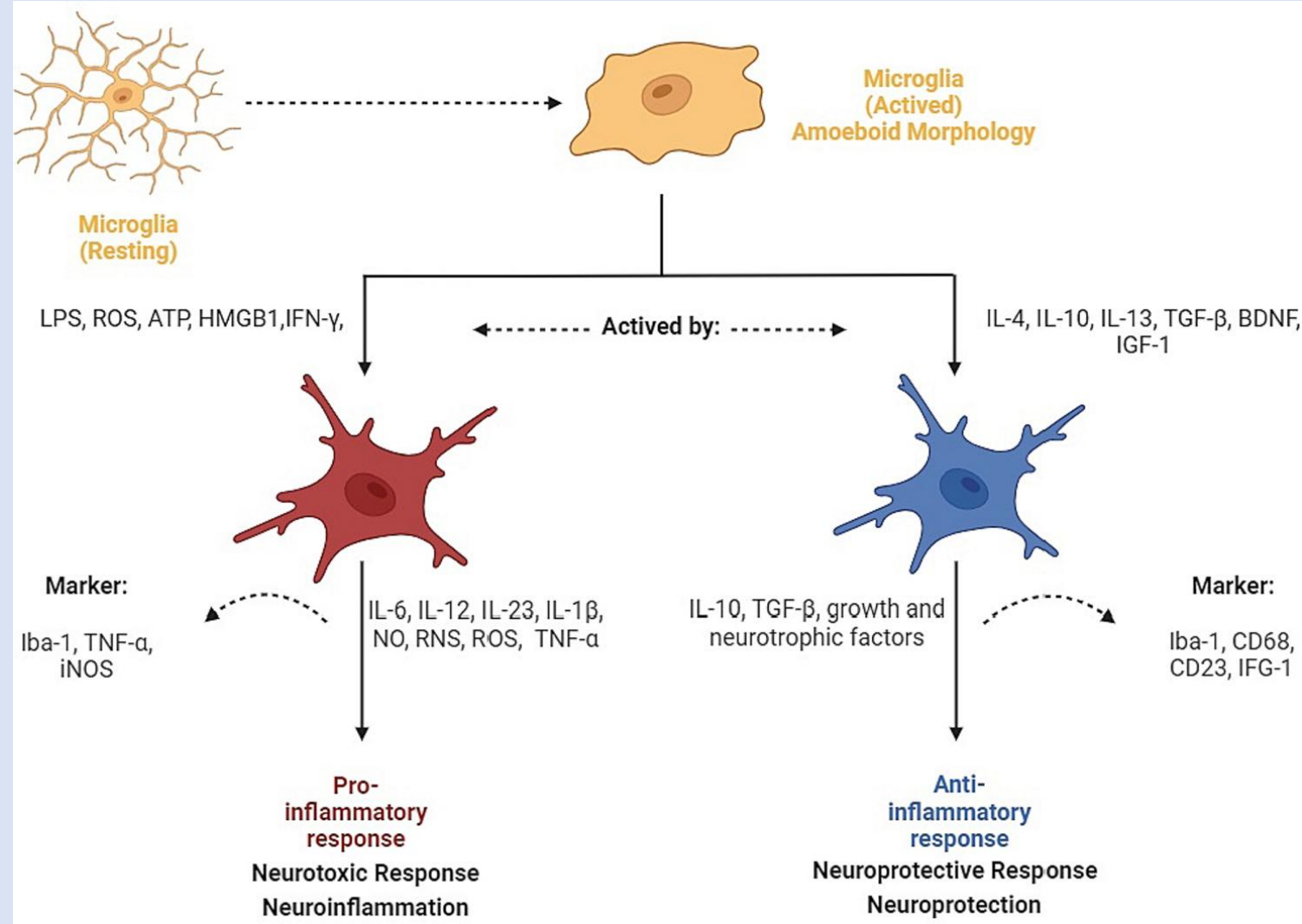
- **Microglia:** “housekeeping cells”
  - Related to macrophages.
  - Constitute the main pool of immune cells within the CNS.
  - It participates in brain development, neuromodulation, synaptic plasticity, and contributes to learning and memory processing.
- **Astrocytes:**
  - Have many different functions.
  - Essential for both the developing and adult brain.
  - Their most prominent role is to maintain BBB

# Microglial Activation Dynamics

Homeostatic State (M2)

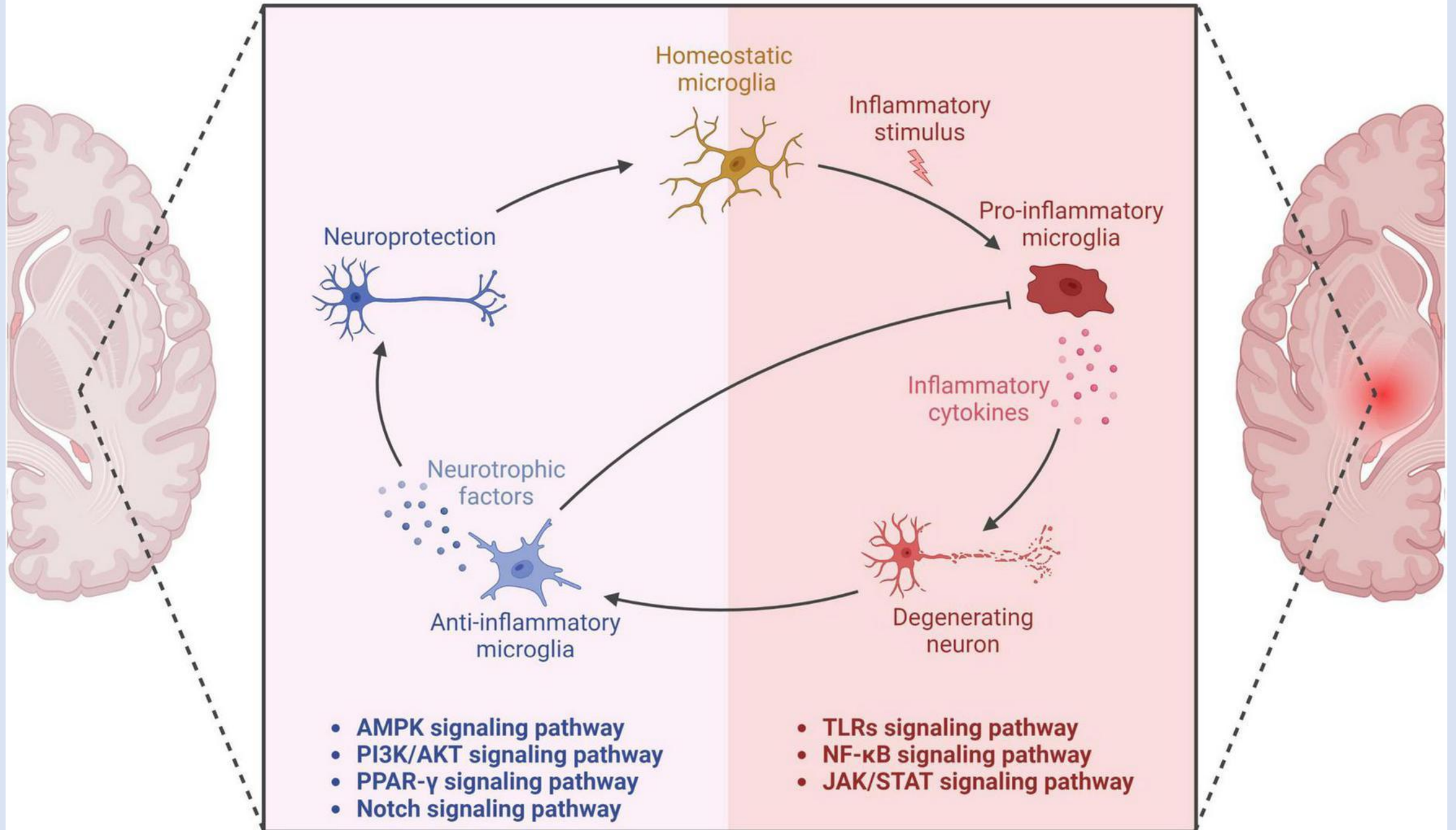
Reactive State (M1)

- Initially, microglia actively phagocytose and clear pathological protein aggregates ( $A\beta$ ,  $\alpha$ -synuclein), releasing anti-inflammatory factors to protect and support neuronal survival.
- Chronic stimulus overrides clearance capacities. Sustained receptor signaling switches microglia to a persistent pro-inflammatory state, releasing neurotoxic  $TNF-\alpha$ ,  $IL-1\beta$ ,  $IL-6$ , and ROS.



M2

M1



# Astrocyte Polarization States

- **Neurotoxic A1 Astrocytes:** Induced by activated microglia-derived cytokines (IL-1 $\alpha$ , TNF). A1 astrocytes lose homeostatic functions and actively release potent mediators that drive neuronal apoptosis.
- **Neuroprotective A2 Astrocytes:** Promoted during transient ischemic or trophic signals. A2 cells upregulate neurotrophic factors (such as BDNF) that facilitate synaptic regeneration and cell survival.
- **Glial Cross-Talk:** In all chronic NDDs, the feedback loop between reactive microglia and neurotoxic astrocytes amplifies and sustains tissue injury over time.

Release of aggregated pathogenic proteins  
(amyloid- $\beta$ , tau,  $\alpha$ -synuclein, mSOD1, TDP-43)  
in neurodegenerative diseases

Induce microglia toward  
pro-inflammatory phenotype

Induce astrocytes toward  
pro-inflammatory phenotype

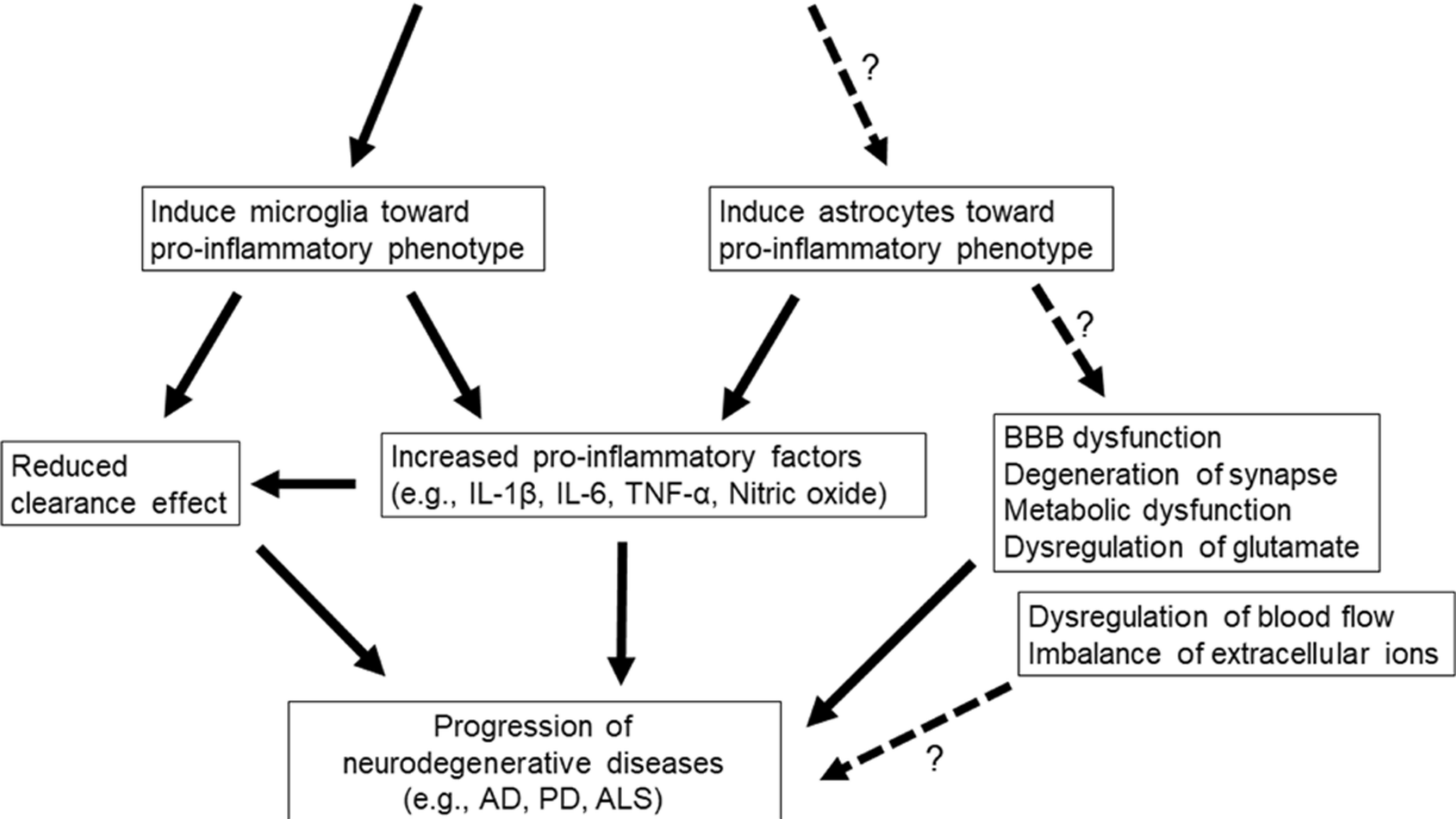
Reduced  
clearance effect

Increased pro-inflammatory factors  
(e.g., IL-1 $\beta$ , IL-6, TNF- $\alpha$ , Nitric oxide)

BBB dysfunction  
Degeneration of synapse  
Metabolic dysfunction  
Dysregulation of glutamate

Dysregulation of blood flow  
Imbalance of extracellular ions

Progression of  
neurodegenerative diseases  
(e.g., AD, PD, ALS)



# The impact of neuroinflammation

- In diseases like multiple sclerosis (MS), chronic inflammation leads to demyelination and axonal loss, contributing to progressive disability.
- Although neuroinflammation initially serves a protective role, chronic and excessive activation in conditions like NDDs leads to significant neurological damage and disability.
- The activation of microglia and astrocytes, along with the release of **cytokines, chemokines, and neuroactive substances**, enhances neuronal excitability and increases pain sensitivity. As a result, the interaction between the nervous and immune systems plays a key role in amplifying pain, driving neuroplastic changes, and contributing to chronic pain, as well as its emotional and cognitive impacts.

# Disease-Specific Pathology

The Key Inflammatory  
Pathways in Major  
Neurological Disorders



# Alzheimer's Disease: A $\beta$ & Tau Cycle

## Amyloid & Tau Triggering

- Extracellular A $\beta$  aggregates stimulate microglial TLR4 and RAGE receptors → inflammatory signaling cascades promote kinases → Tau-hyperphosphorylation and formation of neurofibrillary tangle, microglial activation, and neurotoxicity.

## The Chronic Loop

- As cortical and hippocampal neurons die, they spill intracellular DAMPs into the surrounding parenchyma. This consistently reactivates neighboring microglia, sustaining a chronic inflammation and neurodegenerative loop.

# PD Dopaminergic Neurodegeneration



## Aggregated $\alpha$ -Synuclein

Misfolded  $\alpha$ -synuclein is released into the synaptic space, directly triggering microglial receptors and initiating neuroinflammation.

## Astrogliosis

Reactive microglial signals drive astrocyte conversion to the neurotoxic A1 phenotype, releasing excessive pro-inflammatory cytokines.



## Selective Cell Death

High oxidative stress and localized cytokine storms selectively destroy dopaminergic neurons in the substantia nigra pars compacta.

# Potential treatments and prevention

- To reduce neuroinflammation, a customized, integrated approach is needed that includes:
  - Medication
  - Non-pharmacological lifestyle modifications
  - Natural therapies targeting inflammation.
- Targeting microglia phenotypes to reduce harmful pro-inflammatory effects and boost neuroprotective anti-inflammatory activities may offer promising therapeutic options.

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# Thank you

