COUNCIL ON DIAGNOSIS AND INTERNAL DISORDERS

Faces of neuroinflammation: a closer look at the glial system

2024 CDID Symposium on Mental Health

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Case Study: 18 y/o female

Diagnosed with cerebellar ataxia 4 years prior to first visit. Just prior to the onset of symptoms, she reported injury on the soccer field

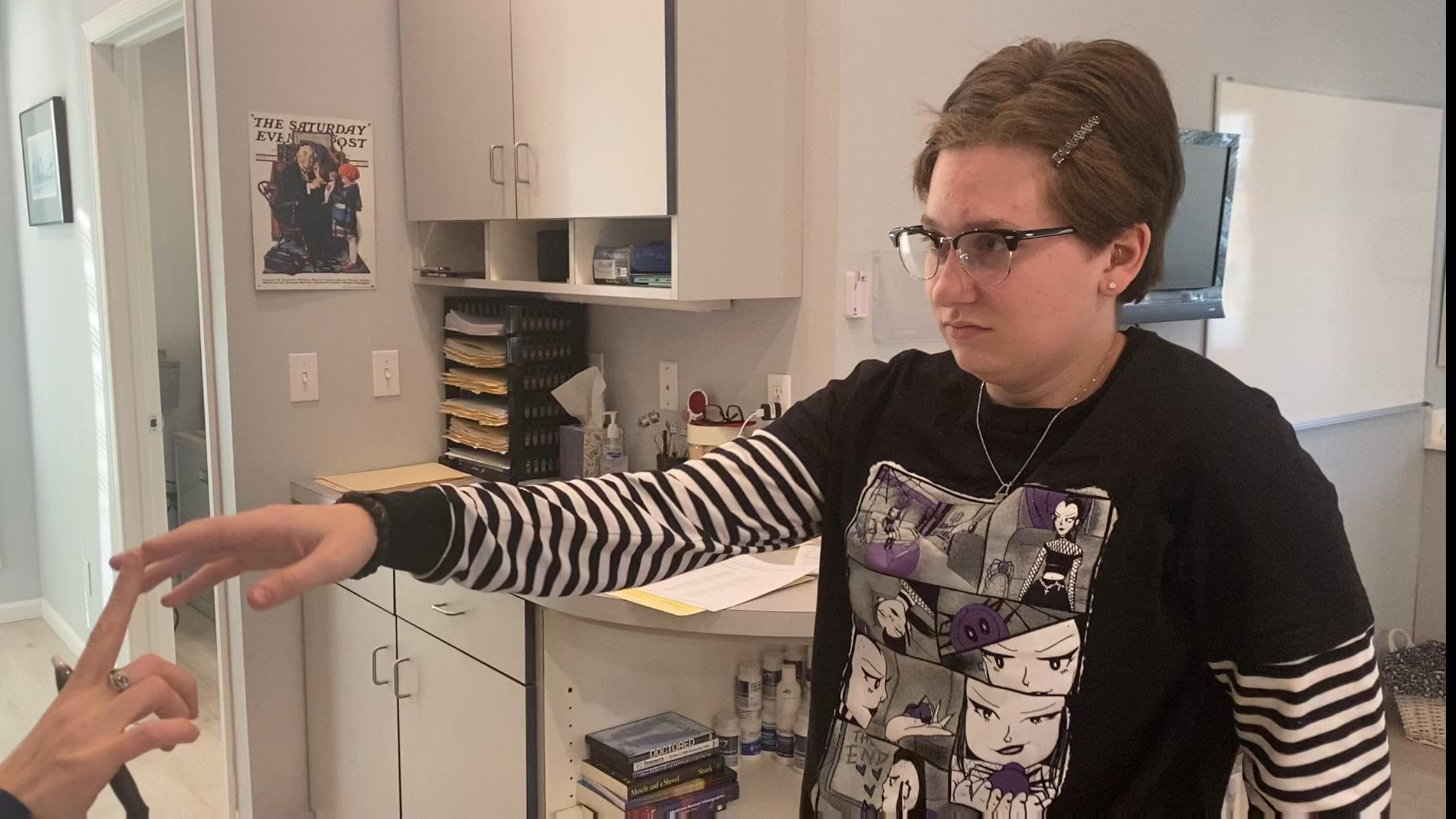
Multiple neurologist appointments with meds prescribed which led to further anxiety/depression – list the meds with side effects

Condition deteriorated to migraine headaches, tics, seizures and episodes of passing out. The patient was confined to a wheelchair or walker, depending upon the day

Had to leave public school

She received upper cervical care, which had a significant impact in reducing her migraine headaches. The upper cervical chiropractor referred her to me.

Patient reports chronic constipation since birth


THE SATURDAY
THE END

Case report:

81 y/o female

Movement disorder of unknown origin began 9 months prior to first visit

Patient reports several episodes per week lasting for minutes to hours.

Patient/family concerned about dementia

Faces of Neuroinflammation Outline

- Microglia activation
- Neurophysiology
- Signs and symptoms
- Conditions
- Clinical web
- Cases

Faces of Neuroinflammation Outline

- **Microglia activation**
- Neurophysiology
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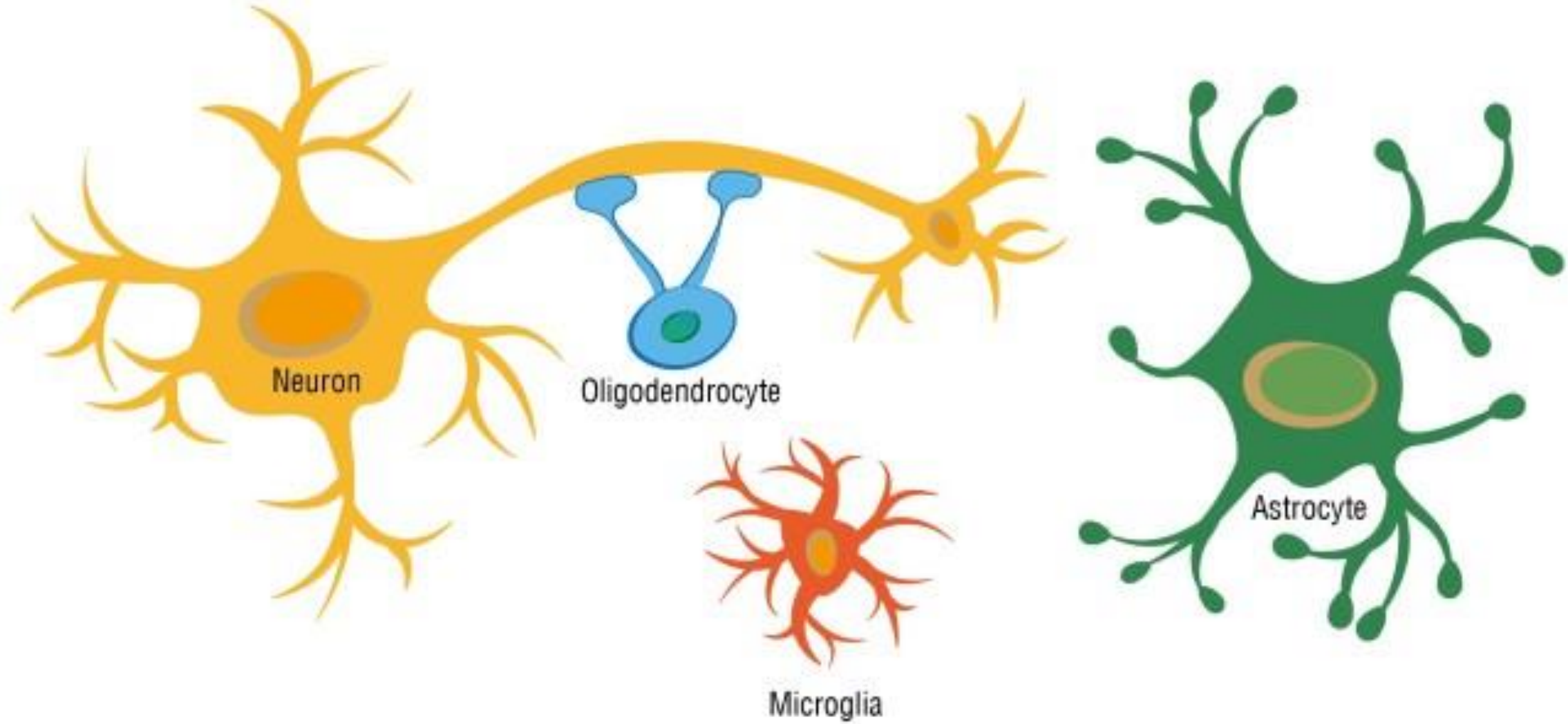
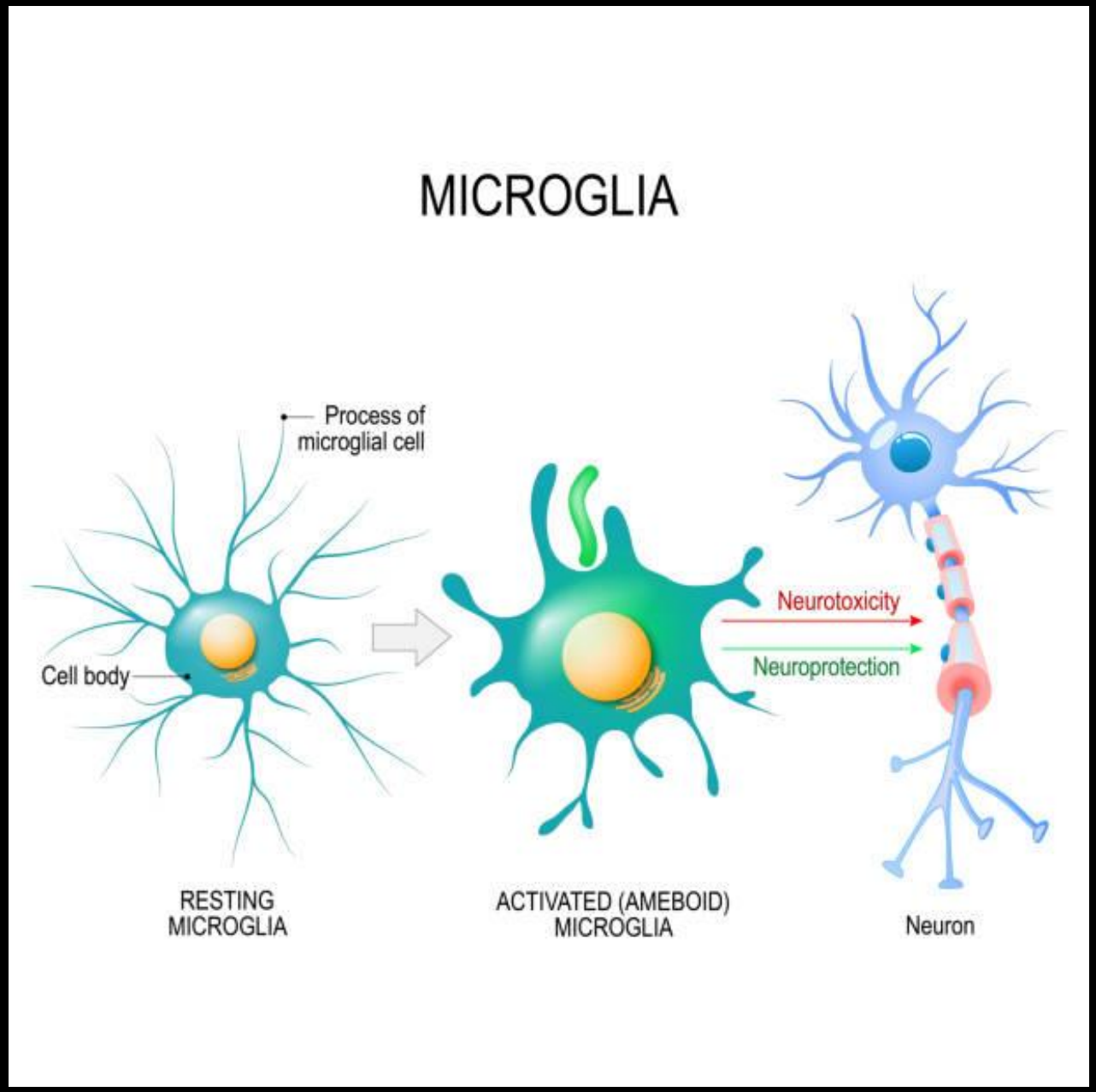
The Glia system: The “glue”





What is Microglia Activation

- The inflammatory response mediated by the brain's resident immune cells, microglia.

Microglia activation

"Microglia are activated by pathological states in the CNS, such as injury, ischemia, and infection, and produce pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α."

Mediated Inflammation in Microglia Contributes to Spared Nerve Injury (SNI)-Induced Pain Initiation. J Neuroimmune Pharmacol. 2022 Dec;17(3-4):453-469

Microglia activation

"Microglia are direct responders to both IL-6 and IFN-α"

The cytokines interleukin-6 and interferon-α induce distinct microglia phenotypes. *J Neuroinflammation* **19**, 96 (2022).

Microglia activation

In acute lesions the peak of microglial activation occurs 2-3 days post insult, but if the pathological stimulus persists microglial activation continues[9].

MNeuropathological imaging: in vivo detection of glial activation as a measure of disease and adaptive change in the brain. *Brit. Med. Bul.* 65, 121–131 (2003).

Microglia activation

Microglia can become chronically activated by either a single stimulus (LPS) or multiple stimuli exposures to result in cumulative neuronal loss with time.

Lull ME, Block ML. Microglial activation and chronic neurodegeneration. Neurotherapeutics. 2010 Oct;7(4):354-65.

Physical threats
(injury, infections, trauma)

Lifestyle
(Standard American Diet, poor sleep, smoking, alcohol, stress, lack of exercise)

Environmental Pollutants or irritants
(chemicals, toxins)

Ongoing Stimulus

Acute Inflammation
(Innate Immunity)

Chronic Inflammation
(Adaptive Immunity)

Healthy Inflammatory Response

Local immune surveillance
Immune cells migrate to site of injury
Neutralizing pathogens
Clearance of local debris and tissue repair
Enhanced synaptic plasticity
Neuroprotection

Chronic Inflammation

Systemic Inflammation ->Increased gut & BBB permeability
Activation of microglia --> perpetuation of inflammatory response
Anxiety & Depression, Metabolic Dysfunction
Reduced neuroplasticity, Neurodegenerative Diseases

Microglia activation

Activation of microglia is a hallmark of brain pathology

Microglial activation and its implications in the brain diseases. Curr Med Chem. 2007;14(11):1189-97

Microglia activation

"It is now generally acknowledged that all CNS disorders are characterized by microglial activation"

Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. Int J Environ Res Public Health. 2011 Jul;8(7):2980-3018. Kraft AD, Harry GJ.

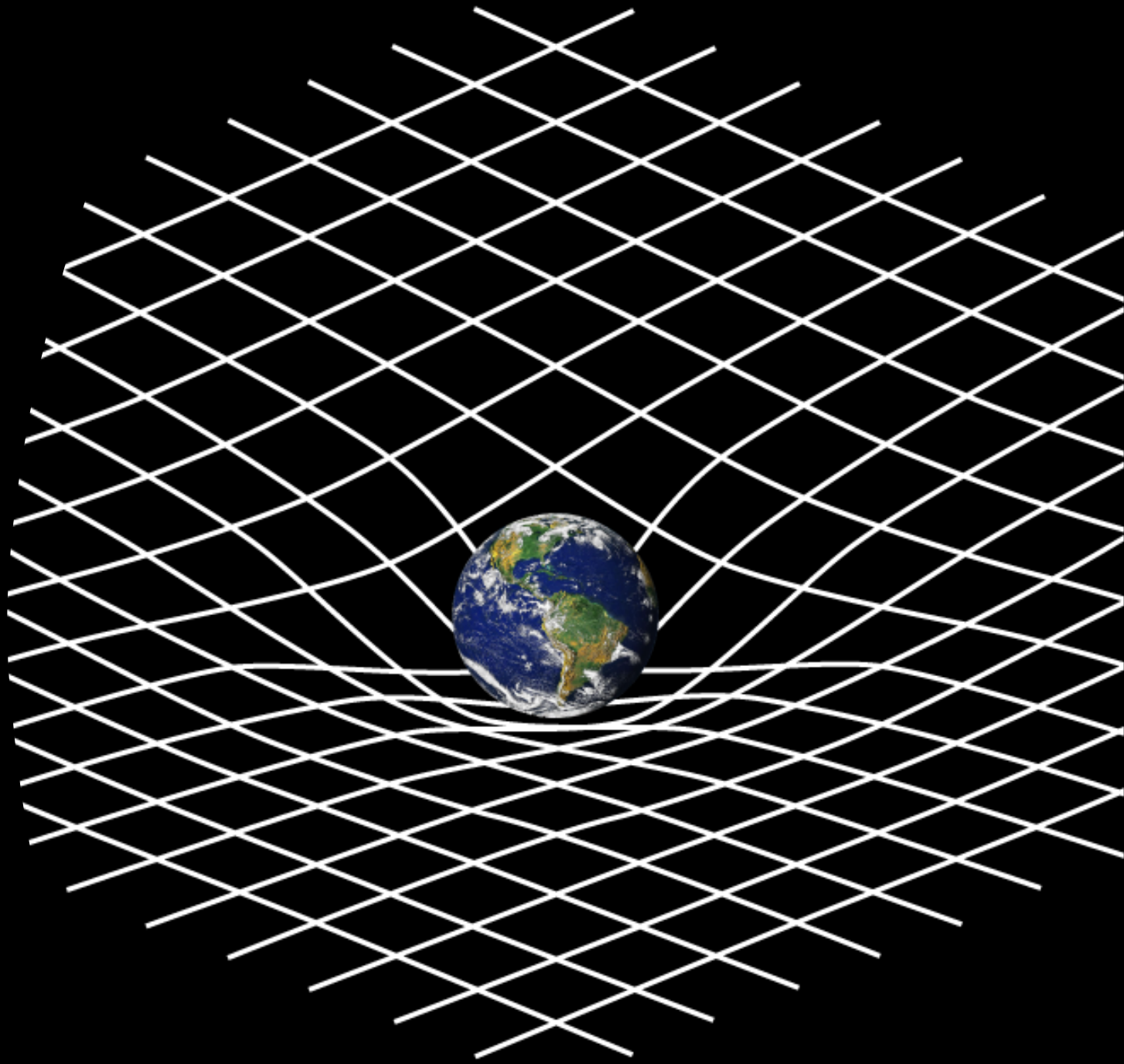
Microglia activation

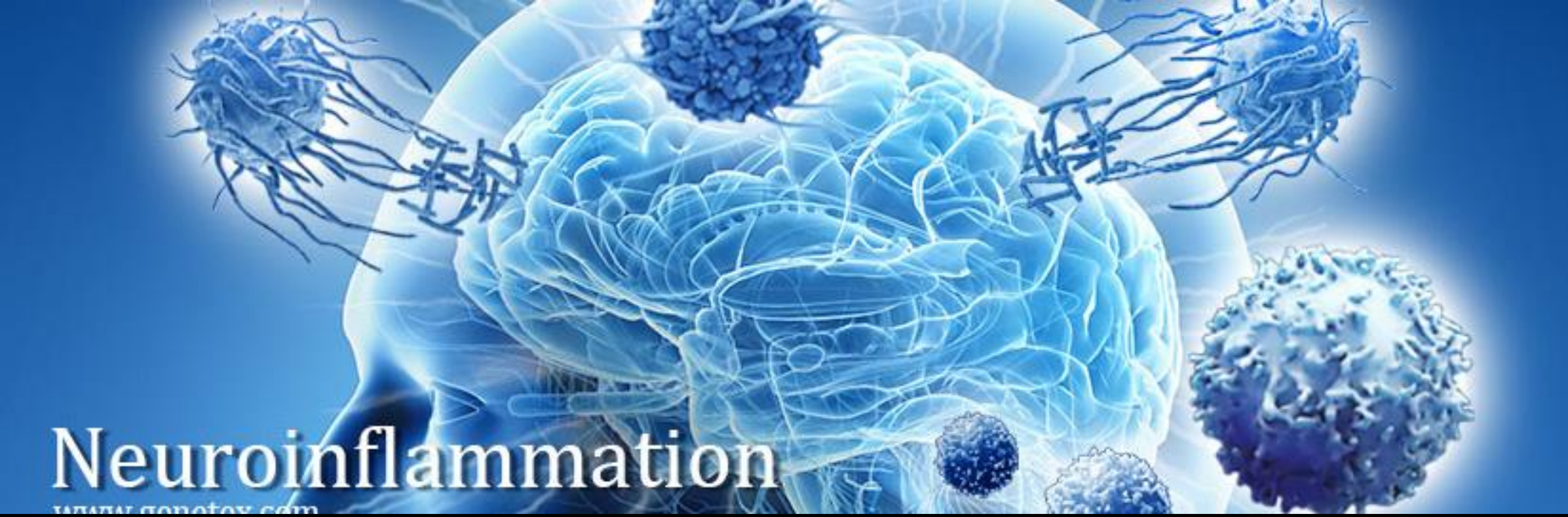
"the progression and resolution of many diseases is contingent, in part, on the activity of microglia."

Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. Int J Environ Res Public Health. 2011 Jul;8(7):2980-3018. Kraft AD, Harry GJ.

Microglia activation

Is it a unifying theory?





3 common complaints

- Fatigue (mental activity)
- Brain fog
- Depression

History: Functional complaints

- Fatigue
- Brain fog
- Poor memory
- Inability to handle stimulation
- Poor brain endurance
- A need for excessive sleep
- Inability to focus or concentrate

History: Diagnosed conditions

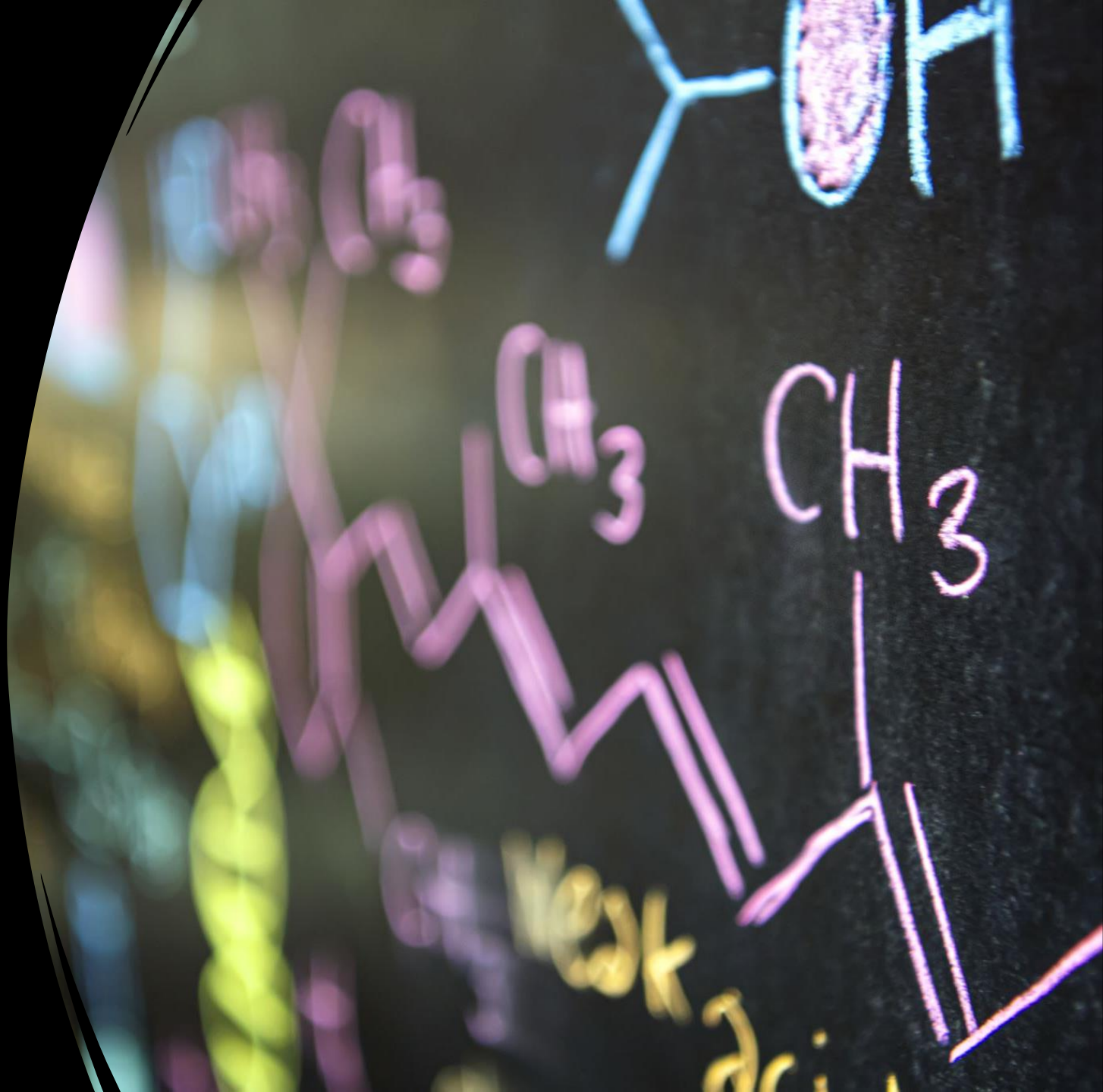
- Depression
- Anxiety
- Chronic fatigue syndrome
- Fibromyalgia
- Chronic pain syndrome
- Stroke
- Neurodegenerative disease (AD, PD)
- PTSD
- Autism
- ADHD

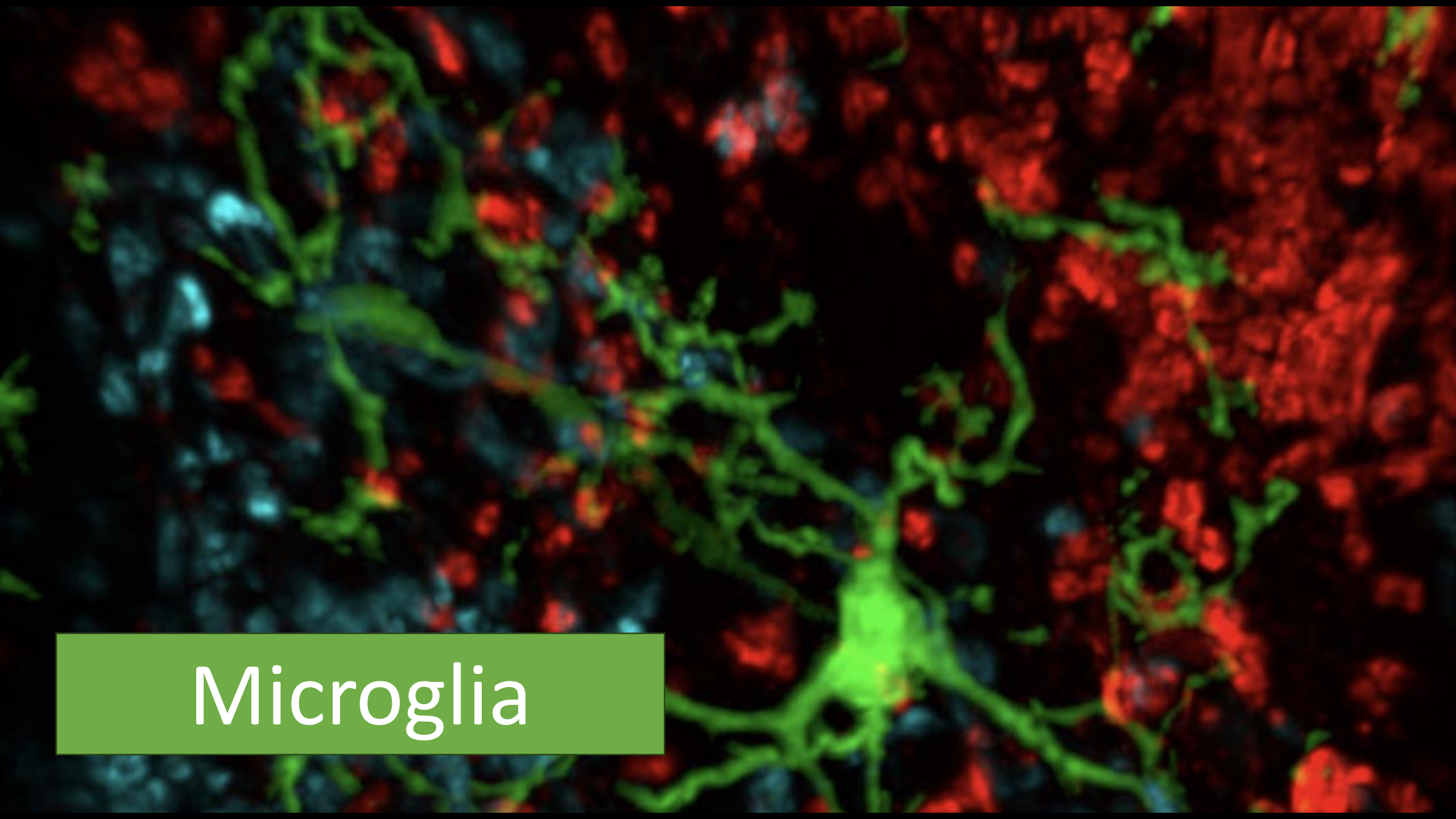
Faces of Neuroinflammation Outline

- Microglia activation
- **Neurophysiology**
- Signs and symptoms
- Conditions
- Clinical web
- Cases

Neurophysiology

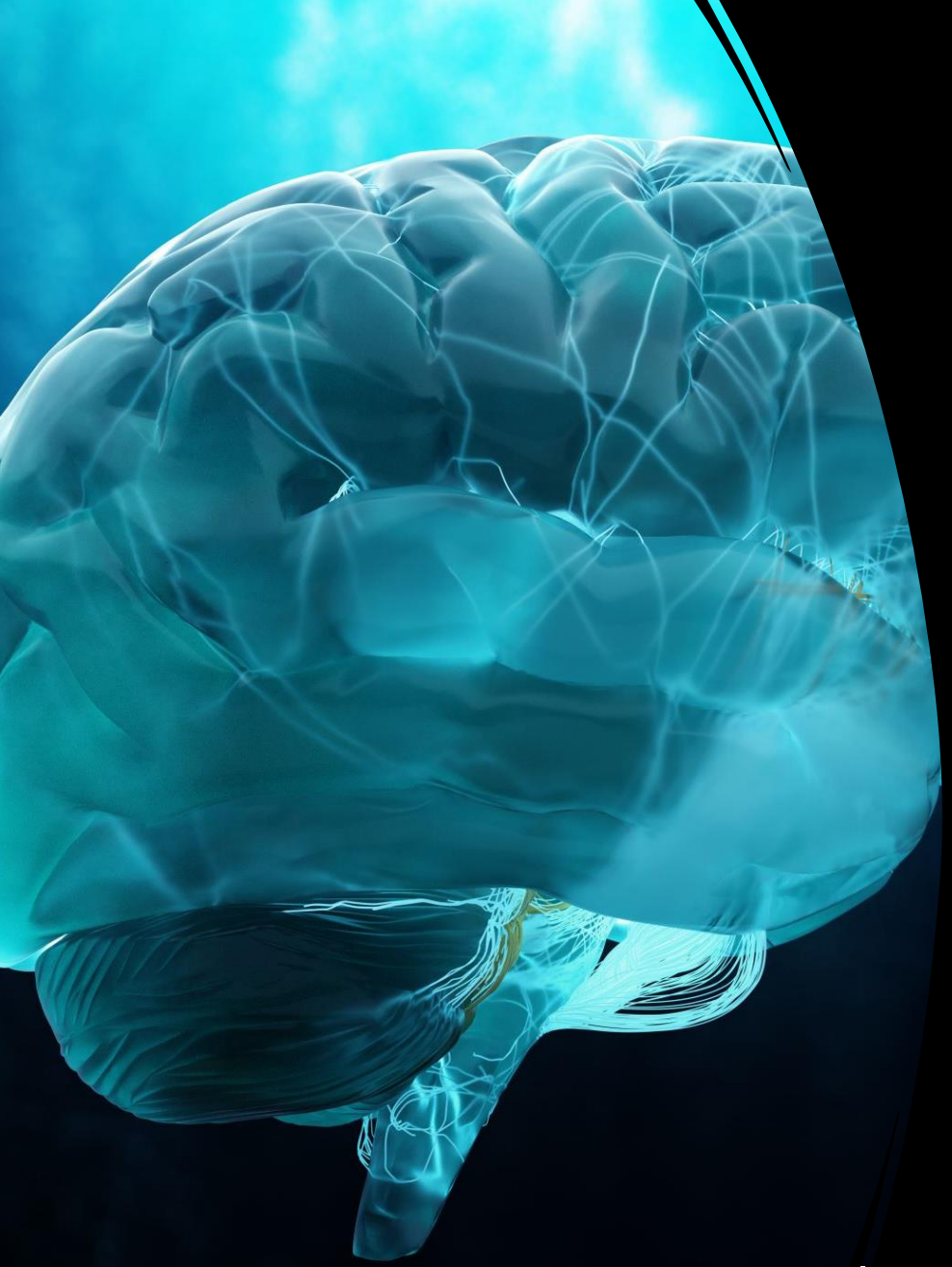
- **Function**
  - Priming




Microglia

Microglia actively survey the brain microenvironment for disruptions in homeostasis.

Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. Neuropharmacology. 2015 Sep;96(Pt A):29-41. Norden DM, et al



Microglia patrols and eliminates:

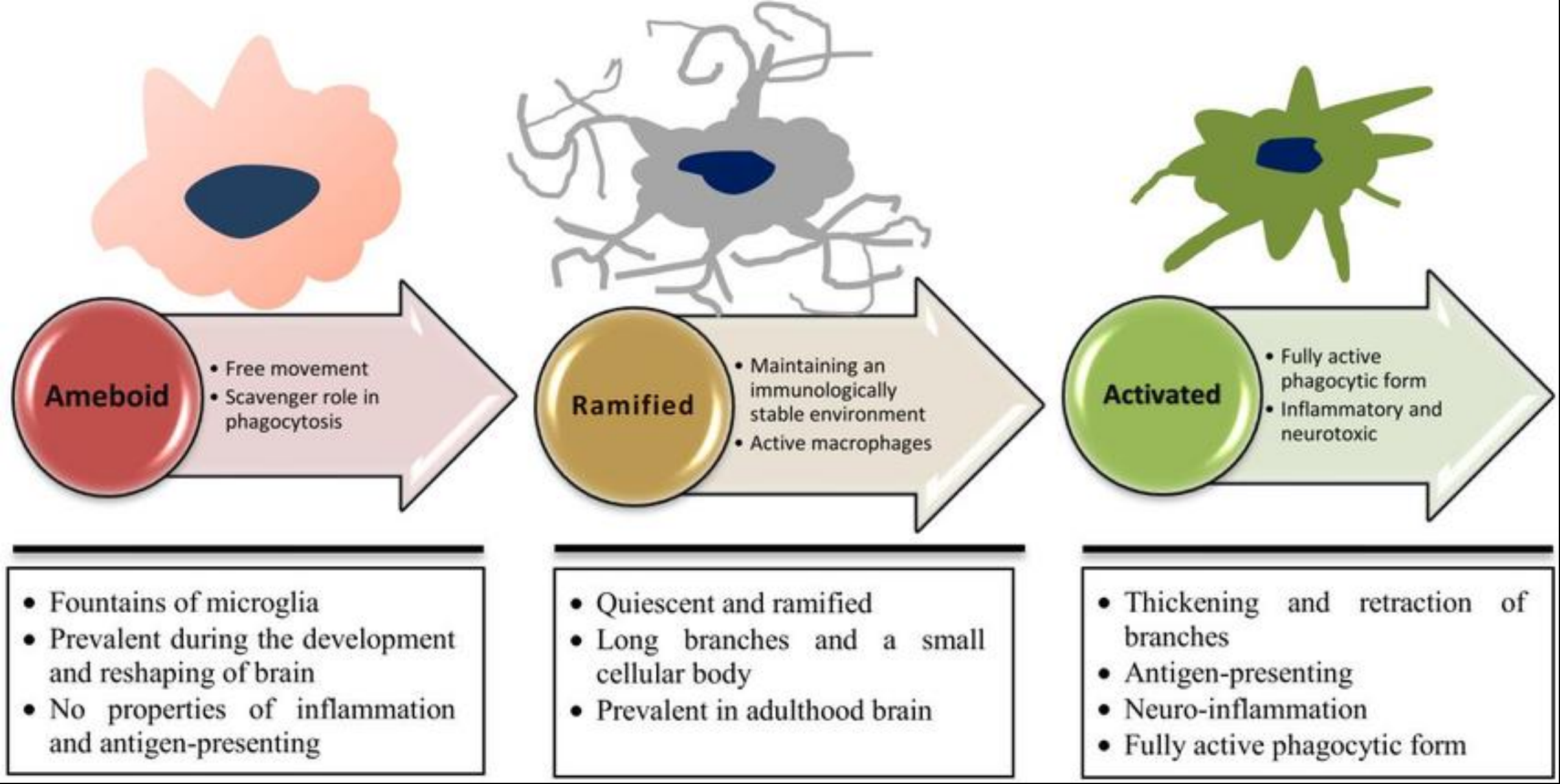
- Microbes
- Dead cells
- Redundant synapses
- Protein aggregates
- Particulates and soluble antigens that may endanger the CNS

Microglia Function in the Central Nervous System During Health and Neurodegeneration. Annu Rev Immunol. 2017 Apr 26;35:441-468. Colonna M, Butovsky O.

Microglia influences…

- Brain development
- Synaptic plasticity
- Neurogenesis
- Memory
- Mood

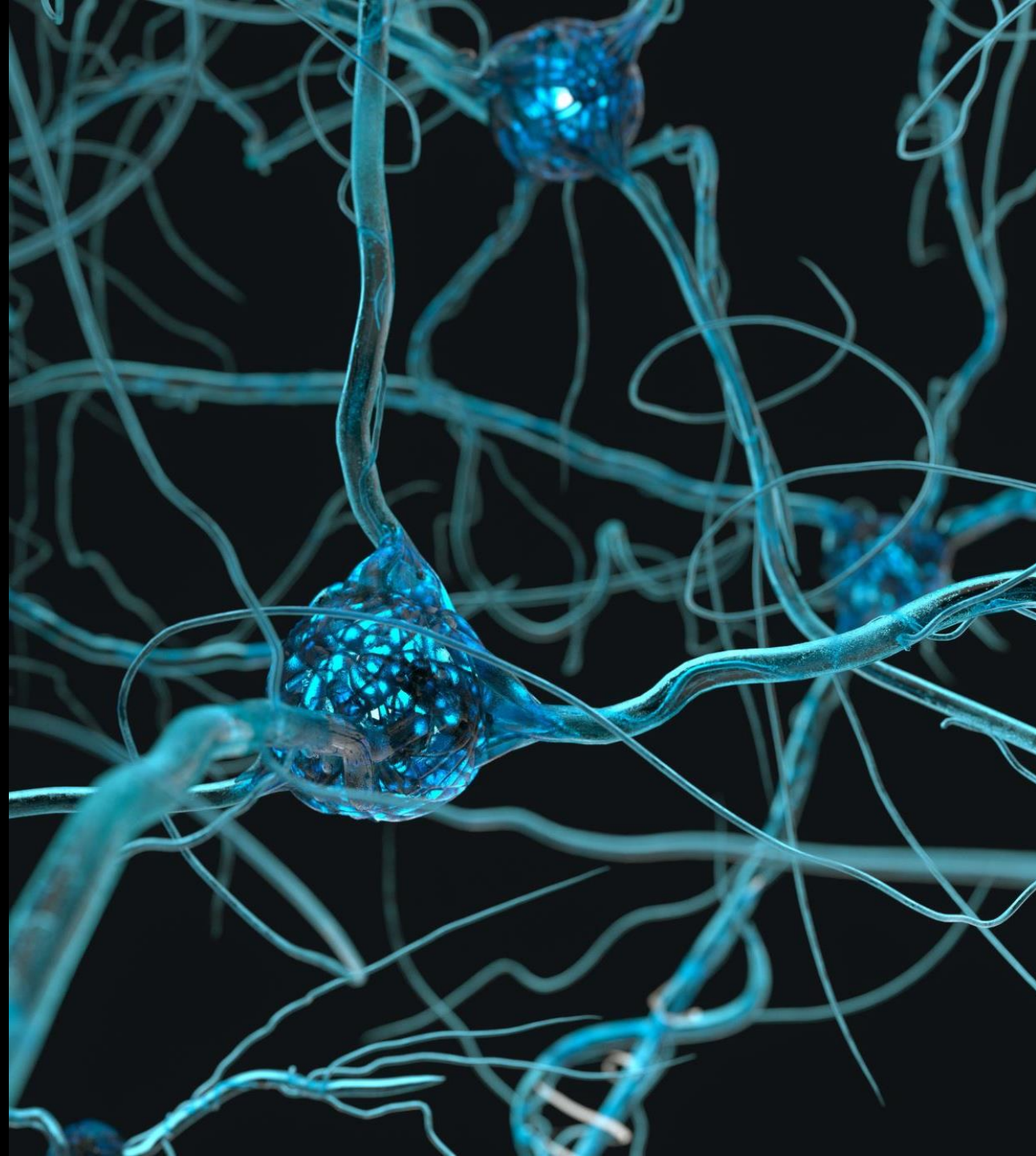
Depression as a Microglial Disease. Neuroimmunology
VOLUME 38, ISSUE 10, P637-658, OCTOBER 2015

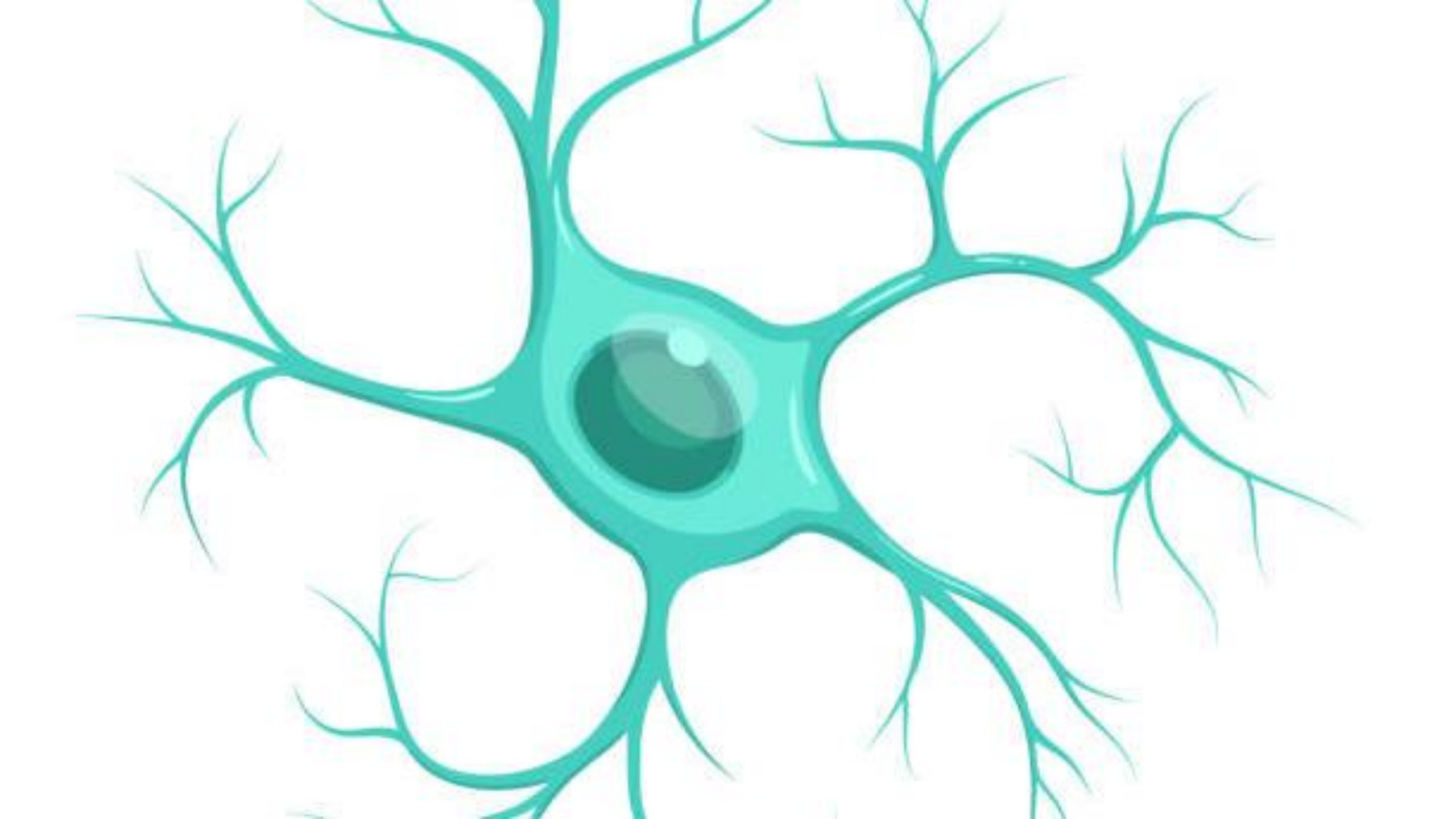


Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease. Int J Neurosci. 2014 May;124(5):307-21.

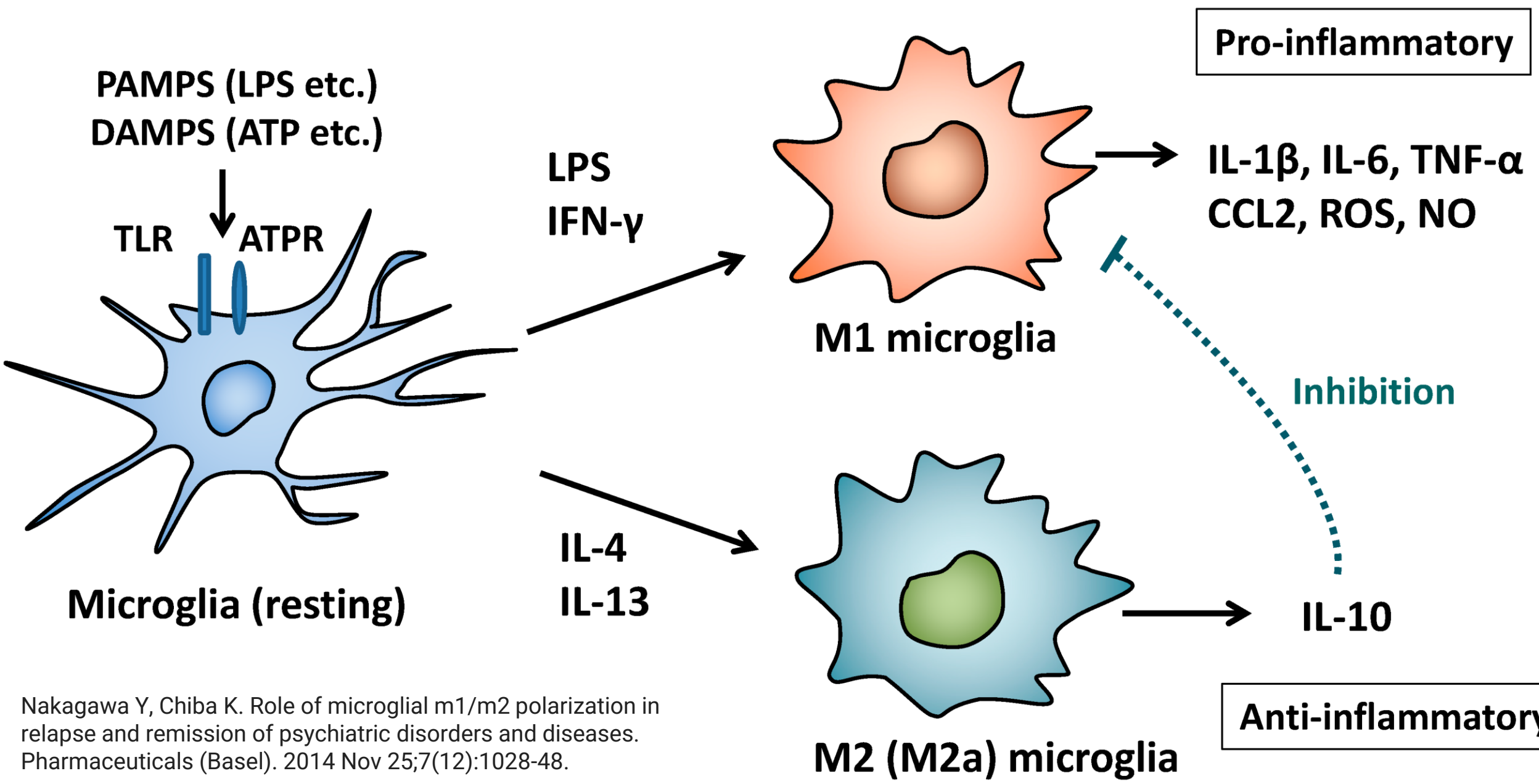
Microglia states

- **Ameboid** Histogenesis, brain development
- **Ramified** toxin clearance, metabolite removal
- **Activated** injury or pathogen invasion, if pathological stimulus persists MA continues





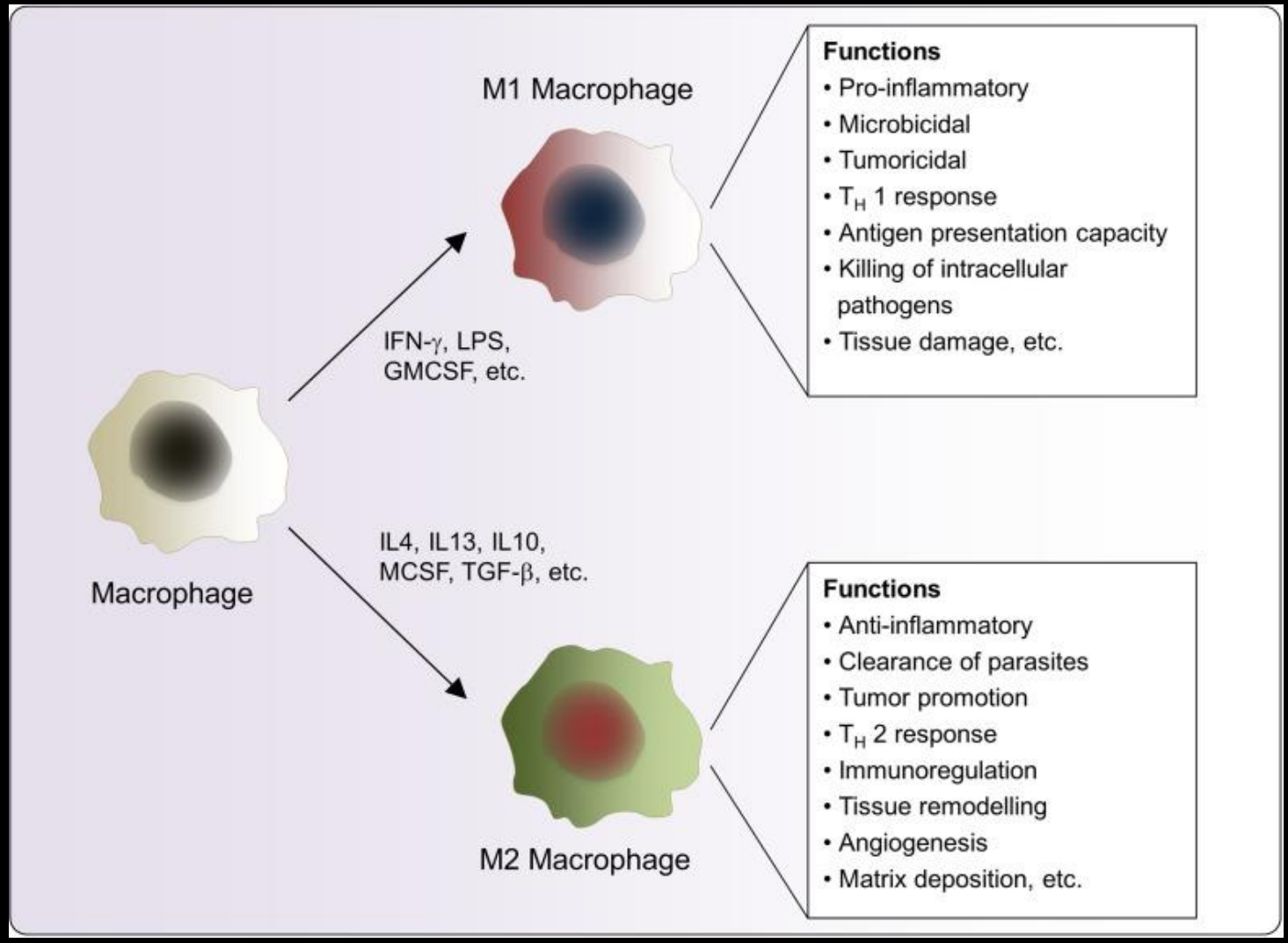

2 µm
02:24 min

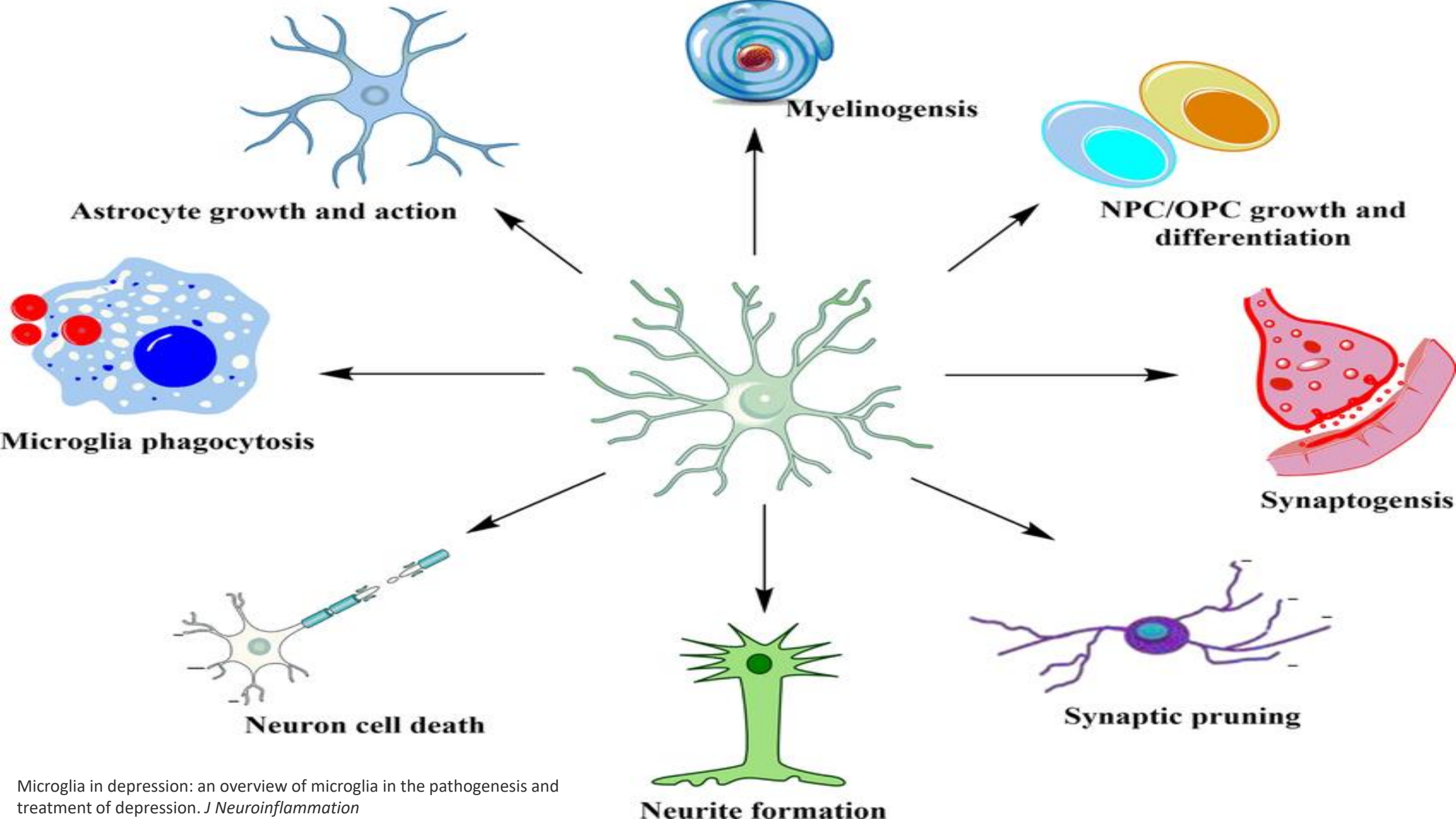


Nakagawa Y, Chiba K. Role of microglial m1/m2 polarization in relapse and remission of psychiatric disorders and diseases. Pharmaceuticals (Basel). 2014 Nov 25;7(12):1028-48.

M1 vs. M2

- Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018 Apr 3;9(25):17937-17950 Saqib U, et al





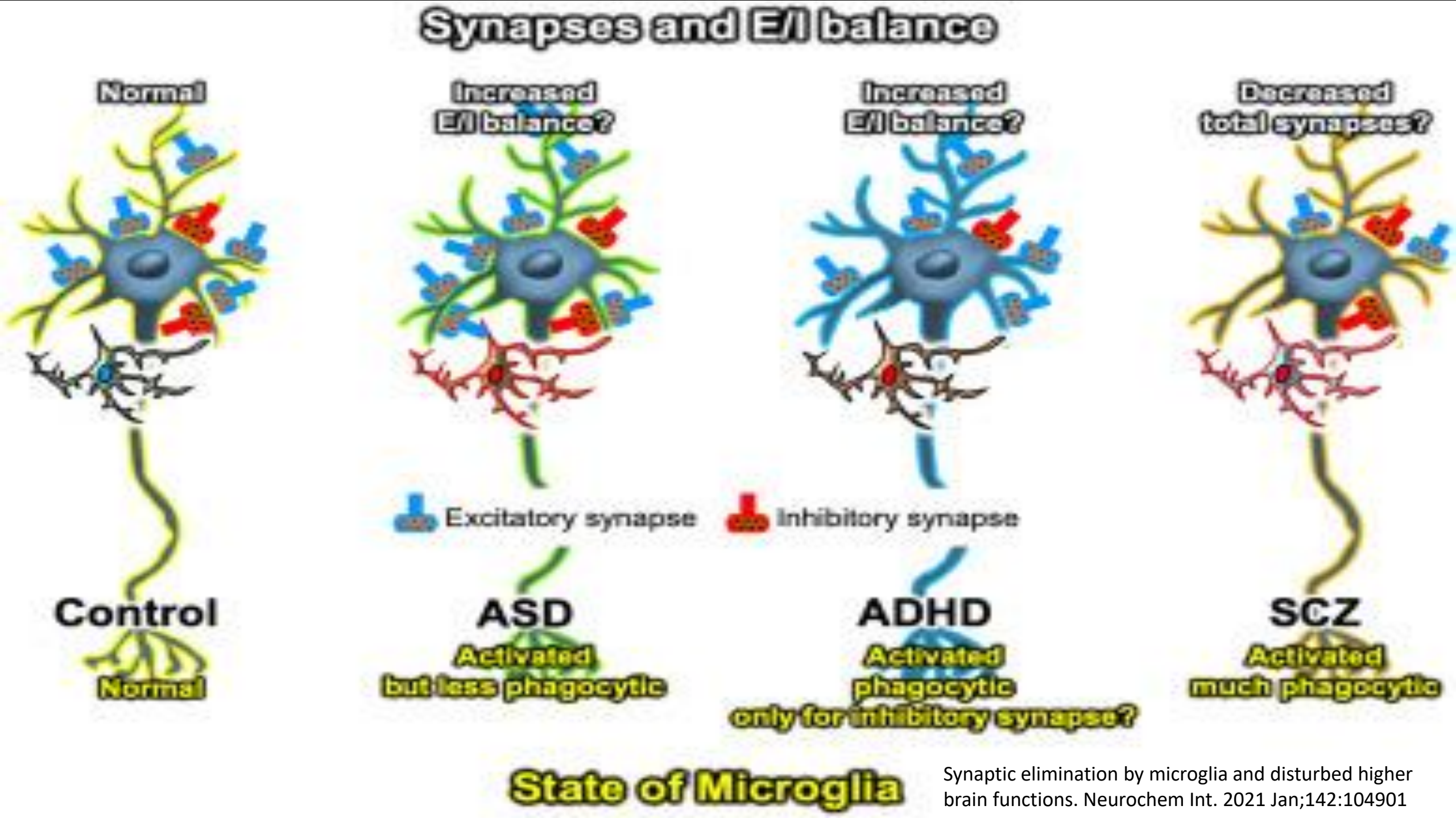
Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J Neuroinflammation*

The E/I balance

Highlights

- Microglia engage in synaptic elimination by phagocytosis in mature brains.
- Selective synaptic elimination changes excitatory/inhibitory (E/I) balance.
- Microglia modulate neuropsychiatric disorders by synaptic elimination.
- This review discusses Parkinson's and Alzheimer's diseases, ASD, ADHD, and schizophrenia.

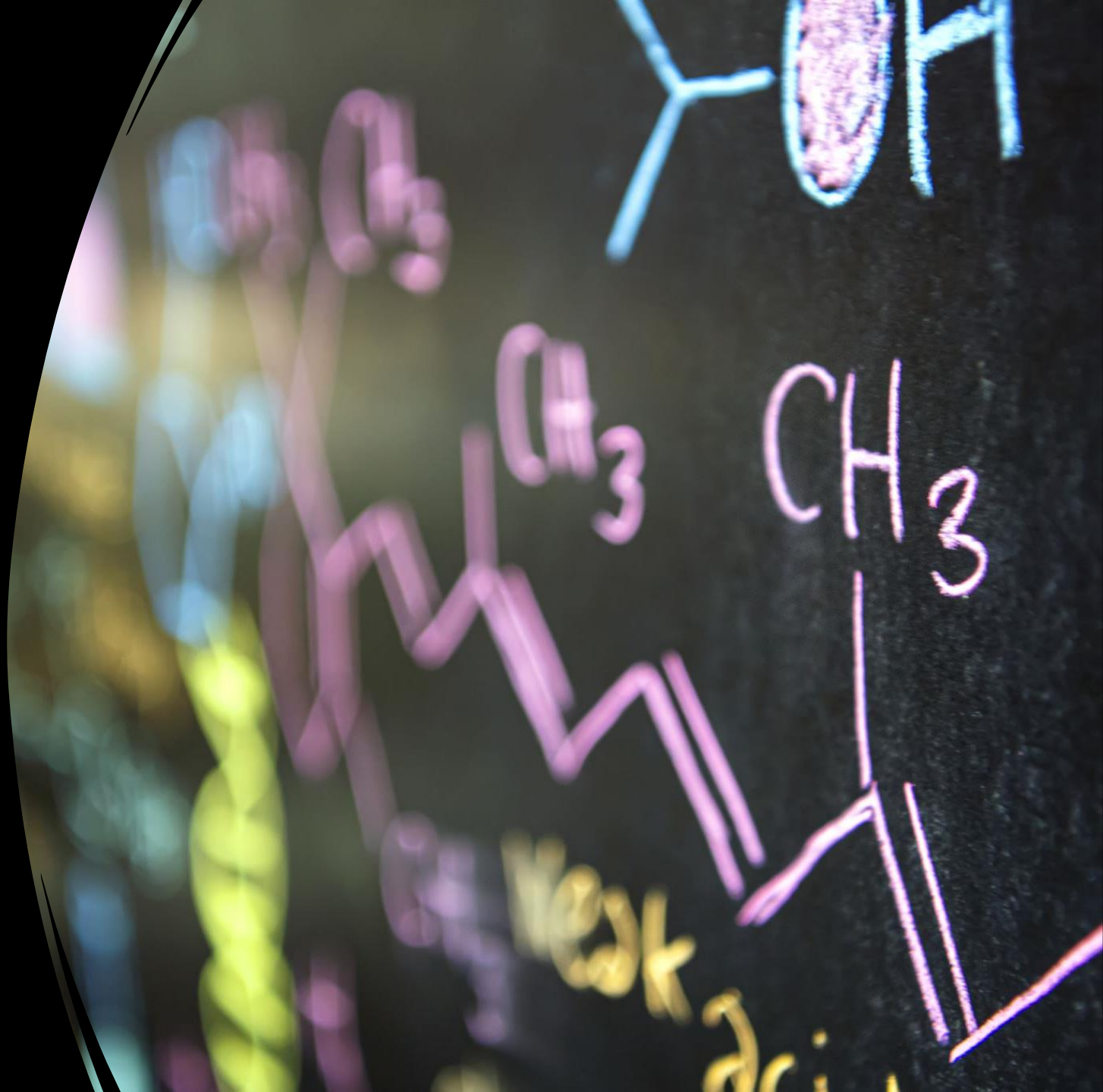
Synaptic elimination by microglia and disturbed higher brain functions. Neurochem Int. 2021 Jan;142:104901



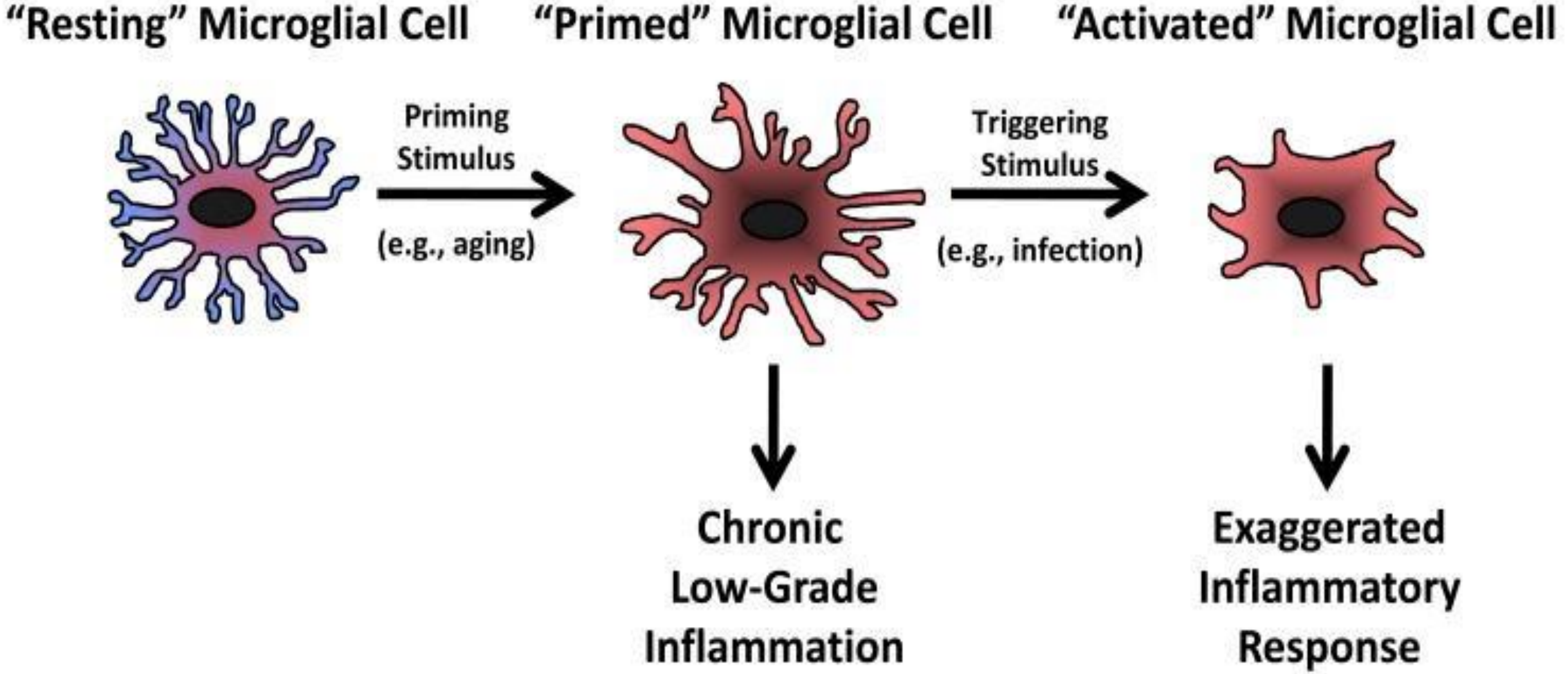
Synaptic elimination by microglia and disturbed higher brain functions. Neurochem Int. 2021 Jan;142:104901

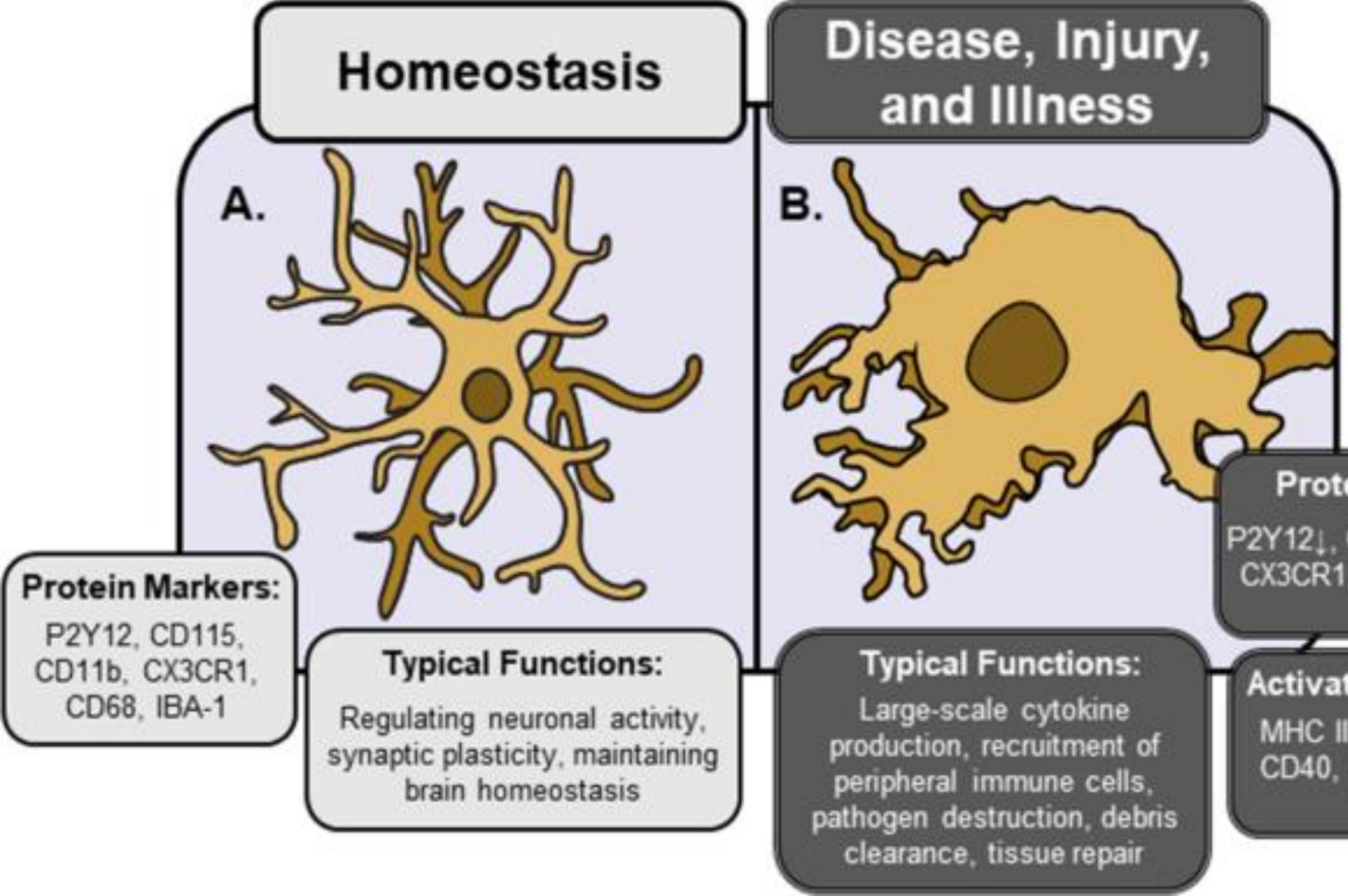
Neurophysiology

- Function
- **Priming**



A. Age-Related Priming of Microglia



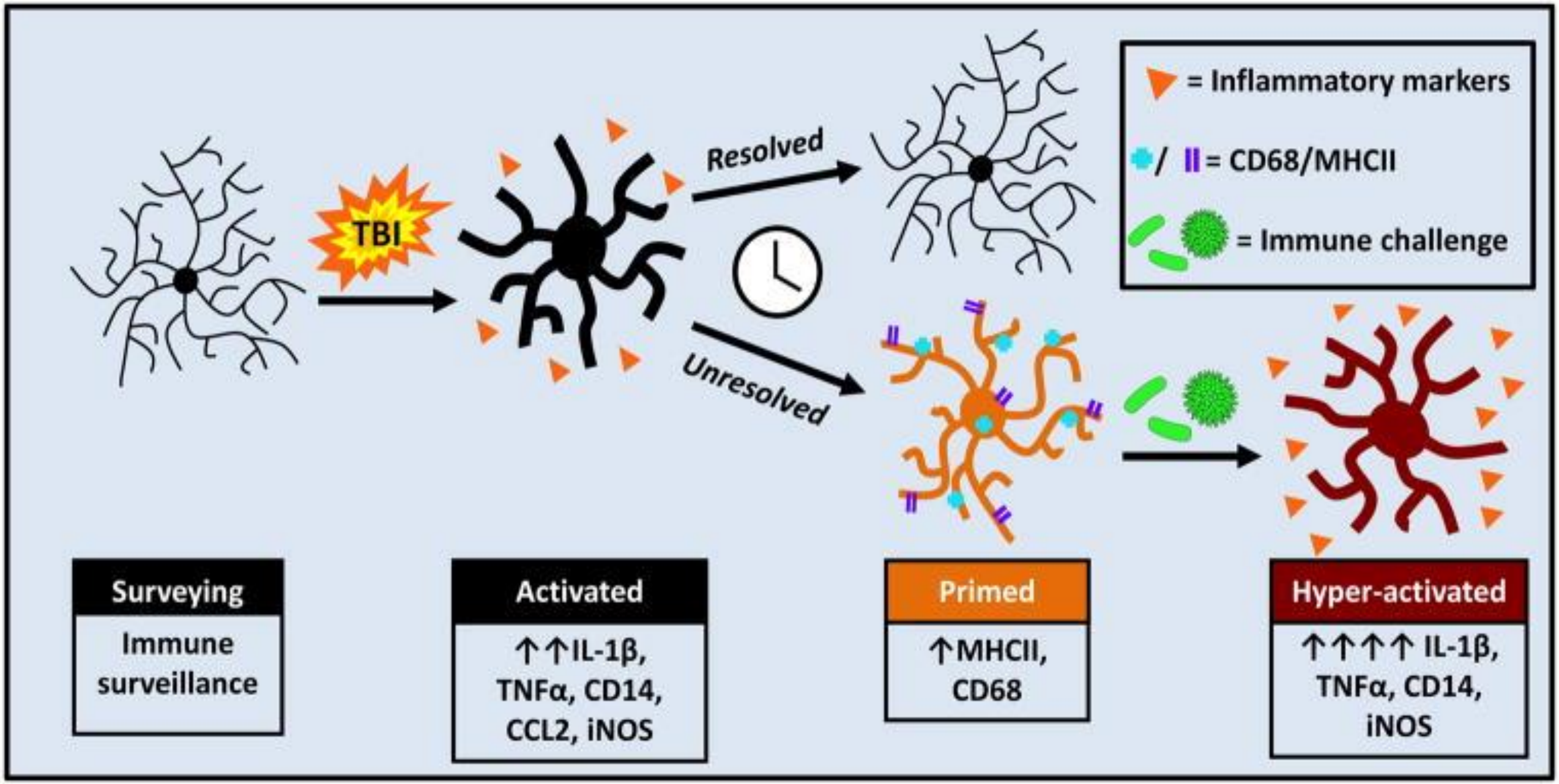


The semantics of microglia activation: neuroinflammation, homeostasis, and stress. *J Neuroinflammation* **18**, 258 (2021)

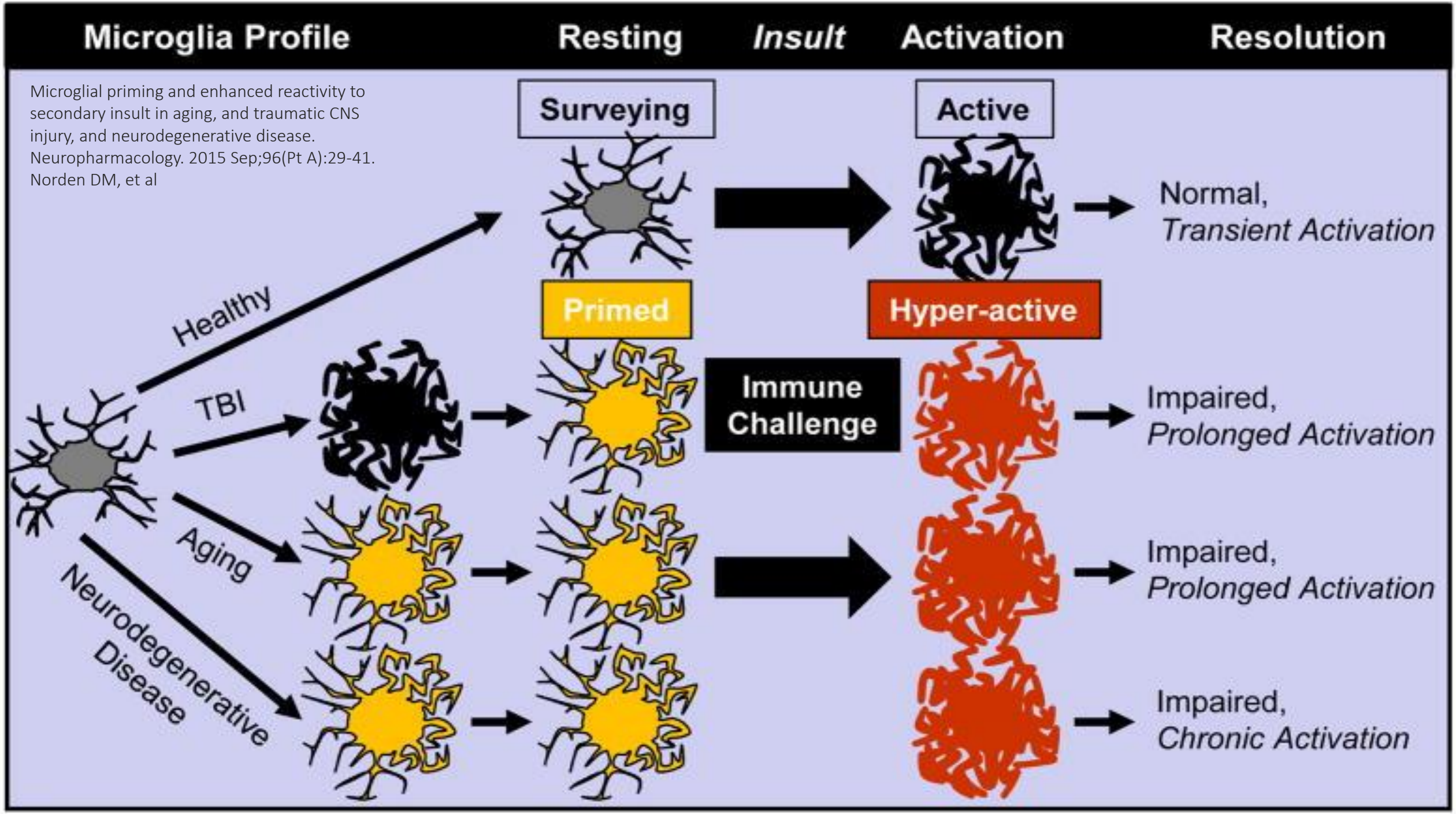
Second hit syndrome

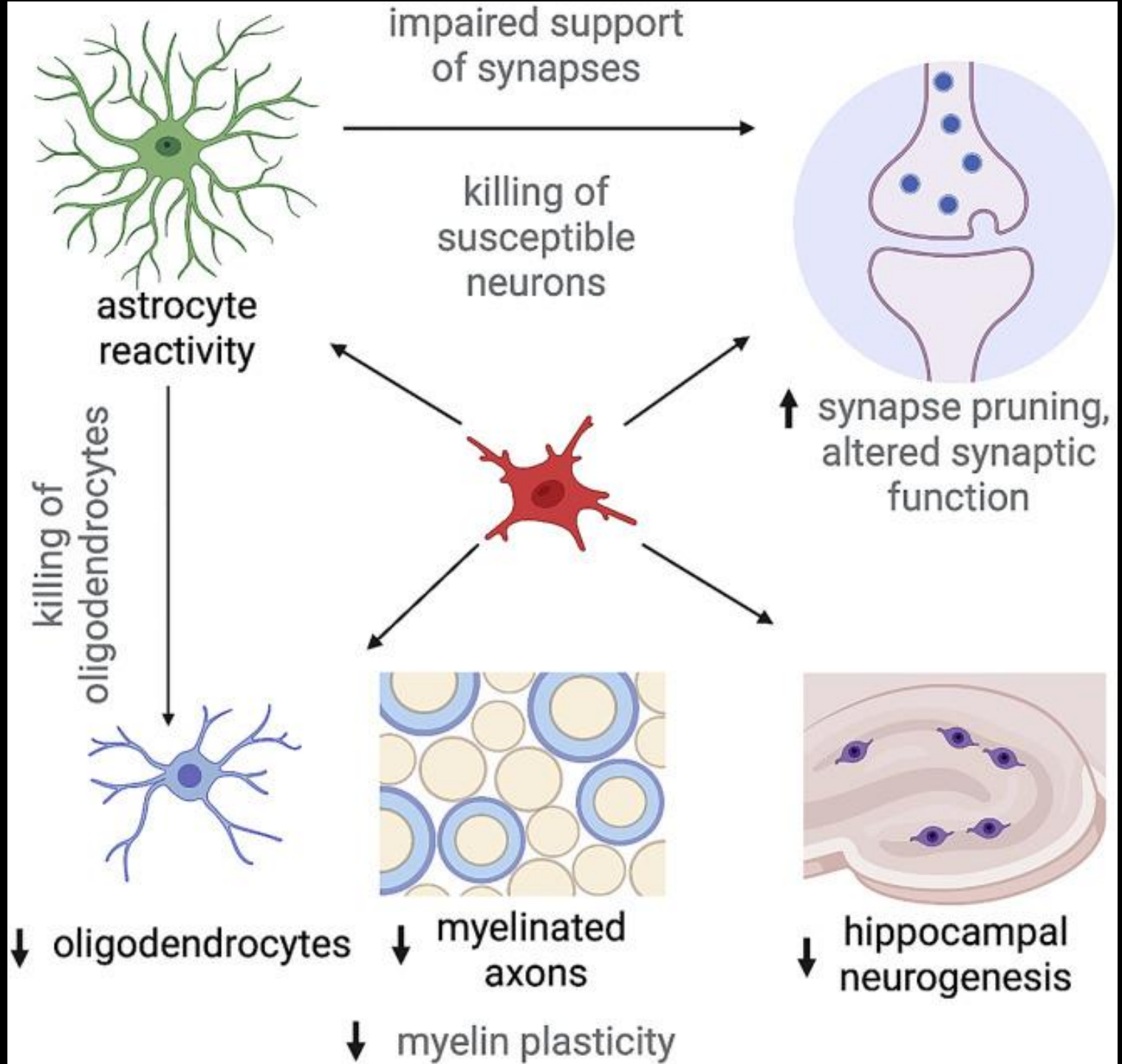
- “Microglia contribute to this inflammation by maintaining a primed profile long after the acute effects of the injury have dissipated. This may set the stage for glial dysfunction and hyperactivity to challenges including subsequent head injury, stress, or induction of a peripheral immune response.”

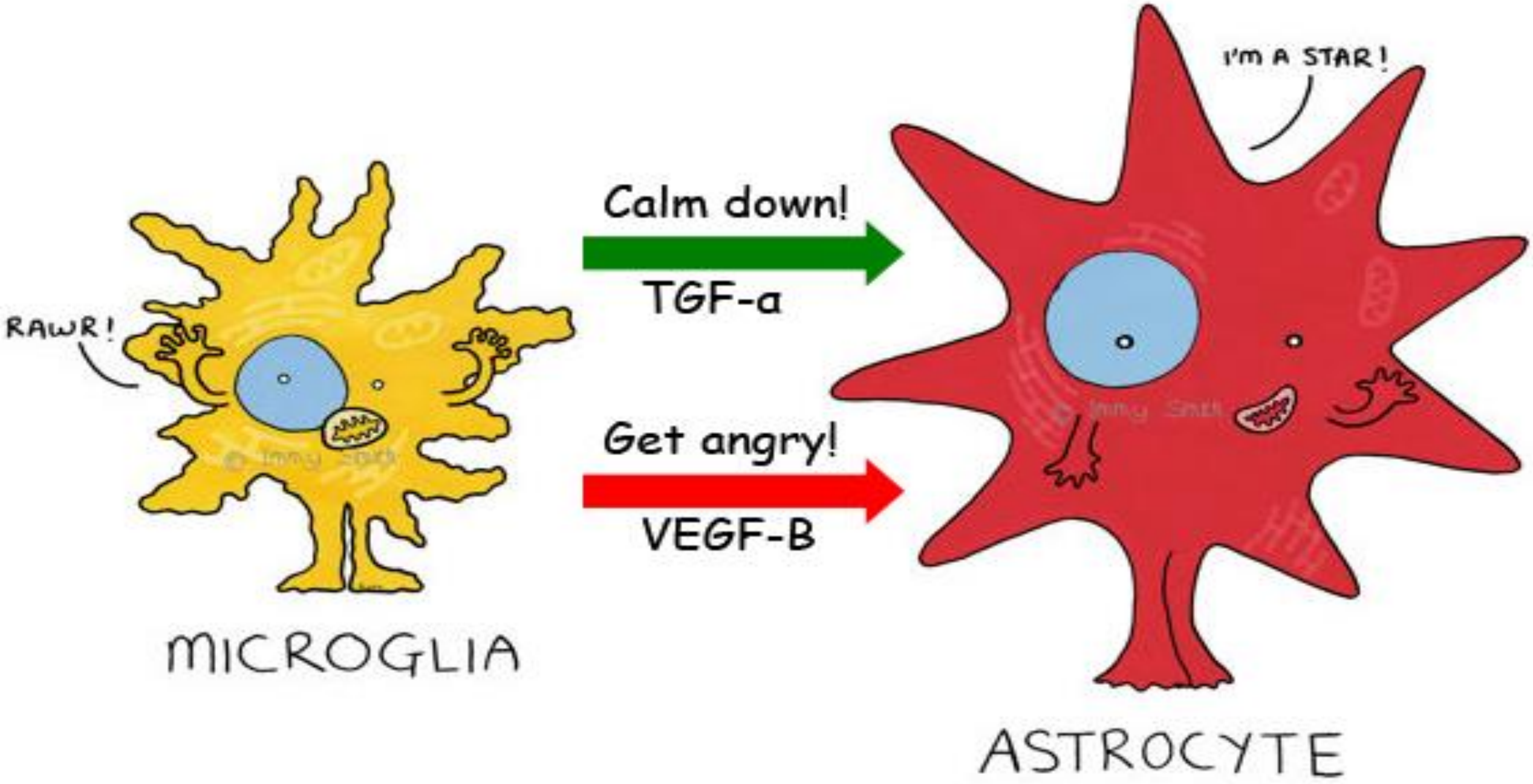
Priming the inflammatory pump of the CNS after traumatic brain injury. Trends Neurosci. 2015 Oct;38(10):609-620.



Priming the inflammatory pump of the CNS after traumatic brain injury. Trends Neurosci. 2015 Oct;38(10):609-620.


Microglia Profile
Resting
Insult
Activation
Resolution
Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. Neuropharmacology. 2015 Sep;96(Pt A):29-41. Norden DM, et al
Surveying
Active
Primed
Hyper-active
Healthy
TBI
Aging
Neurodegenerative Disease
Immune Challenge
Normal, Transient Activation
Impaired, Prolonged Activation
Impaired, Prolonged Activation
Impaired, Chronic Activation


impaired support of synapses
killing of susceptible neurons
astrocyte reactivity
killing of oligodendrocytes
synapse pruning, altered synaptic function
oligodendrocytes
myelinated axons
hippocampal neurogenesis
myelin plasticity


RAWR!
MICROGLIA
Calm down!
TGF-a
Get angry!
VEGF-B
I'm A STAR!
ASTROCYTE

Microglia can become activated in several ways, including:

- **Brain damage:** Microglia can become activated and proliferate after brain damage or stimulation by immune mediators.
- **Infection or insults:** Microglia can be rapidly activated in response to infection or insults within the adult CNS parenchyma.
- **Psychological stress:** Psychological stress can activate microglia, which can then take on a primed profile and cause an exaggerated inflammatory response.
- **Neurodegeneration:** Microglia can multiply in response to an accumulation of debris and abnormally folded proteins during neurodegeneration.
- **Developmental:** In spectral disorders, microglia may be underdeveloped with a lower population of ramified

Phases of Microglia activation with clinical relevance

- Transient
- Chronic
- Primed microglia
- Neuroautoimmune

Faces of Neuroinflammation Outline

- Microglia activation
- Signs and symptoms
- Neurophysiology
- **Conditions**
- Clinical web
- Cases

History: Functional complaints

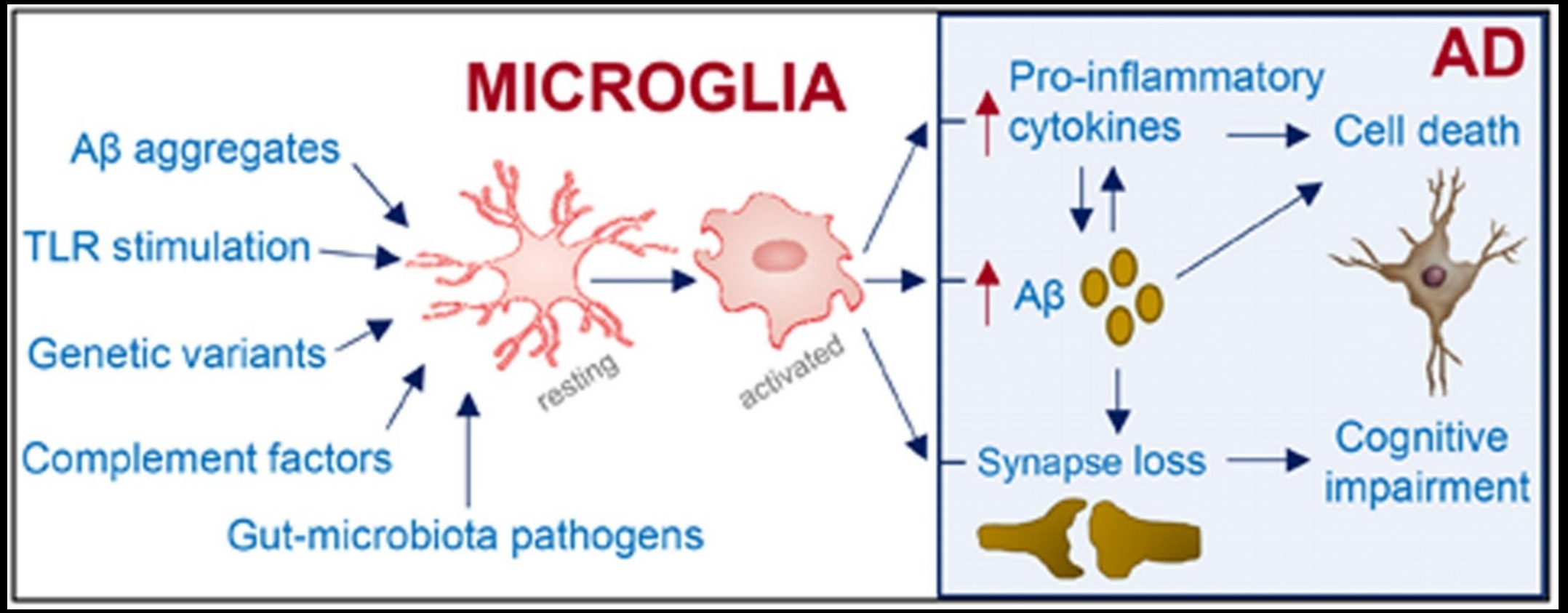
- Fatigue
- Brain fog
- Poor memory
- Inability to handle stimulation
- Poor brain endurance
- A need for excessive sleep
- Inability to focus or concentrate

History: Diagnosed conditions

- Depression
- Anxiety
- Chronic fatigue syndrome
- Fibromyalgia
- Chronic pain syndrome
- Stroke
- Neurodegenerative disease (AD, PD)
- PTSD
- Autism
- ADHD

- Novel targets in Alzheimer's disease: A special focus on microglia. Volume 130, April 2018, Pages 402-413 Pharmocological research.

Microglia activation and AD



Microglia activation and Depression

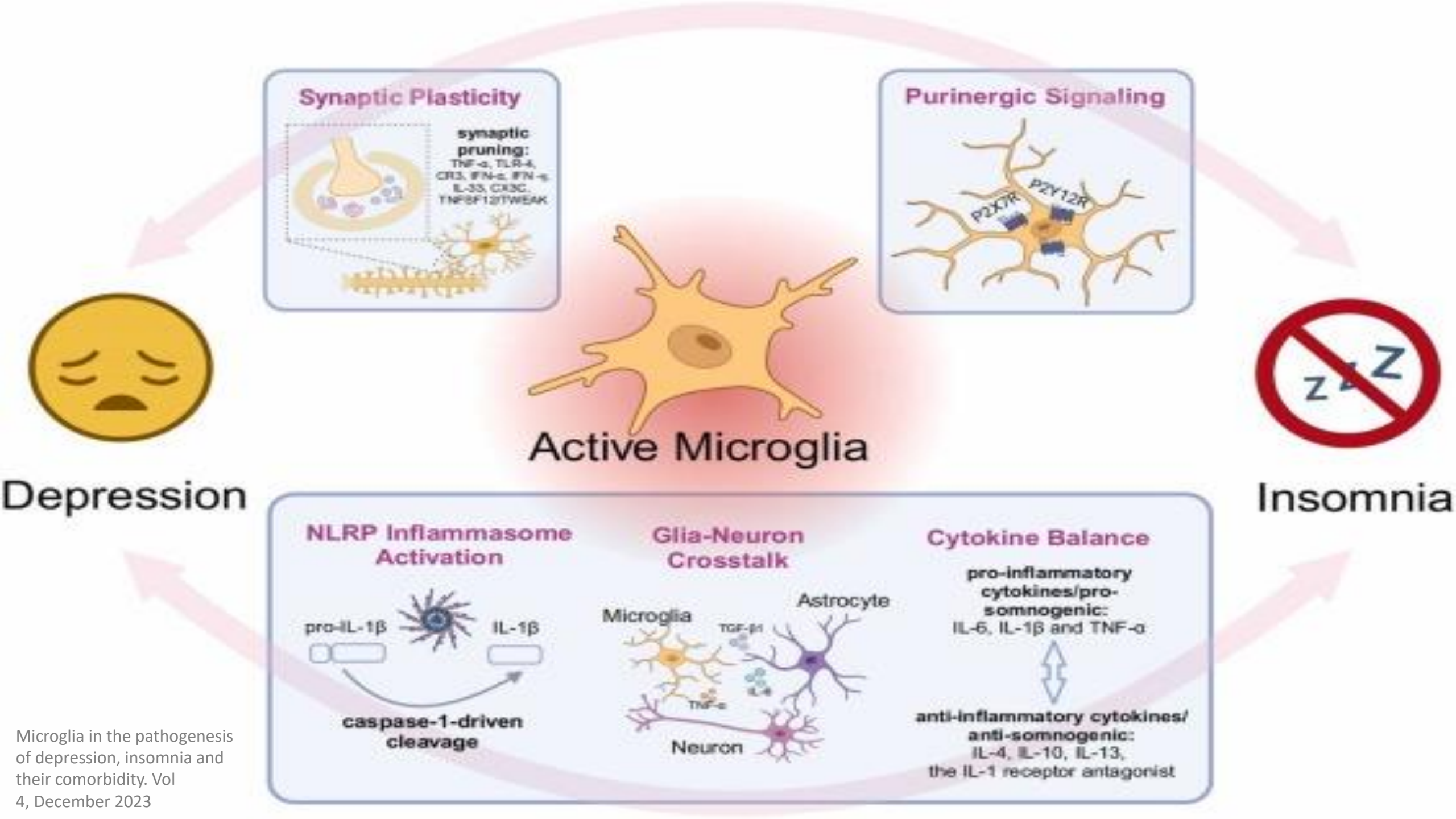
- Microglia regulates:
  - Inflammation
  - Synaptic plasticity
  - Formation of neural networks

Depression as a Microglial Disease. Neuroimmunology
VOLUME 38, ISSUE 10, P637-658, OCTOBER 2015

Microglia activation and mania, depression, psychosis, and anxiety

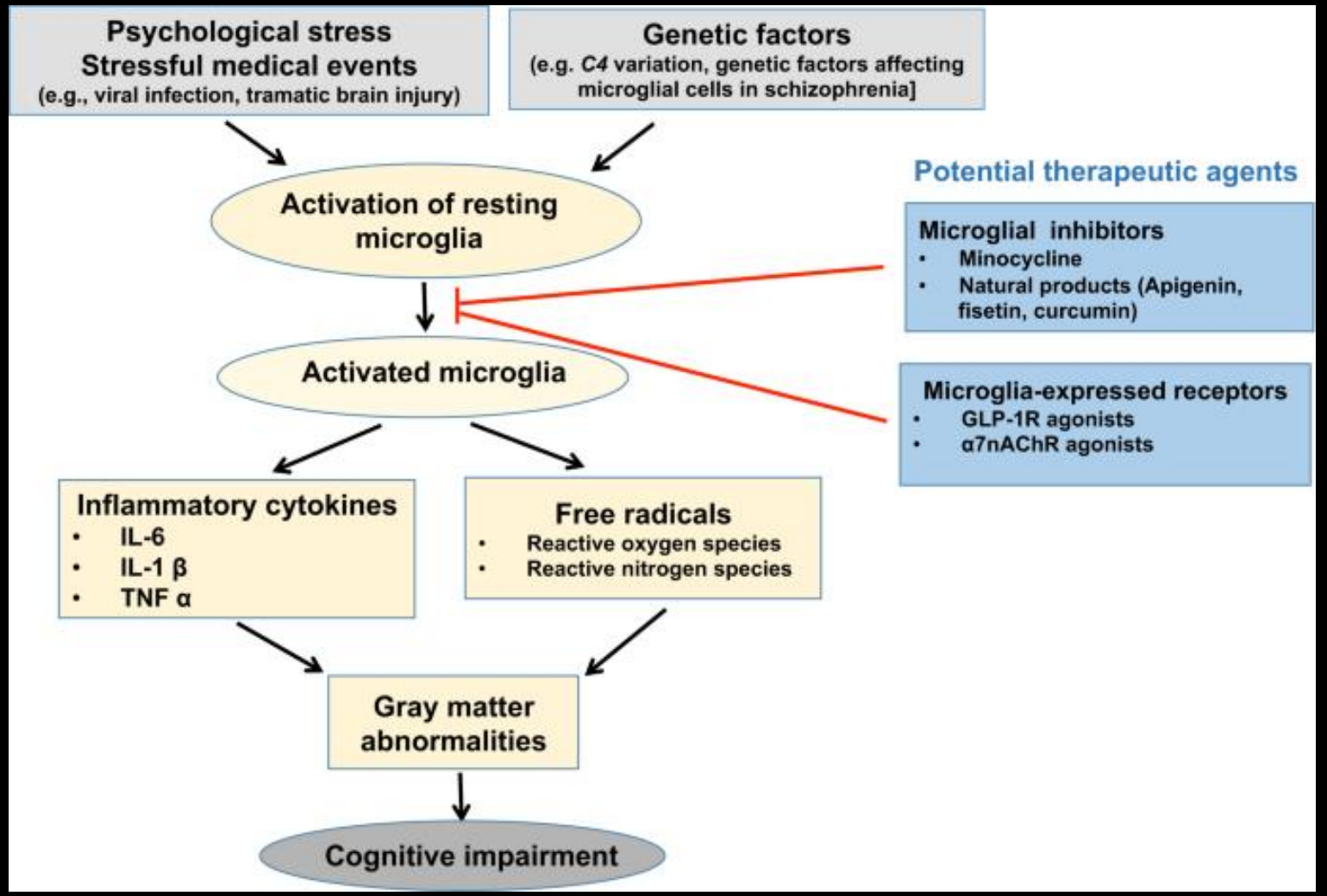
"These results support previous studies suggesting that **microglial activation** plays an important role in the development of psychiatric symptoms such as **mania, depression, psychosis, and anxiety** in a range of psychiatric disorders."[33,34]

Neuropsychiatric Symptoms and Microglial Activation in Patients with Alzheimer Disease. *JAMA Netw Open.* 2023;6(11):e2345175. Schaffer Aguzzoli C, Ferreira PCL, Povala G, et al.



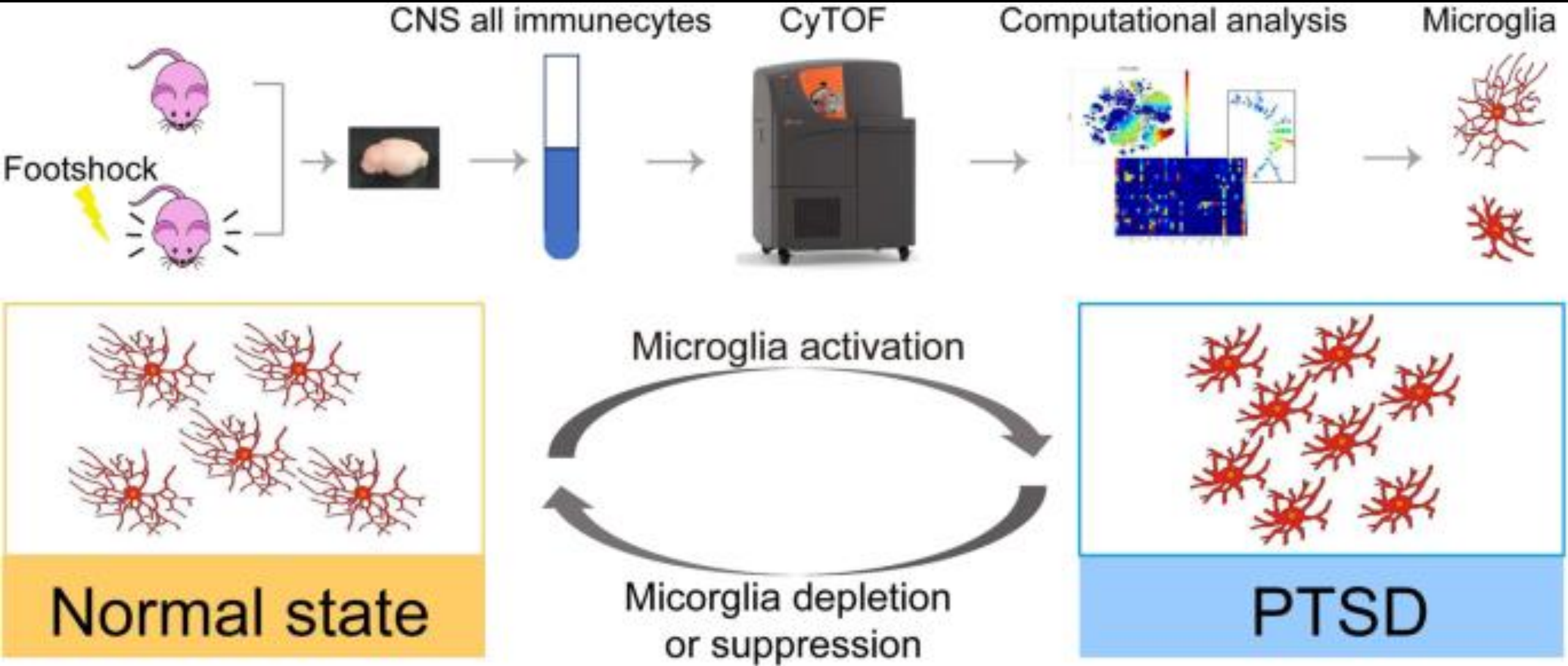
Microglia in the pathogenesis of depression, insomnia and their comorbidity. Vol 4, December 2023

Schizophrenia



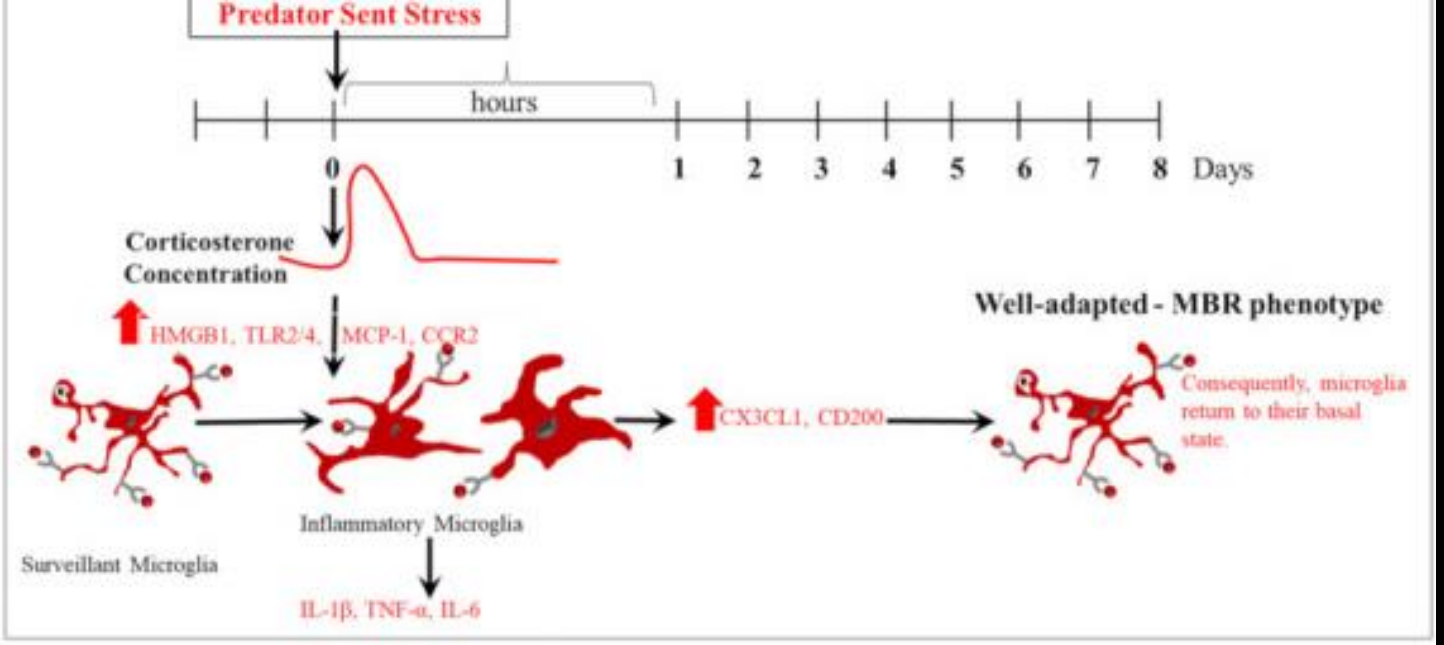
Microglia and cognitive impairment in schizophrenia: translating scientific progress into novel therapeutic interventions. *Schizophr* **9**, 42 (2023).

Microglia activation and PTSD

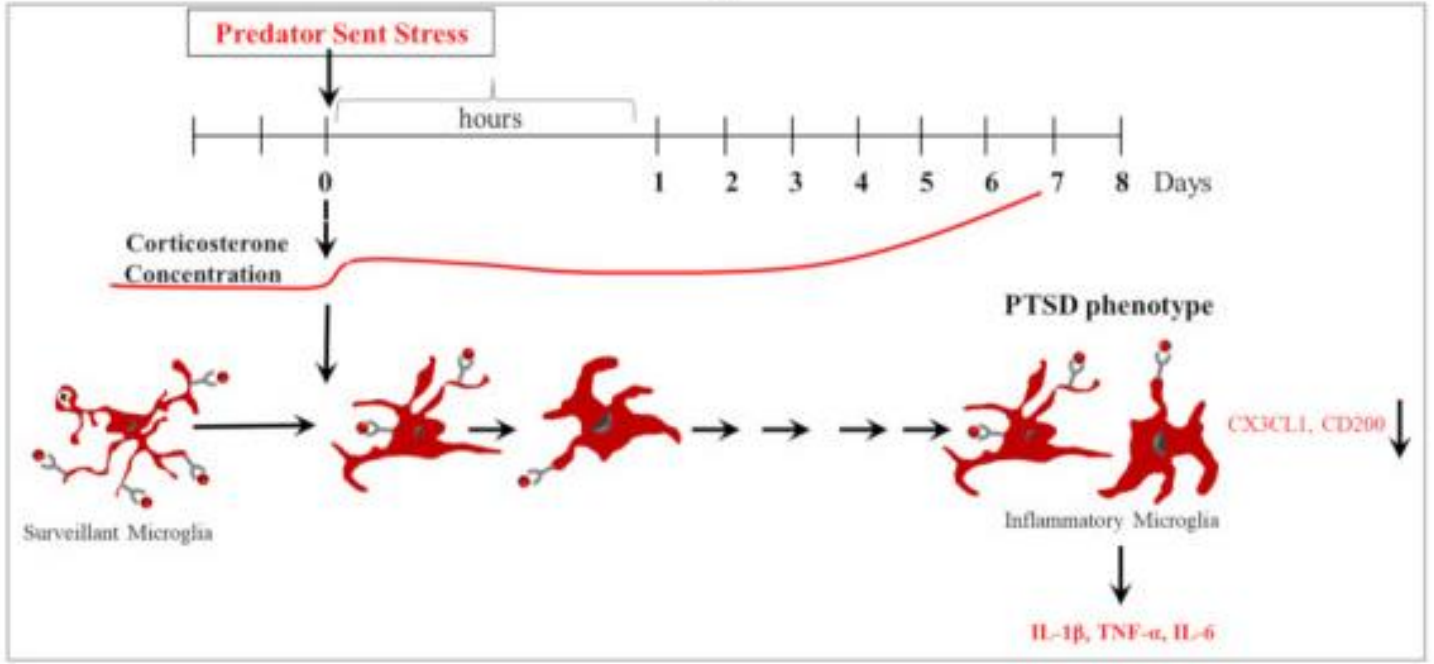


Microglial deletion and inhibition alleviate behavior of post-traumatic stress disorder in mice. *J Neuroinflammation* **18**, 7 (2021).

Microglia adaptation to stress determined PTSD phenotype expression



(a)



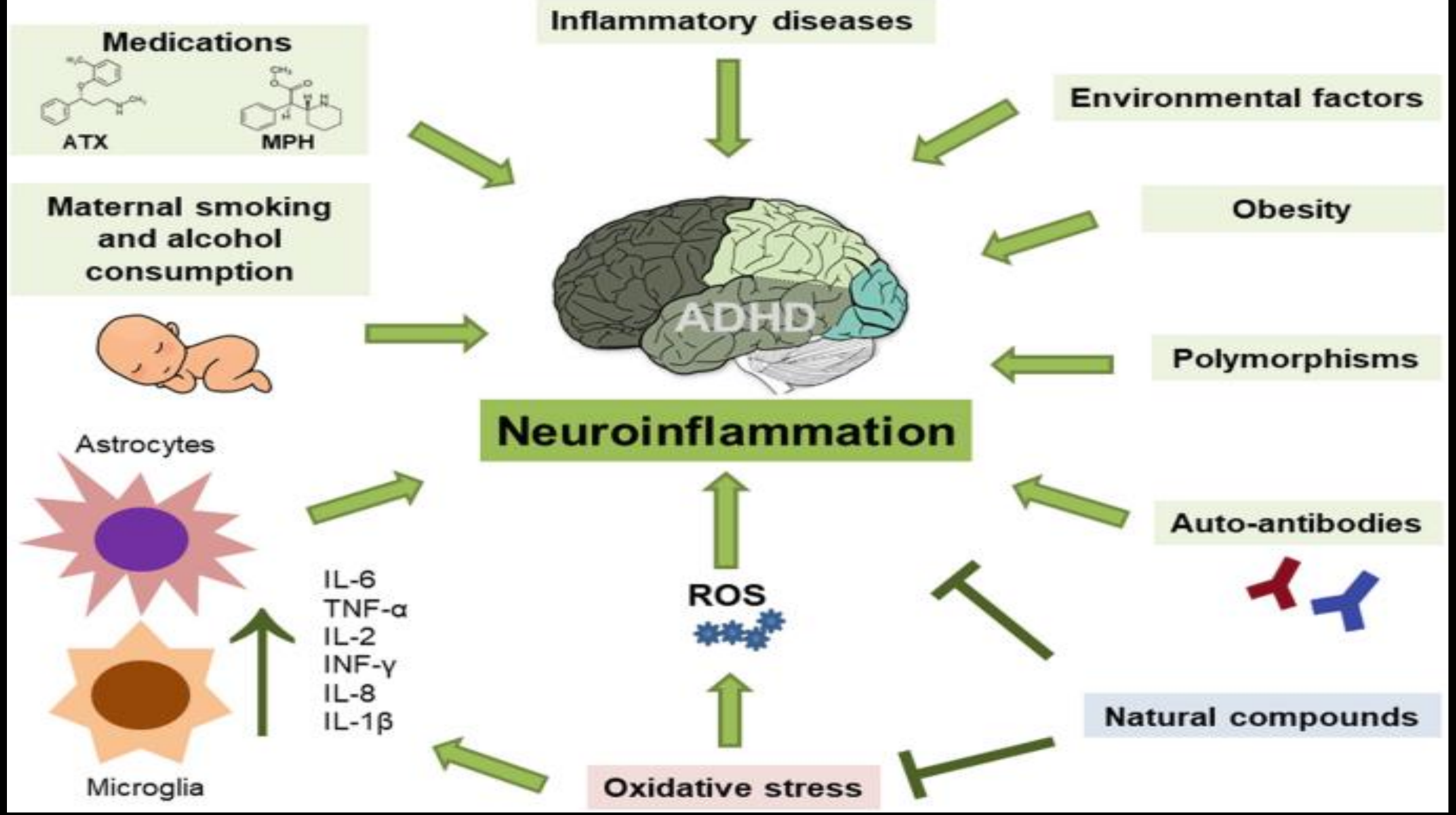
(b)

The Role of Microglia in the (Mal)adaptive Response to Traumatic Experience in an Animal Model of PTSD. Int J Mol Sci. 2022 Jun 28;23(13):7185.

Microglia activation plays key role in fatigue

- Recent evidence from preclinical studies indicates that activated microglia have a key role in the onset of fatigue. In chronic inflammatory conditions, such as infections and senescence, microglia orchestrate an inflammatory microenvironment thereby causing fatigue

Shared microglial mechanisms underpinning depression and chronic fatigue syndrome and their comorbidities. Behavioural Brain Research, vol 372, 17 October 2019, 111975



A Potential Role for Neuroinflammation in ADHD. In: Kim, YK. (eds) Neuroinflammation, Gut-Brain Axis and Immunity in Neuropsychiatric Disorders. Advances in Experimental Medicine and Biology, vol 1411. Springer, Singapore.

Microglia activation and Autism

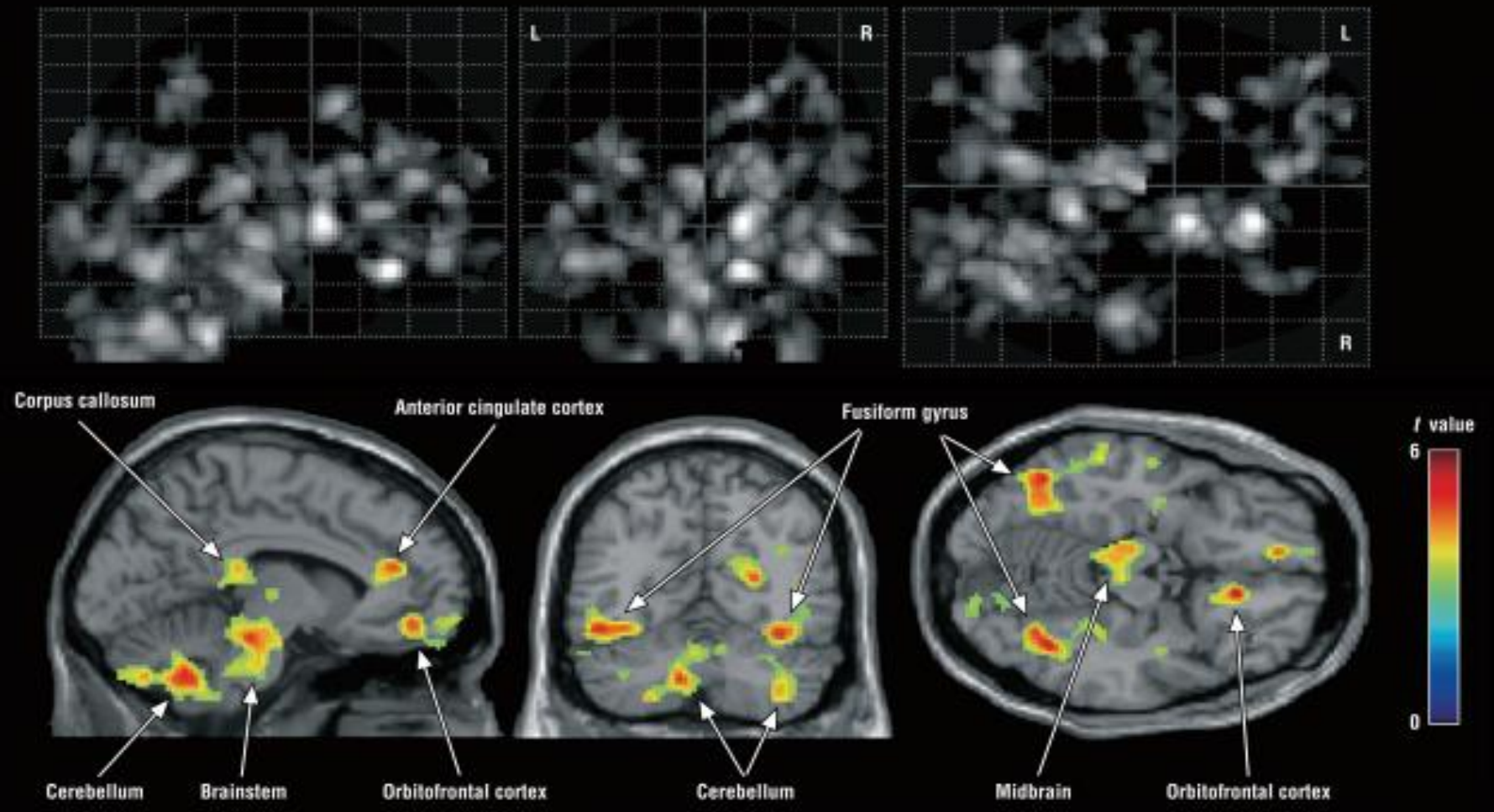
The combination of neuropathological analyses of post-mortem human brain samples and PET scanning of live human **ASD patients** has provided compelling evidence to suggest that **aberrant microglia and astrocyte immune activation** is a common hallmark of ASD.

Yokokura, M., Takebasashi, K., Takao, A. *et al.* In vivo imaging of dopamine D1 receptor and activated microglia in attention-deficit/hyperactivity disorder: a positron emission tomography study. *MolPsychiatry* **26**, 4958–4967 (2021).

Microglia activation and Autism

- A study by Johns Hopkins University School of Medicine found evidence of microglial activation in individuals with autism or autism spectrum disorder

Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neuron Glia Biol. 2011 May;7(2-4):205-13.

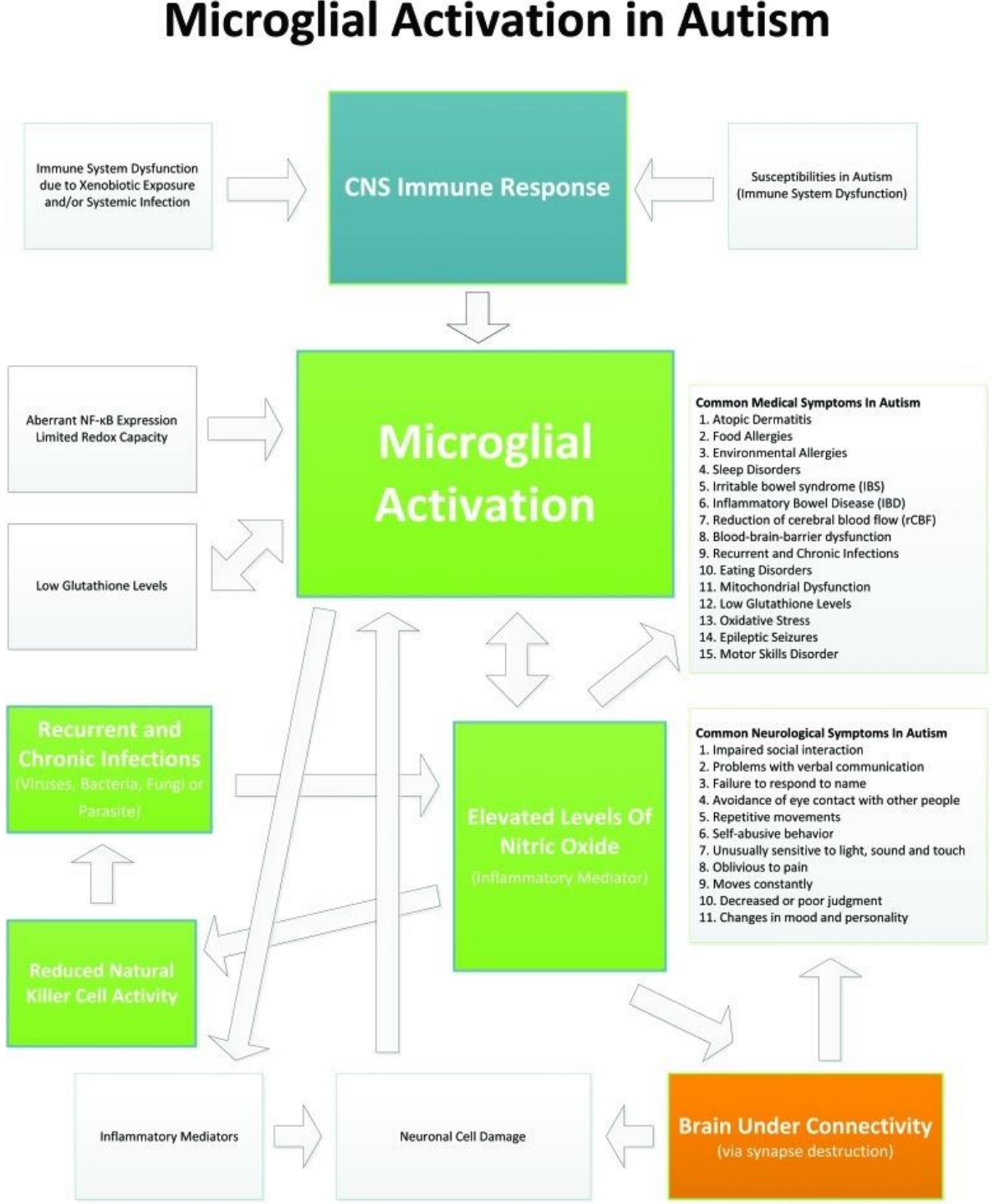


- A neuroimaging study that looked for the location of the translocator protein TSPO, which is expressed in microglia and astrocytes, has found a greater amount in the brains of young people with autism, something that has also been subsequently verified in tissue from autopsies.

Microglia and Autism. Neurobiology, January 2018, Jose Alonso

Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neuron Glia Biol. 2011 May;7(2-4):205-13

- Microglia activation in Autism



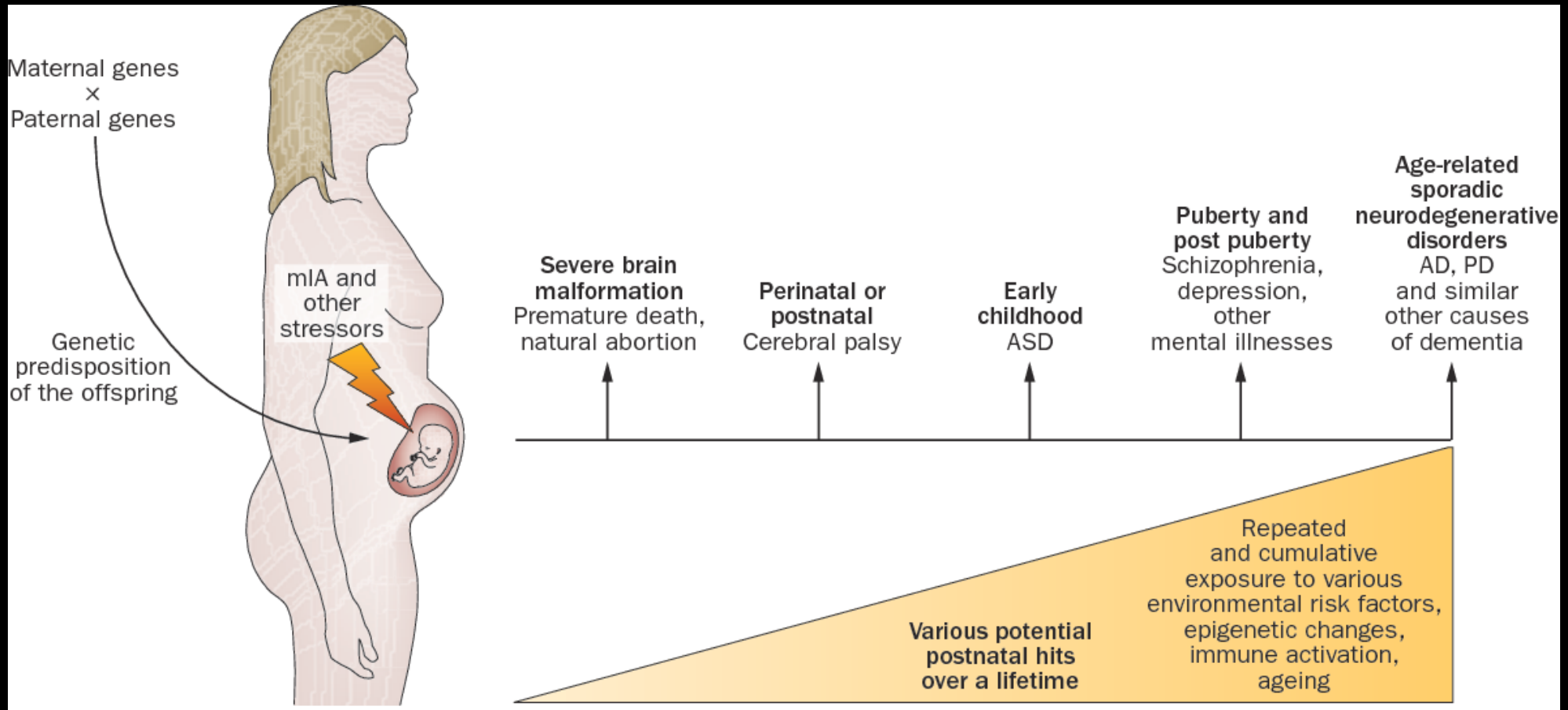


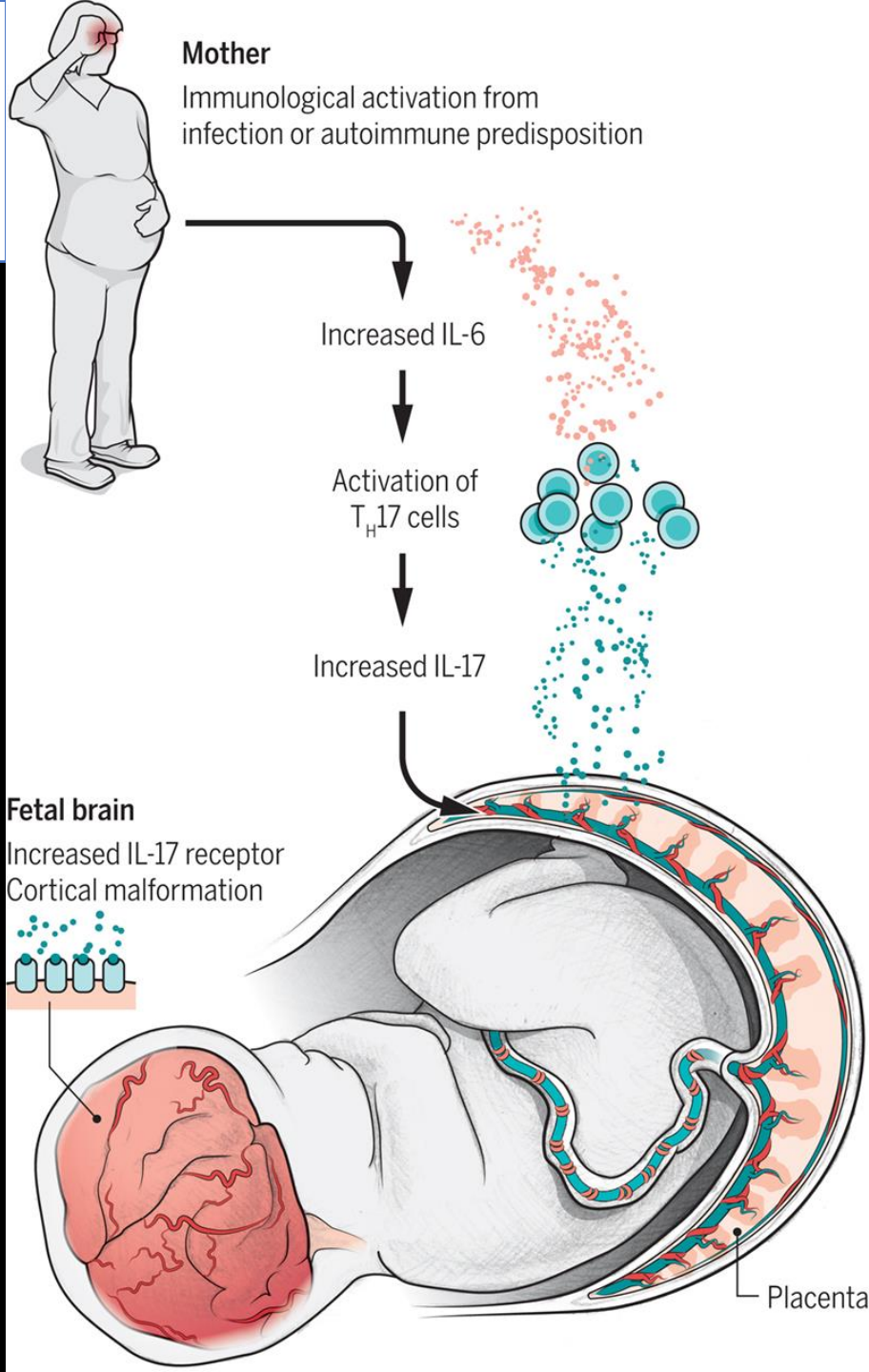
Figure 2 | Proposed causal chain of events. In humans, mIA can lead to the wide spectrum of neuronal dysfunctions and

Maternal immune activation (MIA)

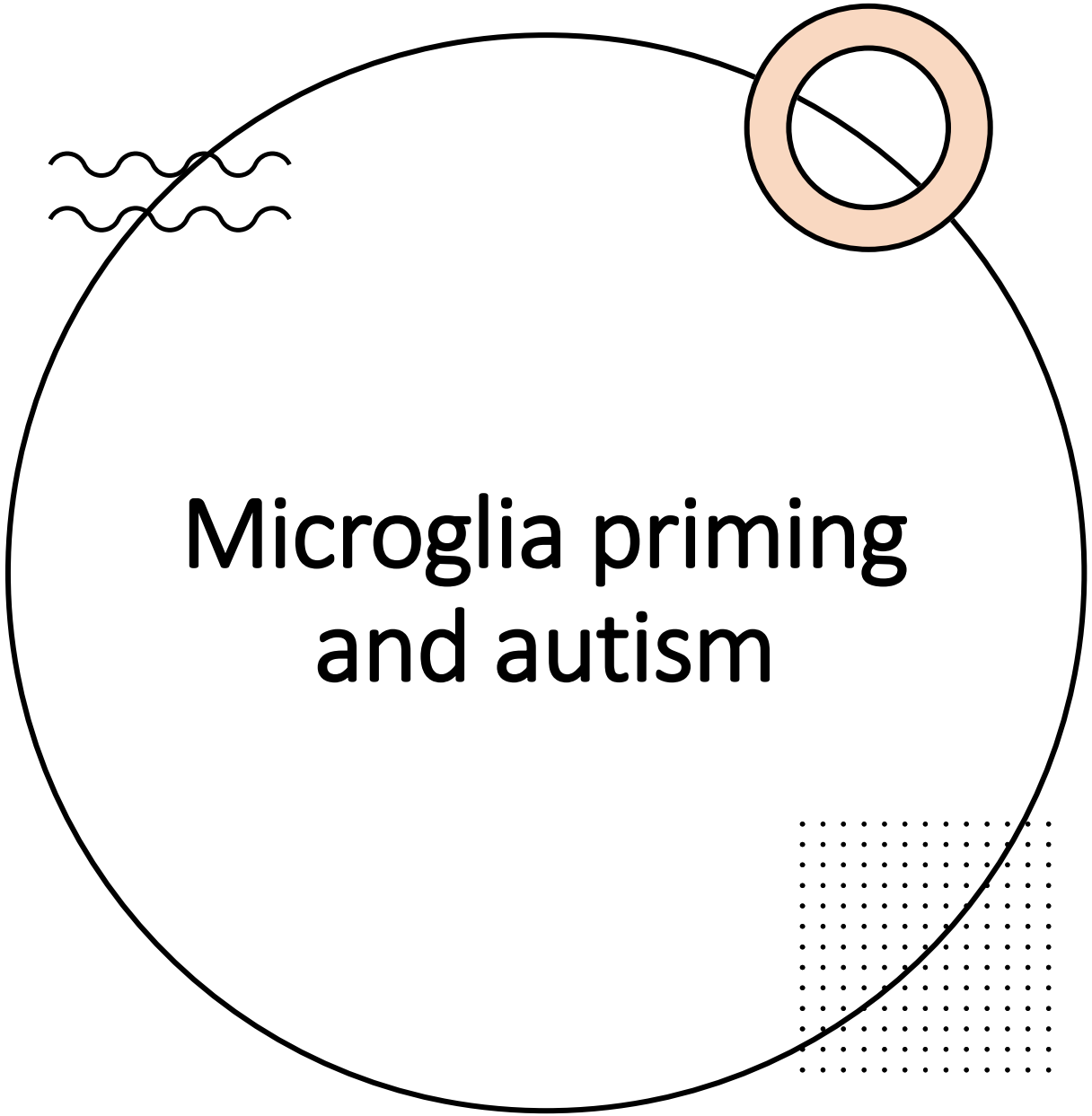
Maternal T_H17 cells take a toll on baby's brain.

Science 26 Feb 2016: 351(6276):919-920 Myka L. Estes, A. Kimberley McAllister

- The hypothetical model shown is based on mouse experiments and illustrates that MIA, possibly in combination with a predisposition for autoimmunity, leads to an increase in T_H17 cells in maternal blood. These cells release IL-17, which crosses the placenta and increases expression of the IL-17 receptor in the offspring's brain. This in turn leads to ASD-related cortical and behavioral abnormalities in the offspring.



Microglia priming and autism



- “there was a significant decrease in ramified microglia in both gray matter and white matter of ASD, and a significant increase in primed microglia in gray matter of ASD compared to typically developing individuals.”

Developmental microglial priming in postmortem autism spectrum disorder temporal cortex. Brain Behav Immun. 2017 May;62:193-202.

Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp Neurol*. 2018;299(Pt A):241–251

- A: Microglia transition from a round/ameboid morphology early development
- B: Diesel Exhaust Particles (DEP) increases the number of round microglia in cortex at E:18, and the number of thick microglia at P30 in males only, suggesting DEP delays their maturation and/or leads to their activation. There are similar effects in other brain regions including hippocampus
- C: Al of the effects of DEP in males are dependent on TLR4

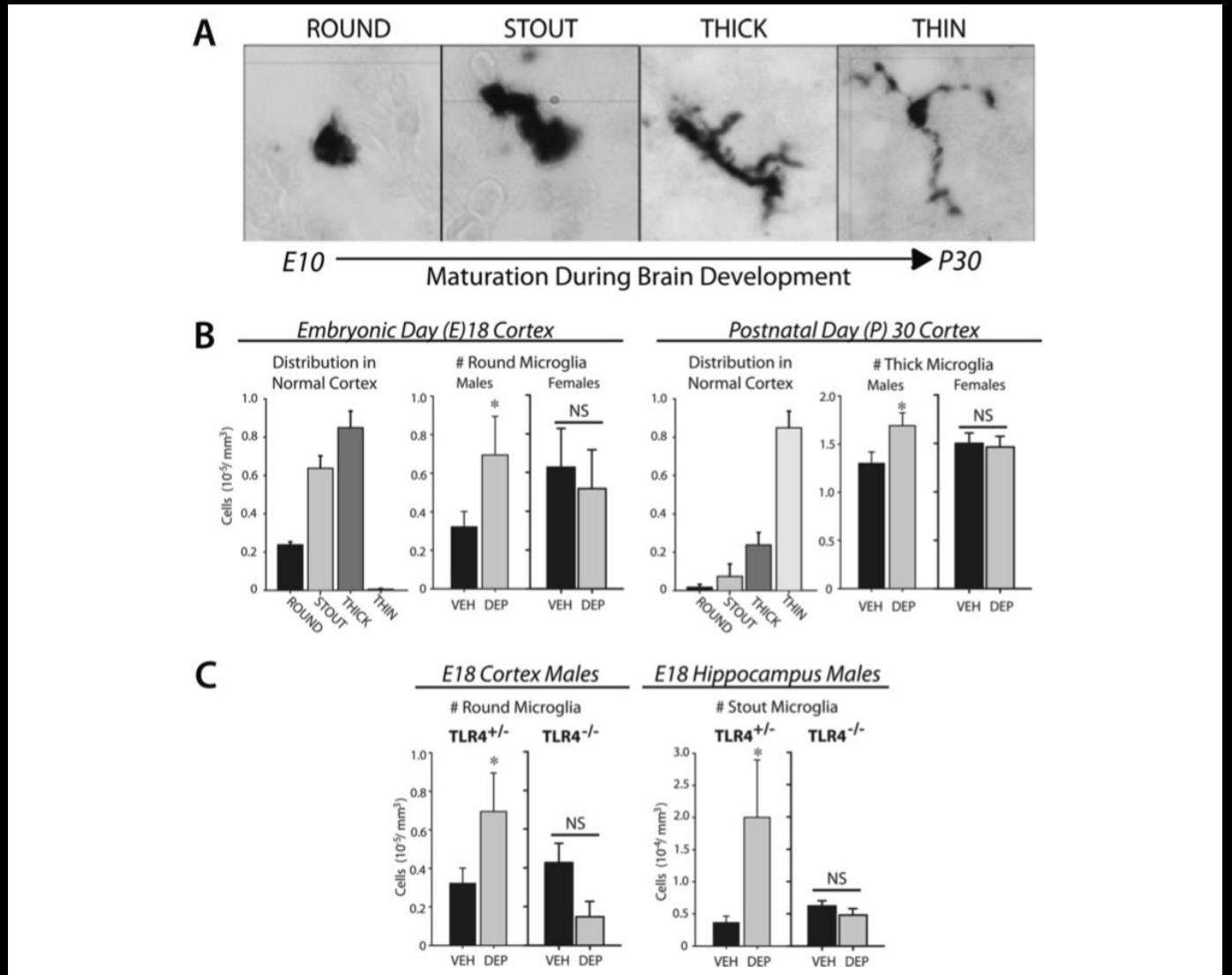


Fig. 1. (A) Microglia transition from a round/amoeboid morphology early in development (~E10, when they first begin to colonize the CNS) to a ramified morphology with small cell bodies and thin processes by P30. (B) DEP increases the number of round microglia in cortex at E18, and the number of thick microglia at P30, in males only, suggesting DEP delays their maturation and/or leads to their activation. There are similar effects in other brain regions including hippocampus (not shown) (C) All of the effects of DEP in males are dependent on TLR4. $^*p < 0.05$ for all; NS = not significantly different.

Please cite this article as: Bilbo, S.D., et al., Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spect..., Exp. Neurol. (2017), http://dx.doi.org/10.1016/j.expneurol.2017.07.002

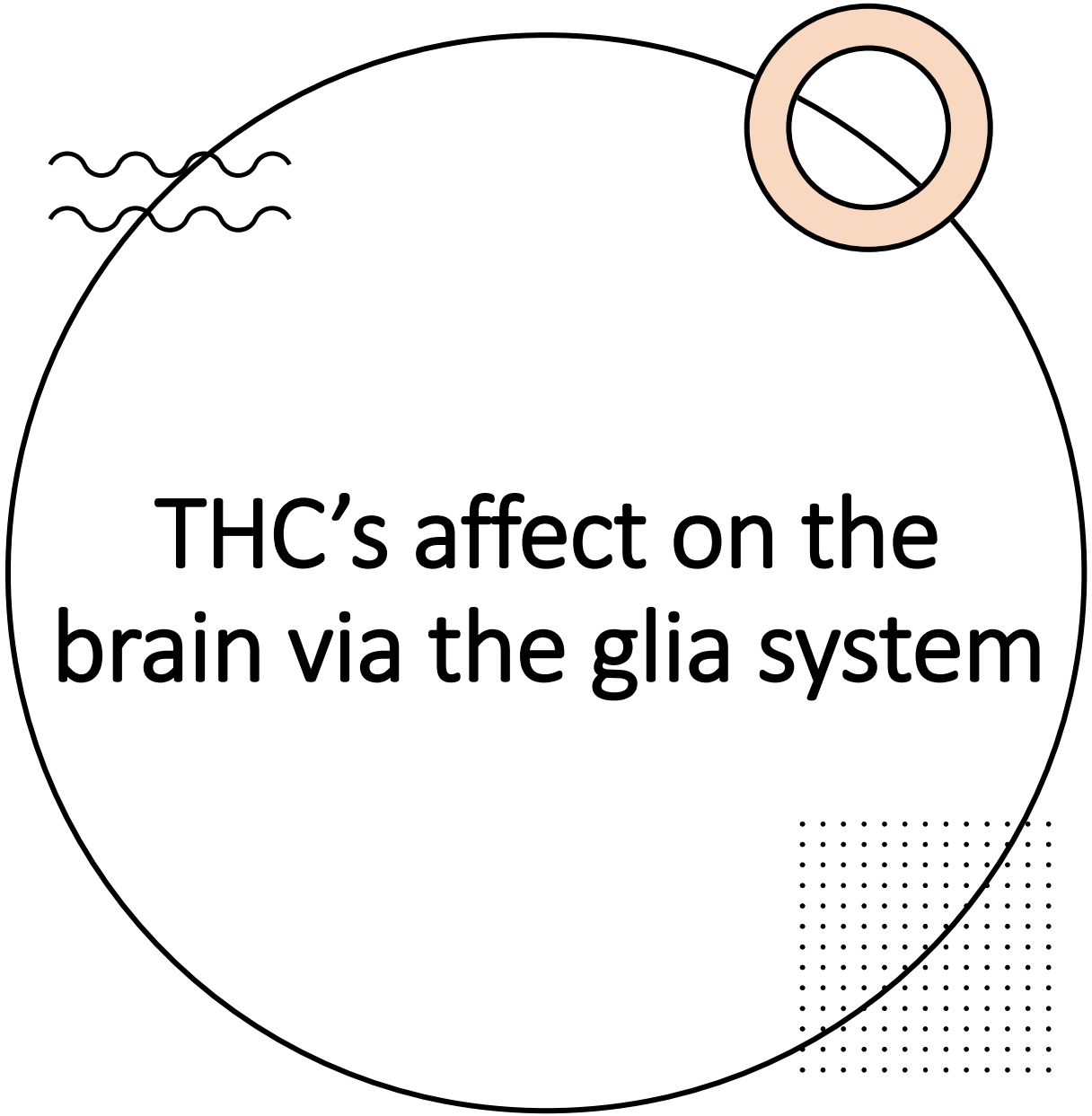
Vaccines and neuroinflammation. International J of Pub Health & Safety, Vol 3(3)1-11. Giannotta G, Giannotta N

- “**Conclusion:** The molecular mechanisms presented here demonstrate **how peripheral cytokines, expressed after vaccination, can cause neuroinflammation** in some subjects, after **microglia activation**, depending on the immunogenetic background and the innate immune memory.”

Microglia activation post stroke

‘The activation of microglia after ischemia involves several stereotypical events including morphological transformation, proliferation and polarization.”

Microglial activation after ischaemic stroke. Stroke Vasc Neurol. 2019 May 10;4(2):71-74.



Conclusion

- Daily low-intensity CB_1 receptor activation by THC during adolescence may disable critical functions served by microglia until young adulthood with potentially wide-ranging consequences for brain and mental health.

Frequent Low-Dose Δ^9-Tetrahydrocannabinol in Adolescence Disrupts Microglia Homeostasis and Disables Responses to Microbial Infection and Social Stress in Young Adulthood. Biol Psychiatry. 2022 Dec 1;92(11):845-860.

Faces of Neuroinflammation Outline

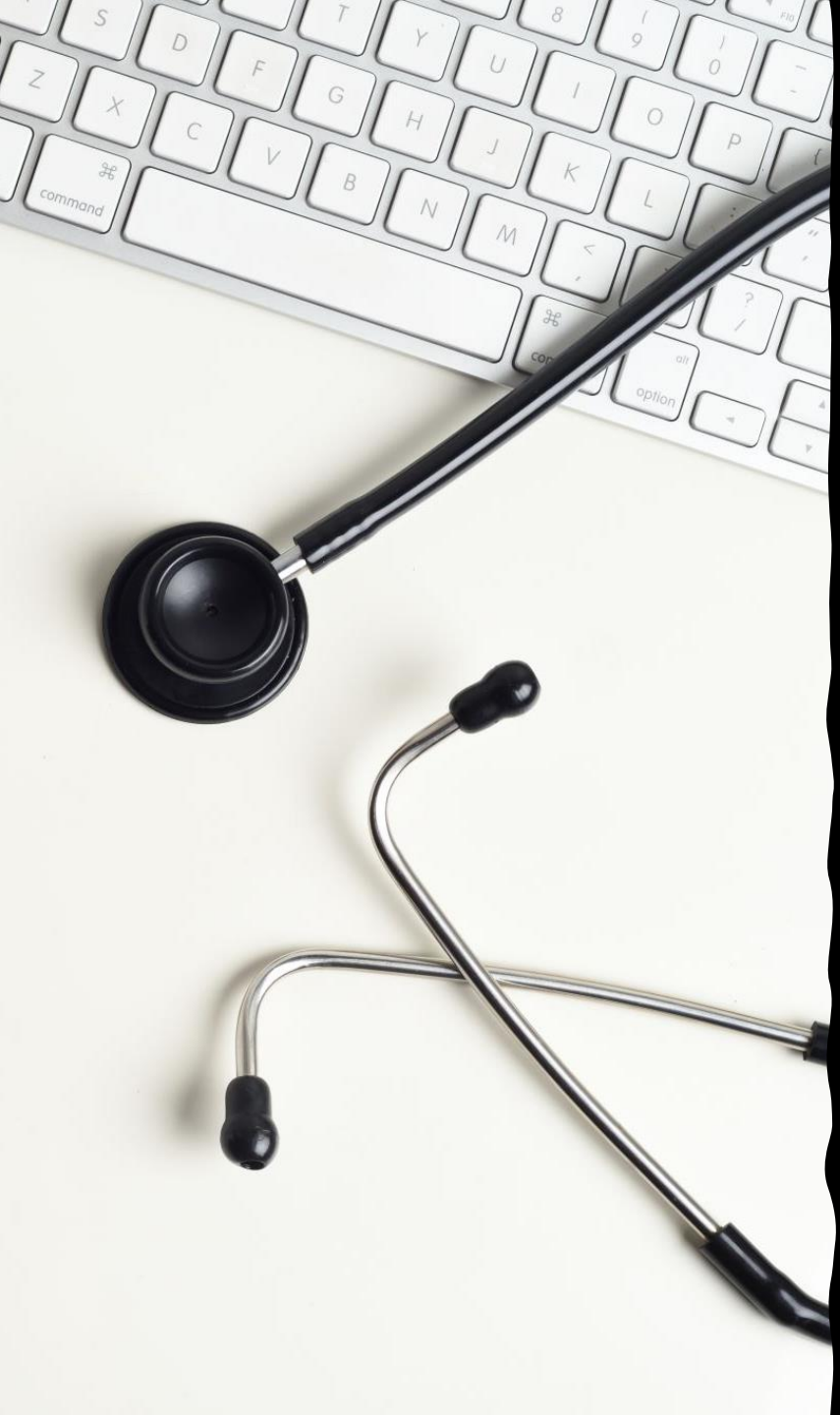
- Microglia activation
- Signs and symptoms
- Neurophysiology
- Conditions
- **Clinical web**
- Cases

Microglia activation:

the clinical web

The Clinical Web

- History
- Physical exam
- Labs/imaging
- Care model: systems biology
  - Diet/lifestyle
  - Nutraceuticals
  - Advanced care



The Clinical Web

- **History**
- Physical exam
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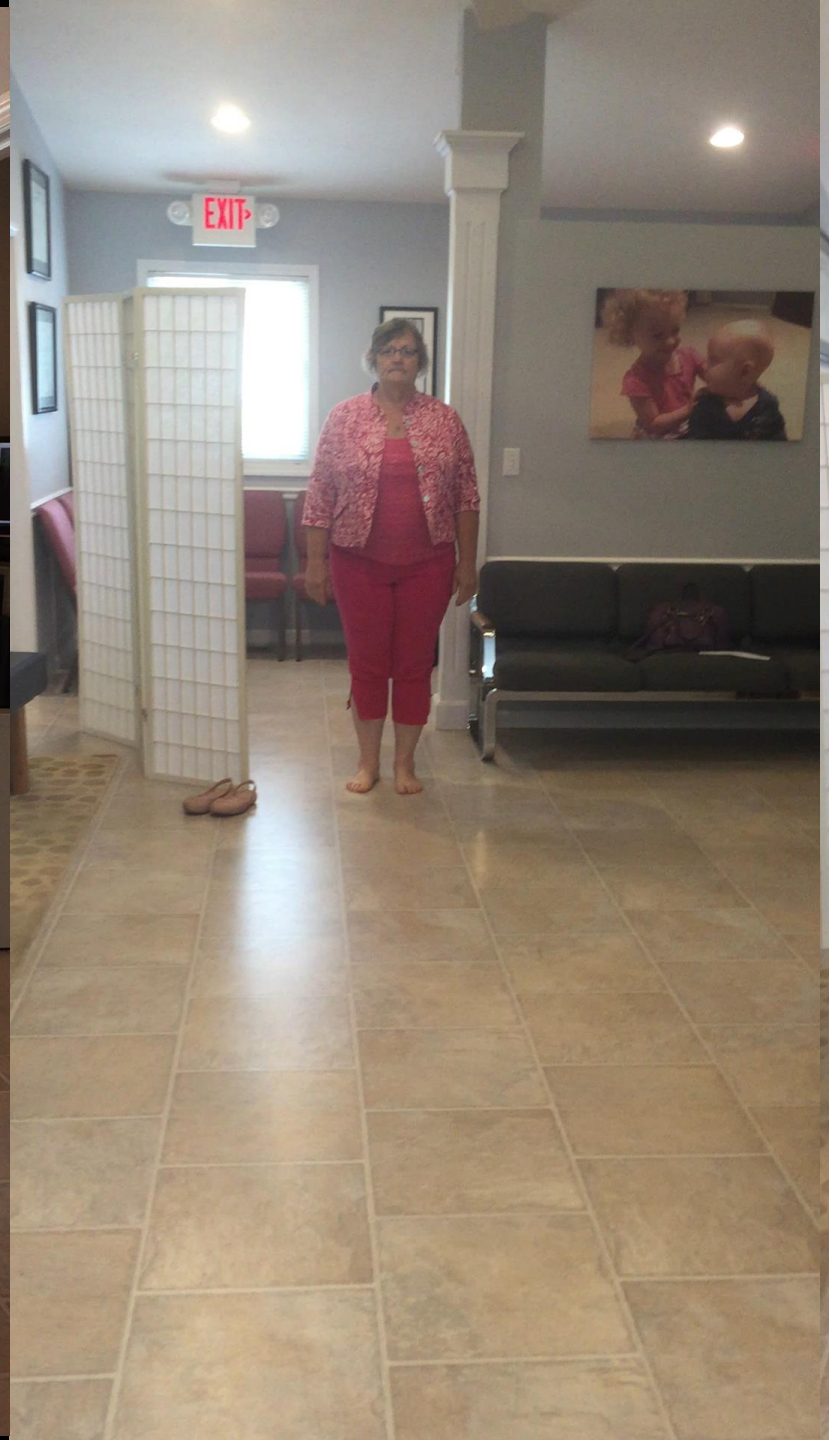
  - Diet/lifestyle
  - Nutraceuticals
  - Advanced care

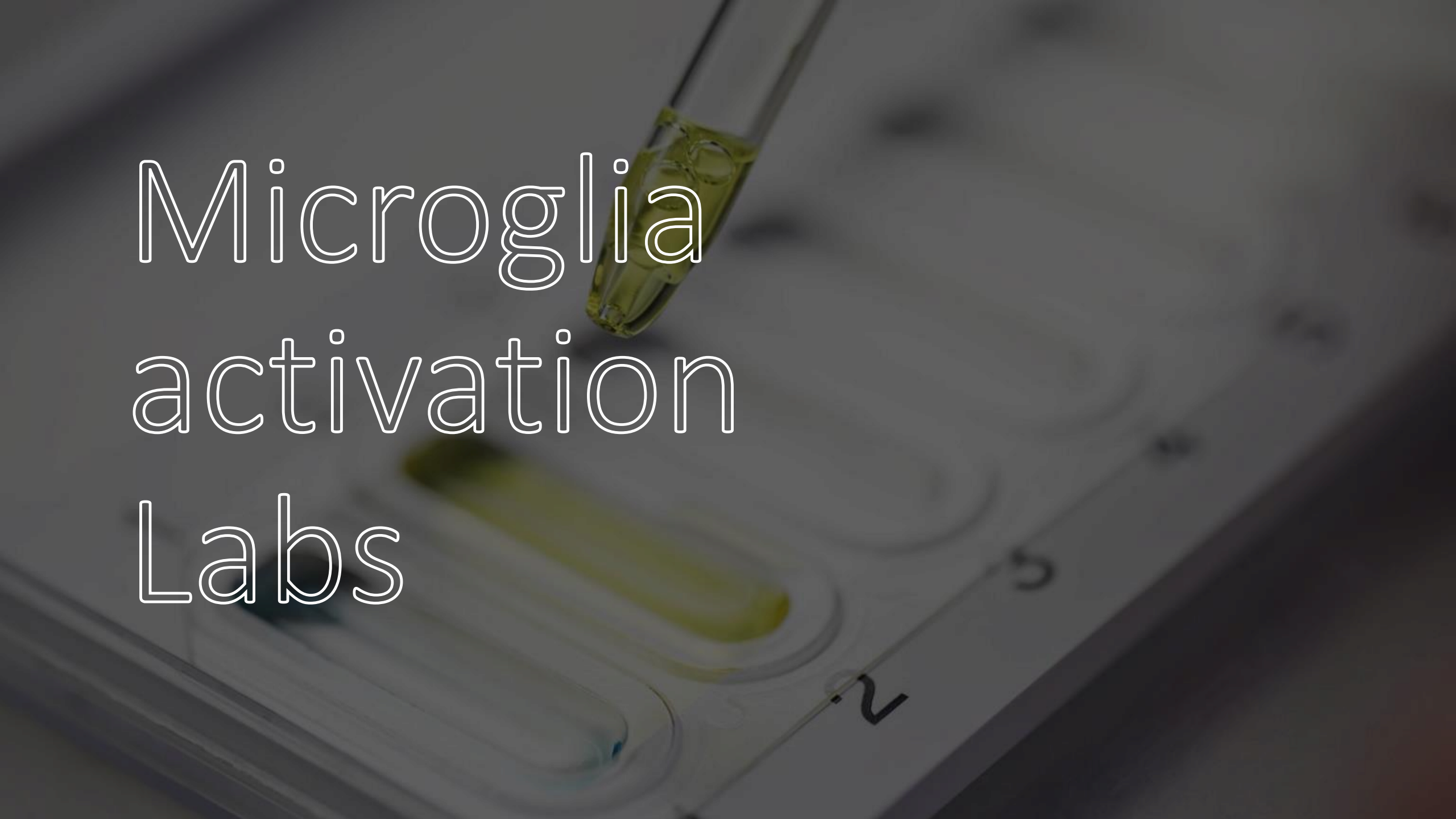
Gait analysis: variability & speed

Balance

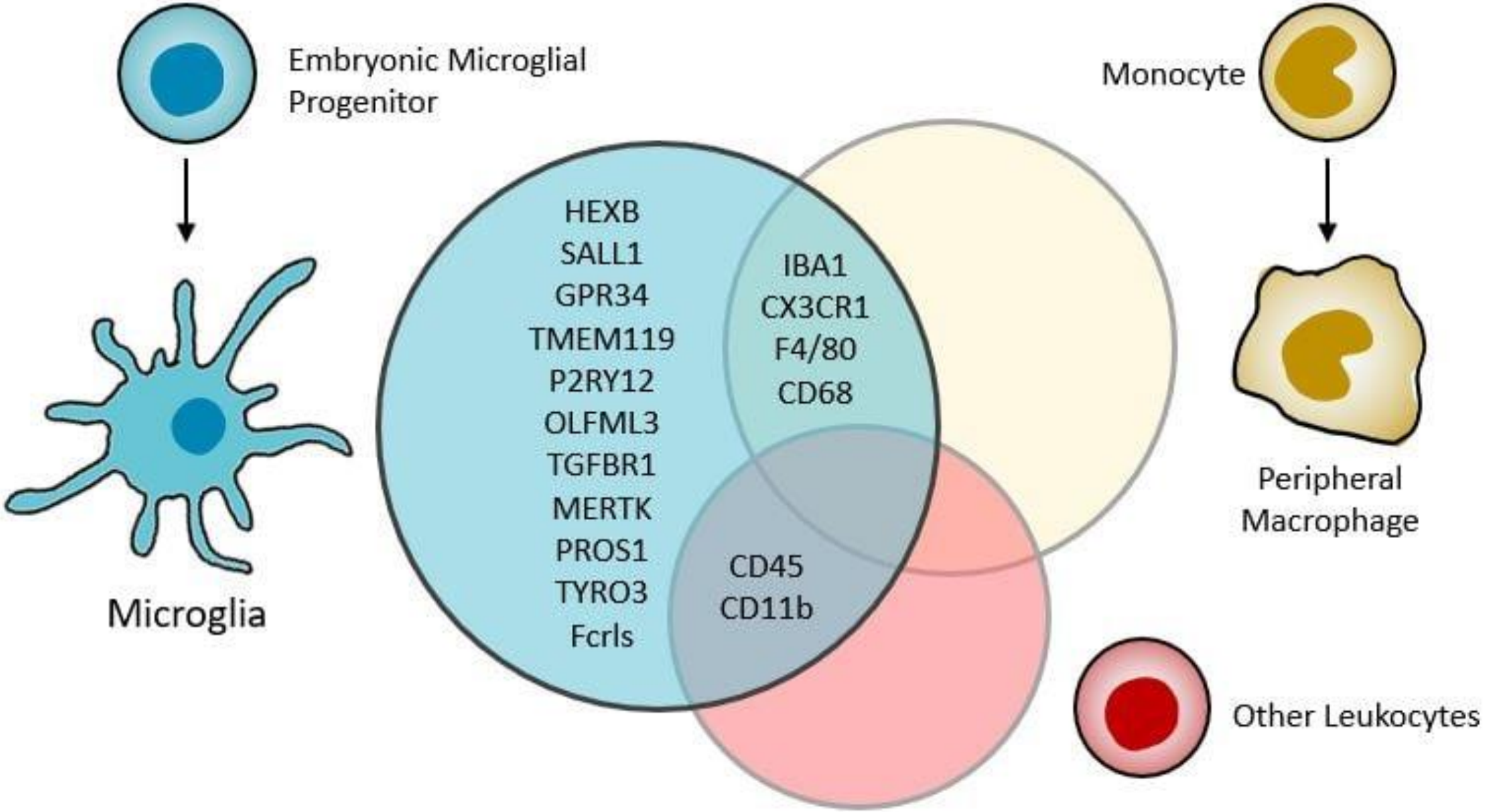
Right arm swing



EXIT

EXIT



Microglia activation Labs


Embryonic Microglial Progenitor
Monocyte
HEXB
SALL1
GPR34
TMEM119
P2RY12
OLFML3
TGFBR1
MERTK
PROS1
TYRO3
Fcrls
IBA1
CX3CR1
F4/80
CD68
CD45
CD11b
Microglia
Peripheral Macrophage
Other Leukocytes

General microglial markers

- Iba1
- CD68
- CD206
- CD45.

Labs to consider

- MMP-9
- C-reactive protein
- Ferritin
- Interleukin-6
- Fibrinogen

Indicators of inflammation

1. elevated ferritin
2. elevated BUN with normal creatinine
3. elevated uric acid
4. elevated cholesterol, LDL
5. elevated ALT, GGT, AST
6. elevated monocytes
7. elevated RDW
8. elevated CRP
9. Insulin resistance marker (Tri/HDL, Chol/Tri, Glucose, HGB A1C, elevated T3 uptake, insulin, C peptide)

Labs to consider

- Blood brain barrier
- Intestinal permeability with LPS evaluation
- Specialty labs

The Clinical Web

- History
- Physical exam
- Labs/imaging
- **Care model: systems biology**
  - Diet/lifestyle
  - Nutraceuticals
  - Advanced care

Systems biology approach

BAIL EM out

BAIL EM out

- Body balance
- Blood sugar management
- Anemia (oxygen)
- Adequate sleep
- Inflammation
- Infection
- Liver (GI N to S)
- Exercise
- Estrogen (hormones)
- Environment (toxic burden)
- Microbiome
- Methylation (genetics)

BAIL EM out

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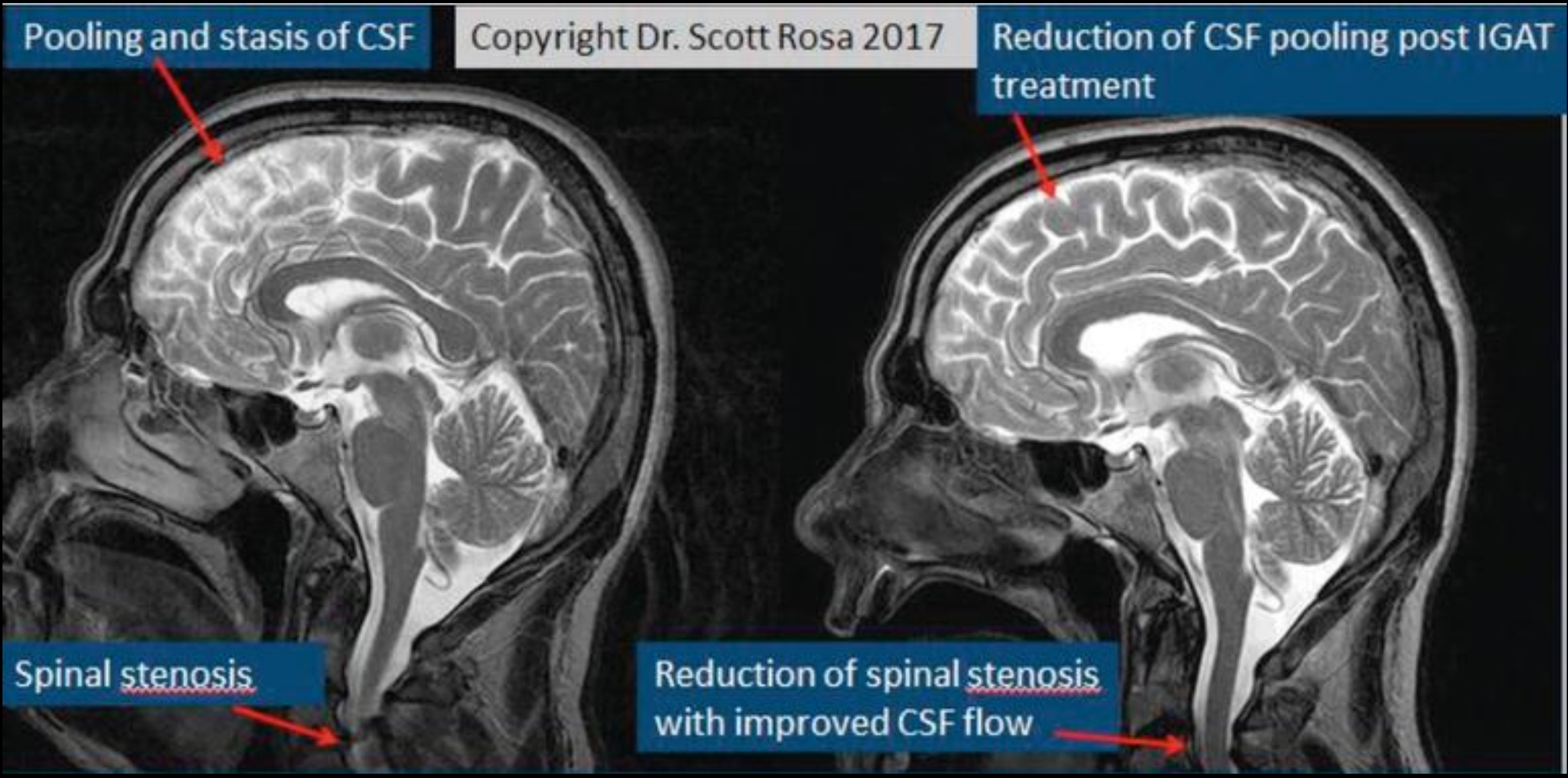
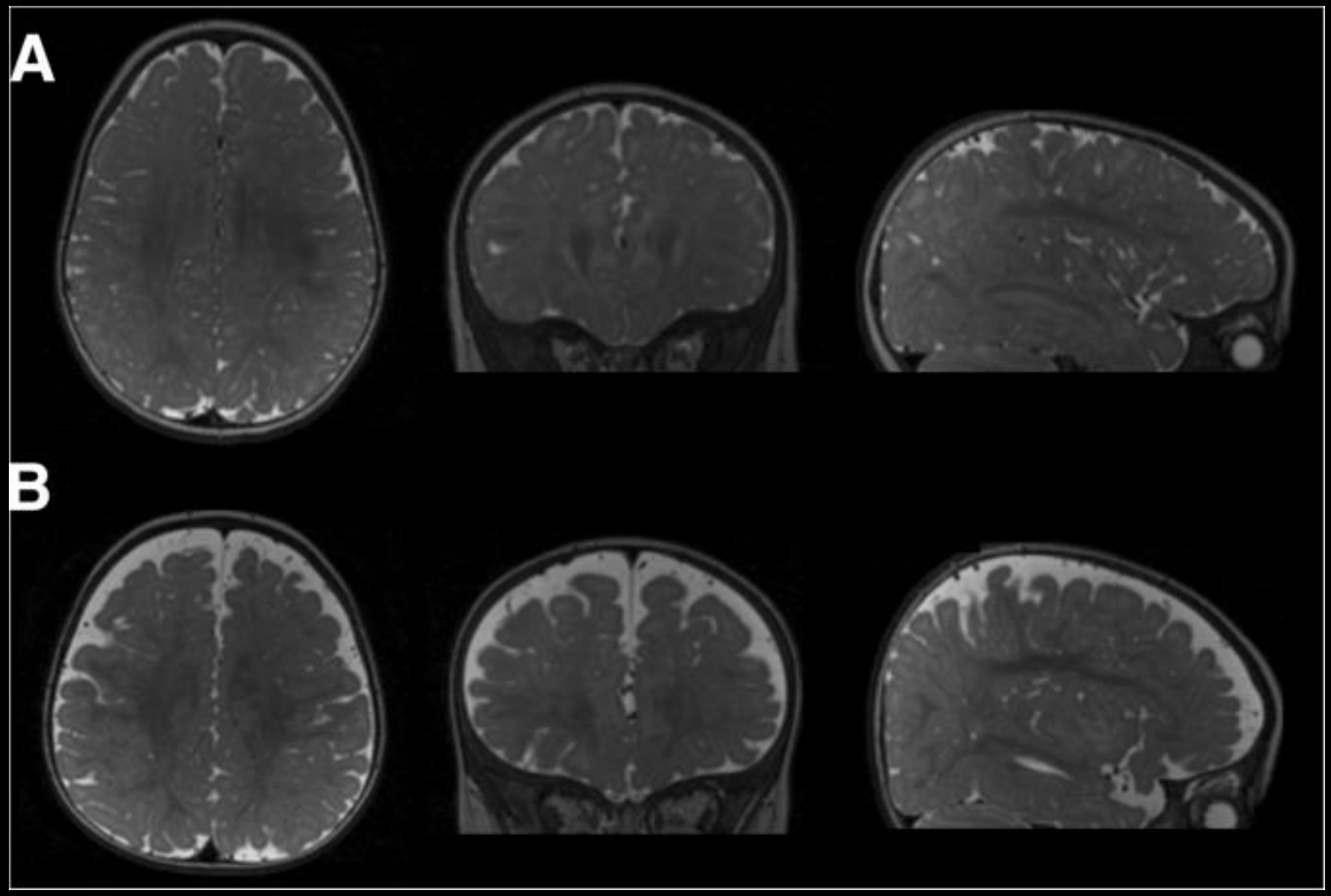

Pooling and stasis of CSF
Copyright Dr. Scott Rosa 2017
Reduction of CSF pooling post IGAT treatment
Spinal stenosis
Reduction of spinal stenosis with improved CSF flow

Shen, M.D. Cerebrospinal fluid and the early brain development of autism. *J Neurodevelop Disord* **10**, 39 (2018).

- **a** T2-weighted images of an infant with a normal MRI at 6 months of age, who was confirmed as having typical development at 2 years of age. **b** Similar T2-weighted images of an infant with excessive extra-axial CSF at 6 months, who was diagnosed with ASD at 2 years of age. [CSF is indicated as brighter regions in these images. Images are of a horizontal section (left), coronal section (middle), and sagittal section (right) through the brain.]



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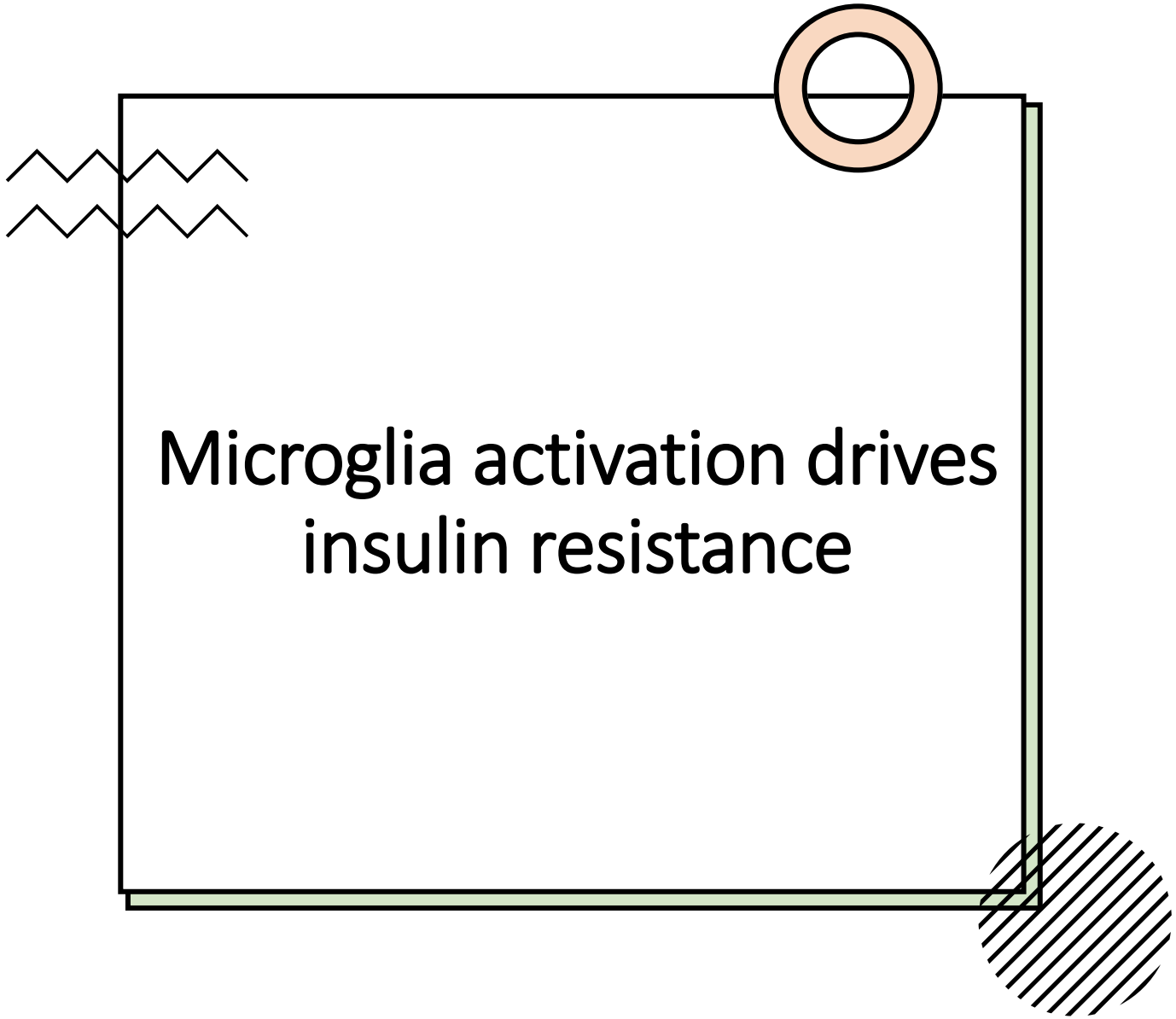

"the disruption between microglia activation by insulin signaling is a new pathological mechanism behind insulin resistance in the aging brain."

Insulin activates microglia and increases COX-2/IL-1β expression in young but not in aged hippocampus. Brain Res. 2020 Aug 15;1741:146884.

Microglia Influences brain control of energy balance

‘Accumulating evidence shows that hypothalamic microglial cells located at the vicinity of these circuits can influence the brain control of energy balance.’

Microgliosis: a double-edged sword in the control of food intake. FEBS J. 2024 Feb;291(4):615-631.

BAIL EM out

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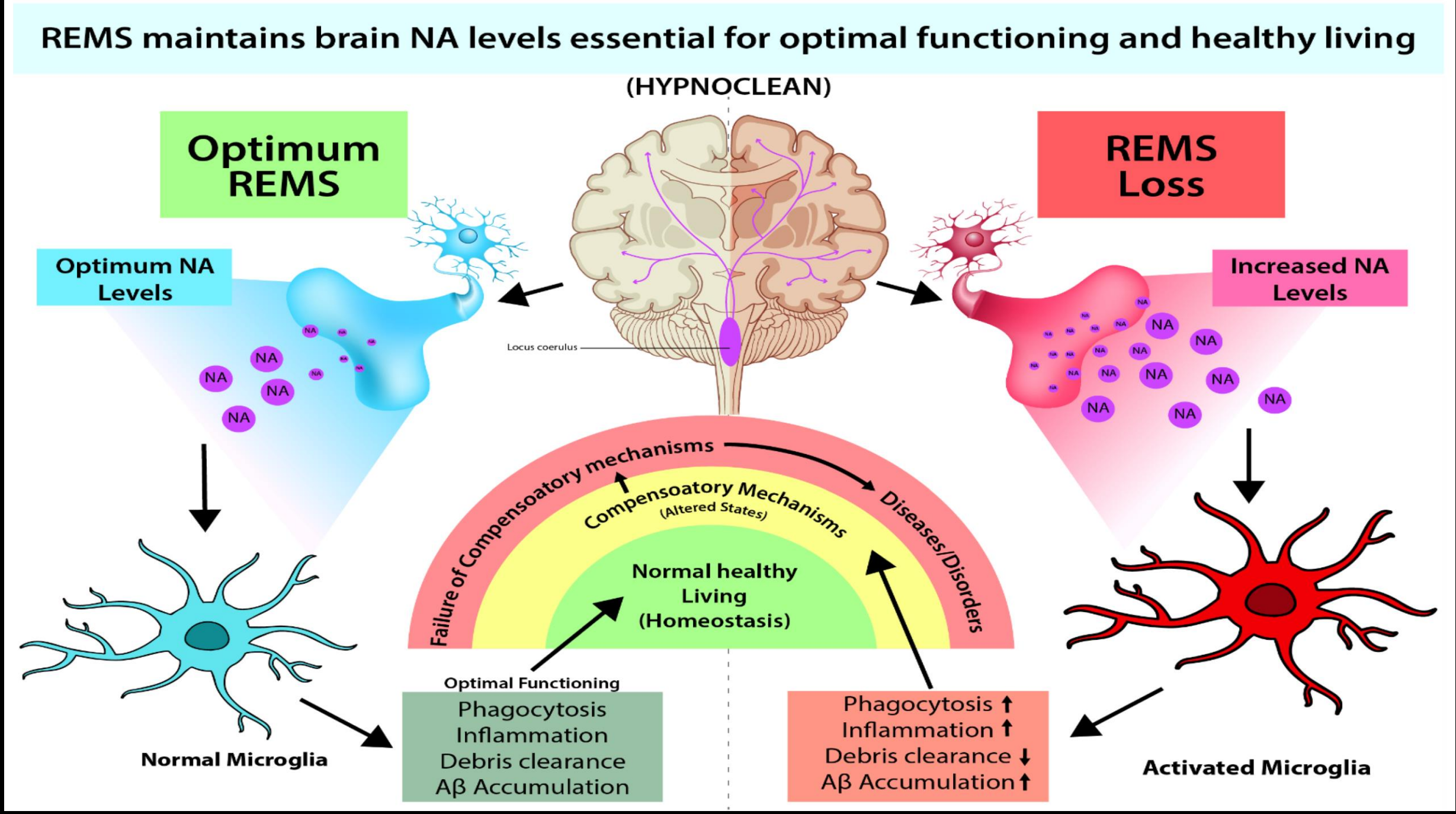
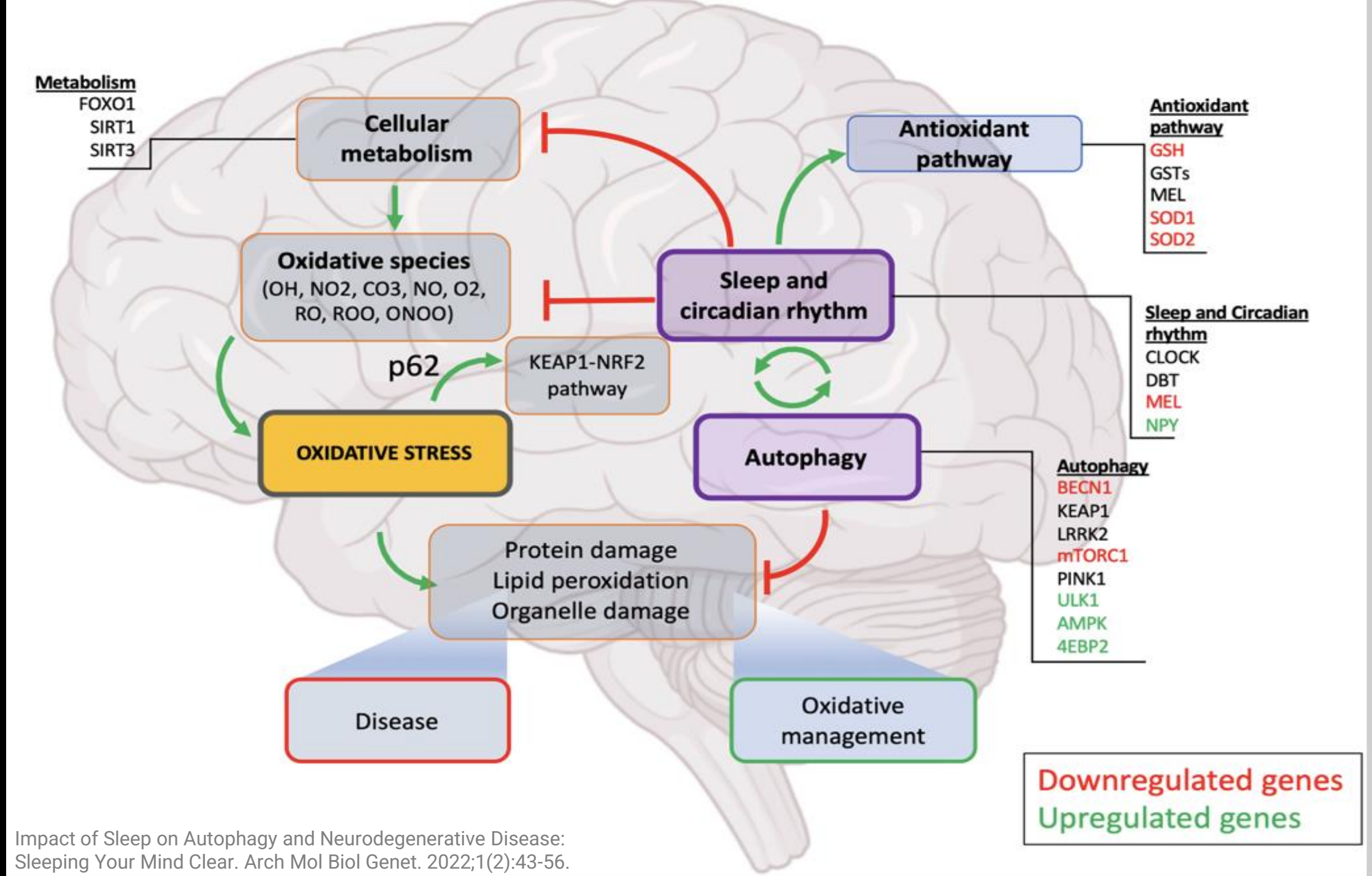


Microglia Activation and Noradrenergic System. Scholarly Community Encyclopedia

Impact of Sleep on Autophagy and Neurodegenerative Disease: Sleeping Your Mind Clear. Arch Mol Biol Genet. 2022;1(2):43-56. Deutsch S, Malik BR.

- Sleep is an evolutionarily conserved phenomenon which has survived tremendous evolutionary pressures. Its disruption has deleterious implications for human health. The importance of sleep is illustrated by the fact that sleep deprivation in many combination of intrinsic old age and in heimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD) and Huntington's disease (HD). One of the key effects of sleep disruption is increased levels of reactive oxygen/nitrogen species (ROS/RNS) and accumulation of protein aggregates, such as Amyloid β and alpha-Synuclein. A possible mechanism of protein plaque clearance is its autophagic degradation through endo-lysosomal pathways. In this review, we will discuss how sleep disruption is intimately linked with neurodegenerative diseases. We will also discuss the evidence that cellular autophagy and antioxidant defense are regulated by sleep, making it a target for future intervention strategies to tackle neurodegenerative diseases.

sleep disruption is intimately linked with neurodegenerative diseases.



Impact of Sleep on Autophagy and Neurodegenerative Disease: Sleeping Your Mind Clear. Arch Mol Biol Genet. 2022;1(2):43-56.

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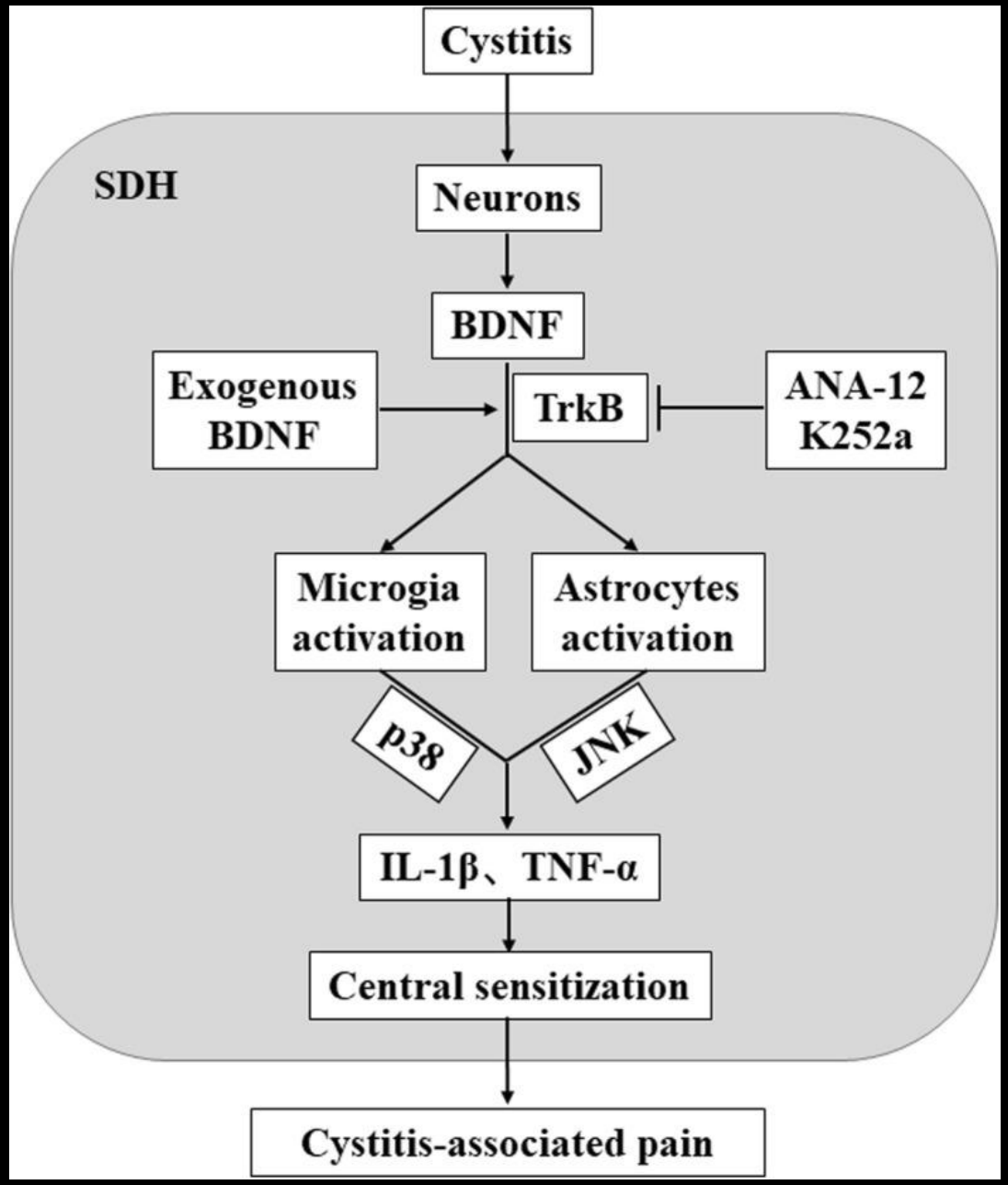
Genitourinary infections drive microglia activation



BDNF promotes activation of astrocytes and microglia contributing to neuroinflammation and mechanical allodynia in cyclophosphamide-induced cystitis. J Neuroinflammation. 2020 Jan 13;17(1):19.

Genitourinary infections drive cognitive decline

"Urinary tract infections are associated with features of cognitive decline and memory deficits"

Urinary Tract Infections Impair Adult Hippocampal Neurogenesis. Biology (Basel). 2022 Jun 9;11(6):891.

Genitourinary infections drive cognitive decline

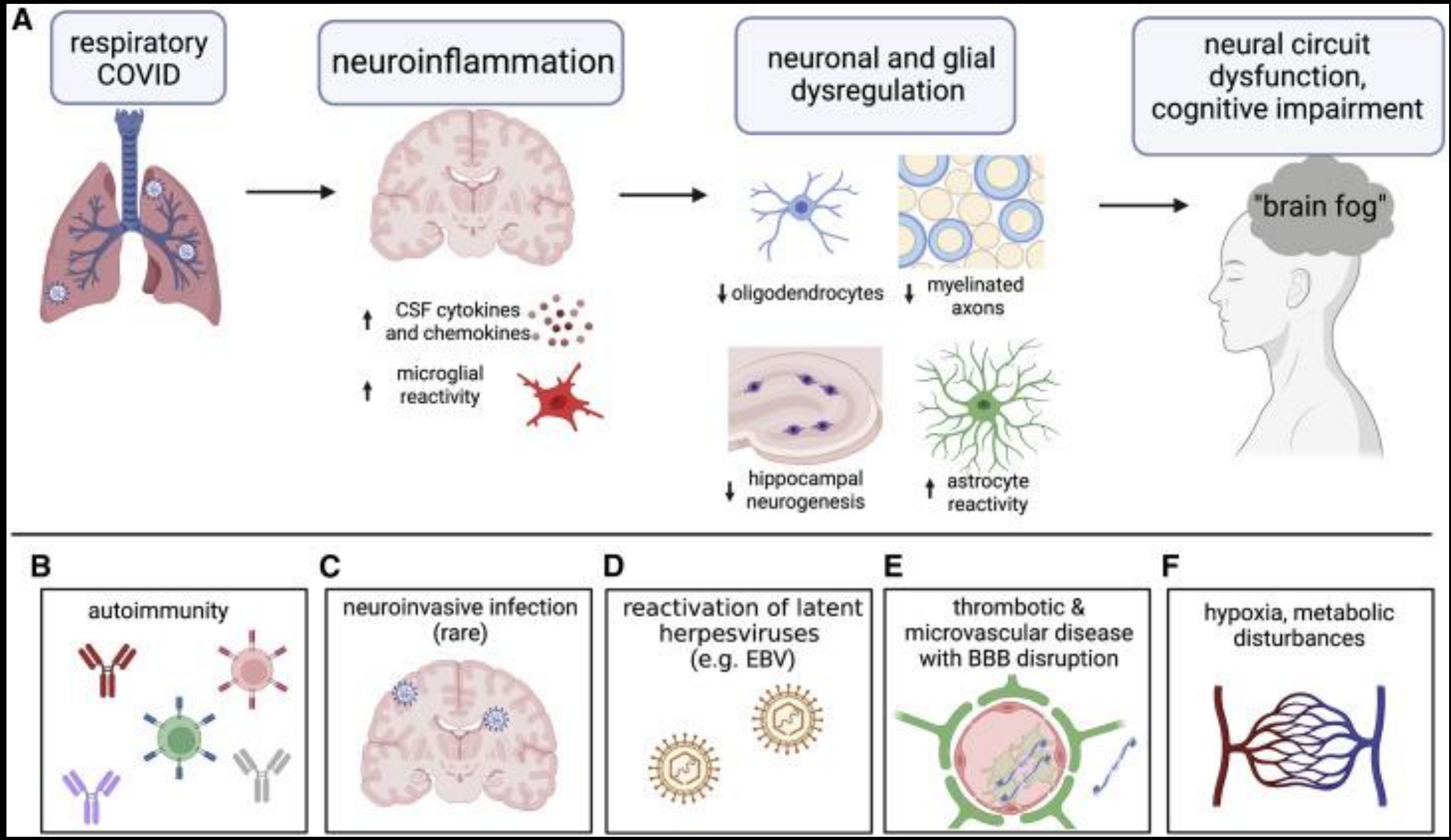
"Here, we present hippocampal neurogenesis as a possible contributor to cognitive changes associated with urinary tract infections."

Urinary Tract Infections Impair Adult Hippocampal Neurogenesis. Biology (Basel). 2022 Jun 9;11(6):891.

Microglia activation and long COVID

‘sustained activation of microglia and astrocytes is likely to play a pivotal role in the chronic neuroinflammation following on from SARS-CoV-2 infection. Inflammatory cytokines are critically involved in the process of learning and memory.”

Long Covid brain fog: a neuroinflammation phenomenon? Oxf Open Immunol. 2022 Sep 27;3(1):iqac007.



The neurobiology of long COVID. Neuron. 2022 Nov 2;110(21):3484-3496.

The Clinical Web

- History
- Physical exam
- Labs/imaging
- Care model: systems biology
  - **Diet/lifestyle**
  - Nutraceuticals
  - Advanced care

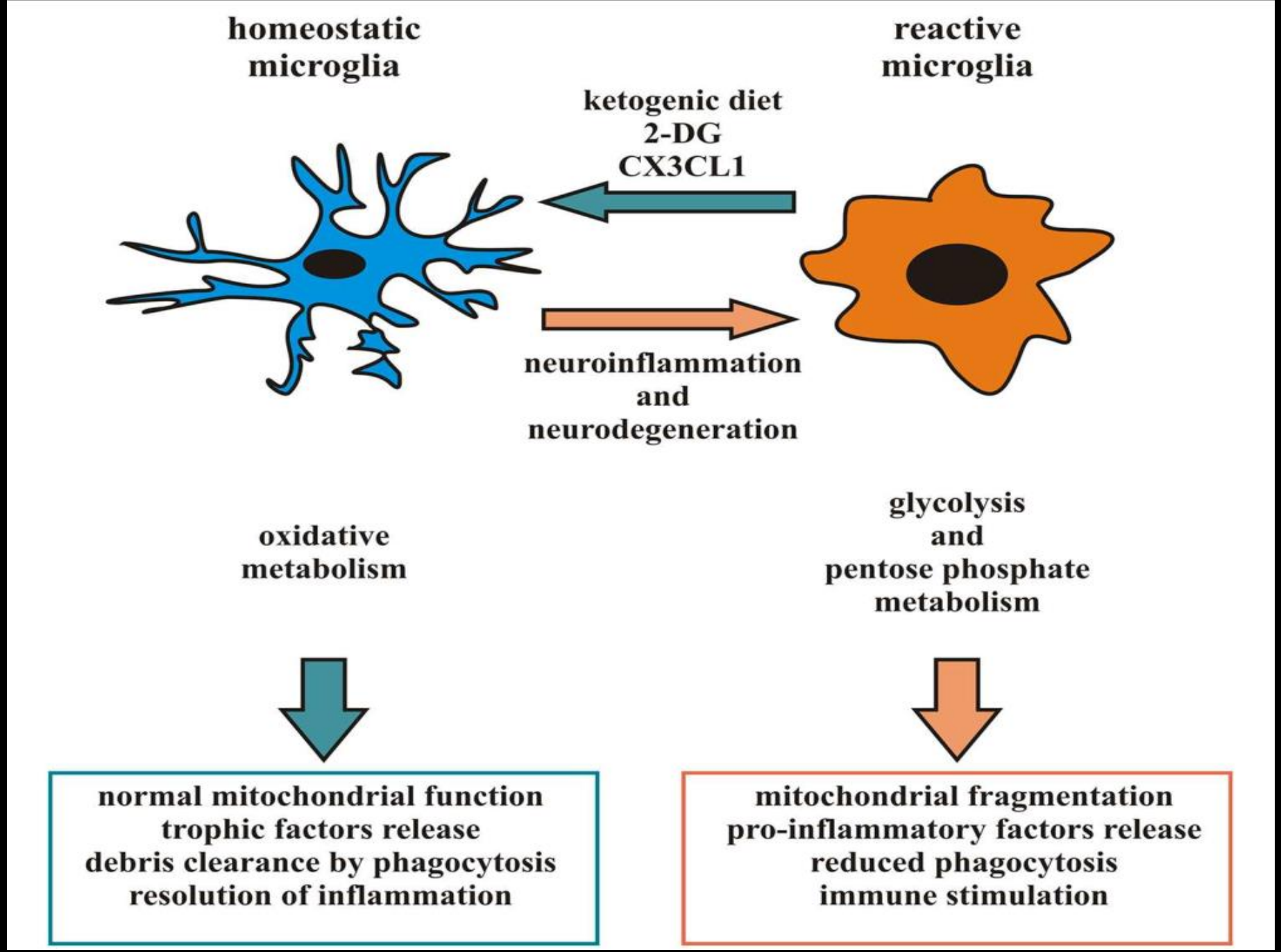
Diet & Lifestyle factors

- Low inflammatory diet
- Intermittent fasting
- Identify IgG food sensitivities
- Sleep
- Reduce stress
- Resistance training

“**Conclusion:** The present study suggests that ketogenic metabolism promotes macrophage polarization to M2, inhibits an inflammatory response, and alleviates the loss of gray matter after SCI.”

SCI – Spinal cord injury

Neuroprotective Effect of Ketone Metabolism on Inhibiting Inflammatory Response by Regulating Macrophage Polarization After Acute Cervical Spinal Cord Injury in Rats. Front Neurosci. 2020 Oct 23;14:583611. Lin J, et al



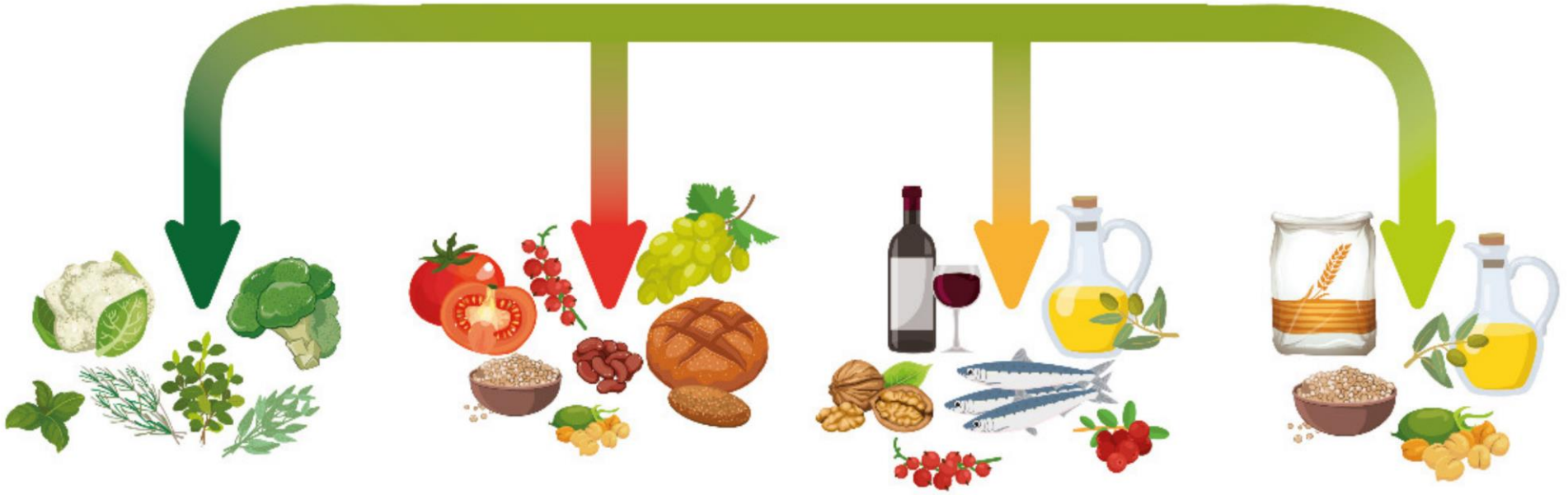
Metabolic Reprograming of Microglia in the Regulation of the Innate Inflammatory Response. Front Immunol. 2020 Mar 20;11:493

Ketogenic diet disrupts glycolysis pathway

- Recent work indicates that several mechanisms may exist for the **ketogenic diet** including disruption of glutamatergic synaptic transmission, **inhibition of glycolysis**, and activation of ATP-sensitive potassium channels.

The ketogenic diet: metabolic influences on brain excitability and epilepsy. Trends Neurosci. 2013 Jan;36(1):32-40.

Mediterranean diet



↑ECs

↑ECs

↑ECs

CB2R ← **FAAH-inhibition** → **CB1R** → **GPR55/TRPV1**

cAMP/PKA/CREB/Sirt1

Nrf2

PGC-1α

PPAR-γ

- ↓ proinflammatory mediators
- ↓ ROS and RNS
- ↓ neuronal apoptosis
- ↑ neurogenesis
- ↑ M2 microglia polarization
- ↑ BBB thigtening
- ↑ antioxidant defense
- ↑ neurotrophin production

- ↑ neuroprotection
- ↑ cognitive performance
- ↑ synaptic plasticity
- ↑ neurotrophin production

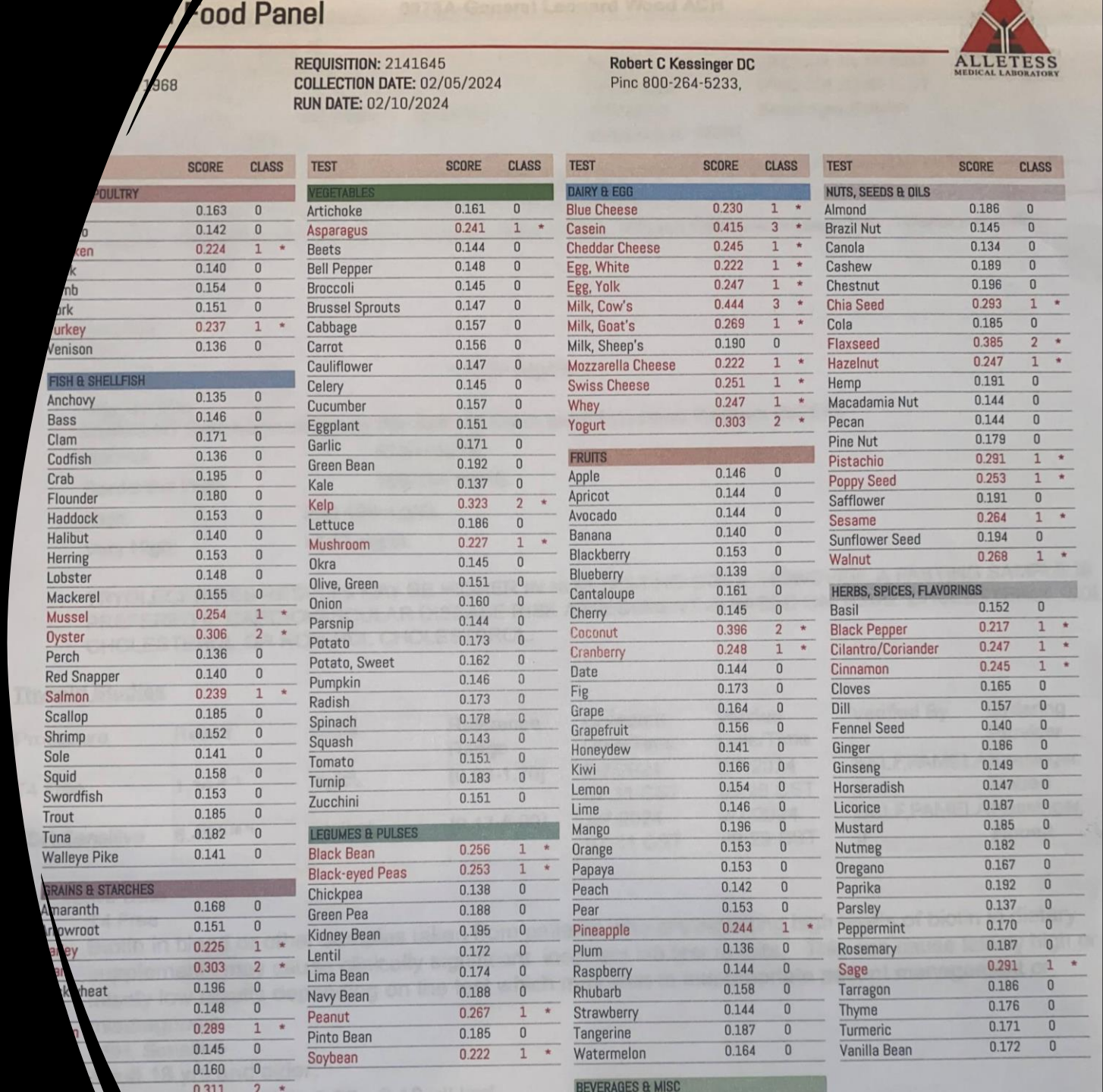
- ↓ neuroinflammation
- ↓ neuronal apoptosis
- ↑ synaptic plasticity
- ↑ downstream neuroprotective signalling

“**Conclusions:** Taken together, our results suggest that IF induces adaptive responses in the brain and periphery that can suppress inflammation and preserve cognitive function in an animal model of systemic bacterial infection.”

IF – Intermittent Fasting

Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. J Neuroinflammation. 2014 May 6;11:85. Vasconcelos AR, et al

IgG Food Sensitivity Testing



Food Panel

ALLETESS MEDICAL LABORATORY

1968

REQUISITION: 2141645
COLLECTION DATE: 02/05/2024
RUN DATE: 02/10/2024

Robert C Kessinger DC
Pinc 800-264-5233,

	SCORE	CLASS
POULTRY		
	0.163	0
	0.142	0
ken	0.224	1 *
k	0.140	0
nb	0.154	0
rk	0.151	0
urkey	0.237	1 *
Venison	0.136	0
FISH & SHELLFISH		
Anchovy	0.135	0
Bass	0.146	0
Clam	0.171	0
Codfish	0.136	0
Crab	0.195	0
Flounder	0.180	0
Haddock	0.153	0
Halibut	0.140	0
Herring	0.153	0
Lobster	0.148	0
Mackerel	0.155	0
Mussel	0.254	1 *
Oyster	0.306	2 *
Perch	0.136	0
Red Snapper	0.140	0
Salmon	0.239	1 *
Scallop	0.185	0
Shrimp	0.152	0
Sole	0.141	0
Squid	0.158	0
Swordfish	0.153	0
Trout	0.185	0
Tuna	0.182	0
Walleye Pike	0.141	0
GRAINS & STARCHES		
maranth	0.168	0
owroot	0.151	0
ey	0.225	1 *
	0.303	2 *
heat	0.196	0
	0.148	0
	0.289	1 *
	0.145	0
	0.160	0
	0.311	2 *

TEST	SCORE	CLASS
VEGETABLES		
Artichoke	0.161	0
Asparagus	0.241	1 *
Beets	0.144	0
Bell Pepper	0.148	0
Broccoli	0.145	0
Brussel Sprouts	0.147	0
Cabbage	0.157	0
Carrot	0.156	0
Cauliflower	0.147	0
Celery	0.145	0
Cucumber	0.157	0
Eggplant	0.151	0
Garlic	0.171	0
Green Bean	0.192	0
Kale	0.137	0
Kelp	0.323	2 *
Lettuce	0.186	0
Mushroom	0.227	1 *
Okra	0.145	0
Olive, Green	0.151	0
Onion	0.160	0
Parsnip	0.144	0
Potato	0.173	0
Potato, Sweet	0.162	0
Pumpkin	0.146	0
Radish	0.173	0
Spinach	0.178	0
Squash	0.143	0
Tomato	0.151	0
Turnip	0.183	0
Zucchini	0.151	0
LEGUMES & PULSES		
Black Bean	0.256	1 *
Black-eyed Peas	0.253	1 *
Chickpea	0.138	0
Green Pea	0.188	0
Kidney Bean	0.195	0
Lentil	0.172	0
Lima Bean	0.174	0
Navy Bean	0.188	0
Peanut	0.267	1 *
Pinto Bean	0.185	0
Soybean	0.222	1 *

TEST	SCORE	CLASS
DAIRY & EGG		
Blue Cheese	0.230	1 *
Casein	0.415	3 *
Cheddar Cheese	0.245	1 *
Egg, White	0.222	1 *
Egg, Yolk	0.247	1 *
Milk, Cow's	0.444	3 *
Milk, Goat's	0.269	1 *
Milk, Sheep's	0.190	0
Mozzarella Cheese	0.222	1 *
Swiss Cheese	0.251	1 *
Whey	0.247	1 *
Yogurt	0.303	2 *
FRUITS		
Apple	0.146	0
Apricot	0.144	0
Avocado	0.144	0
Banana	0.140	0
Blackberry	0.153	0
Blueberry	0.139	0
Cantaloupe	0.161	0
Cherry	0.145	0
Coconut	0.396	2 *
Cranberry	0.248	1 *
Date	0.144	0
Fig	0.173	0
Grape	0.164	0
Grapefruit	0.156	0
Honeydew	0.141	0
Kiwi	0.166	0
Lemon	0.154	0
Lime	0.146	0
Mango	0.196	0
Orange	0.153	0
Papaya	0.153	0
Peach	0.142	0
Pear	0.153	0
Pineapple	0.244	1 *
Plum	0.136	0
Raspberry	0.144	0
Rhubarb	0.158	0
Strawberry	0.144	0
Tangerine	0.187	0
Watermelon	0.164	0
BEVERAGES & MISC		

TEST	SCORE	CLASS
NUTS, SEEDS & OILS		
Almond	0.186	0
Brazil Nut	0.145	0
Canola	0.134	0
Cashew	0.189	0
Chestnut	0.196	0
Chia Seed	0.293	1 *
Cola	0.185	0
Flaxseed	0.385	2 *
Hazelnut	0.247	1 *
Hemp	0.191	0
Macadamia Nut	0.144	0
Pecan	0.144	0
Pine Nut	0.179	0
Pistachio	0.291	1 *
Poppy Seed	0.253	1 *
Safflower	0.191	0
Sesame	0.264	1 *
Sunflower Seed	0.194	0
Walnut	0.268	1 *
HERBS, SPICES, FLAVORINGS		
Basil	0.152	0
Black Pepper	0.217	1 *
Cilantro/Coriander	0.247	1 *
Cinnamon	0.245	1 *
Cloves	0.165	0
Dill	0.157	0
Fennel Seed	0.140	0
Ginger	0.186	0
Ginseng	0.149	0
Horseradish	0.147	0
Licorice	0.187	0
Mustard	0.185	0
Nutmeg	0.182	0
Oregano	0.167	0
Paprika	0.192	0
Parsley	0.137	0
Peppermint	0.170	0
Rosemary	0.187	0
Sage	0.291	1 *
Tarragon	0.186	0
Thyme	0.176	0
Turmeric	0.171	0
Vanilla Bean	0.172	0

Exercise and microglia activation

- Regardless of the type of exercise, treadmill running, resistance training, or swimming promote reduction in microglial activation, Aβ amyloid plaques, and pro-inflammatory cytokines after exercise.

CAUTION

A systematic review of exercise modalities that reduce pro-inflammatory cytokines in humans and animals' models with mild cognitive impairment or dementia. Exp Gerontol. 2023 May;175:112141.

Foods that can help reduce neuroinflammation include:

- Omega3, found in oily fish
- Calming minerals, such as magnesium, zinc, and potassium, found in greens, cashew nuts, almonds, coconut water, and lamb
- Blueberries (anything with the last name berry)
- Leafy greens
- Olive oil
- Curcumin, found in turmeric

The Clinical Web

- History
- Physical exam
- Labs/imaging
- Care model: systems biology
  - Diet/lifestyle
  - **Nutraceuticals**
  - Advanced care

Nutraceuticals management of neuroinflammation

- **Polyphenols** – Resveratrol (lipo), Curcumin (lipo), Apigenin, Luteolin, Baicalein, Rutin
  - Decreases NF-kB, free radicals, increases MB diversity, Balance M1 & M2 Polarization
- **Essential Fatty Acids** – EPA/DHA
  - Decreases Lipid Peroxidation, Protects Neuron Membranes, Modulates Prostaglandin Inflammation, Improves Neuron Membrane Function
- **Short Chain Fatty Acids** – Butyrate, Acetate, Propionate
  - Increase T Reg Function, Balance M1 & M2 Polarization

Nutraceuticals management of neuroinflammation

- **Nutrients** – Magnesium
  - NMDA Receptor Antagonist, Reduces Neuron Injury
- **Cannabinoids** – CBD oil
  - Neuroprotective, anti-inflammatory, immunomodulatory
- **Antioxidants** – Glutathione, Polyphenols
  - Decreases NF-kB, Free Radicals, Balance M1 & M2 Polarization, Prevent Mitochondrion, Uncoupling, Protect BBB, Protect Neurons

Blood Brain Barrier Permeability: NADPH oxidase inhibitors

- Quercetin
- Resveratrol
- Luteolin
- Berberine
- Ginkgo Biloba
- Alpha lipoic acid
- Carnitine
- Butyrate

Polyphenols promote M2 expression

- Resveratrol
- Curcumin
- Apigenin
- Baicalein
- Quercetin
- Luteolin
- Rutin

Ginkgo Biloba

- GBE has been shown to have anti-neuroinflammatory properties.

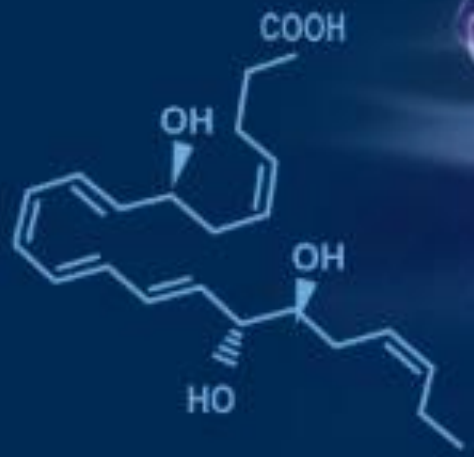
Conclusion

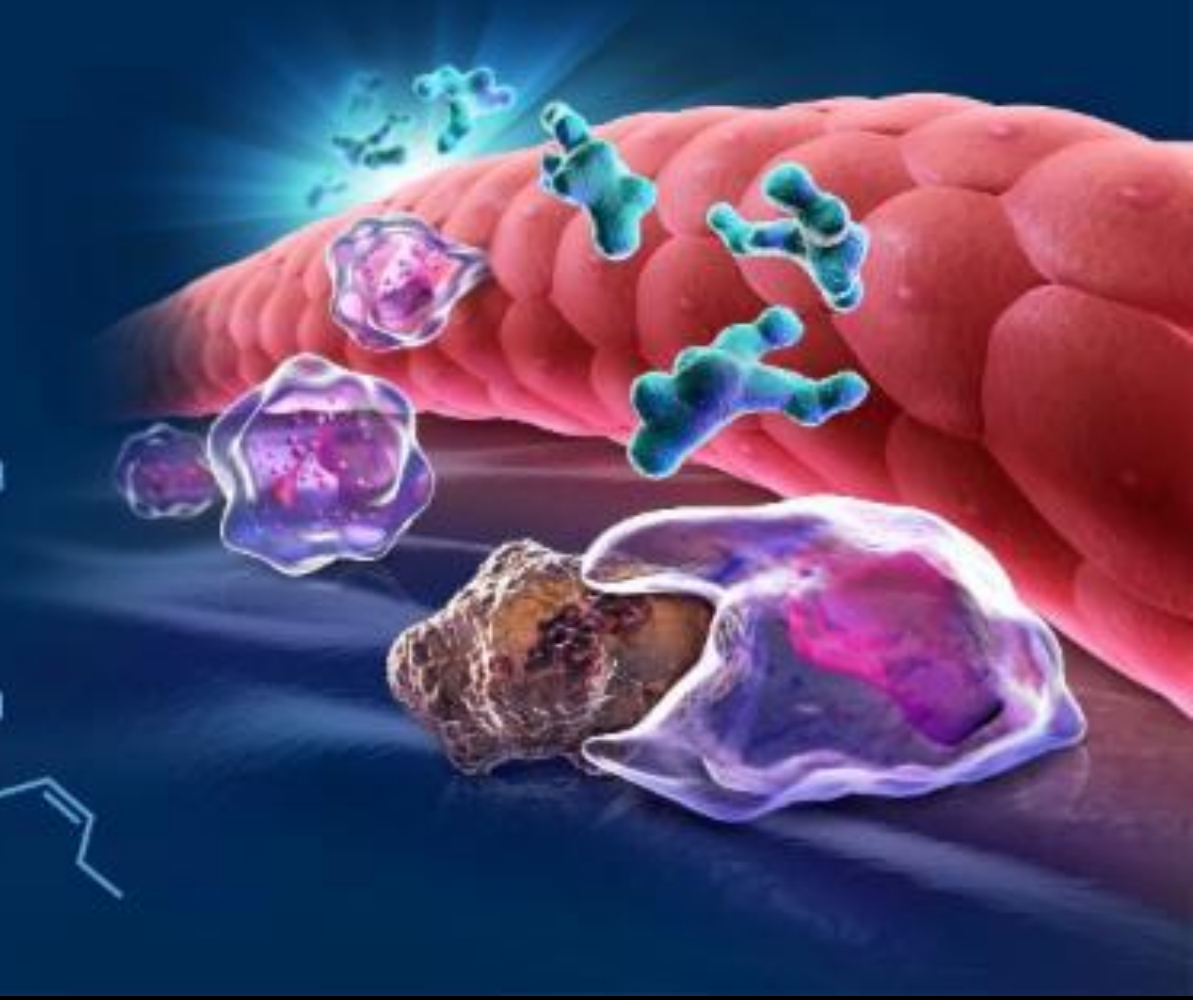
- "was able to reduce neuroinflammatory activation by targeting the COX/PGE_2 pathway."

Anti-neuroinflammatory effects of *Ginkgo biloba* extract EGb761 in LPS-activated primary microglial cells Volume 44, 15 May 2018, Pages 45-55

SPECIALIZED PRO-RESOLVING MEDIATORS

SPMs

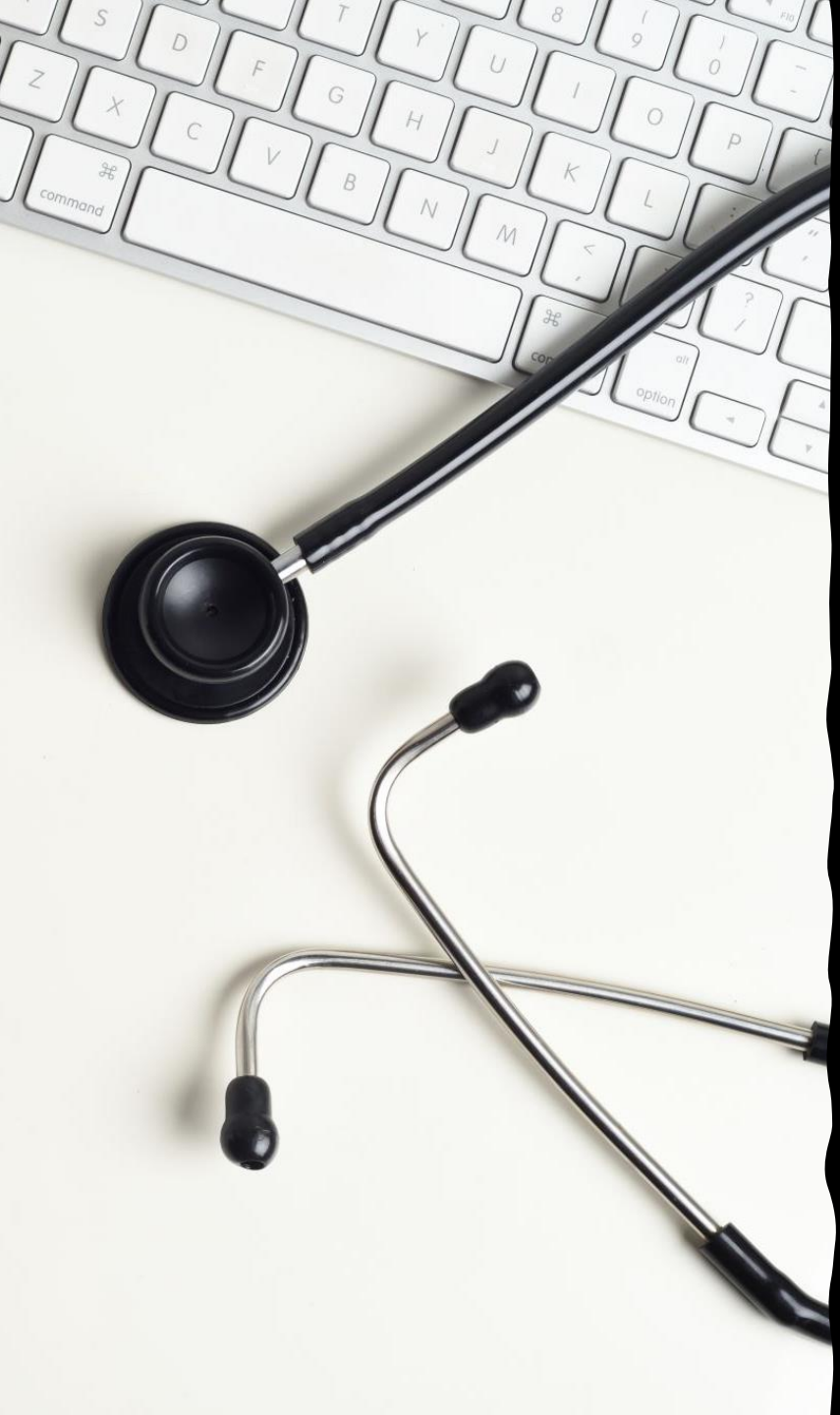




Low dose naltrexone & MA

- “Related to its anti-neuroinflammatory properties, the mechanism of action is possibly mediated via Toll-like receptor 4 antagonism, which is widely expressed on microglial cells.”

Immunometabolic Modulatory Role of Naltrexone in BV-2 Microglia Cells. Int J Mol Sci. 2021 Aug 5;22(16):8429



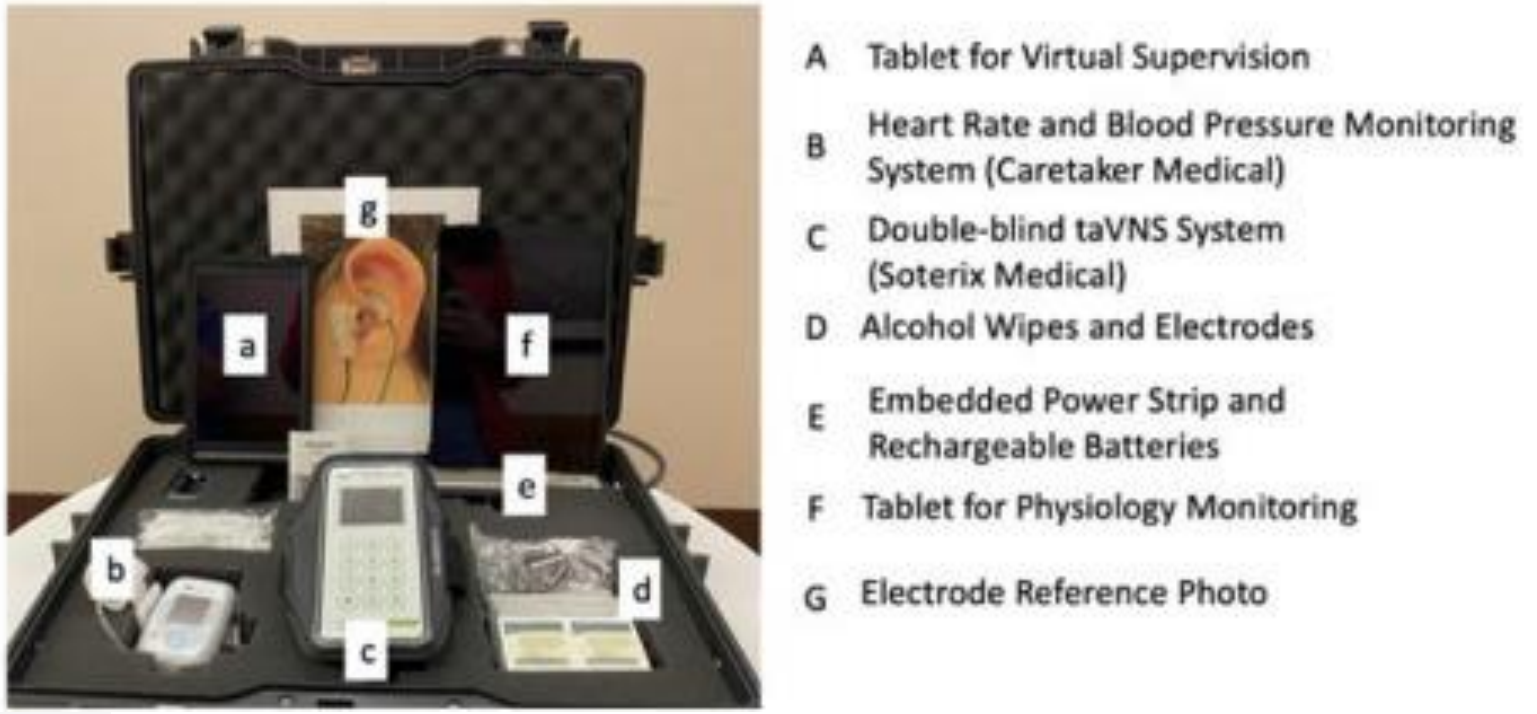
The Clinical Web

- History
- Physical exam
- Labs/imaging
- Care model: systems biology
  - Diet/lifestyle
  - Nutraceuticals
  - **Advanced care**

Vagal activation

- Upper Cervical Chiropractic
- Gargling
- Tens unit on the left tragus
- Coffee enemas
- Deep breathing exercise
- Contrast heat/cold
- Cold plunges
- Exercise

a



b

- **Overview of Stimulation Methodology.**A) we created an at-home taVNS kit that included all the components required to safely self-administer taVNS, as well as real-time monitor safety via physio monitoring. B) taVNS was administered to participant's left ear, with the anode placed on the cymba conchae of the ear, and the cathode on the tragus.

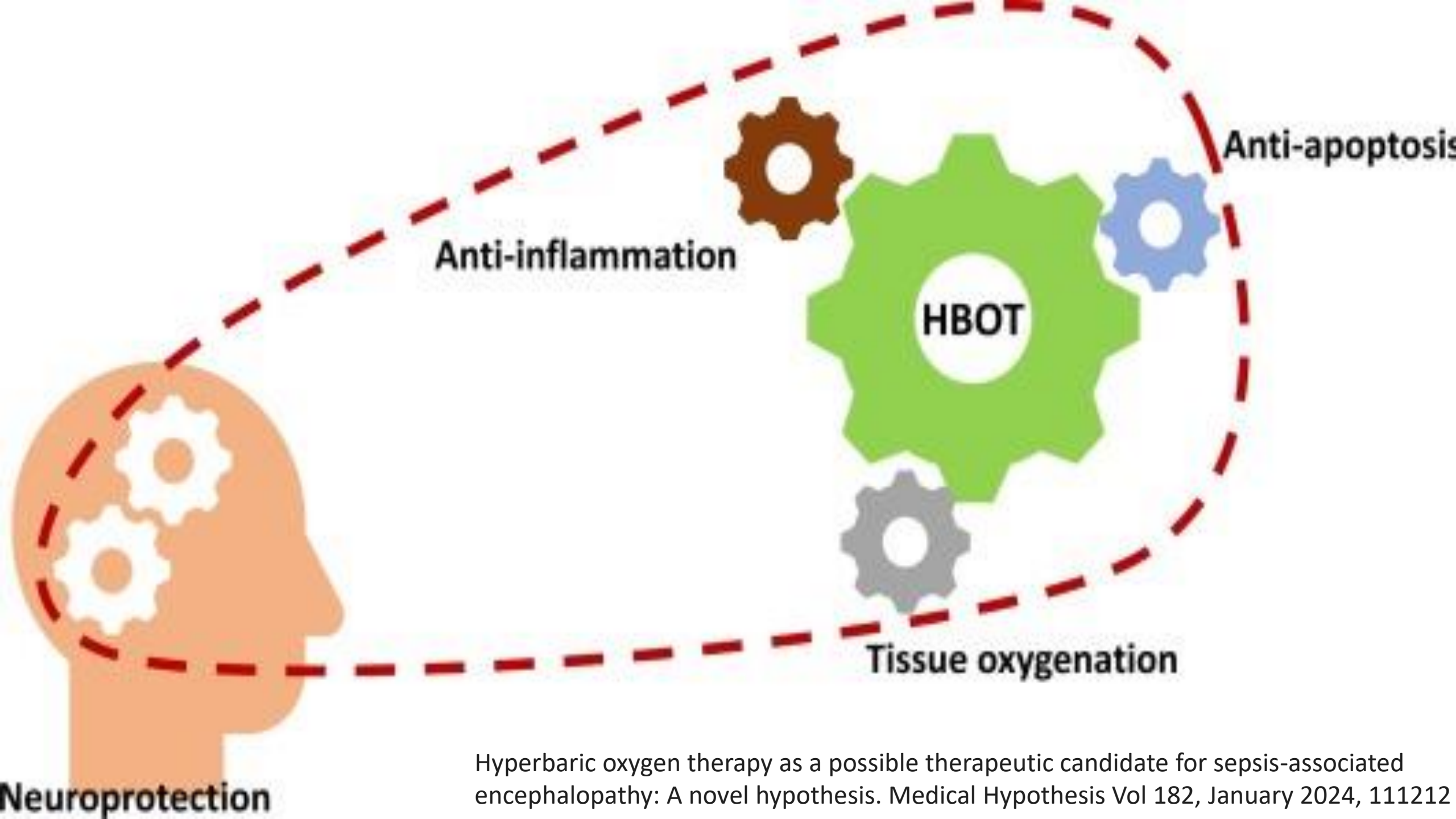
Badran BW, et al A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. Res Sq [Preprint]. 2022 Jun 21:rs.3.rs-1716096.

Vagal nerve activation

- HBOT exerts immunomodulatory actions through attenuation of microgliosis
- HBOT may induce polarization of activated microglia toward the anti-inflammatory M2 phenotype rather than the proinflammatory M1 phenotype.

HBOT Therapy

Hyperbaric oxygen therapy as a possible therapeutic candidate for sepsis-associated encephalopathy: A novel hypothesis. Medical Hypothesis Vol 182, January 2024, 111212



Hyperbaric oxygen therapy as a possible therapeutic candidate for sepsis-associated encephalopathy: A novel hypothesis. Medical Hypothesis Vol 182, January 2024, 111212

Amniotic exosomes

- Conclusion: We demonstrated that hAFSC-exo mitigated an inflammatory injury caused by microglia and significantly recovered the neurotoxicity, suggesting that hAFSC-exo may be a potential therapeutic agent for inflammation-related neurological conditions, including AD.

- hAFSC-exo: human amniotic fluid stem cells exosomes

Exosomes Derived from Human Amniotic Fluid Mesenchymal Stem Cells Preserve Microglia and Neuron Cells from Aβ. Int J Mol Sci. 2022 Apr 29;23(9):4967.

Amniotic exosomes

- Interestingly, the hAFSC-exo pretreatment significantly inhibited the oxidative stress rise and apoptosis occurring in the neurons in presence of both microglia and Aβ

- hAFSC-exo: human amniotic fluid stem cells exosomes

Exosomes Derived from Human Amniotic Fluid Mesenchymal Stem Cells Preserve Microglia and Neuron Cells from Aβ. Int J Mol Sci. 2022 Apr 29;23(9):4967.

Faces of Neuroinflammation Outline

- Microglia activation
- Signs and symptoms
- Neurophysiology
- Conditions
- Clinical web
- **Cases**

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