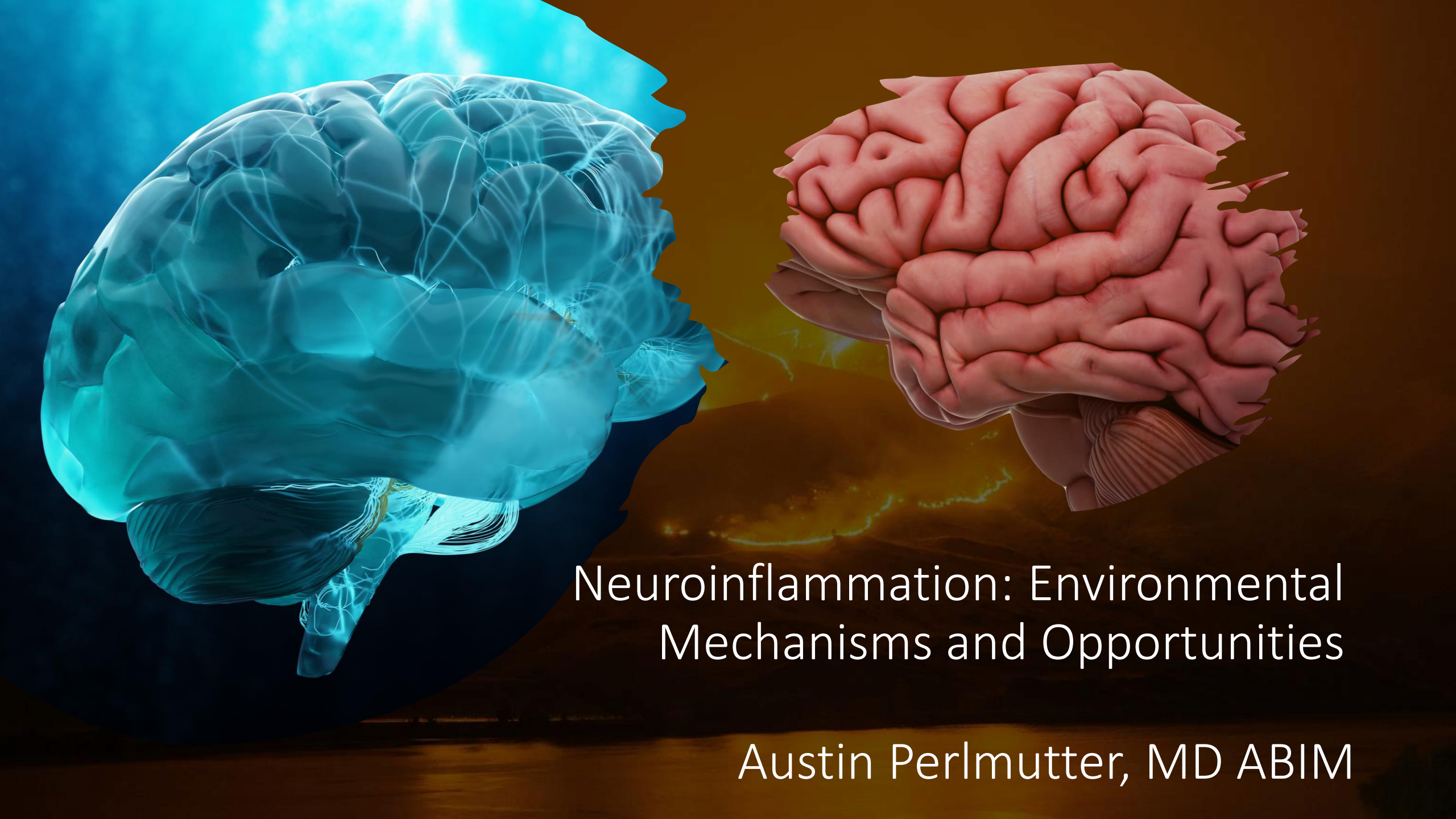
Neuroinflammation: Environmental Mechanisms and Opportunities

Austin Perlmutter, MD, ABIM



Neuroinflammation: Environmental Mechanisms and Opportunities

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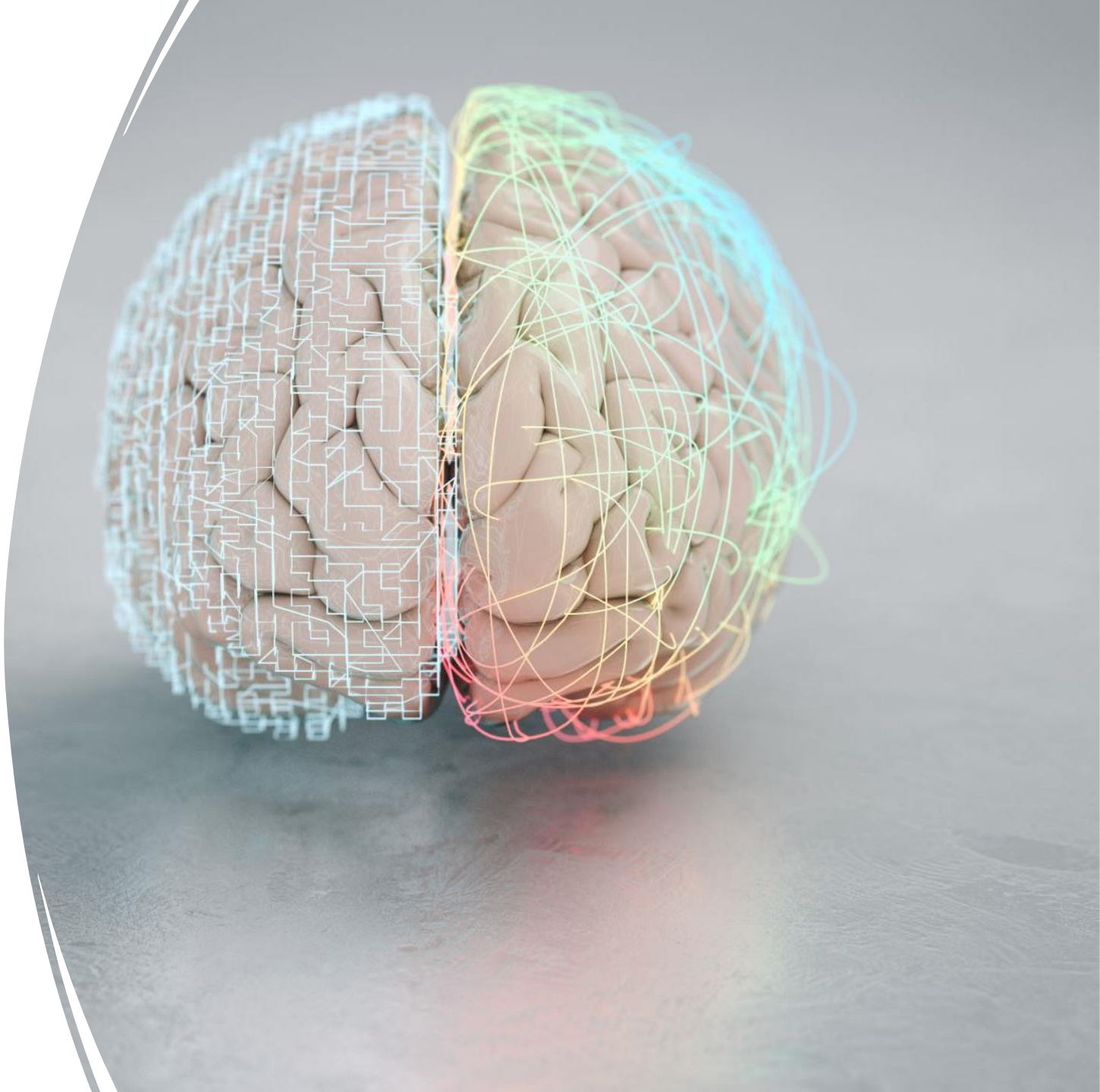
Learning points

- Develop an awareness of the current landscape of neuroinflammation-related diseases.
- Review major systemic contributing pathways to neuroinflammation.
- Recognize the current neurobiological mechanisms behind brain inflammation.
- Investigate the role of “hidden” environmental factors bearing on neuroinflammation.
- Recognize the role of climate change as a driver of brain disease via neuroinflammation.
- Review evidence for environmental interventions to reduce neuroinflammation.

Background ideas

- The brain is full of immune-active cells and signals (neurons and glial cells)
- Systemic immunity impacts brain immunity
- “Immunity” in the brain modulates far more than pathogen defense



What is neuroinflammation?

- Increased level of inflammatory cytokines (e.g., IL-1, TNF-alpha)
- Increased glial cell activation (especially M1 macrophage polarization)
- Increased peripheral immune cell infiltration (e.g., autoreactive T cells in MS)
- Damage to brain tissue
- Damage to/increased permeability of blood-brain barrier

Why care about neuroinflammation?

Pathway to understanding current and future

- Neurodegenerative diseases
- Cognitive function
- Mood
- Decision-making
- Motivation
- Social connectivity/empathy
- And what makes us…us!

Diseases associated with neuroinflammation [1,2]

- Alzheimer’s disease
- Parkinson’s disease
- Multiple Sclerosis
- ALS
- Aging
- Depression
- Schizophrenia
- Bipolar
- ADHD
- PTSD

Neuroinflammation is a real, major health consideration. But how do we know it’s happening?

How does brain inflammation correlate with systemic inflammation?

Systemic-central inflammation

- Delirium highly correlated with severe illness and high systemic inflammation
- “Sickness behavior” occurs acutely in illness
- Administration of LPS (endotoxin) reliably induces systemic inflammation and behavioral changes consistent with depression
- Higher systemic inflammation correlates with higher risk for neuroinflammatory conditions (Alzheimer’s, depression)

Systematic Review | Published: 06 February 2023

Early systemic inflammation induces neurodevelopmental disorders: results from ARTEMIS, a French multicenter study of juvenile rheumatisms and systemic autoimmune and auto-inflammatory disorders and meta-analysis

Pierre Ellul ✉, Isabelle Melki, Stephanie Antoun, Laura Lavialle, Eric Acquaviva, Florence A. Aeschlimann, Brigitte Bader-Meunier, Alexandre Belot, Glory Dingulu, Cecile Dumaine, Albert Faye, Marie-Louise Frémond, Ulrich Meinzer, Hugo Peyre, Pierre Quartier, Michelle Rosenzwajg, Isabelle Savioz, Caroline Vinit, Nicolas Tchitchek, David Klatzmann & Richard Delorme

Molecular Psychiatry **28**, 1516–1526 (2023) | Cite this article

Early systemic inflammation induces neurodevelopmental disorders…

- Meta-analysis of 46,267 children with juvenile autoimmune/rheumatic disorders, 213930 children with neurodevelopmental disorder, >6 million controls
- Positive OR 1.44 between juvenile immune disorders and neurodevelopmental delay
- Age of onset of juvenile immune disorders and timing of disease-modifying therapy mediate neurodevelopmental delay risk

Molecular Psychiatry (2017) 00, 1–7

www.nature.com/mp

ORIGINAL ARTICLE

Selective increase of cerebrospinal fluid IL-6 during experimental systemic inflammation in humans: association with depressive symptoms

H Engler[1], P Brendt[2], J Wischermann[2], A Wegner[3], R Röhling[1], T Schoemberg[4], U Meyer[5], R Gold[6], J Peters[2], S Benson[1] and M Schedlowski[1]

Selective increase of cerebrospinal fluid IL-6 during experimental systemic inflammation in humans: association with depressive symptoms

- Healthy volunteers (10 active, 8 placebo) injected with LPS (endotoxin)
- Increases in serum IL-6, IL-10, TNF-α.
- After latency, increased CSF IL-6
- IL-6 elevation in CSF correlates with depressive symptoms

Molecular Psychiatry (2017) 00, 1–7

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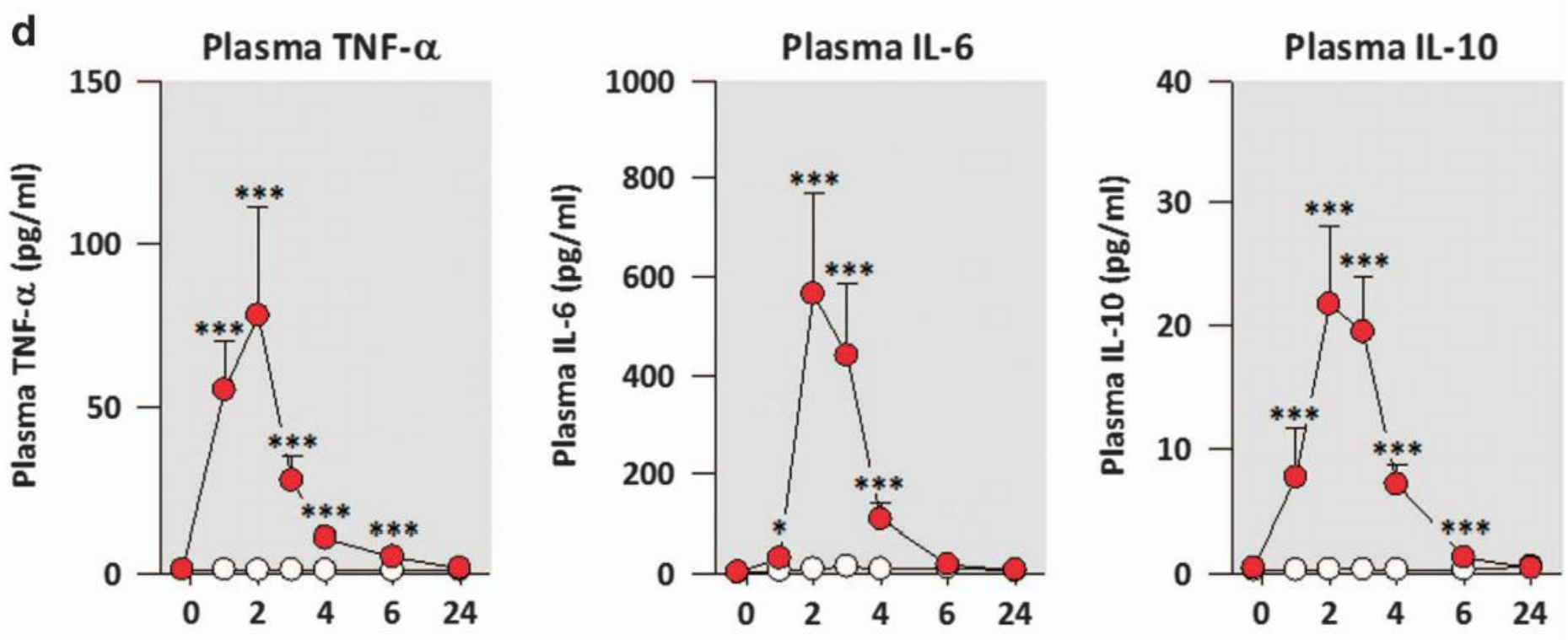

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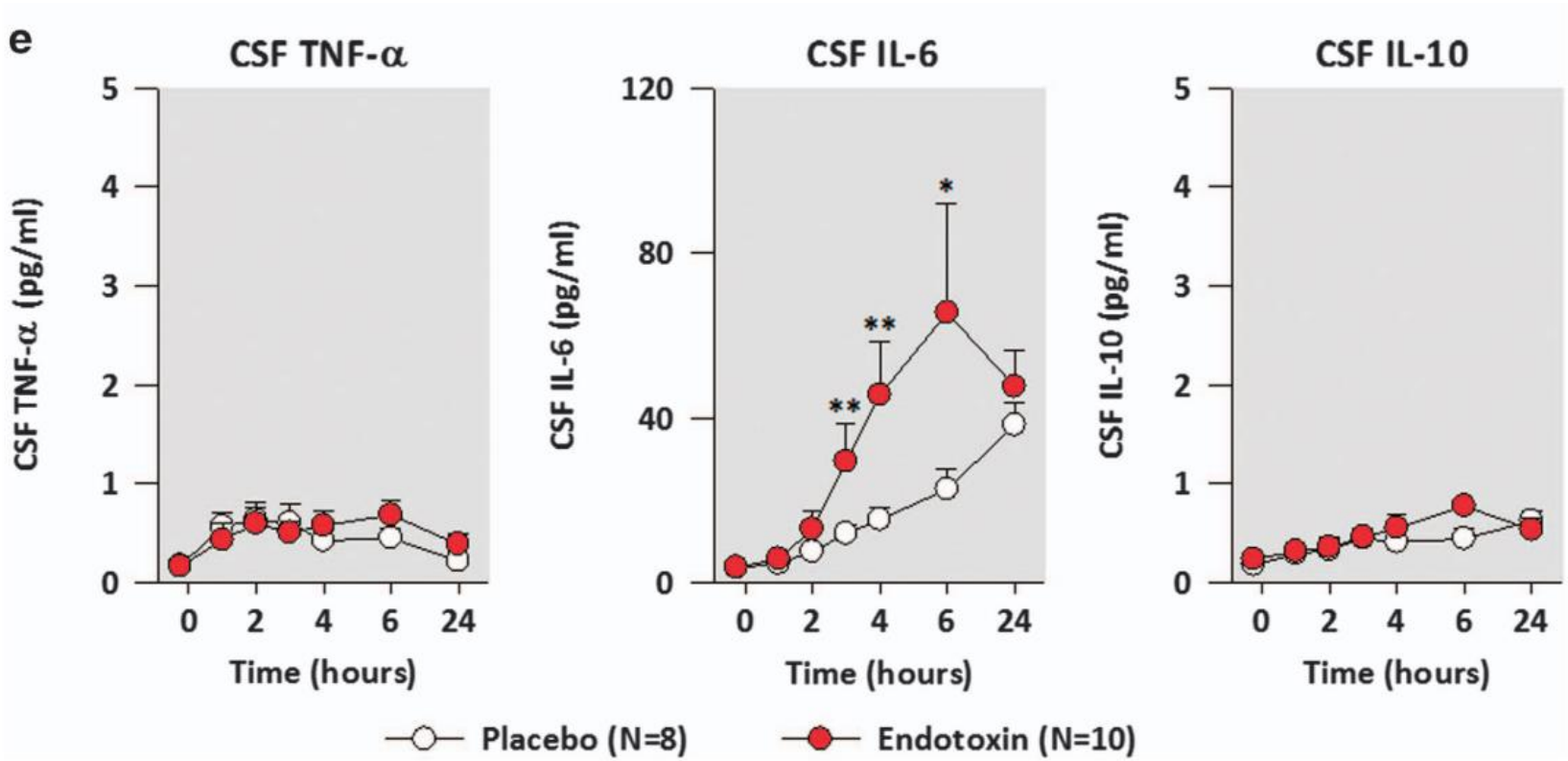


How does inflammation enter the brain?

Review Article | Open Access | Published: 30 September 2021

The blood–brain barrier in systemic infection and inflammation

Ian Galea

Cellular & Molecular Immunology **18**, 2489–2501 (2021) | Cite this article

The blood–brain barrier in systemic infection and inflammation

- Preclinical data show correlations with systemic inflammation and damage to blood brain barrier including endothelial glycocalyx
- Endothelial cells of BBB have receptors responsive to systemic inflammation
- Systemic inflammation appears to promote leukocyte migration into brain
- Systemic inflammation appears to disrupt tight junctions by increasing matrix metalloproteinases (MMPs) activity
- There are areas where BBB may be more “incomplete”

Systemic->neuroinflammatory takeaways

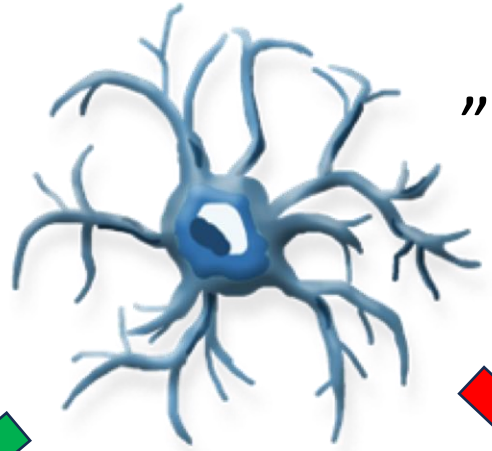
- Systemic-> central inflammation is not 1:1 but there are overlaps
- Systemic inflammation may lead to neurocognitive effects through pathways that are less clearly defined
- Damage to BBB, increase in microglial activation and entrance of systemic immune cells into brain are key pathways

Know your players

Microglia

- Key orchestrators of the brain's immune state
- Key brokers of systemic->CNS immunity
- Involved in plasticity, pruning, phagocytosis and programmed cell death
- Produce chemokines, cytokines, neurotransmitters and neurotrophins like BDNF
- On detection of PAMPs/DAMPs, mount specialized responses

Microglial differentiation

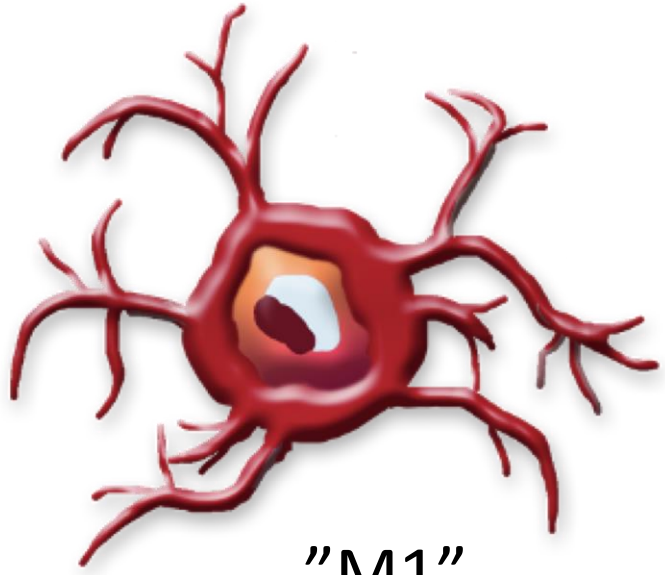


”M0”

LPS, IL-1B, IL-6, TNF-alpha IFN-gamma, IFN-alpha

IL-4, IL-10, IL-13 TGF-beta

”M2”



”M1”

Neuronal immunity [1,2,3,4]

- HPA neurons impact systemic and local immune state (e.g. leukemoid reaction)
- Damaged neurons upregulate inflammatory signaling pathways and amplify microglial activation
- Exosomal transfer of microRNA from neurons to microglia activates M1 polarization
- LPS-activated neurons produce NPY which suppresses inflammation

How do we measure neuroinflammation?

- Neuroimaging
  - PET TSPO, MRI Free Water Fraction[1]
- Histology/biopsy
- CSF analysis
- Peripheral surrogates
  - Peripheral blood immune cells/cytokines/acute phase reactants/KYN pathway metabolites[2]
  - Zonulin, HbA1c, BMI, insulin resistance

Neuroimmune modulators [1,2]

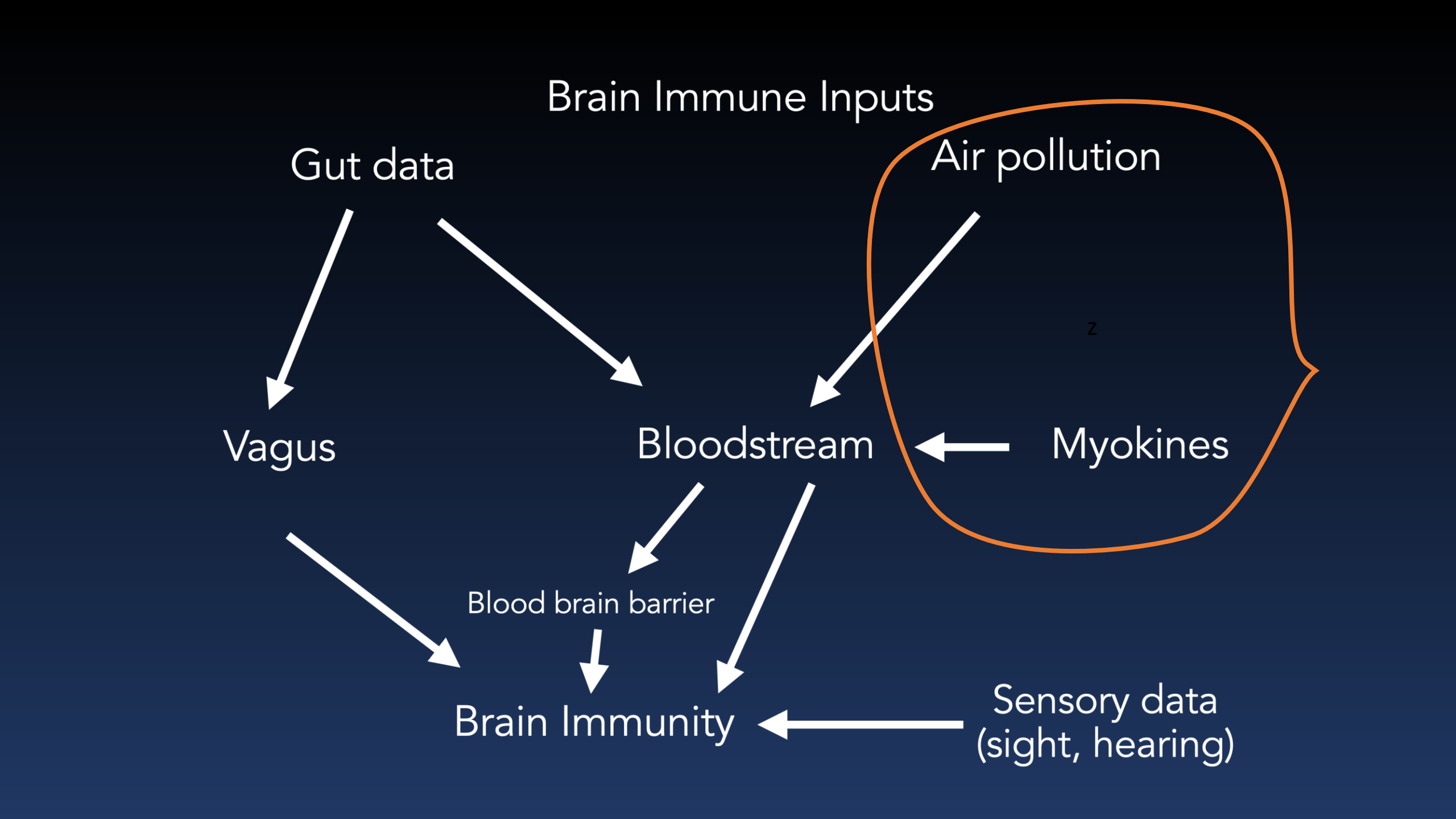
Conventional modulators[1]	Newer therapeutics [2]
• NSAIDS (Prostaglandin/COX inactivators) • Steroids (e.g., prednisone) • Biologics (e.g., interferons, monoclonal abs) • Antibiotics (minocycline, ceftriaxone)	• Complement inhibitors (e.g., pegcetacoplan) • Progranulin augmentation (neuronal/glial regulatory protein) • Small-molecule pathway inhibitors (e.g. NLRP3 inhibitors)

Variables associated with neuroimmune state

- Smoking
- PM 2.5. exposure
- Pharmaceuticals
- Substance use (e.g EtOH)
- Heavy metal exposure
- Traumatic head injury
- Infectious agent exposure (e.g. COVID-19)
- High sugar diet
- Diabetes
- Sedentary behavior/exercise
- Obesity
- HTN
- High fat diet
- Dysbiosis
- Aging
- Stress
- Psychedelics

Systemic->CNS pathways activating neuroinflammation

- Gut-brain via vagus
- Gut-brain via microbiome metabolites
- Gut-brain via gut immune system
- Gut-brain via microbes (e.g., porphyromonas gingivalis)
- Psychological stress (ears and eyes)
- Olfactory nerve (retrograde invasion)
- Binding to/penetrating through BBB
- Lung-brain
- Skin-brain


Brain Immune Inputs
Gut data
Air pollution
Vagus
Bloodstream
Myokines
Blood brain barrier
Brain Immunity
Sensory data
(sight, hearing)

Air quality and neuroinflammation

Air pollution is associated with increased risk for brain issues including

- Dementia [1]
- General worsened cognition [2]
- Depression/anxiety [3]
- Violent crime [4]

Neurotoxic Air Pollutants

- Particulate Matter (PMs)
  - PM $_{10}$, **PM $_{2.5}$, UFPM (< than 0.1 µm)**
- Volatile Organic Compounds (organic gas)
  - E.g Ethanol, formaldehyde, benzene
- NO_x
- CO
- Sulfur dioxide
- O_3
- Lead/heavy metals

Neurotoxic Air Pollutants

- **Particulate Matter (PMs)**
  - **PM_{10}, $PM_{2.5}$, UFPM (< than 0.1 µm)**

Particulate Matter (PMs)

- Primary driver of air pollution mortality [1]
- Stays suspended in atmosphere (smaller longer, farther spread)
- Carries microbes, chemicals, heavy metals
- Can penetrate through BAB, BBB, may damage placenta/fetal development
- Higher exposure linked to worse verbal learning,[2] depression, dementia

Particulate Matter (PMs)

- Leads to localized inflammation in lung, systemic inflammation and may induce alterations in blood brain barrier, gut microbiome [1]
- In human neuronal cells (in vitro), PM2.5 increases expression of TNF-α, IL-1β, and NF-κB [2]
- In humans, higher PM 2.5 exposure correlates with higher circulating fibrinogen, IL-6[3]

scientific reports

Article | Open access | Published: 07 August 2023

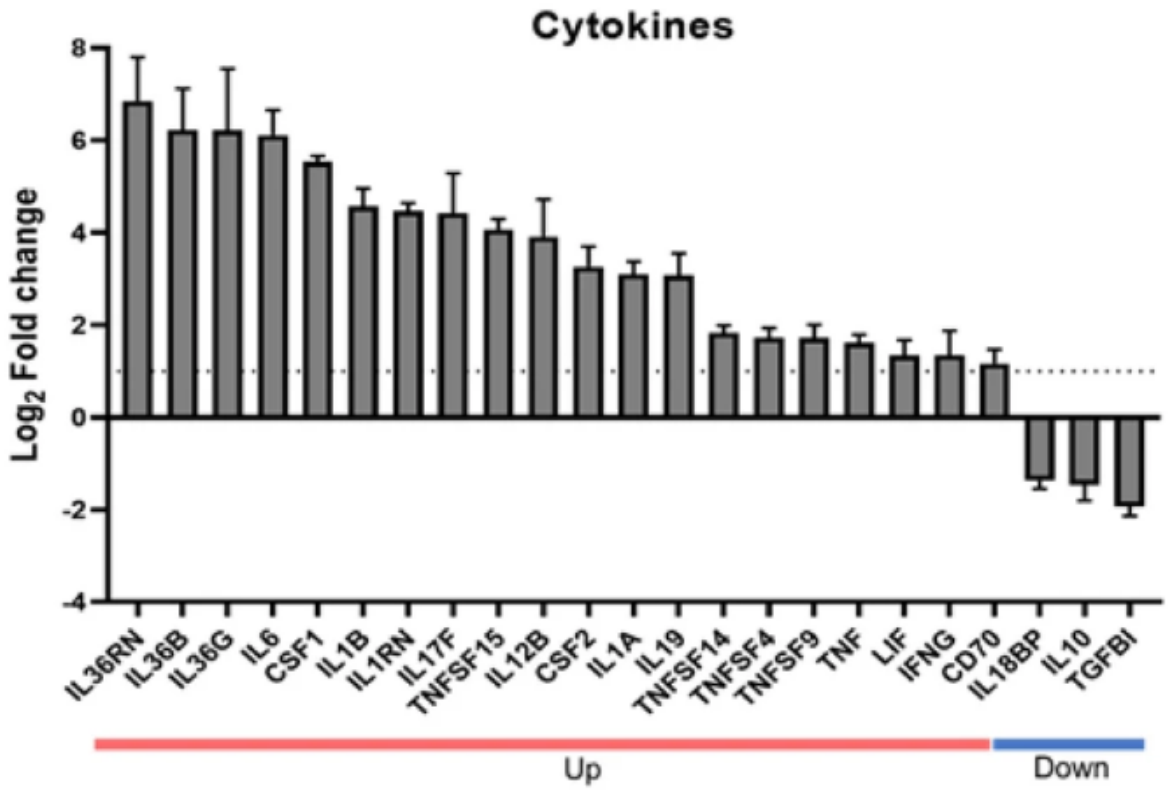
Particulate matter impairs immune system function by up-regulating inflammatory pathways and decreasing pathogen response gene expression

Damariz Marín-Palma, Geysson Javier Fernandez, Julian Ruiz-Saenz, Natalia A. Taborda, Maria T. Rugeles & Juan C. Hernandez

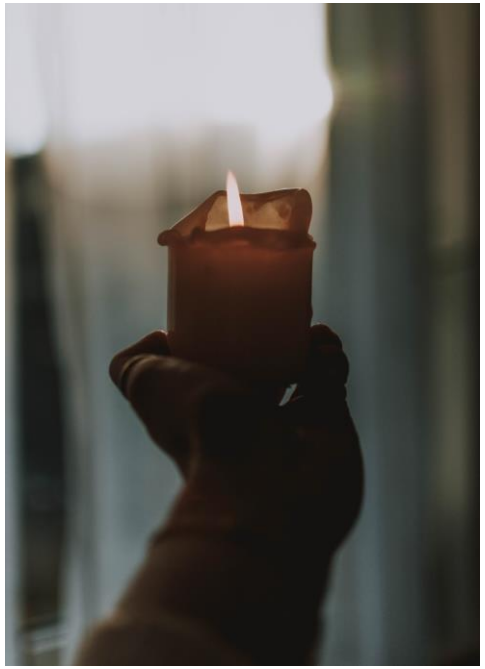
Scientific Reports **13**, Article number: 12773 (2023) | Cite this article

Particulate matter impairs immune system function by up-regulating inflammatory pathways and decreasing pathogen response gene expression

- “Our analyses showed that PM10 was able to reprogram the expression of 1,196 genes in immune cells, including activation of a proinflammatory state with an increase in cytokines and chemokines"



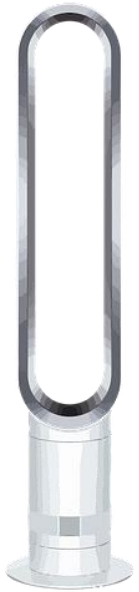
PM sources

Gas pollutants (O3, NOx SO2)

- Higher CRP, TNF-α found for short-term exposure, most for SO_2[1]

Gas pollutant sources



VOCs (Volatile Organic Compounds)

- Made of carbon plus functional groups like oxygen, nitrogen, sulfur
- Not always an issue!
- Examples: benzene, methane
- Often higher **inside** than outside
- Trigger reactions in the air that create air pollutants
- No federal/state standards for testing
- Come from: building supplies, paint, air fresheners, cleaning products, perfumes/cosmetics, candles

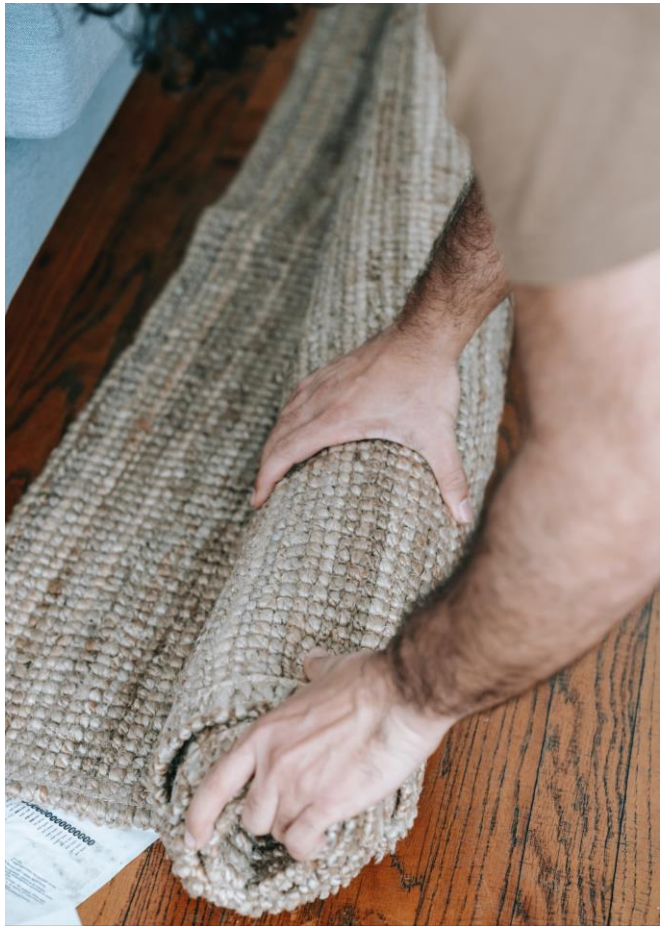
VOCs (Volatile Organic Compounds)

- VOCs react chemically with amines in respiratory epithelium to cause inflammation (in vitro)[1]
- Exposure correlates with increased markers of oxidative stress in humans [2]
- VOCs shown to bind to human TLR4 (known NFKB inflammatory activator) in silico [3]
- TLR4 on immune cells and neurons activates inflammatory pathways

Side note on VOCs…

- Our exhaled breath contains 100’s of VOCs
- Exhaled VOCs represent gene transcription, protein expression, health and diseases
- Breath research now focused on “volatilome”
  as a way to identify disease

Unhealthy VOC Sources



Briefly: mold and other fungi

- Mycotoxins (.1 um) (may
  - increase BBB permeability (in vitro), [1]
  - Impair neuroplasticity in hippocampus (animal) [2]
- Mold spores (1-2 uM) may
  - Alter cognition (animal) [3]
  - Impair neuroplasticity and impair cognition (mice) [4]

Cardiopulmonary Benefits of Reducing Indoor Particles of Outdoor Origin: A Randomized, Double-Blind Crossover Trial of Air Purifiers

FREE ACCESS

Original Investigation

Renjie Chen, Ang Zhao, Honglei Chen, Zhuohui Zhao, Jing Cai, Cuicui Wang, Changyuan Yang, Huichu Li, Xiaohui Xu, Sandie Ha, Tiantian Li, and Haidong Kan

J Am Coll Cardiol. 2015 Jun, 65 (21) 2279–2287

- "Air purification was significantly associated with decreases in geometric means of several circulating inflammatory and thrombogenic biomarkers..." **68.1% decrease in serum interleukin-1β**

Rethinking exercise: Myokines as neuroimmune modulators?

Known benefits of exercise

Systemic: longevity, cardiovascular health, lung function, lower frailty

Brain: better mental health, better cognition, lower risk of dementia

Immune: lower systemic inflammation

How does exercise improve health?

Vascular benefits

Enhanced neuroplasticity (BDNF)

Metabolic regulation

Myokines: brain messages from muscles

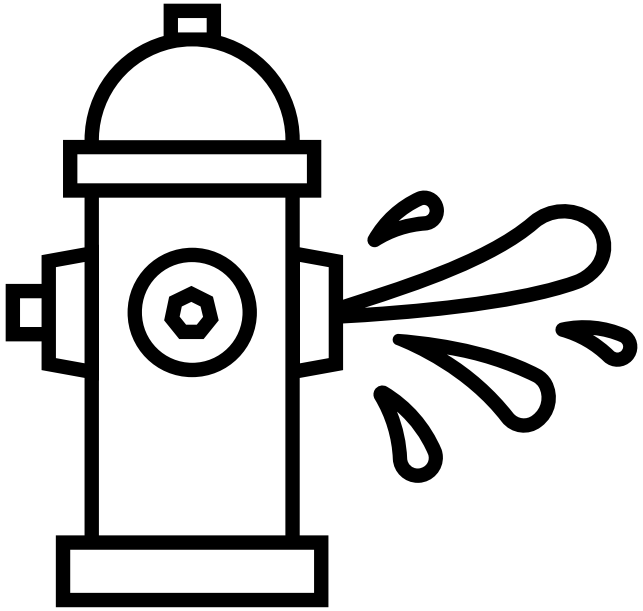
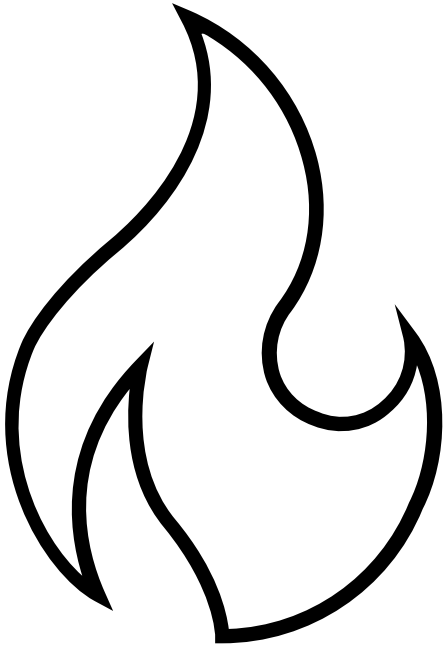
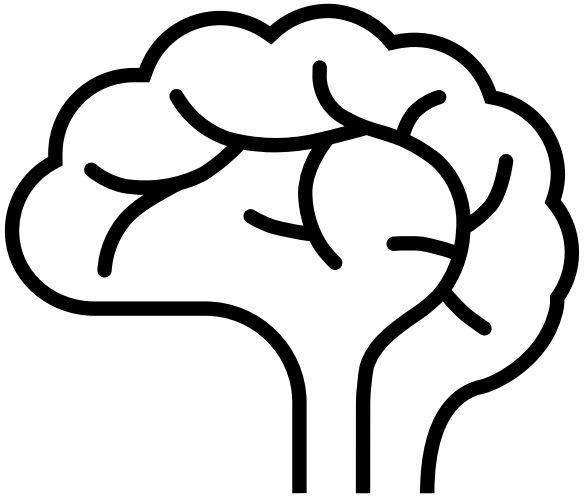
- Over 600 known molecules produced by muscle (likely thousands) (1)
- Skeletal muscle is about 40% of body weight, up to 75% body proteins (2)
- Some myokines are immune cytokines, many may impact immunity
- Have auto, para and endocrine function
- Some cross BBB, others have indirect brain effects

Myokines: brain messages from muscles[1]

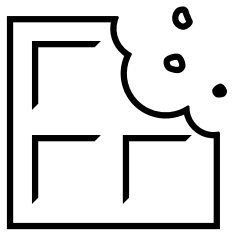
- BDNF production is upregulated in context of myokines Irisin, Lactate and Cathepsin B
- IGF-1 produced during exercise and crosses BBB
- IL-6 increases after exercise and crosses BBB (note sIL-6R differential)
- Lactate generated from exercise crosses BBB

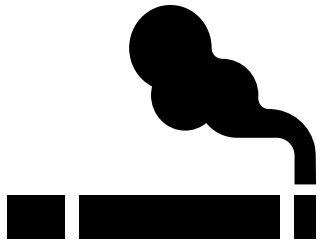
Myokines: brain messages from muscles

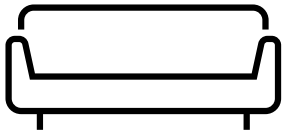
- Irisin has immunoregulatory effect on brain [1]
- IGF-1: immunoregulatory effect on brain [2]
- IL-6: immunoregulatory effect on brain
- Lactate has immunomodulatory effects [3]

What can you do today?







Target the “6 S” approach

- Stress
- Sugar
- Smoke
- Substances
- Sedentarism
- Sleep

Specific to air pollution

- Reduce exposure (air filtration, ventilation, behavior modification)
  - E.g., indoor incense, scented candles, air freshers, vent cooktop
  - Purifiers (skip the UV/Ionizers)
  - E.g., VOC-free materials
- Increase biochemical countermeasures (sleep, diet, exercise)
  - E.g., Mediterranean diet
  - E.g., foods rich in B vitamins

Specific to myokines

- Reduce sedentary behavior
- Both aerobic and anaerobic exercises show benefits to myokine production (weights are good!)
- Mild-moderate exercise best for healthy immunomodulation
- Engage habits > cyclical patterns or overdoing it
- Engage large muscle groups with compound exercises (legs)

Specific to microglia

- **Decrease air pollution exposure** [1]
- **Decrease excess alcohol consumption**[2]
- Tetracyclines (minocycline), ceftriaxone [3, 4*]
- **Exercise** [5]
- **Polyphenolics (Mediterranean diet components)** [6]
- COX inhibitors, monoclonal antibodies, cannabinoids ** [7]

What's coming next

- Better measurements of neuroimmunity?
- Better peripheral surrogates for brain immunity?
- More nuanced conversations re: "inflammation"
- New targeted drugs/nutraceuticals

Putting it together

- Neuroimmune state influences thoughts, behaviors, actions and life experience
- Blanket concerns for inflammation including brain inflammation needs to transition to discussion of immune setpoint
- Mapping and accurately diagnosing brain immune state is still difficult, but will provide increasing insights for patients and providers for disease prevention and management
- Microglia are key to brain immunity, but other brain cells play major roles

Putting it together 2

- Air pollution is a clear source of immune disruptors that promotes chronic inflammation and is likely a key driver of neuroinflammation and resultant pathology
- Myokines are increasingly recognized as mediators of overall and brain immune state and health outcomes and can be modulated through exercise
- Basic lifestyle strategies for better neuroimmune state should be implemented now, with updates in diagnostics, protocols and pharmaceuticals as informed by evidence

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My Free Brain Health Newsletter

Integrative Healthcare SYMPOSIUM

Saturday 10:00am – 11:00am

Neuroinflammation: Environmental Mechanisms and Opportunities

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

Neuroinflammation: Environmental Mechanisms and Opportunities