Webinar Will Begin Momentarily

TODAY'S AGENDA:

- Welcome
- Speaker Introduction
- Presentation
- Q&A
- Closing

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Optimizing Brain Health through Nutrition: Harnessing The Power of Metabolism and Immunity

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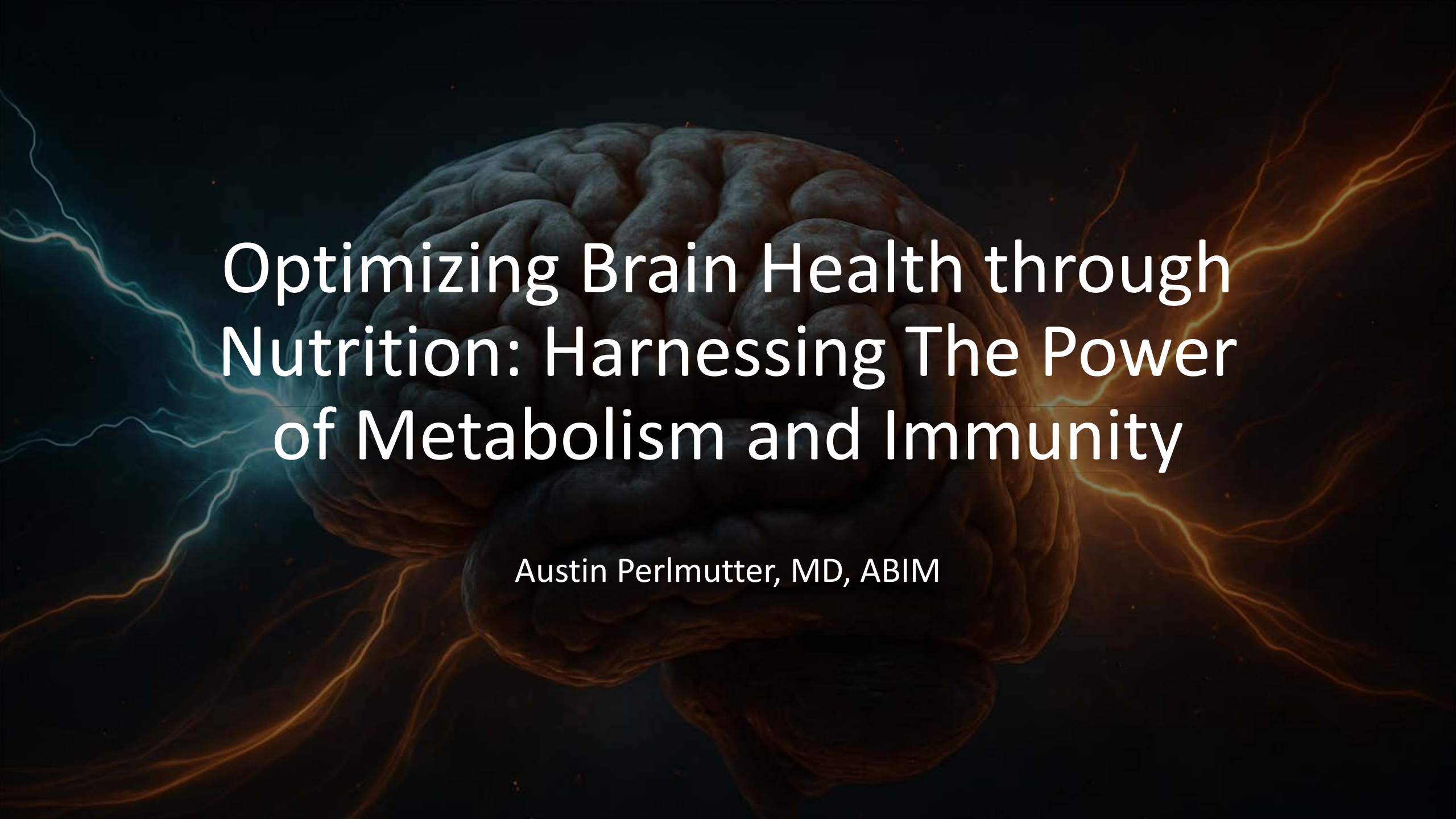

Optimizing Brain Health through Nutrition: Harnessing The Power of Metabolism and Immunity

Austin Perlmutter, MD, ABIM

Financial Disclosures

- Chief Science Officer/shareholder: Big Bold Health
- Shareholder/Principal: Science of Prevention, LLC
- Shareholder: Empowering Nutrients LLC
- CEO: Lichen Air LLC

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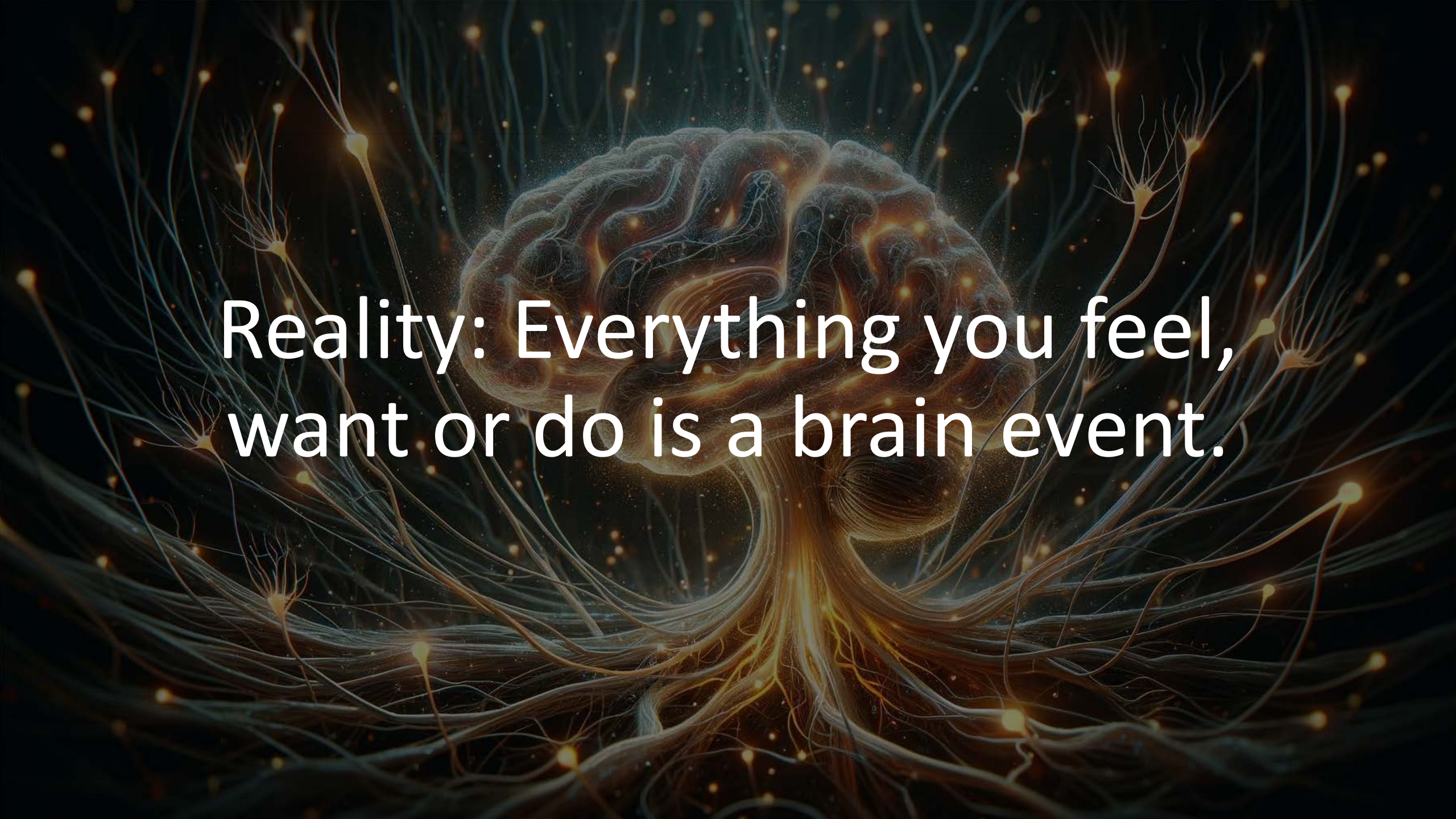
The Brain as the Center of Health


Reality: Everything you feel,
want or do is a brain event.

How we think, act and feel is a dynamic reflection of moment-to-moment brain state that includes

- Neurotransmitters
- Neuromodulators
- Endocrine pathways
- The microbiome
- Neuroplasticity
- Metabolic state
- Neuroimmunity
- Vasculature/oxygen availability

Level setting

- Roughly **300 million people** around the world have depression, **over 300 million** with anxiety disorders
- **57** million people have dementia right now, rates to **153 million** by 2050
- **16%** of people over age 50 have mild cognitive impairment
- **1/3** of American adults report overwhelming stress most days

Cognitive Decline is a Global Public Health Crisis

- Over 57 million people worldwide live with dementia [1]
- Lifetime risk for dementia after age 55 is now 42% in US [2]
- Alzheimer's is the 7th leading cause of death in the US, and #6 over age 65 [3]
- Risk for Alzheimer's is 1/14 over age 65, 1 in 6 over age 80 [4]

How do we approach brain health?

- Wait, wait, wait… then seek medical care

Dementia

MCI

Depression

Stroke

Stress

Anxiety

What’s upstream?

What are key pathways modulating brain state?

- Immune
- Metabolic
- Neuroplastic
- Endocrine
- Neurotransmitter
- Vascular
- Epigenetic

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Key pathways linking diet and brain health

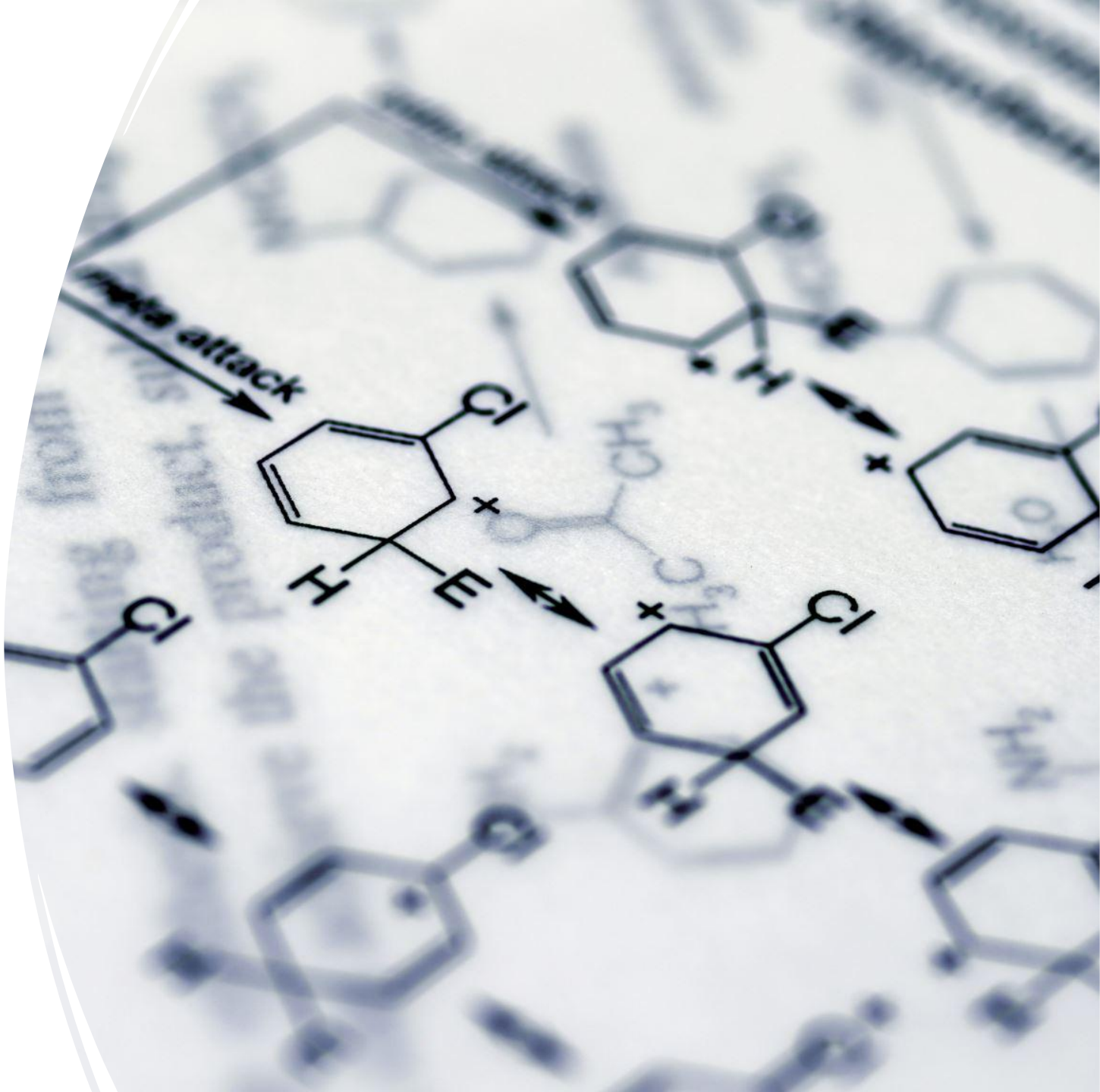
- Our brains are made from our food
- Our food turns into our neurotransmitters
- Our food alters our brain immunity
- Our food impacts brain metabolism
- Our food influences our brain vasculature
- Our food alters neuroplasticity

Structural considerations

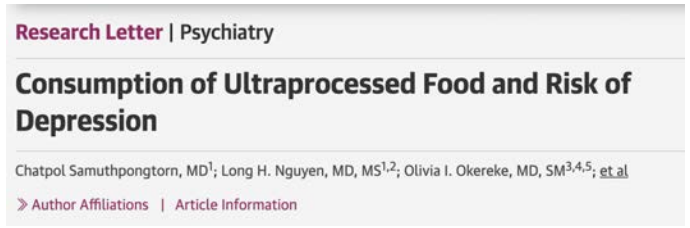
- The brain is about 60% fat weight (after removing water)
- 35% of this fat is omega-3 fatty acids
- 40% of brain omega-3s are DHA (docosahexaenoic acid)

Neurotransmission

- Tryptophan*-> Serotonin
- Tyrosine->Dopamine
- Tyrosine->Dopamine-> Norepinephrine
- Glutamate
- Glutamate + B6-> GABA
- *= essential



How much does diet matter? A lot!



Today

Immunity + metabolism (**immunometabolism**) is the key intersection between diet and brain health.

Metabolism

- Technically, all chemical reactions that sustain life
- Practically, the way that our bodies use food for energy, building and repair.

How’s our metabolic health?

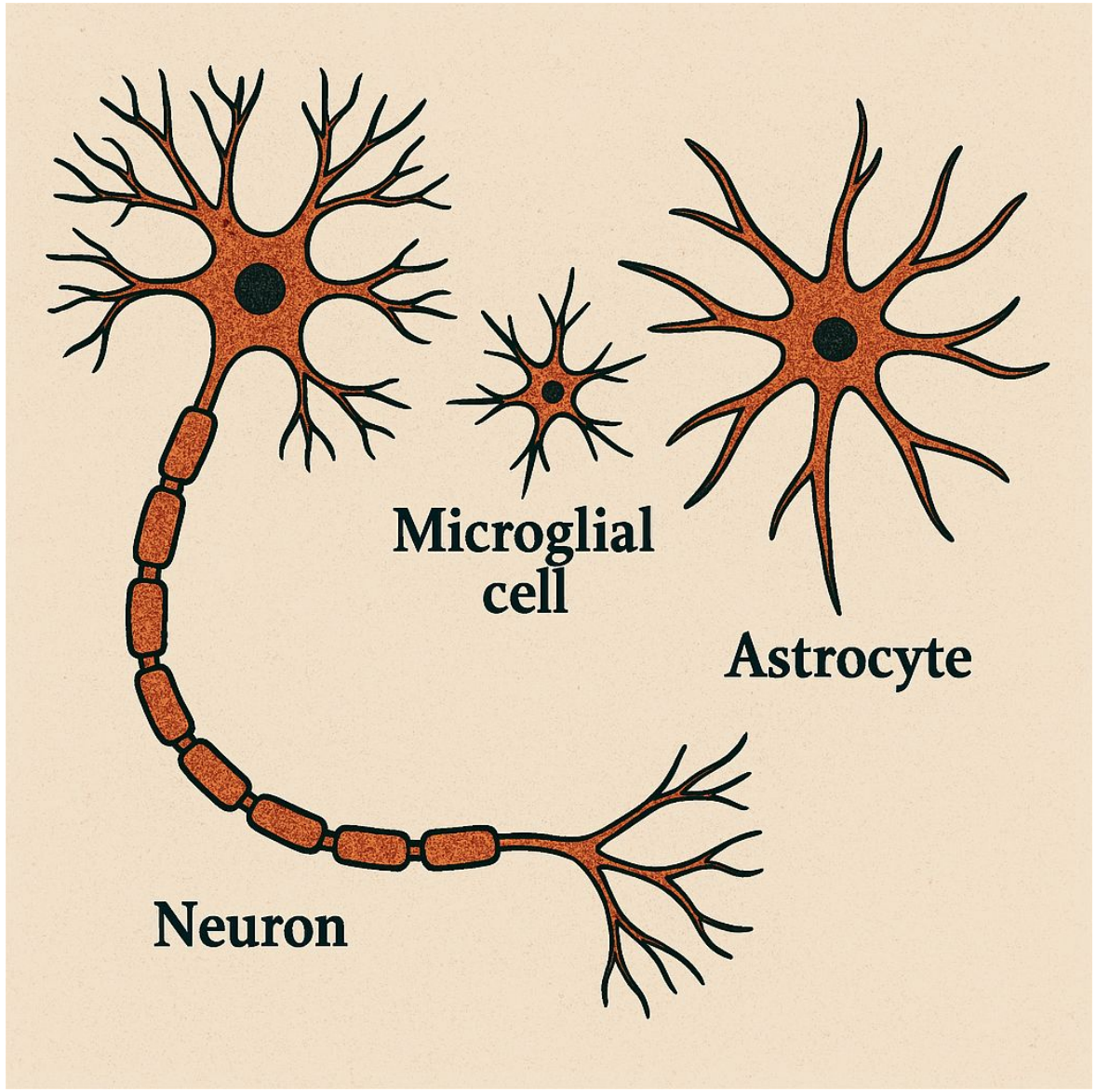
Rates of suboptimal metabolic health= 88-92% of Americans [1,2]

Type 2 diabetes + prediabetes = 50% of Americans [3]

Obesity rates 40.3% Americans [4]

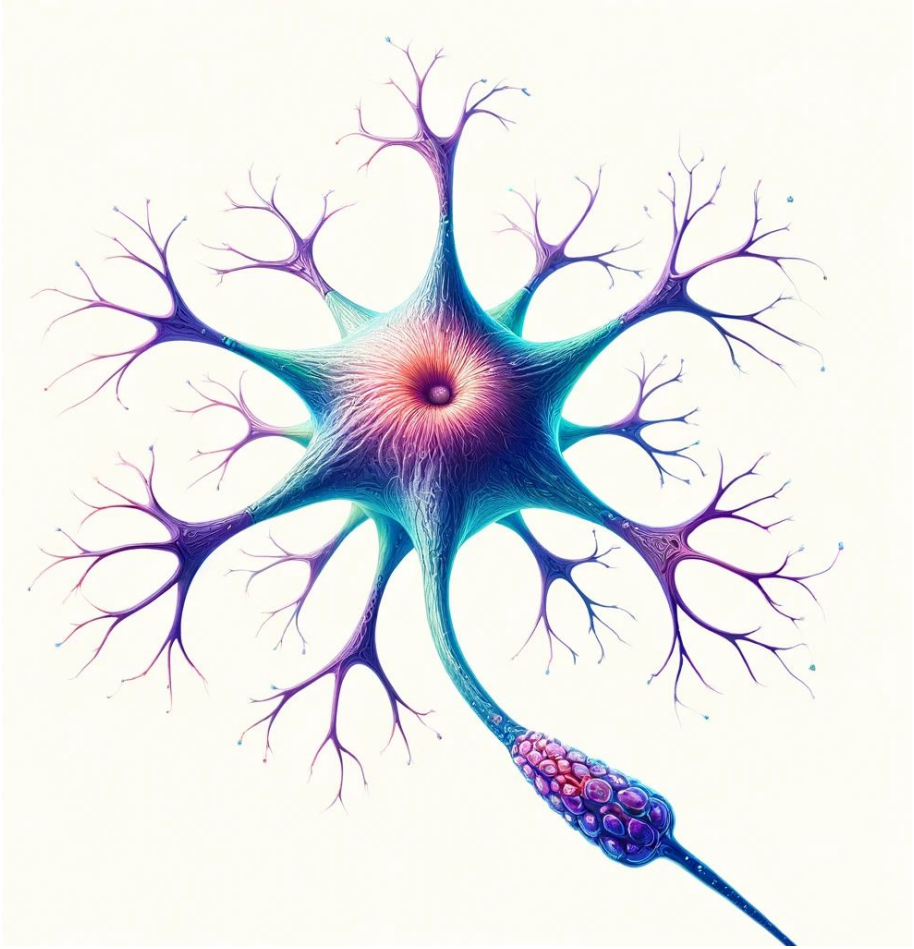
Brain metabolism cast:

- Astrocytes: primary metabolic glial cell



Brain metabolic tenets

- Brain is 2% weight and uses 20% of glucose
- 70% of energy use is by neurons
- Ketones are used during development and under conditions of fasting (up to 60%), lactate is used during exertion (8% at rest, 20% under exertion)
- Brain cells dynamically change metabolic use in real-time as a function of external and internal needs
- Energetic use dramatically changes during periods of immune activation in glial cells



Variables that influence neuroimmunometabolism

- Diet
- Epigenetics
- Infections
- Air quality
- Heat/cold exposure
- Exercise/sedentary behavior
- Sleep quality
- Psychological stress
- Heavy metal exposure
- Microbiome
- OTC
- Supplements
- Rx
- Age
- Many more!

SYSTEMATIC REVIEW

Effects of exercise on cognitive function and glycated hemoglobin A1c among patients with type 2 diabetes mellitus and cognitive impairment: A systematic review and meta-analysis

Xiaoxue Li, Bin Chen, Xinyuan Liu, Jingya Ma

First published: 05 January 2025 | https://doi.org/10.1111/ggi.15061

CLINICAL CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL RESEARCH | MAY 23 2019

The Mediterranean Diet and 2-Year Change in Cognitive Function by Status of Type 2 Diabetes and Glycemic Control FREE

Josiemer Mattei; Sherman J. Bigornia; Mercedes Sotos-Prieto; Tammy Scott; Xiang Gao; Katherine L. Tucker

Check for updates

Corresponding author: Josiemer Mattei, jmattei@hsph.harvard.edu

Diabetes Care 2019;42(8):1372–1379

https://doi.org/10.2337/dc19-0130 **Article history**

PubMed:31123154

Meta-Analysis > Neurosci Biobehav Rev. 2017 Jan:72:87-94.

doi: 10.1016/j.neubiorev.2016.11.017. Epub 2016 Nov 24.

Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis

Nicola Veronese [1], Silvia Facchini [2], Brendon Stubbs [3], Claudio Luchini [4], Marco Solmi [5], Enzo Manzato [6], Giuseppe Sergi [2], Stefania Maggi [7], Theodore Cosco [8], Luigi Fontana [9]

Advances in Nutrition

Volume 15, Issue 2, February 2024, 100169

Review

Diet Overall and Hypocaloric Diets Are Associated With Improvements in Depression but Not Anxiety in People With Metabolic Conditions: A Systematic Review and Meta-Analysis

Tonya Paris [1], Robin M Daly [1], Gavin Abbott [1], Surbhi Sood [1], Christine L Freer [1], Marno C Ryan [2 3], Elena S George [1]

RESEARCH ARTICLE | Open Access

HbA_{1c} variability associated with dementia risk in people with type 2 diabetes

Chris Moran, Rachel A. Whitmer, Zoe Dove, Mary E. Lacy, Yenee Soh, Ai-Lin Tsai, Charles P. Quesenberry, Andrew J. Karter, Alyce S. Adams, Paola Gilsanz

First published: 03 July 2024 | https://doi.org/10.1002/alz.14066 | Citations: 4

The Journal of nutrition, health and aging

Volume 28, Issue 8, August 2024, 100306

Review

Effects of ketogenic diet on cognitive function of patients with Alzheimer's disease: a systematic review and meta-analysis

Liyang Rong [a b], Yating Peng [c], Qi Shen [a], Keying Chen [a], Bangjiang Fang [d], Weirong Li [a]

Optimizing metabolism improves + protects brain health

Immunity

- Far more than a defense system
- Impacts every organ system across body
- Educated and substantially altered by the outside world
- Innate and Adaptive immune lines are blurring

Immune Issues

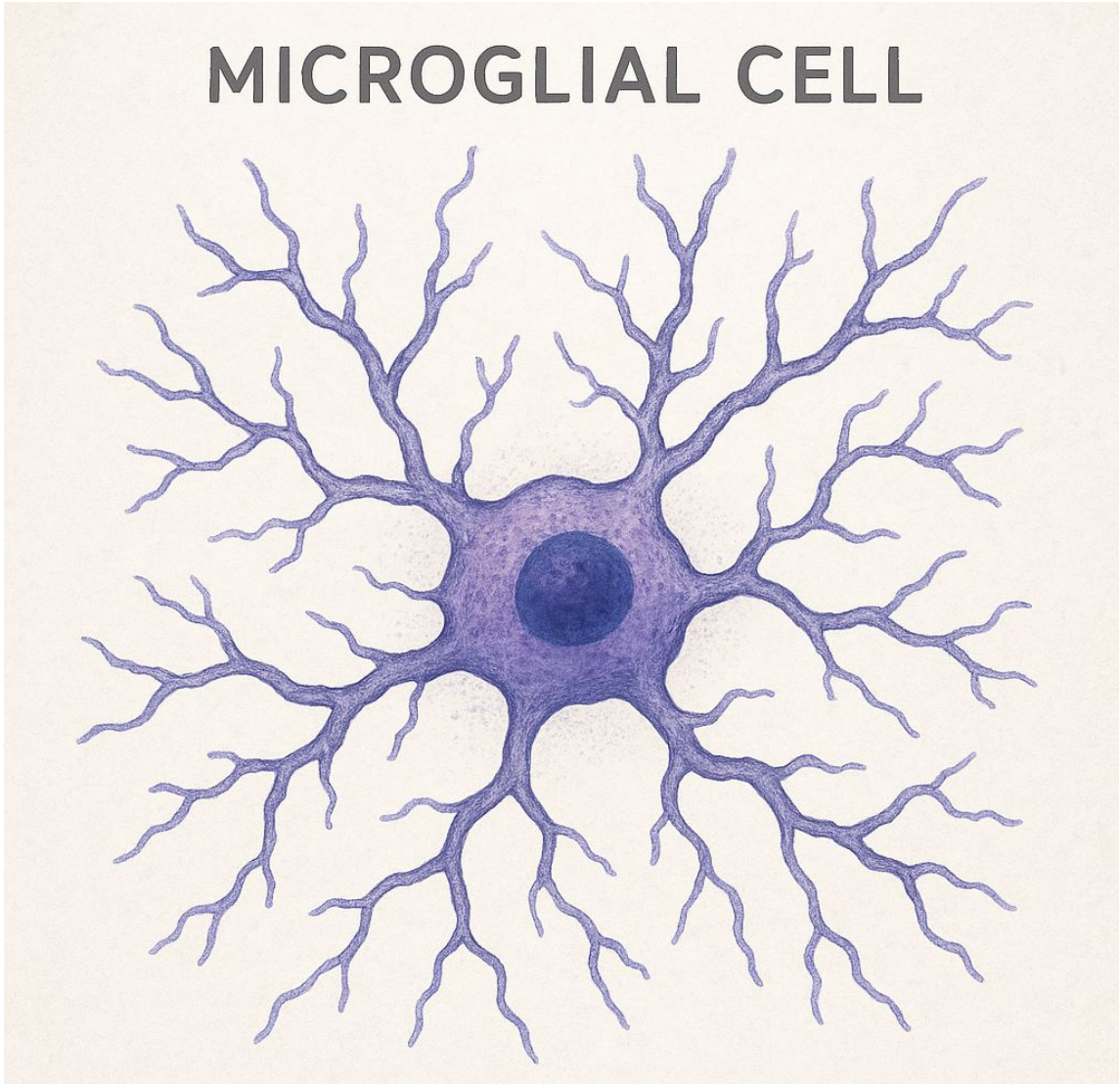
Allergies: 32% of American adults.[4]

Autoimmune: 4.6% of American adults diagnosed [5]

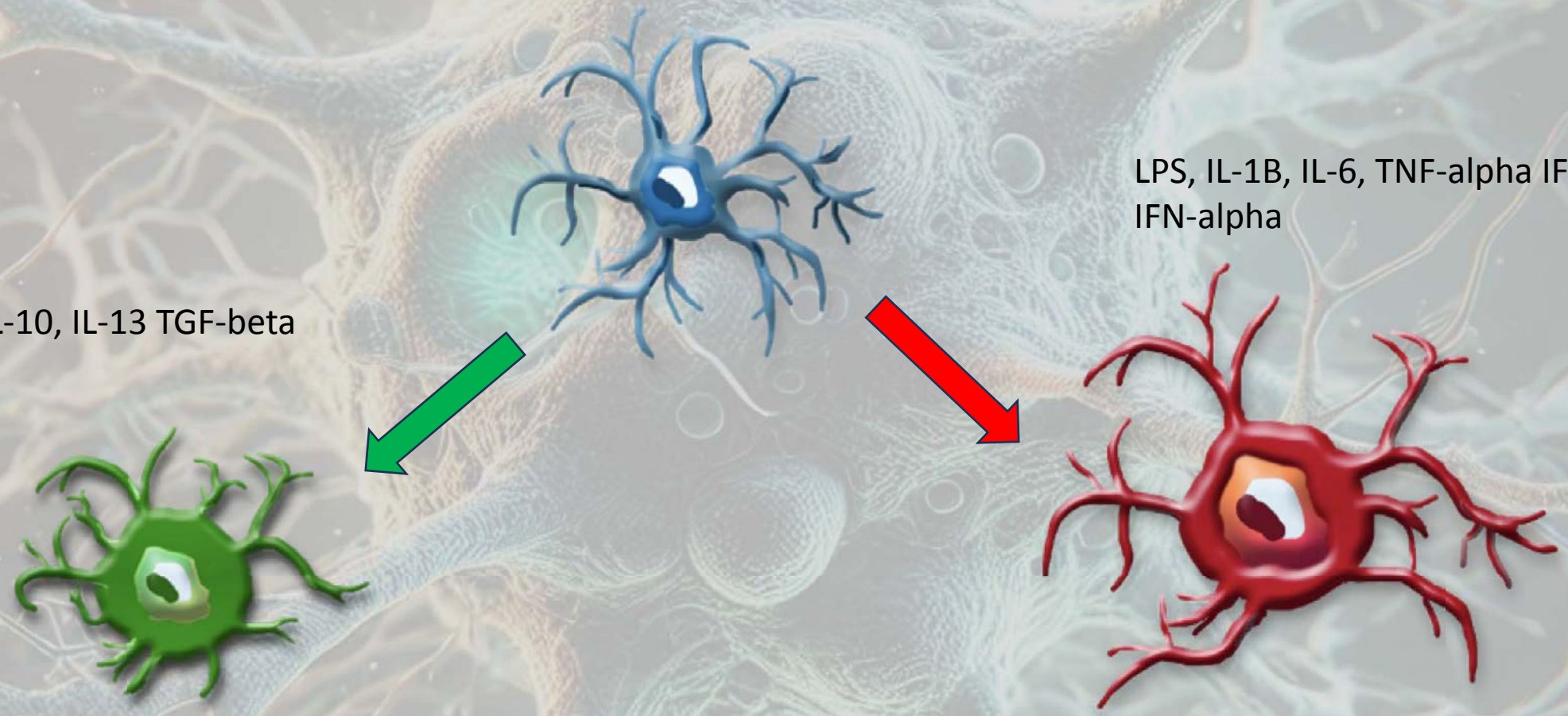
Systemic inflammation: 35% of American adults (HsCRP levels >0.30 mg/dL)[6]

The Brain’s Immune System

- Roughly 10% of our brain cells are immune cells called microglia
- Microglia influence memory, neuroplasticity, cell cleanup, brain aging, mood, cognition and more



Microglial differentiation

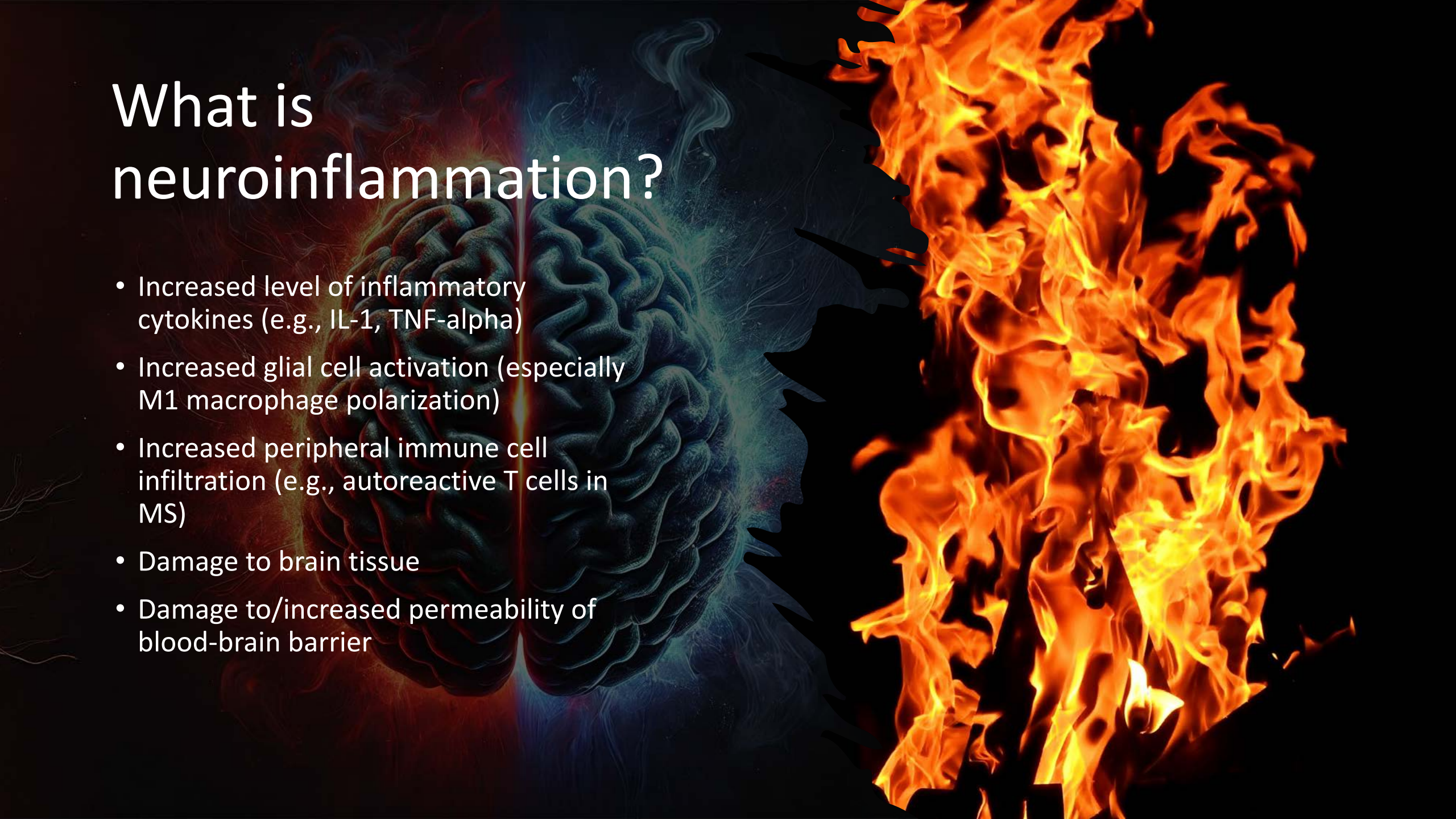


IL-4, IL-10, IL-13 TGF-beta

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

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



Diseases associated with neuroinflammation [1,2]

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

What impacts brain immunity?

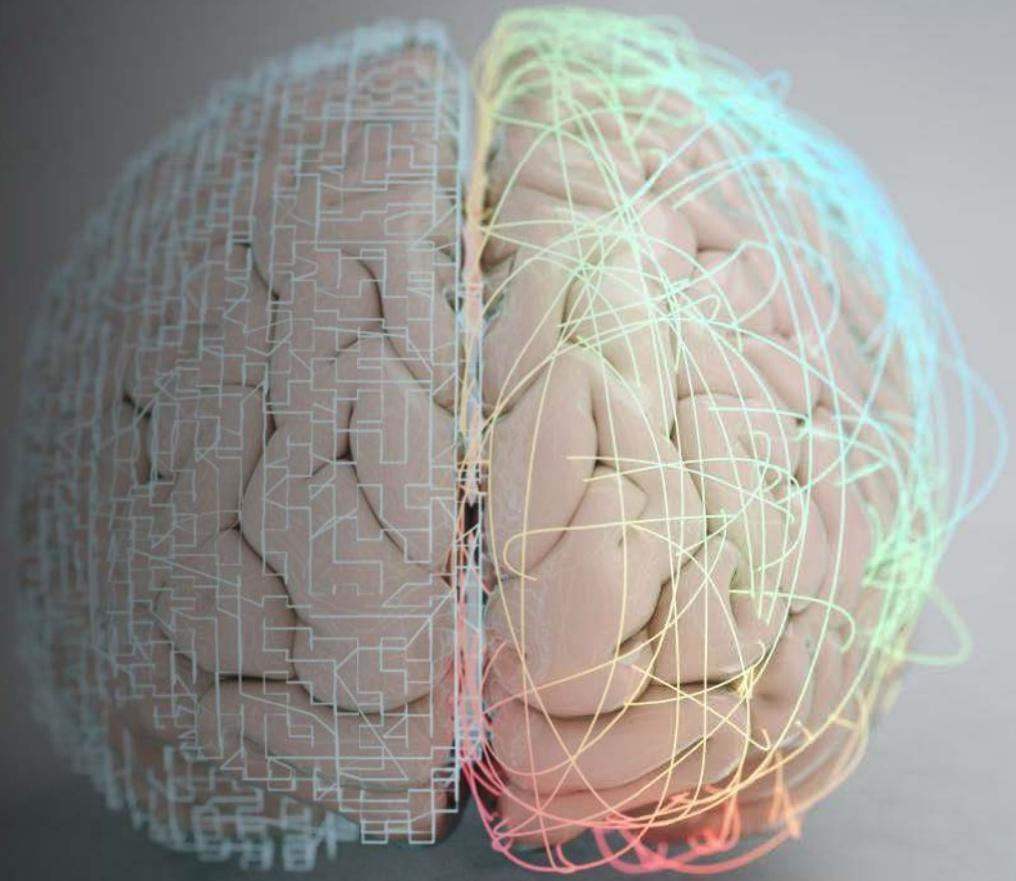
- Smoking
- PM 2.5. exposure
- Pharmaceuticals
- Substance use (e.g., EtOH)
- Heavy metal exposure
- Traumatic head injury
- Infectious agent exposure (e.g. COVID-19)
- High sugar diet

- Diabetes
- Sedentary behavior/exercise
- Obesity
- HTN
- High fat diet
- Dysbiosis
- Aging
- Stress
- Psychedelics

Ok, how do we intervene to enhance immunometabolic and especially neuroimmunometabolic health?

- Rx/OTC/Supplements
- Epigenetics
- Infection prevention/treatment
- Biological aging
- Environmental exposures (temperature, pollutants)
- Stress
- Sleep
- Microbiome
- Endocrine system
- Exercise
- Diet

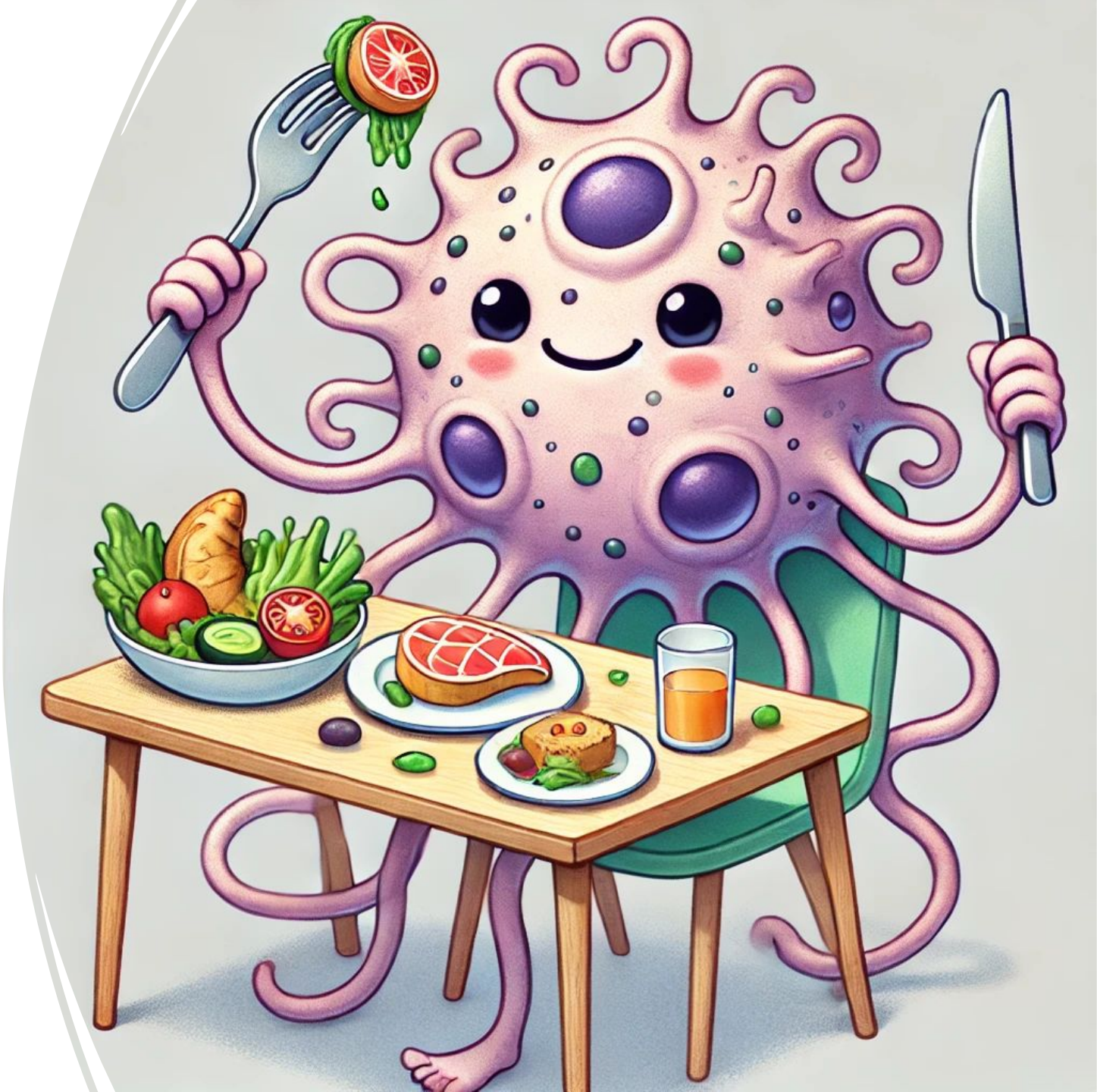
Dietary optimization for brain health through immunometabolism




GUT-BRAIN
CONNECTION

How does diet impact immunometabolism?

- Alters physical composition of immune cells and metabolically-active tissue
- Energy supply
- Biases immune cells towards signaling state, function, differentiation (e.g., Th1/Th2)
- Biases metabolic programming (e.g., mTOR/AMPK)
- **Non-caloric elements may speak directly to immunometabolism**



Specifics

- Optimize peripheral metabolic health
- Keep inflammation in check
- Promote a healthy gut

Optimize peripheral metabolic health

- Decrease risk for development of new metabolic dysfunction, improve existing function
  - Decrease added sugar, refined carbohydrates, ultraprocessed foods, promote skeletal muscle health (glucose sink + myokine production)
  - Protein at minimum 0.8 grams of protein per kilogram of body up to 2 grams/kg for older active adults building muscle (plant or animal sources good)

Decrease chronic inflammatory risk and burden

- Decrease sources of new chronic inflammation
  - Decrease intake of ultra-processed foods, decrease refined carbohydrates, decrease added sugar, decrease trans-fats consumption. Decrease alcohol consumption.
- Quell existing sources of inflammation
  - Increase unsaturated fat consumption, especially DHA/EPA omega-3 intake (500 mg a day)
  - Increase polyphenol intake (1500+ mg a day)
  - Increase fiber intake ~ 30 grams a day
  - Olive oil at around 1-2 tsp (15-30 ml) of EVOO daily.

Promote a healthy gut

- Microbiome support
  - Probiotic-rich foods (yogurt, kefir, sauerkraut)
  - Prebiotic-rich foods (spices, herbs, fiber)
- Gut immune support
  - Minimize added sugar (glucose, fructose)
- Gut lining support
  - Production of short-chain fatty acids (certain microbes, polyphenols, resistant starches, other prebiotic fibers)
  - Amino acids, e.g., Glutamine? Colostrum?
  - Minimize alcohol consumption


Go beyond the basics into the “dark matter” of food

Polyphenols

- 8000+ “secondary metabolites” found in plants
- Higher in Mediterranean “blue zones” type diets
- Bind to immune cells directly
- Metabolized by and influence the gut microbiome
- Intracellularly engage metabolic and immune longevity pathways (e.g., mTOR)
- At level of DNA, regulate epigenetic machinery involved in metabolic and immune outcomes

REVIEW article

Front. Immunol., 14 March 2024

Sec. Nutritional Immunology

Volume 15 - 2024 | https://doi.org/10.3389/fimmu.2024.1360065

This article is part of the Research Topic

Immunometabolism: Bridging the Gap Between Immunology and Nutrition

View all 12 articles >

Polyphenols: immunonutrients tipping the balance of immunometabolism in chronic diseases

 Carolina Ferreira[1,2,3,4]

 Pedro Vieira[1,2,3,4,5]

Helena Sá[2,3,6]

 João Malva[1,2,3,4]

 Miguel Castelo-Branco[4,7,8]

 Flávio Reis[1,2,3,4]

 Sofia Viana[1,2,3,4,5*]

Polyphenols

- Evolutionary mechanism enabling our immunometabolism to respond to environmental data?

What do we know about brain-polyphenol links?

- Polyphenol interaction with the gut modulates satiety hormones [1]
- Animal data suggest gut polyphenols can augment GLP-1 secretion/signaling [2]
- In vitro data suggest immune-modulating effect of polyphenols on microglial cells (decreased inflammatory expression) [3]
- Observational data suggest a diet rich in polyphenols linked to lower rates of dementia (up to 50% lower), especially Alzheimer's. [4,5]

1. https://www.sciencedirect.com/science/article/abs/pii/S0308814624003881
2. https://academic.oup.com/bbb/article/88/5/493/7611688
3. https://www.mdpi.com/2072-6643/14/15/3012
4. https://www.neurology.org/doi/10.1212/WNL.0000000000005607
5. https://www.neurology.org/doi/abs/10.1212/wnl.0000000000008981

Polyphenol-rich foods

- Berries (blueberries, blackberries, raspberries, strawberries, cranberries)
- Grapes and red wine
- Cherries and plums
- Pomegranates
- Spinach, kale, broccoli, onions
- Artichokes
- Fresh herbs (oregano, thyme, mint, parsley, rosemary, sage)
- Walnuts, hazelnuts, almonds
- Soybeans and other legumes
- Flaxseeds
- **Tartary buckwheat**
- Green tea, black tea, oolong tea
- **Coffee**
- Dark chocolate and cocoa
- Olives and extra-virgin olive oil
- Whole grains (rye, oats, barley)
- **Spices** (cloves, star anise, cinnamon, turmeric)

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 18 November 2024
DOI 10.3389/fnut.2024.1474597

Check for updates

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The impact of a polyphenol-rich supplement on epigenetic and cellular markers of immune age: a pilot clinical study

Austin Perlmutter[1]*, Jeffrey S. Bland[1], Arti Chandra[1], Sonia S. Malani[1], Ryan Smith[2], Tavis L. Mendez[2] and Varun B. Dwaraka[2]*

Uniquely Brain-Boosting Nutrients

- Omega-3s (EPA/DHA): balance immunity, improve membrane fluidity, promote neuronal health. Most don’t consume enough in diet
- Magnesium, B-vitamins, choline: essential for neuroplasticity and cognition
- Creatine: may boost brain energy supply by augmenting availability of brain ATP

What about….

Some increasing consideration for low-carb/keto for certain subgroups in focused dosing

Vegan diet is beat by omnivorous diet for most metrics but can be enhanced with additional nutrients (B12, omega-3s etc)

Little to no good evidence for carnivore for long-term brain health compared to other better-studied healthy diets

No diet has proven better for brain health at scale than a balanced, minimally-processed Mediterranean diet

Key Tenets

- Diet: Mediterranean or MIND, consideration for low-carb/keto for metabolic dysfunction
- Pre/Probiotics including fiber, polyphenols, diversity vs individual strains
- Postbiotic considerations?
- Reduction/elimination of alcohol
- Reduce/remove trans-fats
- Increase/consume omega-3 fats in diet or supplement (500 mg-1 gram EPA/DHA baseline)
- Saturated fats << olive oil, avocados, nuts, fish
- Some consideration for magnesium , creatine (5-10 grams a day)

What does the future hold?

- Immunometabolism is emerging as central to our understanding of brain health and disease
- Lifestyle and environment majorly shapes immunometabolic programming
- The effect of diet on brain cognitive and mental health is increasingly viewed through integrated immunometabolic circuitry
- Polyphenols, historically viewed as antioxidants, are now understood to act through immunometabolic pathways.

Thank you for joining us today.

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