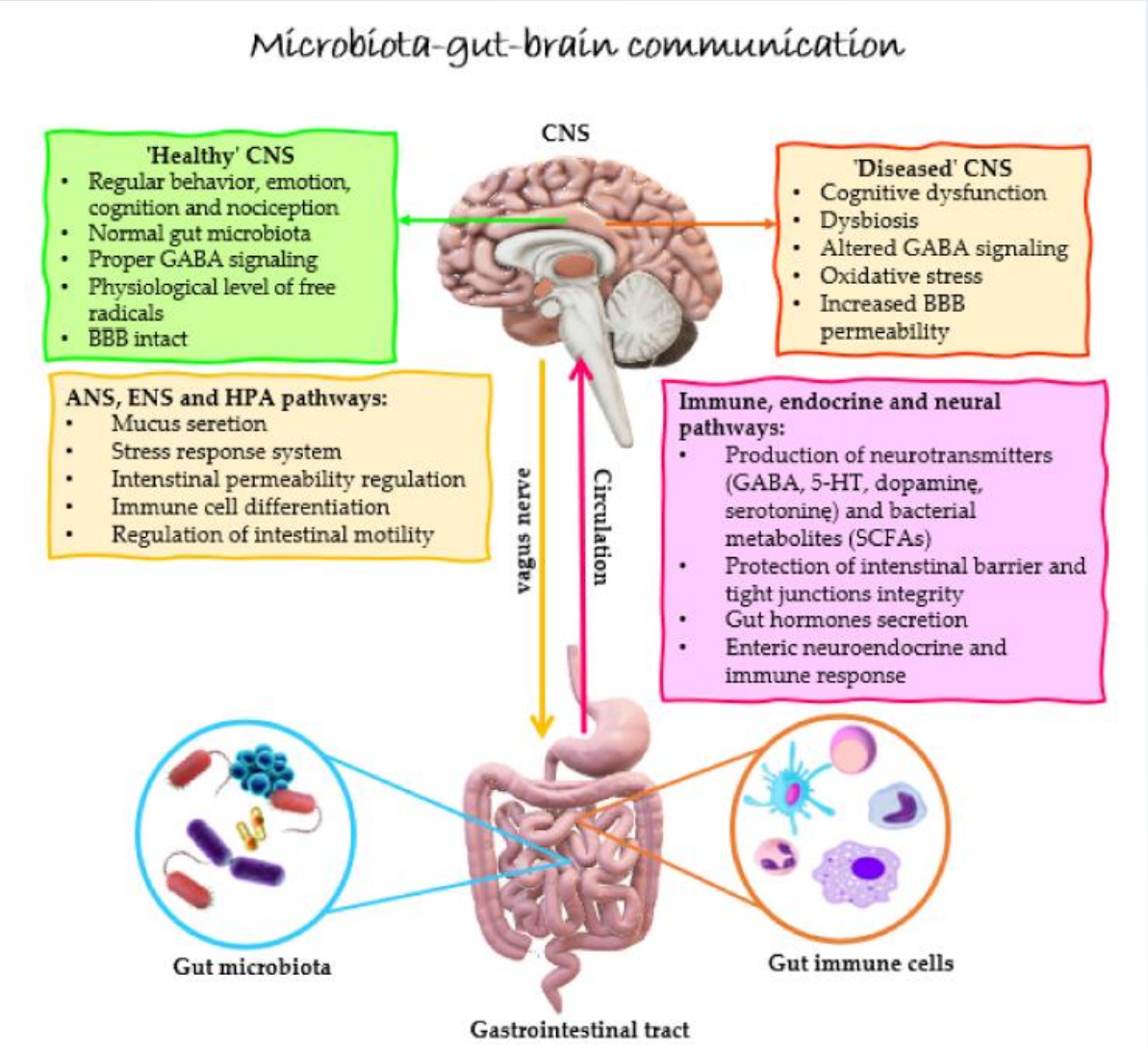
Connection between Gut Biome and MS Pathophysiology?

Gut biome affects CNS through multiple mechanisms

- Connection between autonomic nervous system, enteric nervous system, and hypothalamic-pituitary-adrenal axis
- Immune system
- Neuroendocrine pathways

In CNS, circulating microbes, microbial products, and inflammatory factors, can lead to

- Increased BBB permeability
- Demyelination, axonal damage, and neurodegeneration



5-HT, serotonin; ANS, autonomic nervous system; BBB, blood-brain barrier; CNS, central nervous system; ENS, enteric nervous system; GABA, gamma-aminobutyric acid; GBA, gut-brain axis; HPA, hypothalamic-pituitary-adrenal; SCFAs, short-chain fatty acids.

Ullah H et al. *Curr Neuropharmacol*. 2021;19:1966-1983.

Gut Biome and MS

Altered Gut Biome with MS

Identical twin studies

- ↑Akkermansia, *Acinetobacter, Methanobrevibacter*
- ↓*Parabacteriodes*, *Butyricimonas*

Consistent changes across other studies:

- ↓Bacteroidaceae family, *Faecalibacterium*, *Clostridium*, and *Prevotella*

Altered Levels of Microbial Metabolites

- ↓**SCFAs**:
  Gut – SCFAs maintain intestinal barrier, ↓inflammation
  Brain – cross BBB, modulate immune homeostasis
- ↓**Propionate**, resulting in ↓in SCFAs and Treg and ↑in IL-17 producing T cell proportion in blood
- ↑**Acetate**: ↑IL-17 producing $CD8^+$ cell proportion
- ↓**Bile acid metabolites**, which modulate microglial and myeloid cell activation; neuroprotective role in CNS[1,2]

Impaired Intestinal Barrier

- MS associated with impaired intestinal permeability
- MS associated with ↑concentration of *A. muciniphila*, which are known to degrade the intestinal mucosal lining

BBB, blood-brain barrier; CNS, central nervous system; IL, interleukin; SCFA, short chain fatty acid; Treg, regulatory T cell.

1. Ghezzi L et al. *J Clin Invest*. 2021;131:e143774; 2. Bhargava P, et al. *J Clin Invest*. 2020;130:3467-3482.

Probiotics and MS Symptoms and Disease Severity

Major findings from small, preliminary, placebo-controlled trials in patients with MS

Probiotics	N		Key Outcomes (Probiotics relative to placebo)
	Probiotic	Placebo	
L. acidophilus, *L. casei*, *B. bifidum*, *L. fermentum*	20	20	Down-regulated gene expression of IL-8 and TNF-α in PBMCs
L. acidophilus, *L. casei*, *B. bifidum*, *L. fermentum*	30	30	Improved EDSS and physical and mental health scales, ↓serum insulin, ↑insulin sensitivity and HDL levels, ↓hs-CRP, NO metabolites, MDA
Visibiome blend of *Lactobacillus spp, Bifidobacterium spp, S. thermophilus*	9	13	↓$CD14^+CD16^+$, $CD45^+/LIN^-/CD11c^+$, ↑$CD8^+$ T cells
B. infantis, *B. lactis*, *L. reuteri*, *L. casei*, *L. plantarum*, *L. fermentum*	24	24	↑mental health parameters, ↓EDSS, improved insulin resistance and lipid metabolism, ↓hs-CRP, NO, and MDA
Blend of *Lactobacillus spp, Bifidobacterium spp, S. thermophilus*	35	35	↑mental health parameters

EDSS, expanded disability status scale; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; IL, interleukin; MDA, malondialdehyde; NO, nitric oxide; PBMCs, peripheral blood mononuclear cells; TNF-α, tumor necrosis factor α.

Dziedzic A et al. *Int J Mol Sci*. 2022;23:14478.