
Simposio scientifico

ItPROM

Microbiota intestinale e salute:

nuove frontiere nella prevenzione e nella terapia

28 marzo 2026 • Villa Quaranta • Ospedaletto, Verona

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Neuroinfiammazione e medicina probiotica

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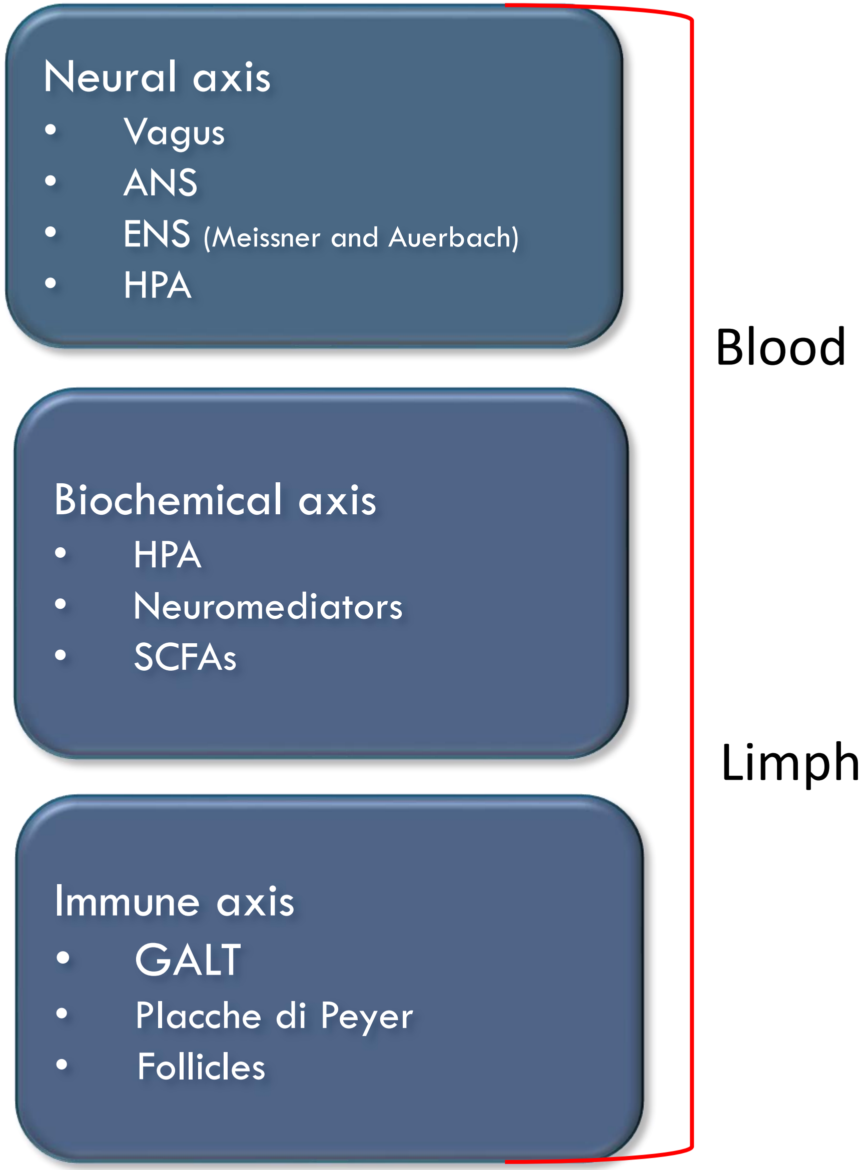
Microbiota-Gut-Brain Axis

Mangia e Stai Meglio, CONTENT ED NET, 2021

K.Stopínska et al JCM,oct 2021



Neural axis
- Vagus
- ANS
- ENS (Meissner and Auerbach)
- HPA

Biochemical axis
- HPA
- Neuromediators
- SCFAs

Immune axis
- GALT
- Placche di Peyer
- Follicles

Blood

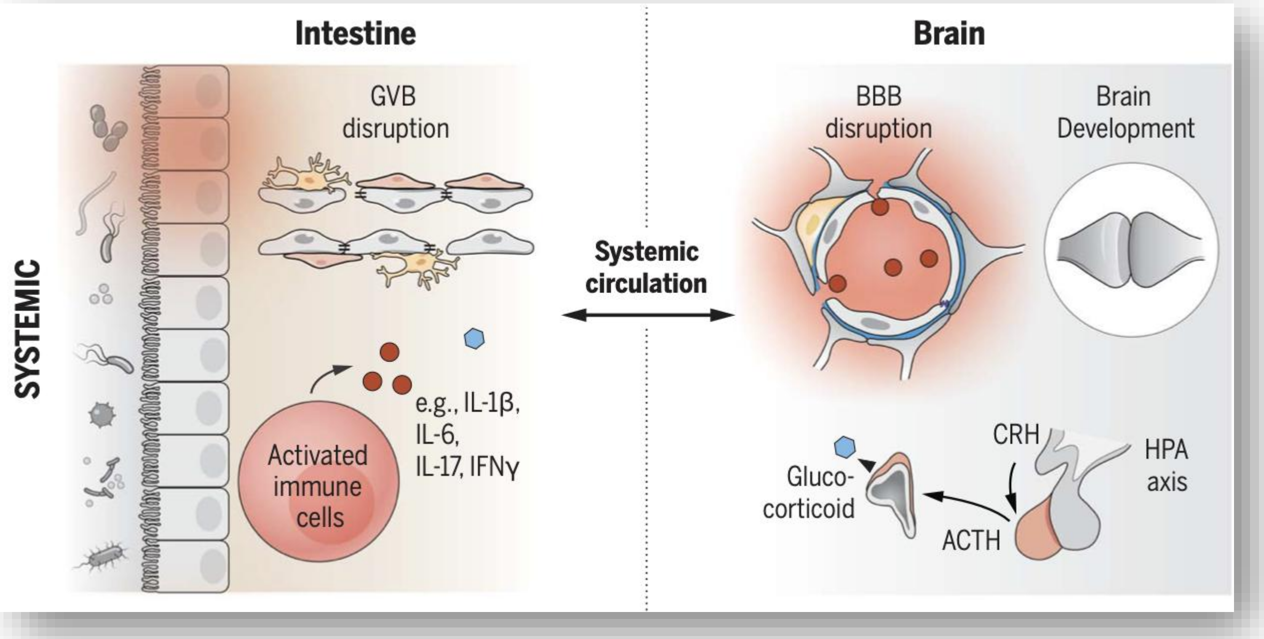
Limph

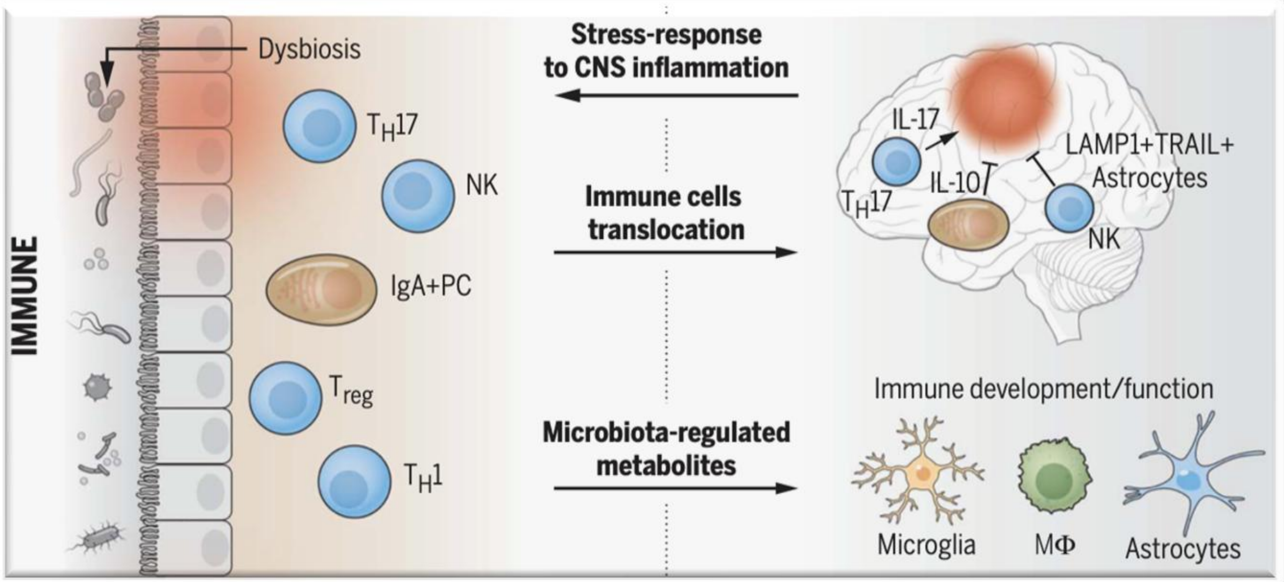
REVIEW

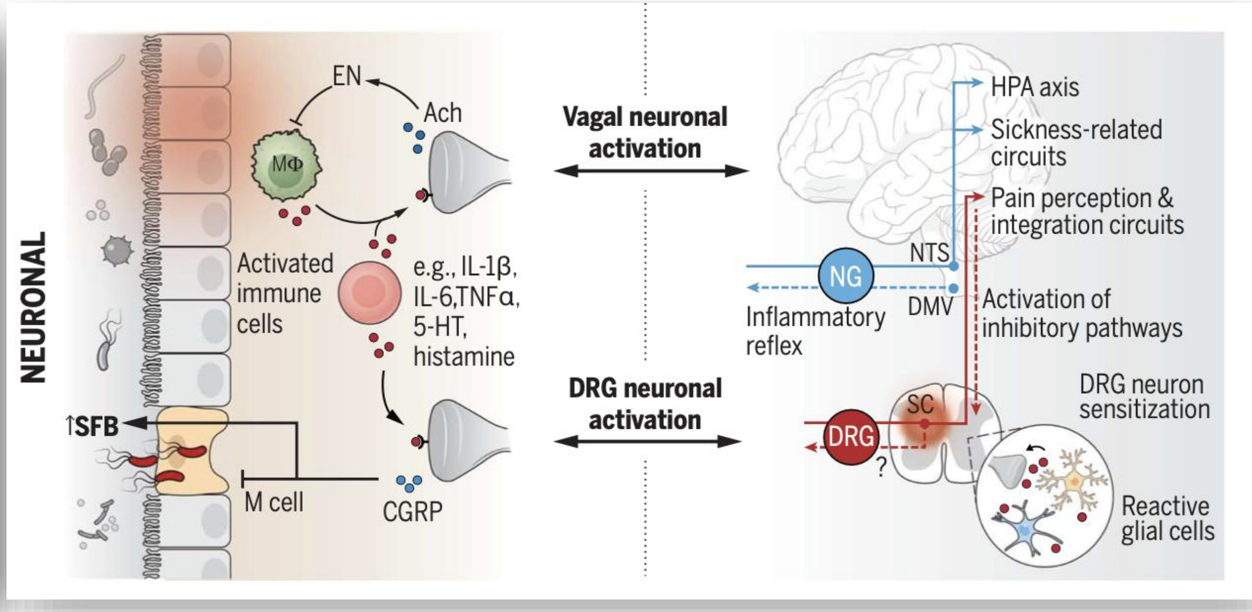
Signaling inflammation across the gut-brain axis

Gulistan Agirman*, Kristie B. Yu, Elaine Y. Hsiao

MICROBIOTA-GLIA AXIS





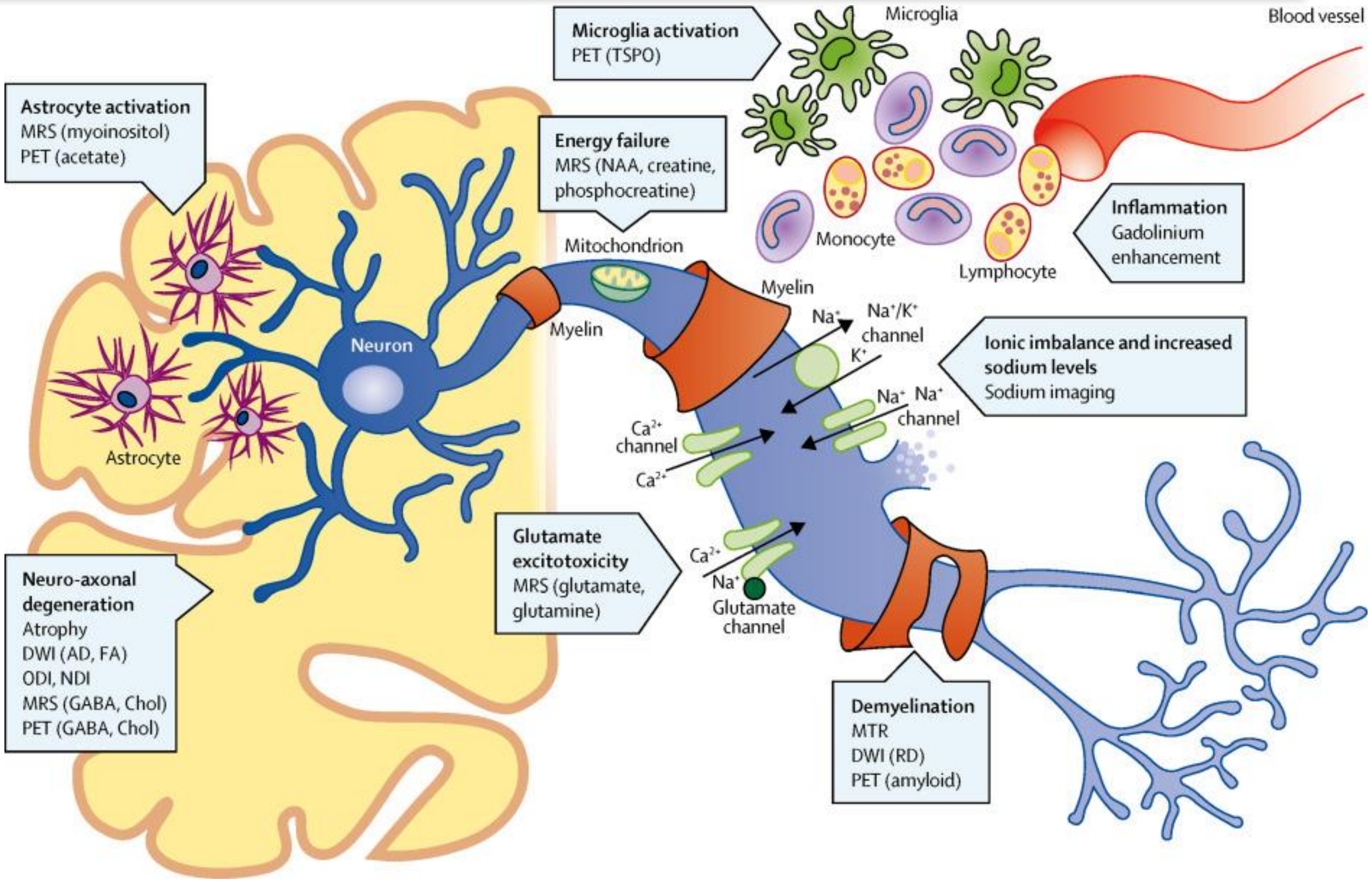


Agirman et al., Science 374, 1087–1092 (2021) 26 November 2021

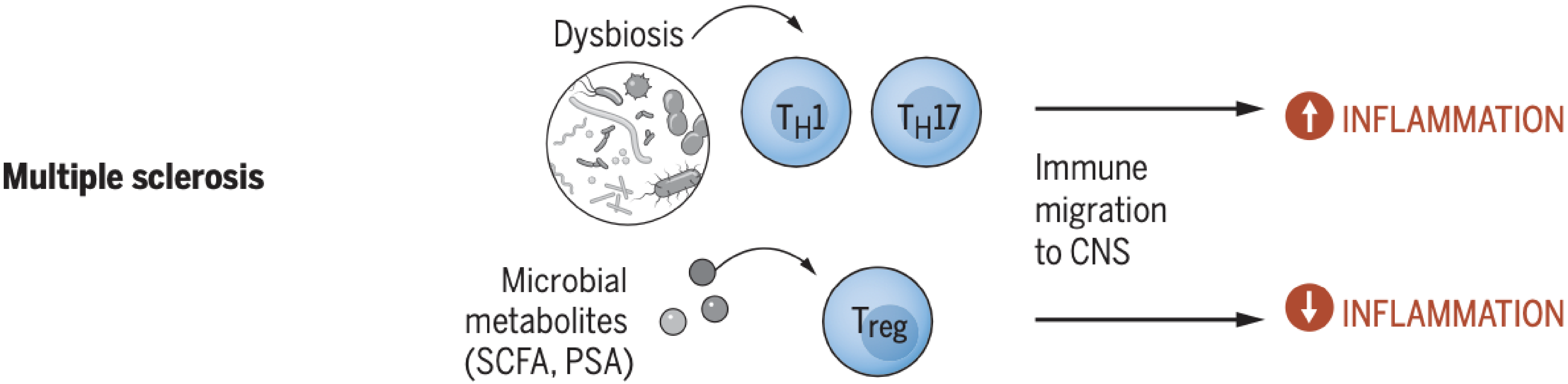
Multiple Sclerosis

Multiple **Sclerosis (MS)** is a chronic autoimmune inflammatory disease of the CNS with major epidemiological and social impact, characterized neuropathologically by three distinctive features:

1. Neuroinflammation
2. Demyelination
3. Axonal degeneration



Thompson A. J., Baranzini S. E., Geurts J., Hemmer B., Ciccarelli O. (2018). Multiple sclerosis. The Lancet, 391(10130), 1622–1636



Multiple sclerosis

Dysbiosis

T_H1 T_H17

Microbial
metabolites
(SCFA, PSA)

T_{reg}

Immune
migration
to CNS

⬆ INFLAMMATION

⬇ INFLAMMATION

Agirman et al., Science 374, 1087–1092 (2021) 26 November 2021

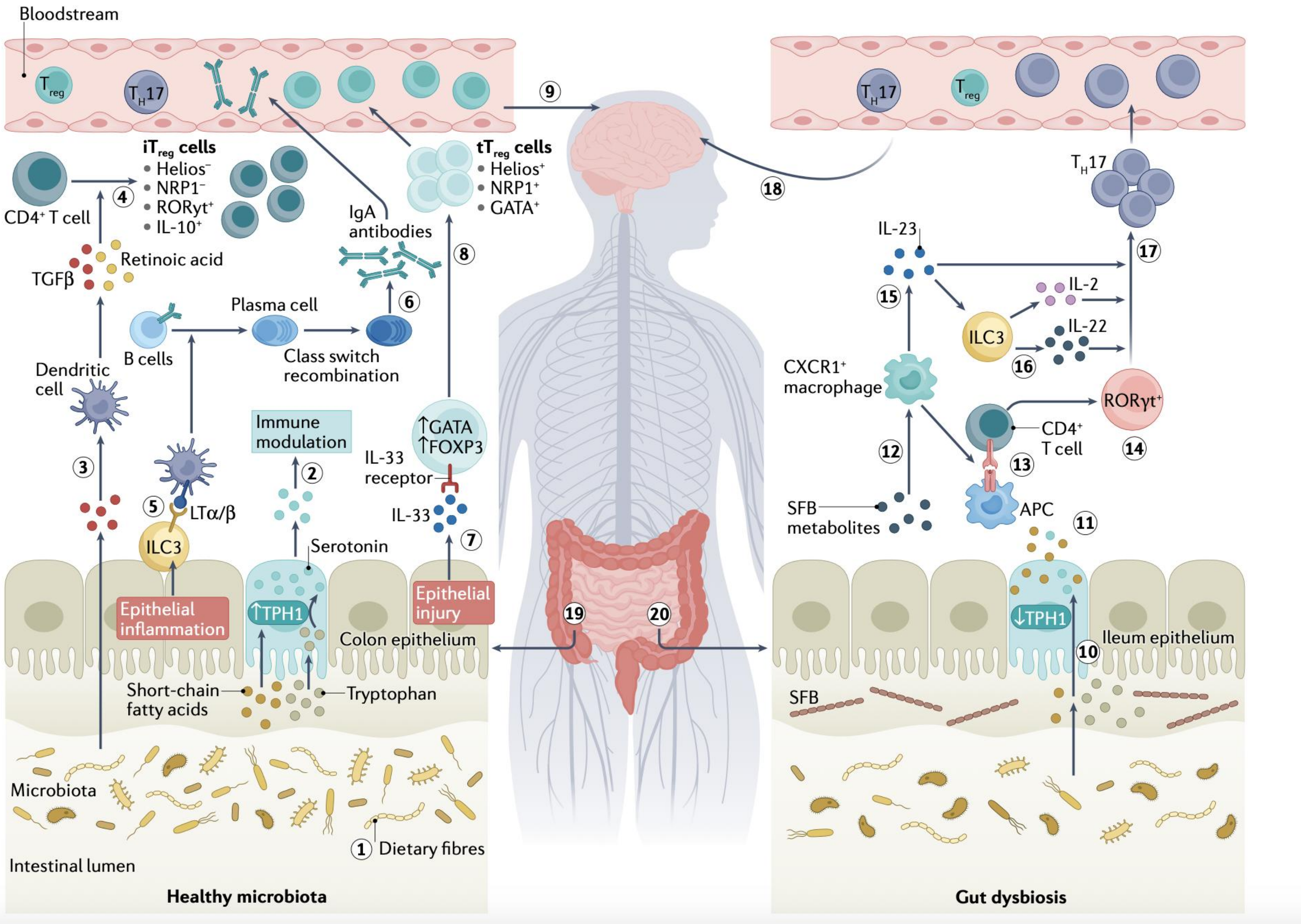
The role of the gut microbiota in multiple sclerosis

Jorge Correale[1], *Reinhard Hohlfeld*[2,3] *and Sergio E. Baranzini*[4] ✉

Key points

- The colony of bacteria that inhabit the gut — known as the gut microbiota — varies in composition according to genetic factors and, more importantly, envorinmental influences, particularly diet.
- The composition of the gut microbiota influences the production of serotonin in the gut, which in turn influences serotonin-mediated regulation of systemic immune function.
- Gut microbiota are also involved in complex interactions with the gut and immune cells in the small intestine and the colon, thereby influencing immune responses in the periphery and the central nervous system.
- Abundant evidence indicates that the gut microbiota has a role in multiple sclerosis (MS) through its influence on immune function.
- Therapeutic strategies that target the microbiota — including dietary interventions, probiotics, short-chain fatty acids and faecal microbial transplantation — seem promising for the treatment of MS, but further work is needed to assess their effectiveness.

The Gut Microbiota Controls Neuroinflammation in MS



Key Mechanisms

- SCFAs promote **Treg cells** that suppress CNS inflammation
- Tryptophan metabolites modulate **TH17/Treg balance**
- Dysbiosis drives **TH17 expansion** and pro-inflammatory cytokines
- Gut IgA+ plasma cells recirculate to **dampen CNS inflammation**
- Disrupted **gut barrier** amplifies systemic + CNS inflammation

Source: Boziki et al., Nat Rev Neurol 2022

Boziki et al., Nat Rev Neurol 2022

IgA$^+$ B Cells Recirculate to the CNS & Reduce Inflammation

Gut-educated IgA-producing plasma cells traffic to the brain and suppress inflammation via IL-10

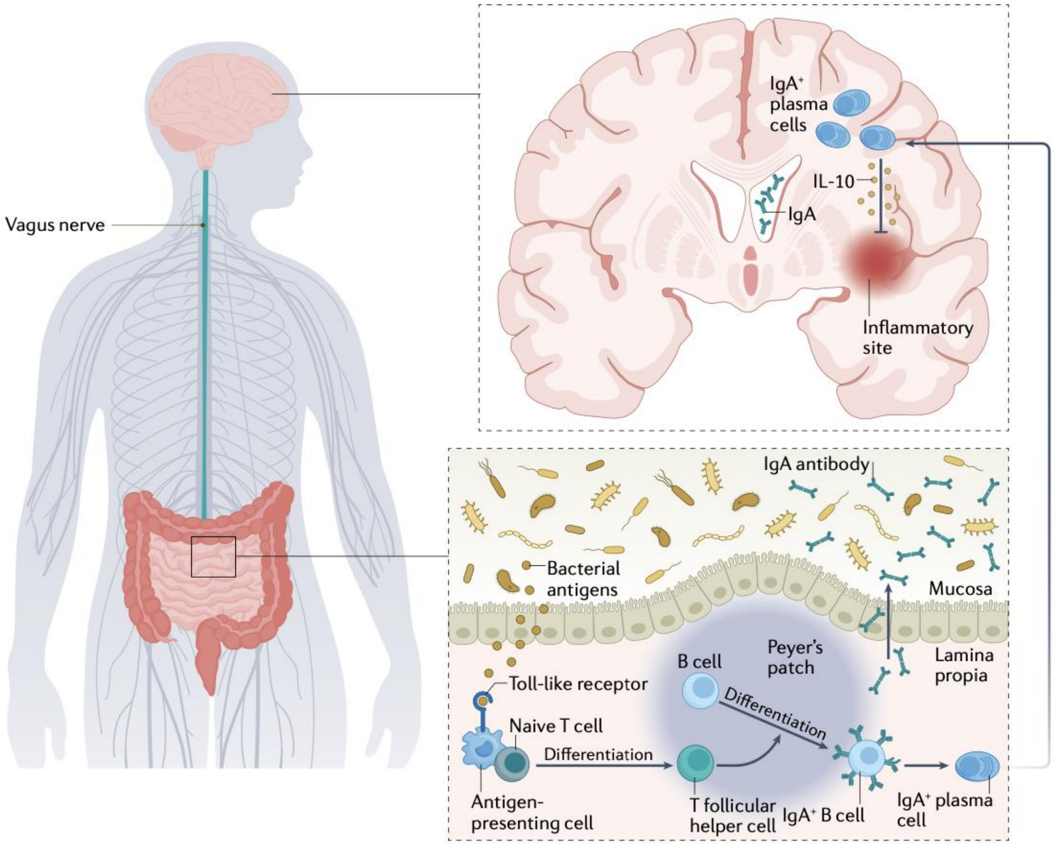


Fig. 2 | **Recirculation of IgA-producing-plasma cells in MS.** Bacterial antigens activate antigen-presenting cells, which lead to differentiation of naive T cells into T follicular helper cells. These cells in turn promote differentiation of B cells into IgA$^+$ B cells and plasma cells that produce IgA antibodies. The plasma cells and antibodies enter the circulation and reduce inflammation in the brain owing to IL10 release by the plasma cells.

Diet

Ketogenic, anti-inflammatory & Mediterranean diets alter microbiome composition

Probiotics

Restore depleted taxa (e.g. Lactobacillus); reduce Akkermansia & Blautia

SCFAs

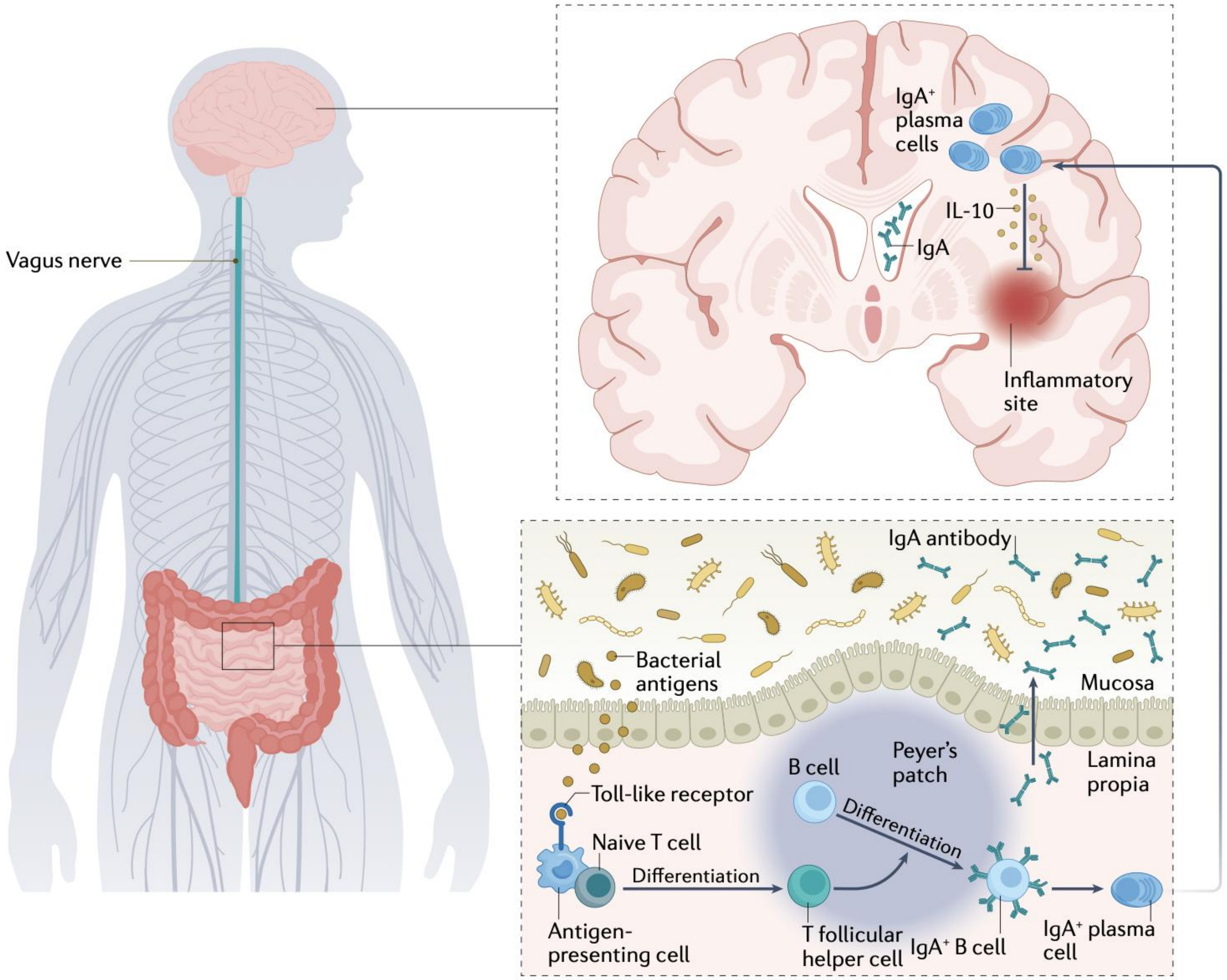
Propionate & butyrate expand Treg cells and suppress CNS inflammation

FMT

Faecal microbiota transplant resets dysbiotic state — trials ongoing in MS

Fig. 2 | Correale et al., Nature Reviews Neurology, 2022

IgA+ Plasma Cells: A Protective Gut-Brain Loop in MS



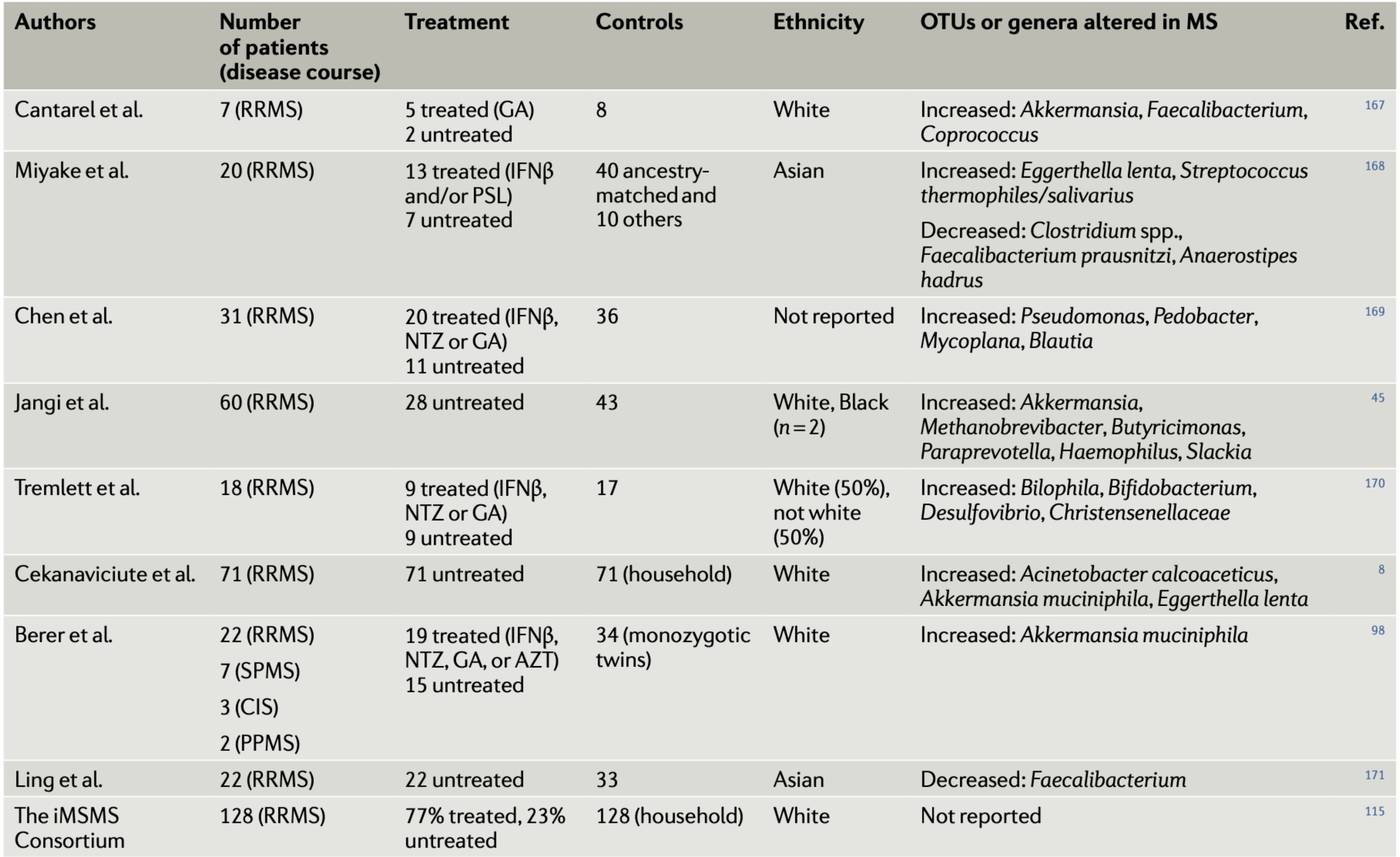
The Circuit

- Bacterial antigens in gut **activate APCs** in Peyer's patches
- T follicular helper cells drive **IgA+ B cell differentiation**
- IgA+ plasma cells enter circulation and reach **inflamed CNS**
- IL-10 secretion by plasma cells **reduces brain inflammation**
- **MS patients** show reduced IgA+ cells — a key deficit

Source: Boziki et al., Nat Rev Neurol 2022

Boziki et al., Nat Rev Neurol 2022

Gut Microbiome Alterations Consistently Found in MS Patients



Authors	Number of patients (disease course)	Treatment	Controls	Ethnicity	OTUs or genera altered in MS	Ref.
Cantarel et al.	7 (RRMS)	5 treated (GA) 2 untreated	8	White	Increased: *Akkermansia*, *Faecalibacterium*, *Coprococcus*	167
Miyake et al.	20 (RRMS)	13 treated (IFNβ and/or PSL) 7 untreated	40 ancestry-matched and 10 others	Asian	Increased: *Eggerthella lenta*, *Streptococcus thermophiles/salivarius* Decreased: *Clostridium* spp., *Faecalibacterium prausnitzi*, *Anaerostipes hadrus*	168
Chen et al.	31 (RRMS)	20 treated (IFNβ, NTZ or GA) 11 untreated	36	Not reported	Increased: *Pseudomonas*, *Pedobacter*, *Mycoplana*, *Blautia*	169
Jangi et al.	60 (RRMS)	28 untreated	43	White, Black (*n* = 2)	Increased: *Akkermansia*, *Methanobrevibacter*, *Butyricimonas*, *Paraprevotella*, *Haemophilus*, *Slackia*	45
Tremlett et al.	18 (RRMS)	9 treated (IFNβ, NTZ or GA) 9 untreated	17	White (50%), not white (50%)	Increased: *Bilophila*, *Bifidobacterium*, *Desulfovibrio*, *Christensenellaceae*	170
Cekanaviciute et al.	71 (RRMS)	71 untreated	71 (household)	White	Increased: *Acinetobacter calcoaceticus*, *Akkermansia muciniphila*, *Eggerthella lenta*	8
Berer et al.	22 (RRMS) 7 (SPMS) 3 (CIS) 2 (PPMS)	19 treated (IFNβ, NTZ, GA, or AZT) 15 untreated	34 (monozygotic twins)	White	Increased: *Akkermansia muciniphila*	98
Ling et al.	22 (RRMS)	22 untreated	33	Asian	Decreased: *Faecalibacterium*	171
The iMSMS Consortium	128 (RRMS)	77% treated, 23% untreated	128 (household)	White	Not reported	115

Consistent Findings

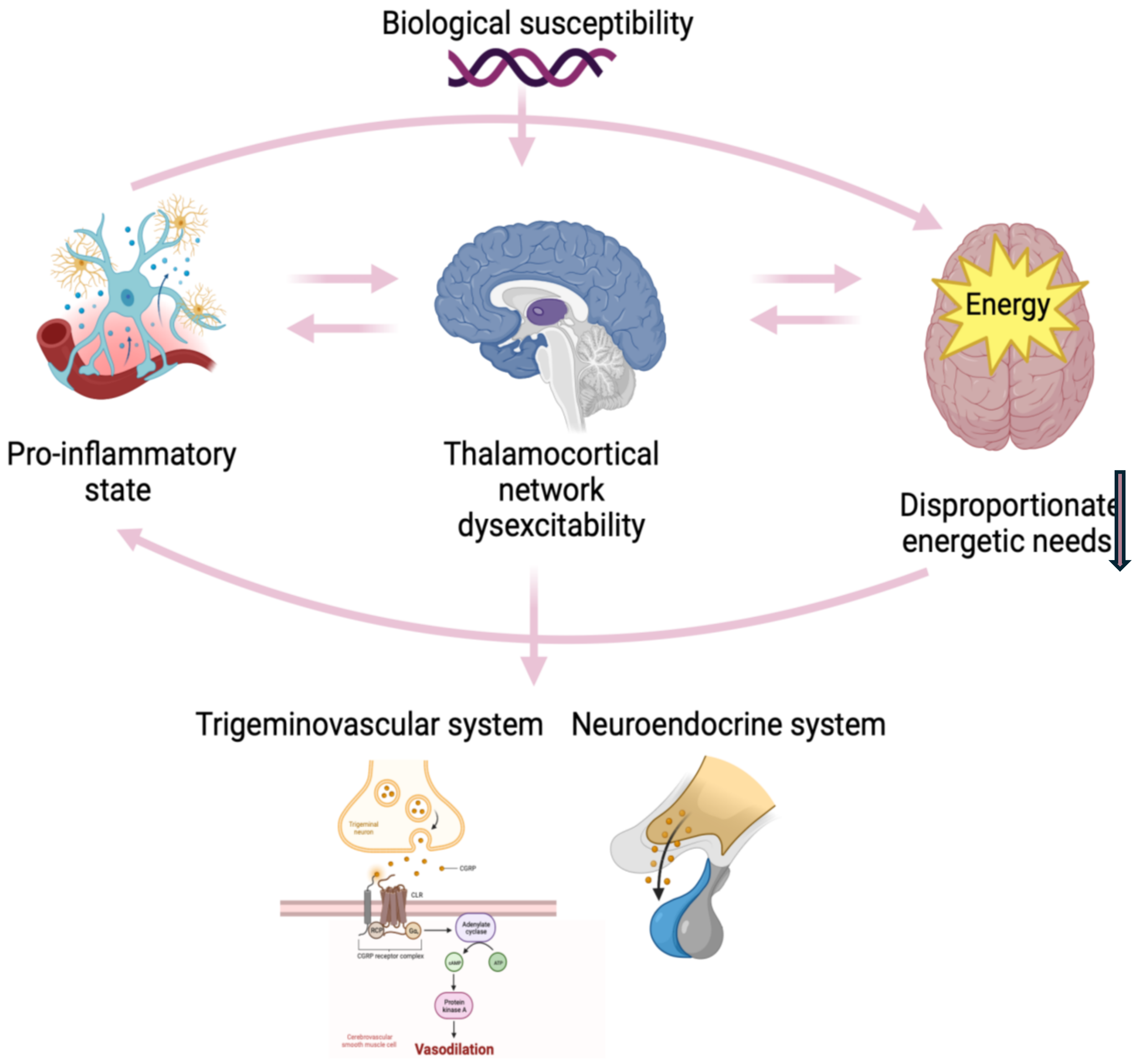
▲ Increased in MS:
- Akkermansia muciniphila
- Acinetobacter calcoaceticus
- Methanobrevibacter spp.

▼ Decreased in MS:
- Faecalibacterium prausnitzii
- Prevotella copri
- Clostridium spp.

→ **8 independent studies**
→ **Multiple ethnicities**

Boziki et al., Nat Rev Neurol 2022

Pathophysiological Mechanisms



The variable combination of:

1. Multiorgan proinflammatory state
2. Dysexcitability of the thalamo-cortical network
3. Disproportionate energy demands from comorbid pathologies

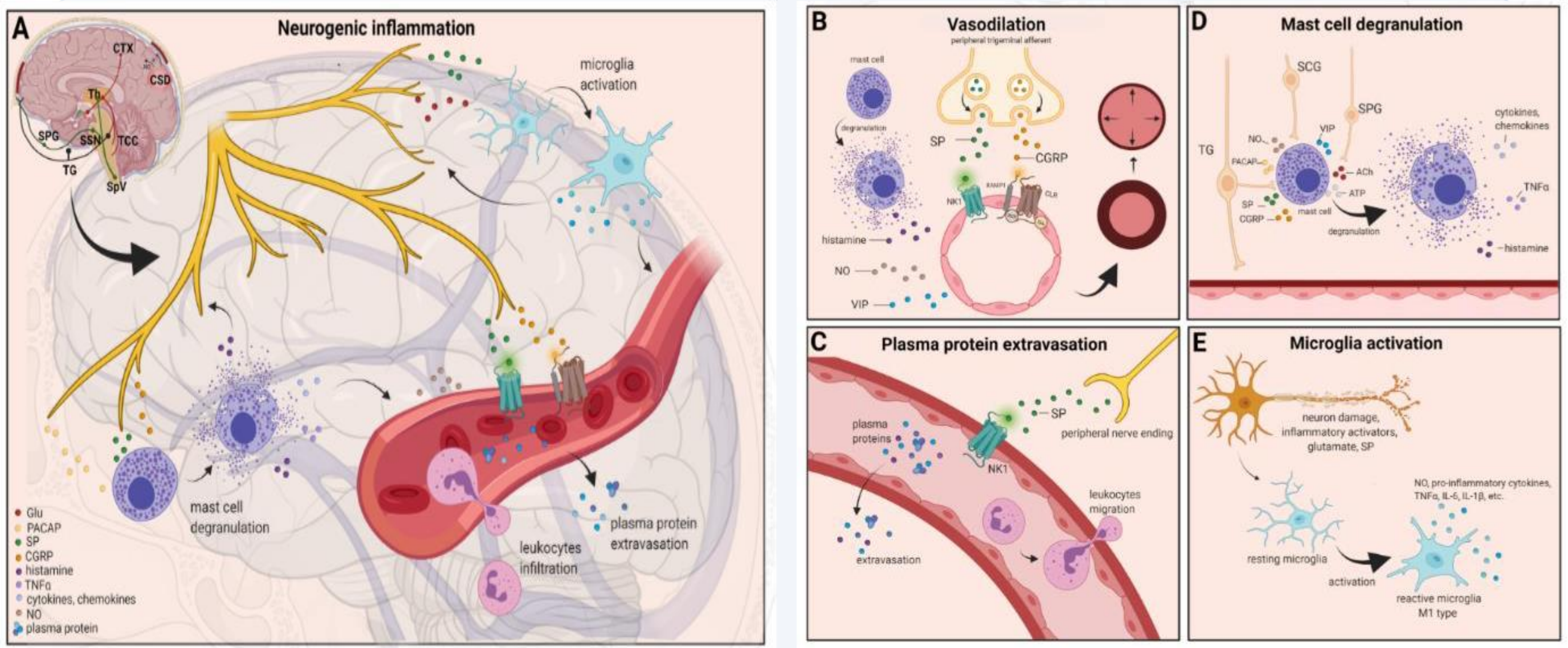
→ Activates:

- Trigeminovascular system
- Hypothalamic neuroendocrine system

↳ Lead to migraine attacks through neurogenic inflammation

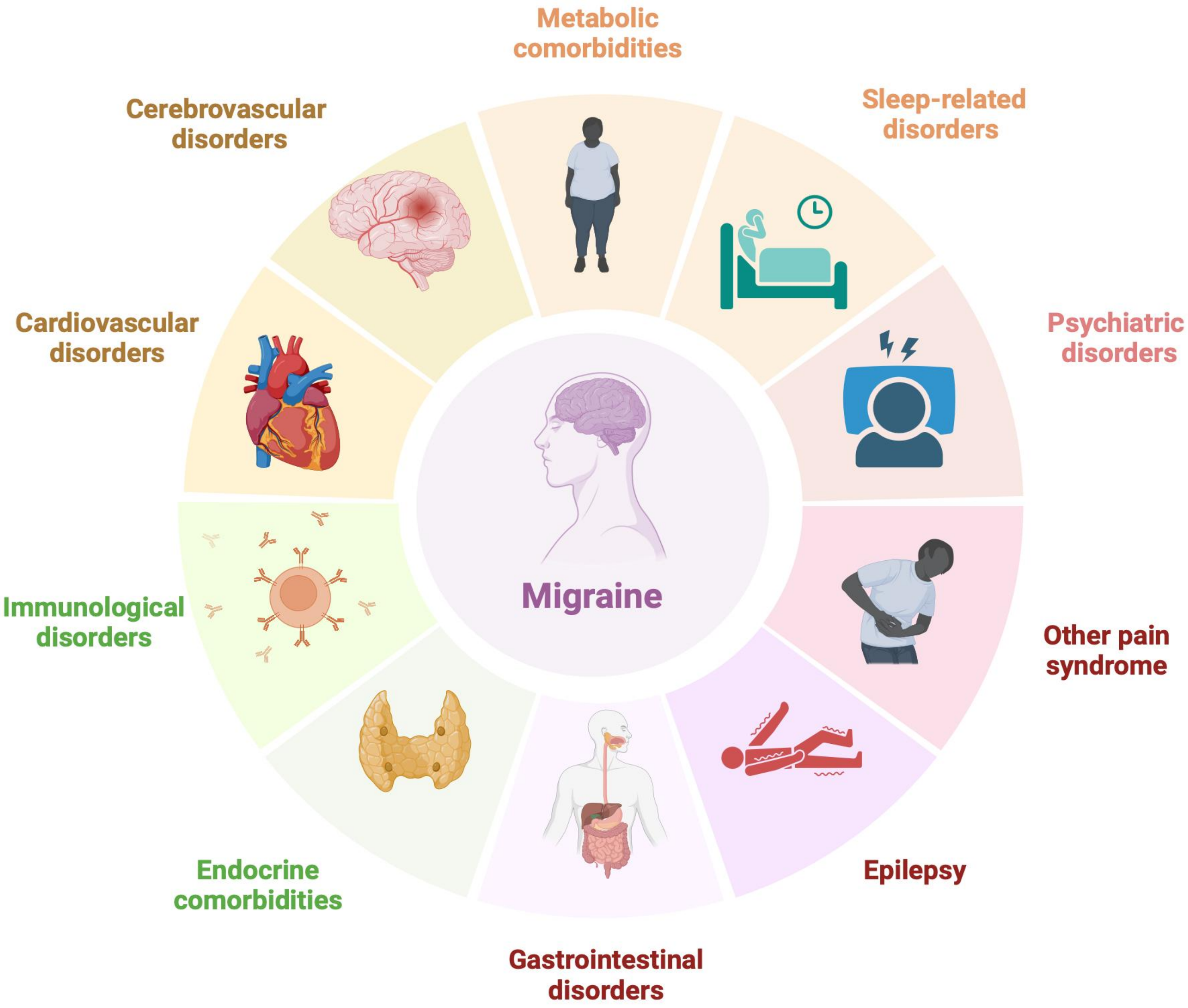
Altamura C et al. Front Hum Neurosci. 2021 Apr 20;15:640574

Neurogenic Inflammation in Migraine



Spekker E. et al, Biomedicines. 2021 Dec 30;10(1):76

Comorbidities of migraine



dysbiosis

inflammation

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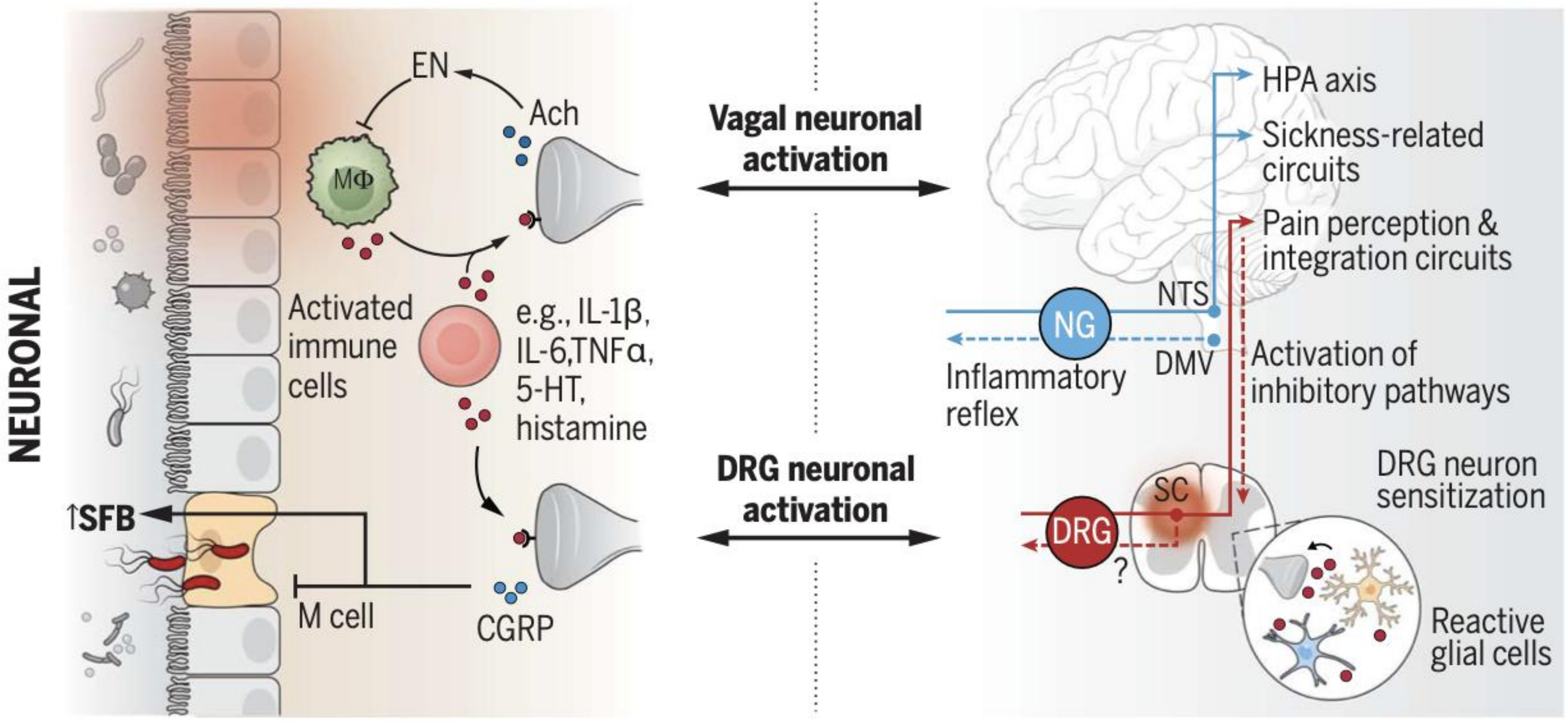

NEURONAL
EN
Ach
MΦ
Activated immune cells
e.g., IL-1β, IL-6,TNFα, 5-HT, histamine
↑SFB
M cell
CGRP
Vagal neuronal activation
DRG neuronal activation
HPA axis
Sickness-related circuits
Pain perception & integration circuits
NTS
NG
DMV
Inflammatory reflex
Activation of inhibitory pathways
DRG neuron sensitization
SC
DRG
?
Reactive glial cells

Evidence from the gut-brain axis research

📊 EVIDENCE

1. The gut microbiota is altered in migraine patients.

2. Migraine comorbidities are characterized by dysbiosis.

3. The gut microbiota could be a diagnostic marker in migraine patients.

💊 THERAPEUTIC

4. If the gut microbiota is able to modulate neuroinflammation and pain...

5. Intervention on the gut microbiota can provide therapeutic support for migraine.

Gut Microbiota & Migraine:
a link through TNF-α

- **Gut dysbiosis prolongs migraine-like pain** — depleting the microbiota (antibiotics or germ-free mice) amplifies trigeminal sensitivity
- **The key mechanism: TNF-α** — dysbiosis upregulates TNF-α in the spinal trigeminal nucleus (Sp5C), sustaining pain
- **Probiotics reverse the effect** — restoring the microbiota normalizes TNF-α and reduces pain chronification

Tang et al., Molecular Neurobiology 2020

Gut Dysbiosis

TNF-α ↑ in Sp5C

Migraine Pain

Gut Microbiota & Pain: 3 Key Insights

01

BROAD PAIN INFLUENCE

Gut microbiota shapes visceral, inflammatory, neuropathic and headache pain — including opioid tolerance

02

NEURO-MODULATION

Modulates dorsal root ganglia excitability and regulates neuroinflammation in both CNS & PNS

03

THERAPEUTIC TARGET

Diet, probiotics, pharmabiotics & fecal microbiota transplantation as new pain strategies

Tang et al., Molecular Neurobiology 2020 — Gut Microbiota Dysbiosis Enhances Migraine-Like Pain Via TNF-α Upregulation

Gut Microbiota Changes in Menopause · Yang et al., Disease Markers 2022

Study Design

Systematic review & meta-analysis
3 case-control studies · 156 women

Phylum Level

No significant changes in Firmicutes, Bacteroidetes or Proteobacteria

Genus Level

↑ Odoribacter & Bilophila significantly increased post-menopause

Estrogen Axis

Estradiol positively correlates with gut microbiota diversity

Clinical Impact

Dysbiosis linked to osteoporosis, metabolic disease & depression

Therapeutic Potential

Probiotics & prebiotics as adjuvant therapy for menopause

Study Objectives · Migraine & Microbiota in Perimenopause — M.E.D.E.A. Trial

PRIMARY ENDPOINT

Assess whether an **anti-inflammatory diet + pre/probiotics** reduces migraine attack frequency & headache days/month in perimenopausal women with gut dysbiosis

SECONDARY ENDPOINTS

- Migraine intensity, disability (MIDAS, HIT-6)
- Quality of life & mood (EQ-5D, MENO-D)
- Sleep quality & fatigue (PSQI, FSS)
- Gut microbiome composition & body composition (BIA)

Study Protocol — Assessment Timeline

BASELINE

T0

- Blood tests
- Headache diary (last 3 months)
- Questionnaires (EQ-5D, VAS, HIT-6, MIDAS, HEADWORK, PSQI, MENO-D, FSS)
- Weight & height (BMI)
- Bioimpedance analysis
- Dietary plan review
- Gut microbiota composition

3 MONTHS

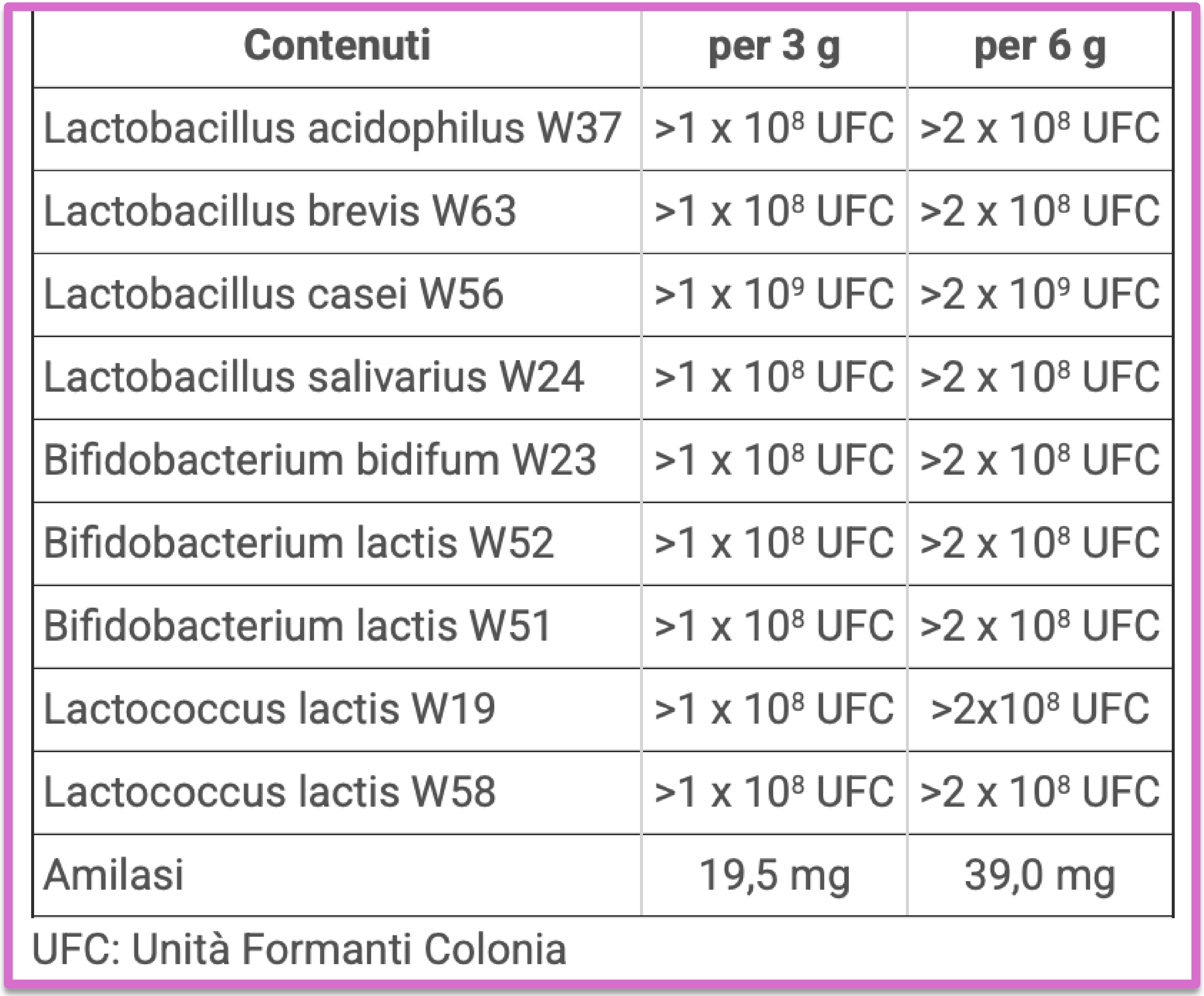
T1

- Blood tests
- Headache diary (last 3 months)
- Questionnaires (EQ-5D, VAS, HIT-6, MIDAS, HEADWORK, PSQI, MENO-D, FSS)
- Weight & height (BMI)
- Bioimpedance analysis
- Dietary plan review

6 MONTHS

T2

- Blood tests
- Headache diary (last 3 months)
- Questionnaires (EQ-5D, VAS, HIT-6, MIDAS, HEADWORK, PSQI, MENO-D, FSS)
- Weight & height (BMI)
- Bioimpedance analysis
- Dietary plan review
- **Gut microbiota composition ★**



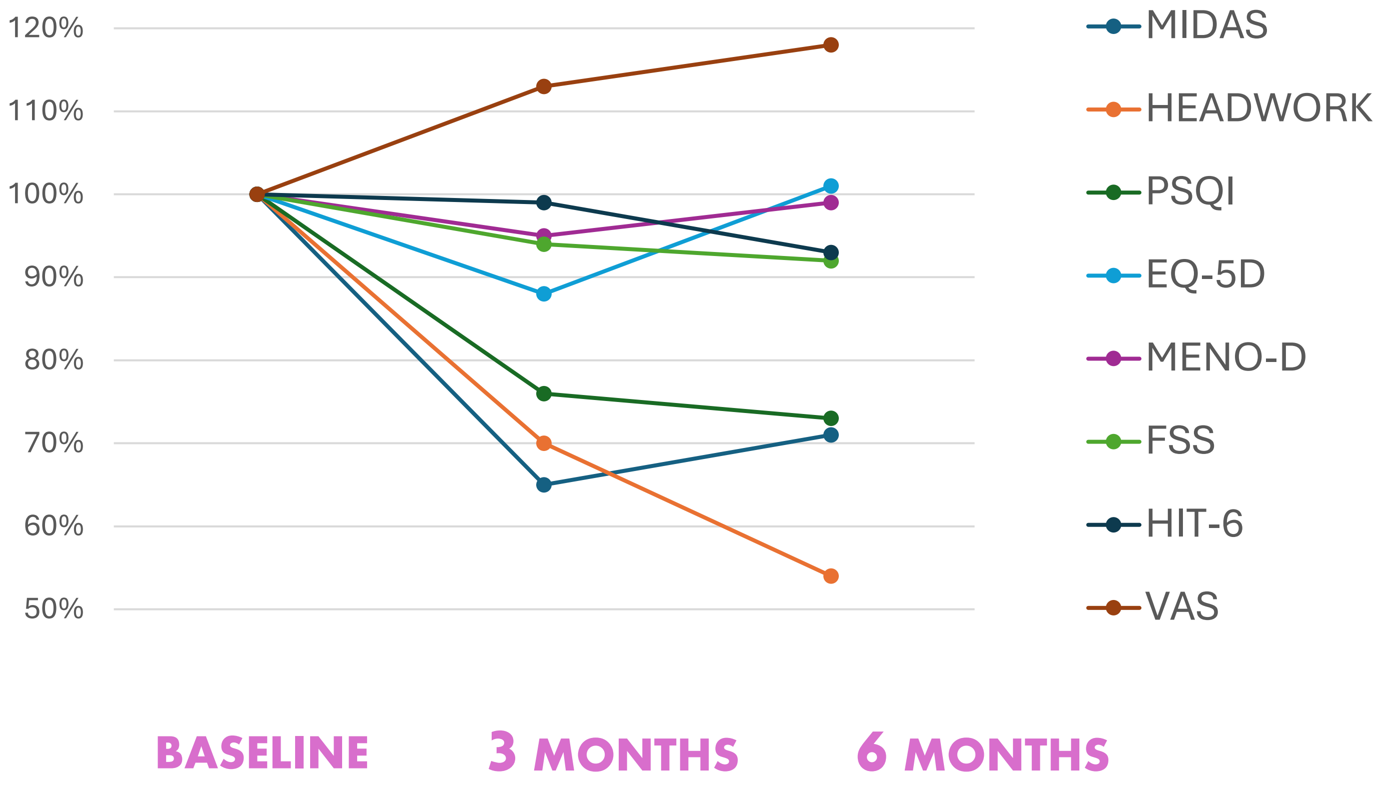
Contenuti	per 3 g	per 6 g
Lactobacillus acidophilus W37	>1 x 10^8 UFC	>2 x 10^8 UFC
Lactobacillus brevis W63	>1 x 10^8 UFC	>2 x 10^8 UFC
Lactobacillus casei W56	>1 x 10^9 UFC	>2 x 10^9 UFC
Lactobacillus salivarius W24	>1 x 10^8 UFC	>2 x 10^8 UFC
Bifidobacterium bidifum W23	>1 x 10^8 UFC	>2 x 10^8 UFC
Bifidobacterium lactis W52	>1 x 10^8 UFC	>2 x 10^8 UFC
Bifidobacterium lactis W51	>1 x 10^8 UFC	>2 x 10^8 UFC
Lactococcus lactis W19	>1 x 10^8 UFC	>2x10^8 UFC
Lactococcus lactis W58	>1 x 10^8 UFC	>2 x 10^8 UFC
Amilasi	19,5 mg	39,0 mg

UFC: Unità Formanti Colonia

SAMPLE

- No. of patients: 17
- Female sex
- Age: 52 ±2.6 years

QUESTIONNAIRES (% CHANGE FROM BASELINE)



TAKE HOME MESSAGES

01

THE GUT–BRAIN AXIS IS REAL

Gut microbiota communicates with the CNS via neural, immune and biochemical pathways, directly shaping neuroinflammation.

02

DYSBIOSIS DRIVES NEUROLOGICAL DISEASE

MS, migraine and menopause all show reduced anti-inflammatory taxa (Faecalibacterium, Prevotella) and expanded pro-inflammatory species.

03

PROBIOTICS & DIET MODULATE CNS INFLAMMATION

Restoring the microbiome via probiotics and anti-inflammatory diet normalises SCFAs, Treg cells and TNF-α, reducing neurogenic pain.

04

MENOPAUSE AMPLIFIES GUT DYSBIOSIS

Oestrogen decline reduces microbial diversity; pre/probiotics targeting the gut-hormone axis may alleviate perimenopausal neurological symptoms.

05

THE M.E.D.E.A. TRIAL — PROOF OF CONCEPT

Preliminary data (n=17) from diet + pre/probiotic intervention in perimenopausal migraineurs show promising trends at 3 and 6 months.