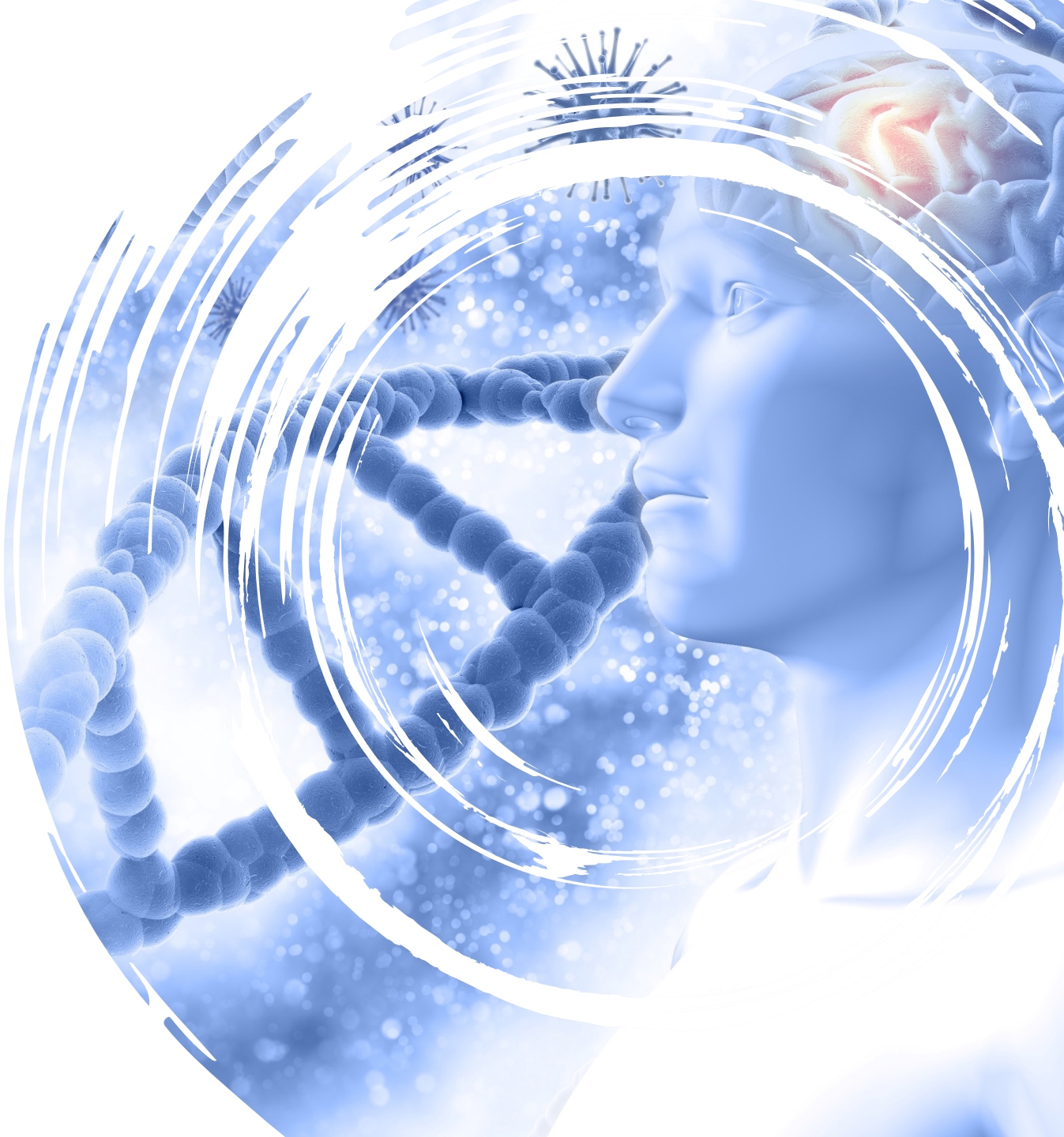
MICROBIOTA AND THE GUT–BRAIN AXIS: FROM PSYCHOLOGICAL DISORDERS TO MOTION SICKNESS

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DR HOSEIN FAZELI

PRESENTER:
MOHSEN POUDINEH

1405.7.26



Content:

- PSYCHOLOGICAL DISORDERS
- Microbiota and Microbiome
- History of the human microbiome
- Colonization of microbiota
- The microbiota-gut-brain axis
- Autism Spectrum Disorder and The intestinal microbiota
- Alzheimer's disease and The intestinal microbiota
- Gut Microbiota and Motion Sickness Susceptibility
- Clinical trials
- Conclusion



PSYCHOLOGICAL DISORDERS

A diverse group of conditions affecting brain function, potentially involving disturbances in cognition, behavior, sensory processing, and physiological responses



These conditions can affect cognitive abilities, sensory processing, daily activities, and overall quality of life, with varying degrees of severity.

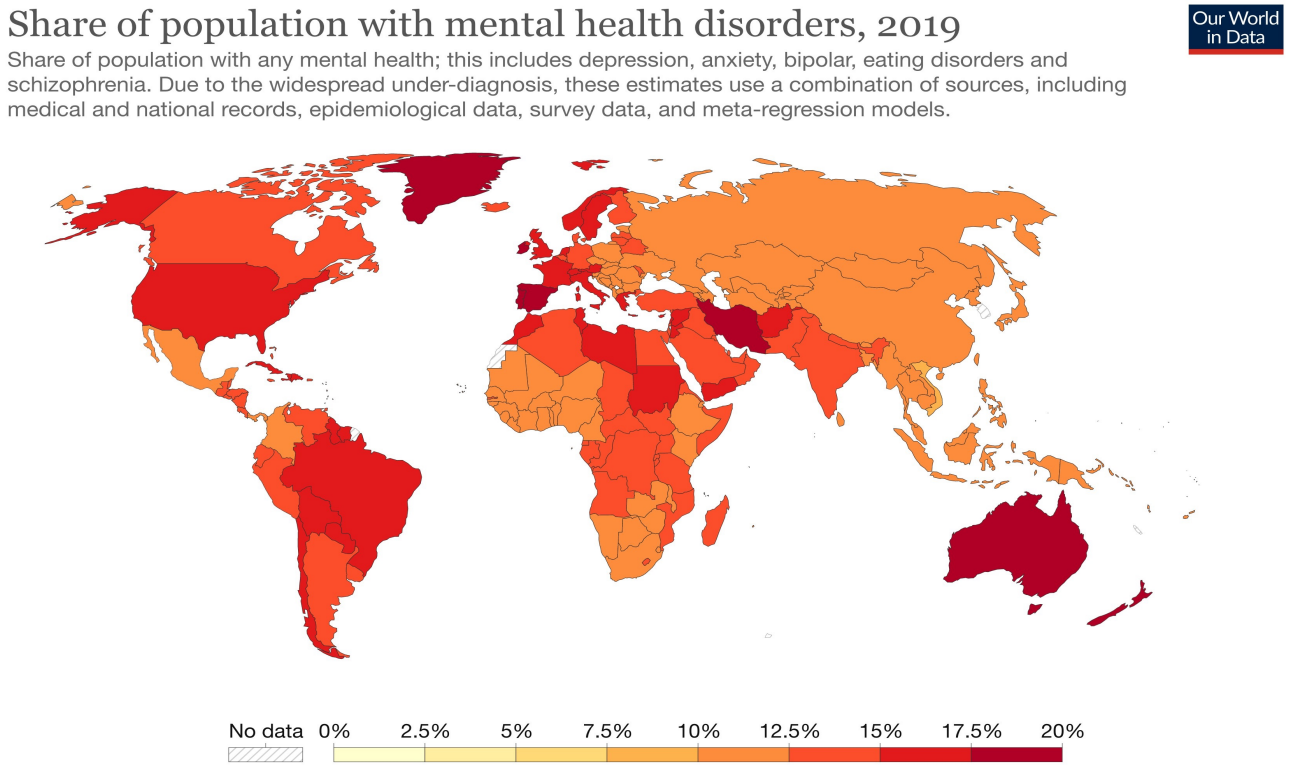
- 57 million people worldwide were living with dementia in 2021.
- 1 in 127 people worldwide has autism
- Up to two-thirds of the population may experience motion sickness.

The common PSYCHOLOGICAL disorders

- Autism spectrum disorder (ASD)
- Alzheimer's disease
- Motion Sickness (MS)

PSYCHOLOGICAL DISORDERS

- **More than a Third** of people reporting sufficient criteria to be diagnosed at some points of their lives.
- Epidemiological research has shown that about **3–18%** of children suffered psychiatric disorders



PSYCHOLOGICAL DISORDERS

Biological factors

- Heredity
- Disturbance in neurotransmitttters
- Brain damage
- Physiological changes

Psychological factors

- Strained interpersonal relationships
- Stress and Frustration
- Childhood insecurities

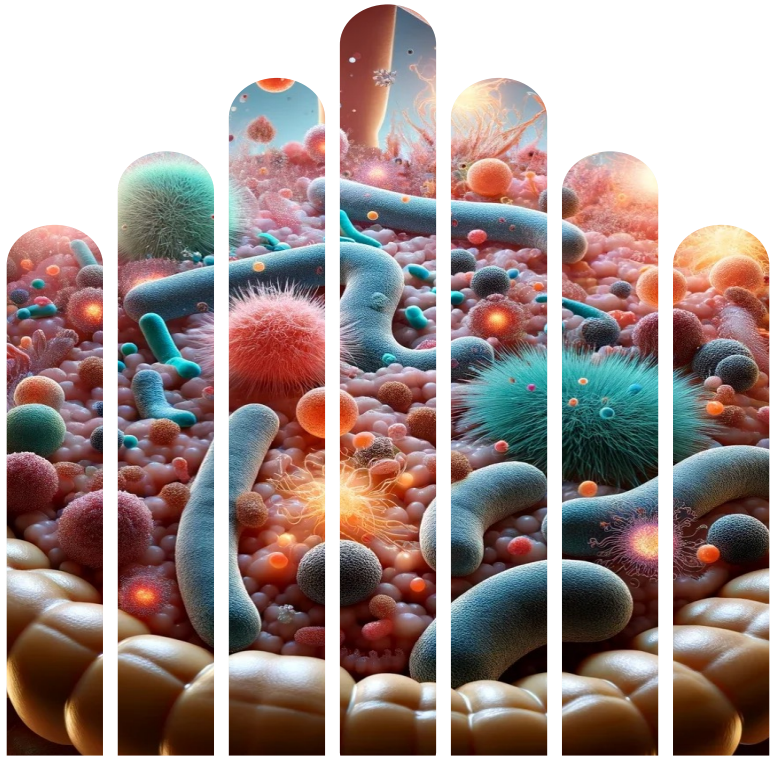
Environmental factors

- Poverty
- Alcoholism
- Urbanization
- Family instability
- Unemployment

MICROBIOTA

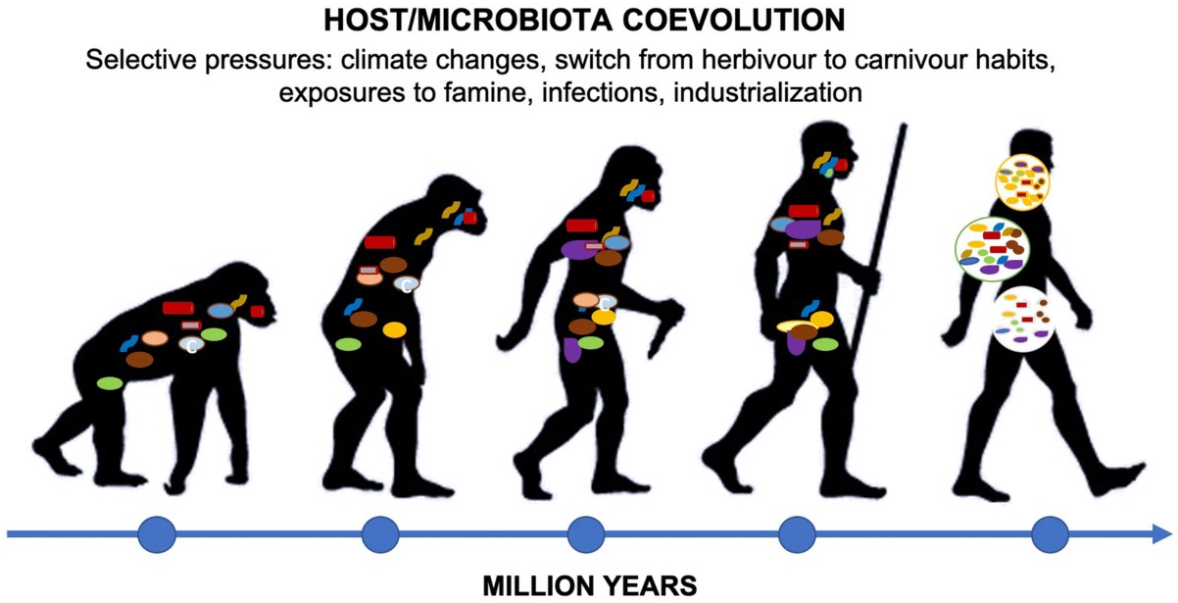
MICROBIOTA AND MICROBIOME

- **Microbiota** describes Microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body
- **Microbiome** refers to The collection of all microbes, such as bacteria, fungi, viruses, and their genes, that naturally live on body
- Estimated to be approximately 10^{13} cells with a 1:1 ratio of bacterial to human cells
- The gastrointestinal tract is the most colonized district of the human organism



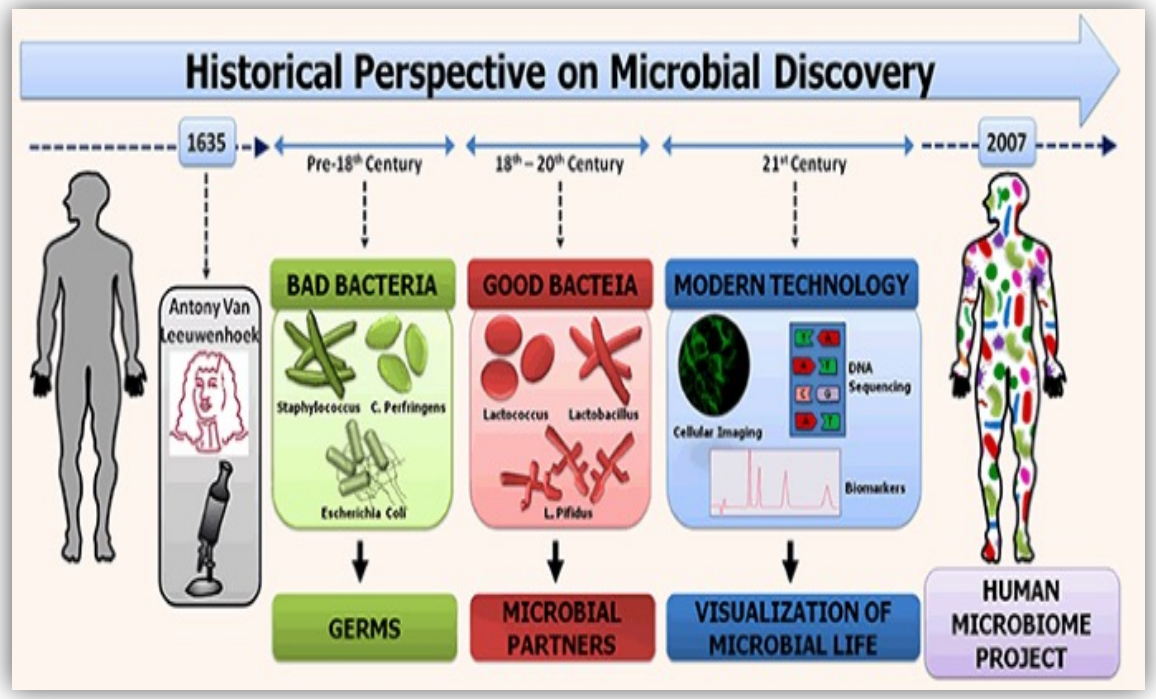
COLONIZATION OF MICROBIOTA

- The onset of the relationship between human species and the microbes residing in our guts goes back into the past to the origin of mankind
- Numerous bacterial taxa inhabiting our intestine developed with primates and humans by cospeciation over the last 15 million years.
- Creating a superorganism



HISTORY OF THE HUMAN MICROBIOME

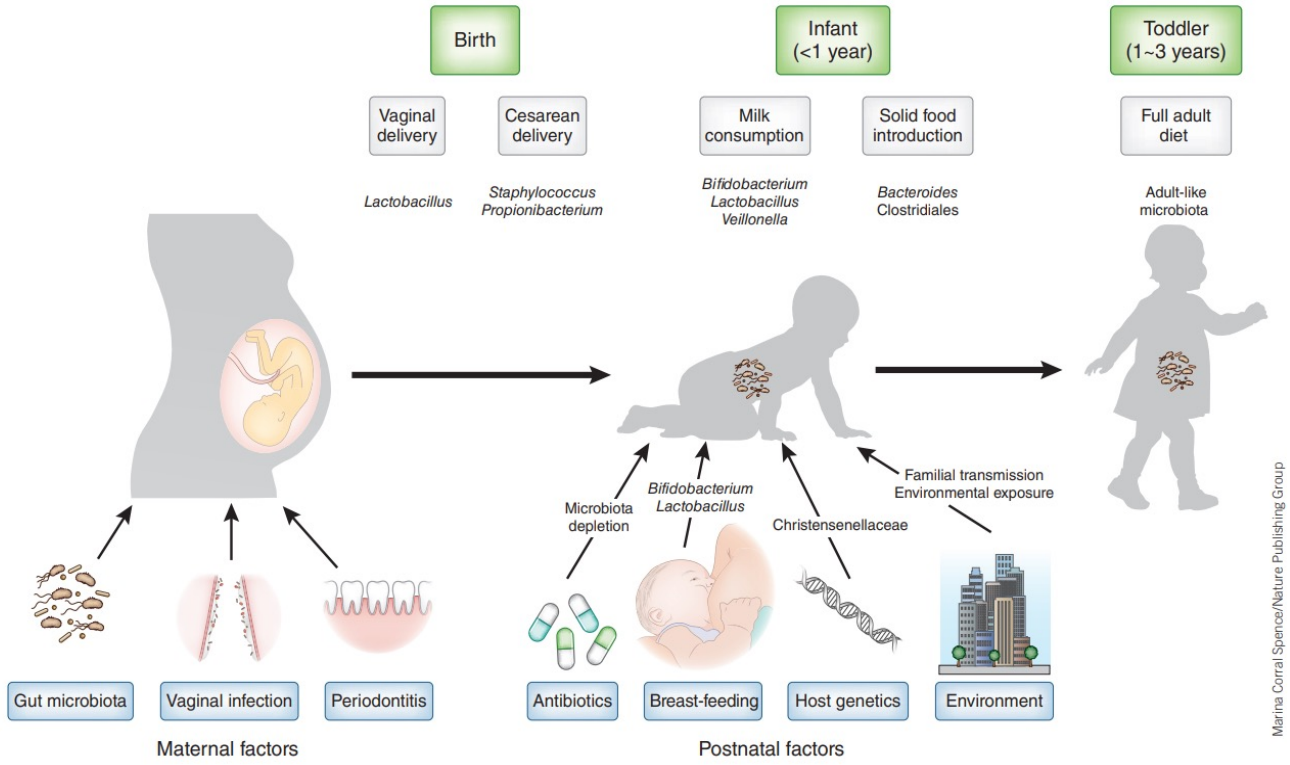
- 17th Century: The first descriptions of human-associated microbiota date back to the 1670s–1680s
- 1988: Whipps and colleagues used the term microbiome to describe the collection of microbes and their activities within a given environment.
- 2001: Joshua Lederberg, first coined the term "microbiome" in 2001
- 2007: the Human Microbiome Project



DEVELOPMENT AND MATURING OF INTESTINAL MICROBIOTA

- Gut microbiota composition depends on several factors, such as:

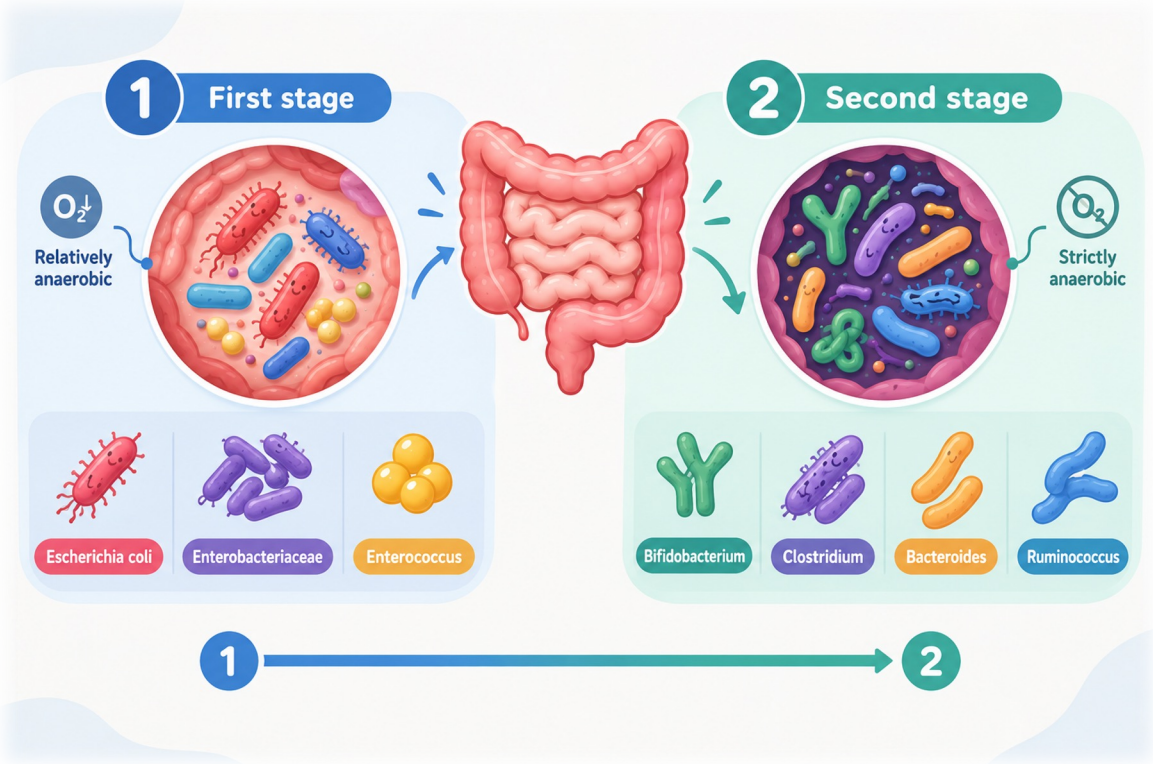
1) Mode of delivery
2) Genetic predispositions
3) Age, nutrition
4) Environmental factors, stress
5) Infections, other diseases
6) Use of antibiotics



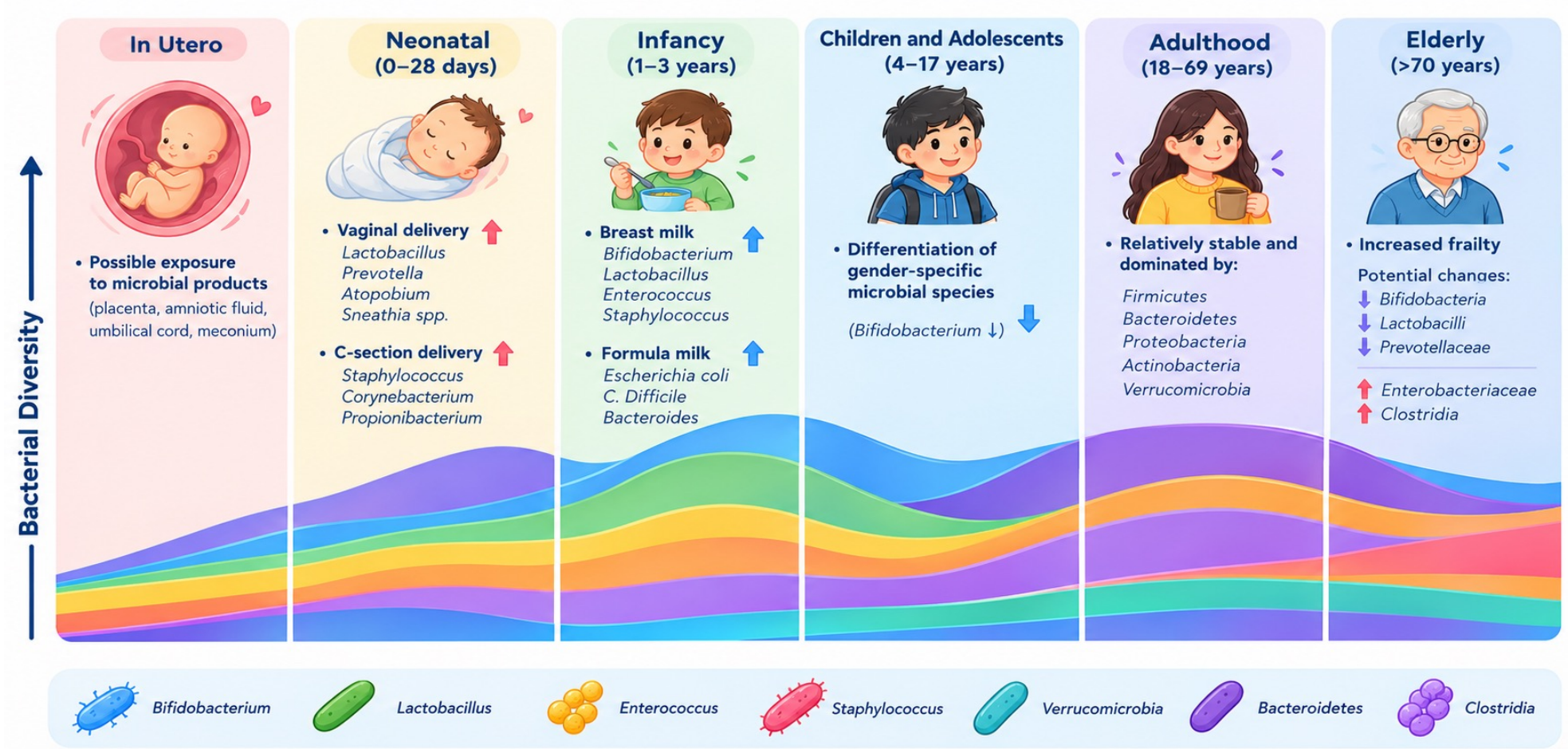
DEVELOPMENT AND MATURING OF INTESTINAL MICROBIOTA

- The development of intestinal microbiota can be classically divided into two stages :
- **First** stage :Growth of relatively anaerobic bacteria such as *Escherichia coli* and other of *Enterobacteriaceae* and *Enterococcus* species.
- **Second** stage: The growth of strictly anaerobic bacteria such as *bifidobacterium*, *clostridium*, *bacteroides* and *ruminococcus*



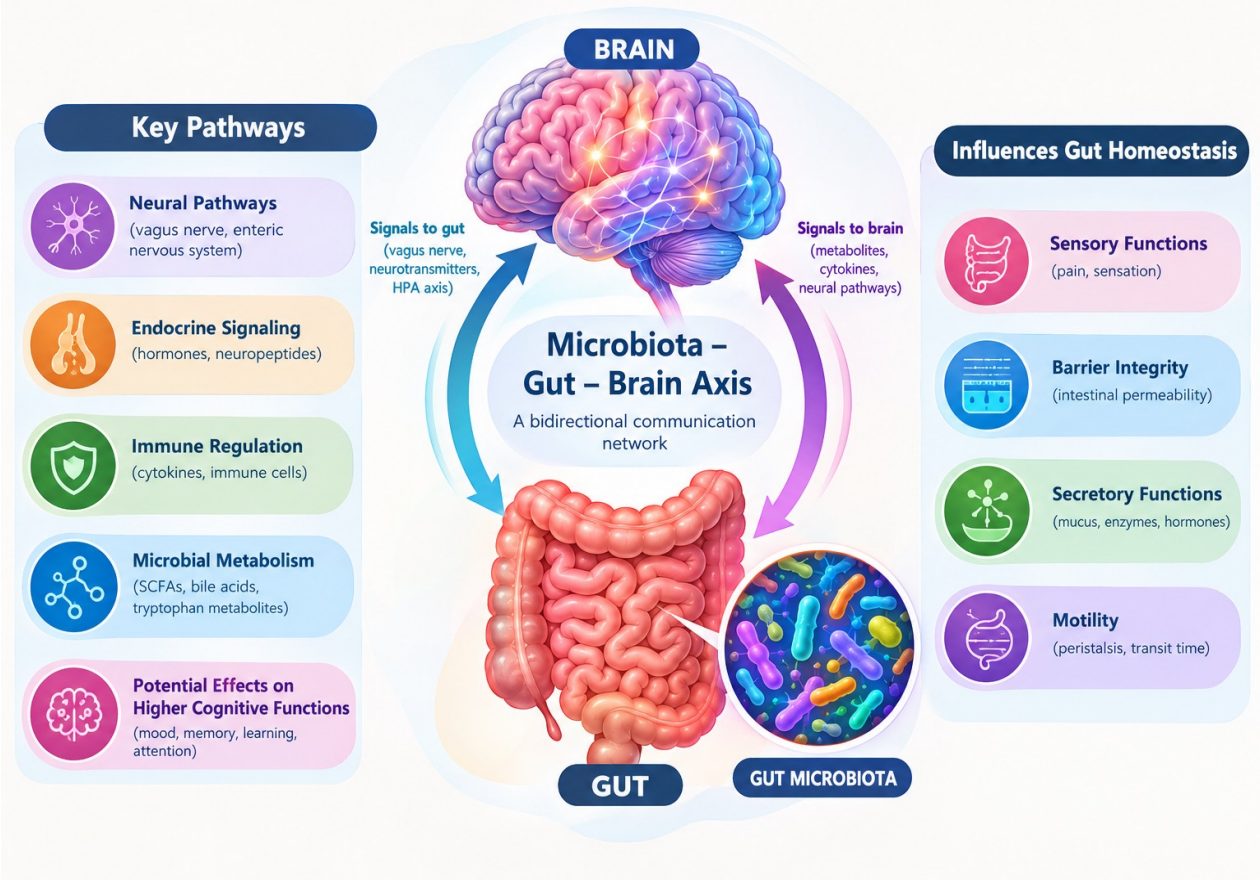


DEVELOPMENT AND MATURING OF INTESTINAL MICROBIOTA



THE MICROBIOTA-GUT-BRAIN AXIS

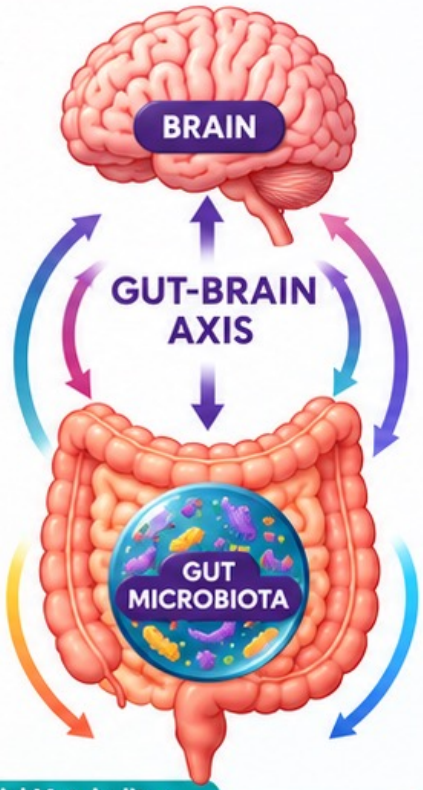
- Microbiota-gut-brain axis consists of a network that regulates not only the gastrointestinal homeostasis, including the gut sensorial, barrier, secretory and motor functions
- The endocrine system,
- The immunity
- Metabolic pathways
- Higher cognitive activities
- Neural pathways



THE MICROBIOTA-GUT-BRAIN AXIS

- **The Intestinal Microbiota Can Bidirectionally Communicate With The Central Nervous System Via Numerous Mechanisms:**

1. Changes in Microbial Content & Immune Stimulation
2. Tryptophan Metabolism
3. Gut Hormonal Response
4. Neuroactive Molecules and Neural Signaling
5. Bacterial Metabolites



1 Changes in Microbial Content & Immune Stimulation

Healthy microbiota (higher diversity) → Dysbiosis (lower diversity) → Immune activation

- Dendritic cells
- Macrophages
- T cells
- Cytokines (IL-6, TNF-α, IL-10)

Microbial components (PAMPs)
- LPS
- Flagellin
- Peptidoglycan
- CpG DNA

2 Tryptophan Metabolism

Tryptophan (from diet) → Gut microbiota (enzymes) → Metabolites
- Kynurenine
- Serotonin (5-HT)
- Indole
- Indole-3-acetic acid (IAA)

Kynurenine pathway (immune regulation)	Serotonin pathway (gut motility & mood)	Indole pathway (barrier function)
↓ Treg cells ↓ Inflammation	↑ 5-HT (enteric & CNS)	↑ IL-22 ↑ Epithelial integrity

3 Gut Hormonal Response

Enteroendocrine cells (release gut hormones) →
- GLP-1 • PYY • GIP
- Ghrelin • CCK • 5-HT

Appetite & satiety · Insulin secretion · Gastric emptying · Gut motility

4 Neuroactive Molecules and Neural Signaling

Microbial production of neuroactive compounds
- GABA
- Dopamine
- Norepinephrine
- Acetylcholine
- Histamine

Signaling pathways
- Enteric nervous system
- Vagus nerve
- Spinal pathways
- Brain neurotransmitters

Effects on CNS
- Mood & anxiety
- Cognition
- Stress response
- Behavior

5 Bacterial Metabolites

Key metabolites and their effects

Short-chain fatty acids (SCFAs) (acetate, propionate, butyrate)	Bile acids (secondary bile acids)	Polyphenols (metabolites) (phenylvaleric acid, benzoic acid)	Other metabolites (IAA, ammonia, (produced by microbes)
• Barrier function • Anti-inflammatory • Energy source	• FXR/TGR5 signaling • Metabolic regulation • Immune modulation	• Antioxidant • Anti-inflammatory • Neuroprotection	• Epithelial signaling • Vascular tone • Neural effects

Local & systemic effects

AUTISM SPECTRUM DISORDER AND THE INTESTINAL MICROBIOTA

- **Autism spectrum disorder (ASD)** is a neurodevelopmental disorder characterized by heterogeneous cognitive, behavioral and communication impairments.
- It is estimated that worldwide about **1 in 100** children has autism
- **CHD8** is an ATP-dependent chromatin-remodeling factor encoded by the most frequently mutated gene in individuals with autism spectrum disorder (ASD)



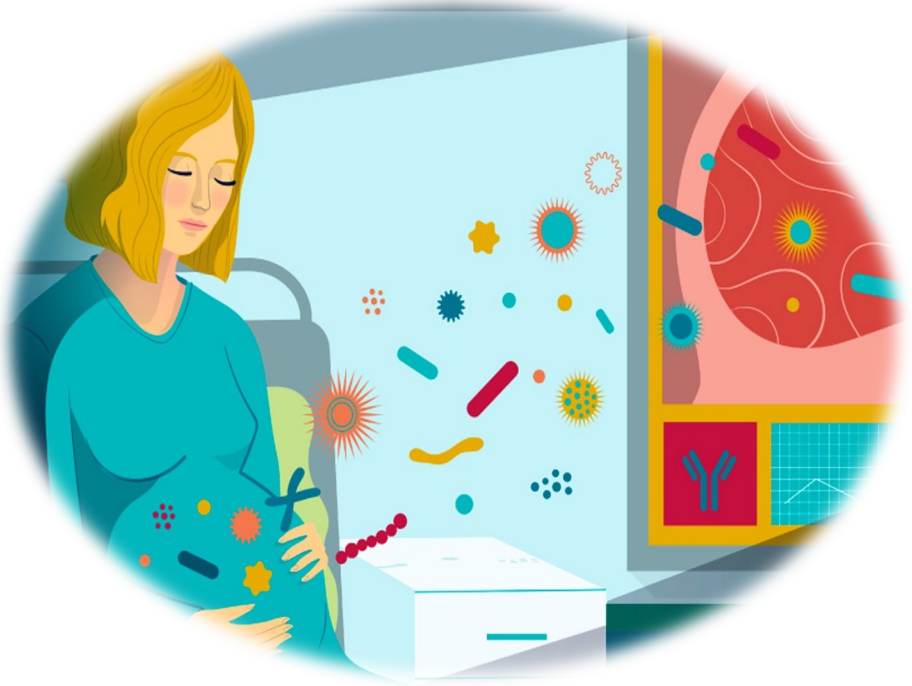


THE EFFECT OF MICROBIOTA ON THE DEVELOPMENT OF AUTISM

BEFORE BIRTH

- Microbial colonization starts during prenatal development inside the mother's womb, in the placenta and amniotic fluid.
- Factors affecting the development of autism:

1. Maternal nutrition
2. Stress
3. Genitourinary tract infection
4. Indiscriminate use of antibiotics



THE EFFECT OF MICROBIOTA ON THE DEVELOPMENT OF AUTISM

- At birth, the fetus' microbiota is almost identical to the mother's microbiota
- Babies born via C section were dominated by ***Enterococcus faecalis***, ***Enterococcus faecium***, ***Clostridium spp***, *Staphylococcus epidermidis, Streptococcus parasanguinis, Klebsiella oxytoca*
- Child born via C-section delivery has a **23% risk** of developing ASD compared with a child born via vaginal delivery

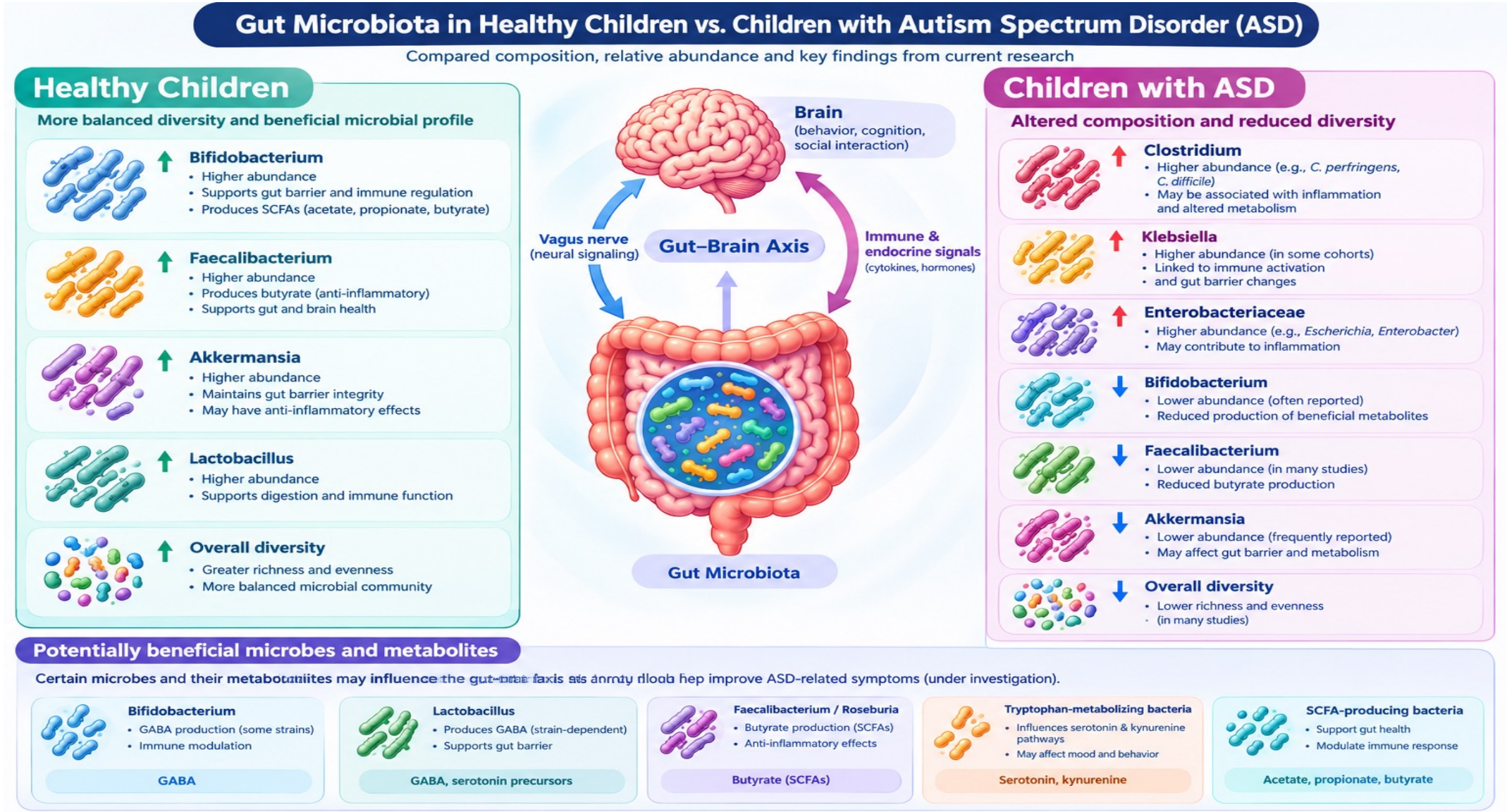
AFTER BIRTH

- Factors affecting the development of autism :

1. Type of delivery
2. Breast milk microbiota
3. Environmental stresses of the baby and distance from the mother

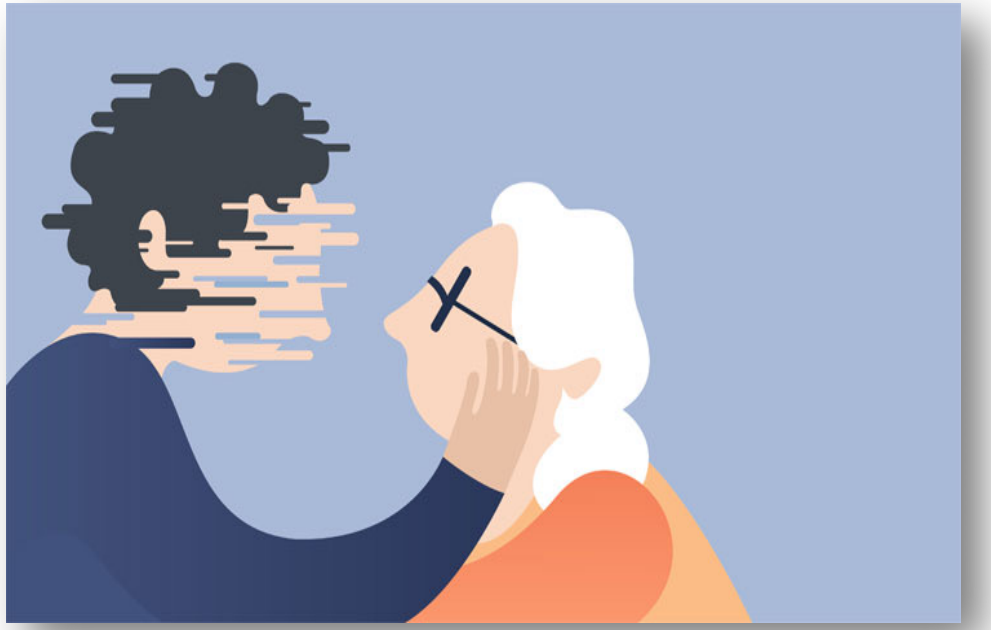


THE EFFECT OF MICROBIOTA ON THE DEVELOPMENT OF AUTISM



ALZHEIMER'S DISEASE AND THE INTESTINAL MICROBIOTA

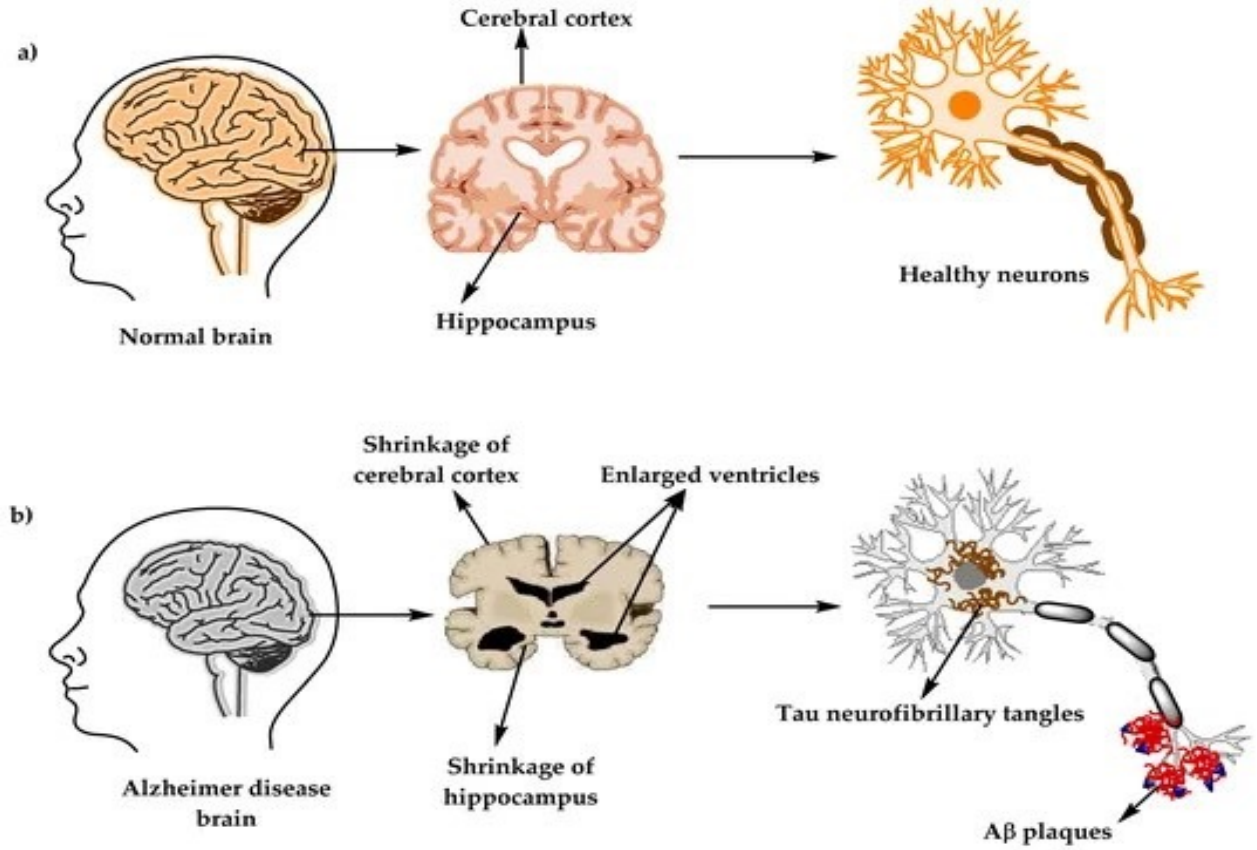
- The most common form of age-related dementia
- Characterized clinically by insidious onset of memory and cognitive impairment, emergence of psychiatric symptoms and behavioral disorders, and impairment of activities of daily living



ALZHEIMER'S DISEASE AND THE INTESTINAL MICROBIOTA

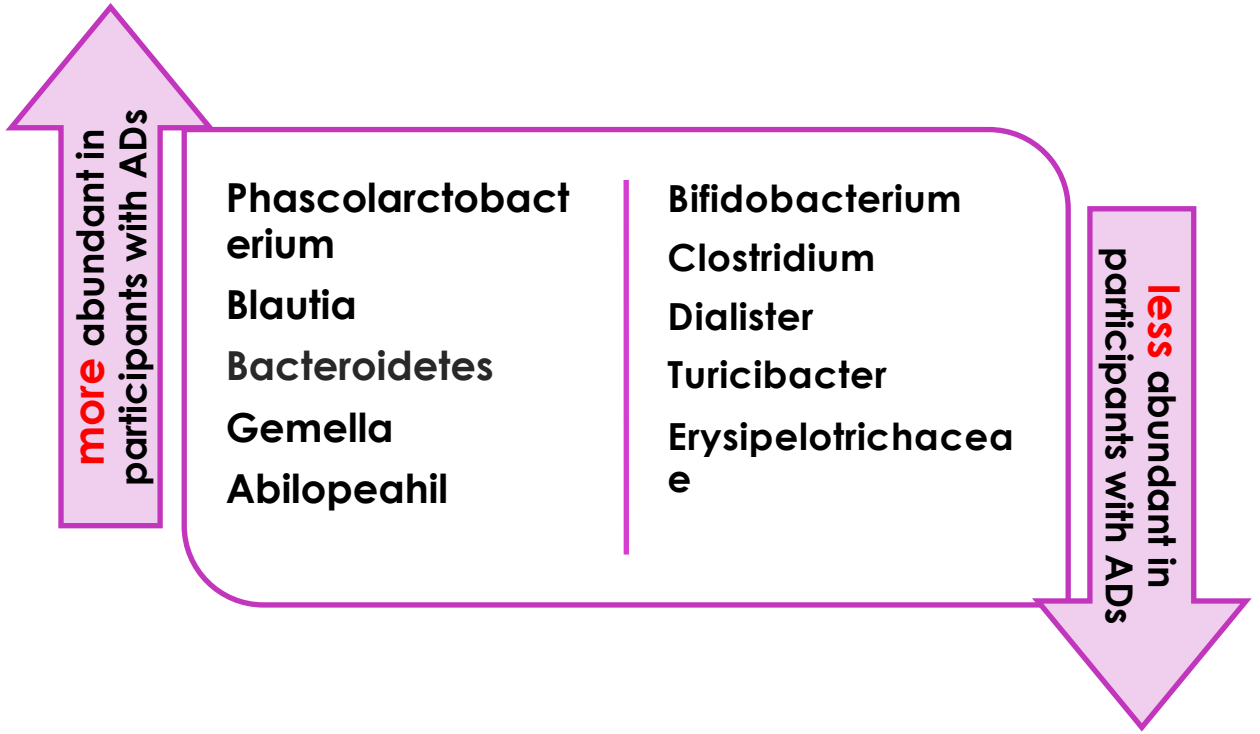
- **Alzheimer's disease** is believed to occur when:

1) Abnormal amounts of amyloid beta (Aβ) accumulating extracellularly as amyloid plaques
2) Accumulating tau proteins
3) Mitochondrial dysfunction
4) Chronic oxidative stress



ALZHEIMER'S DISEASE AND THE INTESTINAL MICROBIOTA

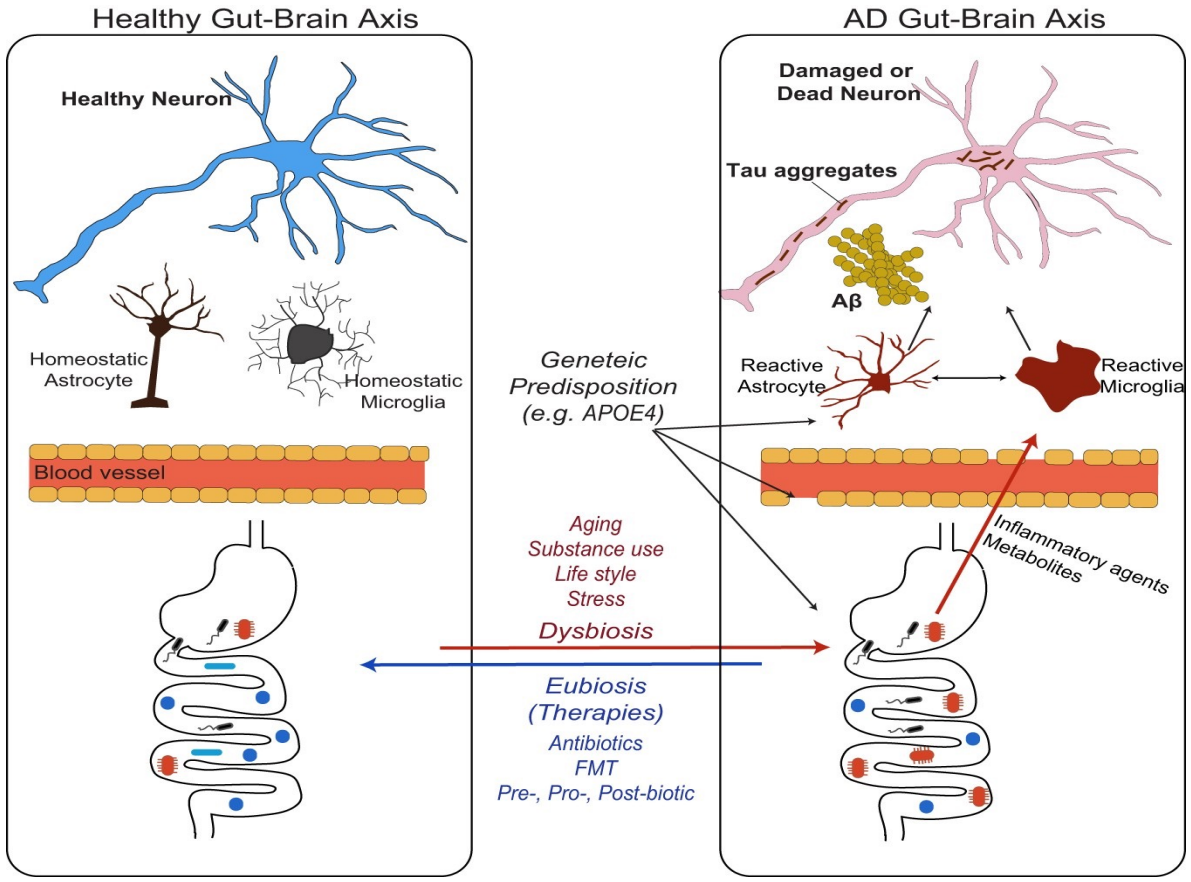
- 85% of patients with dementia have different gut microbiota compositions from the healthy population.
- The phylum abundance of Firmicutes and Actinobacteria decreased significantly, whereas Bacteroidetes were enriched in patients with AD.



ALZHEIMER'S DISEASE AND THE INTESTINAL MICROBIOTA

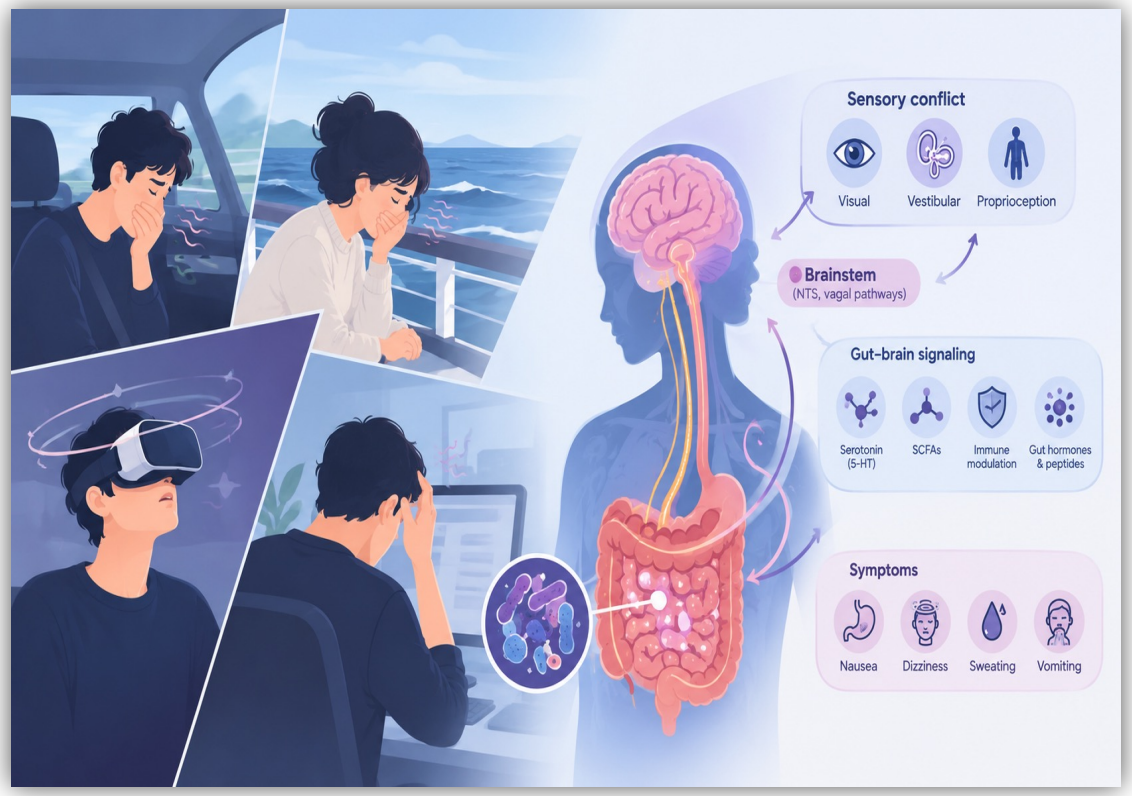
The role of microbiota in the development of Alzheimer's disease:

1. **Amyloid production similar to CNS amyloids**
2. **Suppression of Treg response and enhancement of inflammatory response**
3. **Production of neurotransmitters**
4. **Production of metabolites**

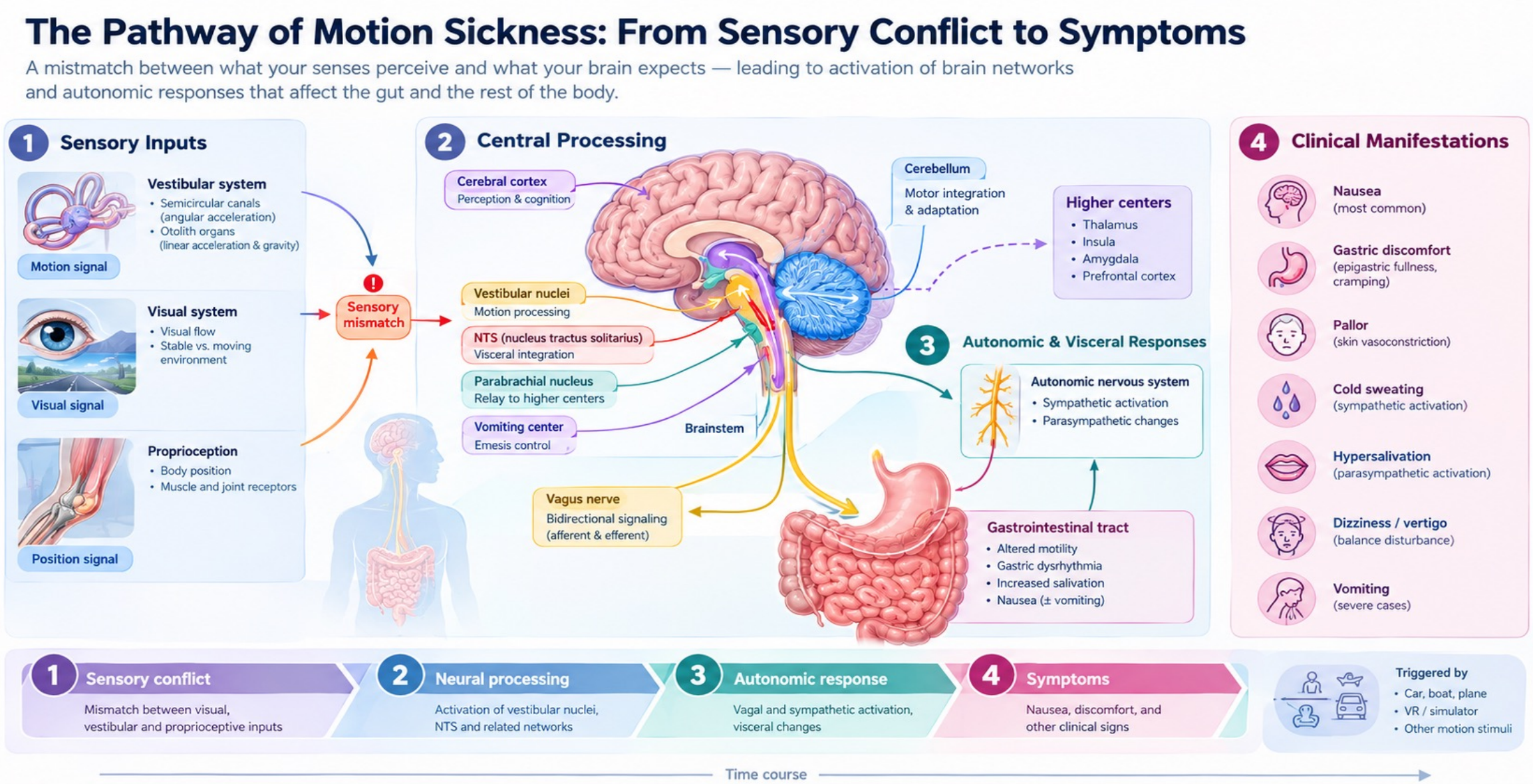


Gut Microbiota and Motion Sickness Susceptibility

- A common physiological response to real or perceived motion
- Caused by a mismatch between visual, vestibular, and proprioceptive signals, leading to nausea, dizziness, sweating, and sometimes vomiting
- Can impair comfort, performance, and daily activities during travel, maritime operations, and virtual reality (VR) exposure
- Individual susceptibility varies, raising questions about the physiological factors that influence symptom severity



Gut Microbiota and Motion Sickness Susceptibility



Gut Microbiota-Gut-Brain Axis in Motion Sickness

Potential microbial mediators and signaling pathways

1 Microbial metabolites

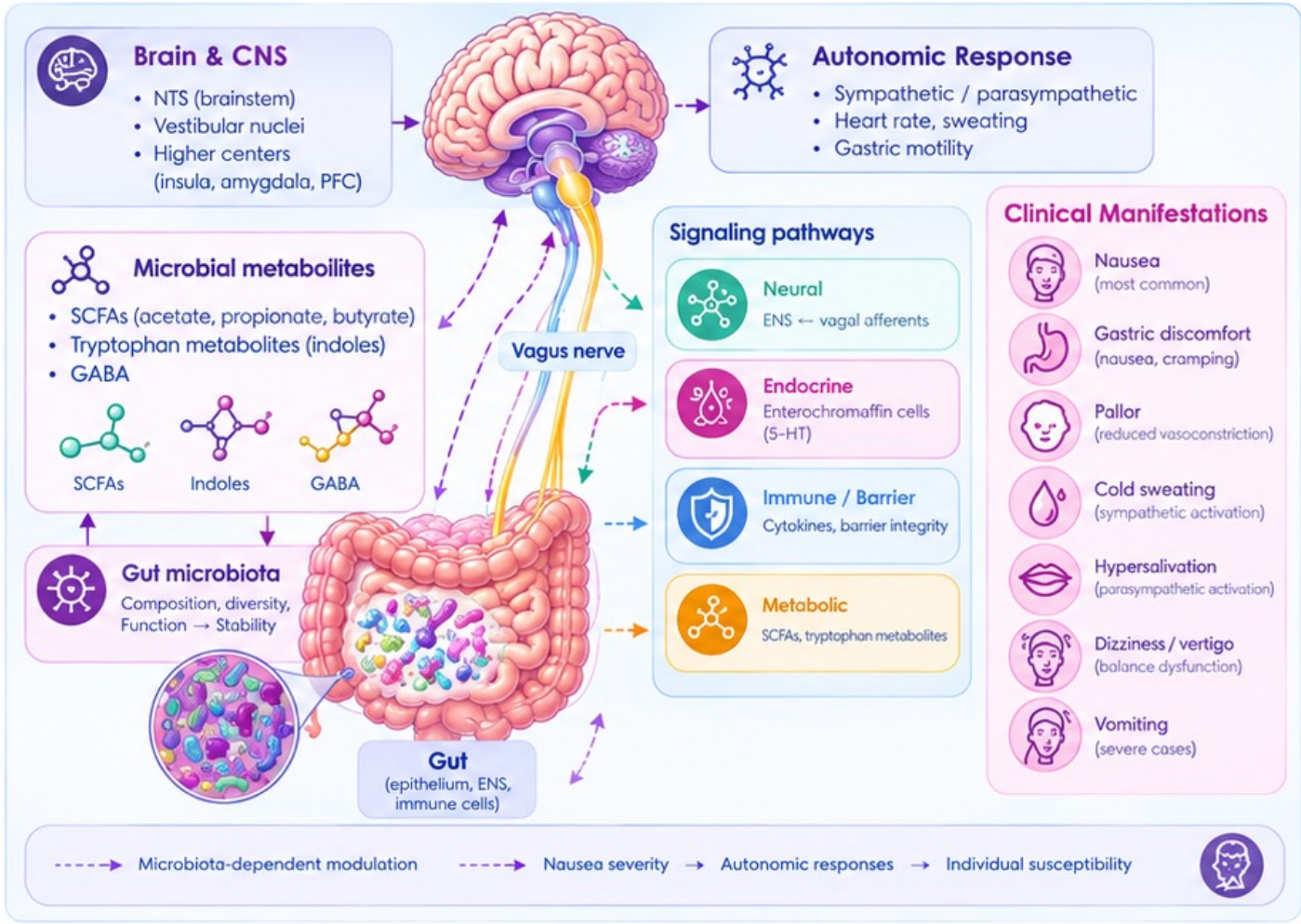
- **SCFAs** (acetate, propionate, butyrate): support epithelial integrity, immune activity and gut–brain signaling.
- **Tryptophan metabolites** (indoles): may affect epithelial and immune signaling.
- **GABA**: produced by some strains: potential neuromodulator, but its role in motion sickness is unproven.

2 Four potential routes from gut to brain

Neural	ENS ← vagal afferents → NTS → brainstem networks
Endocrine	Enterochromaffin cells → 5-HT signaling
Immune / Barrier	Gut barrier function & immune mediators
Metabolic	Microbial metabolites → visceral & autonomic regulation

3 Proposed outcome

These pathways may modulate nausea severity, autonomic responses and individual susceptibility to motion sickness.



CLINICAL TRIALS

Controlled Clinical Trial > Pharmacol Res. 2020 Jul:157:104784. doi: 10.1016/j.phrs.2020.104784. Epub 2020 Apr 17.

Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder

Ying Wang [1], Ning Li [2], Jun-Jie Yang [3], Dong-Mei Zhao [4], Bin Chen [5], Guo-Qing Zhang [6], Shuo Chen [7], Rui-Fang Cao [8], Han Yu [9], Chang-Ying Zhao [10], Lu Zhao [11], Yong-Sheng Ge [12], Yi Liu [13], Le-Hai Zhang [14], Wei Hu [15], Lei Zhang [16], Zhong-Tao Gai [17]

Affiliations + expand

PMID: 32305492 DOI: 10.1016/j.phrs.2020.104784

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Randomized Controlled Trial > BMJ Paediatr Open. 2025 Mar 4;9(1):e003045.
doi: 10.1136/bmjpo-2024-003045.

Impact of probiotic supplements on behavioural and gastrointestinal symptoms in children with autism spectrum disorder: A randomised controlled trial

Himani Narula Khanna [1 2], Sushovan Roy [3], Aqsa Shaikh [3], Rajiv Chhabra [4], Azhar Uddin [3]

Affiliations + expand

PMID: 40037934 PMCID: PMC11881170 DOI: 10.1136/bmjpo-2024-003045

Abstract

Objective: To investigate whether probiotic supplementation can improve behavioural and gastrointestinal (GI) symptoms in children with autism spectrum disorder (ASD) aged 2–9 years and further explore the correlation between these symptoms.

Design: Single-blinded, randomised, placebo-controlled study.

Setting: Five developmental paediatric outpatient clinics of 'Continua Kids'.

Patients: Children aged 2–9 years diagnosed with ASD along with their caregivers.

Interventions: Probiotic or placebo sachet reconstituted in 50 mL of lukewarm milk/water, taken two times per day for 3 months.

PROBIOTIC FOOD
Supplement Facts

Nutritional Information Per Serving (Approximate Values)

Nutrients	Qty. Per Serving 5g	Qty. Per 100g	%*RDA Per Serving
Energy	0 Kcal	0 Kcal	0%
Fats & Its Derivatives	0 g	0 g	0%
Protein	0 g	0 g	0%
Total Carbohydrates	4.45 g	89 g	**
Added Sugar	0 g	0 g	0%
*Polyols (Erythritol)^*	4.45 g	89 g	**

Ingredients Information (Approximate Values)

Ingredients	Qty. Per Serving 5g	Qty Per 100g	%*RDA Per Serving
Probiotic Blend	9 billion cfu	180 billion cfu	**
Lactobacillus delbrueckii subsp. Bulgaricus ATCC 11842	0.91 billion cfu	18.2 billion cfu	**
Lacticaseibacillus casei - ATCC 393	0.88 billion cfu	17.6 billion cfu	**
Limosilactobacillus reuteri - ATCC 55730	0.88 billion cfu	17.6 billion cfu	**
Lacticaseibacillus rhamnosus - ATCC 21052	0.83 billion cfu	16.6 billion cfu	**
Lactiplantibacillus plantarum - ATCC 8014	0.83 billion cfu	16.6 billion cfu	**
Lactobacillus acidophilus - ATCC 4356	0.83 billion cfu	16.6 billion cfu	**
Bifidobacterium breve ATCC 1570	0.75 billion cfu	15 billion cfu	**
Bifidobacterium bifidum - ATCC 29521	0.7 billion cfu	14 billion cfu	**
Bifidobacterium animalis subsp. Lactis - ATCC 27536	0.7 billion cfu	14 billion cfu	**
Bifidobacterium longum subsp. Infantis -ATCC 15707	0.7 billion cfu	14 billion cfu	**
Streptococcus thermophilus - ATCC 19258	0.49 billion cfu	9.8 billion cfu	**
Saccharomyces boulardii	0.47 billion cfu	9.4 billion cfu	**
Excipients	q.s.	q.s.	

** Recommended Daily Allowances (RDA) not established.
* RDA of nutrients as per guidelines of Indian Council of Medical Research (ICMR) 2020.
Ingredients : Polyols (Erythritol), Probiotic Blend, Antioxidants (INS 320), Preservative (INS 202).

CLINICAL TRIALS

frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 31 October 2022
DOI 10.3389/fnagi.2022.1032494

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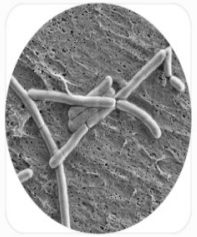
CITATION
Akhgarjand C, Vahabi Z, Shab-Bidar S, Etesam F and Djafarian K (2022) Effects of probiotic supplements on cognition, anxiety, and physical

Effects of probiotic supplements on cognition, anxiety, and physical activity in subjects with mild and moderate Alzheimer's disease: A randomized, double-blind, and placebo-controlled study

Camellia Akhgarjand[1], Zahra Vahabi[2,3], Sakineh Shab-Bidar[4], Farnaz Etesam[5] and Kurosh Djafarian[1]*

[1]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, [2]Cognitive Neurology and Neuropsychiatry Division, Department of Psychiatry, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Geriatric, Ziaeeian Hospital, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, [5]Sina MS Research Center, Brain and Spinal Injury Research Center, Tehran University of Medical Sciences, Tehran, Iran

۱. *Lactobacillus rhamnosus* HA-114



سویهٔ پروبیوتیکی اول

- مقدار هر کپسول: 10^{15} CFU طبق گزارش مقاله
- مصرف: روزی دو بار
- مدت: ۱۲ هفته

۲. *Bifidobacterium longum* R0175



سویهٔ پروبیوتیکی دوم

- مقدار هر کپسول: 10^{15} CFU طبق گزارش مقاله
- مصرف: روزی دو بار
- مدت: ۱۲ هفته

۳. گروه دارونما (Placebo)



کپسول حاوی زایلیتول، مالتودکسترین و اسید مالیک، بدون پروبیوتیک زنده.

CLINICAL TRIALS



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Article | Open access | Published: 22 September 2021

Probiotics maintain the gut microbiome homeostasis during Indian Antarctic expedition by ship

Ashish Kumar Srivastava, Vishwajeet Rohil, Brij Bhushan, Malleswara Rao Eslavath, Harshita Gupta, Sudipta Chanda, Bhuvnesh Kumar, Rajeev Varshney & Lilly Ganju

Scientific Reports **11**, Article number: 18793 (2021) | Cite this article

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6947 Accesses | **13** Citations | **9** Altmetric | Metrics

- *Lactobacillus acidophilus*
- *Lactobacillus rhamnosus*
- *Bifidobacterium longum*
- *Saccharomyces boulardii*
- *Bacillus coagulans*

شرکت‌کنندگان: ۱۹ مرد سالم ۲۷ تا ۴۵ ساله در سفر ۲۴روزهٔ دریایی به قطب جنوب.

گروه پروبیوتیک: ۱۰ نفر.

گروه دارونما: ۹ نفر.

روش بررسی میکروبیوم: توالی‌یابی متاژنومیک شاتگان نمونه‌های مدفوع در ابتدا و انتهای سفر.

نتیجهٔ بیماری حرکت دریایی: علائم دریازدگی در ۱۰٪ گروه پروبیوتیک در مقایسه با ۴۴٫۴٪ گروه دارونما گزارش شد.

نتیجهٔ میکروبیوم: تغییر ترکیب میکروبی در گروه پروبیوتیک محدودتر بود؛ در گروه دارونما تغییرات بیشتری در ترکیب و برخی عملکردهای میکروبی مشاهده شد.

1+ ...ific Reports

CONCLUSION

- The microbiota–gut–brain axis is an emerging area of research in neuroscience and mental health.
- Gut microbiota imbalances (dysbiosis) have been associated with several neurological and psychiatric conditions, including depression, anxiety, autism spectrum disorder, and Alzheimer's disease.
- Probiotics, have the potential to restore balance to the gut microbiota.
- Probiotics can have positive effects on mental health, potentially by reducing inflammation, improving gut barrier function, and modulating neurotransmitters
- Probiotics should not replace established treatments for neurological or psychiatric disorders



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MICROBIOTA AND THE GUT–BRAIN AXIS: FROM PSYCHOLOGICAL DISORDERS TO MOTION SICKNESS

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