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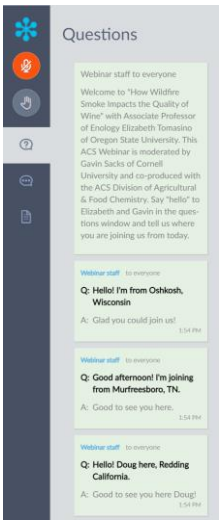

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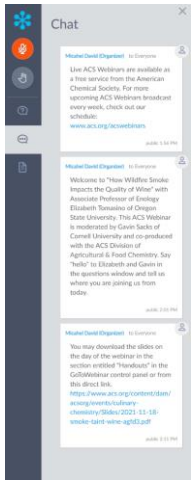
Announcements and hyperlinks from our team



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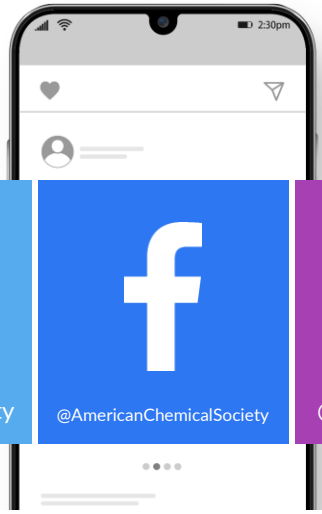

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A Career Planning Tool For Chemical Scientists

ChemIDP is an Individual Development Plan designed specifically for graduate students and postdoctoral scholars in the chemical sciences. Through immersive, self-paced activities, users explore potential careers, determine specific skills needed for success, and develop plans to achieve professional goals. **ChemIDP** tracks user progress and input, providing tips and strategies to complete goals and guide career exploration.

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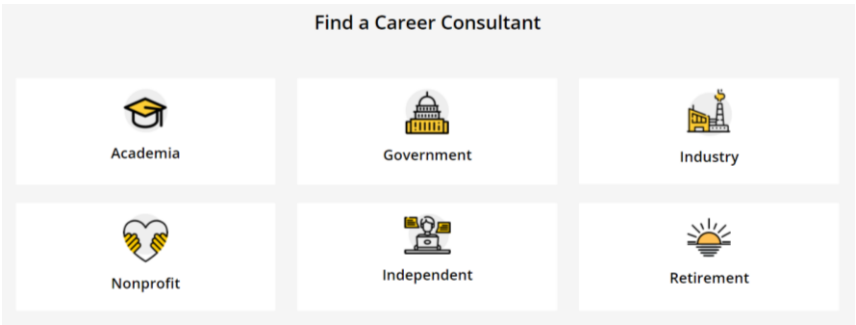
Career Consultant Directory



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ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)

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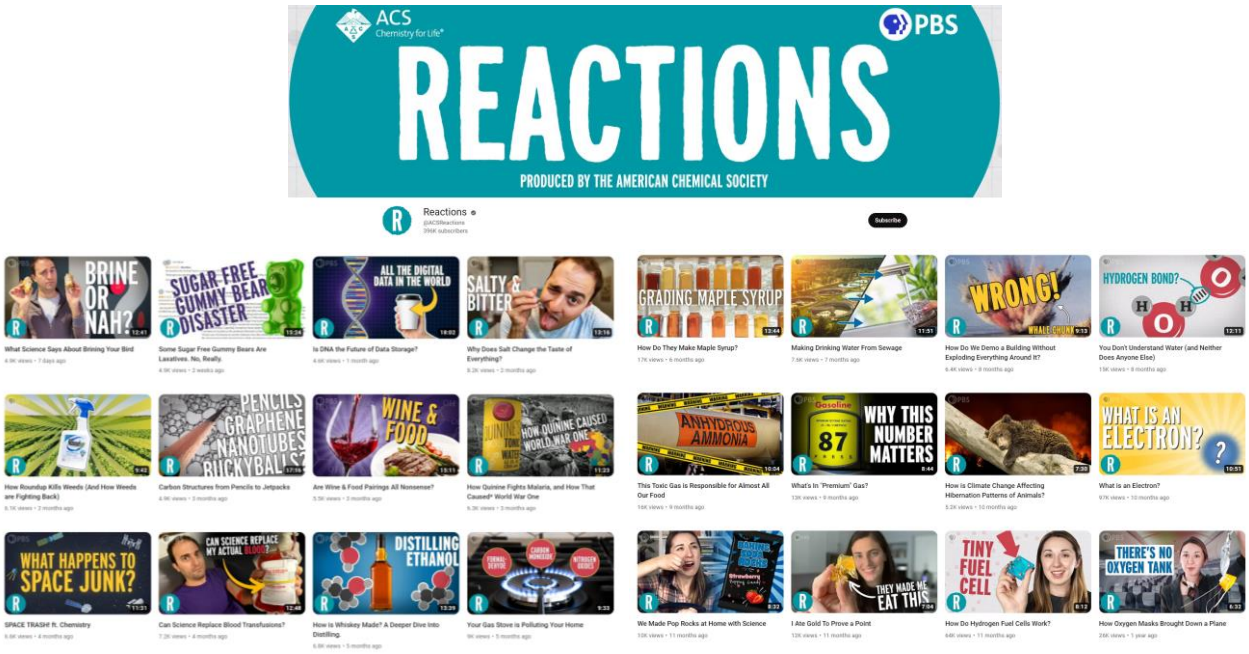

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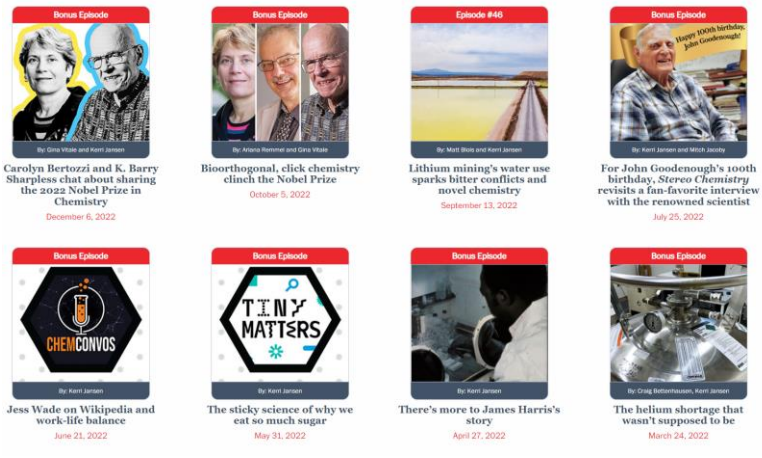

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ACS on Campus is the American Chemical Society's initiative dedicated to helping students advance their education and careers.

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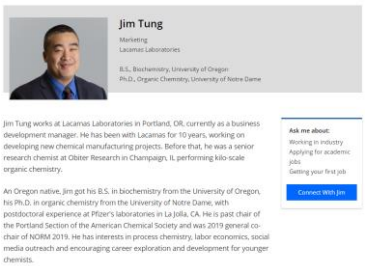
Personal Career Consultations



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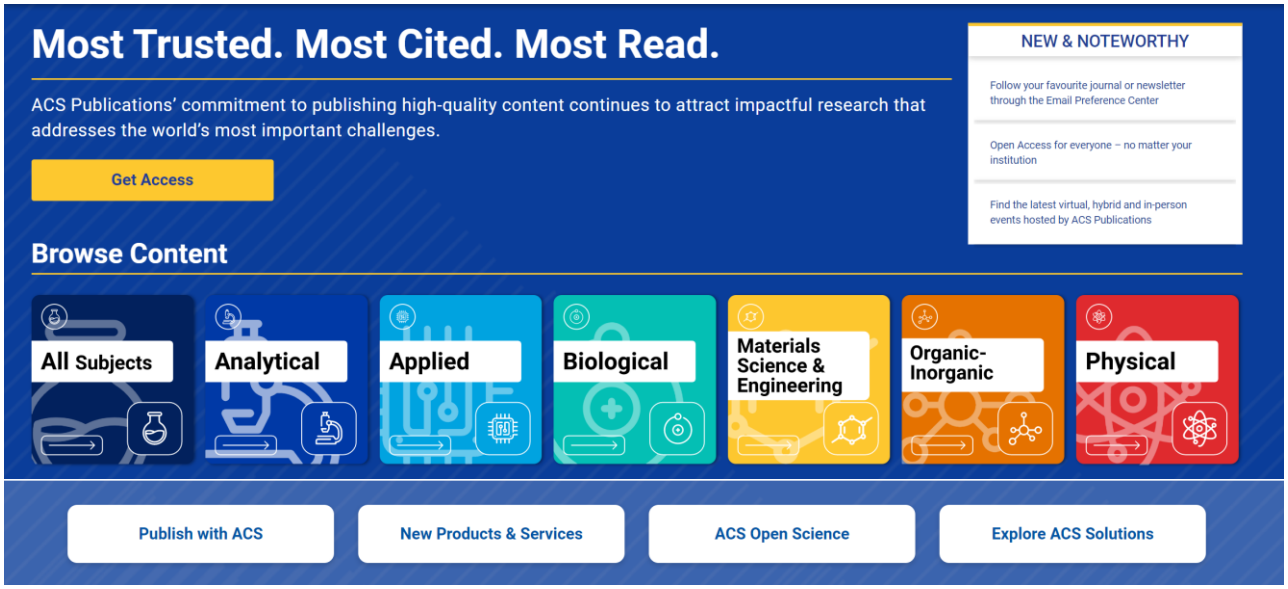

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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

- **Inclusivity Style Guide** — Designed to help staff and members use language and images that respect diversity in all its forms.
- **ACS Webinars on Diversity** — Covering diversity and inclusion at the workplace
- **ACS Publications DEIR Hub** — See what ACS Publications is doing for fostering inclusivity in scholarly publishing
- **ACS Volunteer and ACS Meetings Code of Conduct** — Fostering a positive and welcoming environment for attendees, volunteers and staff.
- **C&EN Trailblazers** — C&EN highlights scientists from different backgrounds who are making an impact in chemistry.
- **NEW! Download DEIR Educational Resources** — Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics.
- **Quick Guide: Inclusion Moments** — Learn more about what Inclusion Moments are and see ideas to host them during your meetings.
- **Quick Guide: How to host inclusive in-person events** — Recommendations and best practices to ensure that your events can accommodate everyone.

Diversity, Equity, Inclusion, and Respect

**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**
Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**
The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socio-economic status, thinking and communication styles, etc.), collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**
Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect
Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

https://www.acs.org/diversity

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See your influence in action!

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The impact and results of **ACS member advocacy** outreach and efforts by the numbers!

2439+	1739+	49	2000
Members participated In Act4Chemistry	ACS Advocacy Workshops participants or enrollees	Years of Public Policy Fellows	Letters sent to Congress
Get Involved	Enroll in a workshop	Become a Fellow	Take Action

https://www.acs.org/policy

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Wednesday, September 27, 2023 | 2-3pm ET

Adapting to AI in Peer Review and the Publishing Process

Co-produced with ACS on Campus

Thursday, September 28, 2023 | 2-3pm ET

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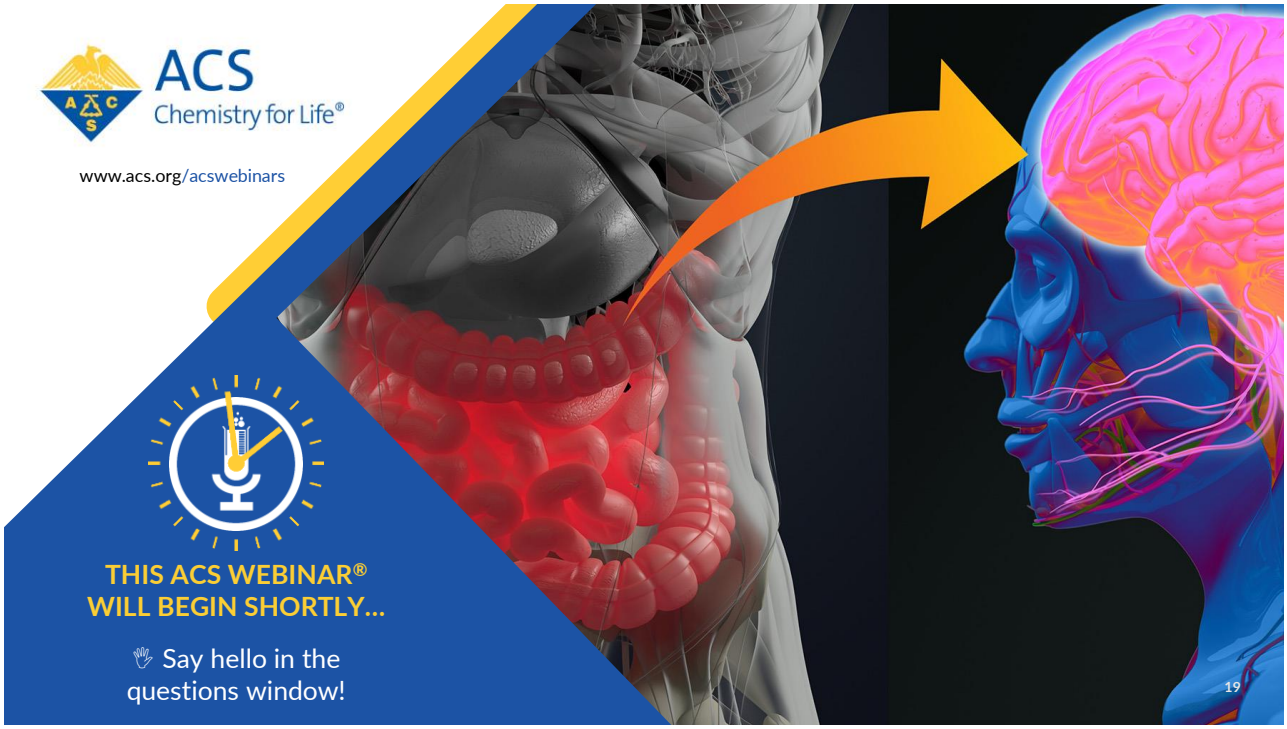
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The Gut Microbiome-Brain Alliance:
The Connection to Health and Disorders
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Information Scientist, CAS, a division of the American Chemical Society
RAMY AMMAR, PHD
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Luis & Nelly Soux Professor of Microbiology, California Institute of Technology
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CAS connects the world's science

At CAS, our passion is advancing scientific progress.

We are proud to partner with innovators across industries, enabling them to maximize the power of connected scientific information to advance discovery and get solutions to market faster.

BETWEEN PROBLEMS AND PROGRESS
ARE CONNECTIONS THAT MATTER

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CAS connect you to the world's published science for better insights

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Over **250** million substances

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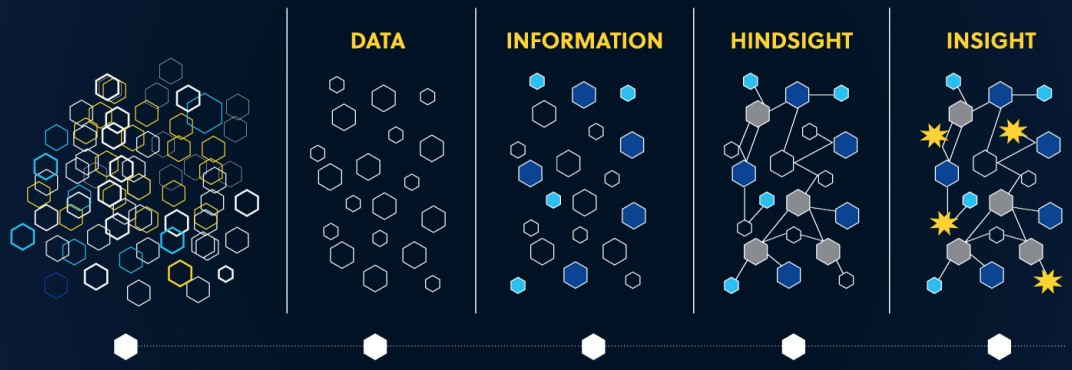
Data is valuable only when it is transformed into insight



CURATE to give data meaning

CONNECT information across disciplines

ANALYZE to reveal insights

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GUT MICROBIOME-BRAIN ALLIANCE

A landscape view

Janet Sasso, Information Scientist, CAS

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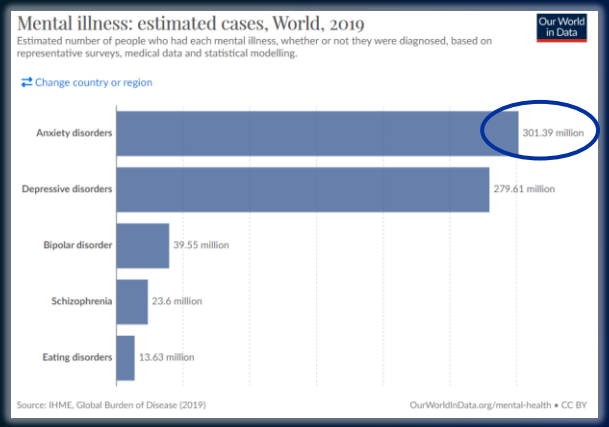
Anxiety and depression alone

Cost the global economy 1 trillion $USD annually



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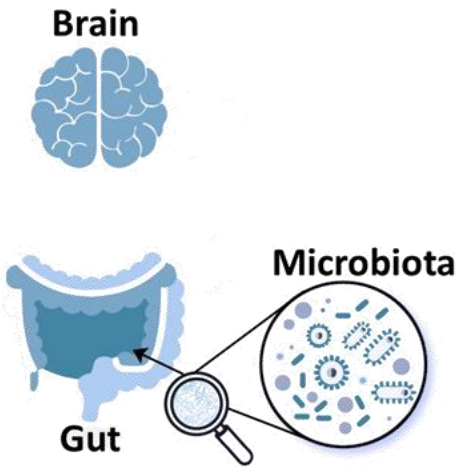
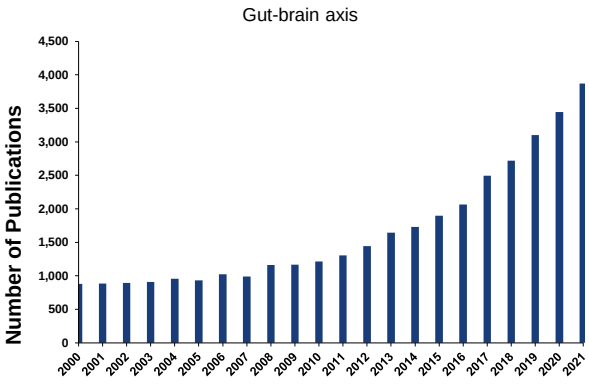
Science shows that there is a connection

With rising interest





Braniste, V.; Al-Asmakh, M.; Kowal, C.; Anuar, F.; Abbaspour, A.; Tóth, M.; Korecka, A.; Bakocevic, N.; Ng, L. G.; Kundu, P.; et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci. Transl. Med. 2014, 6, 263ra158−263ra158

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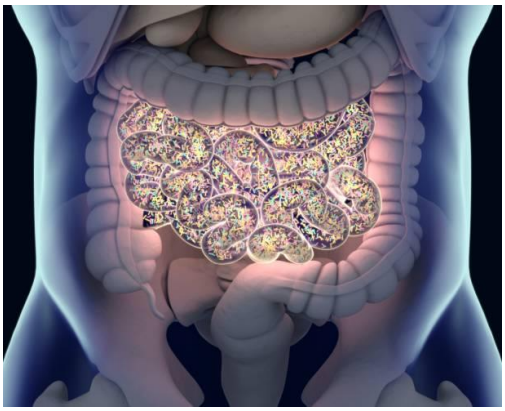
What is the gut microbiome?

The forgotten organ

- Large collection of microorganisms inhabiting the human body
- Up to 100 trillion bacterial cells vs 30 trillion human cells
- Weighs 4.4 pounds / 2 kilograms
- Collective metabolic activity of an organ
- 150 times the number of genes than the human genome



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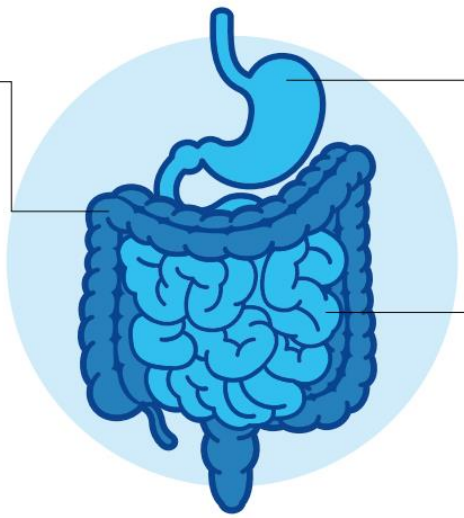
Gut environments and participant bacteria

Firmicutes dominate

Large Intestine
10^{10}-10^{12} CFU/ml

- High diversity and density
  - Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia, and Proteobacteria



Stomach
10^{1}-10^{3} CFU/ml

- Least diversity and density
  - Firmicutes, Bacteroidetes

Small Intestine
10^{4}-10^{8} CFU/ml

- Low diversity and density
  - Firmicutes, Proteobacteria, Bacteroidetes

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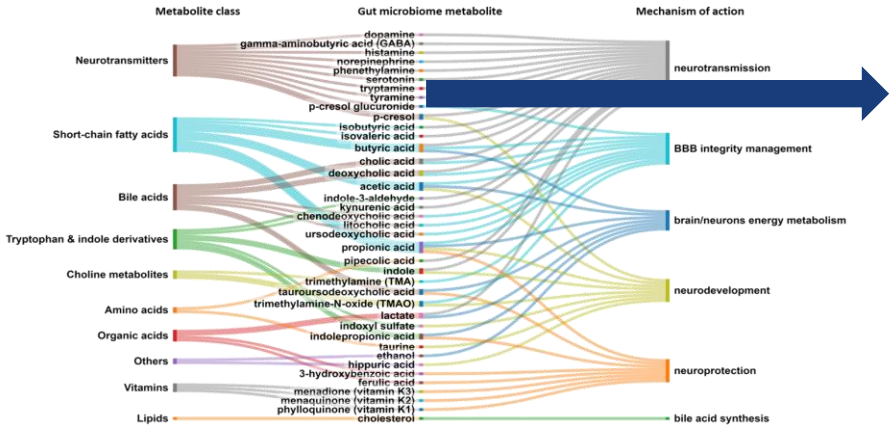
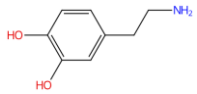
Gut microbiome metabolites

Generate a wide spectrum of bioactivities

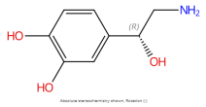


Neurotransmitters

- Dopamine



- Norepinephrine



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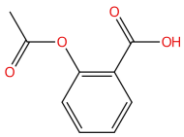
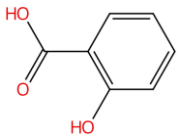
Gut microbiome metabolites

Have 2-way interactions with active pharmaceuticals

GUT impact to an API

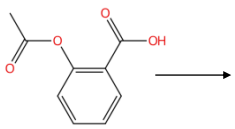


Aspirin



Salicylic acid

API to Gut



Aspirin

Increasing Bacteria
- Akkermansia

Decreasing Bacteria
- Parabacteroides
- Dorea

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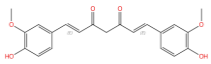
Microbiome therapies

Probiotics

- live microorganisms

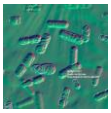
Prebiotics

- substrates selectively utilized by host microorganisms



Curcumin

DHA

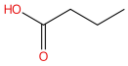


Postbiotics

- bioactive compounds produced when probiotics consume prebiotics

Acetic acid

Butyric acid



Fecal microbiota transplantation

- transplantation of healthy fecal bacteria from a donor

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Gut dysbiosis

Disease effect on the gut microbiome

Diseases	↓ Decreasing Bacteria	↑ Increasing Bacteria	Clinical Trial Example
Digestive system diseases			
Irritable bowel syndrome (IBS)	Bifidobacterium Faecalibacterium	Ruminococcus Dorea Enterobacteriaceae Lactobacillaceae Bacteroides Firmicutes: Bacteroidetes ratio	Evaluated the effectiveness and safety of multi-strain probiotic mixture of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus strains for the treatment of diarrhea-predominant irritable bowel syndrome: NCT04662957
Mental health disorders			
Anxiety	Bacteriodetes Ruminococcus gnavus Fusobacterium	Bacteroidaceae Enterobacteriaceaem Burkholderiaceae	Will evaluate the efficacy of a multi-strain postbiotic capsule in the management of moderate self-reported anxiety: NCT05562739
Post-traumatic stress disorder	Actinobacteria Lentisphaerae Verrucomicrobia		Investigated the use of a Lactobacillus reuteri probiotic to treat symptoms of co-occurring mTBI and PTSD: NCT02723344
Depression	Prevotella Dialister	Eggerthella Holdemania Turicibacter Paraprevotella	Will investigate oral fecal microbiota transplantation in adults with treatment resistant depression: NCT04805879

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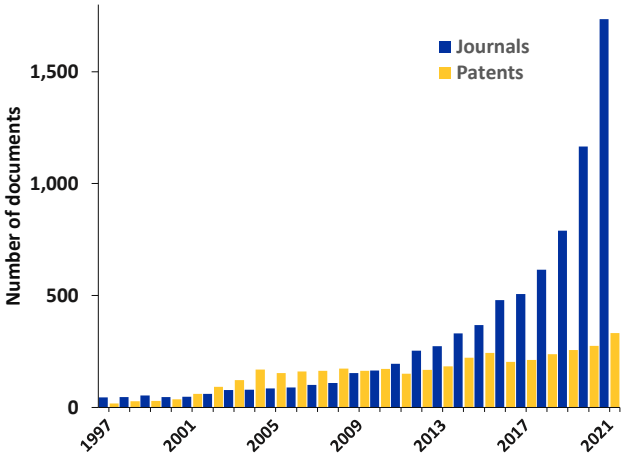
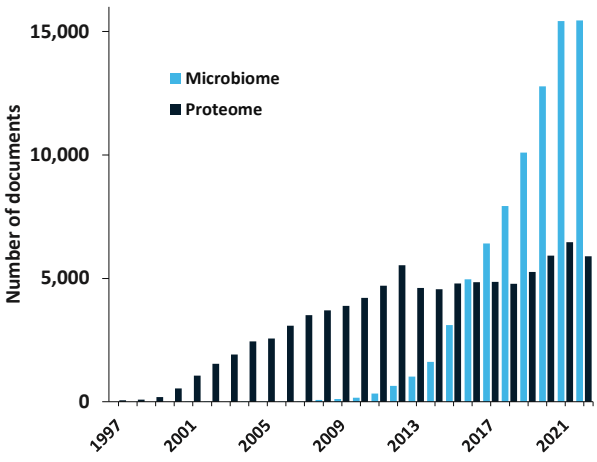
Microbiome publications have increased over time

Research on the microbiome is outpacing other “omics”





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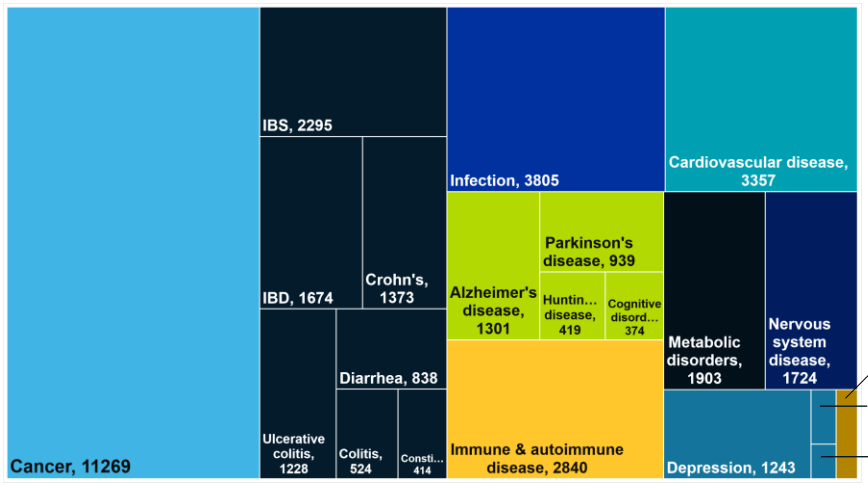
Gut-microbiome-associated diseases

Covers a wide spectrum from cancer, to digestive to neuro



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Top 10 Patent Assignees

Companies	Number of patents
Merck KGaA/ Ares Trading	65
Smithkline Beecham	30
Sanofi-Aventis	24
Merck & Co. (MSD)	24
Mondobiotech Laboratories	23
Inpharmatica	20
Glenmark Pharmaceuticals	20
Dana-Farber Cancer Institute	13
Abbott Laboratories	13
Nitromed	12

Universities & Hospitals	Number of patents
University of California	36
Johns Hopkins University	25
University of Texas	22
Cedars-Sinai Medical Center	18
Yale University	15
Harvard College	14
Southeast University	12
University of Florida	10
Jiangnan University	10
California Institute of Technology	9

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Microbiome therapeutic clinical trials

IBS is leading

Disorder	Clinical trials
Irritable Bowel Syndrome	142
Functional Constipation	110
Functional Diarrhea	84
Functional Dyspepsia	28
Cognition Impairment	31
Anxiety	30
Depression	27
Stress	22
Sleep Disorder	8

Focus of each microbiome intervention

50% of mental health postbiotic trials

50% of mental health FMT trials

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In Summary

Gut-Microbiome Brain Alliance

- Each gut microbiome is unique and highly dynamic
- Gut-brain axis: central nervous system and gastrointestinal tract in constant bidirectional communication
- Journal article publication trends for journal articles related to gut microbiome research and mental and gut health have shown exponential growth
- Gut microbiome therapeutics are being investigated for a wide range of disorders and diseases and have recently gained regulatory approval

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Acknowledgement

CAS and Bayer colleagues and teammates

- Ramy M. Ammar
- Rumiana Tenchov
- Steven Lemmel
- Olaf Kelber
- Malte Grieswelle
- Qiongqiong Angela Zhou

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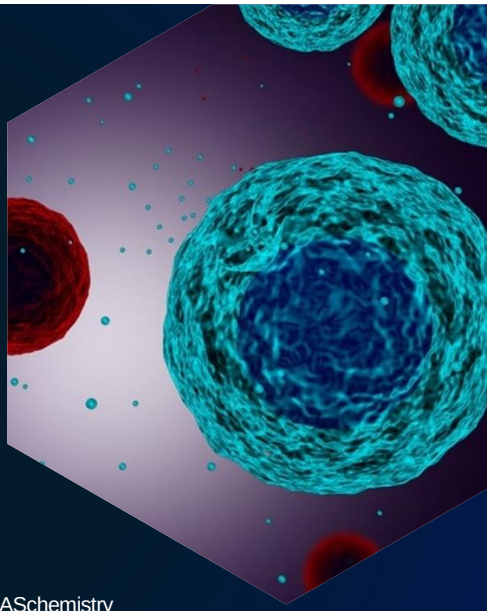
Gain insights on the microbiome and more

Janet Sasso
Information Scientist
jsasso@cas.org

Peer reviewed journal article
cas.org/microbiome-journal



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Microbiome- Gut-Brain Axis

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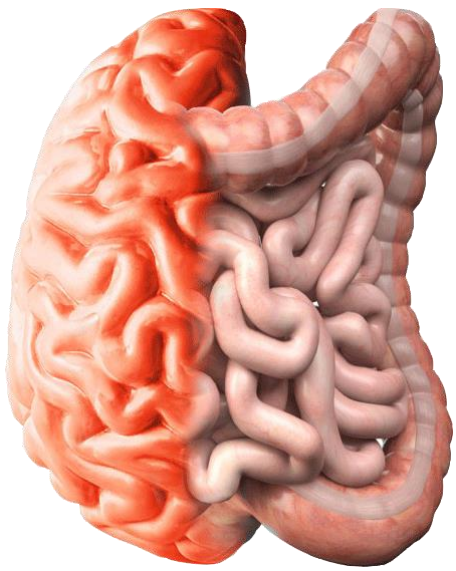
Global R&D,
Emerging Science & Innovation Director,
Digestive Health
Bayer Consumer Health



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AGENDA

1. Introduction to the Gut Brain Axis
2. Gut Health Influences Brain Function
3. Microbiome Based Treatment Landscape
4. Future Outlook

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Introduction to the Gut-Brain Axis

42

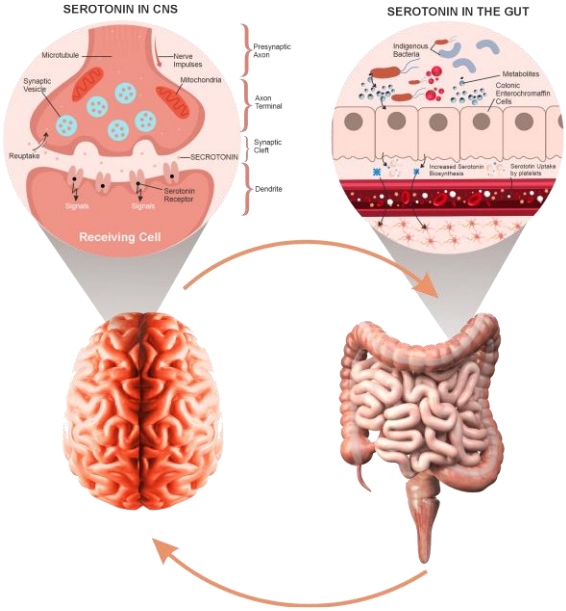
42

Gut and Brain Have the Same Embryological Origins[1]

Neural Ectoderm ⟹ **Neural Tube-Neural Crest** ⟹ **Brain, Spinal Cord, Gut, Peripheral Nerves**

43 1. Elshazzly M LM, *et al.* StatPearls. 2023.

Did You Know?



- GI tract colonization by the microbiota has a parallel developmental trajectory to the brain for up to 3 years of age[1]
- Similar number of neuronal cells in the gut and spinal cord[3]
- **90% - 95%** of serotonin (5-HT) is produced by **gut mucosal enterochromaffin cells**[1]
- Peripheral serotonin helps in the **regulation of gastrointestinal secretion, motility**, **and pain perception**[1]
- Single-nucleotide polymorphisms in **peripheral serotonin**, have been associated with an increased susceptibility to **depression, post-traumatic stress disorders, and alcohol abuse**[2]
- Lack of peripheral serotonin can affect brain functions[2]

CNS: Central nervous system; 5-HT: 5-hydroxytryptamine
1. Jena A, *et al. Front Hum Neurosci.* 2020;14; 2. Sbrini G, *et al. Int J Mol Sci.* 2022;23(9),
3. Elshazzly M LM, *et al.* StatPearls. 2023

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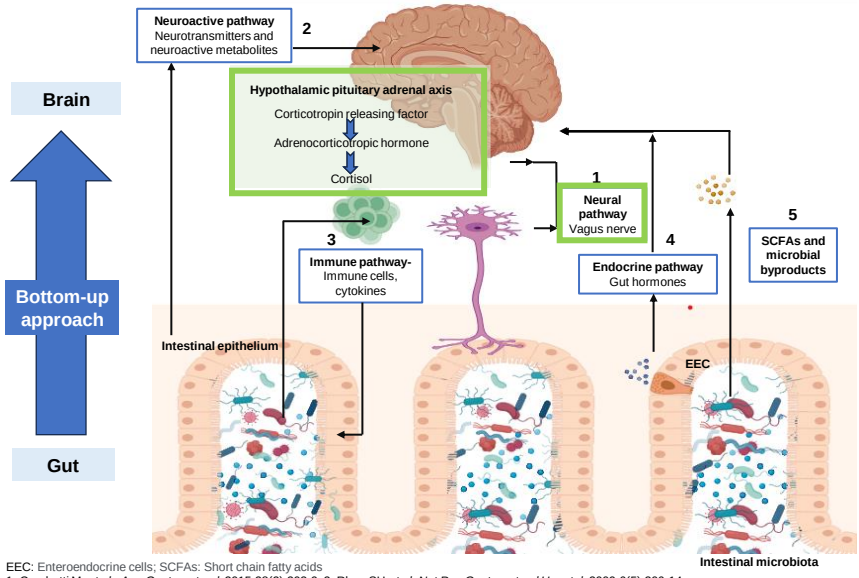
Gut-Brain Axis: A Bidirectional Communication Between Brain and Gut



Gut-Brain axis links emotional and cognitive centers of the brain with peripheral intestinal functions[1,2]

45 EEC: Enteroendocrine cells; SCFAs: Short chain fatty acids

1. Carabotti M, *et al. Ann Gastroenterol.* 2015;28(2):203-9. 2. Rhee SH *et al. Nat Rev Gastroenterol Hepatol.* 2009;6(5):306-14.

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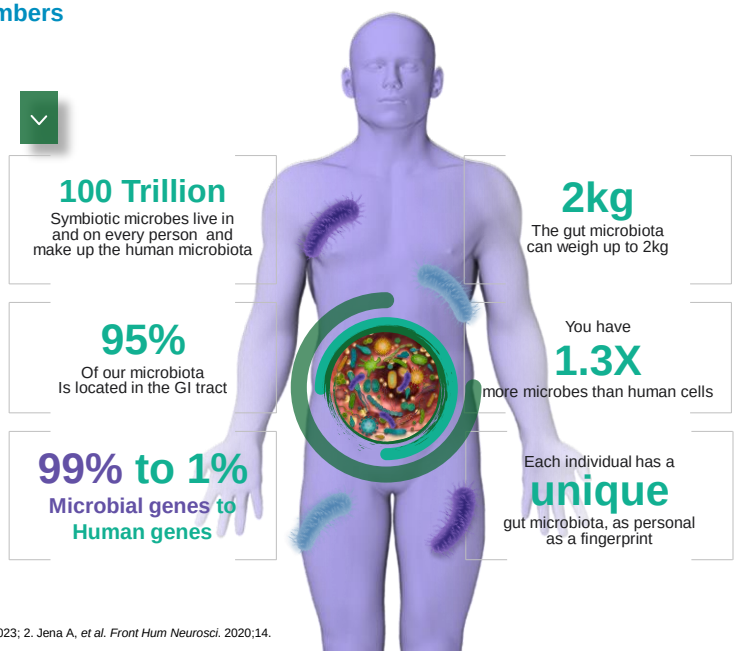
Microbiome in Numbers



46 GI: Gastrointestinal

1. Elshazzly M LM, *et al.* StatPearls. 2023; 2. Jena A, *et al. Front Hum Neurosci.* 2020;14.

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Gut Health Influences the Brain Function

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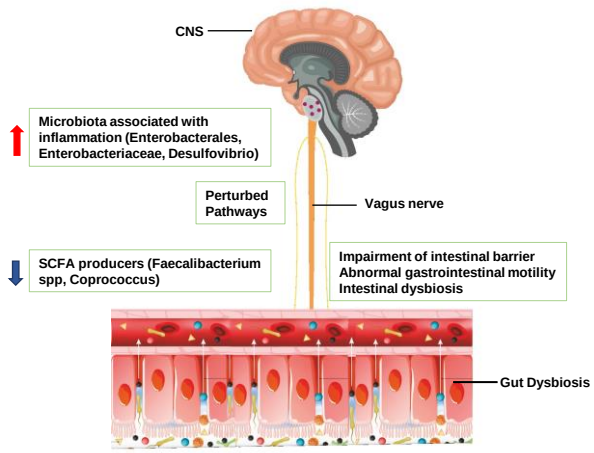
Increased HPA activation is associated with stress and anxiety[2]



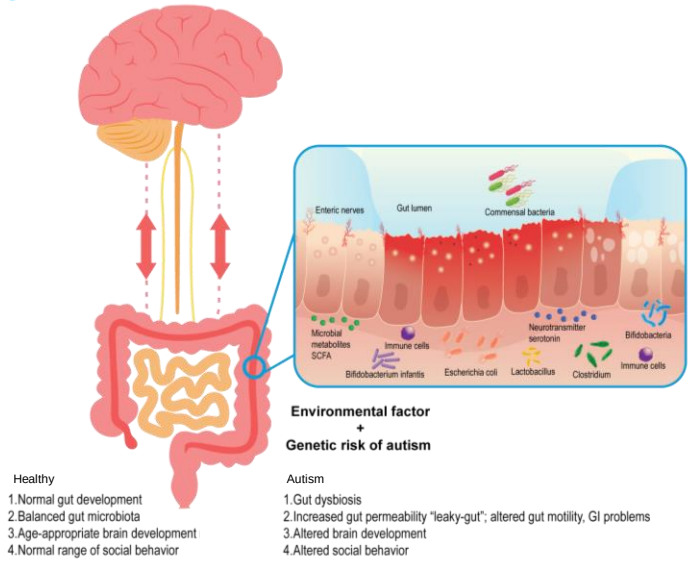
- Gut dysbiosis leads to **increased cortisone, and proinflammatory cytokines** including **Interluekin-6,** which acts as an HPA activator[1]
- Gut microbiota like *Lactobacillus* **alter central GABA receptor expression**[2]
- In a colitis model, *Bifidobacterium longum* was responsible for **anxiolytic effect through the vagus nerve**[2]
- *Bacteroides fragilis* (gut microbiota) **reduces neurotoxic metabolite levels correcting gut permeability and ameliorating anxiety-like behaviour**[3]

About **60%** of patients with **anxiety and depression** are described to have **intestinal function disturbance**, such as IBS[4]

48 CNS: Central nervous system; GABA: Gamma-aminobutyric acid; HPA: Hypothalamo-pituitary-adrenocortical, IBS: Irritable bowel syndrome; SCFAs: Short chain fatty acids

1. Bear T, *et al. Microorganisms*. 2021; 9(4):723. 2. Carabotti M, *et al Ann Gastroenterol*. 2015;28(2):203-209. 3. Zhu S, *et al. J Neuroinflammation*. 2020;17(1)17-25; 4. Liu, L., & Zhu, G. *Front. Psychiatry*. 2018. 9. 223.

GI disorders are approximately 4-fold more prevalent in children with ASD[1]



Mothers of children with ASD harbor an altered gut microbiome during pregnancy

- Significant increase in the relative abundances of *Moraxellaceae* and *Enterobacteriaceae* (at the family level) and *Acinetobacter* (at the genus level)
- Significant reduction in *Faecalibacterium* [2]

Children with ASD harbor unique gut bacterial biomarkers

- Relative abundance of genus Clostridium with high levels of *Epulopiscium, Sphingobium xenophagum, Anaeroplasma, Adlercreutzia, Solirubrobacterales, Mesorhizobium, Hydrogenophilus, Salinicoccus*, and *Promicromonosporaceae* [2]

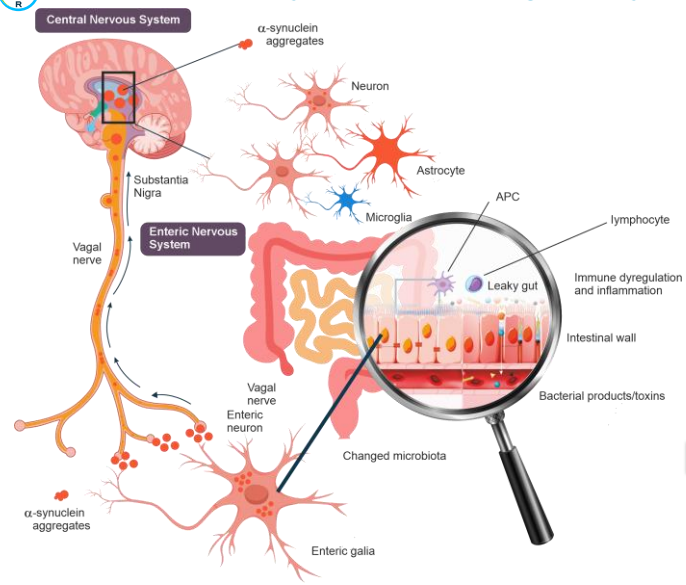
Clostridium bacteria in the colon indicate higher risk and severity of ASD

- It produces TeNT, which passes through the vagus nerve to the CNS
- Blocks neurotransmitters by the proteolytic cleavage of synaptobrevin, a synaptic vesicle membrane protein
- Precipitates a whole range of behavioral deficits [3]

[49] ASD: Autism spectrum disorder; CNS: Central nervous system; GI: Gastrointestinal; TeNT: Tetanus neurotoxin

1. Madra M, *et al. Child Adolesc Psychiatr Clin N Am*. 2020;29(3):501-13., 2. Li N, *et al. GBP*. 2019;17(1):26-38; 3. Taniya MA, *et al. Front Cell Infect Microbiol.* 2022;12:91570.

Intestinal permeability in PD patients is significantly correlated with α-synuclein



EECs contain α-synuclein – synapse with Enteric nerves

↓

Misfolded α-synuclein in enteric nerves

↓

Vagus nerves

↓

Brain

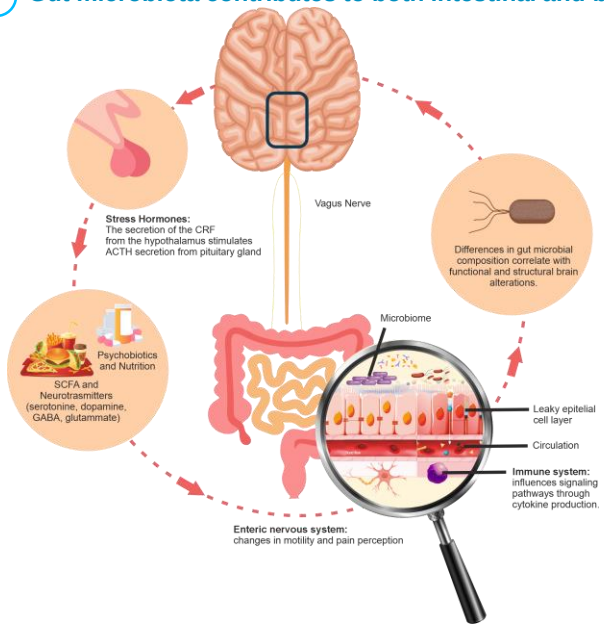
Overexpression of α-synuclein leads to constipation which is the early indicator of PD

Parkinson's **manifests in the gut** before hitting the **CNS**

[50] APC: Adenomatous polyposis coli; CNS: Central nervous system; EECs: Enteroendocrine cells; PD: Parkinson's disease

Klann EM, *et al. Front. Aging Neurosci.* 2022;13.

Gut microbiota contributes to both intestinal and behavioural manifestations of IBS



- **IBS is linked to a higher risk of mood disorders**
- **94%** of patients with IBS have been reported to have mood disorders
- Gut microbiota of patients differ as per IBS subtypes
- Reduced IBS symptoms were observed after FMT resulting in lower depression scores, whereas depression scores of placebo treatment remained unchanged

Gut microbiome-directed therapies have a **higher potential** for better treatment outcomes

51

ACTH: Adrenocorticotropic Hormone, CRF: Corticotropic releasing factor; GABA: Gamma-aminobutyric acid; FMT: Faecal microbiota transplantation; IBS: Irritable bowel syndrome; SCFAs: Short chain fatty acids
1. Ancona A, *et al. Dig Liver Dis.* 2021;53(3):298-305.

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Functional gastrointestinal disorders (FGDI) are now recognized as disorders of gut-brain interaction (DGBI)

> Microbiome. 2021 Nov 30;9(1):236. doi: 10.1186/s40168-021-01188-6.

Cognitive behavioral therapy for irritable bowel syndrome induces bidirectional alterations in the brain-gut-microbiome axis associated with gastrointestinal symptom improvement

Jonathan P Jacobs [1 2 3 #], Arpana Gupta [# 1 2 3], Ravi R Bhatt [1], Jacob Brawer [1 2 3], Kan Gao [1 2 3], Kirsten Tillisch [1 2 3], Venu Lagishetty [2 3 4], Rebecca Firth [5], Gregory D Gudleski [6], Benjamin M Ellingson [2 7 #], Jennifer S Labus [1 2 3], Bruce D Naliboff [1 2 3], Jeffrey M Lackner [# 8], Emeran A Mayer [9 10 11 12]

> Sci Rep. 2019 Sep 19;9(1):13590. doi: 10.1038/s41598-019-50024-3.

Elucidating the putative link between prefrontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome

Adriane Icenhour [1 2 3], Sofie Tapper [4 5], Olga Bednarska [6], Suzanne T Witt [4], Anders Tisell [4 7 8], Peter Lundberg [4 7 8], Sigrid Elsenbruch [9], Susanna Walter [6 9]

> Psychosom Med. Feb/Mar 2019;81(2):146-154. doi: 10.1097/PSY.0000000000000655.

Altered Brain Structure and Functional Connectivity and Its Relation to Pain Perception in Girls With Irritable Bowel Syndrome

Ravi R Bhatt [1], Arpana Gupta, Jennifer S Labus, Lonnie K Zeltzer, Jennie C Tsao, Robert J Shulman, Kirsten Tillisch

> Brain Imaging Behav. 2020 Oct;14(5):1566-1576. doi: 10.1007/s11682-019-00087-7.

Changes of the postcentral cortex in irritable bowel syndrome patients

Jiaofen Nan [1], Wenya Yang [2], Panting Meng [2], Wei Huang [2], Qian Zhang [2], Yongquan Xia [3], Feng Lu [4]

Review > Wien Med Wochenschr. 2018 Mar;168(3-4):62-66. doi: 10.1007/s10354-017-0592-0. Epub 2017 Sep 8.

Intestinal microbiome-gut-brain axis and irritable bowel syndrome

Gabriele Moser [1], Camille Fournier [2], Johannes Peter [2]

> Curr Pathobiol Rep. 2018 Mar;6(1):1-13. doi: 10.1007/s40139-018-0160-3. Epub 2018 Feb 12.

Targeting the Microbiota, from Irritable Bowel Syndrome to Mood Disorders: Focus on Probiotics and Prebiotics

M M Pusceddu [1], K Murray [1], M G Gareau [1]

> Neurogastroenterol Motil. 2015 Dec;27(12):1796-803. doi: 10.1111/nmo.12692. Epub 2015 Sep 25.

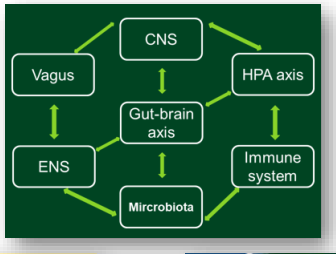
Abnormal regional homogeneity in patients with irritable bowel syndrome: A resting-state functional MRI study

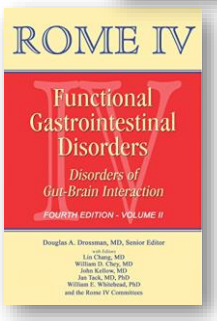
J Ke [1], R Qi [1], C Liu [2], Q Xu [1], F Wang [2], L Zhang [1], G Lu [1]

Review > J Gastrointestin Liver Dis. 2021 Nov 23;30(4):517-525. doi: 10.15403/jgld-4090.

Neuromodulators in the Brain-Gut Axis: their Role in the Therapy of the Irritable Bowel Syndrome

Mihaela Fadgyas Stanculete [1], Dan Lucian Dumitrascu [2], Douglas Drossman [3]





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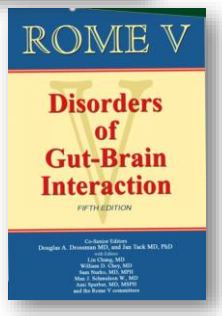

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CNS: Central nervous system; DGBI: Disorders of gut-brain interaction; ENS: Enteric nervous system; FGID: Functional gastrointestinal disorders; HPA: Hypothalamic–Pituitary–adrenal
Drossman DA, *et al. A Rome Foundation Working Team Report. Gastroenterol.* 2018;154(4):1140-71.e1.

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Treatment Landscape for Gut-Brain Interaction Disorders

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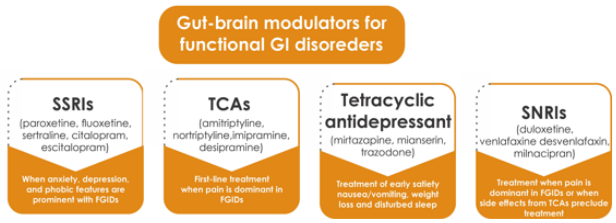
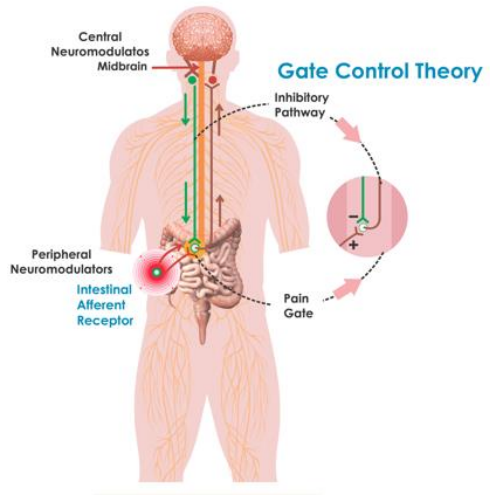
Treating Disorders of Gut-Brain Interaction – ROME Guidelines





54 DGBI: Disorders of gut-brain interaction; FGID: Functional gastrointestinal disorders; GI: Gastrointestinal; SNRIs: Serotonin noradrenergic reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressant
Drossman DA, *et al. A Rome Foundation Working Team Report. Gastroenterol.* 2018;154(4):1140-71.e1.

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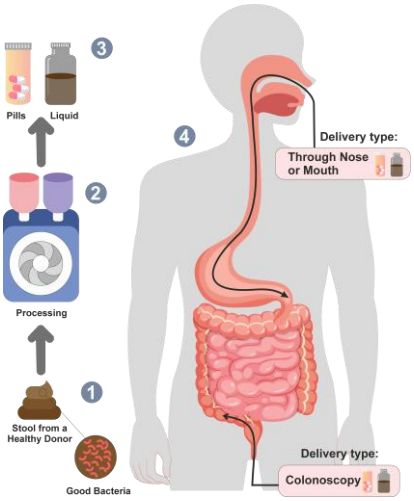
Reconstruction of healthy gut microbiota using FMT - a promising new strategy for treating cerebral diseases[1]



- **Improvement** in **mood, memory**, and **cognitive function** have been reported in patients with **Alzheimer's Disease** after FMT
- **MMSE** score of the FMT recipient increased from 20 (**mild cognitive impairment**) to 26 (**normal cognitive function**) two months after the transplant [2]

- **FMT via colonoscopy** showed **significant improvements** and **relieved the motor and non-motor** symptoms with acceptable safety in **Parkinson's disease**[3]

- FMT **significantly improved fatigue and the quality of life in patients with IBS**[4]

FMT treatment is the most effective way to correct **gut microbiota** dysbiosis

55 APP: Amyloid precursor protein; FMT: Faecal microbiota transplantation; IBS: Irritable bowel syndrome; MMSE: Mini-Mental State Examination; SCFA: Short chain fatty acids
1. Xu H-M, *et al. Gastroenterol. Res. Prac.* 2021;2021:6699268; 2. Nassar, S T., *et al. Cureus*, 2022. 14(10), e29968; 3. Xue, L. J *et al. Medicine*, 2020. 99(35), e22035; 4. El-Salhy, *et al. Gut*, 2020. 69(5), 859–867.

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Gut-Brain Axis- Interventions

Autism	Probiotics	*L plantarum* PS128	DB RCT. (n= 80, 7-15 yr old Boys with ASD, Taiwan)	• Improvements in some autism symptoms, primarily those linked to rule-breaking behaviors such as hyperactivity/impulsivity[1] • PS128 intervention is age-related, with more considerable results noticed in younger cases, suggesting the importance of early interventions [1, 5]
	Prebiotics	*B. longum* subsp.infantis (UCD272); BCP	DB RCT. (n= 8, 2 – 11 yr old children with ASD)	• Reduction in the GI symptoms with remarkable improvement in stereotypy and irritability scores • Reduction in TNF-α and IL-13 production might be an improvement factor [2, 5]
Schizophrenia	Probiotics	Combined *B.animalis* subsp. lactis strain Bb12 and *L.rhamnosus* strain GG	Placebo-controlled RCT (n= 56, 18–65 yrs, patients with at least moderately severe psychotic symptoms)	• Candida albicans seropositivity was associated with worse psychiatric symptoms • Reduction of elevated Candida yeast antibody levels • Relieved yeast-related bowel discomfort compared to placebo [3, 5]
	Synbiotics	Synbiotic (15 g prebiotics, 5 g probiotic containing L. acidophilusT16, *B bifidum* BIA-6, *B. lactis* BIA-7, and *B. longum* BIA-8 [synbiotic group] versus 15 g/20 g maltodextrin [placebo])	Three-arm parallel design, placebo-controlled, DB RCT (n= 75, clinically stable hemodialytic patients with MDD, aged 30 to 65 yrs)	• Improvement in serum BDNF level and depression symptoms [4, 5]

56 ASD: Autism spectrum disorder; BCP: bovine colostrum product; BDNF: Brain-derived neurotrophic factor; DB RCT: Double-blind randomised control trial; GI: Gastrointestinal; IL: Interleukin; MDD: Major depressive disorder; TNF: Tumor necrosis factor
1. Lui *et al. Behav Brain Res.* 2019; 298: 202–209; 2. Sanctuary *et al. PLoS One*. 2019; 14:e0210064 3. Severance *et al., Brain Behav Immun*. 2017. 62:41–45; 4. Haghighat *et al. Nutr Neurosci.* 2019; 24:490–410; 5. Sorboni SG, *et al. Clin. Microbiol. Rev*. 2023; 35(1) e00338-20.

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Gut-Brain Axis- Interventions

Parkinson's Disease	Probiotics	Probiotic capsule *(B. bifidum, L.acidophilus, L. reuteri, L. fermentum)*	DB RCT (n= 60, with Parkinson's Disease, aged 50-90 yrs)	• Improvement of the Movement Disorder Society-Unified Parkinson's Disease rating scale, and insulin metabolism [1, 5]
	Synbiotics	*L. rhamnosus GG, L.acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subsp. bulgaricus, and *Bifidobacterium* (fermented milk), *S. salivarius* subsp. thermophilus, *E. faecium*	DB RCT (n= 80, patients with Parkinson's Disease)	• Alleviated constipation [2, 5]
Irritable Bowel Syndrome	Probiotics	Bifico® (*B. longum, Lb. acidophilus, E. faecalis*; ≥1.0*107 cfu) 20 mg 3 X daily	Pilot study (n= 15, patients with IBS-D diagnosed as per Rome III criteria)	• Changes in gut microbiota and SCFA concentrations • Reduced severity of abdominal symptoms Decreased plasma levels of cytokines [3, 6]
	Prebiotics	Short-chain fructooligosaccharides (scFOS) two times 2.5 g/d	Parallel, DB RCT (n= 79, patients with IBS-D as per Rome III criteria)	• Increased number of *Bifidobacterium* spp. • Decreased anxiety • Attenuated severity of IBS symptoms • No effect on rectal hypersensitivity [4, 6]

57 CFU: Colony forming units; DB RCT: Double-blind randomised control trial; IBS: Irritable bowel syndrome; SCFA: Short chain fatty acid
1. Tamtaji *et al. Clin Nutr*. 2019; 38:1031–1035; 2. Barichella *et al., Neurol.* 2016; 87:1274–1280; 3. Zhang *et al., Chin. Med. J.* 2019, 132, 346; 4. Azpiroz et al., Neurogastroenterol. Motil. 2017, 29, e12911; 5. Sorboni SG, *et al. Clin. Microbiol. Rev*. 2023; 35(1) e00338-20; 6. Chlebicz-Wójcik A, *et al., Biomol.* 2021; 11(8):1154.

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Gut-Brain Axis- Interventions

Stress	Psychobiotics	*B. longum* 1714	n = 22 healthy men	• Decreased stress • Enhanced memory [1, 4]
		L. rhamnosus (JB-1)	n = 29 healthy men	• Decreased stress-related behaviors, corticosterone release, and altered expression of central GABA receptors [2, 4]
		Multi-strain probiotic (*B. coagulans* Unique IS2**,** *L. rhamnosus* UBLR58, *B. lactis* UBBLa70, *L. plantarum* UBLP40, *B. breve* UBBr01, *B. infantis* UBBI01	n = 63 women, n=17 men	• Reduction in depression anxiety stress scale and state-trait anxiety inventory [3, 4]

58 GABA: Gamma-aminobutyric acid
1. Allen *et al. Transl. Psychiatry*. 2016 6:e939–e939; 2. Kelly *et al., Brain Behav Immun* 2017; 61:50–59; 3. Venkataraman *et al., Antimicrob Proteins*. 2021 13:12–18; 4. Oroojzadeh P, *et al., J Mol Neurosci*. 2022; 72(9): 1952–1964.

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Future outlook

Artificial Intelligence and Language Models in Drug- Microbiome Therapeutics

Identification of potential biomarkers or therapeutic targets

AL and LLMs can play a significant role in:

- Analyzing large volumes of microbiome data
- Identifying patterns
- Making sense of complex microbial communities

With their ability to process vast amounts of information, AI systems can unveil hidden relationships between microbiota and diseases, helping in the identification of potential biomarkers or therapeutic targets

Drug Discovery and Development

Incorporating AI into the drug discovery process can expedite the identification of potential microbiome-targeted therapeutics.

Language models can assist in predicting the effects of specific compounds on microbial communities and provide insights into potential drug-microbiome interactions.

[60] AI: Artificial intelligence; LLM: Large language models

Gut-Brain Axis- AI, LLM – Future Scope

Disease Prediction and Early Detection

Leveraging AI algorithms, and microbiome data to be analyzed alongside clinical and genetic information to develop predictive models for disease risk assessment

Enabling earlier detection of certain conditions and providing personalized intervention strategies

Precision Probiotics and Microbiome Engineering

Strategies to guide the development of precision probiotics designed to modulate specific microbiome components

Understanding the complex interactions within the microbiome, help engineer targeted interventions for restoring microbial balance in diseased states

Treatment Optimization and Personalized Medicine

AI can facilitate the development of personalized treatment plans based on an individual's unique microbiome profile

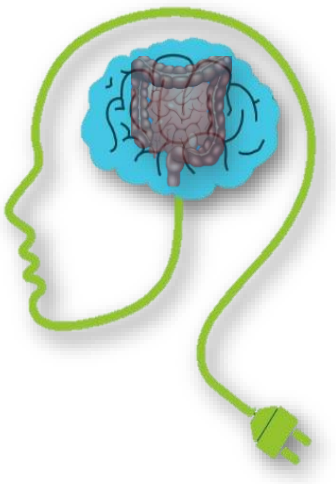
Analyze microbiome data to predict optimal therapeutic approaches, tailor interventions, and enhance treatment outcomes

Patient Stratification

AI can aid in categorizing patients based on their microbiome profiles and other relevant clinical data, allowing for more precise disease subtyping and personalized treatment strategies

[61] AI: Artificial intelligence; LLM: Large language models

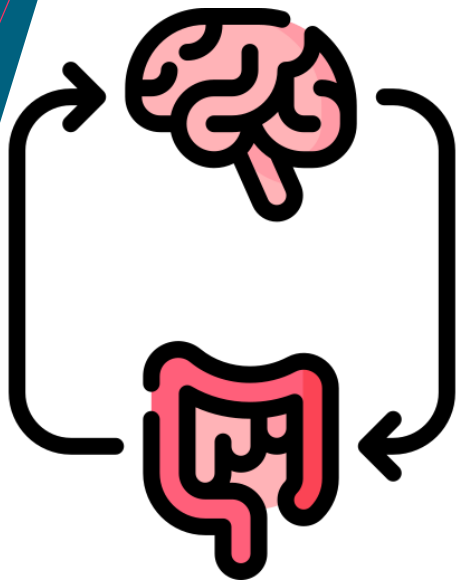
Key Takeaway



- Gut microbiota plays a crucial role in maintaining our overall health, including influencing brain function, behavior, and mental well-being
- This bi-directional communication occurs through various pathways, including the immune system, the enteric nervous system, and the production of neurotransmitters and metabolites.
- Imbalances in the gut microbiota have been linked to various mental health disorders such as anxiety, depression, and even neurodegenerative diseases like Alzheimer's.
- Functional gastrointestinal disorders (FGDI) are now recognized as disorders of gut-brain interaction (DGBI)
- Targeting the gut microbiota through interventions such as probiotics, prebiotics, fecal microbiota transplantation, or dietary modifications holds promise for potential therapeutic interventions in mental health.
- Further research is needed to fully understand the complex mechanisms of the microbiome-gut-brain axis and to develop personalized treatments that harness the potential of this communication network.

[62] ASD: Autism spectrum disorder; DGBI: Disorders of gut-brain interaction; FGID: Functional gastrointestinal disorders; GI: Gastrointestinal; GABA: Gamma-aminobutyric acid; HPA: Hypothalamo-pituitary-adrenocortical; IBS: Irritable bowel syndrome; 5-HT: 5-hydroxytryptamine

Thank You!



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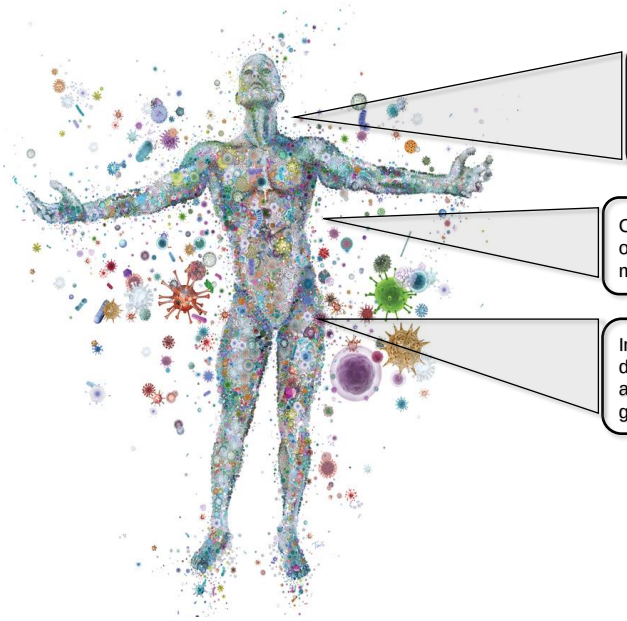
The gut microbiome is linked to immune, metabolic and neurologic conditions

The human gut harbors 10^{11}-10^{12} bacteria per gram of colonic content (>10^{14} total bacteria)

The microbiota contains more cells than the human body, with a 150X as many genes families than our genome

Human gut bacterial communities have the metabolic capacity of the liver, and same weight as the brain



Autism spectrum disorder, anxiety, depression, cognition, Alzheimer's disease, Parkinson's disease

Cardiovascular disease, obesity, type II diabetes, metabolic syndrome

Inflammatory bowel disease, rheumatoid arthritis, psoriasis, gastrointestinal infections

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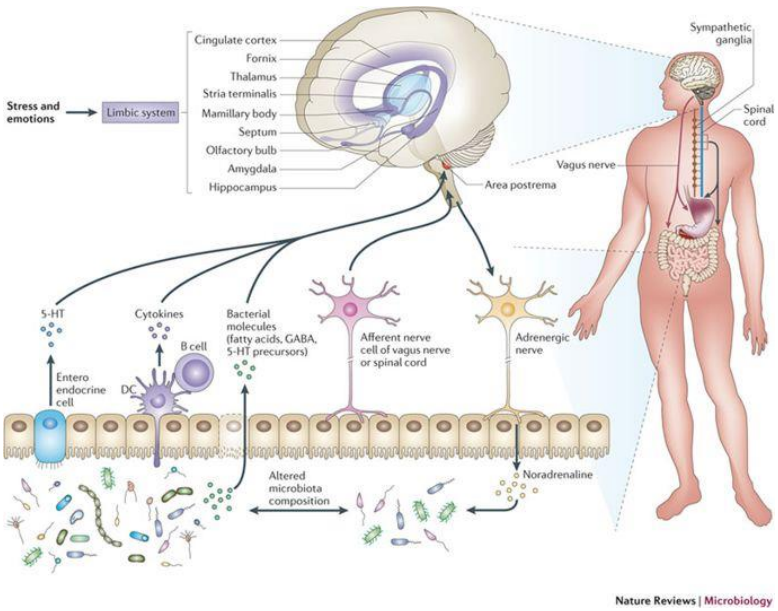
The gut-brain connection includes various conduits for communication



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Autism involves a spectrum of clinical symptoms

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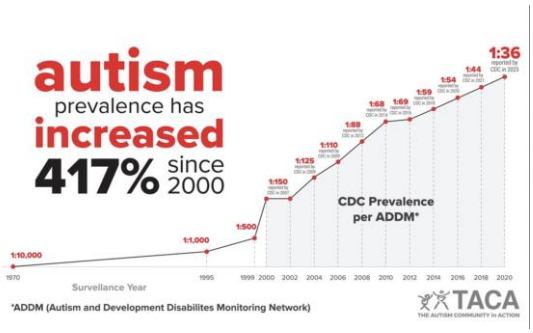
The prevalence of ASD is rising dramatically

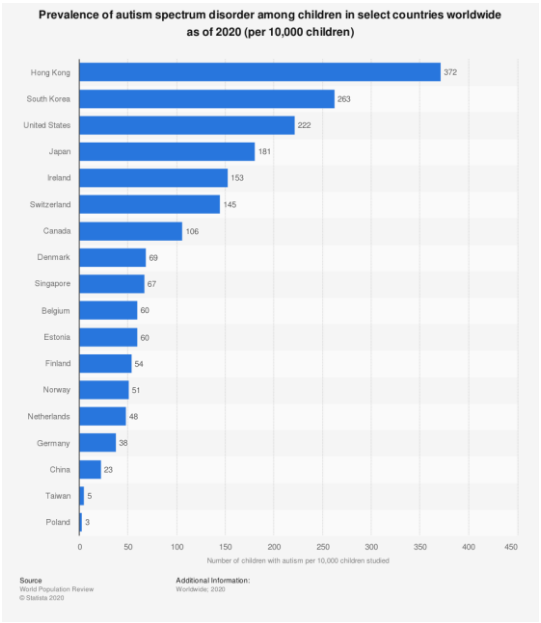


ASD affects over 3 million individuals worldwide, though many projections suggest this is an underestimate

The diagnosis of ASD is rising. Current estimates reveal an ASD incidence of 1 in 36 births in the US, making it the fastest growing developmental disorder

Annual cost of ASD is $236 billion in the U.S., with a lifetime cost of $2.5 million per person

Many children with ASD have gut issues, and the microbiome of ASD subjects is altered compared to healthy controls



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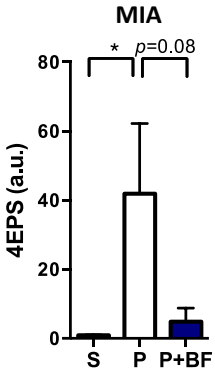
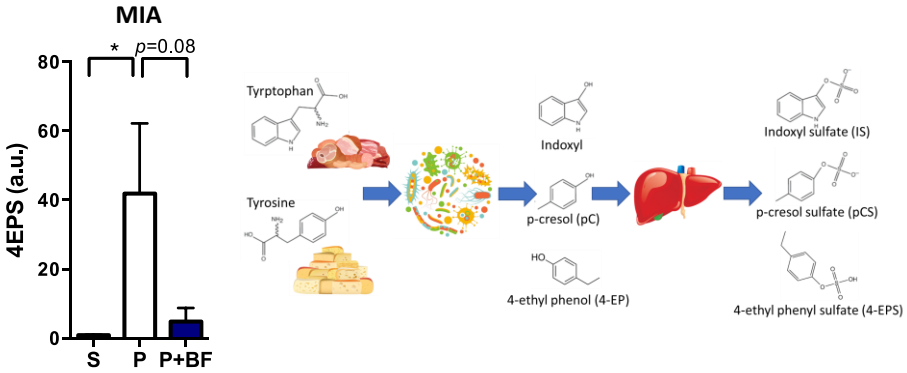
The gut microbial metabolite, 4-ethylphenylsulfate (4EPS) is elevated in mouse models of ASD



69

Hsiao et al, *Cell* (2013)

The gut microbial metabolite, 4-ethylphenylsulfate (4EPS) is elevated in mouse models of ASD



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Hsiao et al, *Cell* (2013)

Plasma and fecal metabolomes in a large human ASD cohort show elevation of 4EPS

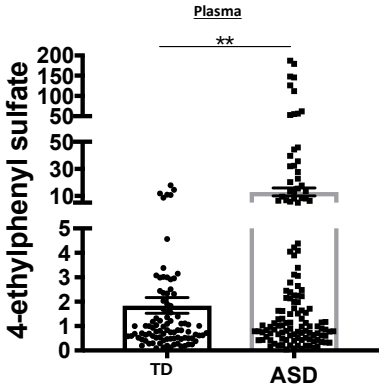
(and many other metabolomic changes)

Plasma

Compared to TD	↑	↓	Total
All ASD	62	248	310
ASD-GI	72	182	254
ASD+GI	54	206	260

Feces

Compared to TD	↑	↓	Total
All ASD	25	87	112
ASD-GI	28	53	81
ASD+GI	14	66	80



Human Plasma Metabolites	Fold of Change ANOVA Contrasts			
Biochemical Name	All ASD TD	ASD-GI TD	ASD+GI TD	ASD+GI ASD-GI
4-ethylphenylsulfate	6.89	5.81	9.2	1.58

with Paul Ashwood, Alessio Fasano

Needham et al, *Bio. Psychiatry* (2020)

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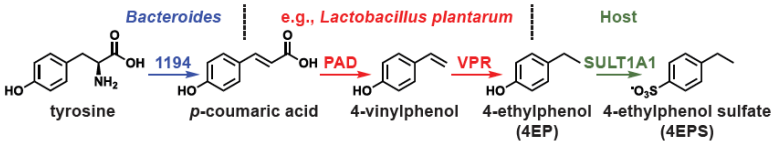
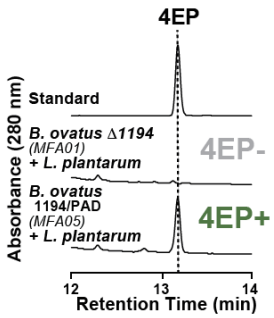
Discovery of a biosynthetic pathway for 4EPS synthesis and bioengineered production strains





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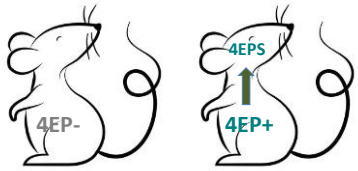
with Michael Fischbach

Needham et al, *Nature 2022*

72

Colonization of mice with 4EP-producing bacteria leads to 4EPS in circulation and the brain



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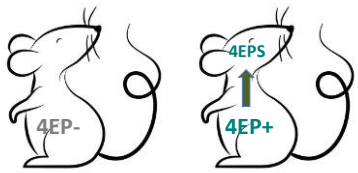
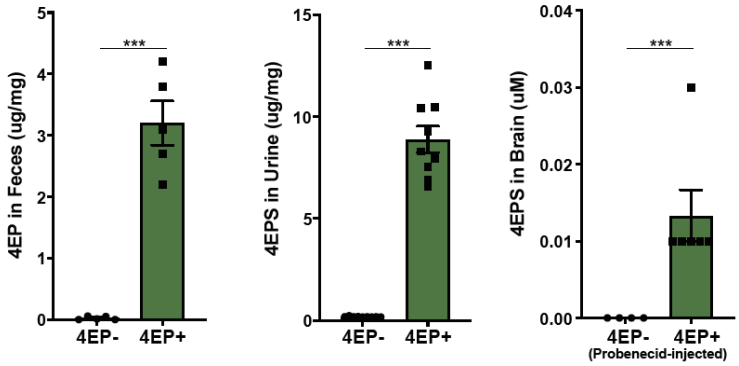
Needham et al, *Nature 2022*

Colonization of mice with 4EP-producing bacteria leads to 4EPS in circulation and the brain





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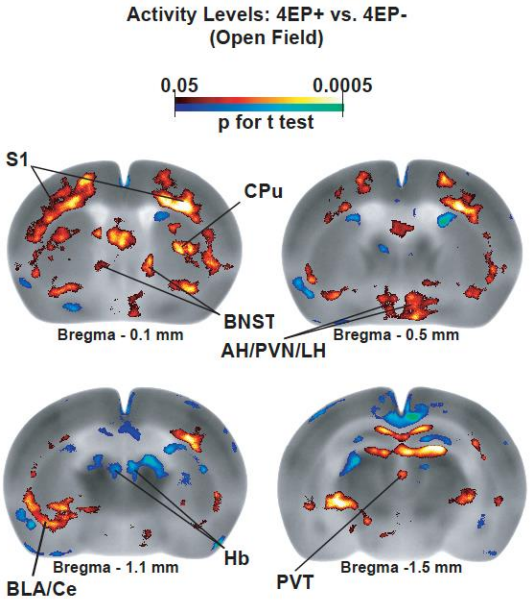
Needham et al, *Nature 2022*

4EPS activates brain regions linked to emotional behaviors in mice



Hypothalamus
anterior area(AH)
lateral (LH)
paraventricular nucleus (PVN)
Amygdala
basolateral (BLA)
central (Ce)
Bed nucleus of the stria terminalis (BNST)
Paraventricular nucleus of the thalamus (PVT)

Habenula areas (Hb)
medial Prefrontal Cortex (mPFC)

75

with Daniel Holshneider

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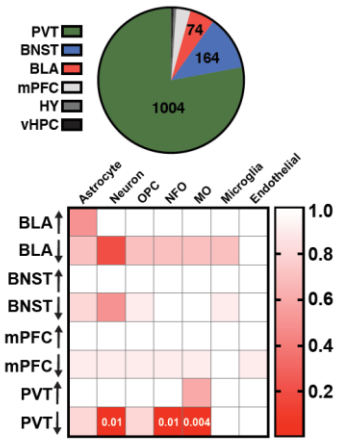
Gene expression in the brain reveals that 4EPS impacts oligodendrocyte maturation

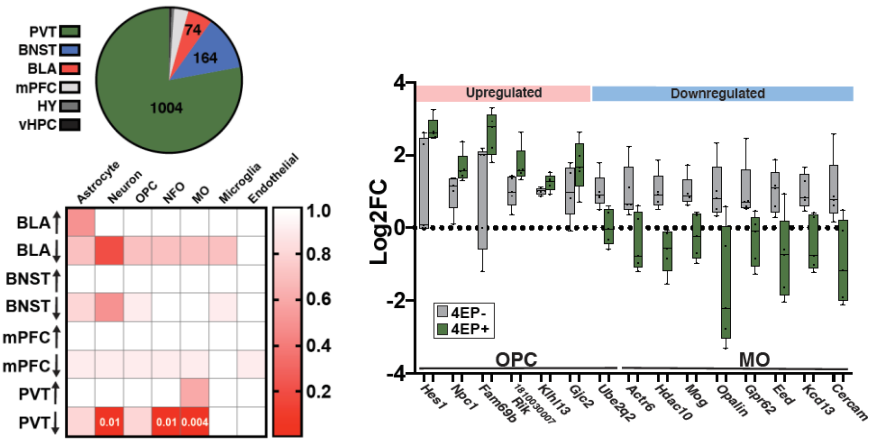


76

with Daniel Geschwind

76

Gene expression in the brain reveals that 4EPS impacts oligodendrocyte maturation



with Daniel Geschwind

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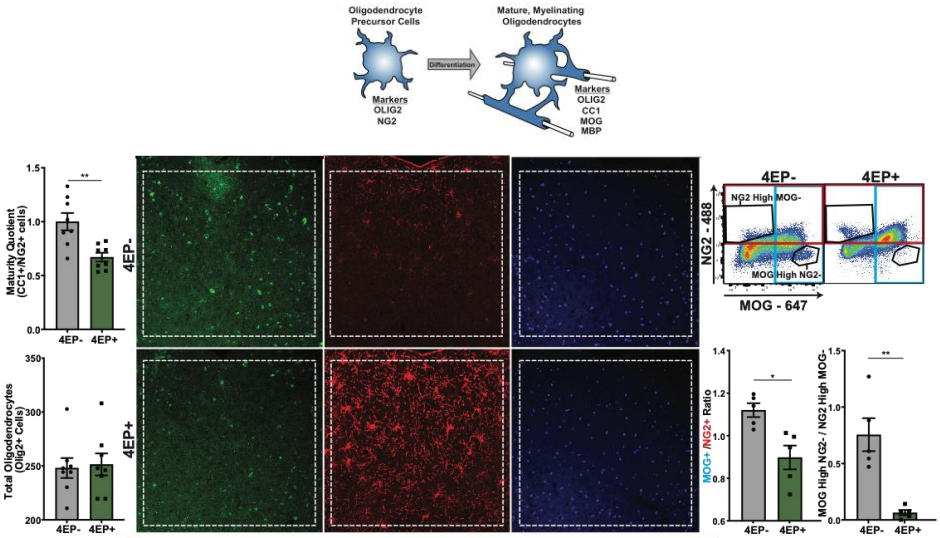
4EPS inhibits maturation of oligodendrocytes in the brains of mice



Red = NG2/immature or OPC
Green = CC1/mature
Blue = Olig2/pan-oligodendrocyte

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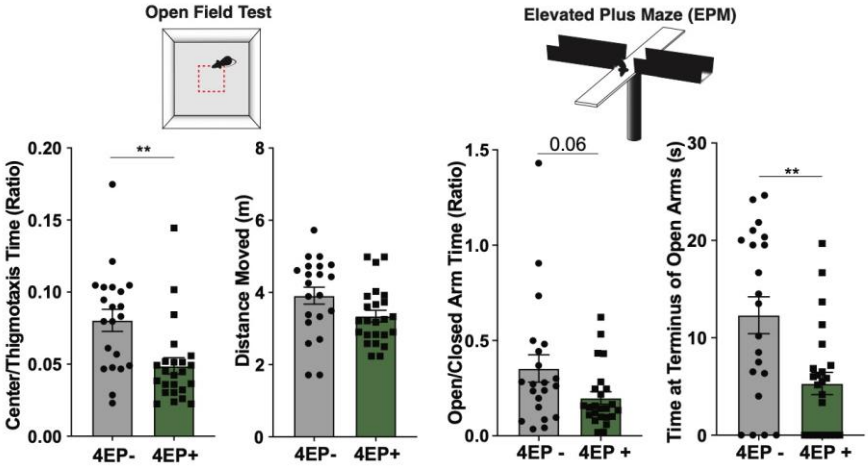
4EPS induces anxiety-like behaviors in mice



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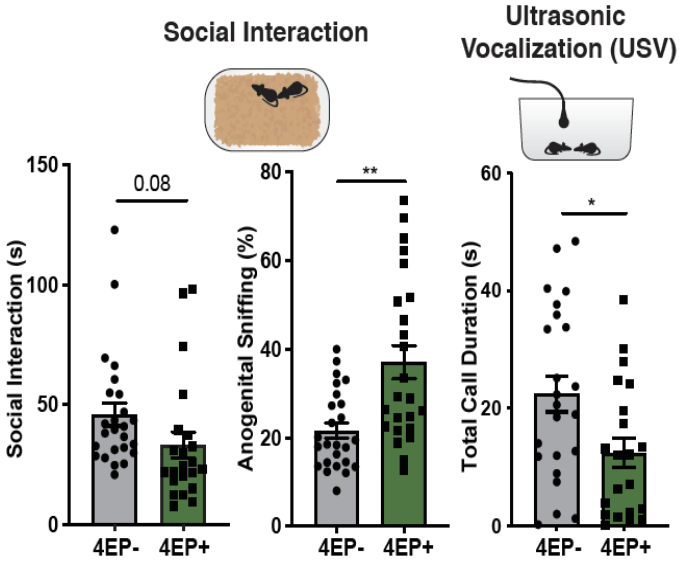
Light Dark Box

79

4EPS promotes autism-like behaviors in mice



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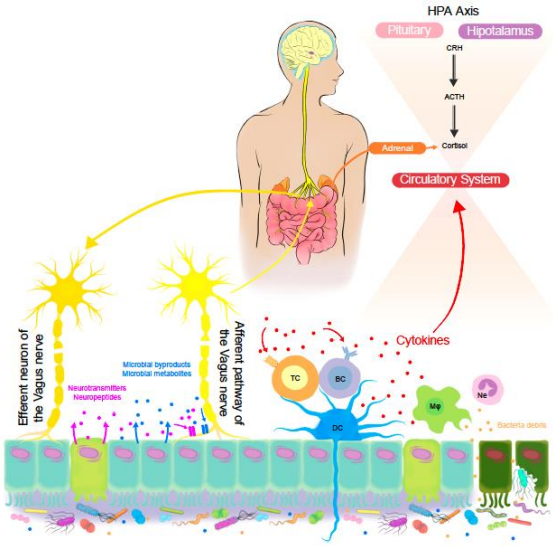
Proposed model for the behavioral effects of a gut microbial neurotransmitter(?)



5. 4EPS arrests oligodendrocyte maturation, leading to reduced myelination and altered behaviors

4. Concentrations of 4EPS increase in the circulation and enter the brain

3. 4EP is sulfated to 4EPS, likely in the liver

2. Altered compositions of microbial metabolites cross the gut epithelial barrier

1. Changes in the gut microbiome lead to increased 4EP (and related metabolites)

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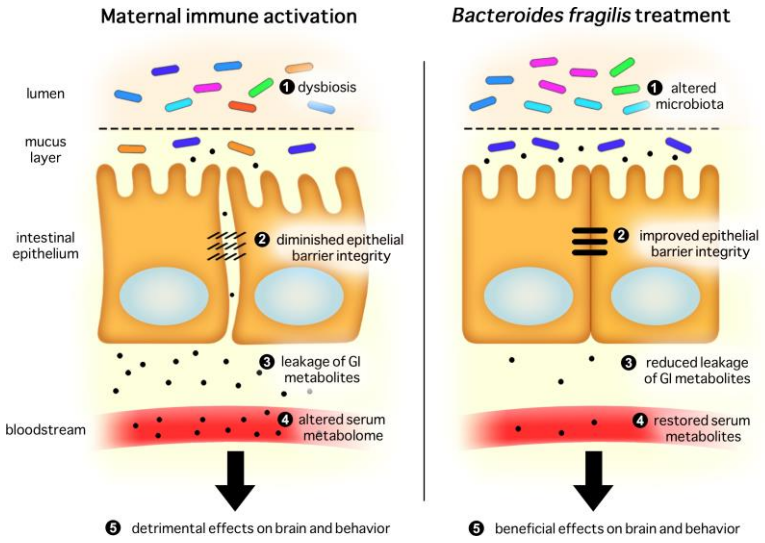
Proposed model for *B. fragilis* treatment of neurodevelopmental disorders



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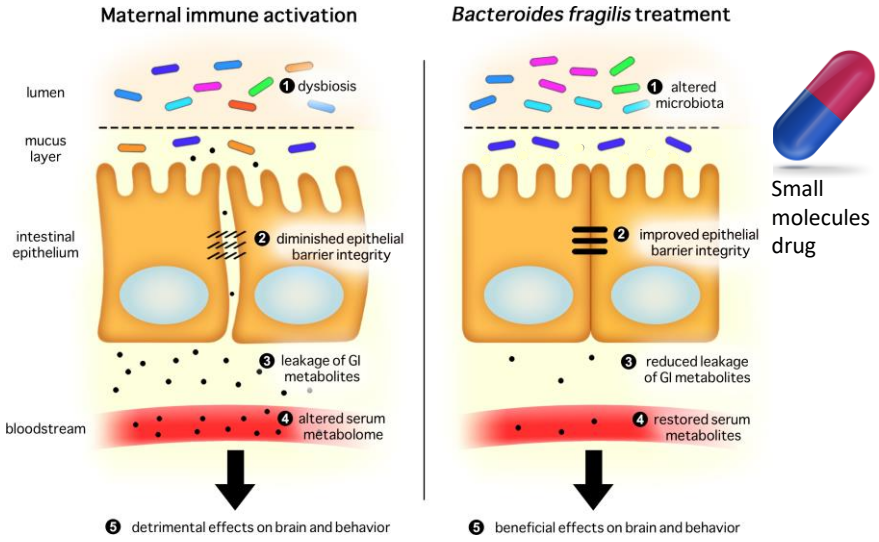
Proposed model for *B. fragilis* treatment of neurodevelopmental disorders



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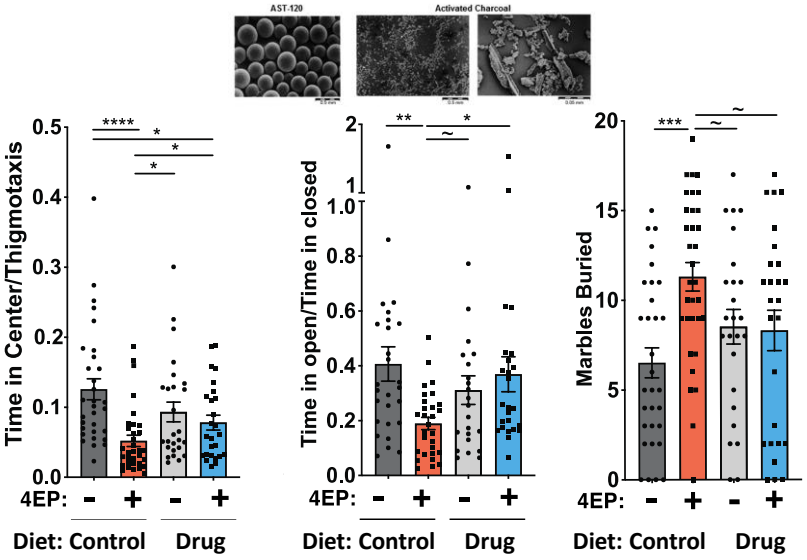
Sequestering microbial metabolites in the gut prevents 4EPS-induced behaviors in mice



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Drug: oral, non-absorbable sequestrant that binds phenolic molecules

Campbell et al, *Nature Medicine 2022*

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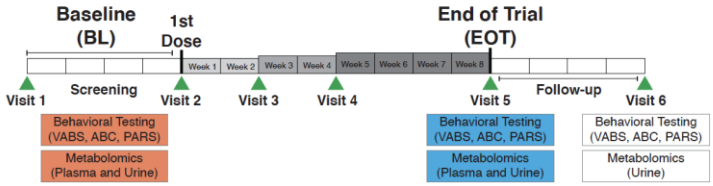
Proof-of-concept clinical trial: open-label, ascending dose design

Trial Demographics	
Sample Size	26
Location (no. individuals)	Brisbane (10); Sydney (4); Auckland (12)
Mean age, years (range)	14.3 (12.1-17.3)
Sex	All Males
Mean BMI (SD)	20.6 (4.9)
ADOS Severity	69% Severe; 27% Moderate; 4% Mild
Adherence to Dosing	74-100%; Median 97.5%



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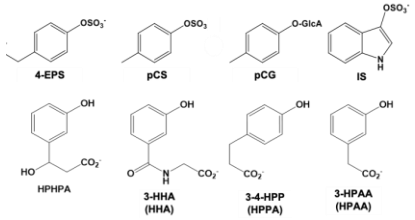
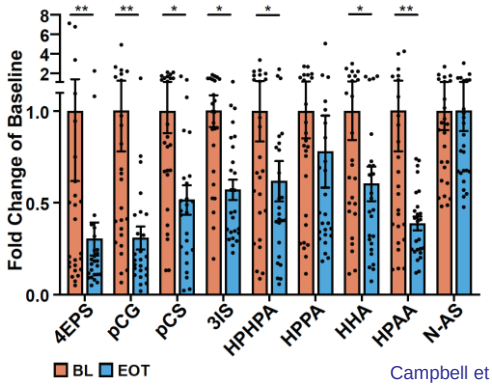
Reduction of key microbial metabolites in plasma of ASD individuals



Target Microbial Metabolites

4-EPS: 4-ethyl phenyl sulphate
pCS: para-cresol sulfate
pCG para-cresol glucuronidase
IS: indoxyl sulfate
HPHPA: 3-hydroxypropionic Acid
3-HHA: 3-hydroxyanthranilic Acid
3-4-HPP(HPPA): 4-Hydroxyphenylpyruvic Acid
3-HPAA (HPAA): Hydroxyphosphonoacetic Acid
N-AS: N-acetyl serine



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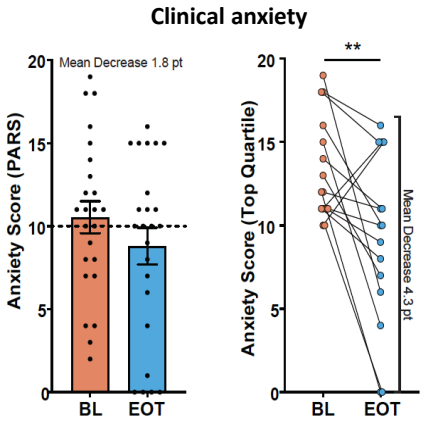
Campbell et al, *Nature Medicine 2022*

86

Improvements in anxiety and irritability in a subset of ASD individuals on drug



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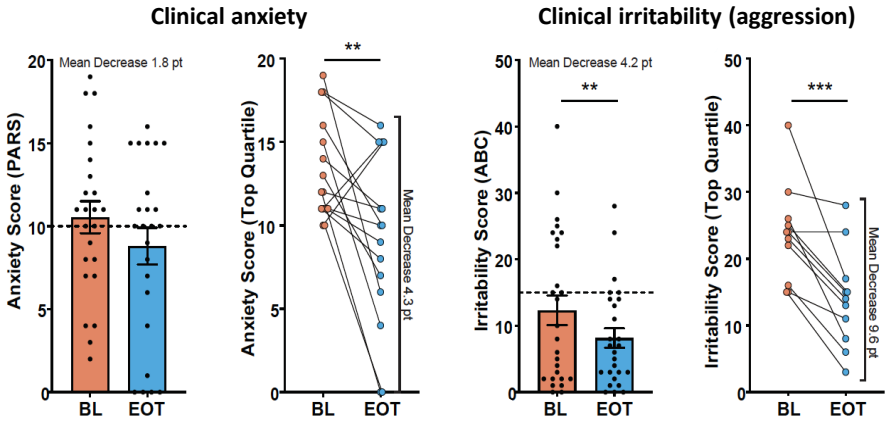
Improvements in anxiety and irritability in a subset of ASD individuals on drug



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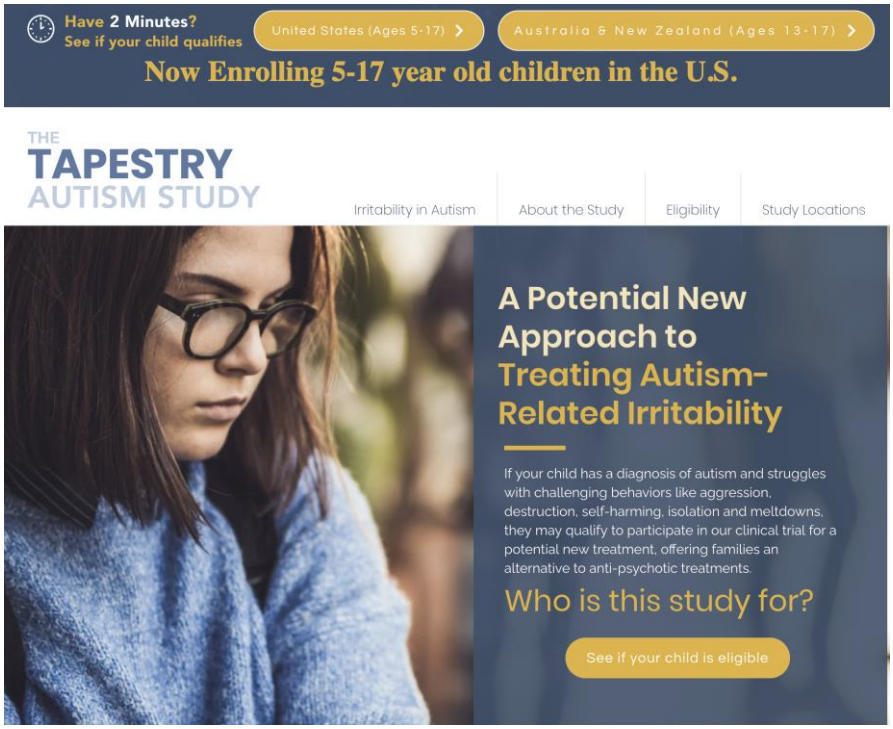

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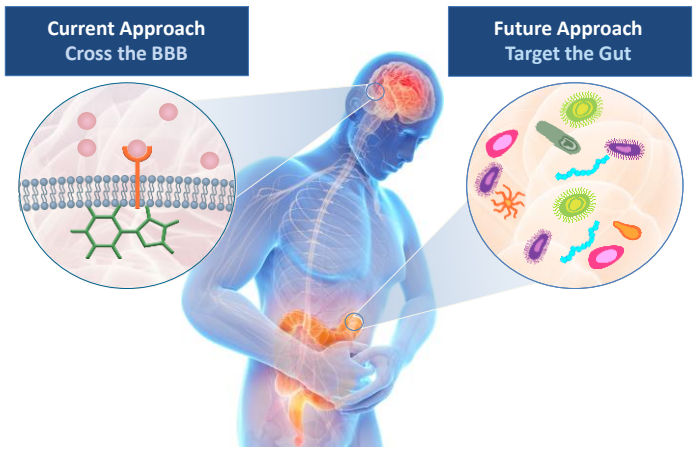
Future treatments for behavioral disorders may target drugs to the gut



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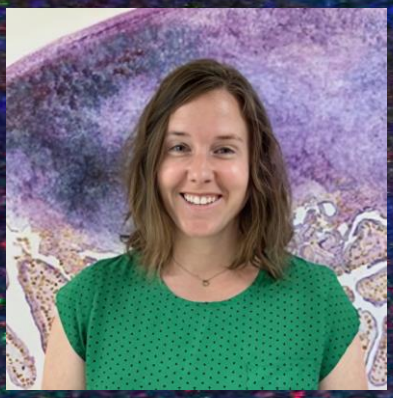
Brittany Needham (Caltech)
Mark Adame (Caltech)
Wei-Li Wu (NCKU)

Paul Patterson (Caltech)
Elaine Hsiao (UCLA)
Daniel Geschwind (UCLA)
Stewart Campbell (Axial)
David Donabedian (Axial)
Alessio Fasano (MGH)
Paul Ashwood (UC Davis)
Mark Ladinsky (Caltech)
Pamela Bjorkman (Caltech)
Daniel Holschneider (USC)
Michael Fischbach (Stanford)
Mikhail Shapiro (Caltech)



NIA, NIMH, NIDDK
Autism Speaks
Heritage Medical Research Institute
Axial Biotherapeutics
The Brain Foundation

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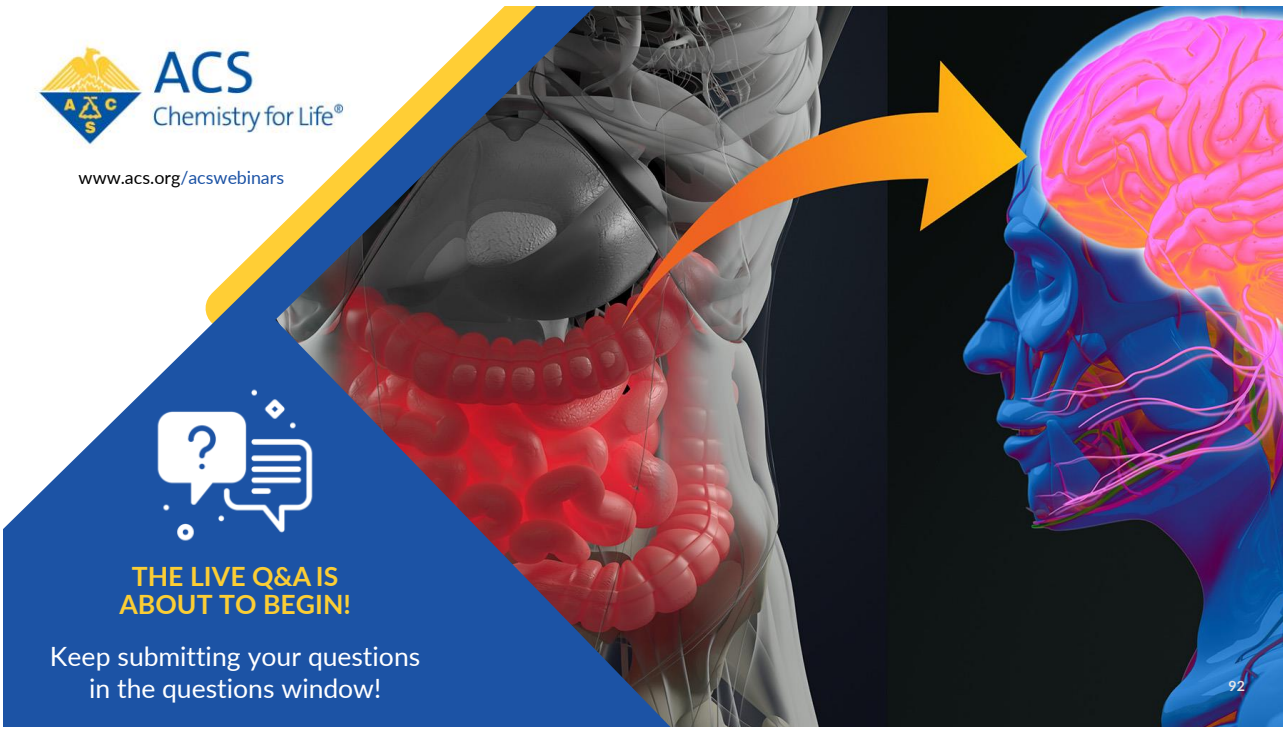

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