

Gut health and Alzheimer's disease

WAI Annual Update, 2024

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Overview

- Microbiome intro
- Microbes and neurodegenerative disease
- Recent findings
- Interventions
- Future directions

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Disclosures

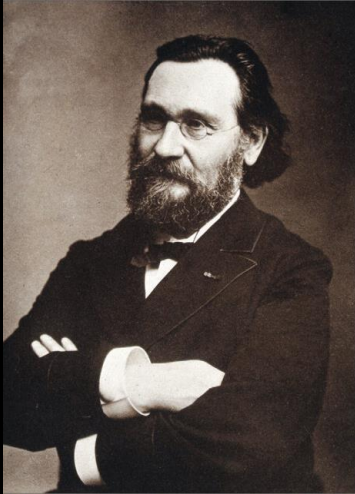
- Funding provided by the Wisconsin Partnership Program, UW Microbiome Initiative, Private donor, National Institute on Aging
- Ad boards for Cognito, New Amsterdam, and MerryLife

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Microbiome in aging and health

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Élie Metchnikoff



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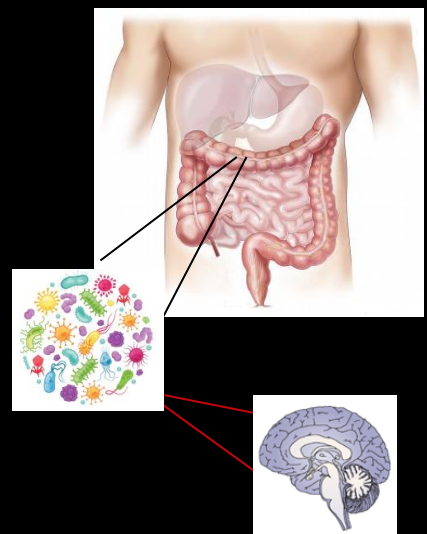
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Human Microbiota

- Some are pathogens but most are either benign or beneficial
- In gut: play role in nutrition, immunity, barriers, toxins
- Altered in disease



Proc. Natl Acad. Sci. USA (2015)

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Gut microbiome and obesity



Federico Rey, PhD



How do we study microbiome in relation to AD?



Patient or mouse samples or defined communities

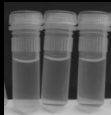
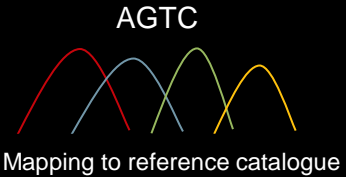


Germ-free mice

Antibiotic-treated mice

16S ribosomal RNA

Metagenomics (function-based analysis)



Metabolomics, proteomics, lipodomics, foodomics

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Microbiome & Alzheimer's Risk Study

- Perform mechanistic experiments in germ-free AD mice.

(AKA: what happens if we keep an AD mouse germ free?)



- Assess fecal microbiota composition in Wisconsinites



Funded by the UW Institute for Clinical and Translational Research, the Wisconsin Microbiome Initiative and the Wisconsin Partnership Program

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Lower amyloid in antibiotic treated mice

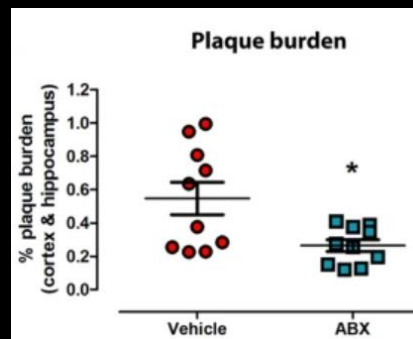
SCIENTIFIC REPORTS

Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease

Myles R. Minter, Can Zhang, Vanessa Leone, Daina L. Ringus, Xiaoqiong Zhang, Paul Oyler-Castrillo, Mark W. Musch, Fan Liao, Joseph F. Ward, David M. Holtzman, Eugene B. Chang, Rudolph E. Tanzi & Sangram S. Sisodia

Scientific Reports 6, Article number: 30028 (2016)
doi:10.1038/srep30028

Received: 03 May 2016
Accepted: 28 June 2016
Published online: 21 July 2016



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Lower amyloid in GF APP/PS1 mice

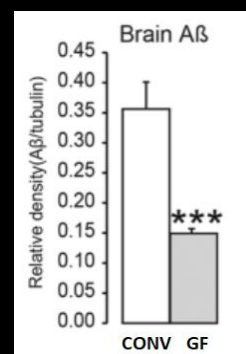
SCIENTIFIC REPORTS

Reduction of Abeta amyloid pathology in APP/PS1 transgenic mice in the absence of gut microbiota

T. Harach, N. Marungruang, N. Duthilleul, V. Cheatham, K. D. Mc Coy, G. Frisoni, J. J. Neher, F. Fåk, M. Jucker, T. Lasser & T. Bolmont

Scientific Reports 7, Article number: 41802 (2017)
doi:10.1038/srep41802

Received: 27 July 2016
Accepted: 28 December 2016
Published online: 08 February 2017



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- Home-dwelling participants with dementia due to AD (n=25) and cognitively-unimpaired participants (n=88)
- Exclusions: antibiotics in previous 6 months, commercial probiotics (>10⁸ cfu/day), immunosuppressive agents, major dietary change in previous month, GI surgery

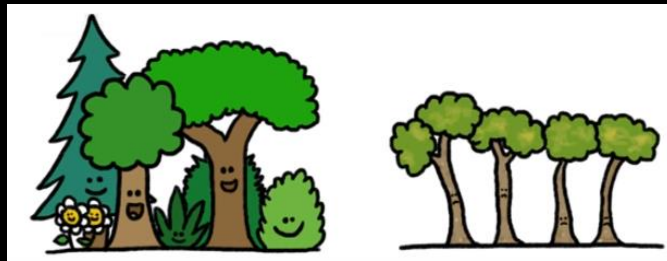
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AGTC

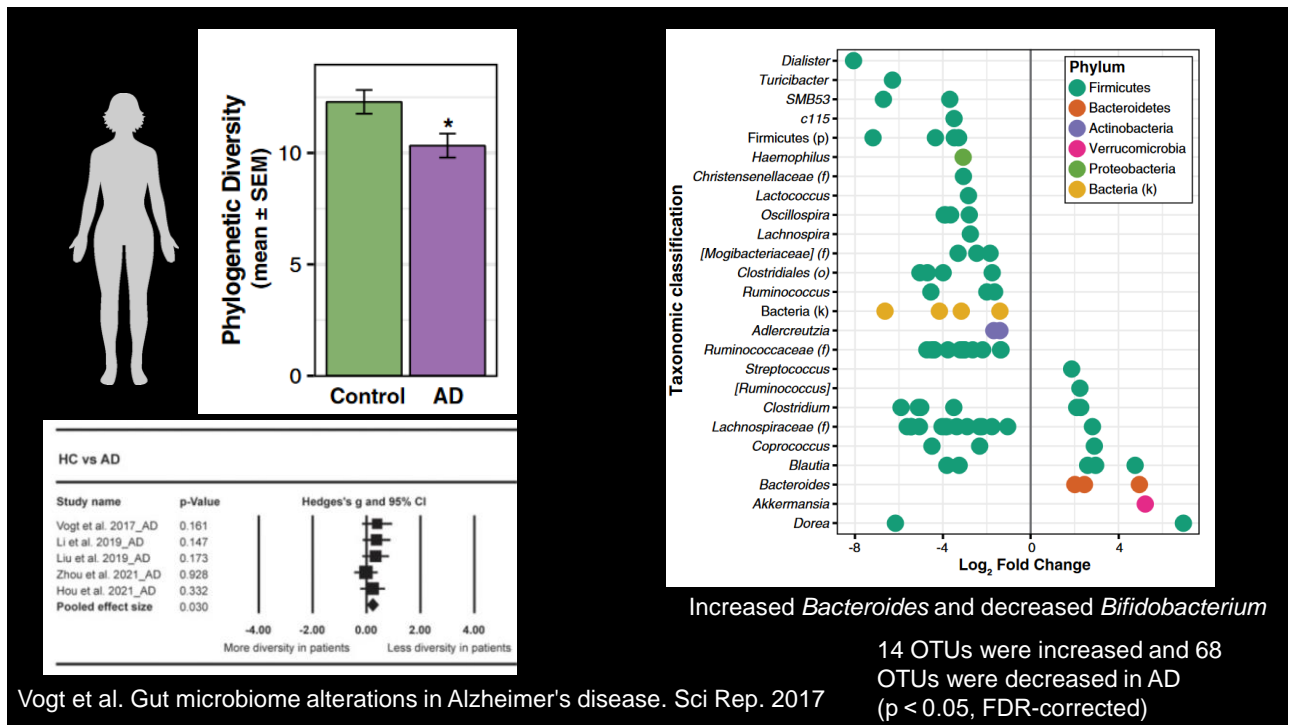


- Performed bacterial 16S rRNA sequencing on DNA isolated from stool
- Compared age- and sex-matched AD participants 1-to-1 with asymptomatic participants

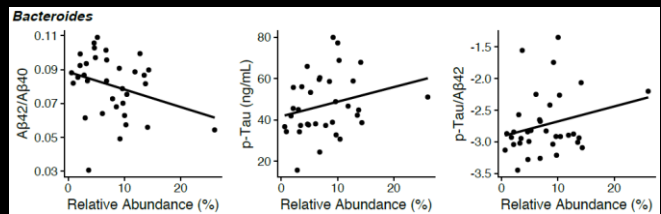
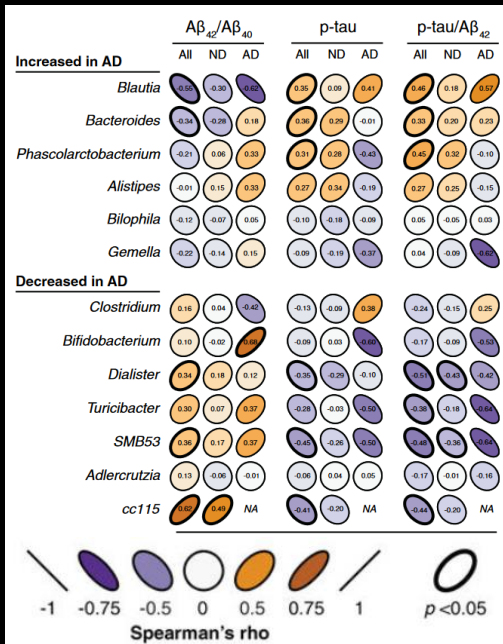
Diversity and Abundance



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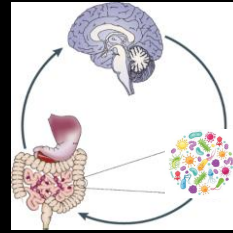


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How does the gut impact the brain?

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- Bi-directional communication
- Vagus nerve
- Microbial metabolites
- Gut permeability
- Translocation of (bacteria) or bacterial products
- Dysregulation of immune function (peripheral and central)

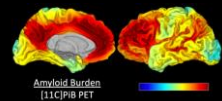
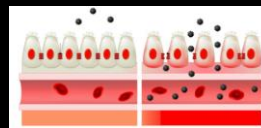
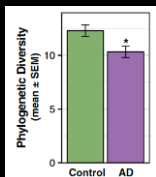


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Gut permeability



Age-associated gut dysbiosis and inflammation impact gut barrier function, leading to dissemination of microbial components driving changes that worsen AD pathology.



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Fecal Aliquot Straw Technique

4°C

Fecal sample

Straws

-80°C

Romano et al, 2018

Macrophages

Monocytes

Neutrophils

Lamina propria

Epithelial cells

Mucus layer

Gut lumen

Stool

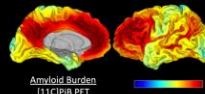
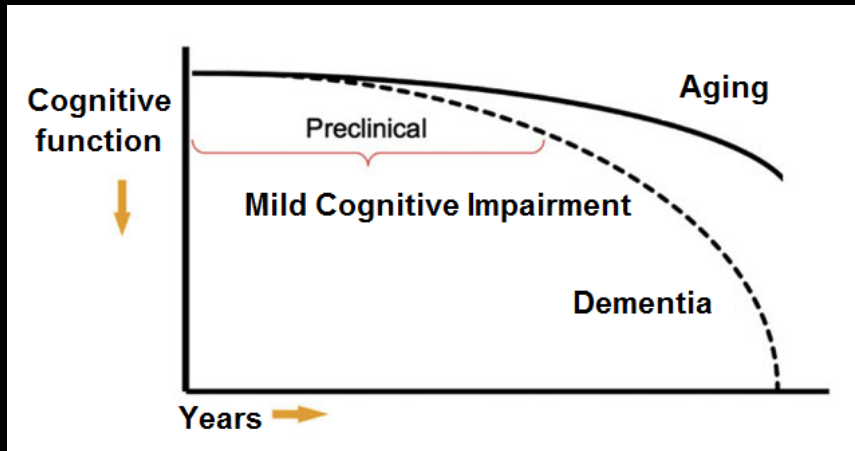
▽ = Faecal Calprotectin

Jeong, 2019

Fecal calprotectin

Sequencing, proteomics, metabolomics, biomarkers and isolation of microbiota.

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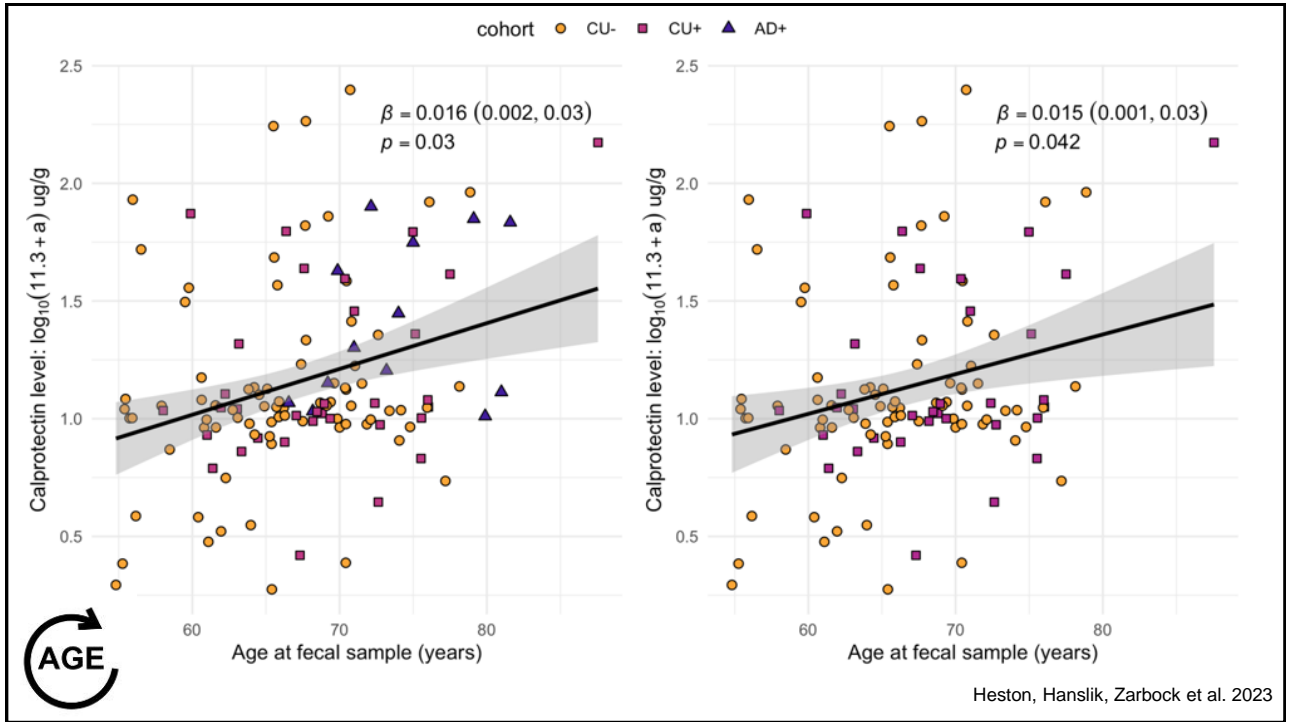


Rey AVLT
TRAILS B

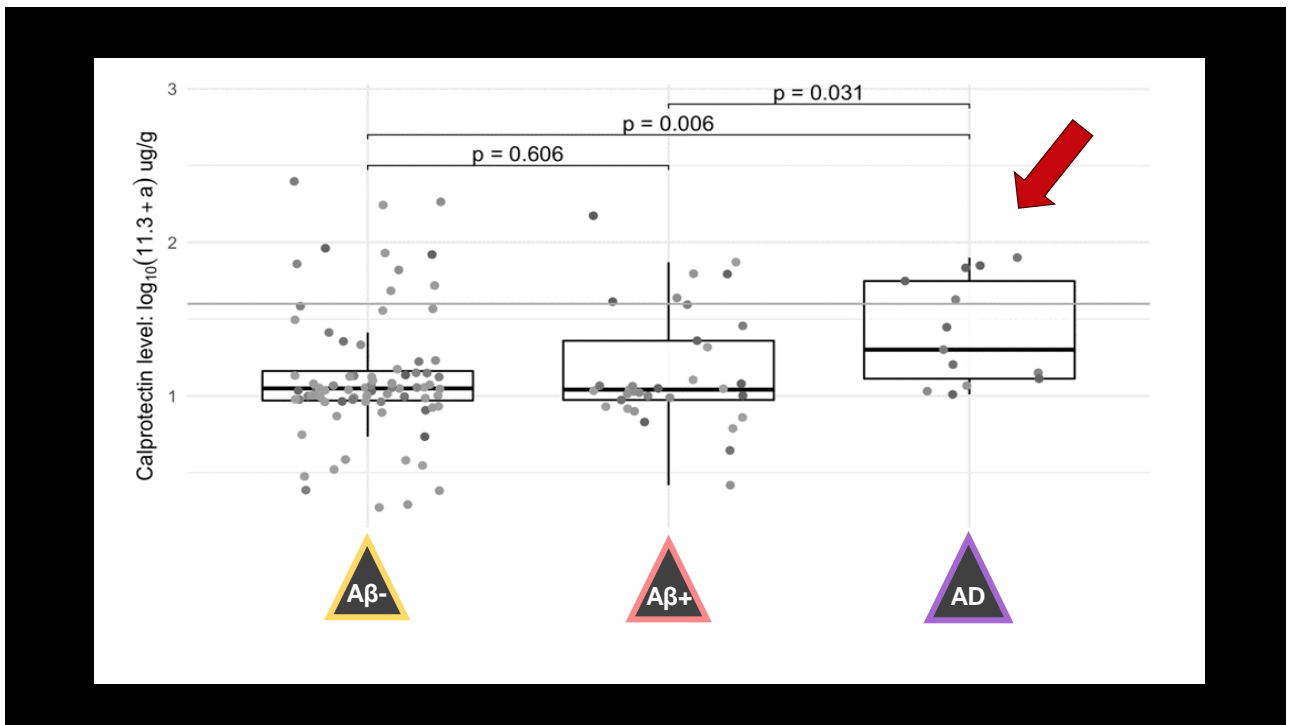
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	CU- N = 79	CU+ N = 33	AD-dementia N = 13	P-value
Age, years	65.92 (5.97)	68.92 (6.34)	73.90 (5.09)	<0.001
Sex				0.9
Female	50 (63%)	22 (67%)	9 (69%)	
Male	29 (37%)	11 (33%)	4 (31%)	
Education, years	16.41 (2.71)	16.18 (2.26)	14.69 (2.02)	0.054
BMI, kg/m ²	27.95 (4.90)	27.68 (5.22)	26.43 (3.63)	0.8
Bristol score	3.89 (1.19)	3.82 (1.21)	3.92 (1.38)	0.9

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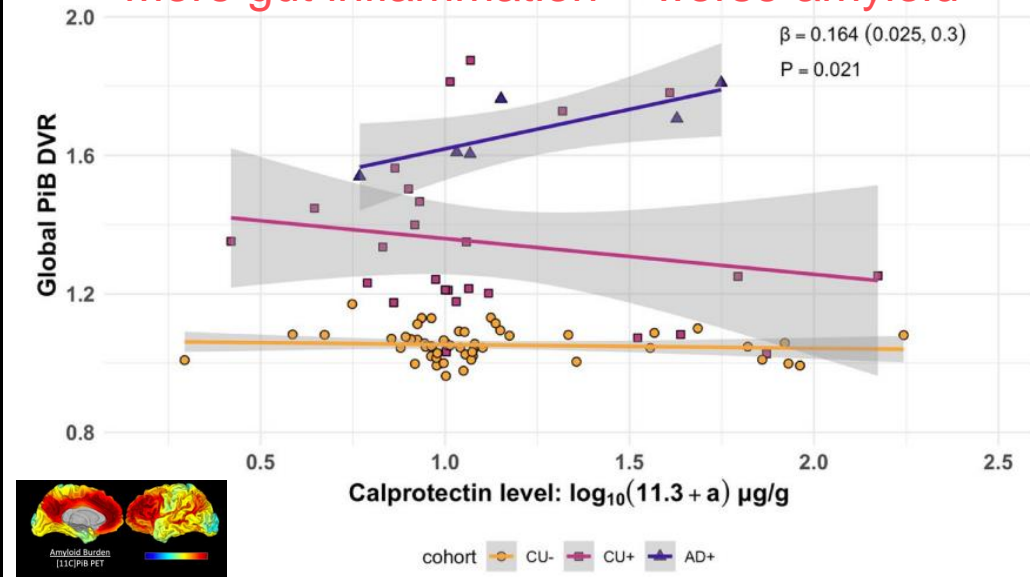


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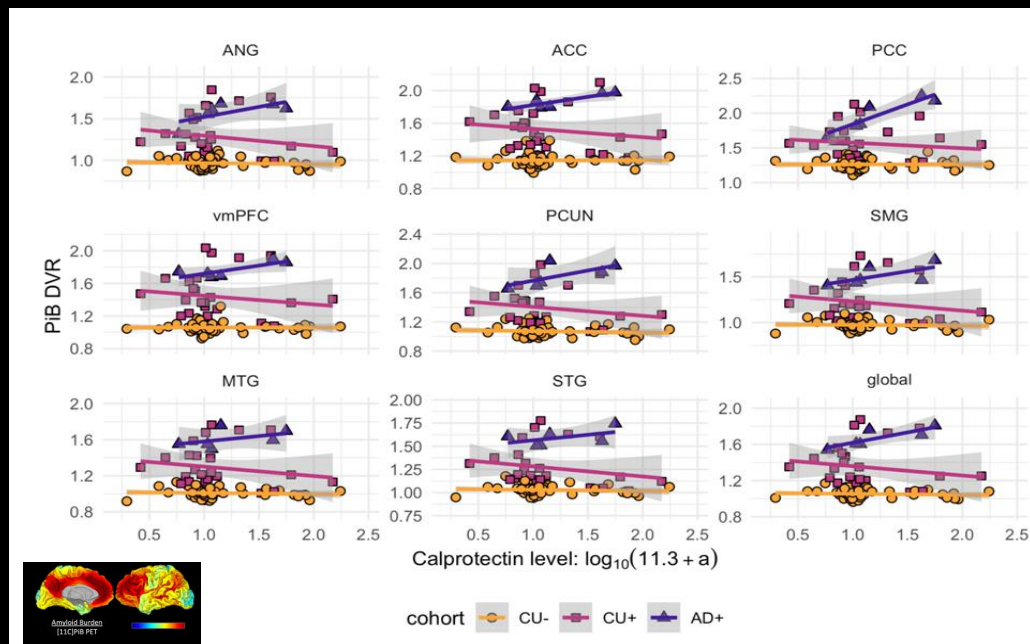


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More gut inflammation = worse amyloid

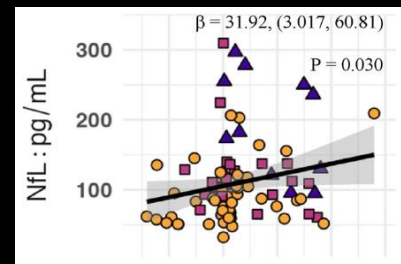
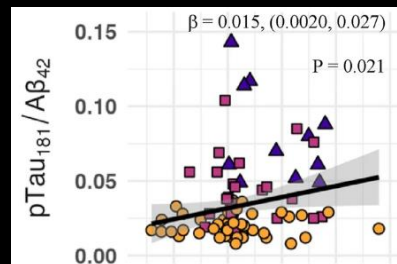
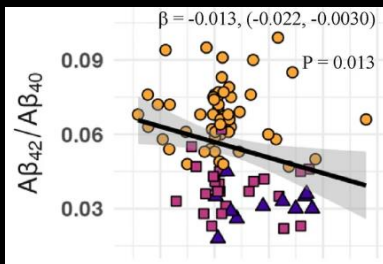


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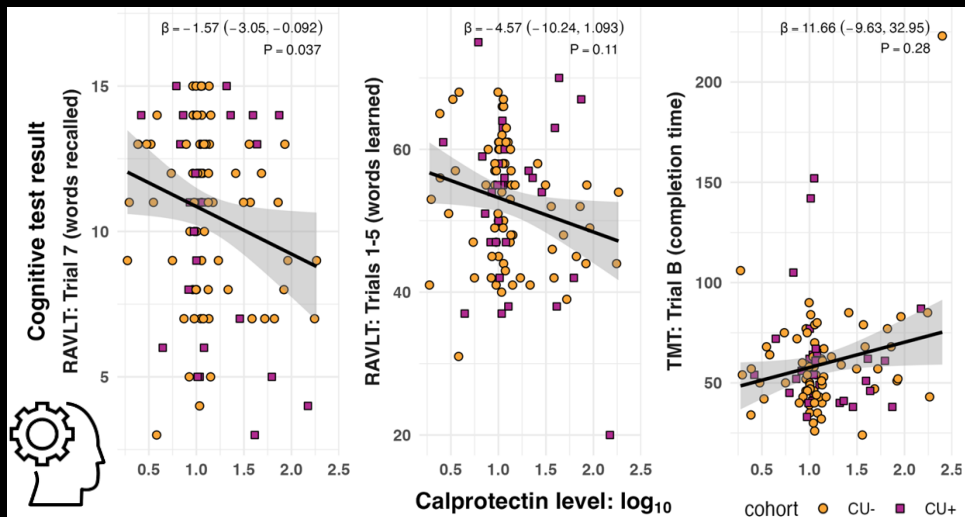


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More gut inflammation = greater amyloid burden and more neurodegeneration



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More gut inflammation = worse long delay recall

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Implications

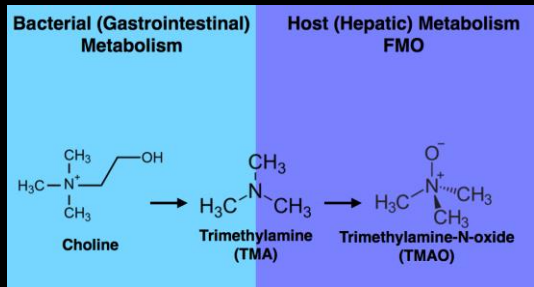
- Increases with age
- Observed in AD
- (May) exacerbate pathology
- Associates with cognition
- Permeability?



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Metabolites

- Metabolites produced/influenced by gut microbiota

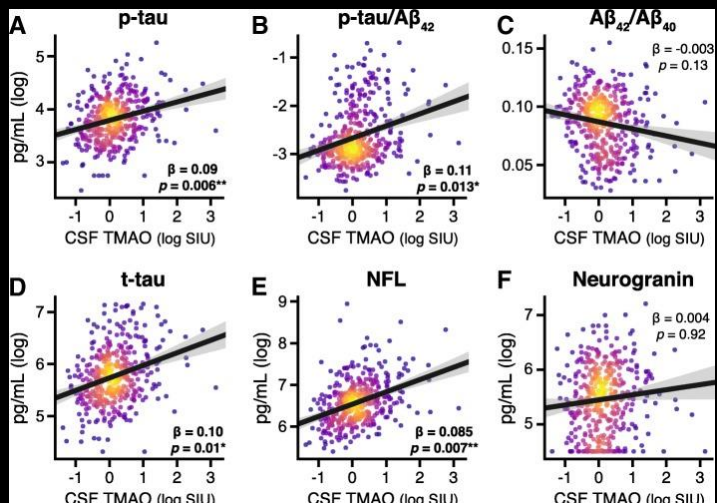
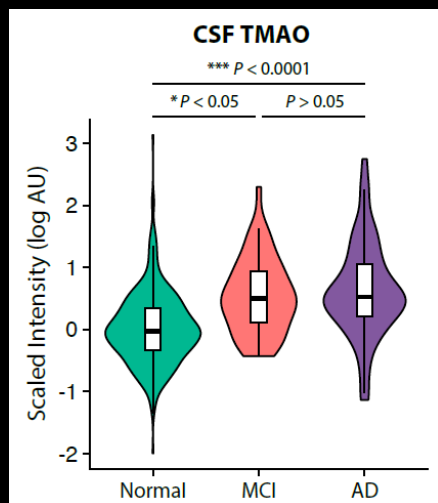


Trimethylamine-oxide (TMAO)

TMAO generation is initiated upon ingestion of foods rich in phosphatidylcholine, choline, and carnitine.

Courtesy F. Rey

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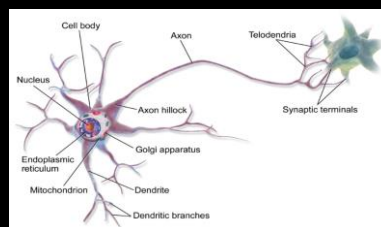
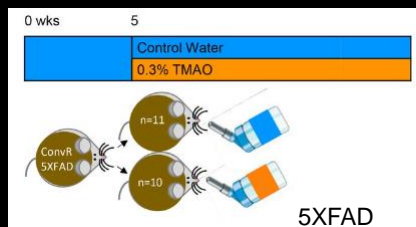


Vogt et al. 2018

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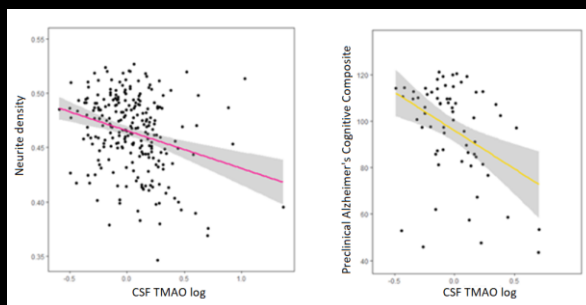
Katie Zarbock



TMAO-treated animals had significantly reduced neurite density in bilateral frontal association cortex, right amygdala, corpus callosum, and the internal capsule.



Jason Moody, PhD



Other metabolites... β -Hydroxybutyrate, imidazole propionate, phenol sulfate, N-formylmethionine associated with cognition and CSF biomarkers

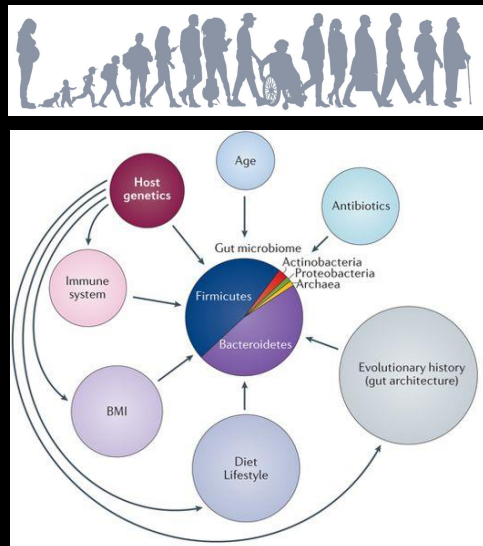
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What factors impact the gut microbiome?

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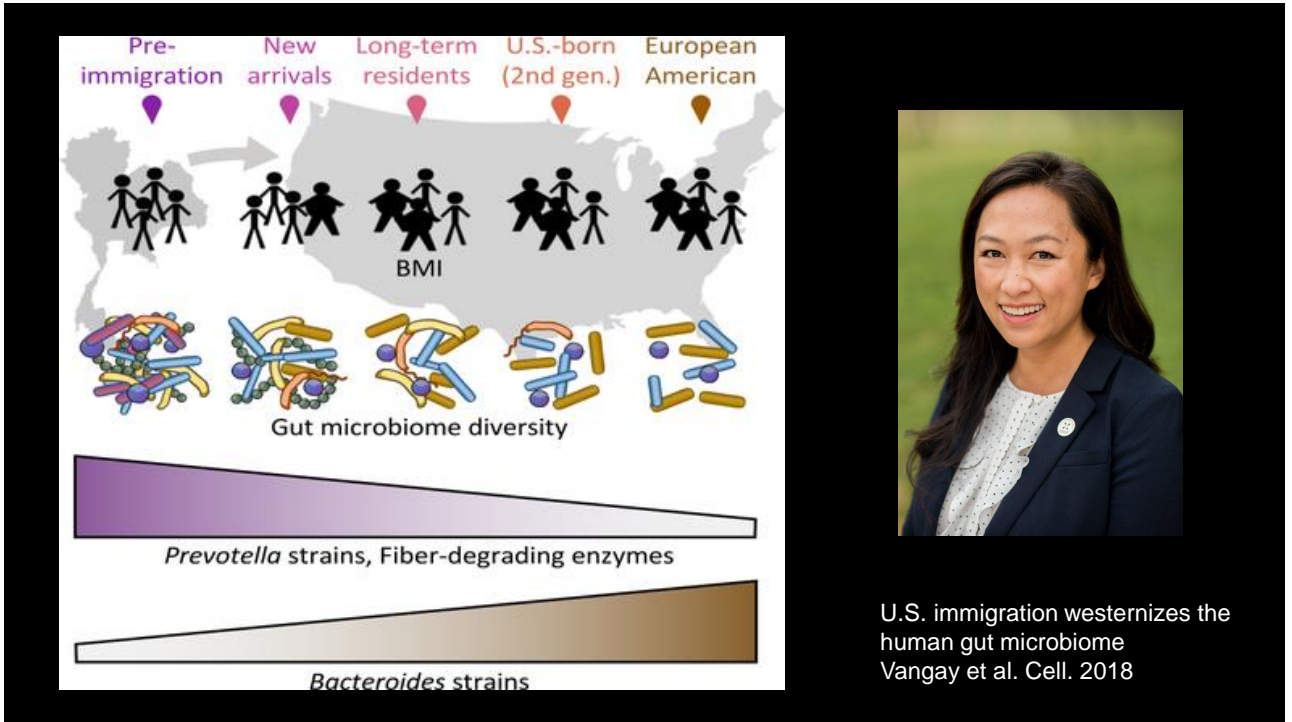
Modifiers of the gut microbiome

- Genetics
- Early life experiences
- Age
- Travel/Residence
- Diet/Alcohol
- Spouse/family members
- Antibiotics
- Probiotics
- Gastric bypass
- Disease
- Pets



Nat. Rev. Microbiol. (2011)

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How do we modify the gut microbiome?

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Faecal microbiota transplantation

Symbiotic microbial consortia

Microbiota-derived proteins and metabolites

Engineered symbiotic bacteria

Diet and prebiotics

Sorbara & Pamer, Nature Reviews Microbiology, 2022

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Self-reported dietary data suggest that the number of unique plant species that a person consumes is associated with microbial diversity.

> 30 per week

AMERICAN GUT BY THE NUMBERS

MAY 2012 MAY 2018

FIVE+ YEARS RUNNING

DISCOVERING THE TYPES OF MICROBES AND MICROBIOMES FOUND IN CITIZEN SCIENTISTS

SITES IN EUROPE AUSTRALIA SINGAPORE

8 COUNTRIES & TERRITORIES REPRESENTED

15,096 SAMPLES

11,336 HUMAN PARTICIPANTS

MORE THAN 467 MILLION 16S GENE FRAGMENTS SEQUENCED

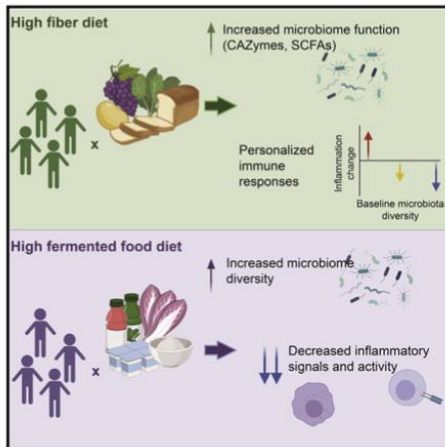
AMERICAN GUT UC San Diego

<https://msystems.asm.org/content/3/3/e00031-18>

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Gut-microbiota-targeted diets modulate human immune status

Graphical abstract



Authors

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In brief

A prospective randomized multiomics study in humans investigating the longitudinal effects of a high-fiber or fermented-food diet shows their differential effects on the diversity of the microbiome, with the latter having a noticeable impact on reducing inflammatory markers and modulating immune responses.



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Take aways

- The gut microbiome is related to numerous health outcomes, including brain outcomes.
- Mechanisms are multifactorial, non-exclusive.
- Gut microbiome provides multiple opportunities for intervention.
- Possibilities for better understanding of disease mechanisms
- Caveats: the gut microbiome is complex, FMT (nor probiotics) are not likely to provide a “miracle cure”.

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