

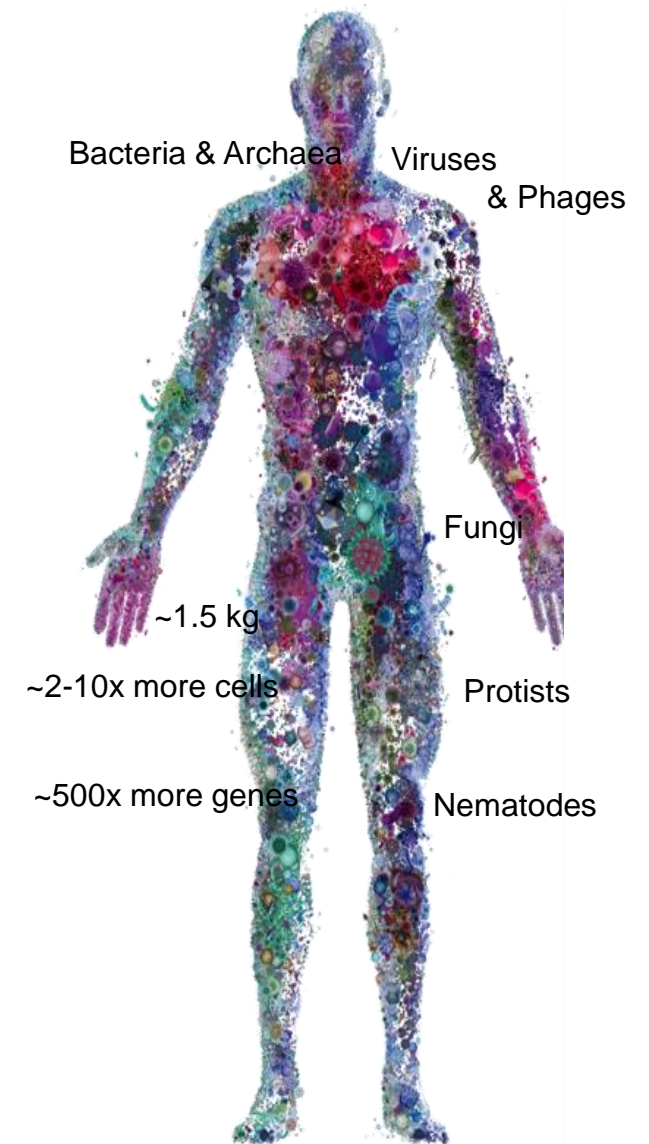
Microbiome and The Social Brain – How the Gut and the Brain Mature Together

Dr. Siobhain O'Mahony

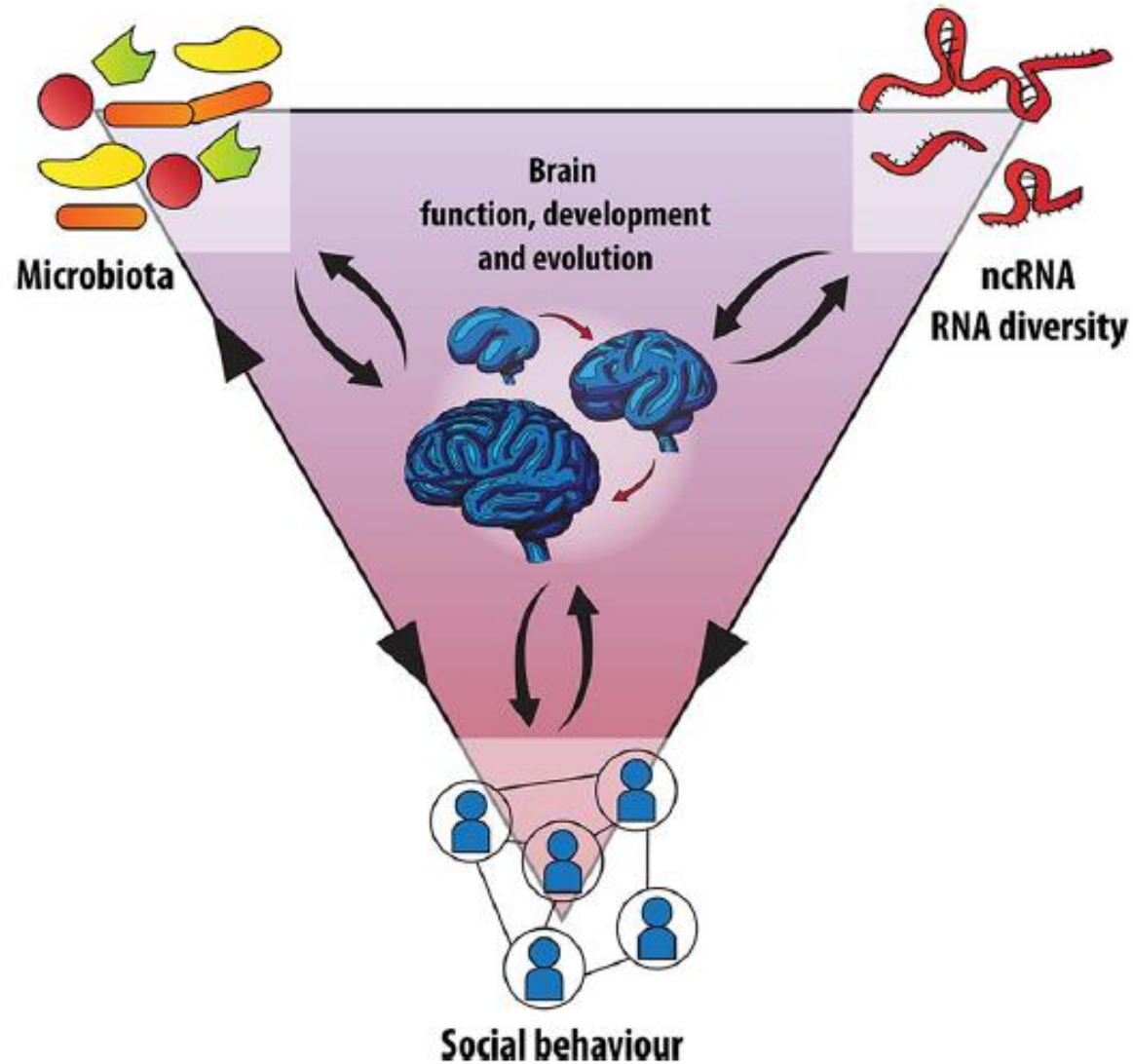
**Snr. Lecturer, Department of Anatomy and
Neuroscience, APC Microbiome Ireland,
University College Cork
Cork
Ireland**

- The gut microbiome
 - Friends with social benefits
 - Development of the microbiome-gut brain axis
 - Influential factors
- Social development
 - Role of microbiome
 - Pre-clinical studies
 - Human studies
- Key messages

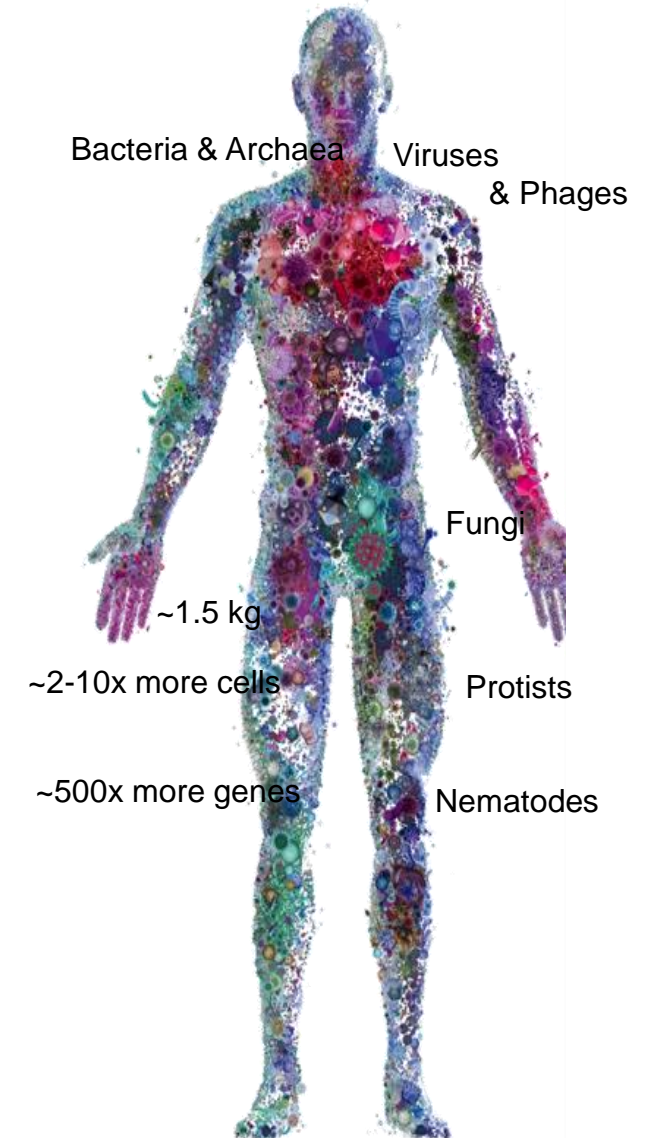
Human Holobiont



The Gut Microbiome-Friends with Social Benefits

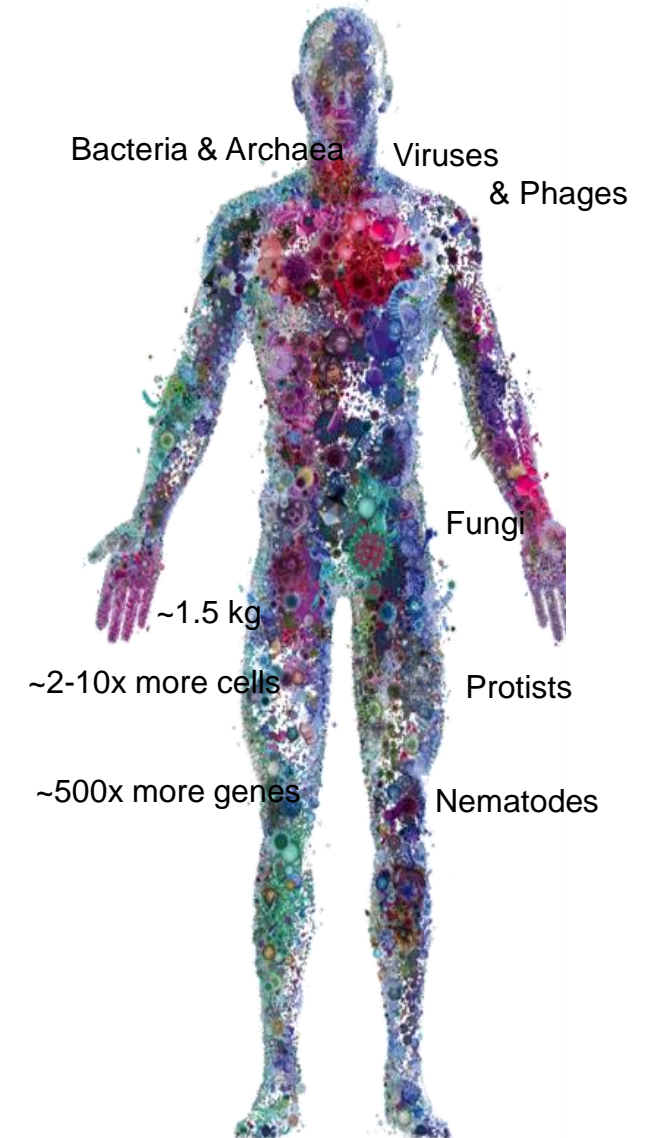
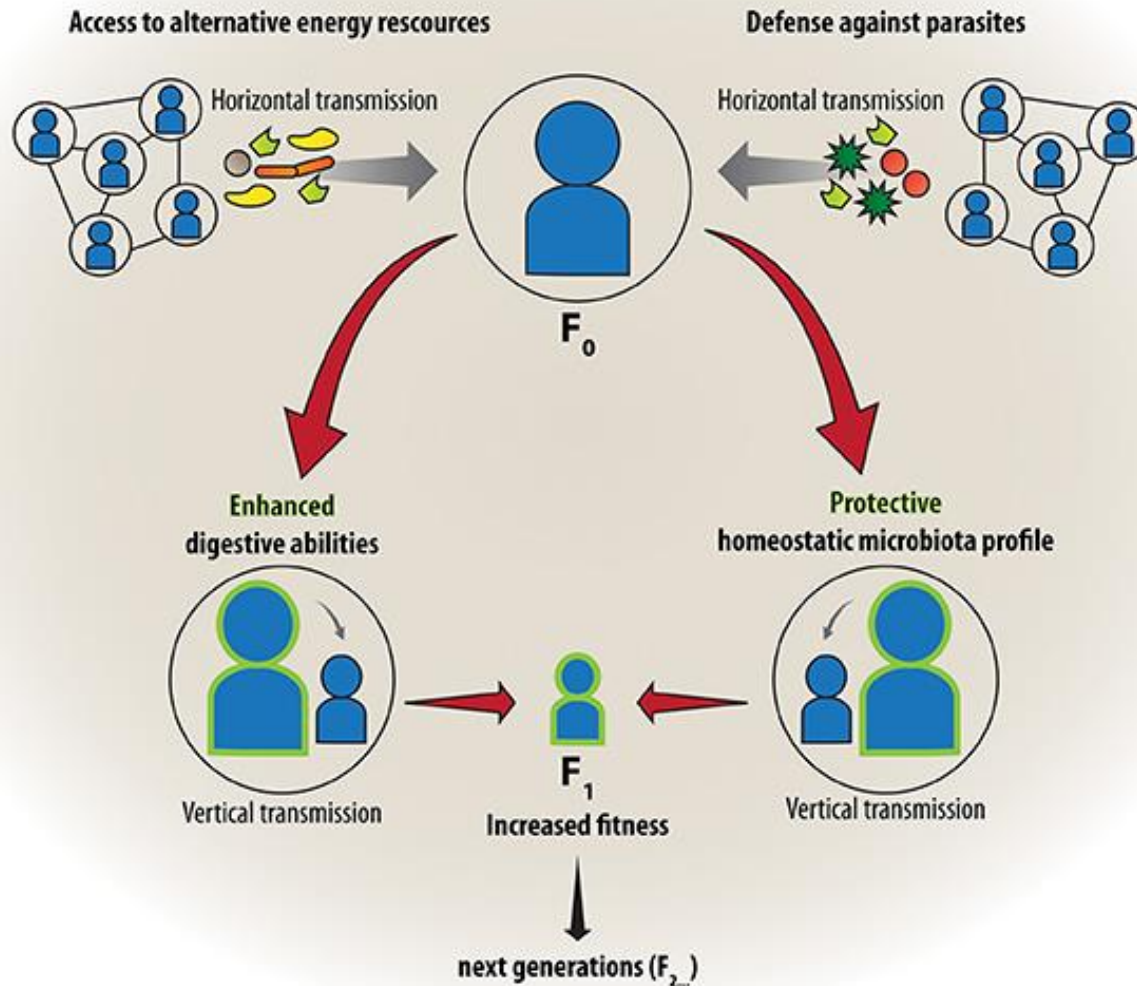


Human Holobiont



The Gut Microbiome-Friends with Social Benefits

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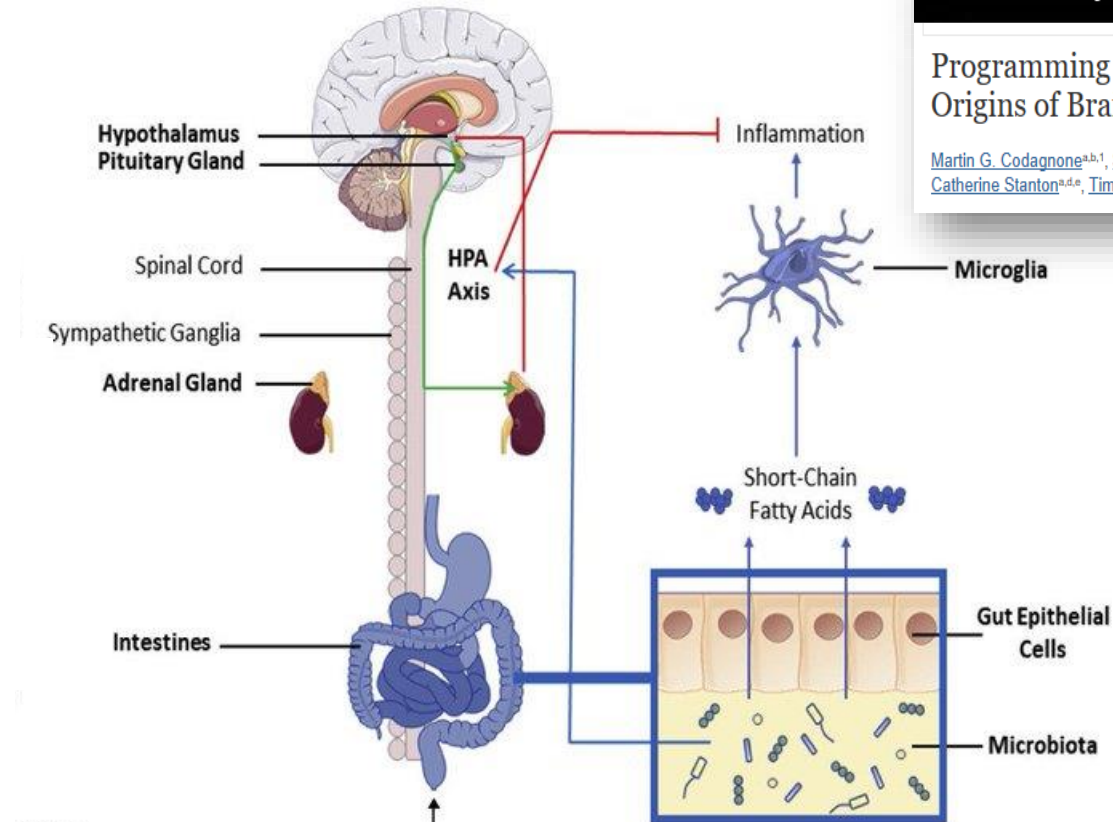
Programming the Microbiome-Gut-Brain Axis

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Programming Bugs: Microbiota and the Developmental Origins of Brain Health and Disease

[Martin G. Codagnone^{a,b,1}](#), [Simon Spichak^{a,b,1}](#), [Siobhain M. O'Mahony^{a,b}](#), [Olivia F. O'Leary^{a,b}](#), [Gerard Clarke^{a,c,d}](#),
[Catherine Stanton^{a,d,e}](#), [Timothy G. Dinan^{a,c}](#), [John F. Cryan^{a,b,*}](#)



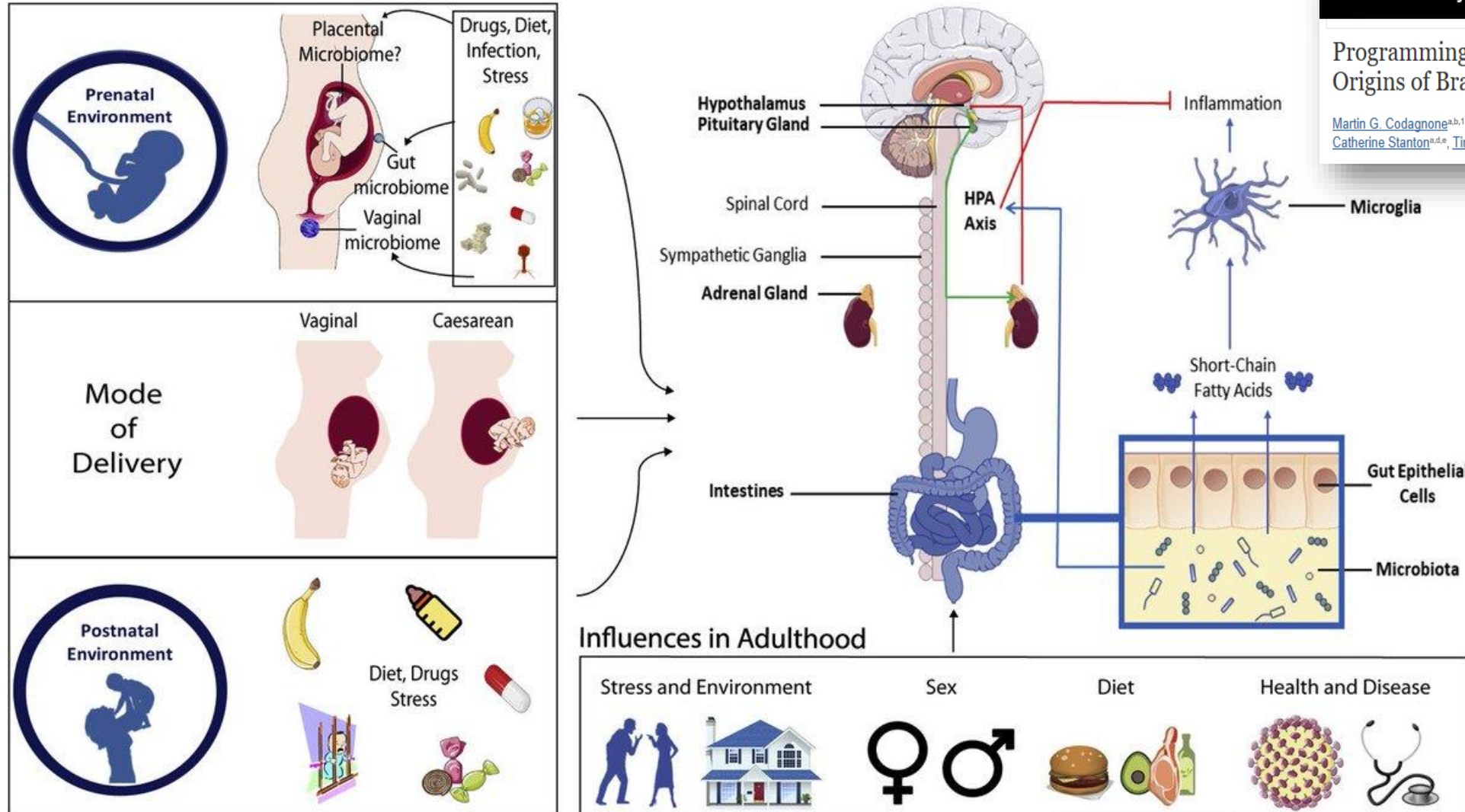
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Programming Bugs: Microbiota and the Developmental Origins of Brain Health and Disease

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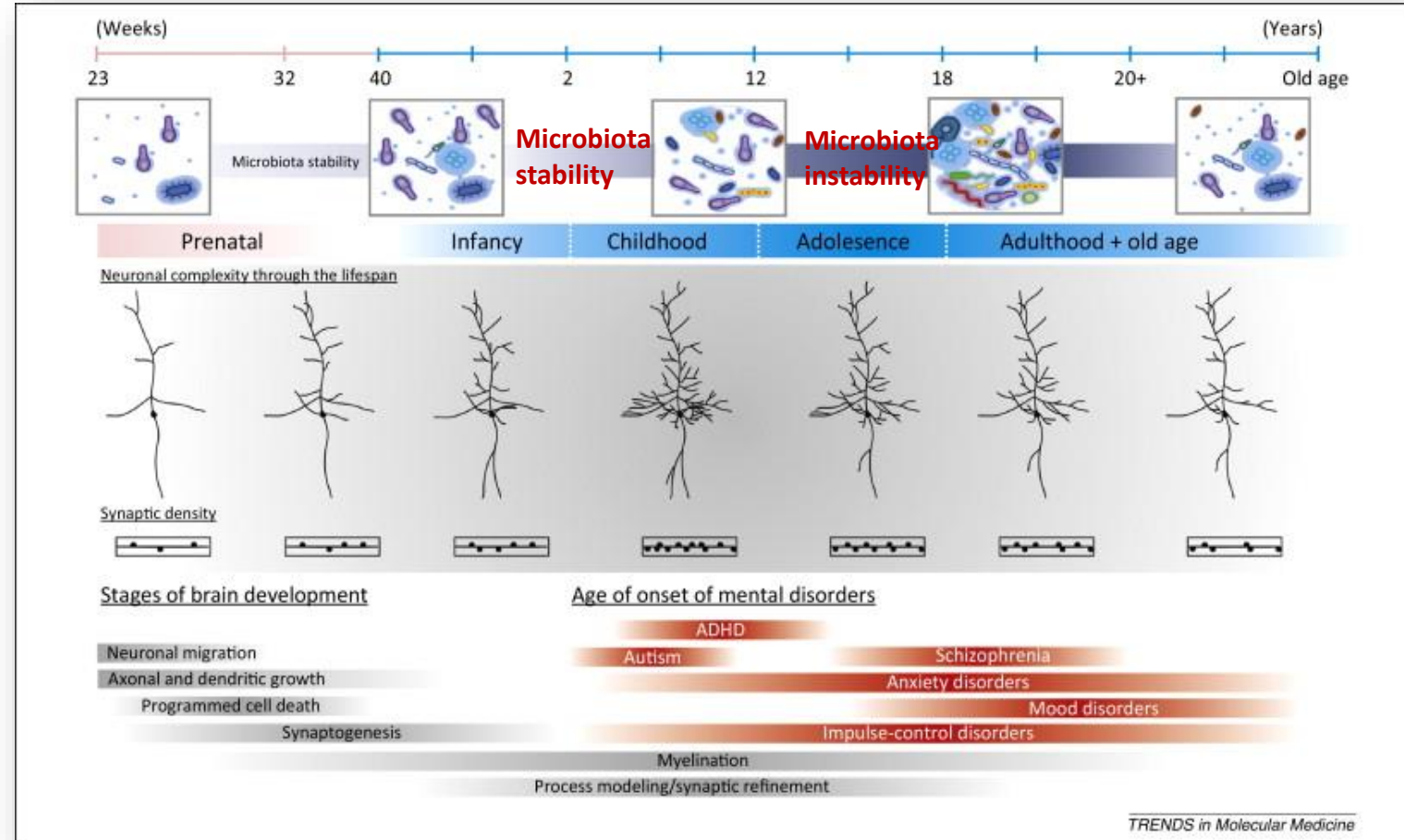
Parallel Development of the Gut Microbiome and the Brain

Brain Development

- ❖ Brain size at birth – 1/3 of an adult; doubles in 1st y; and increases 35% by 3rd y
- ❖ Synaptic density quadruples in 1st and will be 150-200% greater than an adult by 3rd y- to be pruned/selectively strengthened

Microbiome Development

- ❖ Virtually sterile at birth
- ❖ 6-12 mo – increase in α -diversity and reduced β -diversity; microbiomes capable capacity to metabolise nutrients necessary for brain growth
- ❖ 2nd and 3rd y – increase in certain phyla
- ❖ 3 y old – almost reached structural composition and functional capacity of adulthood and is less amenable to change



Neither develop in a vacuum!

Social-Emotional Developmental Milestones

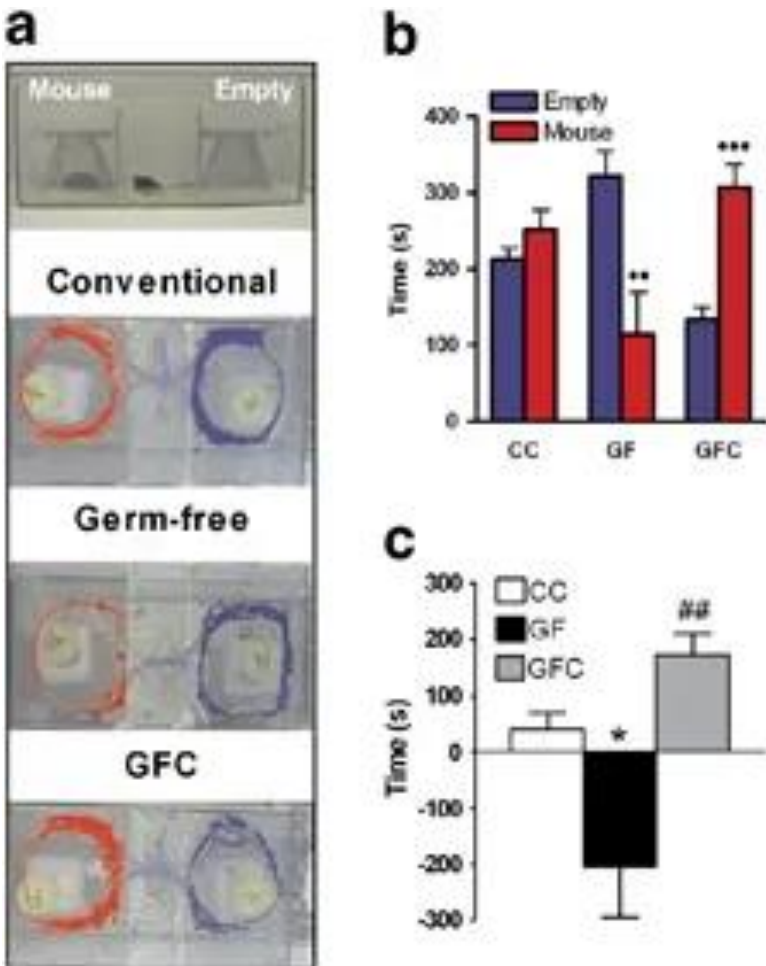
DEVELOPMENTAL MILESTONES



- ❖ <6 mo – Spontaneously orient and respond to social stimuli, beginning of attachment to caregiver
- ❖ 6 mo – Emergence of babbling, pointing, eye contact; attachment has been established
- ❖ 6-12 mo – Joint attention, imitation, orientation to own name, first words, use of gestures
- ❖ 12 mo – 2.5 y – Phrase speech, expansion of vocabulary, instrumental helping, expression of concern, comforting others, self-awareness, self-regulation, impulse control and empathetic understanding
- ❖ 3-5 y – Emergence of theory of mind skills, attributing mental states, social understanding

Microbiome is Essential for Social Development in Mice

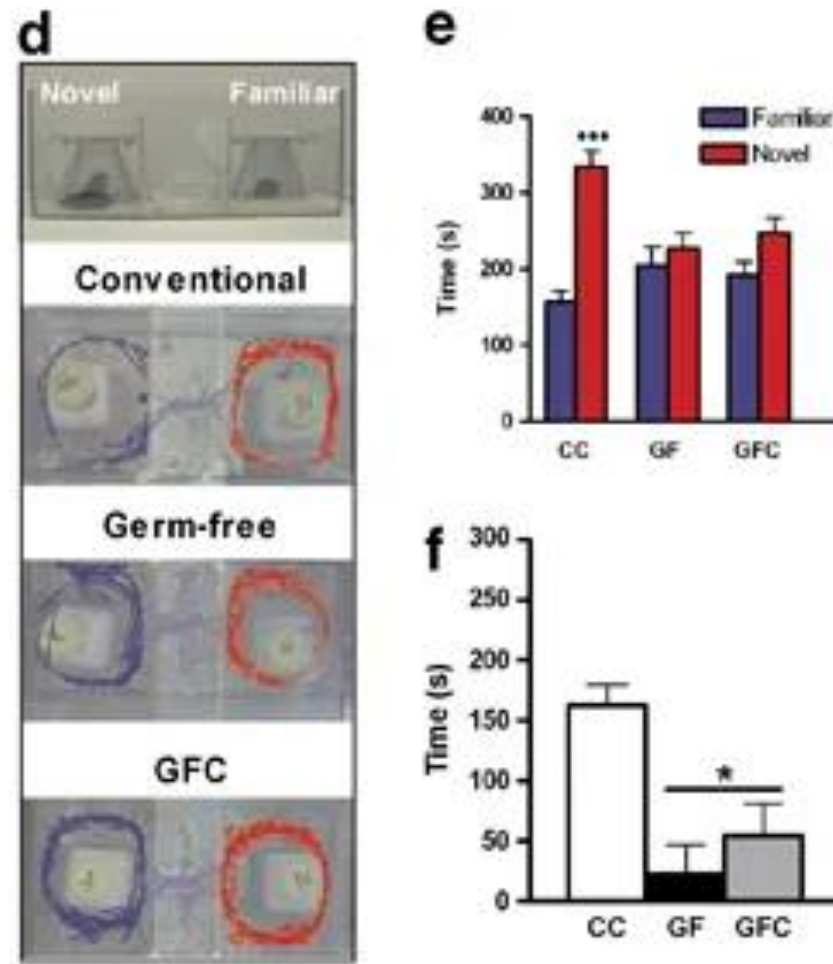
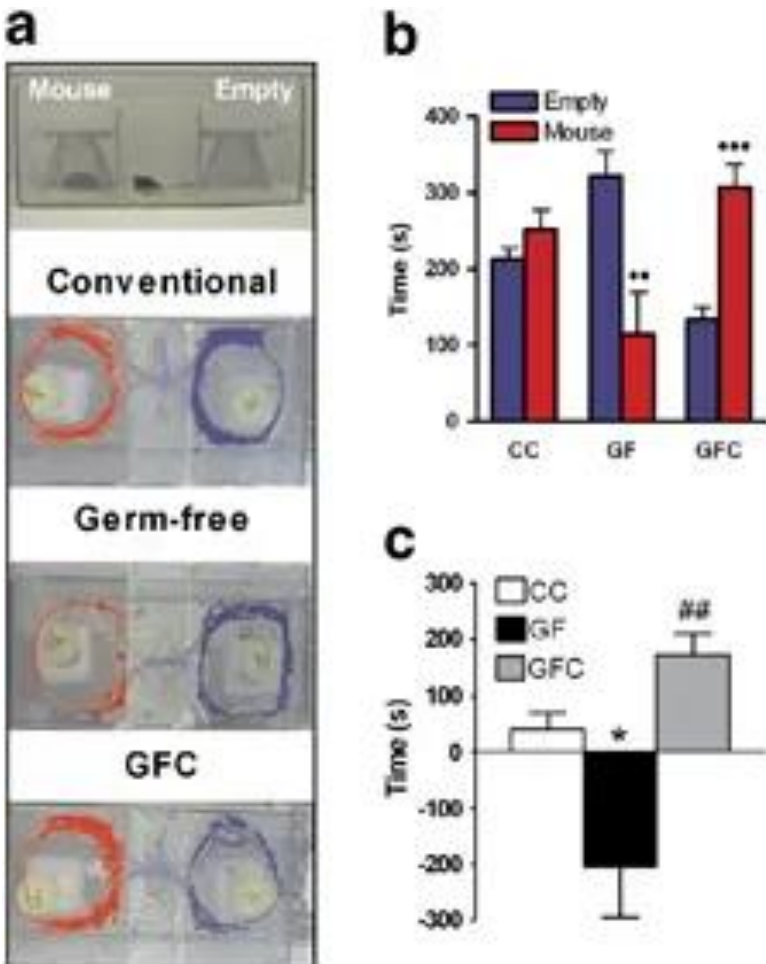
Social Preference



Microbiome is Essential for Social Development in Mice

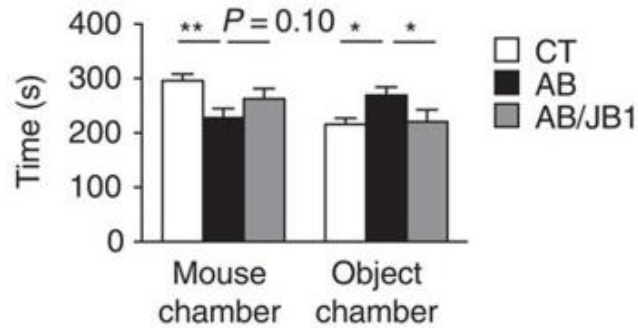
Social Preference

Social Recognition

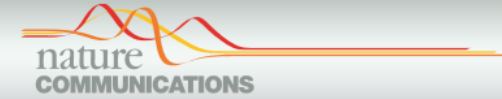
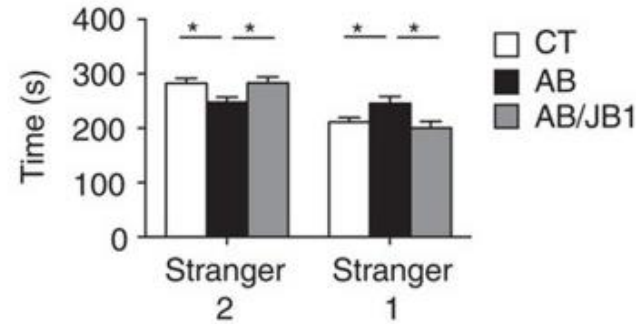


Perinatal Antibiotic Affects Microbiome, Social Behaviour, Brain Tight Junctions and Cytokines

Social Preference



Social Recognition



ARTICLE

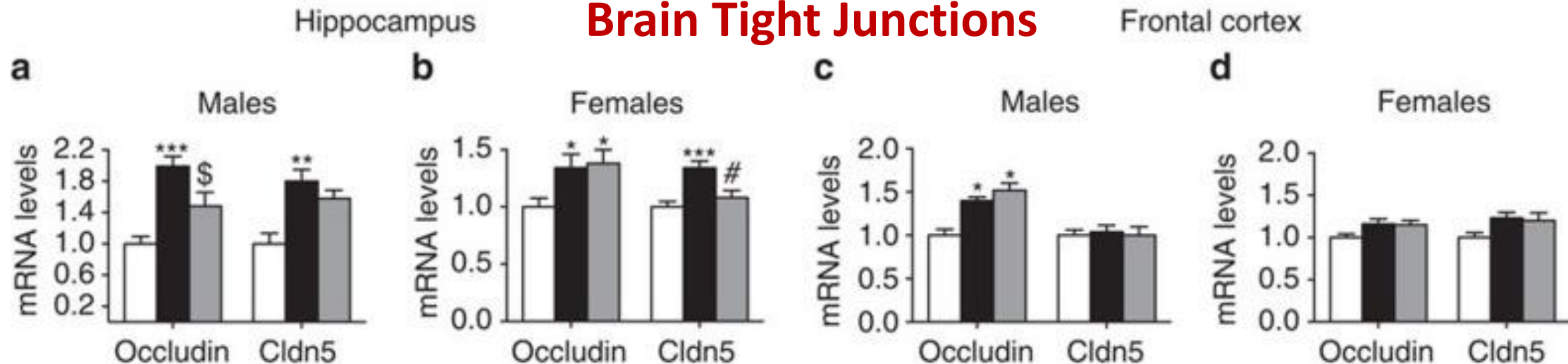
Received 15 Sep 2016 | Accepted 24 Feb 2017 | Published 4 Apr 2017

DOI: 10.1038/ncomms15062 OPEN

Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior

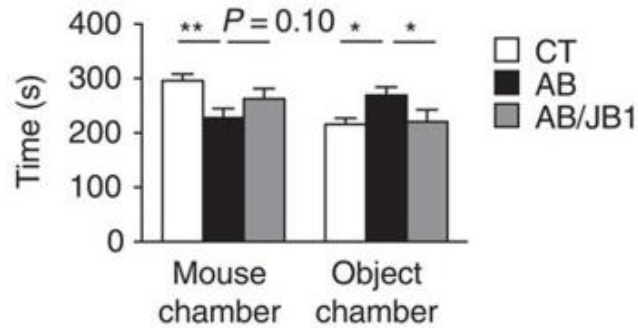
Sophie Leclercq^{1,2}, Firoz M. Mian¹, Andrew M. Stanis¹, Laure B. Bindels³, Emmanuel Cambier⁴, Hila Ben-Amram⁵, Omry Koren⁵, Paul Forsythe^{1,6} & John Bienenstock^{1,2}

Brain Tight Junctions

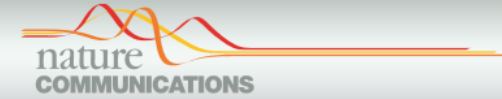
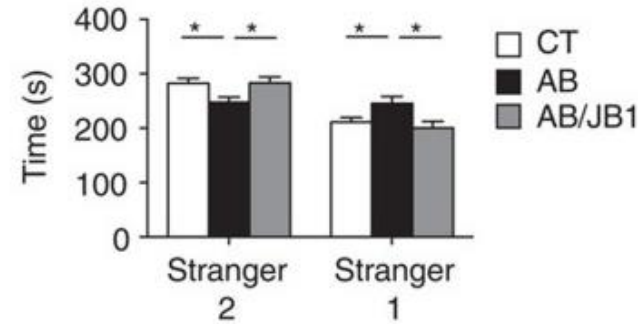


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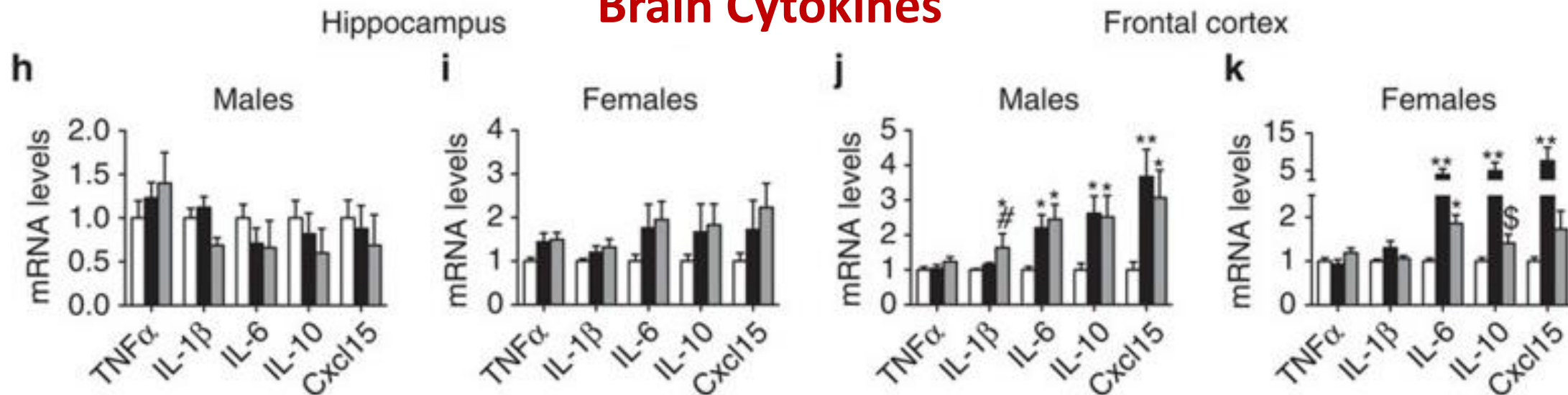
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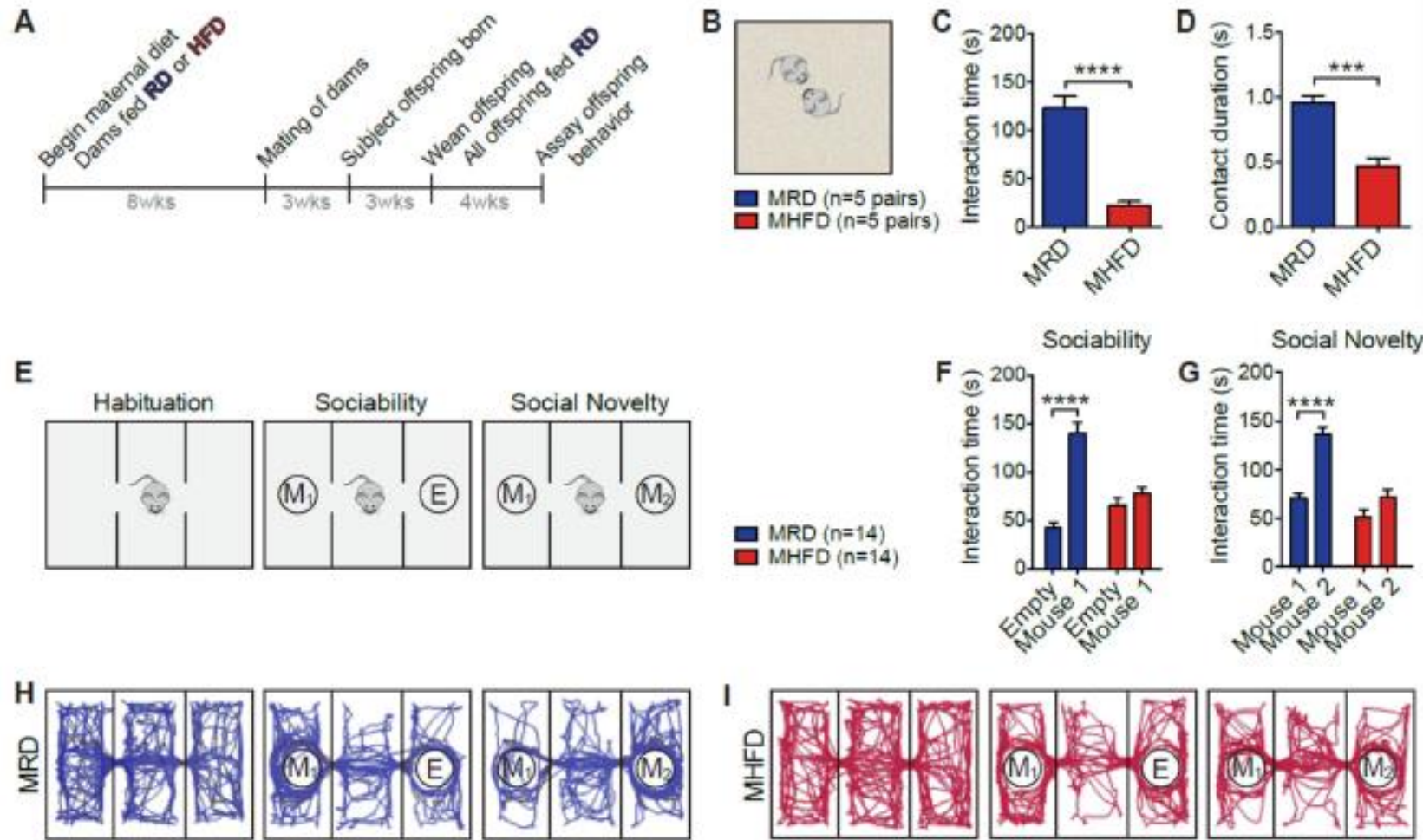
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Brain Cytokines



Maternal high fat diet induces social deficits in offspring



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Cell. Author manuscript; available in PMC 2017 June 16.

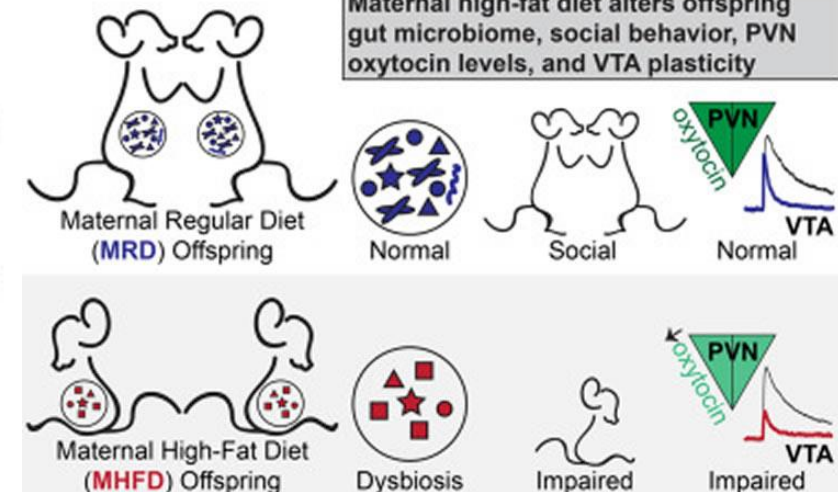
Published in final edited form as:

Cell. 2016 June 16; 165(7): 1762–1775. doi:10.1016/j.cell.2016.06.001.

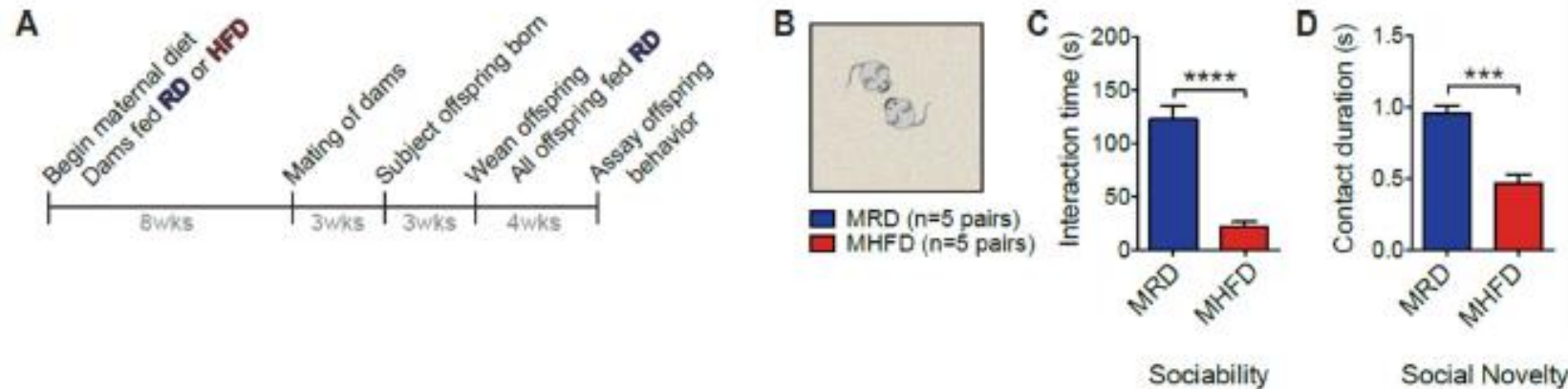
Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring

Shelly A. Buffington^{1,2}, Gonzalo Viana Di Prisco^{1,2}, Thomas A. Auchtung^{3,4}, Nadim J. Ajami^{3,4}, Joseph F. Petrosino^{3,4}, and Mauro Costa-Mattioli^{1,2,*}

Maternal high-fat diet alters offspring gut microbiome, social behavior, PVN oxytocin levels, and VTA plasticity



Maternal high fat diet induces social deficits in offspring



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Author manuscript

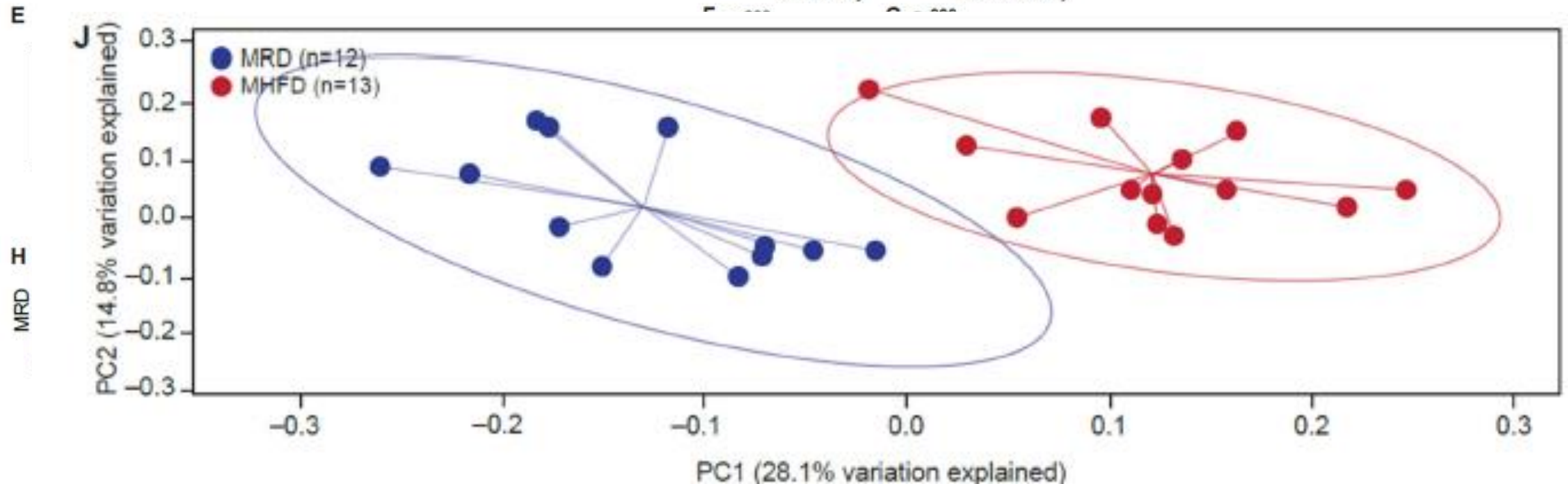
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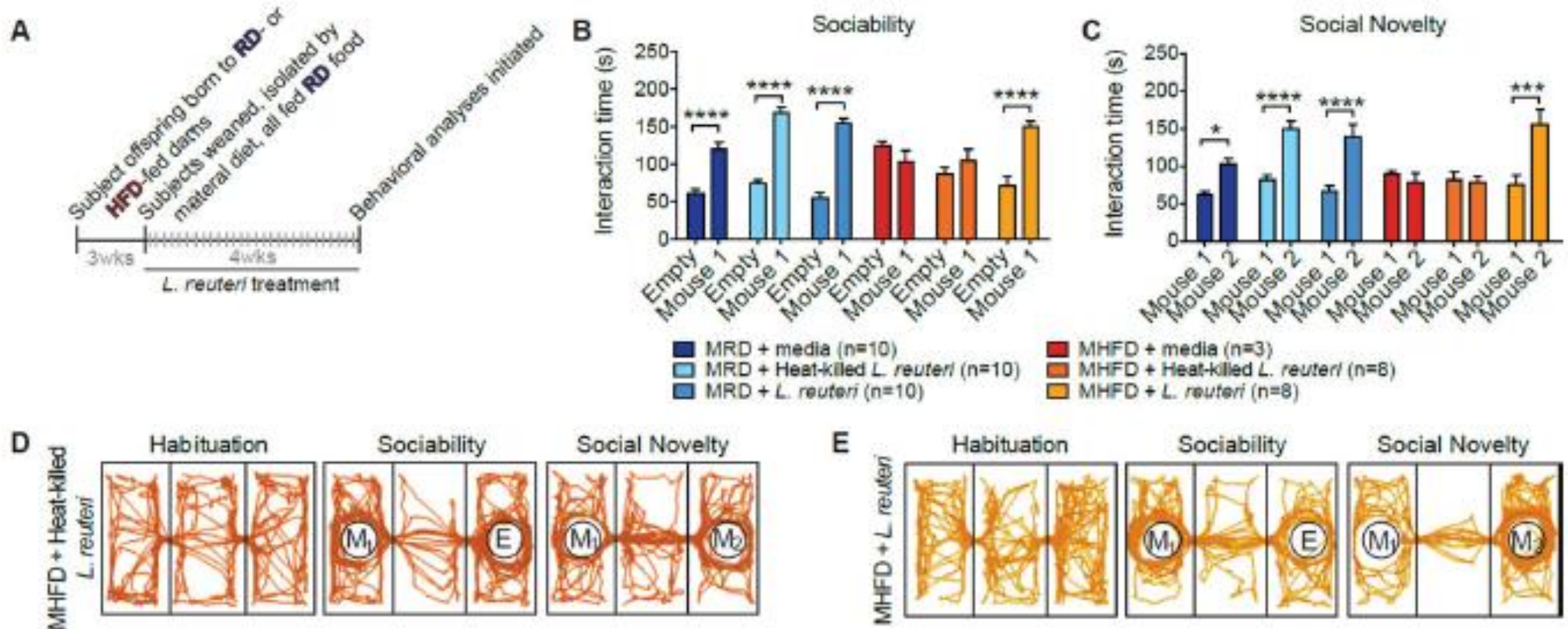
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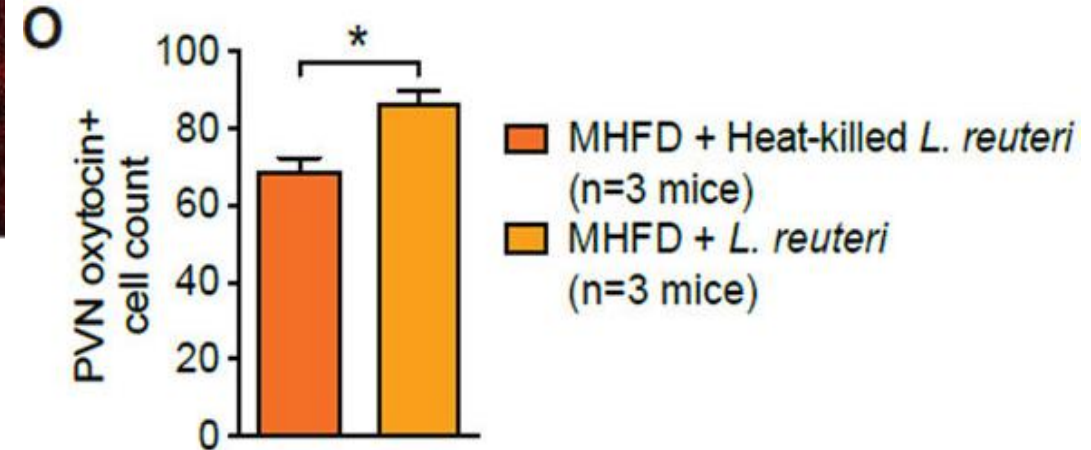
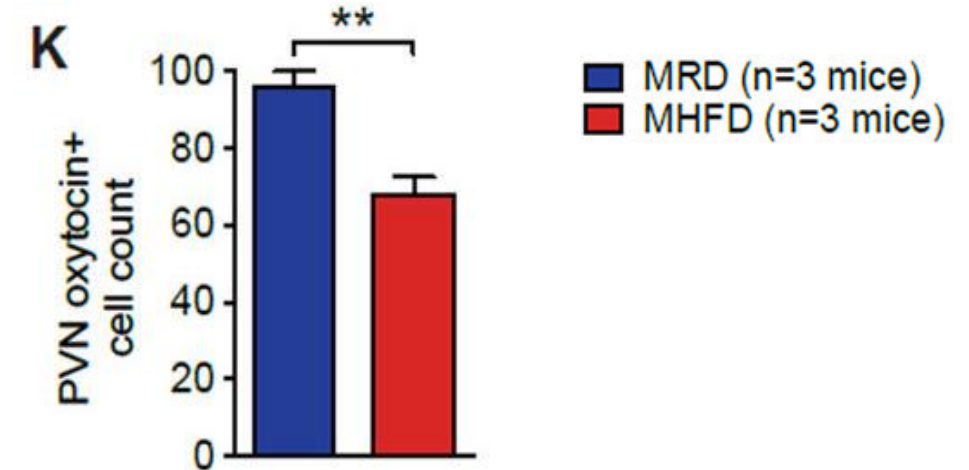
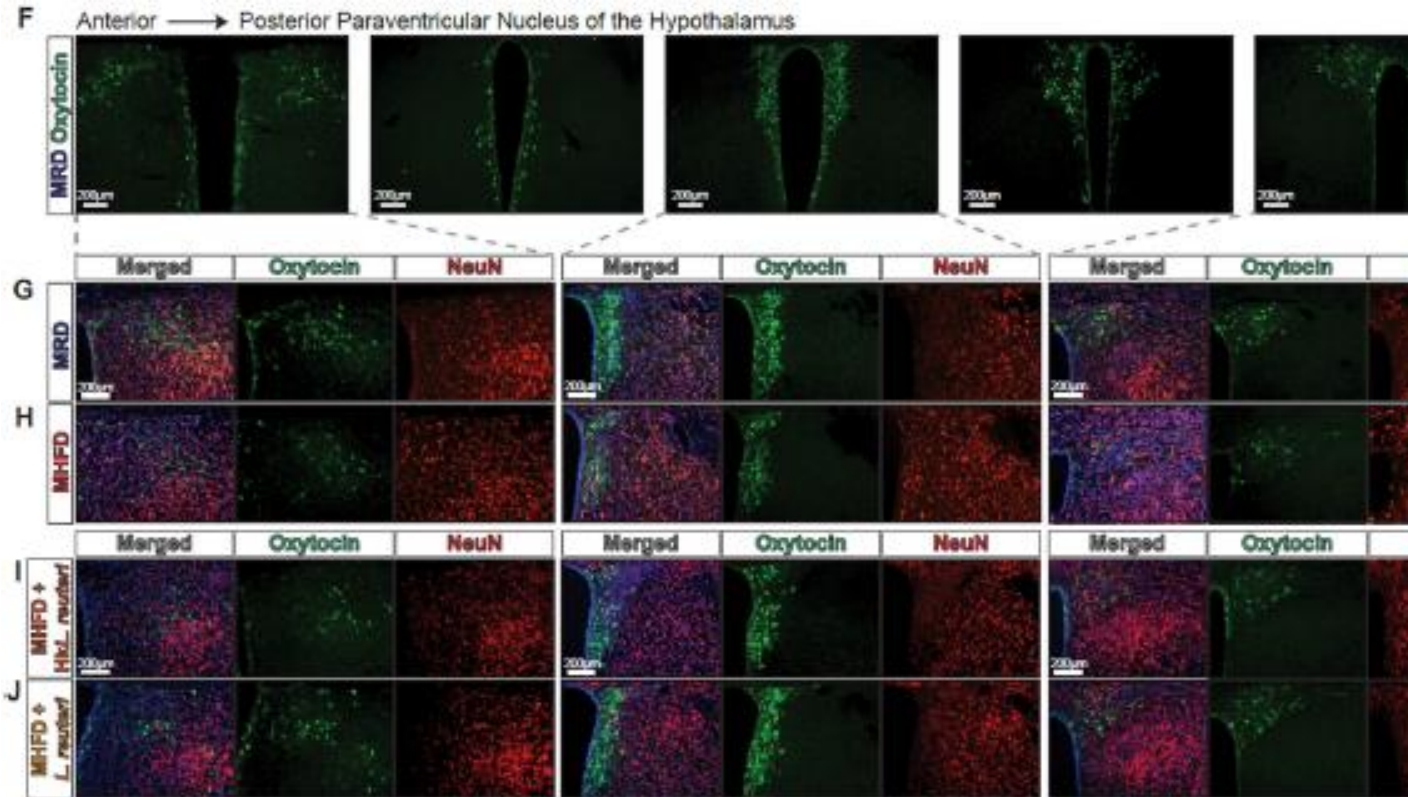


Microbial reconstitution reverses maternal diet-induced social deficits in offspring



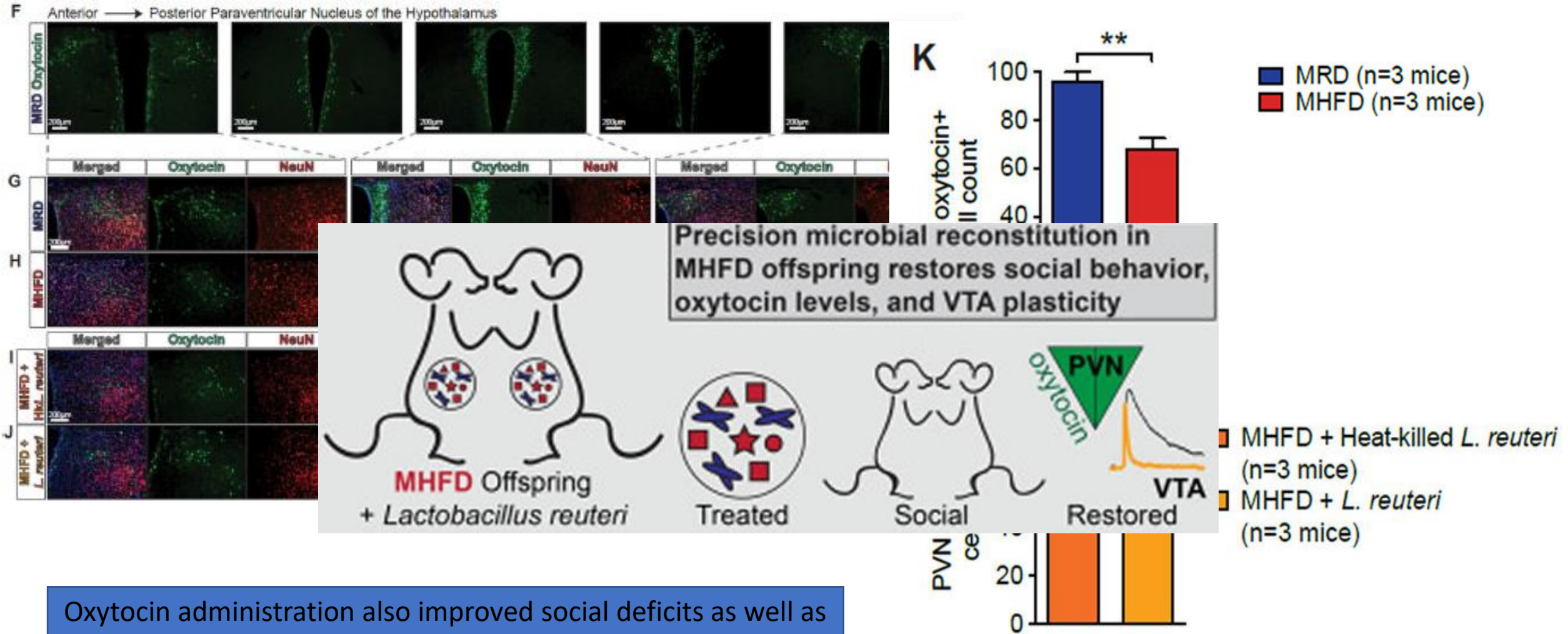
Co-housing MHFD offspring with MRD reduced impact and Fecal Microbiota from MRD, but not MHFD, Offspring Improves Germ-Free (GF) Recipient Social Behavior

Microbial reconstitution reverses maternal diet-induced oxytocin deficits in offspring



Oxytocin administration also improved social deficits as well as synaptic deficits

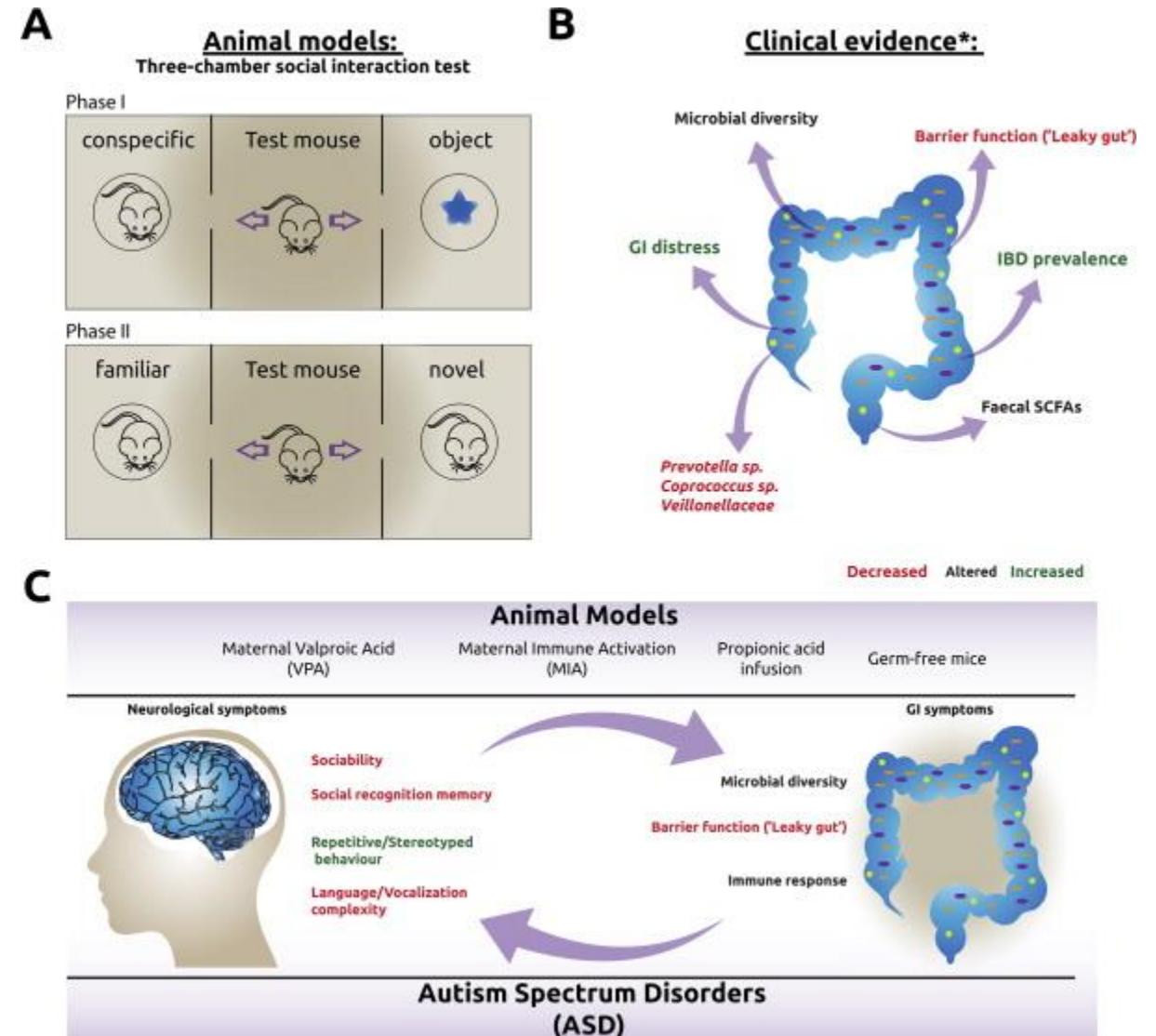
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Human Social Disorders and the Microbiome-Evidence from ASD studies

- ❖ Autism spectrum disorders (ASD)-neurodevelopmental disorders
 - ❖ Deficits in social interaction, communication, presence of limited, repetitive stereotyped interests and behaviors
- ❖ link between ASDs and the microbiota-gut-brain axis
- ❖ Expanding on the evolutionary theory-when microbiota are associated with adverse health-inhibition of social development-reduce transmission
 - ❖ Specific genetic variants might be linked to microbiota-related social deficits



Gut Microbiome and Autism

Desulfovibrio species are potentially important in regressive autism

Sydney M. Finegold

Infectious Diseases Section (111 F), VA Medical Center West Los Angeles, Los Angeles, CA 90073, United States
Departments of Medicine and of Microbiology, Immunology, and Molecular Genetics, UCLA School of Medicine, Los Angeles, CA, United States

Received: January 13, 2011; Accepted: April 23, 2011; Published Online: May 18, 2011



Mol Autism. 2013; 4: 42.
Published online 2013 Nov 4. doi: [10.1186/2040-2392-4-42](https://doi.org/10.1186/2040-2392-4-42)

PMCID: PMC382800

Increased abundance of *Sutterella* spp. and *Ruminococcus torques* in feces of children with autism spectrum disorder

Ly Wang,¹ Claus T Christophersen,² Michael J Soric,¹ Jacobus P Gerber,¹ Manya T Angley,¹ and Michael A Conlon¹

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Reduced Incidence of *Prevotella* and Other Fermenters in Intestinal Microflora of Autistic Children

Dae-Wook Kang^{1,3}, Jin Gyoon Park^{2,3}, Zehra Esra Ilhan¹, Garrick Wallstrom^{2,3}, Joshua LaBaer², James B. Adams⁴, Rosa Krajmalnik-Brown^{1,3,5}

- Clostridia, *Desulfovibrio*, *Sutterella*, and *Bacteroidetes* -elevated in the stool of ASD children
- Firmicutes, *Prevotella*, and *Bifidobacter* -reduced in these patients
- Alterations in fecal concentrations of SCFAs (PPA) and urinary concentrations of amino acids and ammonia
- Conflicting reports exist-antibiotics and probiotics being useful



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Fecal Microbiota and Metabolome of Children with Autism and Pervasive Developmental Disorder Not Otherwise Specified

Maria De Angelis^{1*}, Maria Piccolo¹, Lucia Vannini^{2,3}, Sonya Siragusa¹, Andrea De Giacomo⁴, Diana Isabella Serrazzanetti², Fernanda Cristofori⁵, Maria Elisabetta Guerzoni³, Marco Gobetti¹, Ruggiero Francavilla⁵



GUT IN FOCUS: EXTENDED ABSTRACT

Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders

Early Probiotic Intervention Reduces Development of Neuropsychiatric Disorders

❖ 75 infants

- ❖ Randomized to *Lactobacillus rhamnosus* GG or placebo during the first 6 mo of life were followed-up for 13 y
- ❖ At the age of 13 y, ADHD or AS was diagnosed in 17.1% children in the placebo and none in the probiotic group
- ❖ *Bifidobacterium* species bacteria in feces during the first 6 mo of life was lower in affected children
- ❖ *Bifidobacteria* species are highly prevalent in early life particularly in breast-fed infants
 - ❖ Brain development
 - ❖ Stress system development



Prebiotic Intervention Improves Social Scores in Autistic Children

Grimaldi et al. *Microbiome* (2018) 6:133
<https://doi.org/10.1186/s40168-018-0523-3>

Microbiome

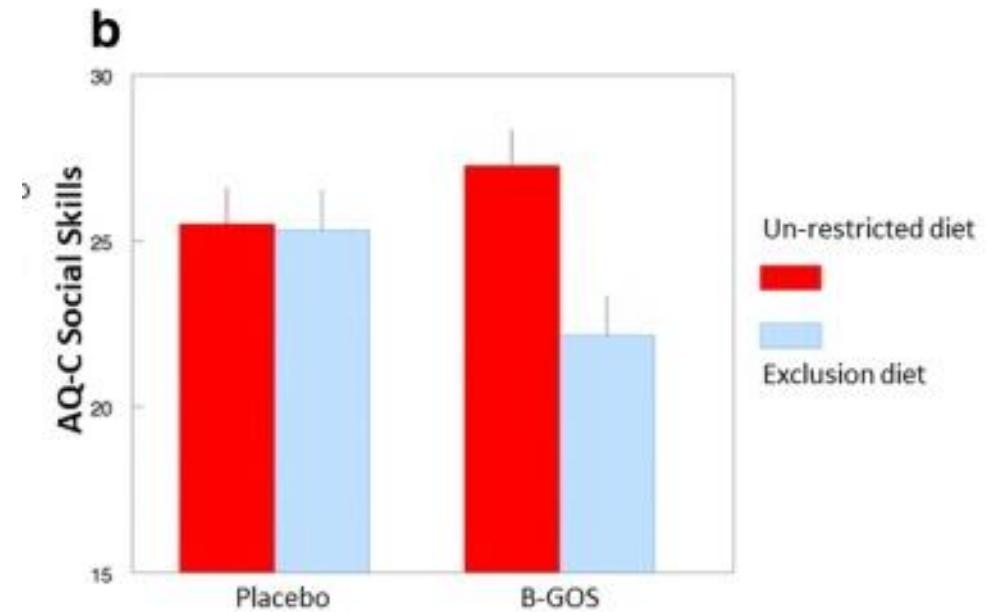
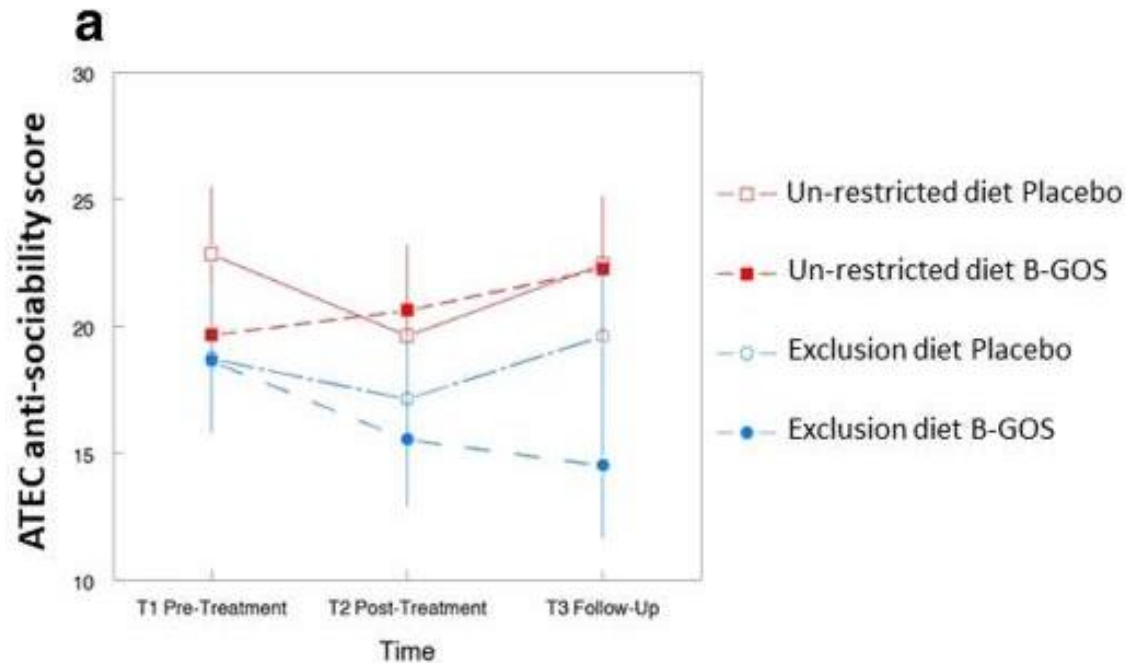
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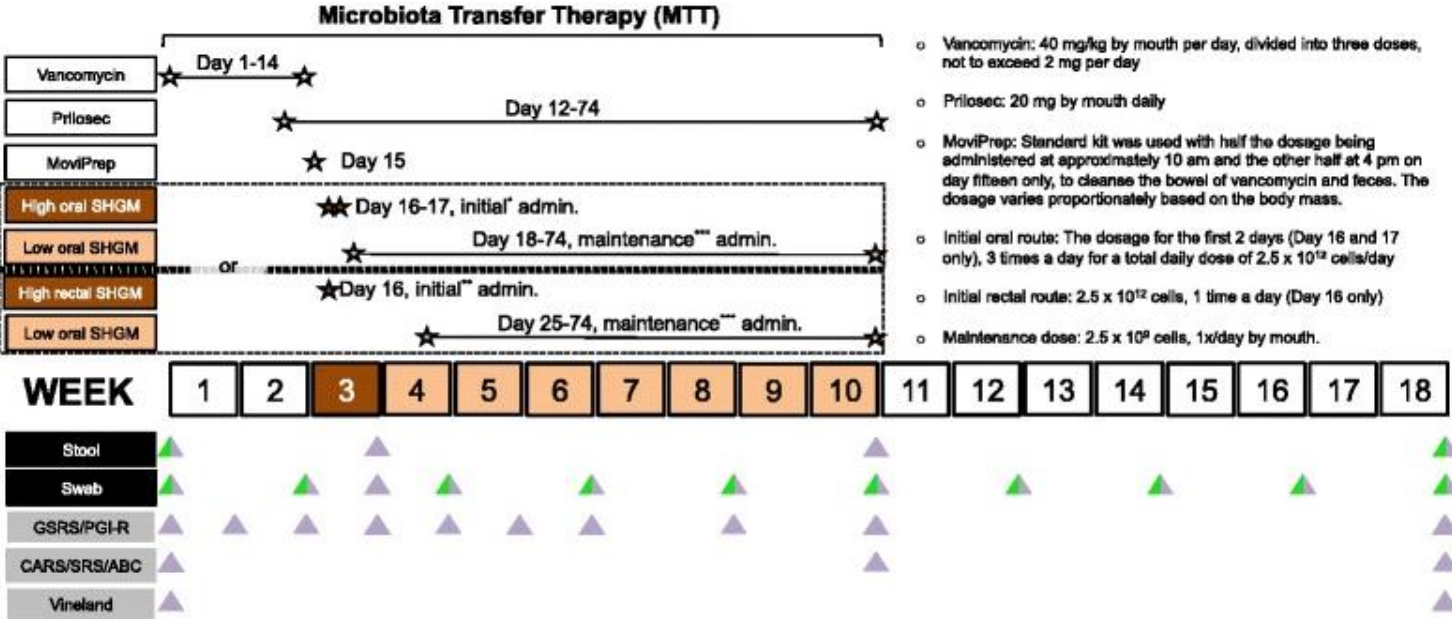
A prebiotic intervention study in children with autism spectrum disorders (ASDs)

Roberta Grimaldi^{1,2*}, Glenn R. Gibson¹, Jelena Vulevic², Natasa Giallourou³, Josué L. Castro-Mejía⁴, Lars H. Hansen⁵, E. Leigh Gibson⁶, Dennis S. Nielsen⁴ and Adele Costabile⁶



- ❖ Exclusion diets had a significant impact on gastrointestinal problems and a general trend of reduction in GI problems was reported after B-GOS®
- ❖ 23% of participants (two ASD following unrestricted diet and one under exclusion diet) benefited from B-GOS®

Microbiota Transfers Improves Gut and Autistic Symptoms in Children



Kang et al. *Microbiome* (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

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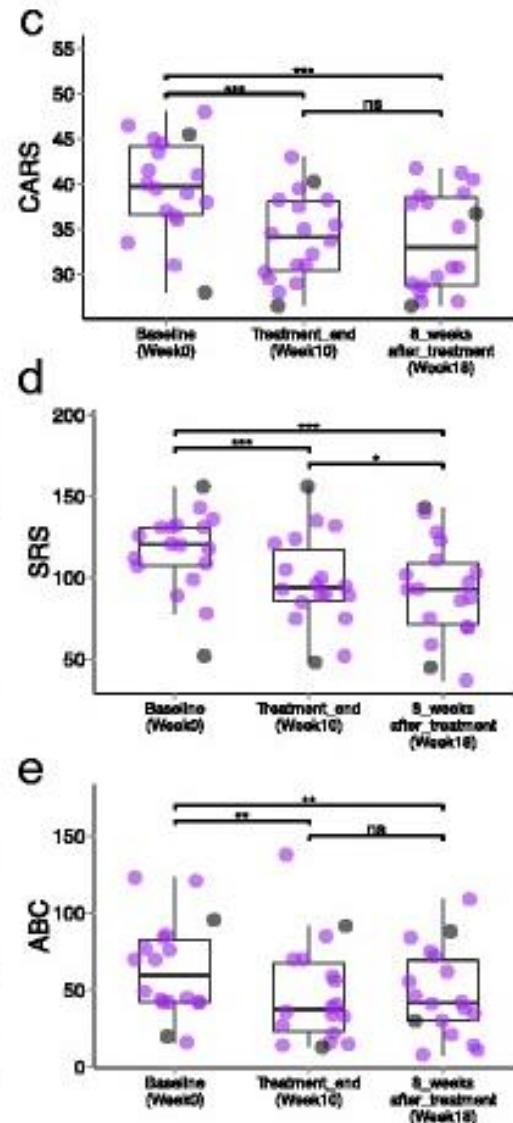
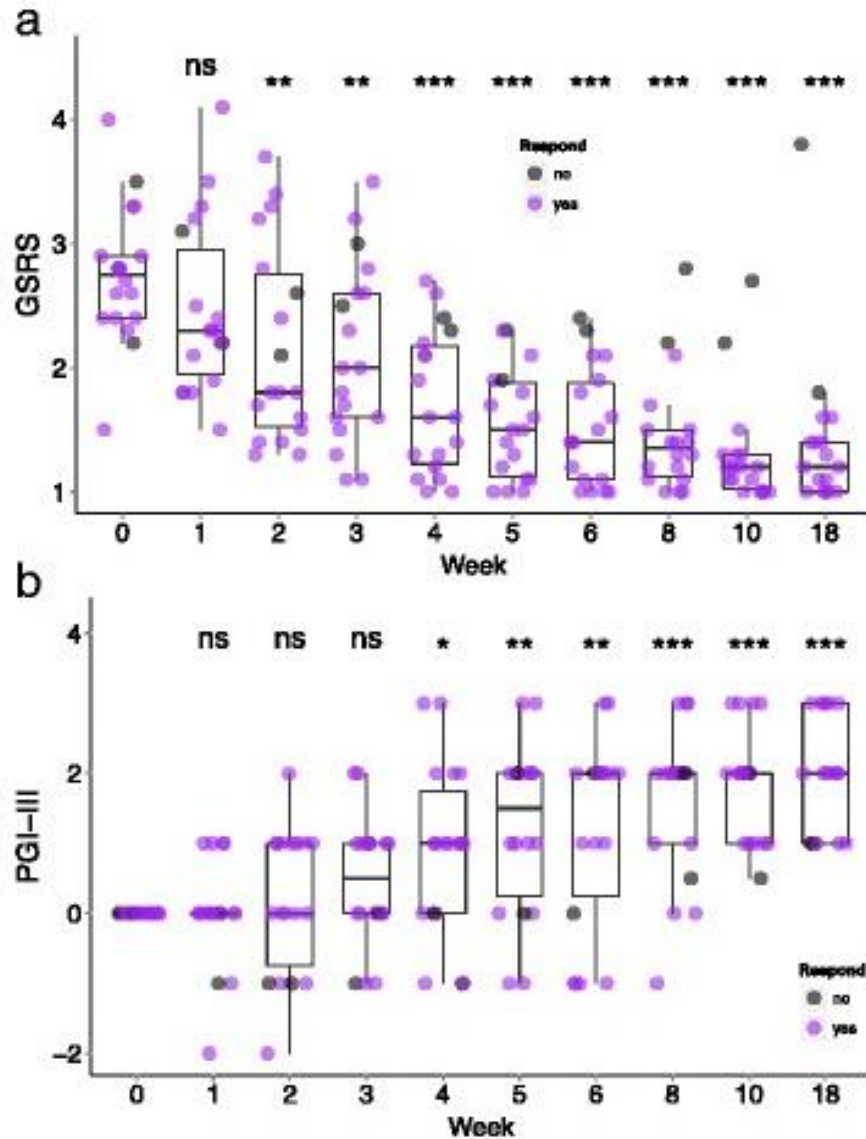
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Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang^{1†}, James B. Adams^{2†}, Ann C. Gregory^{3,15†}, Thomas Borody⁴, Lauren Chittick^{5,15}, Alessio Fasano⁶, Alexander Khoruts^{7,8,9}, Elizabeth Geis², Juan Maldonado¹, Sharon McDonough-Means¹⁰, Elena L. Pollard², Simon Roux^{5,15}, Michael J. Sadowsky^{8,11}, Karen Schwarzborg Lipson¹², Matthew B. Sullivan^{3,5,15,16*}, J. Gregory Caporaso^{12,13*} and Rosa Krajmalnik-Brown^{1,14*}

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Microbiome

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Key Messages

- ❖ Symbiotic microorganisms, specifically the microbiota that reside within the gut, may influence neurodevelopment and programming of social behaviors across diverse animal species
- ❖ This relationship between host and microbes hints that host-microbiota interactions may have influenced the evolution of social behaviors
- ❖ Further understanding of how microbiota influence the brain may be helpful for elucidating the causal mechanisms underlying sociability and for generating new therapeutic strategies for social disorders in humans, such as autism spectrum disorders (ASDs)

