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Health

Neuroscience
& Cell Biology

Host-Microbe Interactions Mediating the Multigenerational Impact of Maternal High-Fat Diet on Offspring Social Behavior

NIEHS Early-Stage Investigators Webinar Series
Zoom – August 10th, 2022

Shelly A. Buffington, Ph.D.

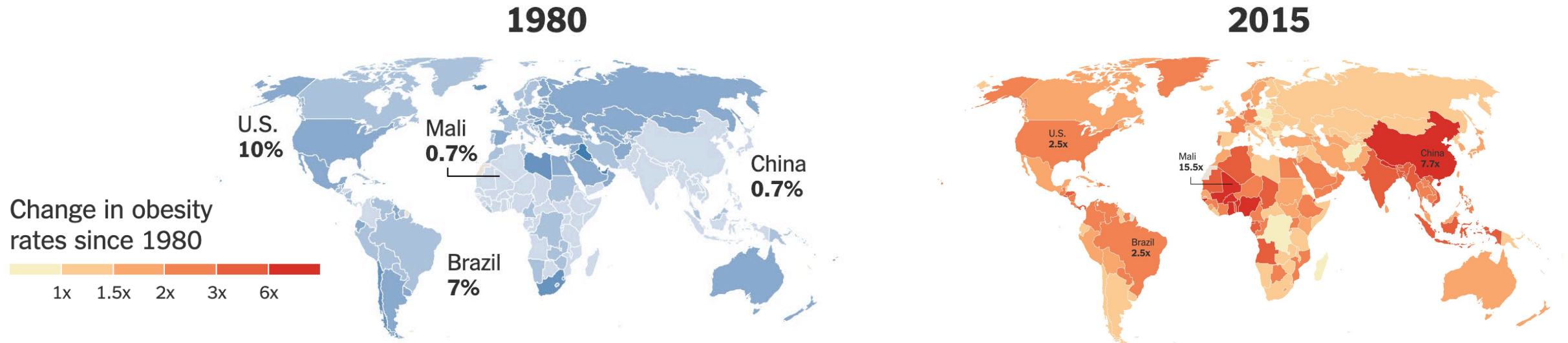
Department of Neuroscience, Cell Biology, & Anatomy

Sealy Center for Microbiome Research

The University of Texas Medical Branch at Galveston (**UTMB**)



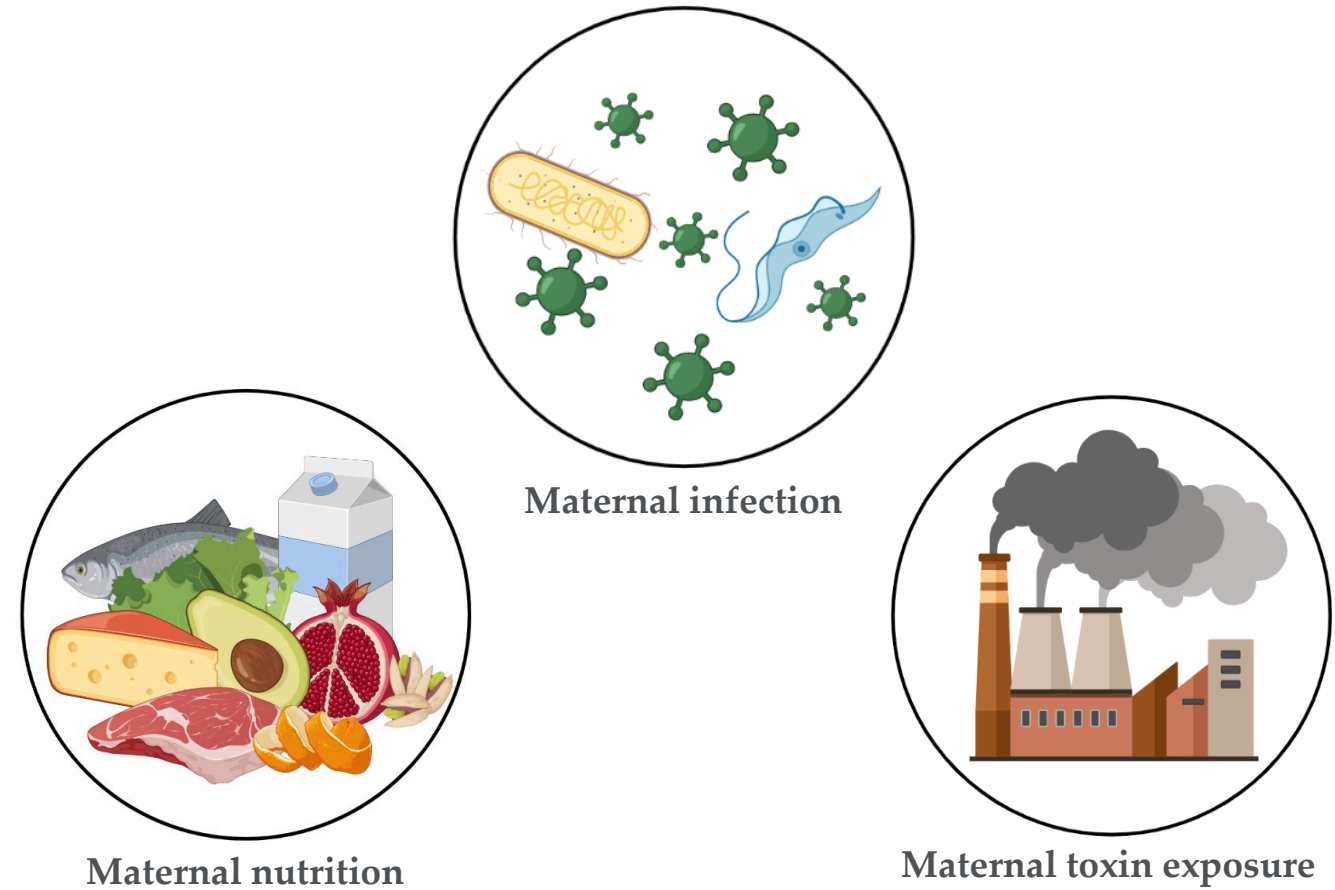
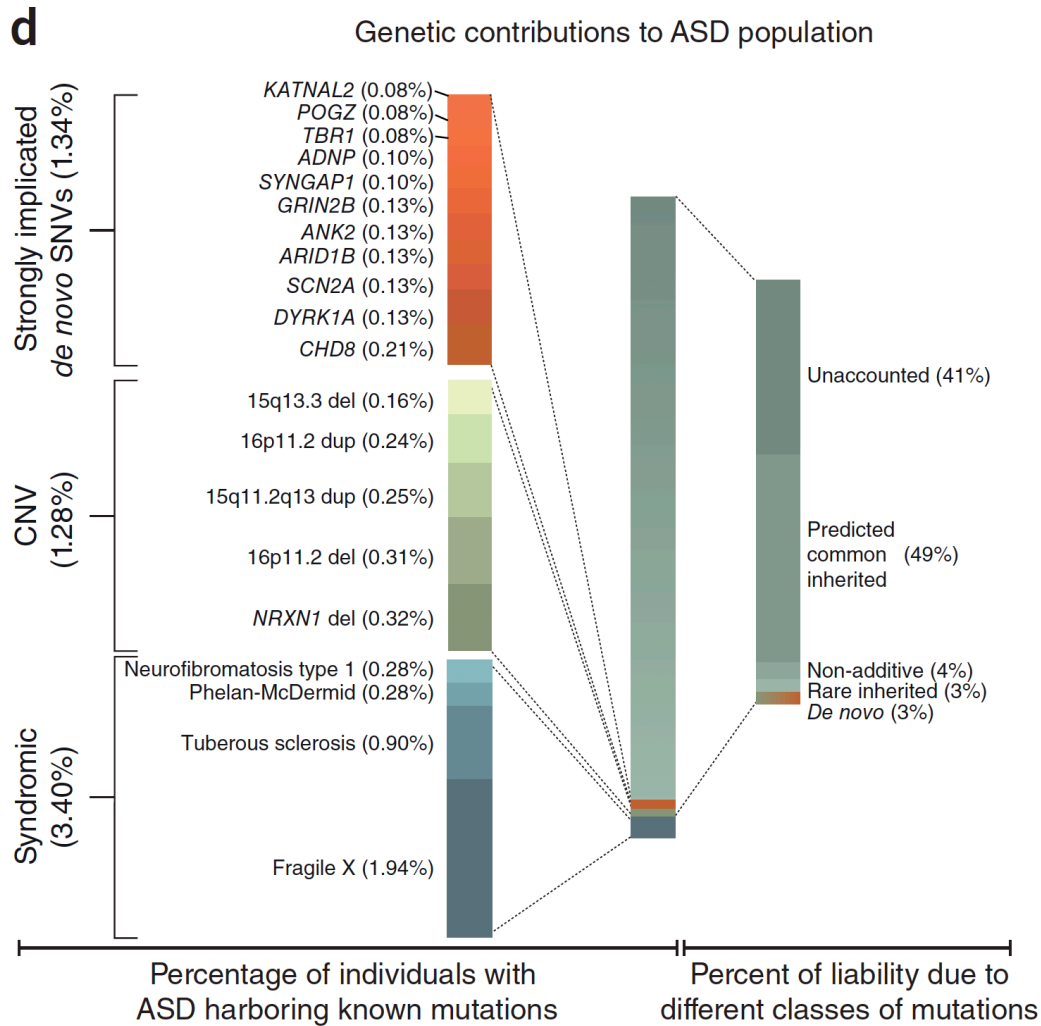
In the US, three in ten children are now born to women with prepregnancy obesity, presenting a mental health challenge



Adapted from *The New York Times*, 2017; NYT Source: Institute for Health Metrics and Evaluation.

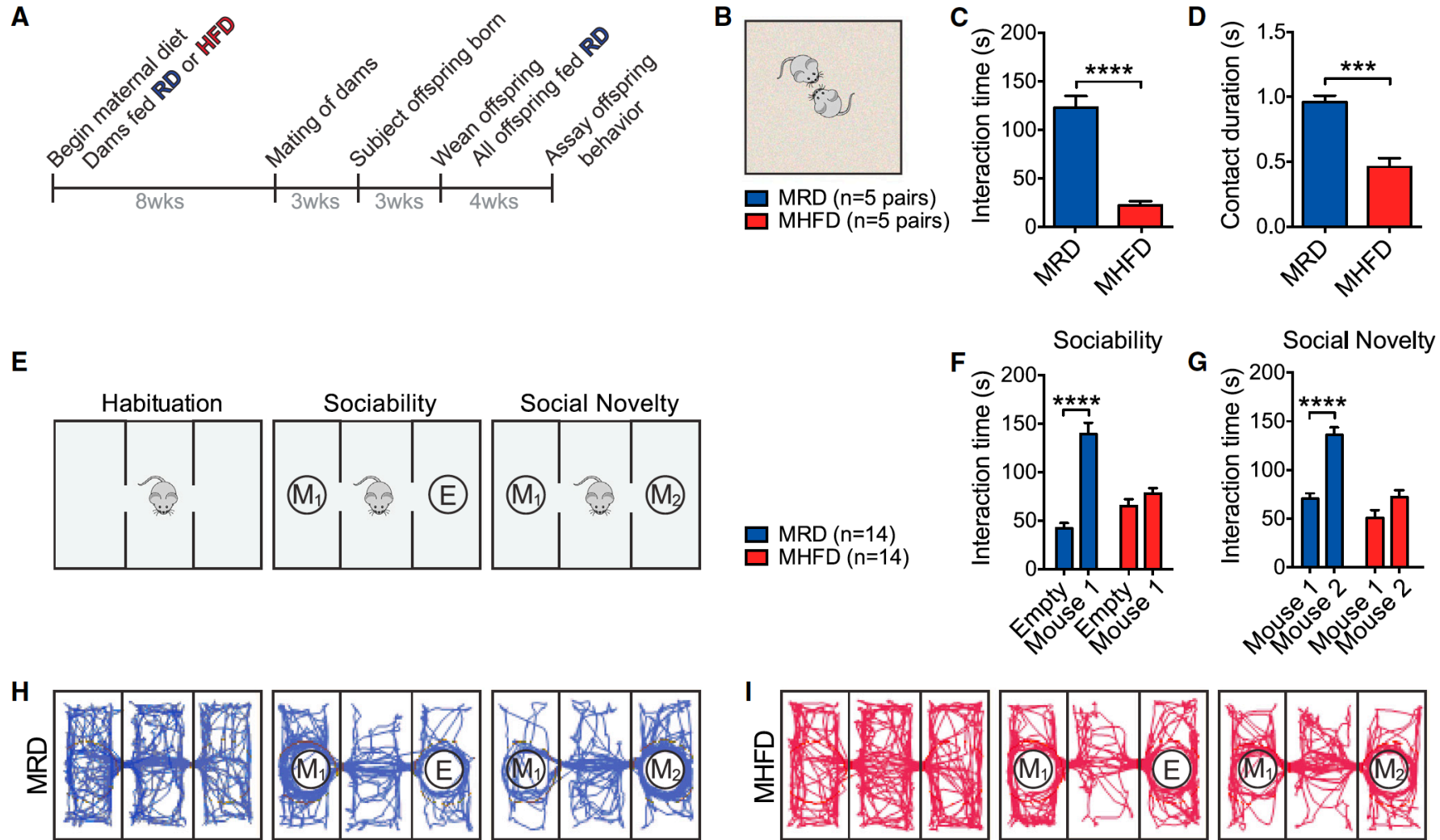
The growing prevalence of maternal diet-associated obesity is a serious mental health concern because it predisposes affected children to neurodevelopmental disorders, including autism spectrum disorder (ASD)

ASD is highly heritable; however, a growing body of evidence suggests that gene-environment interactions contribute to neurodevelopmental pathology and maladaptive behaviors in ASD

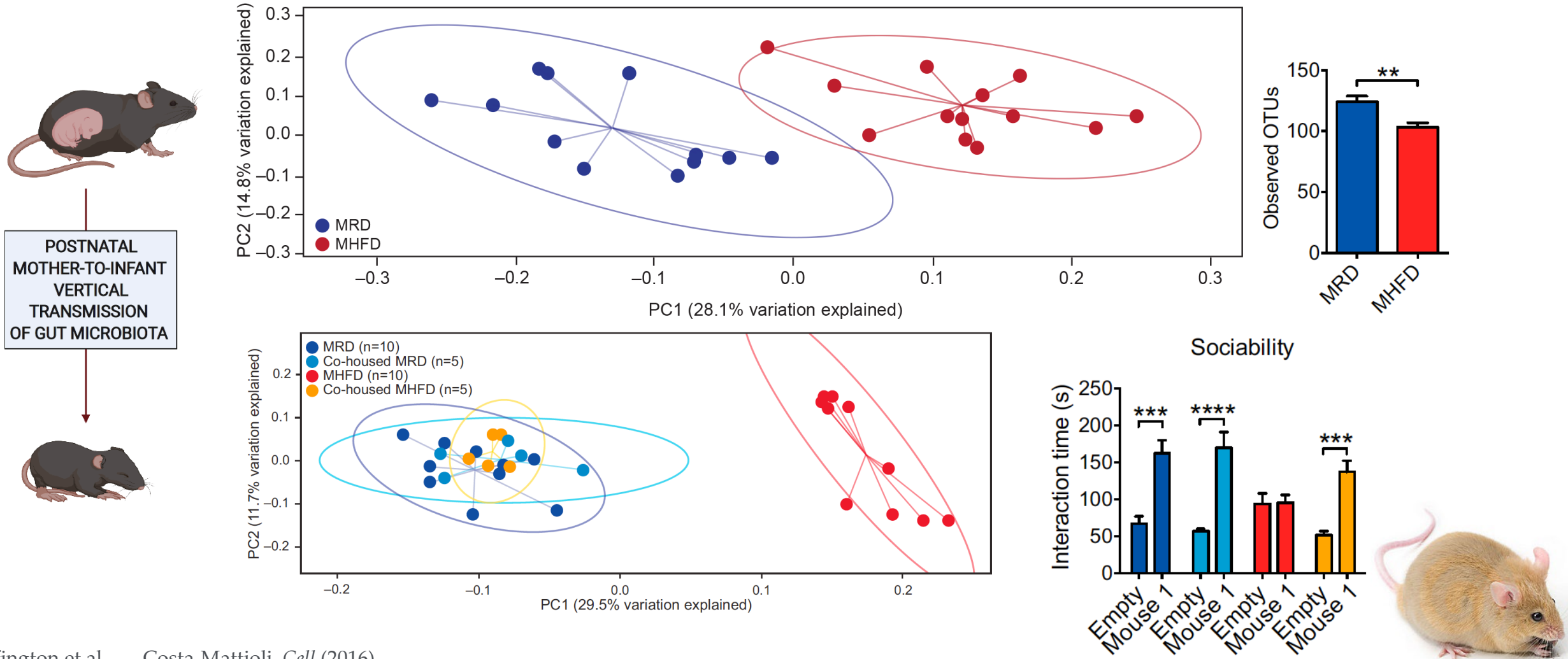


Early-life environmental exposure in genetically predisposed individuals could trigger behavioral dysfunction associated with neurodevelopmental disorders

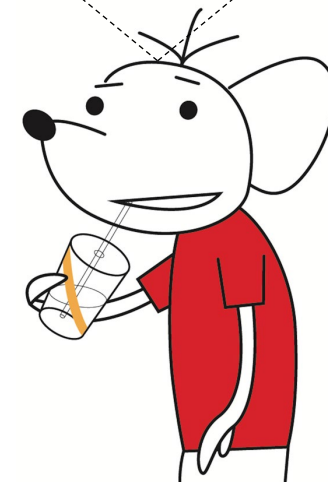
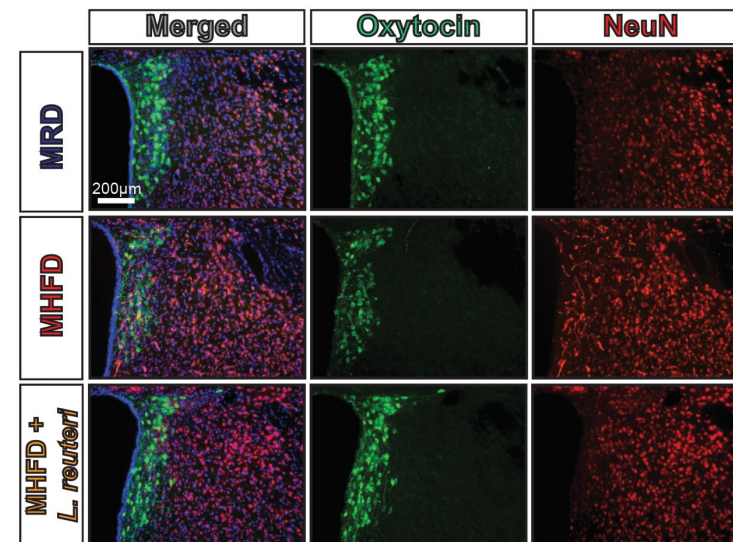
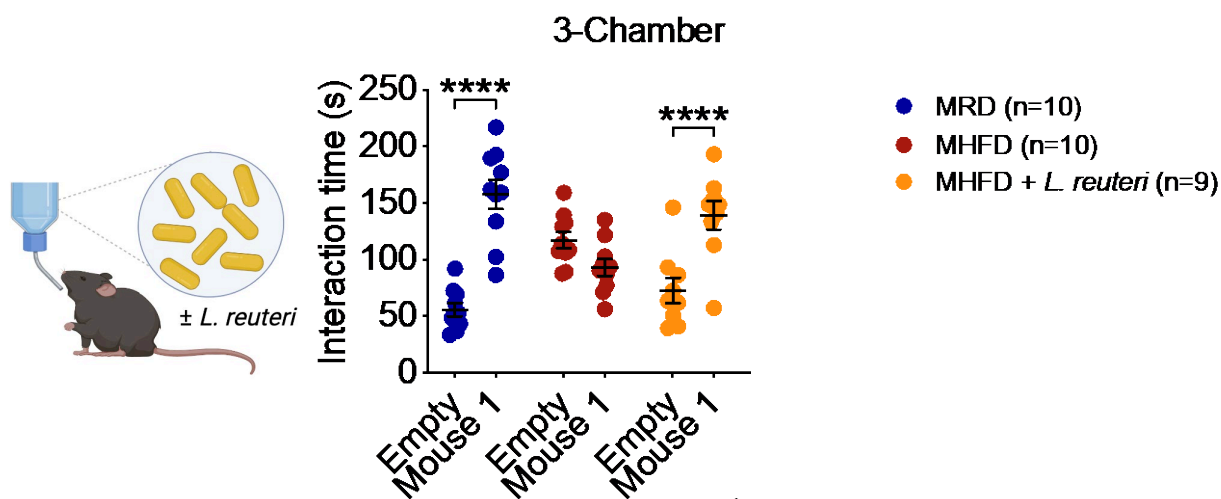
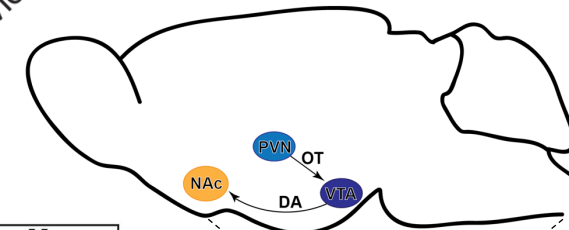
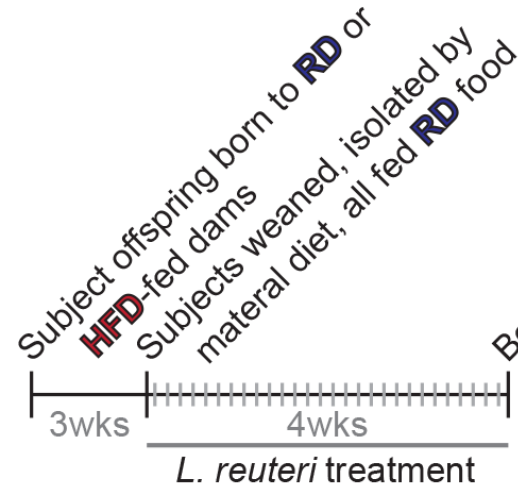
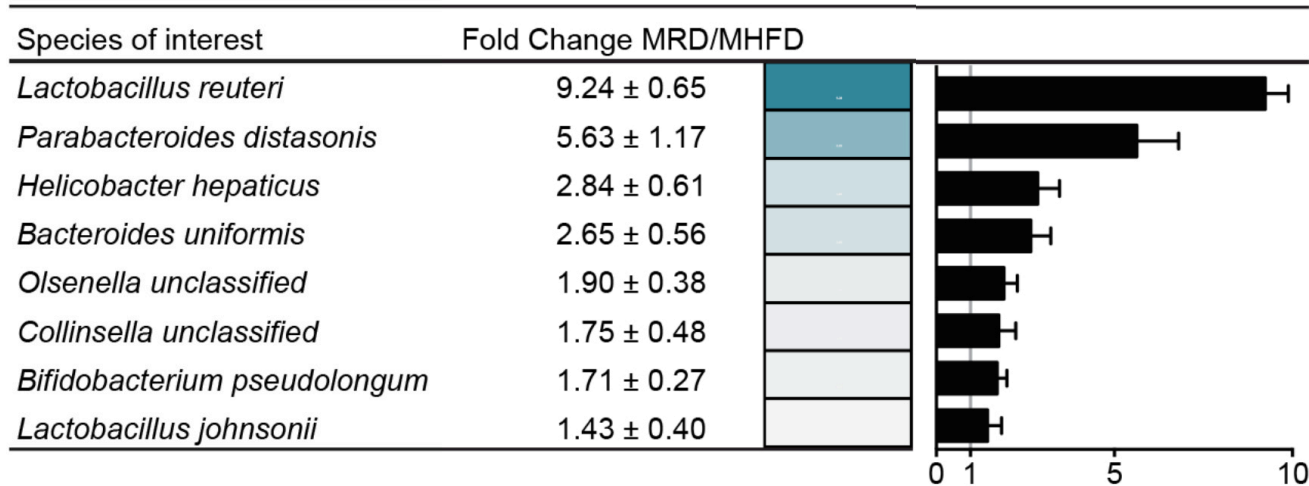
Maternal HFD consumption throughout pregnancy and lactation induces social dysfunction in male offspring



Co-housing resolves MHFD-induced dysbiosis of the offspring gut microbiome and rescues social dysfunction phenotype



Precision reconstitution with human breastmilk isolate *Limosilactobacillus reuteri*-6475 rescues MHFD offspring social deficits



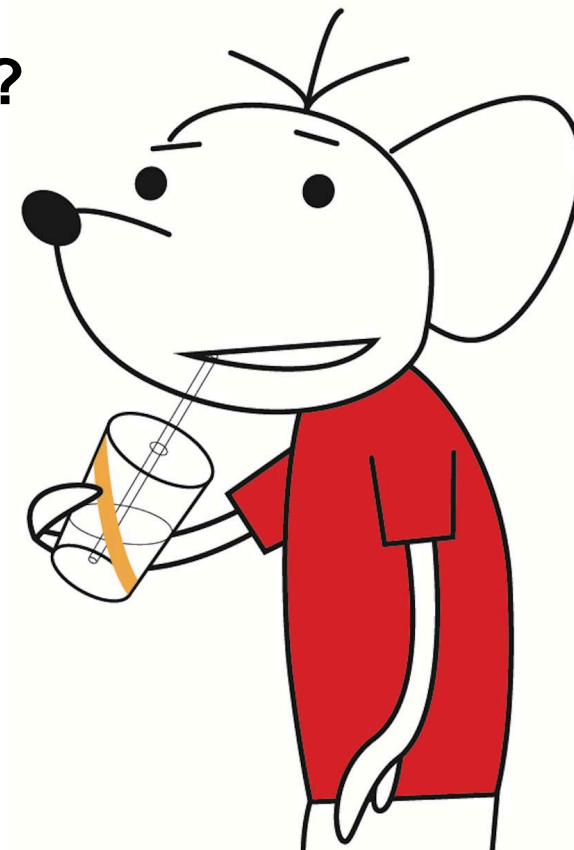
Part I: Remaining Questions

- **Can *L. reuteri* also rescue autism-like phenotypes in genetic and/or idiopathic mouse models for ASD, or is the rescue specific to MHFD offspring?**
 - Sgritta et al., ... Costa-Mattioli, *Neuron* 2019
 - *L. reuteri* rescues social deficits in genetic (*Shank3B^{-/-}*), idiopathic (BTBR), and environmental (GF) models for ASD
 - Buffington, Dooling et al., ... Costa-Mattioli, *Cell* 2021
 - *Cntnap2^{-/-}* model for ASD, case for considering the holobiont
- **What is the mechanism by which *L. reuteri* rescues social dysfunction in mouse models for ASD?**
 - Sgritta et al., ... Costa-Mattioli, *Neuron* 2019
 - The *L. reuteri*-mediated rescue depends on ...
 1. Integrity of the vagus nerve
 2. Oxytocin receptor (OXTR) expression in dopaminergic neurons
 - Buffington, Dooling et al., ... Costa-Mattioli, *Cell* 2021
 - *L. reuteri* restores tetrahydrobiopterin synthesis in *Cntnap2^{-/-}*



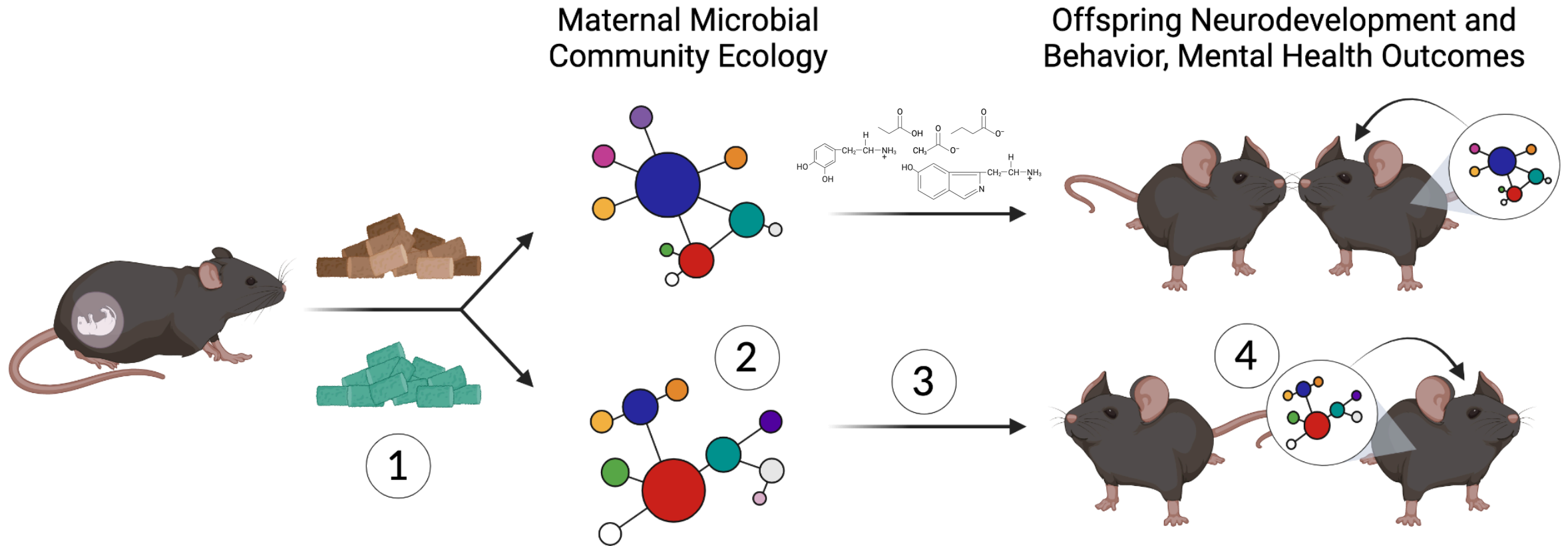
Part I: Remaining Questions, cont'd.

- **Given that *L. reuteri* rescues social dysfunction in multiple mouse models for ASD of diverse etiology, could we be back to Square 1 in our goal to understand how maternal HFD consumption leads to adverse neurodevelopmental and behavioral outcomes in offspring?**
 - Di Gesù, Matz et al., ... Buffington, *Revision under review*
- **What is the mechanism by which *L. reuteri* rescues social dysfunction in mouse models for ASD?**
 - Sgritta et al., ... Costa-Mattioli, *Neuron* 2019
 - Buffington, Dooling et al., ... Costa-Mattioli, *Cell* 2021
 - Di Gesù, Matz et al., ... Buffington, *Revision under review*



[Unpublished content unavailable]

Therapeutic targeting of the gut microbiome is a promising approach to the prevention/treatment of adverse neurodevelopmental outcomes



Acknowledgments

Buffington Lab + Collaborators

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- Robert S. Fultz, Ph.D.
- **Lisa M. Matz, Ph.D.**



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Costa-Mattioli Lab + Collaborators

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- Sean W. Dooling, B.S. (BCM → Altos Labs)
- Martina Sgritta, Ph.D. (BCM → AbbVie)
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- Thomas A. Auchtung, Ph.D. (BCM → University of Nebraska – Lincoln)
- Peter J. Turnbaugh, Ph.D. (UCSF)



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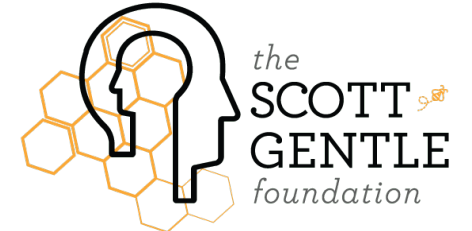
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Institute for Translational Science
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Eunice Kennedy Shriver National Institute
of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.



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