A Distinct Brain-Gut Microbiome Profile Exists for Obese Females with Food Addiction

Tien S Dong[1, 3], Emeran A. Mayer[1-5], Vadim Osadchiy;[3,5] Candace Chang[3], William Katzka[3], Venu Lagishetty[1,3], Kimberly Gonzalez[1,4,5], Amir Kalani[1,2,5], Jean Stains[1,4,5], Jonathan P. Jacobs[1,3,6], Arpana Gupta[1,2,4,5]

[1]Vatche and Tamar Manoukin Division of Digestive Diseases, [2]David Geffen School of Medicine, [3]UCLA Microbiome Center, David Geffen School of Medicine at UCLA,[4]G. Oppenheimer Center for Neurobiology of Stress and Resilience, [5]University of California, Los Angeles, [6]Division of Gastroenterology, Hepatology and Parenteral Nutrition, VA Greater Los Angeles Healthcare System, Los Angeles, CA

INTRODUCTION

- The obesity epidemic continues to be a major public health problem both in the United States (US) and globally.[1]
- Obesity has a complex and multifactorial etiology, and the limited progress in obesity treatments can in large part be attributed to the failure to apply a systems biology-based approach to understand its pathophysiology and to develop individualized strategies to achieve sustained weight loss and prevention.[1-3]
- A growing body of literature has demonstrated bidirectional signaling between the gut microbiome and the brain, mediated via neural, metabolic, endocrine, and immune-related signaling mechanisms.[4,5]
- Perturbations at any level of this system resulting in compromised inhibitory mechanisms that normally regulate food intake, can bias ingestive behaviors towards predominant hedonic ingestion (food addiction), cravings, and overeating.[2,6,7]
- **AIM:** To explore the relationship between food addiction and the brain-gut microbiome using a multi'omics approach in order to show that food addiction is related to alterations in neural communications that are associated with gut microbial and metabolite changes.

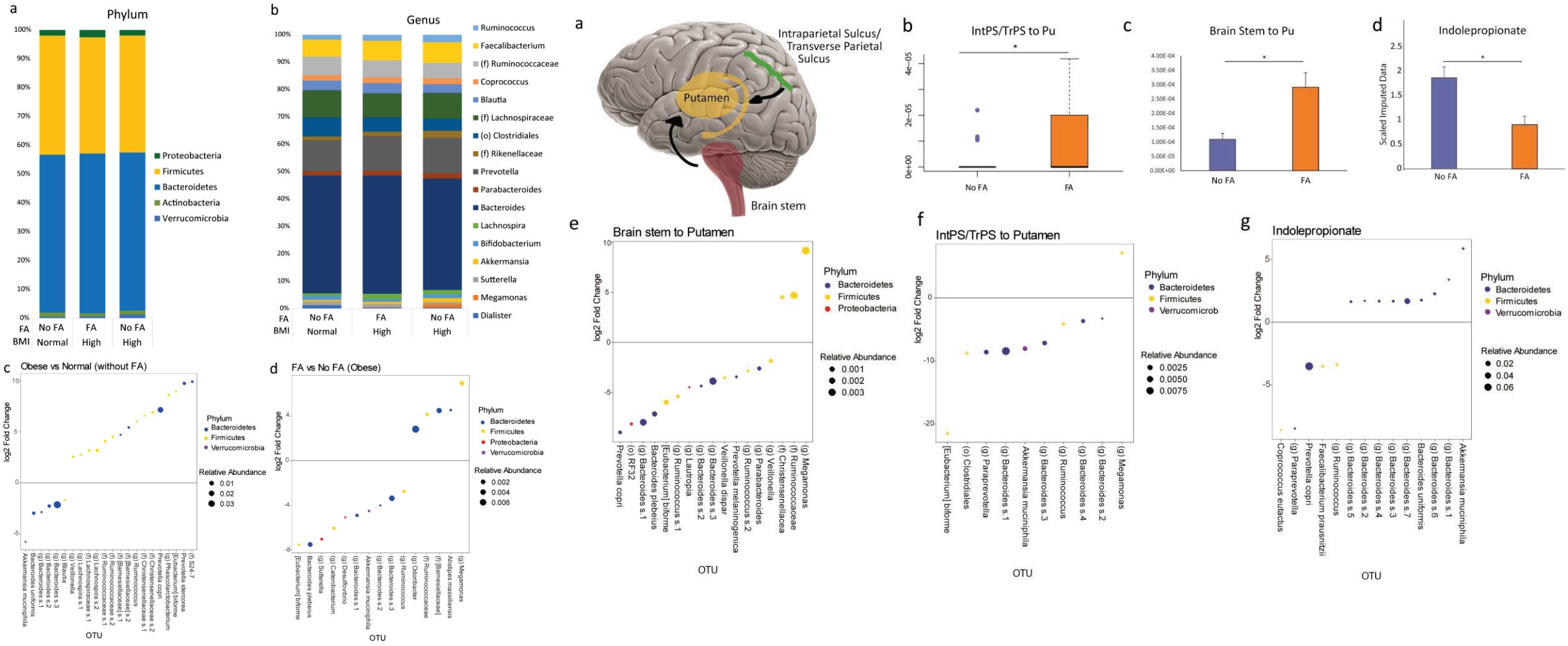
METHODS

- **Subject:** N=105 healthy female subjects.
- Fecal samples were stored at -80 C and shipped to Metabolon for processing and analysis using mass spectrometry and their global metabolomics and bioinformatics platform, focusing on **Tryptophan-related metabolites**.
- 16S rRNA gene sequencing was performed on all fecal samples using Illumina HiSeq platform.
- Structural and diffusion weighted magnetic resonance imaging was conducted at UCLA using a Siemens 3T MRI scanner.
  - Reward networks: caudate, putamen, globus pallidus, amygdala, hippocampus, nucleus accumbens, medial orbital frontal gyrus
- The Yale Food Addiction Scale (YFAS) was administered, and food addiction was defined as a score ≥ 3[8]

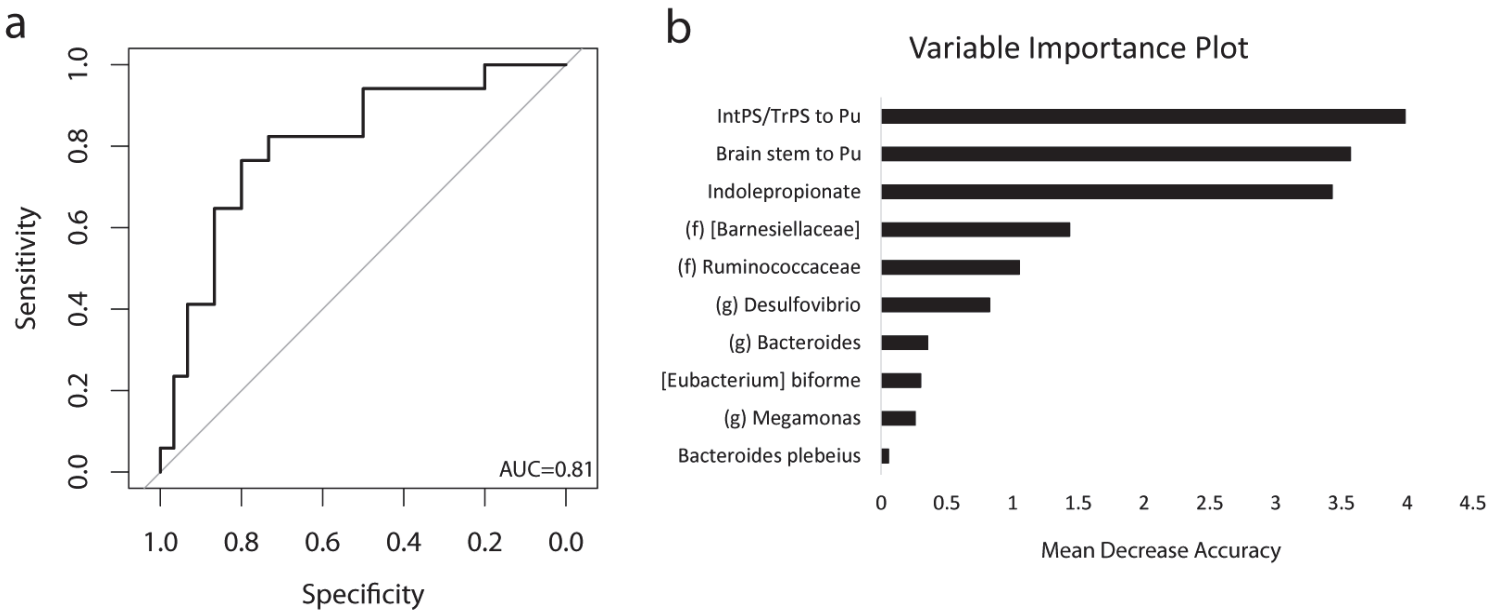
Results: Table 1

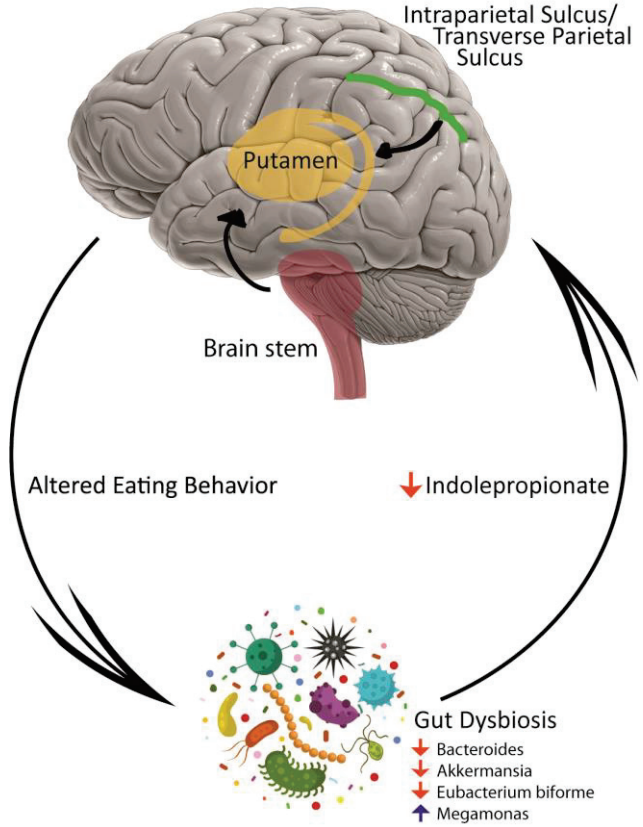
	Low YFAS (n=82)	High YFAS (n=23)	p-value
Age (mean +/- SD) (yrs)	32.95 + 10.02	30.26 + 10.53	0.26
BMI (mean +/- SD)	29.2 + 5.6	34.3 + 5.6	**0.0001**
Normal Weight (n=16) %	19.5	0.0	
Overweight (n=38) %	39.0	26.1	
Obese (n=51) %	41.5	73.9	**0.01**
Race/Ethnicity			
Hispanic (n=41) %	37.80	43.48	
Caucasian (n=28) %	24.39	34.78	
African American (n=13) %	13.41	8.70	
Asian (n=21) %	21.95	13.04	
Other (n=2) %	2.44	0.00	0.75

Results: FA is Associated with Changes in the Brain-Gut-Microbiome Axis



Results: Brain-Gut-Microbiome Axis Changes Accurately Identifies FA





Conclusion

- Overall, food addiction behaviors in females were associated with a distinct microbial profile, increase signaling between the intraparietal sulcus/transverse parietal sulcus, brainstem and the putamen of the reward center of the brain, and a decrease in indoleproprionate, a tryptophan derived microbial metabolite.
- Using the significant findings on brain imaging, fecal metabolite, and DESEq2 analysis of the fecal microbiome, a random forest classifier was created with a high accuracy for predicting patients with food addiction behaviors.
- This data suggests that food addiction behavior may be mediated via effects of the gut microbiome and their metabolites on the reward centers of the brain.
- This suggests the possibility of targeting the brain-gut microbiome axis to combat food addiction behavior and obesity.

References: 1) Ziaudden et al. *Obesity* Review. 2013; 2) Martin et al. *Cell Mol Gastro Hep*. 2018; 3) Sanmiguel et al. *Curr Obes Rep*. 2015. 4) Ley, et al. *Cell.* 2016. 5) Mayer, et al. *J Neurosci.* 2018; 6) Mayer et al. *Psychosom Med*. 2017; 7) Patist et al. *Cogn Affect Behav Neurosci.* 2018; 9) Gearhardt et al. *Psychol Addict Behav*. 2016; 10) Destrieux et al., Neuroimage, 2010; 11) Irimia et al., Neuroimage, 2010;

Supported by National Institutes of Health grants K23106528, R01DK048351, P50 DK 064539, P30 DK 041301

Provisional Patent No. 62/885,010