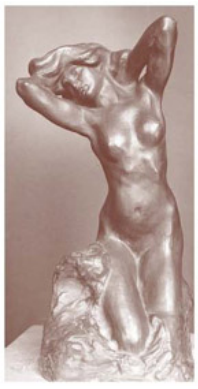
15th Annual CNSR Symposium

Bringing the Brain Back into Medicine: Focus on Obesity, Microbiome and Women's Health

Friday, February 3, 2017 • UCLA California NanoSystems Institute

UCLA CNSR

G. OPPENHEIMER CENTER
FOR NEUROBIOLOGY OF STRESS AND RESILIENCE



IRIS CANTOR-UCLA WOMEN'S HEALTH CENTER

EDUCATION AND RESEARCH CENTER

Acknowledgments

Symposium Chairs

Andrea Hevener, PhD

Claudia Sanmiguel, MD

Poster Reviewers

Basic and Translational

Jonathan Jacobs, MD, PhD
Clinical Instructor of Medicine, Vatche and Tamar Manoukian
Division of Digestive Diseases, David Geffen School of Medicine at UCLA

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Joseph Pisegna, MD
Chief, Division of Gastroenterology and Hepatology, VA Greater Los Angeles Healthcare System;
Professor of Medicine, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Acknowledgments

Sponsors

We gratefully acknowledge the support for this meeting received from:

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UCLA Brain Research Institute

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Program

15TH ANNUAL CNSR SYMPOSIUM

Bringing the Brain Back into Medicine:
Focus on Obesity, Microbiome and Women's Health

G. Oppenheimer Center for Neurobiology of Stress and Resilience
Vatche and Tamar Manoukian Division of Digestive Diseases,
Department of Medicine, David Geffen School of Medicine at UCLA

In collaboration with the Iris Cantor – UCLA Women's Health Center, the UCLA California NanoSystems Institute and the UCLA Microbiome Center

With the generous support from UCLA Vatche and Tamar Manoukian Division of Digestive Diseases, CURE Foundation, Gerald Oppenheimer Foundation, Morris A. Hazan Family Foundation, Executive Advisory Board of the Iris-Cantor – UCLA Women's Health Center and UCLA Clinical and Translational Science Institute (CTSI)

Friday, February 3, 2017
CALIFORNIA NANOSYSTEMS INSTITUTE AUDITORIUM

Symposium Chairs	**Claudia Sanmiguel, MD** Director, Ingestive Behavior and Obesity Program, G. Oppenheimer Center for Neurobiology of Stress and Resilience, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA **Andrea Hevener, PhD** Professor, UCLA Program on Genomics and Nutrition, Division of Endocrinology, Diabetes, and Hypertension, David Geffen School of Medicine at UCLA; Iris Cantor - UCLA Women's Health Center
7:30 am – 8:00 am	**CONTINENTAL BREAKFAST**
8:00 am – 8:15 am	**INTRODUCTIONS**
	Eric Esrailian, MD, MPH Lincy Foundation Chair, Clinical Gastroenterology; Co-Chief, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA
	Janet Pregler, MD Director, Iris Cantor - UCLA Women's Health Center; Health Sciences Clinical Professor, David Geffen School of Medicine at UCLA
SESSION I **8:15 am – 10:15 am**	**STATE OF THE ART LECTURES, Part I** (Each 25 minutes + 5 minutes discussion)
Session Chairs	**Zhaoping Li, MD, PhD** (Director, Center for Human Nutrition; Chief, Division of Clinical Nutrition, David Geffen School of Medicine at UCLA) **Wenyuan Shi, PhD** (Professor and Chair, School of Dentistry, Section of Oral Biology; Professor, School of Medicine, Molecular Biology Institute and Department of Microbiology, Immunology and Molecular Genetics)

8:15 am – 8:45 am ***The Sex and Gender Integral***
Janine Clayton MD
NIH Associate Director for Research on Women's Health; Director, NIH Office of Research on Women's Health

8:45 am – 9:15 am ***The Gut-Brain Axis - Role of Diet, Microbes and Sex Differences***
Helen Raybould, PhD
Professor, Departments of Anatomy, Physiology and Cell Biology, UC Davis

9:15 am – 9:45 am ***Sex Differences in Food Addiction***
Ashley Gearhardt, PhD
Assistant Professor, Department of Psychology, University of Michigan

9:45 am – 10:15 am ***Sex Differences in Gut Microbiome and Metabolic Syndrome***
Jake Lusis, PhD
Professor, Departments of Medicine, Cardiology, Human Genetics, Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA

10:15 am – 10:30 am **COFFEE BREAK**

SESSION II **UCLA Campus Initiatives**
10:30 am – 11:45 am (Each 15 minutes)

Session Chair **Lin Chang, MD** (Director, Functional GI Disorders Program, G. Oppenheimer Center for Neurobiology of Stress and Resilience; Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

10:30 am – 10:45 am ***UCLA Healthy Campus Initiative***
Michael Goldstein, PhD
Former UCLA Associate Vice Provost, Healthy Campus Initiative; Professor Emeritus, Community Health Sciences and Sociology

10:45 am – 11:00 am ***VA Women's Health Initiative (EMPOWER QUERI)***
Tannaz Moin MD, MBA, MSHS
Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, David Geffen School of Medicine at UCLA; HSR&D Center for the Study of Healthcare Innovation, Implementation & Policy, VA Greater Los Angeles Healthcare System

11:00 am – 11:15 am ***UCLA Microbiome Center Initiative***
Jonathan Jacobs, MD, PhD
Clinical Instructor of Medicine, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:15 am – 11:45 am **STATE OF THE UCLA CNSR**
Emeran Mayer, MD, PhD
Director, G. Oppenheimer Center for Neurobiology of Stress and Resilience; Co-Director, CURE: Digestive Diseases Research Center; Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:45 am – 1:15 pm **LUNCH AND POSTER SESSION**

1:15 pm – 1:30 pm **POSTER AWARDS**

Joseph Pisegna, MD
Chief, Division of Gastroenterology and Hepatology, VA Greater Los Angeles Healthcare System; Professor of Medicine, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Andrea Hevener, PhD

SESSION III **CORPORATE ROUNDTABLE**
1:30 pm – 3:00 pm

Moderators **Emeran Mayer, MD, PhD**

Jeffrey F. Miller, PhD
Director, California NanoSystems Institute; Fred Kavli Chair, NanoSystems Sciences; Professor, Microbiology, Immunology and Molecular Genetics

C3J Therapeutics
A biotechnology company developing novel products to diagnose, treat and prevent human and animal diseases
Brian Varnum, PhD (Chief Development Officer)

The Dannon Company Inc.
Maker of more than 200 different flavors, styles and sizes of cultured refrigerated dairy products
Miguel Freitas, PhD (VP Scientific Affairs)

Bell Institute of Health & Nutrition - General Mills Inc.
An American multinational manufacturer and marketer of branded consumer foods
Ravi Menon, PhD (Senior Principal Scientist)

Kallyope
Developing an industry-leading platform to harness the gut-brain axis
Nancy Thornberry (CEO)

Prolacta Bioscience, Inc.
Develops clinically proven, high-value products derived from human milk to meet the needs of premature infants in the NICU
Victoria Niklas, MD, MA (Chief Medical and Scientific Officer)

Whole Biome
A microbiome company focused on enabling better patient care through targeted equilibration of human microbiomes
Colleen Cutliffe, PhD (CEO and Co-Founder)

SESSION IV **STATE OF THE ART LECTURES, Part II**
3:00 pm – 4:30 pm (Each 25 minutes + 5 minutes discussion)

Session Chairs **Paul Micevych, PhD** (Distinguished Professor, Head and Neck Surgery Chair, Distinguished Professor, Neurobiology, David Geffen School of Medicine at UCLA)

Catia Sternini, MD (Professor, Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA)

3:00 pm – 3:30 pm ***Sleep and Irritable Bowel Syndrome: A Metabolomics Approach***
Margaret Heitkemper, PhD, RN, FAAN
Chair, Department of Biobehavioral Nursing and Health Systems, Affiliate Professor, Division of Gastroenterology, School of Medicine, University of Washington School of Nursing

3:30 pm – 4:00 pm ***The Role of ERα in the Regulation of Feeding and Energy Homeostasis***
Stephanie Correa, PhD
Assistant Professor, Department of Integrative Biology and Physiology, UCLA

4:00 pm – 4:30 pm ***The Role of ERα in the Protection Against Metabolic Disease***
Andrea Hevener, PhD

4:30 pm – 4:35 pm **CLOSING COMMENTS**
Lin Chang, MD

4:35 pm **END OF SYMPOSIUM**

Summaries of Presentations

Symposium Chairs: Andrea Hevener, PhD (Financial Disclosure: None)
Claudia Sanmiguel, MD (Financial Disclosure: None)

SESSION I: STATE OF THE ART LECTURES, PART I

Chairs: Zhaoping Li, MD, PhD (Financial Disclosure: None)
Wenyuan Shi, PhD (Financial Disclosure: Founding Scientist - C3J Therapeutics)

The Sex and Gender Integral

Janine Clayton MD
NIH Associate Director for Research on Women's Health; Director, NIH Office of Research on Women's Health
Financial Disclosure: None

Sex matters along the entire research pathway, from preclinical studies to translational investigations to clinical trials and implementation studies. However, scientists have overly relied on men and male animals in research, historically believing that any findings from their studies could be applied generally. Sex chromosomes lead not only to distinct anatomical differences, but also crucial physiological variations that can have a direct influence on health. Another important factor in health is gender, which concerns how individuals perceive themselves, unspoken cultural rules that influence behavior, and interpersonal relations between different gender identities. In alignment with its commitment to advancing women's health, the National Institutes of Health (NIH) implemented a policy titled "Consideration of Sex as a Biological Variable in NIH-Funded Research" for all NIH-funded studies. According to the policy, scientists are asked to "explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans." This policy complements NIH's more than 20 years of work in promoting the inclusion of women in clinical studies. Today, the majority of participants in NIH-funded clinical trials are women, in contrast to their being underrepresented in the past. In addition, as the communication of research findings is critical, NIH has encouraged the use of the Sex and Gender Equity in Research (SAGER) guidelines, which assist researchers and editors in reporting sex and gender information in publications.

The Gut-Brain Axis - Role of Diet, Microbes and Sex Differences

Helen Raybould, PhD
Professor, Departments of Anatomy, Physiology and Cell Biology, UC Davis
Financial Disclosure: None

Vagal afferent neurons innervating the GI tract represent the afferent arm of the gut–brain axis, providing the brain with information about the state of the gut. These neurons transmit information about the composition and activity of the gut microbiota; this information is important in regulation of numerous types of behavior. Here I will present information to show that microbial dysbiosis induced by a high fat, low fiber diet attenuates information transfer in vagal afferent neurons, resulting in hyperphagia. Treatment with prebiotics, either inulin or milk oligosaccharides, improves the dysbiosis, increases levels of butyrate in the large intestine and attenuates the hyperphagia. Supernatant from growth of beneficial bacteria on prebiotic milk ologisaccharides activates gut enteroendocrine cells and vagal afferent neurons; one possible active factor is indolactate. In culture, indolacetate increases release of GLP-1 and CCK from gut endocrine cell lines. Further, information will be presented on sex differences in vagal afferent neurons. These neurons express estrogen receptor alpha (ERα); expression varies with the phase of the estrous cycle with highest levels of expression when circulating levels of estradiol are high.

Sex Differences in Food Addiction

Ashley Gearhardt, PhD
Assistant Professor, Department of Psychology, University of Michigan
Financial Disclosure: None

The current food environment has more foods with high levels of added sugar and fat than at any other point in human history. Humans are hard-wired to find these high-calorie foods pleasure and reinforcing. Have these foods become so rewarding that they are capable of triggering an addictive response (at least in some people)? Evidence is growing that an addictive process may be contributing to obesity and some forms of pathological eating, although this topic is highly controversial. In the current talk, the state of the literature regarding the validity of "food addiction" will be discussed. The potential role of sex differences in the development of addictive-like eating will also be examined.

Sex Differences in Gut Microbiome and Metabolic Syndrome

Jake Lusis, PhD
Professor, Departments of Medicine, Cardiology, Human Genetics, Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA
Financial Disclosure: None

The composition of the gut microbiota varies greatly among individuals in human populations and also in experimental organisms such as the mouse. This variation appears to be due to a number of factors including diet, maternal seeding, host genetics, and antibiotic use. We have used genetic approaches in both mouse and human populations to try to understand how host genetics influences microbiota composition and also how microbiota influence host physiology and disease susceptibility. Using a panel of about 100 different inbred strains of mice, we have modeled a genetic contribution to gut microbiota composition. We conclude that, given a similar environment, genetics play a very large role in determining the taxa in the intestines of mice, with heritabilities for certain taxa as high as 70%. In this study design, we can also examine relationships between physiologic traits, such as adiposity and plasma lipids, and the abundance of gut microbiota. In this way, we have identified a number of species of microbiota associated with cardiovascular and metabolic traits and have experimentally followed up on some of these. We have also explored pathways by which microbiota can contribute to host functions and disease susceptibility. In particular, we worked with Stan Hazen at the Cleveland Clinic to examine the role of bacteria-derived product, trimethylamine-N-oxide, on cardiovascular and metabolic disorders. Finally, we are complementing our studies in mice by examining a cohort of Finnish men in terms of the relationship between gut microbiota and cardiometabolic traits. In my talk, I will focus on sex differences in gut microbiota composition.

SESSION II: UCLA CAMPUS INITIATIVES

Chair: Lin Chang, MD (Financial Disclosure: Advisory Board Member – Ironwood, Synergy, Synthetic Biologics, IM Healthcare, Bioamerica)

UCLA Healthy Campus Initiative

Michael Goldstein, PhD
Professor Emeritus, Department of Community Health Sciences, UCLA Fielding School of Public Health
Financial Disclosure: None

In January 2013, Chancellor Gene Block launched the UCLA Healthy Campus Initiative (HCI). The UCLA HCI, envisioned and supported by Jane and Terry Semel, prioritizes the health and wellness of students, staff, and faculty. It is a campus-wide effort to draw upon UCLA's world renowned research and teaching, to find new and innovative ways to promote living well on the UCLA campus, and to share that education and research with other communities, locally and beyond. Over the past four years, the HCI has acted as a sparkplug and home for health-related campus-wide work, helping to leverage the strengths of individuals and institutions on and off campus. The HCI promotes living well for the UCLA community by supporting the "healthy choice as the easy choice" through its five major thematic areas, called "pods": MindWell, BEWell, EatWell, MoveWell, and BreatheWell. In the 2014-2015 academic year, the HCI added a sixth pod, ResearchWell, to support the Initiative's research and evaluation needs.

VA Women's Health Initiative (EMPOWER QUERI)

Tannaz Moin MD, MBA, MSHS
Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, David Geffen School of Medicine at UCLA; HSR&D Center for the Study of Healthcare Innovation, Implementation & Policy, VA Greater Los Angeles Healthcare System
Financial Disclosure: None

The VA Quality Enhancement Research Initiative (QUERI) Enhancing Mental and Physical Health of Women through Engagement and Retention (EMPOWER) Program is focused on the implementation of innovative care models in VA women's health, in order to improve engagement and retention in evidence-based care for high priority health conditions. This five year, multisite VA initiative includes three projects that focus on prediabetes/diabetes prevention, cardiovascular risk, as well as anxiety and depression among women Veterans. The projects focus on implementing and evaluating tailored evidence-based care models that are patient-centered, proactive, and personalized, and feasible for VHA providers to deliver.

Microbiome Center Initiative

Jonathan Jacobs, MD, PhD
Professor, Departments of Medicine, Cardiology, Human Genetics, Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA
Financial Disclosure: None

The germ theory of disease developed by Louis Pasteur had a revolutionary impact on human health and made avoidance of microbes a fundamental tenet of daily life. It has now become clear in recent years that microbes are critically important for maintaining health through their effects on the immune system, metabolism, and even behavior. This has raised questions about whether our current lifestyle - replete with antimicrobial household products, frequent antibiotic treatment, germ avoidance, and processed foods - has disrupted our microbiota. There is growing concern that disorders with growing prevalence in recent decades such as obesity, diabetes, asthma, atopy, Crohn's disease, multiple sclerosis, and autism spectrum disorders are being driven by detrimental changes in the human microbiome. This has led to an explosion of research in the microbiome field but we have only scratched the surface in terms of our understanding of how microbes impact human physiology and how we can manipulate the microbiome to improve health. There is a critical need for translational research that identifies specific microbes and their products relevant to disease, new tools to facilitate mechanistic dissection of the pathways by which microbes impact health, and lifestyle programs – including diet and hygiene practices – that cultivate a healthy microbiome. To this end, the UCLA School of Medicine, School of Dentistry, CNSI, Life Sciences, Physical Sciences, and Engineering have come together to establish the UCLA Microbiome Center to foster interdisciplinary collaboration and reduce barriers to entry in the microbiome field. The UCLA Microbiome Center promotes these goals through a monthly seminar series, innovative cores (Microbiome, Gnotobiotic, Bioinformatics), and academic/industry partnerships.

SESSION III: CORPORATE ROUNDTABLE

Chairs: Emeran Mayer, MD, PhD (Financial Disclosure: Advisory Board Member – Axial Biotherapeutics, Dannon, Danone, Prolacta, Whole Biome)

Jeffrey F. Miller, PhD (Financial Disclosure: Co-founder, Board Member – AvidBiotics, Inc; Co-founder, Board Member – Dermalytica, Inc)

C3J Therapeutics

Brian Varnum, PhD
Chief Development Officer

C3J Therapeutics is a clinical-stage biotechnology company based in Los Angeles, California. C3J Therapeutics is focused on improving human health through the development and commercialization of targeted, or pathogen-specific, antimicrobials that treat and prevent diseases caused by microbial dysbiosis. A disrupted or imbalanced microbial ecology due to disease or broad-spectrum antibiotic use can result in negative clinical consequences and prolonged debilitating infections. Recent understandings of the human microbiome have illustrated the importance of a healthy and balanced microbial ecosystem and the link to improvements in human disease outcomes and disease risk.

C3J Therapeutics refers to the targeted compounds as STAMPs: Specifically Targeted Antimicrobial Peptides. The STAMP Platform Technology was pioneered in the lab of Dr. Wenyuan Shi, Chairman of Oral Biology at the University of California Los Angeles (UCLA) School of Dentistry and Professor of Microbiology, Immunology & Molecular Genetics at the UCLA David Geffen School of Medicine.

The Dannon Company Inc.
Miguel Freitas, PhD
VP Scientific Affairs

Headquartered in White Plains, New York, Dannon makes yogurt in Minster, OH, Fort Worth, TX, West Jordan, UT, and Portland, OR, and offers more than 200 different flavors, styles and sizes of cultured refrigerated and frozen dairy products to serve the diverse needs of its retail and foodservice customers. Dannon brings health through food to as many people as possible via its wide offering of delicious and nutritious fresh and frozen yogurts. Dannon is committed to encouraging Americans to eat one yogurt every day with a convenient, popular and nutrient dense food as a simple step that can help Americans achieve healthy dietary patterns. Dannon is a subsidiary of Danone, and Danone is the top-selling brand of yogurt worldwide, sold under the names Dannon and Danone. For more information, visit dannon.com.

General Mills Bell Institute of Health and Nutrition
Ravi Menon, PhD
Senior Principal Scientist, Bell Institute of Health & Nutrition - General Mills Inc.

The global Bell Institute of Health and Nutrition is the source for health, wellness and nutrition expertise for General Mills. Our goal is to create value for General Mills by championing health innovation and advancing nutrition leadership. We believe food should make us better, and work hard to make food people love, while improving the nutrition of our products. The Bell Institute of Health and Nutrition traces its history back to 1963, as a nutrition department within General Mills, created to strengthen the company's health and nutrition expertise. In 1998, the nutrition department was re-organized under the name 'Bell Institute of Health and Nutrition' to continue to advance excellence in nutrition, and advise General Mills on emerging nutrition capabilities. Named in honor of James Ford Bell, a lifelong scientist and former president and chairman of General Mills, our department continues to draw inspiration from his vision and innovative spirit. Recognizing the importance of nutrition, Bell's laboratories studied vitamins and developed a process for producing vitamin D to help increase the nutrient density of General Mills' products. Bell's legacy surpasses his immeasurable contribution to General Mills, to philanthropy, conservation, and the support of science. For more information, visit us at: www.bellinstitute.com/en

Kallyope
Nancy Thornberry
CEO

Kallyope is a new biotechnology company dedicated to unlocking the therapeutic potential of the gut-brain axis. The company was founded by Charles Zuker, Tom Maniatis, and Richard Axel, leading neuroscientists and molecular biologists from Columbia University. Headquartered in New York City, the company integrates cutting-edge technologies in sequencing, bioinformatics, neural imaging, cellular and molecular biology, and human genetics to provide an understanding of gut-brain biology that can be translated into transformational therapeutics and products that improve human health and nutrition.

Prolacta Bioscience, Inc.
Victoria Niklas, MD, MA
Chief Medical and Scientific Officer

Prolacta develops clinically proven, high-value products derived from human milk that are designed to meet the needs of extremely premature infants in the Neonatal Intensive Care Unit.

Whole Biome
Colleen Cutliffe, PhD
CEO and Co-Founder

Whole Biome's mission is to be the trusted brand in bringing the public improved health solutions through microbiome interventions. We are developing microbiome interventions and diagnostics using our proprietary discovery platform.

SESSION IV: STATE OF THE ART LECTURES, PART II

Chairs: Paul Micevych, PhD (Financial Disclosure: None)
Catia Sternini, MD (Financial Disclosure: None)

Sleep and Irritable Bowel Syndrome: A Metabolomics Approach
Margaret Heitkemper, PhD, RN, FAAN
Chair, Department of Biobehavioral Nursing and Health Systems, Affiliate Professor, Division of Gastroenterology, School of Medicine, University of Washington School of Nursing
Financial Disclosure: None

Self-reported sleep disturbances are well documented among persons with irritable bowel syndrome (IBS). Difficulty falling asleep, shorter sleep time, frequent arousal and awakenings, or non-restorative sleep are the most common manifestations. We and others have provided evidence of a positive association between subjective poor sleep quality and increased severity and frequency of gastrointestinal (GI) symptoms in those with IBS. Sleep disturbances are also related to higher risk of have GI complaints in individuals without IBS. However, findings from studies using objective sleep and activity measures, such as polysomnography and actigraphy, are less conclusive in linking objective sleep with IBS symptoms. Our laboratory has shown that the 'first night' effect is greater (e.g., increased time to sleep onset and increased time to REM sleep) in women with IBS relative to healthy control women. In addition, we have shown that cortisol levels are higher during early hours of sleep following exposure to a social stressor in women with IBS. Serotonin (5-HT) and melatonin (MT) are important neurochemicals in the gut and central nervous system. In the GI tract, levels of 5-HT are linked with bowel alterations (constipation, diarrhea) and pain sensitivity. Tryptophan (TRY, an essential amino acid) is the precursor for 5-HT and ultimately MT. A competing pathway in TRY metabolism leads to kynurenine (KYN) and its metabolites. KYN and its metabolites have an array of biological activities and elevations have been associated with inflammation, pain sensitivity and depression. Some evidence suggests that patients with IBS have alterations in both the KYN and 5-HT pathways. In this exploratory study we sought to examine plasma metabolites via liquid chromatography-mass spectrometry (LC-MS) in a group of healthy women (n=20) and women with IBS (n=39; IBS-diarrhea, n=28; IBS-constipation, n=21). Women (ages 18-45) were studied on the third night in a university sleep laboratory. Samples were obtained every 20 minutes, however, for this exploratory study, only 8 sampling time points every 80 minutes apart across the night were assayed and for analyses, collapsed to 4 samples/subject. Targeted metabolomics analyses were performed by the Northwest Metabolomic Research Center at the University of Washington. In the first stage, 107 metabolites were detected. Partial Least Squared Discriminant Analysis (PLS-DA) was used to provide a global test of the null hypothesis that none of the 107 metabolites differed between groups at any time point. This omnibus test showed significant group differences were present. We next performed a separate LC/MS for 14 TRY metabolites. As expected, both 5-HT and melatonin varied by time of night. With respect to group, 5-HT/TRY was lower in the IBS-diarrhea as compared to IBS-constipation group. While no group differences were found in the KYN pathway metabolites tested, there were significant relationships of some metabolites with sleep variables. Similarly, several indolepyruvate metabolites (indole-3-acetic acid and indole-lactic acid) were also related to sleep variables. For example, indolepyruvate/TRY was positively associated with total sleep time (p=.007) and percent time in REM sleep (p =.012). Several TRY metabolites (tryptamine, 5-HT, nicotinic acid) were associated with cortisol and cortisol/ACTH ratio. The results of this exploratory study suggest that targeted metabolomics approaches may be useful in examination of the gut-brain axis. However, this approach necessitates careful attention to sample collection methods, timing, sleep quality, diet (composition and timing) and participant's level of activity.

The Role of ERα in the Regulation of Feeding and Energy Homeostasis

Stephanie Correa, PhD
Assistant Professor, Department of Integrative Biology and Physiology, UCLA
Financial Disclosure: None

Estrogen signaling in the brain has many roles beyond reproduction, including profound effects on metabolism. Indeed, declining estrogen levels are associated with weight gain in postmenopausal women. While estrogen replacement therapy can reverse weight gain, it comes with a higher risk of reproductive cancers. This tradeoff has serious implications for women's health, as lifespan extends and women spend a larger proportion of their lives in a low estrogen, postmenopausal state. Our research aims to develop a mechanistic understanding of how estrogen signaling in the CNS promotes metabolic health.

Work in mice shows that estrogen signaling via estrogen receptor alpha (ERα) suppresses feeding and promotes energy expenditure. Eliminating ERα in mice leads to obesity due to increased feeding and decreased movement. Using gene ablation and chemogenetic tools, we identified a subpopulation of ERα+ neurons that are solely dedicated to promoting locomotion in female but not male mice. This specialized population is located in the ventromedial hypothalamus and is required for maintaining normal body weight. In contrast, the effects of ERα signaling on food intake are not mediated by the hypothalamus. Instead, we find a surprising and female-specific role for hypothalamic ERα in bone homeostasis. Our work has begun to pinpoint the neurons by which estrogen maintains normal body weight and promotes bone health, and has potential applications for combating postmenopausal obesity and osteoporosis.

The Role of ERα in the Protection Against Metabolic Disease

Andrea Hevener, PhD
Professor, UCLA Program on Genomics and Nutrition, Division of Endocrinology, Diabetes, and Hypertension, David Geffen School of Medicine at UCLA
Financial Disclosure: None

The increased life expectancy trends for women in the modern era suggest that we will be challenged with combating postmenopausal disease risk for over three decades of life. The lack of effective treatment strategies to contest the rising incidence of metabolic dysfunction and obesity during the menopausal transition is limiting our ability to restrain chronic diseases including type 2 diabetes, heart disease and certain forms of cancer in women. Improved interrogation of estrogens and their biological actions mediated by estrogen receptors (ERs) in the regulation of cardiometabolic health will enhance novel target discovery and promote the development of therapeutic strategies to curb metabolic related diseases. We and others have clearly shown a protective role of ERα in maintenance of metabolic homeostasis and insulin sensitivity in humans and rodents. For over a decade now, my laboratory has been engaged in a tissue-specific as well as cell autonomous interrogation of ERα to understand its mechanisms of action on metabolism and insulin action. Our recent studies show a strong role of ERα in the control of metabolic homeostasis by regulating mitochondrial remodeling and function. We show these ERα-induced regulatory mechanisms underlie the maintenance of glucose tolerance and insulin sensitivity, and are essential for the metabolic-related health benefit of chronic exercise training.

Thus, from a clinical perspective, refinement of our understanding regarding the biological actions of ERs will lay the framework for the design of better targeted therapies to improve the health of women while reducing undesired complications that have previously limited the efficacy and use of traditional hormone replacement interventions.

About the Speakers

Janine Clayton MD
NIH Associate Director for Research on Women's Health; Director, NIH Office of Research on Women's Health

Janine Austin Clayton, M.D., is Associate Director for Research on Women's Health and Director of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH). Since assuming this role in 2012, Dr. Clayton has strengthened NIH support for research on diseases, disorders, and conditions that affect women. She is the architect of a trans-NIH initiative to require scientists to consider sex as a biological variable across the research spectrum. As co-chair of the NIH Working Group on Women in Biomedical Careers with NIH Director Dr. Francis Collins, Dr. Clayton also leads NIH's efforts to advance women in science careers. Prior to joining ORWH, Dr. Clayton was the Deputy Clinical Director of the National Eye Institute (NEI), and has been an attending physician and clinical investigator in cornea and uveitis at the NEI since 1996. In the course of her research on ocular surface disease, she discovered a novel form of disease associated with premature ovarian insufficiency in young women, which set the stage for her commitment to rigorous, thoughtful exploration of the role of sex and gender in health and disease.

Stephanie Correa, PhD
Assistant Professor, Department of Integrative Biology and Physiology, UCLA

The Correa lab explores how reproductive hormones and reproductive status affect metabolic health and disease. In women, increased risk for obesity, stroke, and other cardiovascular disease often is associated with low estrogen levels at menopause. Work with rodents has established critical roles for central estrogen receptor alpha (ERα) signaling in both energy balance and fertility. We have developed novel mouse models of ERα deficiency to understand how estrogen modulates hypothalamic centers involved in energy intake, energy expenditure, and fertility. Our recent work defined a cluster of ERα-expressing neurons in the ventromedial hypothalamus that selectively drive spontaneous movement in female mice. Current studies continue to dissect the function of estrogen-responsive hypothalamic neurons and their associated circuits using new viral tools that provide spatial, molecular, and temporal specificity. This work will define the mechanisms by which the reproductive axis alters metabolic physiology in females and could ultimately provide potential avenues for combating obesity in women.

Colleen Cutliffe, PhD
CEO and Co-Founder, Whole Biome

Colleen Cutcliffe is the CEO and Co-Founder of Whole Biome Inc. She has over 15 years of experience leading and managing biology teams in academia, pharmaceuticals and biotechnology. Prior to starting Whole Biome, Colleen was the Senior Manager of Biology at Pacific Biosciences and a Scientist at Elan Pharmaceuticals. Colleen received her Ph.D. in Biochemistry and Molecular Biology from Johns Hopkins University and her B.A. in Biochemistry from Wellesley College.

Miguel Freitas, PhD
VP Scientific Affairs, Danone North America

Miguel Freitas is the Vice President of Scientific Affairs for Danone in North America, including The Dannon Company and other Danone subsidiaries in the geography, based in White Plains, NY. Dr. Freitas serves as a liaison between Danone and the scientific community. He is also responsible for ensuring the integrity of the Danone product portfolio with respect to health attributes and serves as a nutrition and scientific spokesperson for convention purposes and media related to brands and category topics. Dr. Freitas and his team manage a network of key opinion leaders and health care professionals (HCPs) on

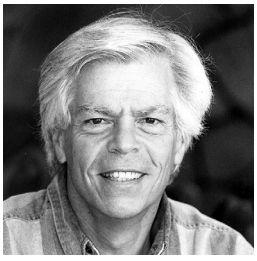
nutrition- and probiotic-related topics and implement scientific affairs programs targeting HCPs on behalf of several Danone brands. Dr. Freitas cooperatively works with Danone's consumer marketing, legal and corporate affairs departments in developing the nutrition and health components of messages, claims, communication tools and events to help inform the opinions and choices of HCPs and consumers.

Dr. Freitas also serves as a liaison between Danone's North American businesses and Danone's global research teams in France and the Netherlands, including the international research center of Danone, where he previously worked as a research project leader. In this capacity, he designed and managed research projects investigating human health and functional foods – in particular, probiotics – and communicated these findings to diverse audiences through business and marketing channels, presentations at scientific conferences, and the publication of studies in scientific journals.

Dr. Freitas earned his Ph.D. from the National Institute of Health and Medical Research (INSERM, Paris, France) and earned his M.S. from the College of Biotechnology (Oporto, Portugal).

Ashley Gearhardt, PhD
Assistant Professor, Department of Psychology, University of Michigan

Dr. Ashley Gearhardt is an Assistant Professor of Psychology in the Clinical Science area at the University of Michigan. She received her Ph.D. in clinical psychology at Yale University with training on the underpinnings of both excess food and alcohol consumption. Dr. Gearhardt currently investigates the contribution of reward dysfunction (e.g., craving, liking) to eating-related problems across the lifespan. She uses a multi-method approach to explore the neurobiological, attentional, and behavioral factors that contribute to problematic eating behavior. Dr. Gearhardt also investigates the role of addictive processes in compulsive overeating and is the Director of the Food Addiction Science and Treatment Laboratory. She has published over 40 peer-reviewed articles and her research has been featured on media outlets including the ABC News, Today Show, and Time Magazine.



Michael Goldstein, PhD
Former UCLA Associate Vice Provost, Healthy Campus Initiative; Professor Emeritus, Community Health Sciences and Sociology

Michael S. Goldstein, PhD (Brown University) is a professor emeritus of public health (Community Health Sciences) and sociology, and as UCLA's first Associate Vice Provost of the Healthy Campus Initiative, he served as the founding director of HCI who was instrumental in defining the core values that guide the initiative, establishing the infrastructure, identifying the major areas of concentration and faculty leaders in these areas. He has also served the campus as interim Vice Provost for Graduate Education and the Dean of the Graduate Division. Goldstein was co-principal investigator and program director of CHIS-CAM, an NCI-funded follow-up study to the 2001 California Health Interview Survey that examines use of complementary and alternative medicine (CAM) among California adults, particularly those with cancer and other chronic illnesses. At UCLA he teaches graduate courses on complementary and alternative medicine, self-help and self-care.

Goldstein's published research on health promotion spans 30 years. During the late 1980s, his research examined factors that led conventionally trained physicians to become involved with CAM. In the early 1990s, Goldstein spent two years conducting research at The Wellness Community, a support center for people with cancer. In the mid-1990s, he was among the first researchers supported by the Office of Alternative Medicine for his study of patient satisfaction with CAM. His current work deals with the potential for CAM providers to assume a greater role in the provision of primary care in the nation's health care system.

Goldstein is the author of two books: *The Health Movement: Promoting Fitness in America* (Macmillan 1992), and *Alternative Health Care: Medicine, Miracle, or Mirage* (Temple Univ. 1999). Both strive to understand changes in the way people seek to prevent and respond to serious illnesses as part of broader social and cultural changes in American society.

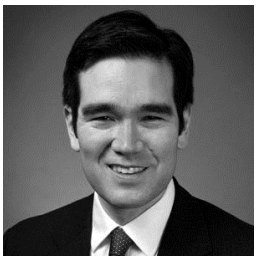
Margaret Heitkemper, PhD, RN, FAAN
Chair, Department of Biobehavioral Nursing and Health Systems, Affiliate Professor, Division of Gastroenterology, School of Medicine, University of Washington School of Nursing

Margaret McLean Heitkemper, PhD, RN, FAAN, is Professor and Chairperson, Department of Biobehavioral Nursing and Health Systems, Adjunct Professor, Division of Gastroenterology, and Co-Director, Center for Innovations in Sleep Self-Management at the University of Washington. Her research has focused on the pathophysiology and biobehavioral treatment of irritable bowel syndrome (IBS) and the interaction of stress and symptoms in children and adults. Current studies are examining blood and fecal metabolite levels in men and women with IBS. This work has been substantially funded by the National Institute for Nursing Research, National Institutes of Health.

Andrea Hevener, PhD
Professor, UCLA Program on Genomics and Nutrition, Division of Endocrinology, Diabetes, and Hypertension, David Geffen School of Medicine at UCLA; Iris Cantor - UCLA Women's Health Center

Dr. Hevener's laboratory studies the transcriptional regulation of metabolism and insulin action with a specific focus on the biological actions of hormone responsive nuclear receptors in metabolic tissues. Recently, Dr. Hevener's team showed that the expression of estrogen receptor (ER) α is dramatically reduced in muscle from women displaying clinical features of the Metabolic Syndrome (glucose intolerance and obesity). To test whether reduced ERα expression levels could promote metabolic dysfunction, the Hevener laboratory generated a mouse model in which ERα was specifically reduced in skeletal muscle. Interestingly, both female and male muscle-specific ERα knockout mice developed glucose intolerance, insulin resistance, and increased adiposity recapitulating the human pre-diabetes syndrome. Subsequent molecular studies conducted in the Hevener laboratory now show that ERα is critical in regulating mitochondrial fission-fusion-mitophagy dynamics and oxidative metabolism in skeletal muscle as well as adipocytes, pancreatic islets, and immune cells. Thus collectively, findings from the Hevener laboratory suggest a conserved action of ERα to control the architecture, health, and function of mitochondria, and these ERα-mediated effects may underlie, at least in part, the protective role of estrogen-ERα in combating chronic diseases associated with metabolic dysfunction.

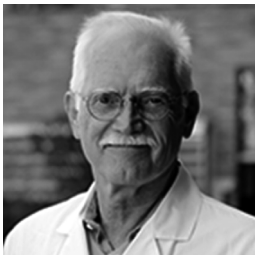
Dr. Hevener is a member of the UCLA Iris Cantor Women's Health Research Center and the executive committee of the NIH-sponsored UCSD-UCLA Diabetes Research Center. Dr. Hevener's laboratory is supported by the National Institutes of Health, UCLA Department of Medicine, the STOP CANCER Foundation I.C.O.N. Award, the UCLA CTSI and the Iris Cantor Women's Health Executive Advisory Board.



Jonathan Jacobs, MD, PhD
Clinical Instructor, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Jonathan Jacobs received a B.A. in Biochemistry from Harvard University and a M.D. from Harvard Medical School. During this time he trained in the laboratory of Diane Mathis and Christophe Benoist, where he investigated the immunologic mechanisms of an autoantibody-mediated model of arthritis. This research was supported by a fellowship from the Howard Hughes Medical Institute and resulted in three first-author publications, including one in Proceedings of the National Academy of Science. He completed a residency in internal medicine at Stanford University then joined UCLA as a gastroenterology fellow in 2010. He pursued additional research training at UCLA through the Specialty Training and Advanced Research program under the mentorship of Jonathan Braun. He was awarded a Ph.D. in Cellular and Molecular Pathology in 2015 for his work on the interactions of the mucosal immune system and the intestinal microbiome in inflammatory bowel disease (IBD).

Afterwards, he joined the UCLA Division of Digestive Diseases faculty as a Clinical Instructor. His ongoing projects employ in vivo models and multi'omics analysis of IBD cohorts to define the role of IBD-associated genes in shaping the intestinal microbiome and to identify microbial products that promote IBD. Dr. Jacobs co-founded the UCLA Microbiome Center in 2015 alongside investigators from the School of Medicine, School of Dentistry, CNSI, Life Sciences, Physical Sciences, and Engineering. He currently serves on the Steering Committee of the UCLA Microbiome Center and is the Director of the Microbiome Core.



Jake Lusis, PhD
Professor, Departments of Medicine, Cardiology, Human Genetics, Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA

Aldons (Jake) Lusis is Professor of Microbiology, Human Genetics and Medicine at the University of California, Los Angeles. He obtained his Ph.D. in Biophysics from Oregon State University and did postdoctoral work in molecular genetics and mouse genetics at Roswell Park Memorial Institute prior to joining the faculty of UCLA. His lab is interested in genetic and environmental interactions contributing to common forms of cardiovascular and metabolic disorders such as atherosclerosis, obesity, and diabetes. Some of the questions they are trying to tackle include: How do gut microbiota contribute to the disorders? Can epigenetic marks such as DNA methylation provide signatures of gene-by-environment interactions? How do sex differences contribute to disease susceptibility? To address such questions, they use a population-based approach, termed "systems genetics", that involves the analysis of intermediate phenotypes, such as global transcript levels, as well as the complex traits. The data are then integrated using correlation, genetic mapping, or various kinds of statistical modeling to generate hypotheses about the molecular pathways and interactions underlying disease. They follow up these hypotheses using standard molecular biology tools such as engineered mice. For studies in mice, they have developed a resource termed the Hybrid Mouse Diversity Panel, consisting of about 100 inbred strains that are well-characterized and highly diverse. These provide sufficient power for genome-wide association analyses. For studies in humans, they primarily use a cohort of about 10,000 Finnish men called METabolic Syndrome In Men (METSIM), developed by their colleague, Markku Laakso.

Ravi Menon, PhD
Senior Principal Scientist, Bell Institute of Health & Nutrition - General Mills Inc.

Ravi Menon is a Senior Principal Scientist in the Bell Institute for Health & Nutrition at General Mills Incorporate in Minneapolis, MN. He joined General Mills R&D in 2000. Ravi earned his doctoral degree in Biochemistry (Cancer Pharmacology) from the Advanced Center for Treatment, Research and Education in Cancer, at the Department of Atomic Energy, Bombay, India. He received his post-doctoral training in the laboratory of Prof. Richard Ham who pioneered the development of serum-free mammalian cell culture systems, at the University of Colorado in Boulder. Prior to joining General Mills, he was a Senior Scientist at Aastrom Biosciences in Ann Arbor, Michigan, where he worked on the development of retroviral vector delivery systems for gene therapy in hematopoietic cells. His current research interest at General Mills is in the area of gut microbes and health – particularly in understanding the impact of diets and dietary ingredients on the composition and resilience of gut microbial communities, and their associations with health. His interests also include the health benefits of probiotics and prebiotics.

Emeran Mayer, MD, PhD
Director, G. Oppenheimer Center for Neurobiology of Stress and Resilience; Co-Director, CURE: Digestive Diseases Research Center; Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Emeran A Mayer is a Gastroenterologist, Neuroscientist and Professor in the Departments of Medicine, Physiology and Psychiatry at the David Geffen School of Medicine at UCLA. He is the Executive Director of the G. Oppenheimer Center for Neurobiology of Stress and Resilience at UCLA, and co-director of the CURE: Digestive Diseases Research Center. As one of the pioneers and leading researchers in the role of mind-brain-body interactions in health and chronic disease, his scientific contributions to U.S. national and international communities in the broad area of basic and translational enteric neurobiology with wide-ranging applications in clinical GI diseases and disorders is unparalleled. He has published more than 300 scientific papers, and co edited 3 books. He is the recipient of the 2016 David McLean award from the American Psychosomatic Society. His most recent work has focused on the dialogue between the gut microbiota and the brain, the role of food addiction in obesity, and the role of the brain in chronic inflammatory diseases of the gut.

Mayer has a longstanding interest in ancient healing traditions and affords them a level of respect rarely found in Western Medicine. He has been involved in documentary film productions about the Yanomami people in the Orinoco region of Venezuela, and the Asmat people in Irian Jaya, and has recently co produced the award

winning documentary “In Search of Balance”.

Dr. Mayer has been interviewed on National Public Radio, PBS and by many national and international media outlets including the *Los Angeles Times*, *Atlantic* magazine and *Stern and Spiegel Online*. He has spoken at UCLA TEDx on the “Mysterious Origins of Gut Feelings” in 2015, and his book *The Mind-Gut Connection* was published by Harper&Collins in July of 2016 and has been translated into 10 languages.

Tannaz Moin MD, MBA, MSHS
Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, David Geffen School of Medicine at UCLA; HSR&D Center for the Study of Healthcare Innovation, Implementation & Policy, VA Greater Los Angeles Healthcare System

Tannaz Moin, M.D., M.B.A, M.S.H.S. is an Assistant Professor of Medicine in the Division of Endocrinology at the David Geffen School of Medicine at UCLA. She is an investigator on several federally funded research studies that focus on the comparative effectiveness research, as well as implementation and evaluation of health system- and health insurance-partnered interventions for patients with diabetes and prediabetes. In addition to seeing patients at the VA Greater Los Angeles, Dr. Moin is also a Core Investigator at the VA HSR&D Center for the Study of Healthcare Innovation, Implementation & Policy. She has led numerous projects to implement and evaluate diabetes prevention programs (DPP) for Veterans with prediabetes. Dr. Moin is a co-principal investigator on the VA Quality Enhancement Research Initiative (QUERI) EMPOWER program focused on the implementation of innovative care models in VA women’s health, in order to improve engagement and retention in evidence-based care for prediabetes, cardiovascular risk, and mental health conditions, which be the subject of her presentation today.

Victoria Niklas, MD, MA
Chief Medical and Scientific Officer, Prolacta Bioscience, Inc.

Dr. Victoria Niklas earned her Master’s Degree from Harvard University and MD from Harvard Medical School. She completed a residency in Pediatrics at the Children’s Hospital of Los Angeles and a fellowship in Perinatal and Neonatal medicine at UCLA.

She is currently the Chief Medical and Scientific Officer at Prolacta Bioscience, where she leads the Research and Development team in developing next-generation products from human milk. She also continues to serve as a Professor of Pediatrics at the UCLA David Geffen School of Medicine.

Dr. Niklas is passionate about uncovering therapeutic potentials in human milk and transforming that knowledge into meaningful solutions in health care. Prior to joining Prolacta, she served as the Director of the Neonatal Intensive Care Unit and Newborn Services at Olive View–UCLA Medical Center. Dr. Niklas’ research has focused on neonatal gastrointestinal immunology and the role of lactoferrin, an immune protein found in high abundance in human milk, in reducing infections and necrotizing enterocolitis in premature newborns. She is an experienced clinical practitioner, educator, mentor and a leader of neonatal intensive care. Dr. Niklas has also been responsible for groundbreaking research in neonatal intestinal immunology and is a recognized expert in mouse models of intestinal immune T cell development and the pathogenesis of necrotizing enterocolitis.

Helen Raybould, PhD
Professor, Departments of Anatomy, Physiology and Cell Biology, UC Davis

Dr. Raybould did her PhD in Physiology with Graham Dockray, FRS at the University of Liverpool in the UK. Her thesis was on the role of gut peptides in the gut-brain axis. She went on to a postdoctoral position at UCLA School of Medicine at the UCLA Digestive Diseases Research Center, then headed by John Walsh where she worked with Yvette Taché on the gut-brain axis. She collaborated with many faculty here at UCLA (1986-2000) including Drs. Mayer, Sternini, Walsh and Reeve. In 2000, she moved to UC Davis School of Veterinary Medicine where she maintains a very active research program. Dr. Raybould has received several recognitions for her research and service. She was a councilor for the American Physiological Society and Associate Editor for American Journal of Physiology Gastrointestinal and Liver Section for 9 years and was

recognized as one of the Inaugural Fellows of the Society in 2015. She has served in leadership roles for several other societies including American Gastroenterology Association, Society for the Study of Ingestive Behavior and the Obesity Society. She has set on several NIH study sections.

I am an integrative physiologist with training in neurophysiology and gastrointestinal physiology. My research focuses on understanding the mechanisms by which the vagal afferent pathway (the gut-brain axis) transmits information about gut luminal contents to the brain to regulate gut physiology and feeding behavior. We study how these pathways are altered in metabolic disease including obesity and type 2 diabetes, and how the gut-brain pathway contributes to altered food intake behavior and metabolism. Recently, we have elucidated how gut microbiota and intestinal permeability are altered in rodent models of microbial dysbiosis and how this may drive changes in signaling in the gut-brain pathway. My laboratory has expertise in *in vivo* and *ex vivo* measurement of gastrointestinal physiology, including gastric motility, GI transit, GI secretion and intestinal permeability in rodents and pigs. My program is committed to understanding how the gut microbiota is influenced by diet, including different types of dietary fiber, and how this influences behavior, as well as gut physiology and whole body homeostasis. I have an active and funded collaboration with the Milk Bioactives Program (Food for Health Initiative, UC Davis) to help elucidate the interactions between prebiotic compounds in milk with probiotic bacteria, and how this interaction produces bacterially-derived factors that are beneficial to the host. The goal of this work is to identify and determine the mechanism of action by which bacterial metabolites influence the gut-brain axis. Our efforts to understand how components of the diet interact with the gut microbiota and the host are not limited to milk bioactives; we have made novel observations on how various dietary fibers, such as nopal and inulin, interact with the gut microbiota to influence intestinal barrier function and the plasma metabolome in rodents and pigs.

Nancy A. Thornberry
CEO, Kallyope

Nancy A. Thornberry is CEO at Kallyope, a biotechnology company headquartered in NYC focused on the gut-brain axis. She was formerly Senior Vice President and Franchise Head, Diabetes and Endocrinology, for Merck & Co. Inc. In this role, she led discovery and clinical research in diabetes, osteoporosis, fertility and contraception. Prior to her role as Franchise Head, Nancy initiated and led Merck's dipeptidyl peptidase 4 (DPP-4) project, which resulted in the discovery of JANUVIA® for the treatment of Type 2 diabetes.

Nancy began her career with Merck Research Laboratories in 1979 as a biochemist and served in many roles of increasing responsibility, culminating in her role as Franchise Head. Beyond her contributions in the metabolic disease areas, she achieved several notable scientific accomplishments, including the identification of the first caspase, interleukin-1β converting enzyme (ICE/caspase-1). For her scientific contributions she has received numerous awards, including the Merck Presidential Fellowship, Merck Directors Award, Heroes of Chemistry Award by the American Chemical Society, and in 2011 received the Pharmaceuticals Research and Manufacturers of America (PhRMA) Discoverers Award, which honors research scientists whose work has been of special benefit to humankind.

In addition to her role at Kallyope, Nancy is currently on the Boards of Directors of Intarcia Therapeutics and Abide Therapeutics.

Brian Varnum, PhD
Chief Development Officer, C3J Therapeutics

Dr. Varnum is a biotech veteran with more than twenty years of experience. He began his career with Amgen, and spent more than 18 years at the biotech pioneer as the company grew from a start-up to the largest and most successful biotechnology company. Brian worked in multiple roles, making contributions from discovery research through product launch with a significant focus on bringing new molecules out of the lab and into the clinic. After this experience, Brian joined startups favoring the dynamic entrepreneurial environment. In the 3+ years since joining C3J, he has contributed to the mechanistic understanding of the lead molecule, advanced formulation development for oral and intestinal delivery, and shaped clinical development and pipeline expansion. Brian obtained his Ph.D. from UCLA studying oncogenes, and his drug development research experience includes hematopoietic growth factor discovery, oncology, auto-immune/inflammatory disorders, personalized medicine in IBD and infectious diseases.

Abstracts of Posters
Basic and Translational

1.

Crohn's Disease-associated Microbes Produces Ascorbate to Regulate Human T Cell Responses

Yu-Ling Chang[1,2], Maura Rossetti[3], Gemalene Sunga[3], David Casero[2], Jonathan Jacobs[4], Jonathan Braun[2]

[1]Molecular Biology IDP, University of California, Los Angeles; [2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles; [3]Immune Assessment Core, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California; [4]Division of Digestive Diseases, Department of Medicine, University of California Los Angeles

The unique microbial composition has been associated with Crohn's Disease (CD) and the CD4+ T cell activation and plasticity are reported to regulate disease progression. However, it remains unclear how microbes crosstalk with host immune responses and regulate disease biology. This study hypothesized that microbial producing metabolites regulate T cell responses to control CD progression. We generated a list of predicted CD-associated microbial producing metabolites using metagenomic analyses and designed an in vitro screening system to look for metabolites regulating human T cell functions. Twelve out of 100 metabolites (12%) were found regulating human CD4+ T cell cytokine productions, including selectively inhibiting (enhancing) specific subsets of cytokines, or a pan-inhibition (enhancement) of all of tested cytokines (Figure 1). A further investigation suggested a novel mechanism of how ascorbate regulates T cell function. Ascorbate reduced the activated T cells, but not resting T cells, by causing apoptosis in the activated CD4+ T cells (Figure 2). A backward bioinformatics search demonstrates a group of bacteria that produces ascorbate and has been reported positively associated with CD disease progression. Together, this study presented that microbes producing ascorbate regulate host CD4 T cell responses and that is a novel mechanism to explain CD pathogenesis.

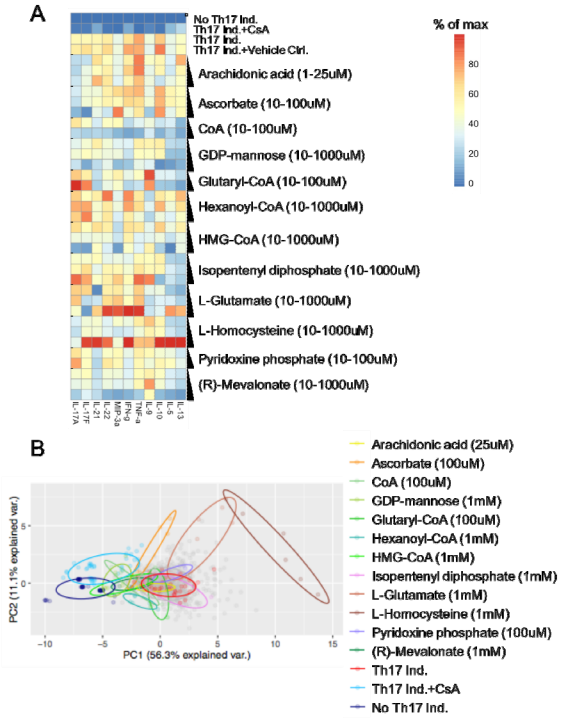
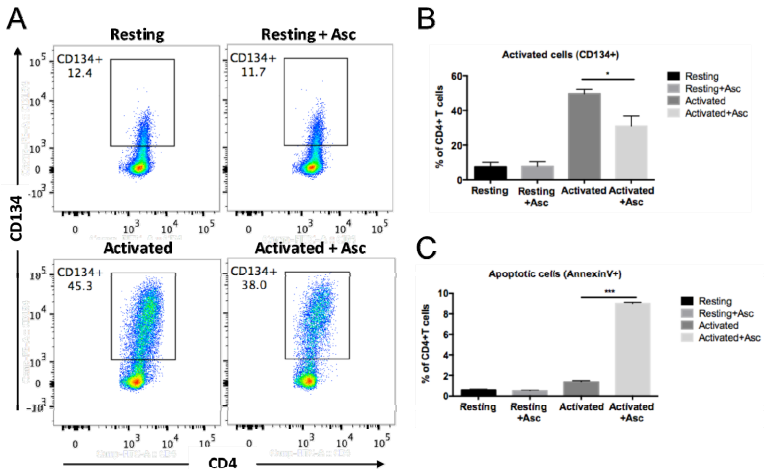


Figure 1 (Left): Twelve metabolites altered CD4+ T cell cytokine secretion. (A) Heat map of relative cytokine releases in metabolite--treated samples. Cytokine production (column) was scaled on the maximum production of each cytokine. Metabolite--treated samples (rows) were ordered by increasing concentrations which tested ranges were indicated. CsA (cyclosporine A) served as control for cytokine inhibition;; 0.01% DMSO was the vehicle control. CoA: Coenzyme A;; HMG--CoA: 3--hydroxy--3--methyl--glutaryl--coenzyme A;; Th17 Ind: Th17 induction. (B) Principal component analysis of relative cytokine release in metabolite--treated samples. Each dot represents a sample, color--coded according to the condition. Only samples treated with the metabolites at indicated concentration(s) were included. Gray dots represent all of the samples that were treated with metabolites but showed no significant differences from the Th17 induction group. Normal contour lines with probability of 68% for each condition are included.

Figure 2 (Below): Ascorbate selectively kills activated T cells. CD4+ T cells were cultured in 10 ng/ml of IL--7 (resting) or activated with 1ug/ml anti--CD3/anti--CD28 antibody (activated) for 48 hours to measure (A and B) T cell activation marker CD134 by flow cytometry. (A) Representative plot (B) Summary of three independent experiments are shown. (C) Cell viability were measured by Annexin V and three independent experiments are shown.



2.

Role of Sex-Dependent Adipose Lipocalin-2 Expression in Regulating Insulin Resistance and Non-Alcoholic Fatty Liver Disease Progression

Karthickeyan Chella Krishnan, Simon Sabir, Calvin Pan, Brian Parks, Nam Che, Sarada Charugundla, Zhiqiang Zhou, Hannah Qi, Simon Hui, Frode Norheim and Aldons J. Lusis

Department of Medicine/Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles, CA; Department of Psychology, University of California, Los Angeles, CA; Department of Nutritional Sciences, University of Wisconsin, Madison, WI

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term encompassing a range of liver abnormalities from simple steatosis (fat accumulation in hepatocytes) to complex non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. The prevalence of NAFLD in the United States has increased dramatically over the past few decades. Population studies have strongly associated obesity, diabetes and insulin resistance (IR) to NAFLD. Regulation of secreted cytokines and proteins from adipose tissue, collectively known as adipokines, is known to contribute to the pathogenesis of several metabolic diseases including obesity, IR and NAFLD via their crosstalk between other tissues like liver and skeletal muscle. Numerous adipokines have been identified so far; however, specific-signalling pathways activated by most of these adipokines and/or mechanism(s) by which they communicate with liver (and other tissues) are currently unknown. It is therefore essential to determine the functional consequences of these adipokines in regulating normal metabolic homeostasis to understand how they are disrupted in patients with obesity, IR and NAFLD. Lipocalin-2 (LCN2) is a 25kDa secretory glycoprotein, first isolated from neutrophils; however, recent evidences have shown LCN2 as a novel adipokine that is up regulated in adipose tissues of genetically obese animals and humans. LCN2 was also proposed to be involved in regulating IR. Moreover, we have recently shown that Adipose Lcn2 expression is negatively regulated by estradiol using female mice from over 100 genetically different inbred mice strains that were maintained on high-fat, high-sucrose (HF/HS) diet for 8 weeks. Recently, LCN2 has also been implicated in recruiting neutrophils to the liver in both alcoholic and non-alcoholic steatohepatitis (ASH and NASH), a severe condition of the liver. To determine the causal mechanistic insights mediating diet-induced obesity, IR, and NAFLD, we have collected phenotypes associated with obesity (fat mass, lean mass and weight of three visceral adipose depots), IR (serum levels of glucose, insulin and HOMO-IR) and liver steatosis (liver triglyceride levels) from both males and females of over 100 different strains of inbred mice subjected to HF/HS diet for 8 weeks. In addition, total RNA from adipose and liver tissues of these 100 strains were subjected to microarray, which after normalization resulted in 22,416 remaining probesets. The goal of our current study is to use a systems genetics approach to investigate the role and mechanism by which LCN2, a secreted adipokine, in response to diet-induced obesity, regulates IR and NAFLD in a sex-specific manner.

Figure 1 HMDP obesity study

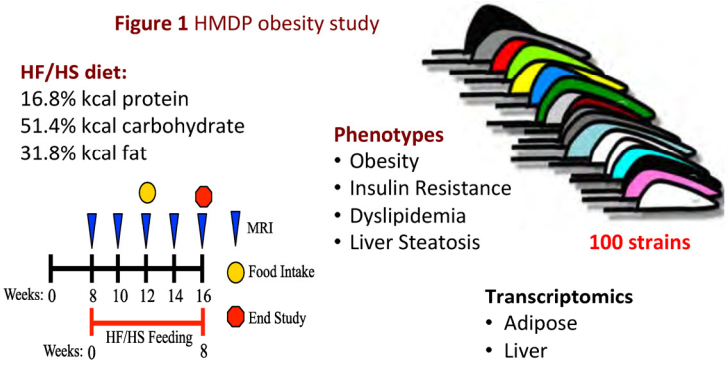
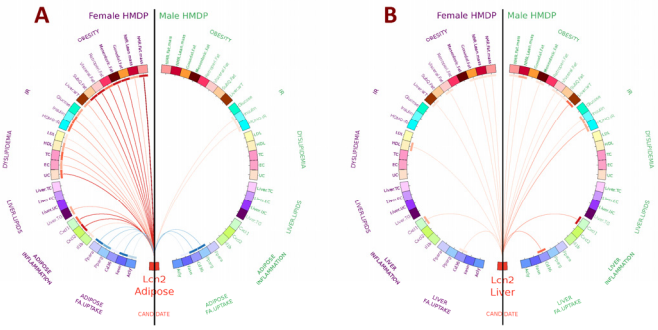


Figure2 Associations between Lcn2 and metabolic traits (FDR<1%)



- Female adipose – stronger associaSons even at higher threshold
- Male adipose – moderate associaSons with IR and FA uptake
- No significant difference between male and female liver
- Liver – moderate associaSons

3.

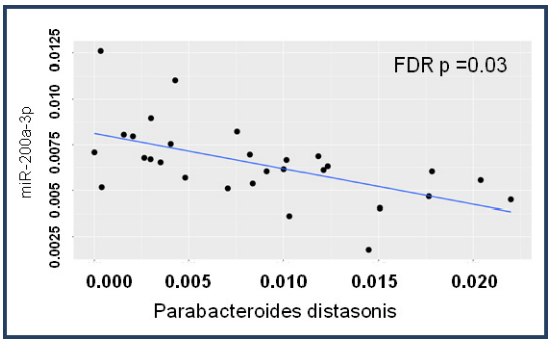
Colonic Mucosal Microbiome is Associated with Mucosal MicroRNA Expression in Irritable Bowel Syndrome

Swapna Mahurkar-Joshi, Jennifer Labus, Jonathan P Jacobs, Elizabeth J Videlock, Dimitrios Iliopoulos, Emeran A Mayer, Lin Chang.

Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

Background: Irritable bowel syndrome (IBS) is a stress-sensitive disorder characterized by altered brain-gut interactions. While alterations in fecal microbiota have been reported in IBS, studies evaluating the role of mucosal microbiota in the pathogenesis of IBS are few. Fecal microRNA (miRNA) plays a role in modulation of the gut microbiota, however, the role of mucosal miRNAs in regulating gut mucosal microbiota is unclear. **Aim:** 1) To compare mucosal microbial alpha and beta diversity between IBS and healthy controls (HCs); 2) To identify clusters driven by microbial composition and their association with clinical traits; and 3) To identify mucosal microbial species that correlate with miRNA expression. **Methods:** 53 Rome III + IBS patients (66% F, mean age 33.2 yrs, 20 IBS-D, 23 IBS-C, 10 IBS-M) and 32 HCs (44% F, mean age 31.31 yrs) underwent sigmoidoscopy with sigmoid colon biopsies. Microbial DNA was extracted and V4 region of 16S RNA genes were sequenced on Illumina HiSeq. RNA was extracted from a subset (N=44, 29 IBS and 15 HCs) of samples. MiRNAs were measured using NanoString nCounter technology. Analyses were performed using Qiime and R. Associations with clinical traits including IBS symptoms were analyzed using linear regression. Spearman correlations were performed between filtered and scaled microbial species (relative abundances) and miRNAs for multi-omics analysis. **Results:** Alpha and beta diversities were not different between mucosal microbiome of IBS patients and HCs ($p>0.05$). Three clusters were identified using hierarchical clustering of unweighted unifrac distances using all subjects. Cluster 1 (62.5% of the samples) was enriched in Bacteroidetes and Firmicutes, Cluster 2 (29.5% of samples) was predominantly enriched in Bacteroidetes and Cluster 3 (8% of samples) was enriched in Proteobacteria. We found 24 species associated with the cluster differences (FDR $p<0.05$). Clusters 1 and 2 were enriched in women compared to Cluster 3 ($p<0.05$). IBS symptom severity, bowel habit subtype and other clinical traits did not differ between clusters when adjusted for sex. Multi-omics analysis identified 7 significantly correlated miRNA-bacteria pairs in IBS that were not seen in HCs (FDR $p<0.1$). Hsa-miR-200a/ Parabacteroides distasonis showed highest correlation (rho= -0.67, FDR p=0.03, Figure). MiR-200a targets transcription factors ZEB1 and ZEB2 which regulate E-cadherin expression, affecting the initiation and stabilization of cell-cell adhesion. Parabacteroides distasonis has been found to be associated with reduced E-cadherin in celiac disease. **Conclusions:** Distinct clusters of microbiota were identified in mucosal biopsies in IBS. Distinct miRNAs may play a role in shaping gut microbial composition in IBS.

Figure: Relationship between miR-200a-3p and Parabacteroides distasonis.



4.

Regulation of Myeloid Immune Cells and Remyelination Are Both Necessary for Neuroprotection in EAE

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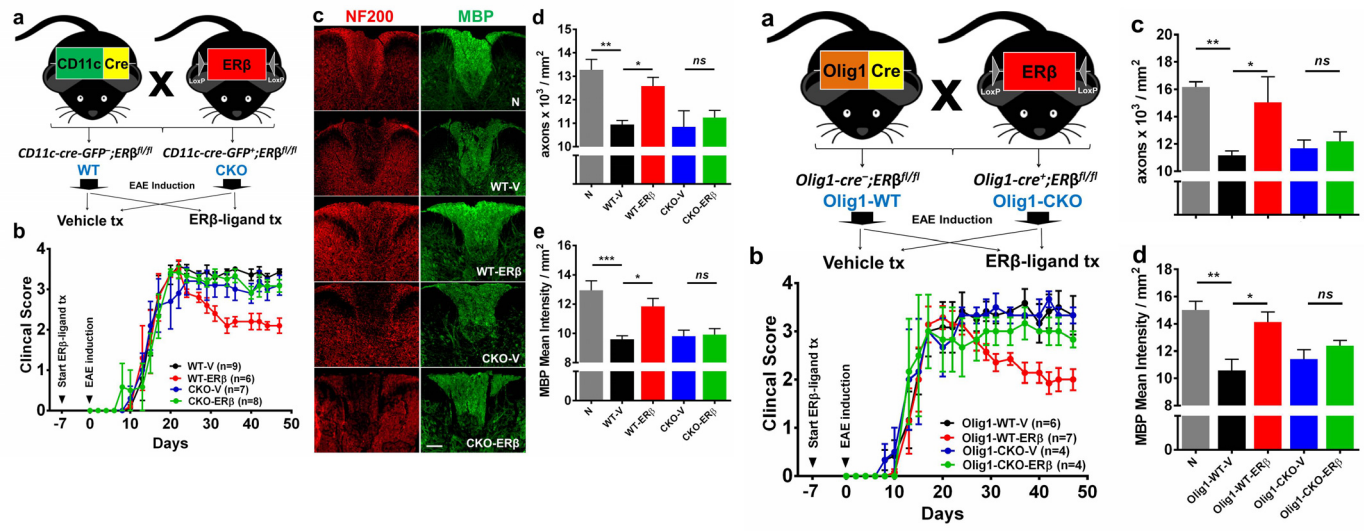
Strategies to induce remyelination in the central nervous system (CNS) during multiple sclerosis (MS) must consider the role of inflammation. In the MS model, experimental autoimmune encephalomyelitis (EAE), treatment with estrogen receptor beta (ERβ)-ligands are neuroprotective. Previous studies using cell specific conditional knockouts (CKO) showed that ERβ in oligodendrocyte lineage cells mediates remyelination. However, whether there are direct effects on microglia or myeloid dendritic cells and macrophages *in vivo* during EAE remained unknown. Here we generate mice with ERβ deleted from CNS resident microglia and peripheral myeloid cells, then use bone marrow chimeras to show that ERβ in $CD11c^+$ peripheral myeloid cells, not microglia, mediates neuroprotection *in vivo* during EAE. Further, we show that ERβ in $Olig1^+$ pre-OPCs is also necessary for neuroprotection. Together these results demonstrate that regulation of the inflammatory microenvironment and remyelination are both needed for neuroprotection, and one without the other will not suffice.



5.

Role of Mu and Delta Opioid Receptors and Their Ligands, B-endorphin and Pro-enkephalin, in Stress-induced Visceral Analgesia in Male and Female Mice

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Background: Repeated exposure to water avoidance stress (WAS), a mild psychological stressor, induces stress-induced visceral analgesia (SIVA) to colorectal distension (CRD) in rodents by recruiting both opioid-dependent and -independent pathways in a sex-dependent manner. However, which opioid receptors and ligands are involved is unknown. **Aims:** To determine the opioid receptors and ligands that contribute to SIVA in a is sex-dependent manner. **Methods:** Male and female mice deficient in mu-opioid receptors (MOR KO), delta opioid receptors (DOR KO), or their ligands; beta-endorphin (BEND KO), pre-pro-enkephalin (pENK KO) and respective wild-type littermates (WT) (6-8 months, 21-25g females, 30-35g males) were used. After a baseline CRD (15, 30, 45 and 60 mmHg, 3 times, 10 sec, 5 min intervals), mice were subjected or not to repeated WAS (rWAS, 1h/day, 4 days), followed by a 2nd CRD immediately after the last stress/no stress session (IMM) and a 3rd CRD 24h later (24h). The visceromotor response (VMR) to CRD was monitored using a non-invasive manometric approach. Results expressed in AUC/min were analyzed using 2-way ANOVA and Bonferroni post-hoc test. **Results:** MOR KO: Male, but not female,WT developed a SIVA at 24h (60 mmHg: 32.1±6.8 vs 64.2±11.2 AUC/min, $p<0.01$), that was abolished in MOR KO males. pENK KO: WT males (60 mmHg: 20.7±5.4 vs 45.9±12.2 AUC/min, $p<0.05$) and females (45 and 60 mmHg: 25.2±6.4 and 24.4±5.1 vs 53.0±10.6 and 51.3±9.4 AUC/min, $p<0.05$) exhibited an IMM SIVA, no longer present in males and females pENK KO. DOR KO: Male WT exhibited an IMM and 24h SIVA (60 mmHg: 11.4±1.8 and 10.9±4.0 vs 27.8±3.7 AUC/min, $p<0.05$, respectively), that was absent in DOR KO males. In females WT and DOR KO, the VMR was not modified compared to baseline. BEND KO: rWAS did not alter the VMR of male WT, male BEND KO and female WT, but induced SIVA in BEND KO females at 24h (60 mmHg: 28.3±6.1 vs 61.8±7.7 AUC/min, $p<0.01$). In all genotypes, repeated CRD per se did not change the VMR to CRD except in male WT of DOR KO which showed an IMM and 24h SIVA (60 mmHg: 22.6±2.8 and 32.5±8.7 vs 55.9 ±8.1 AUC/min, $p<0.05$), and male BEND KO mice which developed IMM visceral hyperalgesia (60 mmHg: 63.5±10.8 vs 33.9±4.0 AUC/min, $p<0.01$). **Conclusions:** Our data support the prevalence of SIVA in WT male compared to female mice. They also highlight the modulatory influence of opioid receptors and their ligands on SIVA in a sex-dependent manner with MOR, DOR and pENK signaling playing a role in males, and pENK in females. BEND knockdown in male mice abolishes SIVA and leads to visceral hyperalgesia in non-stressed animals while revealing SIVA in females. Future work to delineate whether these opioid signaling mechanisms modulating SIVA are localized at supraspinal or spinal sites and their relationship with sex is warranted.

Table: Alterations of visceral sensitivity in MOR KO, DOR KO, pENK KO and BEND KO mice and their wild-type littermates in response to rWAS or repeated CRD (sham).

Genotype		rWAS		sham	
		Male	Female	Male	Female
MOR	WT	SIVA 24h	--	--	--
	KO	--	--	--	--
DOR	WT	SIVA IMM, 24h	--	VA IMM, 24h	--
	KO	--	--	--	--
pENK	WT	SIVA IMM	SIVA IMM	--	--
	KO	--	--	--	--
BEND	WT	--	--	--	--
	KO	--	SIVA 24h	VH IMM	--

SIVA: stress-induced visceral analgesia,
VA: visceral analgesia,
VH: visceral hyperalgesia

6.
Sex-dependent Alterations of Colonic Epithelial Permeability in Irritable Bowel Syndrome

Muriel Larauche, Swapna Mahurkar-Joshi, Mandy Biraud, Tiffany Ju, Nafeesa Islam, Emeran A Mayer, Lin Chang

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Background: Increased intestinal permeability has been identified as a likely pathophysiological mechanism of irritable bowel syndrome (IBS). Increased colonic epithelial permeability is associated with visceral nociception in rodents and abdominal pain severity in IBS patients. Although IBS is more common in women, most studies on IBS-associated epithelial dysfunction have largely overlooked sex as an important variable. **Aims:** To determine if colonic epithelial function differs: 1) between IBS and healthy controls (HCs), 2) by sex, and 3) by bowel habit predominance. **Methods:** Men and women Rome III + IBS patients and HCs completed a bowel symptom questionnaire which assessed GI symptoms including BSQ abdominal pain rating at screening, 24h prior and immediately post procedure. Sigmoid colon biopsies were collected during a flexible sigmoidoscopy and used to determine the epithelial function *ex vivo* in Ussing chambers. Short-circuit current (Isc), transepithelial resistance (TER) and mucosal permeability to FITC-dextran (FD4) were assessed. At the end of the experiment, carbachol (CCh, 10 mM) was added on the serosa to assess tissue viability and responsiveness to a muscarinic agonist. Statistical analyses were performed using linear regression and ANOVA using R software. **Results:** 34 IBS patients (71% F, mean age = 26 yrs) and 11 HCs (45% F, mean age= 27.5 yrs) were enrolled. Even though the IBS group included more women, the difference was not statistically significant ($p>0.05$), with 9 IBS-C, 15 IBS-D, 8 IBS-M and 3 IBS-U. Overall, IBS patients exhibited lower TER (15.8 ± 0.9 vs 21.3 ± 1.8 Ω/cm^2, $p<0.001$) and higher mucosal permeability to FD4 (serosal [FD4]: 258.1 ± 22.7 vs 169.3 ± 21.0 mg/mL; $p<0.05$) compared to HC. Isc was not different. These differences were no longer significant when controlled for sex. When analyzed by sex, IBS men had lower TER vs HC men ($p<0.01$) while it was similar in IBS women and HC women (Table). Within HC, women had lower TER ($p<0.01$) and higher FD4 permeability ($p<0.05$) vs men, while in the IBS, only FD4 permeability was higher in women vs men ($p<0.05$). Both women and men with IBS showed a trend for higher serosal [FD4] ($p=0.059$ and $p=0.057$) vs HC women and men, respectively. Bowel habits had no influence on TER or FD4 permeability but IBS-C patients exhibited higher Isc in response to CCh (191.2 ± 25.3) vs IBS-D (125.1 ± 7.0, $p<0.05$) and IBS-M (122.2 ± 10.1, $p<0.01$). Abdominal pain symptoms at baseline and at time of the procedure were not associated with TER or FD4 concentration ($p>0.05$). **Conclusions:** These data support a major influence of sex on sigmoid colon epithelial permeability independent of IBS diagnosis. Further studies are needed to delineate if intestinal permeability interacts with other factors (e.g., microbiome, immune function) in the pathophysiology of IBS and if these interactions differ by sex.

Table 1: Measures of short-circuit current, TER and FD4 serosal concentration in sigmoid colon biopsies.

Groups	n	Isc (μA/cm^2)	TER (Ω/cm^2)	serosal [FD4] (μg/ml) (2h)
HC men	6	77.2 ± 8.2	25.0 ± 1.6	126.1 ± 16.9
HC women	5	91.7 ± 19.7	14.8 ± 1.0++	221.2 ± 27.4+
IBS men	10	65.8 ± 7.3	18.0 ± 1.4**	186.0 ± 23.8
IBS women	24	79.7 ± 8.6	15.8 ± 1.0	289.4 ± 28.7++

**p<0.01 vs HC men,
+ p<0.05,
++p<0.01 vs respective men group.

7.

Estriol Preserves Axonal Integrity and Cortical Volume in Experimental Autoimmune Encephalomyelitis

Cassandra E. Meyer, Hadley Johnsonbaugh, Josephine L. Gao, Stefano Lepore, Mandavi R. Oberoi, Noriko Ito, Rhonda Voskuhl, Allan MacKenzie-Graham

Department of Neurology, David Geffen school of Medicine at UCLA

Despite wide symptomatic variability in multiple sclerosis (MS), grey matter atrophy has consistently emerged as a strong indicator of clinical disability. In fact, evidence suggests progressive loss of grey matter correlates with physical and cognitive dysfunction better than many other commonly occurring hallmarks of MS, including enhancing lesions and lesion burden. Current treatment options are primarily designed to reduce inflammation and have had only modest success at slowing grey matter atrophy. Sex differences in the prevalence and progression of MS have indicated a possible neuroprotective role for sex hormones. Treatment with the sex hormone, estriol, has been shown to both reduce relapses and preserve grey matter in MS and in its most commonly used mouse model, experimental autoimmune encephalomyelitis (EAE). In this study, we sought to elucidate the mechanism by which estriol treatment preserves grey matter. Our investigation involved implanting either an estriol or placebo pellet subcutaneously in female THY1-YFP+ mice prior to EAE induction with myelin oligodendrocyte glycoprotein (MOG) peptide. *In vivo* Magnetic Resonance Images were collected 20 days after disease induction. Following image acquisition, the mice were sacrificed and Clear Lipid-exchanged Acrylamide-hybridized Rigid Imaging-compatible Tissue-hYdrogel (CLARITY) was performed on the brain and spinal cord. Volumetry analysis revealed preservation of cortical volume in estriol-treated mice with EAE when compared to vehicle-treated mice with EAE. CLARITY images demonstrated that estriol treatment resulted in preservation of cortical layer V pyramidal neurons and reduced formation of axonal ovoids and end bulbs in the spinal cord. Through cross-modality analysis, our results shed light on the relationship between cortical atrophy and axonal transection as well as implicate a neuroprotective role for estriol in EAE.

8.

***In vivo M*agnetic Resonance Images Reveal Neuroanatomical Sex Differences through the Application of Voxel-based Morphometry in C57BL/6 Mice**

Cassandra E. Meyer, Florian Kurth, Stefano Lepore, Josephine L. Gao, Hadley Johnsonbaugh, Mandavi R. Oberoi, Allan MacKenzie-Graham

Department of Neurology, David Geffen school of Medicine at UCLA

Behaviorally relevant sex differences are often associated with structural differences in the brain and many diseases are sexually dimorphic in prevalence and progression. Characterizing sex differences is imperative to gaining a complete understanding of behavior and disease which will, in turn, allow for a balanced approach to scientific research and the development of therapies. In this study, we generated novel tissue probability maps (TPMs) based on 30 male and 30 female *in vivo* C57BL/6 mouse brain magnetic resonance images and used voxel-based morphometry (VBM) to analyze sex differences. Females displayed larger anterior hippocampus, basolateral amygdala, and lateral cerebellar cortex volumes, while males exhibited larger cerebral cortex, medial amygdala, and medial cerebellar cortex volumes. Atlas-based morphometry (ABM) revealed a significant sex difference in cortical volume ($p = 6.97 \times 10^{-9}$) and no difference in whole cerebellar volume. This validated our VBM findings that showed a larger cerebral cortex in male mice and a pattern of dimorphism in the cerebellum where the lateral portion was larger in females and the medial portion was larger in males. These results are consonant with previous *ex vivo* studies examining sex differences, but also suggest further regions of interest. This is the first report of voxel-based morphometry used to identify sex differences in the *in vivo* mouse brain.

9.

Calcium Channel Blockers Decrease Bacterial Pathogenicity: Novel Applications

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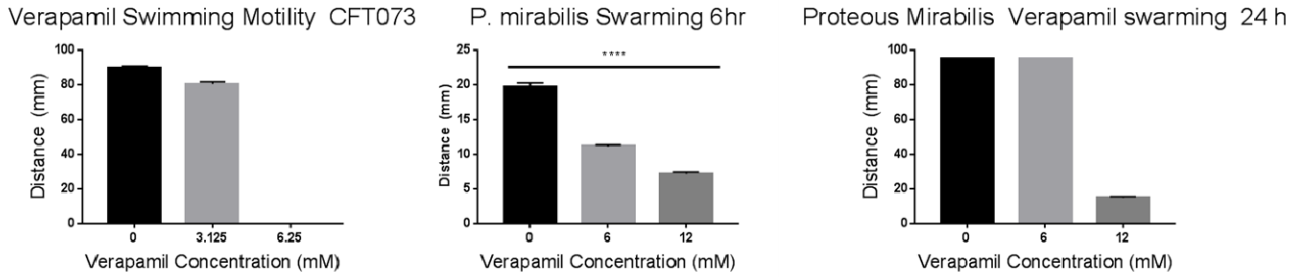
Wake Forest Institute for Regenerative Medicine

Introduction: Calcium channel blockers are widely used in the treatment of cardiovascular diseases. Microbial aggregation and biofilm formation are leading causes of infectious complications in patients with indwelling urinary catheters, central venous catheters and artificial cardiac valves. Calcium homeostasis is critical for multiple functions including motility and biofilm formation in bacteria. We report here that swimming motility in pathogenic *Escherichia coli* and *Proteus mirabilis* is inhibited by verapamil, a calcium channel blocker. The central hypothesis

for this study is that Calcium channel blockers will prevent bacterial motility and biofilm formation. **Methods:** First, we tested the effect of various concentrations of verapamil on growth of common bacterial pathogens *E. coli*, *P. mirabilis* and *Klebsiella pneumoniae*. At high doses (≥12 mM) verapamil was able to inhibit growth of these pathogens. Next, we tested the effect of verapamil, at levels that does not affect bacterial growth (3 and 6 mM), on swimming motility *in vitro*. **Results:** Our results revealed that verapamil inhibits flagella-mediated swimming motility in *E. coli* (strains CFT073 and UTI89) and also in *P. mirabilis*. **Conclusion:** We identified that verapamil decreases motility of tested bacterial pathogens in a dose-dependent manner. Further *ex vivo* and *in vivo* experiments are necessary to determine if Calcium channel blockers could be repurposed as therapeutics or prophylactic target against bacterial pathogens that rely on motility and biofilm formation to induce pathogenesis.



10.

The Genetic and Hormonal Control of Liver Ceramides and Their Role in Insulin Resistance and Sex Differences

Frode Norheim[1], Thomas Bjellaas[2], Simon T. Hui[1], Calvin Pan[1], Brian W. Parks[3], Thomas E. Gundersen[2], Margarete Mehrabian[1], Christian A. Drevon[4], Andrea L. Hevener[5], Aldons J. Lusis[1]

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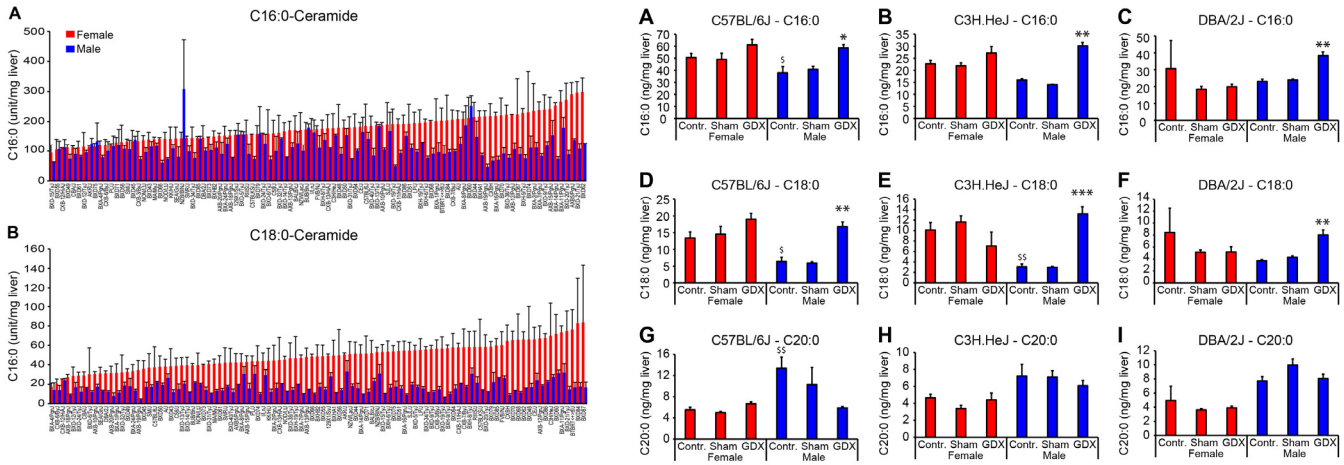
Background and Aims: The etiology of non-alcoholic fatty liver disease (NAFLD) starts with accumulation of fat within hepatocytes (steatosis). Hepatic steatosis coincides with increased ceramide accumulation which again might mediate insulin resistance in humans. Inhibition of ceramide synthesis in liver reduces obesity-induced insulin resistance in male mice. In particular ceramides derived from C16:0 appear to oppose insulin action most potently. However, to our knowledge no study have investigated the connection between liver ceramides and NAFLD or insulin resistance in female mice. We have previously shown that male mice generally have more hepatic steatosis and insulin resistance than female mice in a population of diverse inbred strains known as The Hybrid Mouse Diversity Panel (HMDP). We aimed to study the genetic and hormonal control of liver ceramides and their role in insulin resistance and sex differences in the HMDP. **Methods:** Eight weeks old HMDP mice were fed High-Fat, High-Sucrose diet for 8 weeks to induce obesity, steatosis and insulin resistance. Liver ceramides from 100 strains of mice of both sexes were measured using mass spectroscopy. We also tested if gonadectomy had an effect on hepatic ceramide accumulation in both sexes of three unique strains of mice (C3H/HeJ, C57BL/6J and DBA/2J). The gonadectomized mice were compared to untreated and sham operated controls. **Results:** Surprisingly, most of the female strains showed higher levels of liver ceramide C16:0 (Figure 1A) and particularly C18:0 (Figure 1B) than their male counterpart. Other ceramides, such as ceramide C20:0, showed higher levels in males as compared to females. Ceramide C16:0 showed a positive association with homeostatic model assessment of insulin resistance and hepatic steatosis in both sexes. Genome-wide association mapping on hepatic ceramide C16:0 and C18:0 revealed several sex-specific loci. Gonadectomy increased ceramide C16:0 (Figure 2A-C) and C18:0 (Figure 2D-F) in all three strains of male mice, strongly suggesting that testosterone inhibits the levels of ceramide C16:0 and C18:0 in male livers and can therefor explain the observed sex-difference. No effect of gonadectomy was seen for ceramide C20:0 (Figure 2G-I). **Conclusions:** Our data shows that most female mice strains have higher levels of liver ceramide C16:0 and C18:0 than their female counterpart. This sex difference can probably be explained by the inhibitory effect of testosterone in male mice. Future mechanistic mice studies will show if liver ceramides oppose insulin action more potently in males than in females.


A
C16:0-Ceramide
Female
Male
C16:0 (unit/mg liver)
B
C18:0-Ceramide
C16:0 (unit/mg liver)
A
C57BL/6J - C16:0
B
C3H.HeJ - C16:0
C
DBA/2J - C16:0
D
C57BL/6J - C18:0
E
C3H.HeJ - C18:0
F
DBA/2J - C18:0
G
C57BL/6J - C20:0
H
C3H.HeJ - C20:0
I
DBA/2J - C20:0
C16:0 (ng/mg liver)
C18:0 (ng/mg liver)
C20:0 (ng/mg liver)
Contr. Sham GDX Contr. Sham GDX
Female Male

Abstracts of Posters
Clinical

11.
Altered Brain Structure and Functional Connectivity and its Relation to Pain Perception in Female Adolescents with Irritable Bowel Syndrome

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Background: Irritable Bowel Syndrome (IBS) is a functional disorder of the brain gut-axis with gray matter (GM) reductions in prefrontal, parietal and subcortical brain regions and altered resting-state (RS) functional connectivity (FC) in the subcortex, prefrontal areas, and the precuneus compared to healthy controls (HCs). Additionally differences in quantitive pain testing (QST) and conditioned pain modulation (CPM) have been observed in adults. However, these investigations have been focused mainly in adults and have yet to be adequately investigated in children. The aim of the current study was to explore differences in the brain and pain sensitivity in female children with IBS compared to HCs. **Methods:** Female children diagnosed with IBS using Rome III criteria (N=11, mean age: 14.54yrs) and age-matched female HCs (N=14, mean age: 12.05yrs) were scanned in a 3T scanner. A standard high-resolution MP-RAGE scan along with a 10-minute RS functional scan were obtained. Voxel-Based Morphometry (VBM) analyses were conducted in FSL-VBM to investigate changes in GM. Seeds were selected from regions with significant group GM differences for a seed-to-voxel based whole brain RS-FC analysis implemented in CONN Toolbox. Significance testing was set at $p<.001$ and corrected for multiple comparisons at $p<.05$. **Results:** Patients with IBS had greater trait anxiety ($t=2.054$, $p=.045$, $d=.85$) and higher pain thresholds ($t=1.854$, $p=.078$, $d=.721$). No group differences were observed in CPM. GM differences: Patients with IBS have decreased GM in the thalamus, caudate nucleus, nucleus accumbens, anterior and posterior cingulate, and frontal, inhibitory control regions in comparison to controls. Decreased GM in the caudate nucleus and nucleus accumbens is associated with lower pain thresholds in patients with IBS ($r=.71$, $p=.02$; $r=.83$, $p=.003$) but not HCs. Decreased GM in the thalamus is associated with decreased pain thresholds in HCs ($r=-.72$, $p=.004$) but not IBS. RS differences: IBS patients exhibited decreased connectivity between the caudate nucleus and somatosensory regions. Lower connectivity between the caudate nucleus and somatosensory cortex was associated with decreased amount of time in the cold pressor task in HC ($r=.66$, $p=.03$) but not IBS patients. Lower connectivity between the caudate nucleus and supramarginal gyrus is associated with increased CPM pain threshold marginally in IBS patients ($r=-.49$, $p=.12$) and HCs ($r=-.61$ $p=.06$). **Conclusion:** Female adolescents with IBS have decreased GM in the basal ganglia, associated with decreased pain sensitivity. Additionally they exhibited decreased connectivity from the basal ganglia to somatosensory regions, associated with altered pain sensitivity. This suggests that anomalies in the pain circuitry may be present in adolescents with IBS, warranting further investigation on the mechanisms underlying these pathologies.

12.
Brain Mechanisms Underlying Symptom Improvement in Chronic Visceral Pain After Mindfulness Training

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Background: Irritable Bowel Syndrome (IBS) is a brain-gut disorder characterized by abdominal pain that is associated with altered bowel habits. IBS patients have functional brain alterations in regions associated with salience and emotional processing. Mind-body interventions, such as hypnosis, cognitive behavioral therapy and Mindfulness Based Stress Reduction (MBSR) have been used to successfully treat symptoms in IBS, though the mechanism of this improvement is not known. **Aims:** Discover symptom-related changes in resting state network connectivity (RS-FC) in patients with IBS who have undergone a 9 session MBSR intervention. **Methods:** Men and women aged 18-55 were recruited by advertisement and from clinics at UCLA. A high resolution T1 structural image and 10-minute eyes closed resting state fMRI was performed on a 3T Siemens scanner (TE: 28

ms, TR: 2000 ms, flip angle: 77 degrees, FOV 220mm x 220 mm, acquisition matrix: 64 x 64, slice thickness 4.0mm with a 0.5mm skip) before and after the MBSR intervention. The intervention consisted of eight 2 hour visits and 1 half day retreat using a standardized MBSR model. Mindfulness was measured using the Mindful Attention Awareness Scale (MAAS), and IBS symptoms with the IBS-Severity Scoring System (IBSSSS). Structural images were segmented and parcelled into 165 regions based on Destrieux and Harvard-Oxford atlases. ROI-to-ROI FC analysis was performed in the CONN toolbox. The function network matrix was comprised of z transformed r scores thresholded at z>.3. Network analysis via graph theory was applied using in house MATLAB code and the GTG toolbox to compute the functional network centrality of emotional processing (amygdala) and salience (anterior insula [long gyrus, short gyrus, circular sulcus]) regions. Network centrality indices included Degree strength, Betweenness Centrality, and Eigen vector centrality. Post-Pre intervention change scores in IBS-SSS and network centrality indices were correlated and significance was considered p<.05 corrected using false discovery rate. **Results:** 63 subjects (47 females) completed MBSR training and both scans. Mean age was 33 y (SD=9.80 19-54 years). The mean improvement in IBS-SSS from first to second scan was 74.8 ($t(61) = 5.57$, $p < .001$), with a 50-point change being considered clinically significant. The MAAS increased by 2.5 ($t(59) = 2.41$, $p = .02$). Decreased network centrality of the amygdala and the anterior insula after MBSR was associated with IBS symptom improvement and increased mindfulness. See Figure 1. **Conclusion:** IBS patients undergoing an MBSR intervention have improvements in mindfulness and overall IBS symptoms. These improvements are associated with decreases in emotional processing and salience regions.

Region	Laterality	Network Metric	Symptom Measure	Pearson's Correlation
Amygdala	Right/Left	Strength	IBSSSS	.33 (p=.04) / .44 (p=.0002)
	Left	Eigenvector Centrality	IBSSSS	.43 (p=.0002)
	Right	Node betweenness centrality	MAAS	-.25, (p=.04)
Insula short gyri	Left	Strength	MAAS	-.26 (p = .02)
Insula long gyri	Right	Strength	IBSSSS	.26 (p=.03)
Insula circular sulcus	Right	Strength	IBSSSS	.25 (p=.04)

13.

Reward Sensitivity Facilitates Stress Recovery through Positive Emotion

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Background: Evidence suggests that positive affect plays a significant role in coping processes, facilitating more efficient recovery from stress (Folkman, 2008; Tugade & Fredrickson, 2004). Greater reward sensitivity, or the ability to learn from, respond to, and motivate oneself towards reinforcing stimuli, may also be associated with resilience to stress and stress-induced disorders (Southwick et al., 2005), but the specific mechanisms by which this occurs has not been determined. One possibility is that individual differences in reward sensitivity influence the degree to which people experience positive emotions during stress (Corral-Frias et al., 2016). The current study used mediation analyses to examine whether higher reward sensitivity facilitated stress recovery by promoting positive emotion during an acute psychosocial stressor. **Method:** Participants were 26 female undergraduates, aged 18-23, who completed computerized behavioral tasks prior to undergoing the Trier Social Stress Task (TSST). Reward sensitivity was assessed with the probabilistic reward task, which implicitly assesses reward learning (Pizzagalli et al., 2005). During the TSST, positive emotion was assessed using visual analog scales. After the TSST, negative affect and the State Shame and Guilt Scale were used to assess stress recovery. Mediation models with bias-corrected bootstrapping were used to test the significance of mediated and direct effects. **Results:** In regression analyses, higher reward learning was associated with higher happy emotion during the stressor, $b = 44.94$, $t(26) = 2.11$, $p = .045$. Higher happy emotion during the stressor predicted lower negative affect, $b = -.105$, $t(26) = -2.4$, $p = .025$, shame, $b = -.117$, $t(26) = -2.76$, $p = .011$ and guilt, $b = -.12$, $t(26) = -2.66$, $p = .014$ after the stressor. In mediation analyses, higher happy emotion during the TSST significantly mediated a relationship between higher reward learning at baseline and lower shame $b = -5.26$, 95% CI[-10.46,-.98], guilt, $b = -5.23$, 95% CI[-11.52,-1.19], and negative affect, $b = -4.7$, 95% CI[-10.62,-.03] after the TSST. However, reward learning was not directly associated with lower negative affect, shame, or guilt after the stressor (all p's > .7). **Conclusion:** Results are consistent with emerging work suggesting that individual differences in reward processing are an important predictor of stress recovery, but also suggest that reward sensitivity may only indirectly facilitate recovery from stress through its association with positive emotion.

14.

Added Benefit of Double Reading Liquid-based Cytology Smears As a Triage Strategy Among High-risk HPV Positive Women in Mexico

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Purpose: To evaluate if the detection of histologically confirmed cases of cervical intraepithelial neoplasia or worse (CIN2+) is increased by having each liquid-based cytology (LBC) slide read by two different cytologists. **Methods:** The FRIDA study is an ongoing population-based study that has recruited over 37,117 women aged 30 to 64 years in Tlaxcala, Mexico, between 2013 and 2016. For each participant, two cervical samples were collected during the same clinic visit to test for high-risk human papillomavirus (hrHPV) as the primary screening procedure, and for LBC as a triage procedure. All cytology slides were randomly distributed among five cytologists. Each slide was read independently by two blinded cytologists, and all slides with a result of atypical cells of undetermined significance or worse (ASCUS+) were reviewed by a cytopathologist who reported the final cytology diagnosis. The cytopathologist also read 5% of the slides that were negative in both readings, as a quality control measure. All women with ASCUS+ results were sent to colposcopy for further evaluation and diagnosis. A panel of two pathologist evaluated the biopsy specimens to confirm the final CIN2+ diagnosis. **Results:** A total of 3,606 women had a positive hrHPV test result and were followed up with LBC as a triage procedure. The first and second cytology readings resulted in 44.6 and 41.8 CIN2+ cases detected, respectively, with an average of 43.2 CIN2+ cases identified by each single cytology reading. The double reading strategy detected an additional 7.8 CIN2+ cases, resulting in a total of 51 CIN2+ cases. The CIN2+ detection rate increased from 12.0 per thousand with a single reading to 14.1 per thousand with a double reading. This difference was not statistically significant. **Conclusions:** An 18.1% increase in CIN2+ detection rate was achieved with a double reading of the LBC slides in this sample of hrHPV positive women. Although this difference was not statistically significant, these results suggest that the detection rate of CIN2+ cases could be improved by having two separate cytologists review each LBC slide. The specific costs and benefits of this strategy would have to be evaluated in future studies, in order to determine its value in different cervical cancer screening programs.

Table. CIN2+ cases detected in a single reading vs. double reading

	CIN2+ cases among ASCUS+ cases detected by cytotechnicians and confirmed by cytopathologist[a]	CIN2+ cases detected through reviewing double negative cases[b]	Total CIN2+ cases detected (n)[c]	CIN2+ detection rate (per thousand)[d]
First reading	42	2.56*	44.56	12.35
Second reading	39	2.8	41.8	11.59
Single reading[e]	40.5	2.68	43.18	11.97
Double reading	N/A	N/A	51	14.14
Difference	N/A	N/A	7.8[f]	2.17[g]

[a] All ASCUS positive cases diagnosed by the cytotechnicians are re-read by the cytopathologist; [b] About 8% of the ASCUS negative cases are selected for quality control. *2.56=2+7×0.08; [c] Total CIN2+ cases are the sum of the CIN2+ cases detected through quality control and the CIN2+ cases among ASCUS+ cases detected by cytotechnicians and confirmed by cytopathologist; [d] Defined as the number of CIN2+ cases detected per thousand women divided by the total number of HPV positive women (n=3606); [e] Single reading is the average of first reading and second reading; [f] Difference between the total CIN2+ cases detected in single reading and double reading (51-43.18=7.82); [g] Difference of CIN2+ detection rate in double reading vs. single reading (14.14-11.97=2.17). The percent increase is 18.7% (2.17/11.97×100%=18.2%).

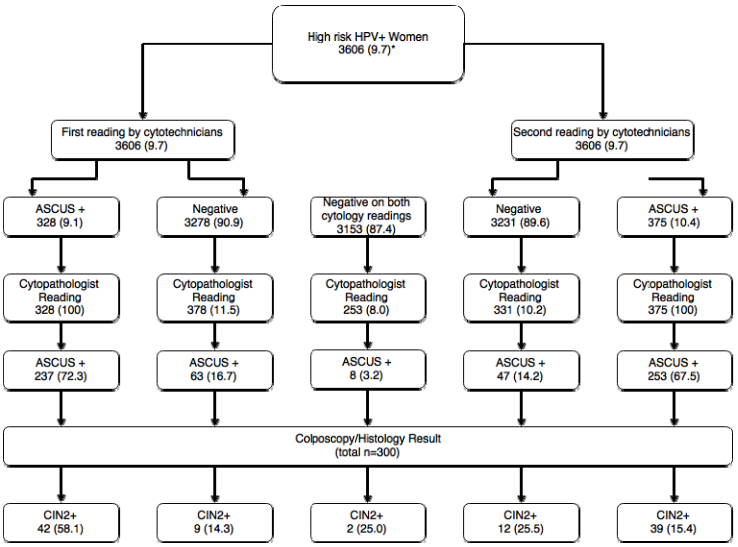

Figure 1. Detailed outcome of cytotechnician double-reading followed by cytopathologist evaluation with histological confirmation of ASCUS+ women. The cytopathologist reviewed all ASCUS+ cases detected in first reading or second reading, in addition to reading all the discordant and sampling about 8% of double negative slides as a quality control measure.
ASCUS +: atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia.
*3606 out of 37117 women aged 30-64 years are HPV positive. Data is presented in n (%).

15.

Sex Differences in Craving, Withdrawal and Reduced-Nicotine Cigarettes

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Smoking is the greatest preventable cause of death in the U.S., and it seems that different strategies for smoking cessation are needed for men and women. Women have more difficulty maintaining long-term abstinence from smoking than men (Smith et al., 2016), partly because they experience greater craving and withdrawal during abstinence (Leventhal et al., 2007). Reduced-nicotine cigarettes (RNCs) alleviate craving and withdrawal in women more than in men (Perkins & Karelitz, 2015), and may effectively aid smoking cessation attempts (Donny et al., 2015), especially in women (Vogel et al., 2014). However, no previous study examined the neural substrates of the sex differences in responses to smoking RNCs.

We measured craving, withdrawal and negative affect, and used fMRI to assess resting state functional connectivity (RSFC) of two brain regions implicated in these symptoms, the insula and striatum. On 4 days, daily smokers (11 men, 10 women, 18-25 yr), were tested before and after smoking the first cigarette of the day - a research cigarette delivering 0.027, 0.110, 0.231 or 0.763 mg nicotine.

Women reported greater negative affect and psychological withdrawal during abstinence than men, and these symptoms were related to right anterior insula and ventral striatal RSFC to the anterior cingulate cortex (ACC) in women more than in men. Smoking RNCs alleviated craving and withdrawal, with no effects of nicotine dose, and reduced negative affect and psychological withdrawal in women more than in men. Smoking RNCs reduced ventral striatal RSFC in men more than in women, with no effect of nicotine dose, and this effect was more related to reductions in craving, psychological withdrawal and negative affect in women than in men.

Our results indicate that smoking-induced reductions in craving and withdrawal do not depend on nicotine in smokers of either sex. They also indicate that the greater negative affect and psychological withdrawal experienced by women during abstinence, and the greater reductions in such symptoms due to non-nicotine factors of smoking, depend on connectivity of the right anterior insula and ventral striatum to the ACC.

16.

Morphological Brain Alterations and Changes in Hedonic Ingestive Behaviors Associated with Bariatric Surgery

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Background: In the United States, 65% of adults are considered either overweight or obese. Neuroimaging studies have identified obesity-related differences in morphological and functional scans, suggesting a possible role of the brain in the pathophysiology of obesity. Obese humans have significantly greater responses in gustatory, somatosensory, and reward-processing regions in response to palatable food and to visual food cues. It has been shown that bariatric surgery decreases the brain's reward network hyperactivity associated with obesity. **Aims**: To investigate morphological changes in the brain's extended reward system one month after undergoing laparoscopic sleeve gastrectomy (LSG) and the associated changes in body mass, weight loss, appetite and hedonic ingestive behaviors. **Methods**: Structural MRI was acquired in 16 female subjects at baseline (mean age=39.5±8.7yrs) and 1 month post surgery. Voxel-based morphometry analyses using a general linear model controlling for age were conducted in FSL-VBM to determine differences in grey-matter pre vs. post surgery and paired t-tests were run to determine the changes in clinical and behavioral variables. All significance testing was conducted at $p<.05$, corrected for multiple comparisons using the Family-Wise Error method. Correlations between significant changes in brain morphometry and changes in obesity and behavioral variables were conducted ($p<.05$). **Results**: Bariatric surgery resulted in significant reductions in BMI (45.0±5.3 before vs. 40.3±5.5 kg/m^2 after surgery (t=16.23, $p<.0001$) and in adiposity (total body fat mass: 119 kg vs. 106 kg, pre vs. post surgery (t=16.82, $p<.0001$). LSG also resulted in decreased hedonic eating (Yale food addiction symptoms count of 3.62 pre vs. 1.19 post-surgery (t=4.80, $p<.0001$). *Brain Morphological Changes*: After surgery, significantly decreased grey matter (GM) densities were observed in the left anterior (t=4.16,p= .03), middle, (t=5.25, p=.02), posterior (t=4.66, p=.03), and inferior insula (t=3.88, p=.04); along with the left hippocampus (t=5.14, p=.02). *Correlations with Clinical variables:* Postoperative reductions in total body fat mass were correlated to changes in middle insula GM (r=.53, p=.04). Changes in lean body mass were correlated with changes to the GM at the posterior insula (r=-.61, p=.01) and the inferior insula (r=-.55, p=.03). Changes in the Yale Food Addiction scores were correlated with changes in the middle insula GM (r=.59, p=.02). **Conclusions**: Bariatric surgery results in a significant decrease in measures of obesity and hedonic eating as well as structural changes at the brain's reward network core regions. Postoperative changes in the brain's reward network were associated with reductions in hedonic eating and adiposity, suggesting an effect of bariatric surgery on brain control of ingestive behaviors.

17.

Morphological Brain Alterations in Anorexia Nervosa

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Background: Anorexia Nervosa (AN) is an eating disorder characterized by abnormally low body weight and a distorted perception of body image. It affects approximately 4.2% of females and has the highest rate of mortality of all psychiatric disorders. Past neuroimaging studies have shown morphological differences and functional connectivity differences within the somatosensory and visual networks. **Aims:** The aims of this study were to determine group-based alterations in morphological brain regions of specific neural networks in individuals currently with Anorexia Nervosa (ANC) compared to subjects who are recovered from Anorexia Nervosa (ANR) and healthy controls (HCs). **Methods:** Structural MRI was obtained in 66 age-matched subjects (12 ANC (BMI mean=19.558, sd=2.545), 11 ANR (BMI mean=21.280, sd =2.575), 44 HC (BMI mean=22.486, sd=5.241)). Image segmentation and regional parcellation was performed using Freesurfer, and resulted in 74 bilateral cortical and 7 subcortical structures, including the cerebellum, with 4 different gray matter metrics (gray matter volume [GMV], cortical thickness [CT], mean curvature [MC], and surface area [SA]). General linear modeling with linear contrasts were used to test for differences between the groups, controlling for mean centered age and total gray matter volume. Based on the literature, a region of interest analyses was done restricting the analyses to 47

regions belonging to the somatosensory, emotional arousal, salience, central autonomic, and executive control networks. Significance was considered as q<.05, corrected for multiple comparisons. **Results: 1)** Clinical Variables: Compared to HCs, ANC were significantly different in age (p=.02) and Eating Disorder Inventory scores for Body Dissatisfaction (p=.000) and Thinness (p=.000). ANR EDI scores for Body Dissatisfaction (p=.003) and Thinness (p=.005) were also significantly different from HCs.**2)** Anorexia Nervosa Current vs. Anorexia Nervosa Recovered: ANC demonstrated smaller SA (q=.031) and GMV (q=.021) of the left subparietal sulcus in the executive control network. **3)** Anorexia Nervosa Current vs. Healthy Control: ANC demonstrated smaller right posterior ventral cingulate gyrus MC (q=.036) in the emotional arousal network, smaller right medial orbital sulcus SA (q=.028) in the central automatic network, and larger right long insular gyrus and central sulcus of the insula SA (q=.004) and GMV (q=.033) in the somatosensory network.**Conclusions:** These findings support previously documented morphological alterations of reduced gray matter and white matter between Anorexia Nervosa patients and healthy controls as well as documented recovery of gray and white matter after weight restoration. Differences in the executive control network between Anorexia Nervosa Current and Recovered may explain the recovery from AN. In addition, changes in the somatosensory network in Anorexia Nervosa Current compared to Healthy Control may explain body image perception distortion.

18.

Caregiver Relationships and General Support Related to Depressive symptoms and BMI

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Supportive relationships have been associated with decreased risk for poor mental and physical health outcomes (Holt-Lunstad et al., 2010; Oliveira et al., 2013). However, the relationship between specific sources of social support at different developmental time periods and health-related outcomes is less clear. Thus, we examined the linkages between support from caregivers early in life, current social support from friends, and current general support, and makers of physical health (i.e., total-body adiposity as a risk factory for a number of chronic diseases) and mental health (i.e., depressive symptoms) among young adults.

Undergraduate students (N = 103, Mage=19.91, SD=1.91) from diverse backgrounds (Asian American = 59, Latino = 21, Other ethnicity = 23) reported on their early caregiver relationships (e.g., During childhood and adolescence, my primary caregiver…" was affectionate to me"), current friend social support (e.g., "I could count on my friend when I needed to talk"), and current general support ("I have someone who understands my problems"). They also reported on their depressive symptoms (e.g., "you felt lonely"), and height/weight, which was used to calculated body mass index (BMI), a validated indicator of total-body adiposity.

Multiple regression analyses controlling for sociodemographic variables (i.e., ethnicity, parent education, and age) revealed that higher current friend support and general support were associated with lower depressive symptoms (bs = -.21, -.26, SE = .06, p < .001). By contrast, support from primary caregivers early in life was not associated with depressive symptoms (b = -.10, SE = .08, p = .24). When all three forms of relationship were entered into the same model, only general support (i.e, having someone), but not support from specific source, was associated with depressive symptoms (b = -.20, SE = .07, p = .01). In terms of physical health, friend and general support were only marginally predictive of BMI (bs = -.77, -89, -.26, SE = .46, .49, p < .10).

These results suggest that having a friend or someone else to rely on from support may decrease risk of depression and perhaps adiposity. Supportive relationships during childhood and adolescence may be less consequential. This may be due to the protective role of social support in the effects of stress. Stressful events often precede depressive episodes, and support is known to be an effective coping mechanism. Current support may be immediately helpful for dealing with current stress whereas support in the past may be less relevant.

19.

Trauma Severity and Lack of Confiding in Others Increases Risk of Having Irritable Bowel Syndrome

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Background: Irritable bowel syndrome (IBS) is a stress-sensitive gastrointestinal (GI) disorder associated with altered brain-gut interactions. IBS patients have a higher prevalence of adverse childhood experiences compared to healthy individuals. However, it is not known if the severity of the trauma or confiding in others about the trauma affects the risk of having IBS or severity of symptoms. **Aims:** To determine in individuals with a history of early adverse life events (EALs): 1) if trauma severity, confiding in others, and first age of EAL are associated with an increased risk of having IBS and with GI and non-GI symptom severity; 2) if the first age of EAL is associated with age of onset of IBS; 3) if sex differences exist. **Methods:** 197 ROME III+ IBS patients (72% F, mean age=30.28 yrs) and 165 healthy controls (HCs, 59% F, mean age=30.77 yrs) completed the Childhood Traumatic Events Scale (CTES), a 6-item measure of traumatic events (e.g., sexual, violence, injury, family events) prior to the age of 17 that asks age of the traumatic event, trauma severity (1=Not at all to 7=Extremely traumatic), and how much one confided in others (1=Not at all to 7=A great deal). Current severity of overall IBS symptoms and abdominal pain were measured as were non-GI symptoms including current anxiety and depression symptoms (HADS), perceived stress scale (PSS), somatic symptom severity without GI symptoms (PHQ-12), and GI symptom anxiety (Visceral Sensitivity Index [VSI]). Multiple logistic and linear regressions were used to adjust these comparisons for sex. Statistical significance was $p<0.05$. **Results:** IBS patients reported a greater number of EALs than HCs (Table, OR=1.30, 95% CI [1.11, 1.53], p=0.001). In the 133 subjects who reported a history of EALs, a greater total trauma burden (the sum of trauma severity ratings) increased the odds of having IBS (Figure, OR=1.11, 95% CI [1.06, 1.17], p<0.001). However, confiding in others decreased the odds of having IBS (OR=0.84, 95% CI [0.73, 0.96], p=0.014). The first age of EAL was not predictive of having IBS and did not correlate with the age of onset of IBS symptoms. There was a trend for an association of increasing total trauma burden with increasing current overall IBS symptoms (p=0.05) and abdominal pain (p=0.07), but there were no other associations between EAL measures and GI symptom severity. No sex differences were found. **Conclusions:** This study confirms that the number of EALs increased the risk of having IBS. Our results suggest that it is also important to assess the perceived severity of trauma and amount of confiding in others as they can significantly affect the risk of having IBS. Our findings are consistent with previous studies that show a beneficial effect of seeking support from others, emphasizing the importance of early intervention to improve health outcomes in individuals with EALs.

Figure: Total trauma burden increases the odds of having IBS (OR=1.11, 95% CI [1.06, 1.17], p<0.001)

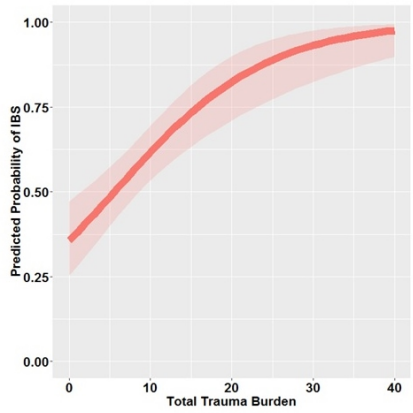

Table: Clinical Characteristics

	HC (n=165)	IBS (n=197)
Age	30.77 (11.057)	30.28 (9.866)
BMI	26.48 (5.018)	24.75 (4.811)**
Female: n (%)	97 (59%)	141 (72%)*
CTES		
First Age of EAL (years)	9.38 (4.71)	8.87 (4.50)
Total Number of EAL (0-6)	1.12 (1.12)	1.61 (1.56)**
Total Trauma Burden (1-42)	6.66 (5.10)	11.34 (8.34)**
Average Trauma Severity (1-7)	3.81 (1.70)	4.51 (1.60)
Average Amount of Confiding (1-7)	3.17 (2.02)	2.58 (1.67)*
HAD Anxiety	3.84 (3.04)	7.86 (4.55)**
HAD Depression	1.52 (1.92)	3.64 (3.27)**
PSS Score	11.72 (6.34)	17.06 (7.30)**
VSI Score	3.90 (6.27)	38.35 (17.61)**
PHQ Score	2.25 (2.47)	11.09 (4.75)**
GI Symptoms		
Overall Severity (0-20)		9.09 (4.38)
Abdominal Pain (0-20)		8.77 (4.27)
Usual Severity (1-5, none-very severe)		3.28 (0.66)

*Difference between IBS and HCs: *p<0.05 and **p<0.01

20.
Paracentral Lobule-insula Connectivity Gradients in Healthy Men and Women

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Introduction: The paracentral lobule (PCL) is the medial continuation of the precentral (anterior PCL) and postcentral gyrus (posterior PCL) and contains the primary motor (anterior PCL) and primary somatosensory cortical (posterior PCL) representations of the pelvis, leg, foot, and genitals. Thus, PCL contains representations of two sexually dimorphic body regions (pelvis, genitals). As preliminary work for studies involving pelvic pain disorders, we aimed to examine sex differences in the functional connection topography of the PCL with the insula, a prominent region in pain, in healthy individuals. **Methods:** Resting fMRI scans (TR=0.72 s, two 15-minute sessions) from 35 healthy men and 35 healthy women of the Human Connectome Project were analyzed using a modified ConGrads approach. The right and left hemisphere were analyzed separately. The time-series of every voxel within the PCL was correlated with the time-series of every voxel within the insula, and the between-voxel similarity (η2 coefficients) in connectivity with the insula was computed for each pair of voxels in the PCL. Similarity matrices were averaged across men and across women for group-level analyses. Non-linear manifold learning (Laplacian Eigenmaps) was used to create spatial maps, with similar values representing similar connectivity patterns. **Results:** The dominant mode of change in connectivity of the right and left PCL with the insula resembled the motor and somatosensory medial homunculus with some anterior/posterior asymmetry (particularly in the genital area) and mainly reflected increasing anterior insula involvement as one moved from one end of the gradient (in the motor/somatosensory pelvic area) to the other end of the gradient (in the somatosenory genital area). Although this basic organization was similarly observed in men and women, some sex differences were observed. Specifically, PCL-insula connectivity changed more gradually from the pelvic area in women than in men. **Conclusions:** Connectopic mapping of sensorimotor and interoceptive brain regions may provide new insights into pain disorders. The results indicate that some sex differences exist in the spatial properties of the functional connectivity between the primary sensorimotor and the primary interoceptive cortex in healthy individuals. Such differences may affect the integration of somatosensory information and contribute to known sex differences in the prevalence of pain disorders.

21.
Heightened Awareness of Body Sensations and Symptoms Distinguishes Brain Morphology in the Somatosensory Cortex Across Gastrointestinal Disorders

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Background: Increased perception of visceral and somatic sensations are seen in a large proportion of patients with irritable bowel syndrome (IBS), while patients with inflammatory bowel disorder (IBD) in clinical remission do not exhibit this viscerosomatic hypersensitivity. The mechanisms of this effect are incompletely understood, but are likely related to altered structural and functional alterations in the brain's sensorimotor network[1-3]. The Pennebaker Inventory of Limbic Languidness (PILL) is a validated self-report questionnaire assessing common physical symptoms and sensations. Generally heightened awareness of physical sensations (higher PILL scores) may distinguish IBS from IBD and healthy individuals and should be reflected in the morphology of sensorimotor areas. **Aims:** To investigate whether increased sensory awareness of normal physical events is associated with brain morphology in the sensorimotor network of patients with IBS, when compared to patients with IBD during symptom-free periods and healthy controls (HC). **Methods:** 297 (88 HC, 158 IBS, 51 IBD) subjects underwent a structural MRI scan. Cortical thickness (CT) and mean curvature (MC) were computed in Freesurfer. All subjects completed the (PILL). Subjects were split into low (N=147) and high (N=150) PILL score groups based on the median score. Using a general linear model (GLM), Pill group differences for the factor PILL low vs. high were assessed across measures of depression (Hospital Anxiety and Depression Questionnaire, HAD), pain catastrophizing (Cognitive Strategies Questionnaire, CSQ), negative/positive affect (PANAS) and brain morphology in sensorimotor cortices (M1, S1). **Results:** A two-factor disease group by PILL score GLM revealed no main or interaction effects on the dependent variables. Across disease groups, scores of depression, negative affect and pain catastrophizing were significantly increased in the high PILL group, whereas positive affect was decreased. In the high PILL group, the right primary sensory cortex (postcentral sulcus) showed stronger Mean

Curvature, while the left primary sensory cortex showed greater Cortical Thickness (see Table). Overall gray matter volume did not differ between the groups (p=.91). **Discussion:** While IBS did not differ from IBD and controls, brain morphology in the primary sensory cortex and measures of negative affect could be distinguished based on self-reported sensitivity to common physical sensory experiences across GI disorders and healthy controls. Alterations in S1 may be a significant marker of hypersensitivity that is common across multiple chronic pain disorders and potentially a risk factor for chronic pain development and maintenance.

References: 1. Mayer et al., Nat Rev Gastroenterol Hepatol 2015;12. 2. Ellingson et al., Pain 2013;154. 3. Orand et al., PLoS One 2015;10.

	Low PILL group		High PILL group		F-value	p-value
	Mean	SEM	Mean	SEM		
Depression (HAD)	2.15	.26	3.38	.26	11.55	.001
Negative affect (PANAS)	12.42	.46	14.2	.45	7.65	.006
Positive affect (PANAS)	31.8	.85	29.09	.83	5.22	.02
Pain catastrophizing (CSQ)	.75	.1	1.28	.11	12.74	.0005
Right postcentral sulcus (mean curvature)	2.1	.01	2.13	.01	2.61	.11
Left postcentral sulcus (cortical thickness)	2.14	.01	2.18	.01	7.56	.006
Left posterior central gyrus (cortical thickness)	2.24	.01	2.2	.01	5.07	.025

22.

Brain Morphometry distinguishes two distinct IBS subgroups

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Background: In IBS patients, subjective clinical symptoms are a poor reflection of the underlying multifactorial pathophysiological mechanisms. The proposed study is based on the general hypothesis that IBS clinical phenotypes are composed of multiple biological endophenotypes and that unsupervised learning methods can be applied to determine biological and therapeutic relevant subgroups. Identifying unique brain-based endophenotype clusters based on brain parameters may provide a pathophysiological mechanism to drive future treatments. **Aim:** To identify brain-based IBS subgroups using unsupervised learning **Methods:** High Resolution T-1 structural images were obtained from 238 IBS patients (62 males, 176 females) undergoing structural imaging. The image was parceled into 165 regions based on Destrieux and Harvard-Oxford atlases. Volume (Vol), surface area (SA), cortical thickness (CT), and mean curvature (MC) were obtained, from which 113 regions associated with central autonomic, autonomic, salience, reward, emotional arousal, and executive control network were utilized. Partitioning around medoids (PAM) clustering was applied to identify subgroups. Using this method, clusters are formed around a central representative object, ensuring minimal average dissimilarity between objects within a cluster. Independent-sample t-tests were applied to determine the brain regions, clinical and symptom data differentiating the clusters. FDR was used to correct the comparison of brain region by clusters. **Results:** PAM revealed two clusters: 1) C1 was comprised of 121 individuals (88F), mean age 33(sd=9.89) and 2) C2 was composed of 117 individuals (88F), mean age 31(sd=10.54). Individual clusters could largely be distinguished by morphometry of sensorimotor regions. Compared to C2, cluster 1 showed higher Vol in the Orbital sulci (q<.01) and left_Pallidum. (q<.01), but lower Vol in the left thalamus (q<.01), lower CT in bilateral Central Sulci, (q's<.01), and lower MC in bilateral inferior precentral sulci, (q's<.01), and left superior precentral sulci. Examining IBS and other physical symptoms, C2 had higher scores for usual symptom severity (p<.01) and a trend for lower duration of disease (p<.07). C2 was comprised of less alternating- and mixed- bowel habits than C1 (p<.045). C1 reported greater levels of widespread pain (p<.05, md= -2.91). Examining behavioral measures, C2 reported higher levels of state (p<.01, md=-1.995) and trait anxiety (p<.01, md= -6.13), depression (p<.05, md= -1.02), gastrointestinal specific anxiety (p<.01, md=-9.69), and pain catastrophizing (p<.05, md=-4.46). **Conclusion:** These findings suggest morphometric data can be used to subgroup IBS patients into two distinct groups: One primarily characterized by greater reports of symptom severity and widespread pain , the other by greater psychological comorbidity, symptom related anxiety and catastrophizing.

23.

Resting State Network Metrics Show Altered Somatosensory Network Centrality in Anorexia Nervosa

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Introduction: Anorexia Nervosa (AN) is a mental disorder characterized by self-induced weight loss and distorted body image perception. Neuroimaging studies have shown alterations in the somatosensory network in AN. These alterations have been implicated in disruptions in awareness of sensations and production of appropriate motor responses (Gupta, 2015). Structural MRI studies have shown differences in gray matter (GM) volume in the primary motor cortex, supplementary motor area, and paracentral lobule (Amianto, 2013, Bar, 2015). Few studies have used graph theory to compare resting state somatosensory networks between patients currently with anorexia nervosa (ANC), healthy controls (HC), and patients recovered from anorexia nervosa (ANR). Graph theory can be used to identify regions central to information flow across the somatosensory network. **Aims:** To quantify differences in measures of centrality of regions of interest (ROIs) in the somatosensory network between individuals with current anorexia nervosa (ANC) compared to those with recovered anorexia nervosa (ANR) and healthy controls (HCs). **Methods:** Resting state functional images were obtained from 66 subjects (12 ANC, 44 HC,10 ANR).The Destrieux and Harvard-Oxford brain atlases were used to perform image segmentation and regional parcellation to divide the brain into 165 regions. The CONN toolbox was used to construct subject-specific functional networks based on existing functional connectivity. Network centrality, defined as the importance of an ROI in the somatosensory network, was analyzed by measuring node degree (number of connections) and node strength (weighted sum of those connections). General linear models with linear contrasts were used to compare the groups, while controlling for age. Significance was considered at $q<.05$ (corrected for multiple comparisons). **Results:** 1) ANC vs. ANR: Compared to ANR, ANC showed decreased centrality in the primary somatosensory cortex (postcentral gyrus/sulcus, central sulcus), secondary somatosensory cortex (subcentral gyrus and sulci), and primary motor cortex (superior precentral sulcus, precentral gyrus). 2) ANC vs. HC: Compared to HC, ANC showed decreased centrality in the primary somatosensory cortex (postcentral gyrus and sulcus, central sulcus), secondary somatosensory cortex (subcentral gyrus and sulci), primary motor cortex (precentral gyrus, superior precentral sulcus), and supplementary motor area (superior frontal gyrus and sulcus). 3) ANR vs. HC: Compared to HC, ANR showed decreased centrality in the primary somatosensory cortex (central sulcus, postcentral gyrus), supplementary motor area (superior frontal gyrus and sulcus), and paracentral lobule and sulcus. **Conclusions:** In ANC individuals, extensive decreased communication was observed between multiple regions of the somatosensory network. In ANR individuals, significant but not as extensive decreases in communication in somatosensory regions were also observed. These findings suggest that treatments for AN should be focused on improving sensory perception and production of motor responses to overcome disrupted organization of the somatosensory network.

24.

Experimental Evaluation of Central Pain Processes in Adolescent Girls and Young Adult Women with Primary Dysmenorrhea

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Extant research shows that women with primary dysmenorrhea (PDM), defined as menstrual pain without an identified organic cause, show enhanced pain sensitivity both in areas of referred pain (abdomen, low back) and areas outside of referred pain (arm, leg). This heightened sensitivity suggests the potential role of central pain mechanisms, which may lead to the development of chronic pain problems in the future. However, no study to date has explored these processes in adolescents. The purpose of the current study was to evaluate indices of pain sensitivity, as indicated by pain threshold from thermal pain, in adolescent girls and young adult women with and without PDM. Seventy participants, ages 16-25 (38 PDM, mean age=21.36, SD=2.10; 32 healthy controls, mean age=20.66, SD=2.05), underwent a series of laboratory pain tasks involving delivery of varying levels of thermal pain via a thermode placed on right forearm during each of three separate phases of the menstrual cycle (menstruation, ovulation, mid-luteal). As expected, girls with PDM reported higher levels of average menstrual

pain compared to healthy controls, on a 0-10 numeric rating scale, M=7.24 (SD=1.60) versus M=0.64 (SD=0.73), respectively, *p*<.01. There were no differences in age of menarche or duration of menstruation in years between girls with PDM and healthy control girls (11.81 v. 12.0 and 9.54 v. 8.66, respectively, all *p*s > .05). Results indicate that girls with PDM demonstrated a significantly *lower* temperature required to achieve a pain rating of 50/100 (Pain50), relative to healthy controls, across all three phases of the menstrual cycle (see Table 1). Additionally, compared to healthy controls, girls with PDM demonstrated a significantly *lower* average pain threshold temperature across all three phases of the menstrual cycle (see Table 2). These data suggest that adolescent girls and young women with PDM experience enhanced pain sensitivity at areas of the body remote from the location of referred pain, as well as during non-painful phases of the menstrual cycle. This provides additional support for the potential role of central sensitization in PDM, even in younger girls.

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Table 1. Mixed models results of temperature required to achieve a pain score of 50/100 by group

Variable	Effect	Estimate (se)	*p* value
Group	Primary dysmenorrhea vs. Control	1.52 (0.64)	0.02
Menstrual Phase	Menstrual v. Mid-luteal	0.26 (0.23)	0.25
	Ovulatory v. Mid-luteal	-0.02 (0.23)	0.91

Table 2. Mixed models results of average temperature required to achieve pain tolerance

Variable	Effect	Estimate (se)	*p* value
Group	Primary dysmenorrhea vs. Control	1.40 (0.54)	0.01
Menstrual Phase	Menstrual v. Mid-luteal	-0.04 (0.20)	0.83
	Ovulatory v. Mid-luteal	-0.03 (0.20)	0.87

25.

Epidemiology of Squamous Cell Carcinoma of the Tongue in Young Females

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Importance: Recent epidemiology studies have revealed an increasing incidence of young tongue cancer patients particularly in women. However, the survival data associated with squamous cell carcinoma of the tongue (tongue SCC) in the young population compared to the older population is scant. **Objective:** To examine the overall survival (OS) and disease-specific survival (DSS) of female patients with tongue SCC stratified by age. D**esign, Setting, and Participants:** A population-based cohort analysis was performed using the Surveillance, Epidemiology, and End Results (SEER) database to identify female patients with tongue cancer from 1973 to 2013. M**ain Outcomes and Measures:** OS and DSS. **Results:** A total of 15,501 cases of tongue SCC in females were identified in the SEER database. Of the total, 9.2% (1428) cases involved young (18-44) patients, whereas 14,070 (90.8%) cases involved patients >45 years of age. The “young” female population had a slightly higher percentage of Stage I cancer compared to those >45 years of age (18.6% versus 15.3%, respectively). A Kaplan-Meier analysis revealed that tongue SCC of young females had an OS of 271.8 months (95% CI, 255.8-287.9 months) whereas females >45 years of age had an OS of 99.8 months (95% CI, 97.1-102.4 months). A similar trend was noted for DSS. The young cohort also had better OS when OS was compared at each cancer stage. A univariate analysis revealed that patient age, stage, radiation therapy, surgery, and primary site of cancer were determinants of OS. In the multivariate analysis, these factors were indeed determinants of survival for tongue SCC patients >45 years of age. However, only radiation therapy was a positive predictor of survival in young tongue SCC patients. C**onclusions and Relevance:** Tongue SCC in young females has a better prognosis compared to tongue SCC in the older population. Radiation therapy was associated with better survival in young female tongue SCC patients. In contrast, age, stage, radiation therapy, surgery, and primary site of cancer were all determinants of survival for female tongue SCC patients >45 years of age.

26.

Higher Household Income May Not Reduce Disparities in Postpartum Cardio-metabolic Risk in African American Women

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Background: Health disparities in pregnancy and birth are well documented for African American/Black versus other races, and for those of lower socioeconomic status. Cardio-metabolic complications of pregnancy may leave a "residue" postpartum so as to increase future cardiovascular disease risk. Identifying at-risk women during the postpartum requires consideration of pregnancy cardio-metabolic complications, and also the health disparities associated with them. As such, the purpose of these analyses was to test whether SES, race/ethnicity, and pregnancy cardio-metabolic disorders interrelate in the prediction of postpartum cardio-metabolic risk. **Methods:** A sample of 1717 women (53% Black, 23% Latina, 25% non-Hispanic White) were recruited at birth in 5 U.S. sites by the Community Child Network. Household income and size, was used to determine poverty status and adjusted for cost of living: Poor (< Federal Poverty Level; 43%), near poor (100-200% Federal Poverty Line; 28%), or low income (>200% Federal Poverty Line; 29%). Women with a pregnancy cardio-metabolic disorder (preeclampsia, gestational hypertension, gestational diabetes) were identified in medical records (18%). Four biomarkers (mean arterial pressure, glycosylated hemoglobin, total cholesterol:HDL ratio, and waist-hip ratio) were collected in home visits at 6 and 12 months postpartum and we calculated an average postpartum cardio-metabolic risk index. Covariates were maternal age, pre-pregnancy body mass index, parity, health behaviors, breastfeeding and employment status. **Results:** Binary logistic regression analyses revealed that Black women were 84% more likely to have had a pregnancy metabolic disorder compared to Latina and White women ($p <$ .001). A 3x3x2 ANCOVA revealed a race x poverty interaction. An inverse gradient for socioeconomic status predicting postpartum cardio-metabolic risk emerged for Black women, such that Black women with higher household income had greater cardio-metabolic risk compared to poor Black and all Latina and White women ($p =$ .001). This pattern was further exacerbated by an additional diagnosis of a pregnancy cardio-metabolic disorder, such that higher income Black women who had a pregnancy metabolic disorder had greater postpartum cardio-metabolic risk compared to all other groups ($p =$ .087). **Conclusions:** Black women emerged as a particularly vulnerable group with respect to postpartum cardio-metabolic risk. Black women were more likely to have been diagnosed with a pregnancy cardio-metabolic disorder, had the highest postpartum cardio-metabolic risk, particularly following a pregnancy cardio-metabolic disorder, and they did not appear to benefit from having greater socioeconomic resources. These findings echo research reporting "reverse" SES gradients among Black samples, and highlight the unique challenges faced by child-bearing Black women.

Variable		F	p
Covariates	Pre-pregnancy BMI	122	< .001
	Parity	5.29	.022
	Age	8.26	.004
	Smoking	3.86	.050
	Alcohol consumption	1.03	.311
	Breastfeeding	1.35	.246
	Employment status	.107	.743
Main effects	Race/ethnicity	15.4	< **.001**
	Poverty Group	.021	.980
	Pregnancy cardio-metabolic Disorder	26.3	< **.001**
2-way interactions	Race/ethnicity x poverty group	4.80	**.001**
	Race/ethnicity x Pregnancy cardio-metabolic Disorder	9.16	**< .001**
	Poverty group x Pregnancy cardio-metabolic Disorder	2.59	*.075*
3-way interaction		2.04	*.087*

Table 1. Results of 3x3x2 ANCOVA predicting postpartum cardio-metabolic risk from maternal race/ethnicity, poverty status and previous pregnancy cardio-metabolic disorder diagnosis, controlling for age, parity, pre-pregnancy BMI, health behaviors (smoking, alcohol consumption), breastfeeding and maternal postpartum employment status.

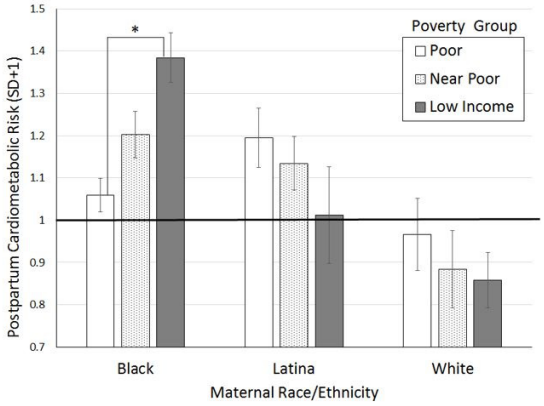

Figure 1. Average metabolic index by the interaction between race/ethnicity and poverty category, independent of pregnancy cardio-metabolic disorder diagnosis and covariates. A trend towards higher income conferring protection in White and Latina women was observed. However, a "reverse" SES gradient was observed in Black women. Higher household income {low income group) Black women had significantly higher postpartum cardio-metabolic risk, *Mn* = .384 SD, *SE* = .059, .95C/{.268, .500) compared to lower household income {poor group) Black women, *Mn* = .059 SD, *SE* = .039, *.95CI(-.017,* .136). Sample average is indicated by the dark line at '1,' and significant group differences by'*.'

27.
Anovulation and Menstrual Pain in Girls with and without Primary Dysmenorrhea

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Objective: Painful menstruation without an identified anatomic cause, or primary dysmenorrhea (PD), is believed to be caused in large part by the overproduction of uterine prostaglandins. The decline in progesterone during the late-luteal phase of ovulatory cycles creates an environment more favorable for prostaglandin production, which has led to the belief that ovulation is necessary for the development of PD. The current study aimed to explore frequencies of anovulation in a sample of menstruating adolescents and young adults with and without PD, and to compare cycle length, number of bleeding days, and levels of pelvic pain during menstruation following both ovulatory (OV) and anovulatory (AO) cycles. **Methods:** Participants in the PD group had self-reported menstrual pain >= 4/10 on a 0-10 (0=none, 10=worst pain possible) numeric rating scale (NRS); control participants' self-reported pain was <= 3/10. Ninety-one participants (52 control, 39 with PD), ages 16-24 years, completed urinary LH surge ovulation predictor kits to determine cycle phase. Cycles were considered AO if the participant never received a positive result prior to beginning menstruation. Participants were tracked for up to three AO cycles and were grouped as AO if they experienced at least one AO cycle. A subset of this group was considered chronically AO if they experienced three AO cycles. Cycle length and number of bleeding days were evaluated for cycles across all participants; pain ratings (0-10 NRS) during menstruation following both OV and AO cycles were evaluated in the PD group. **Results:** One hundred and sixty-nine full menstrual cycles were tracked across the 91 participants. Age, BMI, and race were not significantly different between pain groups, however, the PD group had a higher proportion of Hispanic participants (X^2=6.28, p<.05). There were no group differences in age, race, ethnicity, or BMI between the OV and AO groups. Control girls were significantly more likely to have had at least one AO cycle (44.2%) than were girls with PD (17.9%) (X^2=6.97, p<.01). A greater percentage of control girls were chronically AO compared to those with PD (11.5% vs 2.6%), however this result did not reach statistical significance (p=.12). Cycle length and number of bleeding days did not differ between OV and AO cycles (p's>.05). Within the PD group, maximum pain ratings during menstruation following AO cycles were not significantly different from ratings following OV cycles, either between subjects (4.4 vs 4.8) or within subjects (3.8 vs 5.2; N=6). **Conclusion:** During this observation period, control adolescents and young adult women showed statistically significant increases in the frequency of AO cycles compared to age-matched girls with PD. Girls with PD reported menstrual pain following AO cycles and this pain did not differ significantly from pain they experienced following OV cycles. There were no observed differences in cycle length or number of bleeding days between OV and AO cycles. These data suggest a complex relationship between ovarian sex steroids and menstrual pain. Previous implications of ovulation as a necessary component for the development of menstrual pain are likely incomplete. Given the widespread prevalence and impact of PD, future research should continue to investigate the local uterine and other peripheral and central mechanisms that contribute to dysmenorrhea.

28.

Alterations in the Microbiome with Pregnancy and with Pregnancy-Associated Ectopy

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Background: Pregnancy is a time of increased HIV-1 acquisition and transmission. In this study, we assessed changes in the microbiome in CVL fluid associated with pregnancy, ectopy, pregnancy and ectopy and cytokine production. **Methods:** We conducted a cross-sectional study of healthy pregnant (n=23) and non-pregnant (n=25) women in Los Angeles, California. We collected demographic and clinical data, photographed cervices for ectopy, and collected CVL samples. We performed 16S bacterial metagenomic sequencing and analyzed the data using QIIME 1.9.1. Associations between OTU abundance and metadata covariates were tested using a zero-inflated negative binomial model or a standard negative binomial model as appropriate (e.g. if data did not contain any zeroes or convergence was not achieved). Analyses were performed using the 'pscl' R package and correction for multiple hypothesis testing was done using the Benjamini-Hochberg method. Permutational multivariate ANOVA, using the Jaccard distance metric, was performed with the 'adonis' function of the 'vegan' R package. **Results:** Six bacterial species differed in pregnancy, 12 bacteria differed by ectopy and 4 species differed by pregnancy and ectopy (see Table). Interestingly, the bacterial species that were associated with pregnancy-associated ectopy (n=14) differed from the bacterial species associated with non-pregnancy associated ectopy (n=10) (p=0.05) (See Table.) Immunomodulatory factors, IL5, MCP1, VEGF, IFNa2 and MDC, increased in NP-associated ectopy while IL12p40 and GCF increased and in IP10 and EGF decreased in P-associated ectopy. **Conclusions:** Our results suggest that non-pregnancy-associated ectopy and pregnancy-associated ectopy may be two distinct biologic processes. Additionally, changes in the microbiome in pregnancy and pregnancy-associated ectopy may partially explain the increased risk of HIV-1 in pregnancy.

Bacterial Species	Estimate	Adjusted p-value
Microbiome Changes with Pregnancy		
Prevotella amnii	-3.406485087	0.006189977
Citrobacter koseri	-2.749370123	0.004971256
Klebsiella pneumoniae	-2.303312437	0.048816046
*Aerococcus christensenii**	-2.115696771	0.011521533
*Lactobacillus crispatus**	-1.102708478	0
Fastidiosipila uncultured	2.990049132	0.000108903
Microbiome Changes with Ectopy		
Streptococcus agalactiae	-8.10218267	0.000711002
Streptococcus agalactiae	-7.765710434	0.003992578
Staphylococcus uncultured	-4.395443837	0.023777709
Tyzzerella_4 uncultured	-3.982792076	0.017384907
Citrobacter koseri	-3.556928336	0.00107715
Enterobacter aerogenes	-3.473220807	0.015316211
Klebsiella pneumoniae	-3.084721825	0.016221891
Klebsiella uncultured	-2.963563272	0.014315827
Aerococcus christensenii	-2.337372459	0.020425426
Ezakiella uncultured	5.155001071	0.003101429
Saccharibacteria unknown	6.999665226	5.98E-05
Prevotella amnii	7.84391677	1.92E-08
Microbiome Changes with Pregnancy and Ectopy		
Prevotella sp. S7-1-8	-4.061938314	1.2556E-185
Prevotella amnii	-2.654290456	0.02467061
Lactobacillus crispatus	-1.276071559	0
Fastidiosipila uncultured	3.073072939	0.006192268

29.

Dysregulation of the Long-noncoding RNA, GHRLOS, in Irritable Bowel Syndrome

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Background: Long noncoding RNAs (lncRNAs) are important transcriptional regulators. Changes in epigenetic mechanisms involving methylation/histone modification and microRNA expression have been identified in irritable bowel syndrome (IBS), but expression of lncRNAs has not been studied. **Aims:** 1) To compare expression of lncRNAs in sigmoid mucosal biopsies from patients with IBS vs healthy controls (HCs) using microarray. 2) To

identify potential effectors of GHRLOS from a weighted gene correlation network analysis (WGCNA). **Methods:** 20 Rome III + IBS patients (10 IBS with constipation (IBS-C) and 10 IBS with diarrhea (IBS-D); 5 men and 5 women each) and 10 age and sex matched HCs underwent sigmoidoscopy with sigmoid colon biopsies, from which total RNA was extracted. Gene expression (mRNAs and lncRNAs) was measured using ArrayStar (Agilent platform) microarrays. Differential expression was identified using the limma package in R. A Benjamini-Hochberg-adjusted p-value <0.05 was considered significant. WGCNA analysis was performed in R. **Results:** The number of lncRNAs with fold change at least 2 and raw signal at least 200 in either group were 2, 0 and 96 for IBS (IBS-C+IBS-D), IBS-D and IBS-C. GHRLOS, a lncRNA overlapping the promotor region and part of the first exon of the ghrelin gene, was found to be down-regulated in IBS (Figure 1, FDR<0.05 in IBS-C, p<0.05 in IBS and IBS-D). WGCNA analysis identified a cluster of genes (“floral white module”) having a positive association with GHRLOS and a negative association with IBS status. Interestingly, this module contained the gene for motilin, which is closely related to ghrelin. Motilin was up-regulated in IBS (p<0.005) and negatively correlated with GHRLOS (Figure 2). **Conclusions:** The lncRNA GHRLOS is down-regulated in IBS. Functions and mechanisms of lncRNA are diverse and cannot easily be predicted; however, a WGCNA analysis provides support for a hypothesis that GHRLOS regulates expression of motilin, and this will be tested in planned mechanistic experiments. The role of motilin expression in the colon has not been described. Lower expression than in the upper gut suggest alternate, perhaps paracrine, functions.

Figure 1: *GHRLOS* is down-regulated in IBS

* p < 0.05
** FDR < 0.05

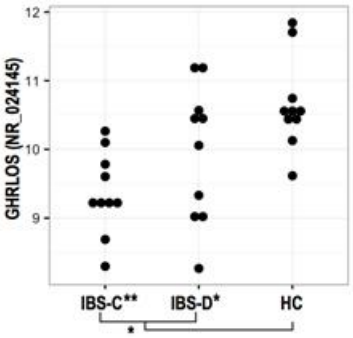
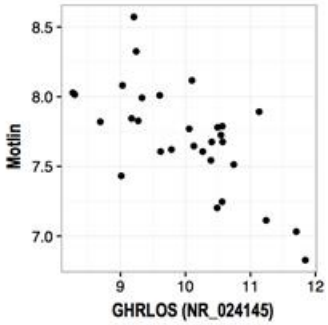


Figure 2: *GHRLOS* and motilin expression are correlated

r = -0.68
p < 0.0001



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