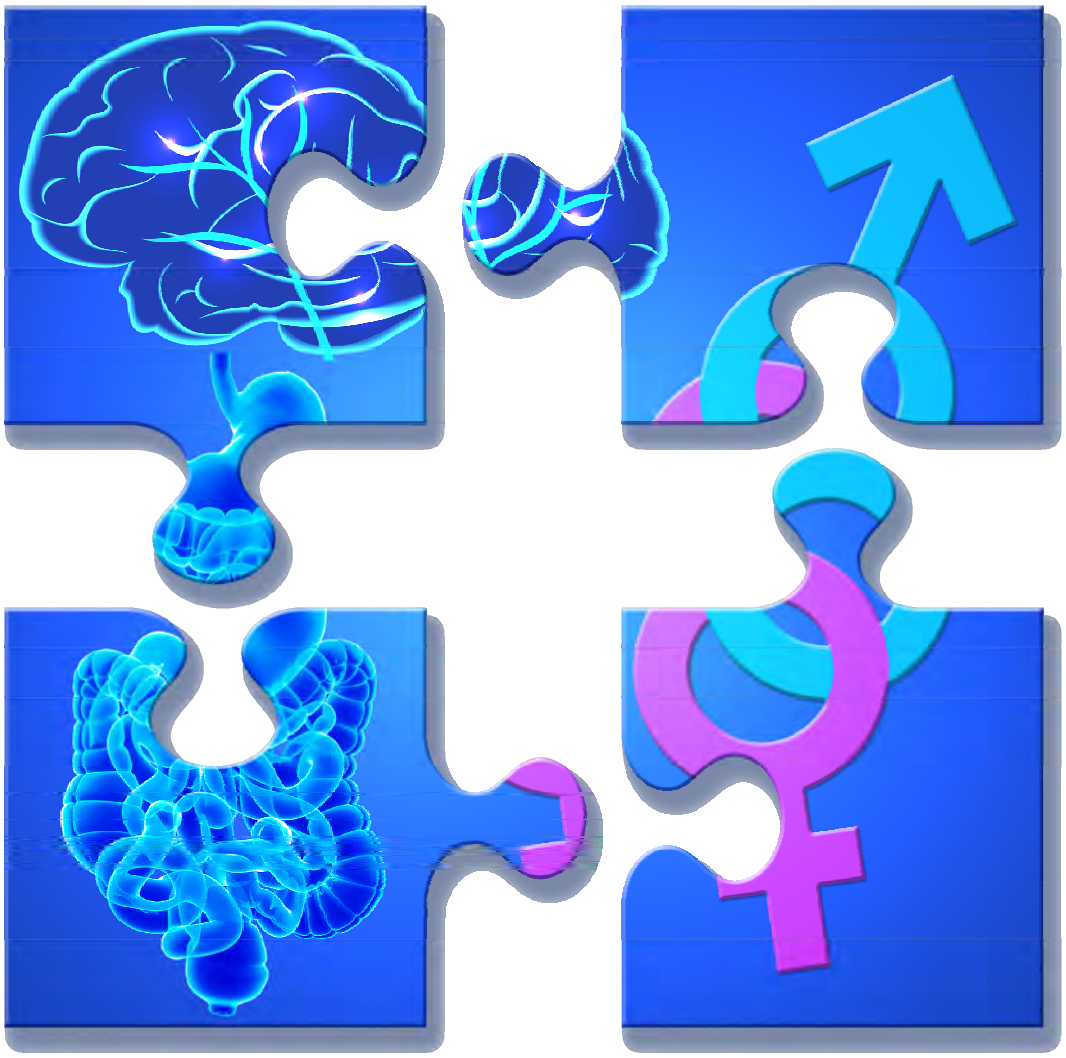
13th Annual CNS
Basic and Translational Science Symposium

SEX DIFFERENCES AND THE BRAIN GUT AXIS



February 27, 2015
UCLA Neuroscience Research Building

UCLA CNS
Gail and Gerald Oppenheimer Family
Center for Neurobiology of Stress

Bringing the Brain
Back into Medicine

Contributors

Symposium Chairs

Claudia Sanmiguel, MD

Million Mulugeta, DVM, PhD

Sponsors

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UCLA Brain Research Institute

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13TH ANNUAL CNS BASIC AND TRANSLATIONAL SCIENCE SYMPOSIUM

SEX DIFFERENCES AND THE BRAIN GUT AXIS

Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress
Division of Digestive Diseases, Department of Medicine
David Geffen School of Medicine at UCLA

With the generous support from the UCLA Brain Research Institute, the UCLA Division of Digestive Diseases, the VA Greater Los Angeles Healthcare System/Brentwood Biomedical Research Institute, CURE Foundation, the Gerald Oppenheimer Family Foundation and the Morris A. Hazan Family Foundation

Friday, February 27, 2015

NEUROSCIENCE RESEARCH BUILDING AUDITORIUM (NRB 132)

8:30 am – 8:45 am **INTRODUCTION**

Symposium Chairs: Claudia Sanmiguel, MD (Director, Ingestive Behavior and Obesity Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA) and **Million Mulugeta, DVM, PhD** (Professor, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA)

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8:45 am – 9:00 am **STATE OF THE CENTER**
Emeran Mayer, MD, PhD
Director, Oppenheimer Center for Neurobiology of Stress; Co-Director, CURE: Digestive Diseases Research Center; Division of Digestive Diseases, David Geffen School of Medicine at UCLA

SESSION I

Session Chairs: Lisa Kilpatrick, PhD (Assistant Researcher, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA) and **Muriel Larauche, PhD** (Assistant Researcher, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

9:00 am – 10:20 am **RESEARCH PROGRAMS OF THE CENTER**
(Program highlights and future direction: each 10 minutes + 5 minutes Q&A)

SCOR SPECIALIZED CENTER FOR NEUROVISCERAL SCIENCES AND WOMEN'S HEALTH & ENTERIC NEUROSCIENCE PROGRAM	**Emeran Mayer, MD, PhD**
FUNCTIONAL GI DISORDERS PROGRAM	**Lin Chang, MD**
INGESTIVE BEHAVIOR AND OBESITY RESEARCH PROGRAM	**Claudia Sanmiguel, MD**
PAIN RESEARCH PROGRAM	**Bruce Naliboff, PhD**
MIND BODY RESEARCH PROGRAM	**Kirsten Tillisch, MD**

10:20 am – 10:35 am **COFFEE BREAK**

SESSION II

Session Chairs: Paul Micevych, PhD (Professor, Surgery, Neurobiology, David Geffen School of Medicine at UCLA) and **Bruce Naliboff, PhD** (Director, Pain Research Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

10:35 am – 12:00 pm **DATA BLITZ – RESEARCH HIGHLIGHTS**
(6 presentations, each 8 minutes + 5 minutes discussion)

Neonatal Stress from Limited Bedding Elicits Visceral Hyperalgesia and Functional Brain Reorganization in Adult Rats
Zhuo Wang, PhD
Assistant Professor of Research, Department of Psychiatry & Behavioral Sciences, Keck School of Medicine, USC

Role of Sex Hormones and Sex Chromosomes in Mechanically-Induced Visceral Hyperalgesia in Mice
Muriel Larauche, PhD

Sex Differences in Anatomical Connectivity Networks Associated with Obesity
Arpana Gupta, PhD
Post-Doctoral Scholar, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

IBD-Associated Changes in Mesenteric Fat and Their Effects on Experimental Colitis
Iordanis Karagiannidis, PhD
Assistant Professor, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

Sex Differences in Dysregulation Hypothalamic-Pituitary-Adrenal (HPA) Axis Associated with Irritable Bowel Syndrome and Early Adverse Life Events
Elizabeth Videlock, MD
Gastroenterology Fellow, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Unraveling a Brain Interface between Skeletal Muscle Function and the Viscera in Humans
Jason Kutch, PhD
Assistant Professor, Division of Biokinesiology and Physical Therapy, USC; Oppenheimer Center for Neurobiology of Stress, UCLA

12:00 pm – 1:30 pm **LUNCH AND POSTER SESSION**

SESSION III

Session Chairs: Lin Chang, MD (Director, Functional GI Disorders Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA) and **Kirsten Tillisch, MD** (Director, Mind Body Research Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

1:30 pm – 3:45 pm **STATE OF THE ART LECTURES**
(Each 25 minutes + 5 minutes discussion)

Sex Biased Cell Signaling
Rita Valentino, PhD
Research Professor of Anesthesiology and Critical Care, Children's Hospital of Philadelphia

Sex Differences in the Genetic and Cellular Mediation of Pain and Analgesia
Jeffrey Mogil, PhD
Professor, Department of Psychology and Alan Edwards Centre for Research on Pain, McGill University

Gender Differences In the Relationship Between Stress and Addictions: Clinical Correlates
Kathleen Brady, MD, PhD
Distinguished University Professor; Associate Provost, Clinical and Translational Research Director, South Carolina Clinical and Translational Research Institute

Neuroimmune Interactions in Stress
John Sheridan, PhD
Professor, Division of Biosciences; Associate Director, Institute for Behavioral Medicine Research, Ohio State University

3:45 pm – 3:55pm **POSTER AWARD**
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

3:55 pm – 4:00 pm **CLOSING COMMENTS**
Yvette Taché, PhD
Director, CURE: Animal Models Core; Professor, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

4:00 pm **END OF SYMPOSIUM**

Summaries of Presentations

Symposium Chairs: Claudia Sanmiguel, MD (Financial Disclosure: None)
Million Mulugeta, DVM, PhD (Financial Disclosure: None)

SESSION I: RESEARCH PROGRAMS OF THE CENTER

Chairs: Lisa Kilpatrick, PhD (Financial Disclosure: None)
Muriel Larauche, PhD (Financial Disclosure: None)

SCOR SPECIALIZED CENTER FOR NEUROVISCERAL SCIENCES AND WOMEN'S HEALTH

Emeran Mayer, MD, PhD

Financial Disclosure: Dannon – Advisory Board

Mission: To study sex -related differences in bidirectional interactions between the brain, the gut and the gut microbiome in health and disease

Background and Rationale:

- Sex related differences in the way the brain, the gut and its microbiome interact normally and during stress have important implications for understanding of and treatment approaches to functional gastrointestinal disorders, in particular irritable bowel syndrome (IBS).
- Attempts to develop new cost effective pharmacologic treatment approaches to functional GI disorders, including IBS have largely failed. This failure has many reasons, including incomplete understanding of the pathophysiology of IBS, failure to take sex related differences and symptom subgroups into account, and undesirable side effects of novel medications.
- This NIDDK/ORW funded research program aims to better understand the pathophysiology of functional GI disorders such as IBS, to characterize sex related differences in their pathophysiology and to develop novel, cost effective treatment strategies based on these insights.

Approach:

- Researchers apply cutting edge technologies to unravel the structure and function of the brain, the immune system, the microorganisms living in our intestine, and visceral adipose tissue, and to identify sex related differences in these areas. These techniques involve multimodal brain imaging, molecular and genetic analyses and gut microbiome related technologies to identify biological intermediate phenotypes. Both clinical and preclinical approaches are employed and an emphasis is placed on interdisciplinary, translational strategies.
- Advanced mathematical analyses strategies are applied to identify the interactions between central and peripheral intermediate phenotypes, and the role of sex related differences in these interactions.
- The long term goal is to extensively phenotype patients and apply machine learning approaches to identify biologically based subgroups of patients which may be responsive to specific therapies. A particular focus in drug development is to take into account identified sex differences in disease mechanisms.

Disease Areas: Irritable Bowel Syndrome

ENTERIC NEUROSCIENCE PROGRAM

Emeran Mayer, MD, PhD

Mission: To characterize the bidirectional interactions between the brain, the gut and the gut microbiome in health and disease to provide rational targets for novel treatments

Background and Rationale:

- This NIDDK funded research program aims to understand how changes in the bidirectional interactions between the brain, the digestive system and the gut microbiome play a role in the pathophysiology and symptom modulation in functional and inflammatory bowel diseases
- The recently suggested role of direct communications between the gut microbiota and the nervous system is largely based on studies in rodent models, while its implications for human gut and brain disorders has not been characterized.
- Treatment strategies aimed at gut microbial disturbances ("dysbiosis") open new therapeutic opportunities for these functional GI disorders.

Approach:

- Researchers apply cutting edge technologies to unravel the structure and function of the brain, the immune system, the microorganisms living in our intestine, and visceral adipose tissue These techniques involve multimodal brain imaging, molecular and genetic analyses and gut microbiome related technologies to identify biological intermediate phenotypes.
- Advanced mathematical analyses strategies are applied to identify the interactions between central and peripheral intermediate phenotypes in health and disease.
- The long term goal is to extensively phenotype patients and apply machine learning approaches to identify biologically based subgroups of patients which may be responsive to specific therapies.

Disease Areas: Irritable Bowel Syndrome, Inflammatory Bowel Diseases, Cyclic Vomiting Syndrome

FUNCTIONAL GI DISORDERS PROGRAM

Lin Chang, MD

Financial Disclosures: Salix – Advisory Board; Ironwood – Advisory Board, Research; QOL Medical – Advisory Board; Drai's – Advisory Board

Mission: To establish a state-of-the-art research and patient-centered care program that works to diagnose, effectively treat and understand the root causes of functional gastrointestinal (GI) disorders and to improve the lives of patients suffering from these medical conditions.

Background and Rationale:

- Functional GI and motility disorders, such as irritable bowel syndrome (IBS), constipation, dyspepsia, gastroparesis and chronic abdominal pain are the most commonly diagnosed GI conditions in clinical practices
- Patient care is provided at the UCLA Digestive Health and Nutrition Clinic where patients can be seen by a multidisciplinary team of dedicated physicians, nurses, and a dietitian who specialize in GI disorders and apply a holistic approach designed to bring a broader and more in-depth dimension to patient care. The physicians are internationally renowned experts in the science, diagnosis and treatment of brain-gut disorders
- The research program is comprised of clinical and translational studies in functional GI disorders, specifically IBS. Clinical studies focus on characterizing clinical symptoms and assessing biologic responses, novel treatments and health outcomes. Translational studies use novel scientific techniques with the goal of identifying biologic markers in the blood and colon to diagnose and predict treatment response in patients with functional GI disorders.

Disease Areas: Irritable Bowel Syndrome, Chronic Constipation, Cyclical Vomiting Syndrome, Functional Dyspepsia, Gastroparesis, Fecal Incontinence

INGESTIVE BEHAVIOR AND OBESITY RESEARCH PROGRAM

Claudia Sanmiguel, MD

Mission: To study the central and peripheral mechanisms involved in the regulation of food intake and eating behaviors in health and obesity. To develop novel treatments aimed to replicate the results of bariatric surgery on weight loss. We also aim to find predictors of successful outcomes for different obesity treatment and then use them to customize weight loss management for individuals

Background and Rationale:

- Obesity and overweight have become a worldwide epidemic affecting grossly the two thirds of the population. The World Health Organization (WHO) predicts that by 2015 there will be 2.3 billion overweight adults in the world and more than 700 million of them will be obese.
- Americans spend $200 billion dollars yearly on obesity related health costs.
- Basic mechanisms regulating ingestive behavior in rodents are well understood, however more complex interactions between internal environment (fat signaling, gut microbiome) and human brain regulating eating behaviors are just partially understood in both health and in obesity.
- The only treatment that has shown a significant and sustained weight loss is bariatric surgery. Despite the dramatic increase in the number of bariatric surgeries performed in recent years around the world, we do not understand the mechanisms underlying weight loss after bariatric surgery

Example Projects:

- Research on mechanisms of weight loss after bariatric surgery with emphasis on changes in the brain function related to fullness/hunger and eating behaviors and their relationship with gut microbiome-visceral fat-brain axis.
- The effect of neuromodulation on eating behaviors
- The role of psychosocial environmental (adverse life events, stress, psychological symptoms, socioeconomic status, diet, physical activity, resilience) and biological (race, sex, genes, microbiota) factors on obesity related changes in brain structure and function

Disease Areas: Obesity, Eating Disorders

PAIN RESEARCH PROGRAM

Bruce Naliboff, PhD

Financial Disclosure: None

Mission: 1) To advance our understanding of brain-body interactions important for the development, maintenance and alleviation of chronic pain. 2) To develop novel brain imaging and behavioral technologies for use in chronic pain research and treatment.

Background and Rationale:

- Chronic pain affects an estimated 116 million American adults and costs the nation up to $635 billion each year in medical treatment and lost productivity.
- This program integrates cutting edge neuroimaging and biological measurements with insights from behavioral sciences to provide new answers for critical questions in chronic pain.

Example Projects:

- Established first NIH funded repository of brain imaging in chronic pain to identify “brain signatures” (changes in brain structure and function) associated with various chronic pain conditions
- Participating as the lead neuroimaging site in a large NIH consortia project examining the psychosocial and biological basis for sex differences and longitudinal symptom change in chronic urological pelvic pain.
- A first of its kind study of neuroimaging and detailed phenotyping of patients with Vulvodynia.
- Perform the largest and most comprehensive study to date of the effects of cognitive behavioral therapy on brain networks involved in visceral pain.
- A neuroimaging study to identify brain signatures of resilience to disease.

Disease Areas: Irritable Bowel Syndrome, Inflammatory Bowel Diseases, Chronic Pelvic Pain, Vulvodynia, Fibromyalgia

MIND BODY RESEARCH PROGRAM

Kirsten Tillisch, MD

Financial Disclosure: None

Mission: To promote excellence and innovation in Mind-Body medicine at through fostering new research on the neurobiology of health and healing.

Background and Rationale:

- Mind-Body and alternative medicine approaches are increasingly sought out by patients to supplement their traditional health care.
- Research on the mechanisms and efficacy of Mind Body interventions lag behind utilization of these treatments, making it difficult to prioritize one treatment over another
- This program applies western science to determine how specific Mind Body and alternative medicine treatments work and how to enhance their effectiveness.

Example Projects:

- Study of brain signatures from neuroimaging associated with successful use of mindfulness meditation for irritable bowel syndrome and for Veteran's with post traumatic headache,
- Study of transcutaneous electrical stimulation as a treatment for anxiety and depression in Veterans
- Study of the utilization of movement therapies (Tai chi, yoga), meditative practices, and acupuncture in the Greater Los Angeles Veterans Administration Outpatient practice
- Study of yoga for women with irritable bowel syndrome
- Study of the effect of mindfulness training on gastrointestinal microbiota in patients with irritable bowel syndrome

Disease Areas: Irritable Bowel Syndrome, Headache, Chronic Pelvic Pain, Widespread Pain, Mood disorders and Trauma

SESSION II: DATA BLITZ – RESEARCH HIGHLIGHTS

Chairs: Paul Micevych, PhD (Financial Disclosure: None)
Bruce Naliboff, PhD

Neonatal Stress from Limited Bedding Elicits Visceral Hyperalgesia and Functional Brain Reorganization in Adult Rats

Zhuo Wang, PhD

Assistant Professor of Research, Department of Psychiatry & Behavioral Sciences, Keck School of Medicine, USC

Financial Disclosure: None

Early life stress is a risk factor for developing functional pain disorders. The “limited bedding” (LB) model (Gilles et al., 1996) elicits psychological stress in the dam and her pups by providing minimal nesting material following delivery. Little is known about what effects this animal model of altered maternal care has on visceral pain and its functional brain responses. Wistar rats (female, male) were exposed to LB on postnatal days 2-9. Electromyographic visceromotor responses (VMR) were recorded by radiotelemetry at age 11-12 weeks during titrated colorectal distension (CRD). LB exposure resulted in significant visceral hyperalgesia in both sexes. Sex differences were demonstrated only in non-stressed controls, with females showing greater VMR.

In addition, cerebral perfusion was mapped in LB and control rats during CRD (60-mm Hg) using [14C]-iodoantipyrine autoradiography. Regional cerebral blood flow-related tissue radioactivity (rCBF) was analyzed in three-dimensionally reconstructed brains by statistical parametric mapping. Preliminary results showed that neonatal stress resulted in significant changes in functional activation during CRD of nodes within the ascending pain pathway (lateral parabrachial n., locus coeruleus, periaqueductal gray, sensory thalamus, primary somatosensory cortex, posterior insula, cingulate and medial prefrontal cortex), with additional significant changes

noted in the amygdala and hippocampus. These changes included alterations in nodes of the emotional-arousal network (amygdala, locus coeruleus), and altered regulation of this network by the medial prefrontal cortex.

Sex differences were present, though less broadly expressed. Significant sex differences were noted at the level of the medial prefrontal cortex, primary somatosensory cortex, retrosplenial cortex, amygdala, dorsal hippocampus, raphe, sensory thalamus, and striatum. A significant interaction of 'stress x sex' was noted in the somatosensory cortex, hippocampus, amygdala and locus coeruleus/lateral parabrachial n. Stressed females compared to stressed males showed greater activation of the raphe, the locus coeruleus/lateral parabrachial n., hippocampus, and amygdala, with decreased activation of somatosensory cortex.

These results in the rodent model show that altered neonatal maternal care is a risk factor for visceral pain in later life, and are consistent with the clinical observation that early life adversity (ELA) affects pain behavior in functional gastrointestinal disorders. Our preliminary results suggest that such difference in pain behavior may be linked to alterations in the brain modulatory circuitry of pain and emotions, and that ELA may show sexually dimorphic effects on brain function.

Role of Sex Hormones and Sex Chromosomes in Mechanically-Induced Visceral Hyperalgesia in Mice

Muriel Larauche, PhD
Assistant Researcher, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Background: Characterized by recurrent abdominal pain and altered bowel habits, irritable bowel syndrome (IBS) is more common in women. The mechanisms underlying this sex difference in prevalence remain unclear. The sex-biased proximate factors causing sex differences in phenotype include direct effects of gonadal hormones (organizational or activational) and of genes represented unequally in the genome because of their X- or Y-linkage. To address the role of sex hormones vs. sex chromosomes in the modulation of visceral sensitivity in rodents, we used the "four-core genotypes" (FCG) mice (XX and XY mice with ovaries, and XX and XY mice with testes). **Aims:** To determine the influence of sex hormones and sex chromosomes on the visceral hyperalgesia induced by repeated noxious colorectal distension (CRD) when monitored non-invasively. **Methods:** Intact and gonadectomized (GDX) FCG male (XY(Sry+) and XX(Sry+), mice with testes) and female (XX and XY mice with ovaries) (4-6 months old; n=6-8/group) were used. Mice were subjected to 4 sets of isobaric phasic distensions (each set: 3 CRDs at 55 mmHg, 10-s duration, 5-min intervals). Visceromotor response (VMR) was recorded using manometry. The 1st CRD set served as a baseline response. Results were expressed in AUC/min. Data were analyzed using 2-way ANOVA and Bonferroni post-hoc test. **Results:** Visceral hypersensitivity developed in response to repeated noxious CRD in intact XX mice at the 3rd set of CRD, in XY(Sry+) at the 4th set, and in XX(Sry+) mice in the 2nd, 3rd and 4th sets but not in XY mice. The VMR between groups of males (XY(Sry+) and XX(Sry+)) and females (XY and XX) was similar. When pooled together, gonadal males exhibited visceral hyperalgesia at the 4th set of CRD ($p<0.01$) and gonadal females at the 3rd set of CRD ($p<0.05$), with males presenting higher VMR than females to all sets of CRD reaching significance at the 4th set ($p<0.01$). Gonadectomy reduced the baseline VMR to the 1st set of CRD in all groups comapred to intact mice. In addition, GDX gonadal males and gonadal females all presented a strong visceral hyperalgesia at the last two sets of CRD, including the 2nd set only for XY female mice. No difference in VMR was detected between groups of GDX males and females. When pooled together, GDX males and females exhibited visceral hyperalgesia at the 2nd, 3rd and 4th set of CRD ($p<0.01$), and their VMR were comparable. Males GDX exhibited lower VMR at all sets of CRD compared to intact males, unlike GDX females which except for the 1st of CRD, had a similar VMR to CRD than intact females. **Conclusions:** These data support a major role of sex hormones, but not sex chromosomes, in the modulation of visceral hypersensitivity in response to repeated noxious colorectal distensions under non stress conditions.

Sex Differences in Anatomical Connectivity Networks Associated with Obesity

Arpana Gupta, PhD
Post-Doctoral Scholar, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Financial Disclosure: None

Obesity is a major worldwide health problem, with more than half of the U.S. population being overweight or obese. Since the economic burden related to obesity continues to rise, various efforts have been directed towards understanding the mechanisms underlying obesity. This is so that treatments and interventions with lasting effectiveness can be developed.

Various studies have identified the homeostatic system of food intake, which is comprised of hormonal regulators of hunger, satiety, and adiposity levels. The hedonic aspect of ingestion behavior, which can become uncoupled from the homeostatic system, also plays an important role in obesity. However, much less in known about how the hedonic system influences the brain, even though the assumption is that excessive consumption of palatable food even after energy requirements have been met can trigger neuroadaptive responses in the brain's extended reward network. The extended reward network is comprised of brain regions in the reward, salience, emotional arousal, executive control, and somatosensory networks. Although, limited, these neuroimaging studies offer some insight into the fact that brain alterations in key regions of the extended reward network may be linked to increased food related behaviors in obesity, especially related to hedonic ingestion.

Using diffusion tensor imaging that measures the connections between brain regions, I propose that significant differences between obese compared to overweight and lean individuals will be found in the connectivities of regions of the reward network and with regions in other networks (salience, executive control, emotional arousal, somatosensory). I will also show significant sex differences in these anatomical connections within these networks. Using powerful visualization tools I will use the brain connectogram as a way to graphically depict and fingerprint average group and sex-based differences in anatomical connections within the extended reward network. These insights may be useful to identify specific targets for future mechanistic studies and treatments aimed at abnormal ingestive behavior and obesity.

IBD-Associated Changes in Mesenteric Fat and Their Effects on Experimental Colitis

Iordanis Karagiannidis, PhD
Assistant Professor, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

Financial Disclosure: None

The development of the "creeping" fat mass that surrounds the involved intestine is a hallmark of active Crohn's disease. We have previously demonstrated the development of a similar mass that is infiltrated by immune cells in animal models of colitis. Despite the emergence of fat as an active regulatory tissue during disease and the acknowledgement of obesity as a leading cause of disease in modern society, the fat-associated changes during IBD as well as the potential effects of obesity in the outcome of these diseases have not been investigated. Indeed, recent clinical studies have demonstrated that obesity at diagnosis is associated with increased need for hospitalization during the course of the disease and shorter time span between diagnosis and surgery in IBD patients. Here, we show that intracolonic introduction of conditioned media from control, obese, ulcerative colitis (UC), and Crohn's disease (CD) patient preadipocyte cultures alter the course of experimental colitis in mice. We also show that these maybe effects may be due to disease-related changes in cytokine release patterns from human preadipocytes. Finally, we demonstrate that the same conditioned media can induce differential cytokine release and intracellular pathway activation when applied to human NCM460 colonocytes. Overall, our data suggest that mesenteric preadipocytes secrete mediators that may affect the outcome of IBD at least via effects on colonocyte function.

Sex Differences in Dysregulation Hypothalamic-Pituitary-Adrenal (HPA) Axis Associated with Irritable Bowel Syndrome and Early Adverse Life Events

Elizabeth Videlock, MD
Gastroenterology Fellow, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Financial Disclosure: None

Background: IBS is a stress related disorder and is more prevalent in women. Dysregulation of the HPA axis has been associated with IBS and other stress-related disorders. EALs are associated with IBS and with HPA axis response. **Aim:** To evaluate the effect of sex, IBS and history of EAL on the response to hormone stimulation and expression of glucocorticoid receptors (GR). **Methods:** Serial collections of plasma cortisol and ACTH were obtained following 1ug/kg of ovine CRF. On a separate date, the cortisol response to 250ug ACTH (Cortrosyn, Organon, West Orange, NJ) was assessed. The magnitude of response (area under the curve) as well as the behavior of the response over time (rate of rise and decline) was compared among groups. GR mRNA was extracted from peripheral blood mononuclear cells. **Results:** 60 IBS patients and 56 HCs (52% and 65% female) completed the hormone challenge study. GR mRNA was studied in 160 subjects: 69 HC (52%F), 74 IBS (65%F). There were significant Sex/IBS and Sex/EAL interaction effects on CRH-stimulated ACTH and CRH- and ACTH-stimulated cortisol. Main findings at the pituitary level were a slower rate of decline in IBS vs HC and this was predominately due to a difference in women. At the level of the adrenal gland, the effect of IBS was opposite for men and women with a slower decline and lower magnitude of response in women and a faster rise and greater response in men. IBS is associated with decreased expression of GR-α. In addition, GR mRNA levels were negatively correlated with magnitude of HPA response. **Conclusions:** The HPA axis is dysregulated in IBS, and IBS-related changes are different in men and women. Some of these changes may result from decreased negative feedback.

Unraveling a Brain Interface between Skeletal Muscle Function and the Viscera in Humans

Jason Kutch, PhD
Assistant Professor, Division of Biokinesiology and Physical Therapy, USC; Oppenheimer Center for Neurobiology of Stress, UCLA

Financial Disclosure: None

Modulating pelvic floor skeletal muscle activity in relation to both visceral and skeletal motor activity is a critical contributor to continence during many postural tasks. However, the neural structures responsible for the synergistic coactivation of pelvic floor muscles are poorly understood, despite the important role that the control of these muscles play in prevalent clinical conditions (Kilpatrick et al., Journal of Urology, 2014). We have recently shown that activity in primary motor cortical regions in the medial wall of the precentral gyrus is associated with the coactivation of pelvic floor muscles during voluntary contraction of gluteal muscles (Asavasopon et al., Journal of Neuroscience, 2014). Here we further interrogate cortical mechanisms of pelvic floor muscle control by examining the even more surprising coactivation of pelvic floor muscles with voluntary toe contraction in healthy human males. We first demonstrate, using electromyographic recordings from the pelvic floor and toe (flexor hallicus longus - FHL), that the pelvic floor contracts automatically during voluntary toe contraction. Using functional magnetic resonance imaging (fMRI) during muscle contraction tasks, we then localized two important motor cortical regions: one that was preferentially active during voluntary toe contraction (posterior region) and one that was active during both voluntary pelvic floor contraction and voluntary toe contraction (anterior region). We then show, using transcranial magnetic stimulation, that the FHL was preferentially activated by the posterior region while the pelvic floor was equally activated by both the anterior and posterior regions of primary motor cortex. Finally, in a repository fMRI dataset of 48 men, we estimated the functional connectivity of the anterior region and posterior region, and found that the anterior region has preferential connectivity to the posterior insula (primary viscerosensory cortex), whereas the posterior region has preferentially connectivity to the primary somatosensory cortex, frontal cortex, and parietal cortex. These results demonstrate that adjacent motor cortical regions project to pelvic floor muscles but are not functionally equivalent, and suggests both that there is a specific region of motor cortex that regulates pelvic floor muscle activity and that this region preferentially communicates with the neural sensory representation of the viscera.

SESSION III: STATE OF THE ART LECTURES

Chairs: Lin Chang, MD
Kirsten Tillisch, MD

Sex Biased Cell Signaling

Rita Valentino, PhD
Research Professor of Anesthesiology and Critical Care, Children's Hospital of Philadelphia
Financial Disclosure: None

Stress-related psychiatric disorders are more prevalent in women compared to men. Because these are characterized by both hypothalamic-pituitary-adrenal axis dysfunctions and symptoms of hyperarousal, the underlying pathophysiology should lie at the intersection of stress and arousal systems. To this end we provided evidence in rat that corticotropin-releasing factor (CRF), the neuropeptide that orchestrates the stress response, serves as a neurotransmitter to activate the nucleus locus coeruleus (LC)-norepinephrine arousal system during stress. We identified sex differences in CRF receptor (CRF1) coupling with its GTP-binding protein (Gs) and with the adaptor protein, β-arrestin 2, that render female LC neurons more sensitive to CRF and less able to adapt to excess CRF by receptor internalization. Because Gs and β-arrestin 2 signaling regulate the dynamics of phosphorylation in cells we hypothesized that CRF1 activation would result in distinct phosphoprotein profiles and that the differences in those profiles would reveal the basis for sex differences in stress-related psychiatric disorders. A global phosphoproteomic approach in CRF-overexpressing mice (CRF-OE) was used to demonstrate that when CRF is in excess, sex biased CRF1 coupling translates downstream to divergent cell signaling that is expressed as different brain phosphoprotein profiles. Cortical phosphopeptides that distinguished female and male CRF-OE mice were overrepresented in unique canonical pathways that were consistent with Gs-dependent signaling in females and β-arrestin2-related signaling in males. Notably, phosphopeptides that were more abundant in female CRF-OE mice were overrepresented in a GABA signaling pathway and in an Alzheimer's disease pathway, implicating sex biased CRF1 signaling in the increased prevalence of affective disorders and Alzheimer's disease in females. This sexual divergence in phosphoprotein profiles was not seen in wild type mice and therefore represented an interaction between sex and excess CRF. Together these results provide evidence that the excess CRF that characterizes stress-related disorders initiates distinct cellular processes in male and female brains. The results underscore the importance of sex as a determinant of stress-related diseases and the power of systems biology approaches to reveal the molecular basis of this.

Sex Differences in the Genetic and Cellular Mediation of Pain and Analgesia

Jeffrey Mogil, PhD
Professor, Department of Psychology and Alan Edwards Centre for Research on
Financial Disclosure: None

Pain researchers have now come to some consensus regarding the existence of small quantitative sex differences in the sensitivity to and tolerance of pain in humans. Differences in the effectiveness of analgesics in men and women are also appreciated. However, broad conclusions regarding the existence and direction of such sex differences are complicated by emerging evidence from laboratory animals that sex differences interact with genetic background. That is, male and female mice of only certain genetic backgrounds display sex differences. Even the direction of sex differences (male>female vs. female>male) may depend on genetic factors. In addition to these quantitative sex differences, evidence is rapidly emerging that the sexes may differ qualitatively in their neural mediation of pain and analgesia. That is, different neural circuits, transmitters, receptors and genes may be relevant to pain processing in males and females. I will present new data from our laboratory demonstrating that the specific genetic, cellular and neurochemical mediation of chronic pain processing in the spinal cord in male and female mice are radically different.

Gender Differences In the Relationship Between Stress and Addictions: Clinical Correlates

Kathleen Brady, MD, PhD
Distinguished University Professor; Associate Provost, Clinical and Translational Research Director, South Carolina Clinical and Translational Research Institute

Financial Disclosure: None

Data from multiple sources have converged to support the idea that exposure to adversity, especially during childhood, can place an individual at increased risk for subsequently developing psychiatric and medical disorders, in particular substance use disorders (SUD). The MUSC SCOR is focused on exploring gender differences in the relationship between stress and substance use disorders in animal models and human laboratory paradigms. This presentation will focus on gender differences in the interaction between stress, adversity and SUDs with a particular emphasis on data from human laboratory paradigms, clinical trials and epidemiologic data. New treatments focused on addressing vulnerabilities at the interface between stress and SUDs will be discussed.

Neuroimmune Interactions in Stress

John Sheridan, PhD
Professor, Division of Biosciences; Associate Director, Institute for Behavioral Medicine Research, Ohio State University

Financial Disclosure: None

Psychological stress contributes to the development and exacerbation of mental health disturbances, including anxiety and depressive disorders. The biological underpinnings of this relationship, however, are not well understood. Recent evidence indicates that bidirectional communication between the brain and immune system contributes to the etiology of many psychiatric symptoms and disorders, particularly related to psychological stress, depression, and posttraumatic stress disorder (PTSD). Social stress-induced alterations in monocyte priming and microglia activation leads to aberrant peripheral and central inflammation. Elevated pro-inflammatory cytokine levels caused by microglia activation and recruitment of monocytes to the brain contribute to development and persistent anxiety-like behavior. Mechanisms that mediate interactions among microglia, endothelial cells, and monocytes and how these contribute to behavioral changes will be discussed.

About the Speakers

Kathleen Brady, MD, PhD
Distinguished University Professor; Associate Provost, Clinical and Translational Research Director, South Carolina Clinical and Translational Research Institute

Kathleen T. Brady, MD, PhD is a Distinguished University Professor and Associate Provost for Clinical and Translational Science at the Medical University of South Carolina (MUSC). Dr. Brady is Director of the Women's Research Center, Director of the MUSC Clinical and Translational Research Center (CTSA), and Director of the Southern Consortium of NIDA's Clinical Trials Network. She received her PhD in Pharmacology from the Medical College of Virginia, Richmond, and her MD degree from the Medical University of South Carolina. Her research interests include gender differences in addictions, innovative treatments for drug and alcohol abuse/addiction and comorbid conditions such as posttraumatic stress disorder and other anxiety disorders.

Lin Chang, MD
Director, Functional GI Disorders Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Lin Chang, MD, is a Professor of Medicine in the Department of Medicine, Division of Digestive Diseases, at the David Geffen School of Medicine at UCLA. She serves as the Co-Director of the Oppenheimer Center for Neurobiology of Stress at the David Geffen School of Medicine at UCLA and Director of the Functional GI Disorders Program. She serves as Program Director of the UCLA Gastroenterology Fellowship Program and Director of the Digestive Health and Nutrition Clinic at UCLA. Dr. Chang's clinical expertise is in functional gastrointestinal disorders which include irritable bowel syndrome (IBS), chronic constipation, and functional dyspepsia. She is a funded NIH-investigator studying the central and peripheral mechanisms underlying IBS. Specifically, her research is focused on the pathophysiology of IBS related to stress, sex differences, and genetic and epigenetic factors and the treatment of IBS.

Dr. Chang is the recipient of the Janssen Award in Gastroenterology for Basic or Clinical Research and the AGA Distinguished Clinician Award, Dr. Chang has authored more than 80 original research articles, 50 review articles, and 20 book chapters on her specialty interests. She is Past President of the American Neurogastroenterology and Motility Society (ANMS), and is also a member of the Rome Foundation Board of Directors, the Rome IV Editorial Board and the Functional Bowel Disorders Committee. Dr. Chang is a fellow of the American Gastroenterological Association and American College of Gastroenterology, and a member of the Society for Neuroscience, and is an Associate Editor of the American Journal of Gastroenterology. She frequently speaks at national and international meetings.

Arpana Gupta, PhD
Post-Doctoral Scholar, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Gupta received her PhD degree in Clinical Neuropsychology from the University of Tennessee, Knoxville and completed her APA accredited clinical internship at Massachusetts General Hospital/Harvard Medical Center, 2010. Consequently she came to University of California, Los Angeles for her postdoctoral research training, and in 2012, she joined the Neuroimaging and Ingestive Behavior and Obesity Programs at the Oppenheimer Family Center for Neurobiology of Stress.

Her research examines the bidirectional influences between the brain and gut (microbiota and metabolite profiles and immune system) that contribute to the pathophysiology of obesity related to increases in the hedonic-related food addiction component of food intake which are no longer driven by homeostatic needs, and are thus likely to play an important pathophysiological role in some obese individuals. Dr. Gupta is dedicated to using advanced automated and mathematical analytic techniques which allows her to integrate information from multimodal neuroimaging data, gene profiles, microbiota and metabolite profiles, clinical behaviors, and adverse environmental factors, while accounting for sex and race differences. Her goal is to develop a comprehensive model that provides a powerful and sensitive biomarker that will increase biological readouts of hedonic eating

behaviors, thus bringing to the forefront those disadvantaged groups and individuals who are at increased risk for this type of obesity.

Iordanis Karagiannidis, PhD
Assistant Professor, Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

Dr. Karagiannides received his Bachelor's degree in Biology at Plymouth State University and his Master's degree in Genetics at University of New Hampshire. He went on to study in the Department of Pathology and Laboratory Medicine at Boston University School of Medicine. During his graduate work, he researched the intrinsic changes in fat cell differentiation with aging and accomplished demonstrating changes in the expression of numerous factors involved in adipocyte differentiation with increasing age in the field of fat tissue physiology.

The main target of his research is to study the extent of abdominal fat tissue involvement in the generation of inflammation during inflammatory bowel disease (IBD). In this research, he found that fat cells respond to proinflammatory stimuli (such as the neuropeptide substance P), shown to be present during IBD, and in turn are able to produce inflammatory cytokines themselves. Such cytokines have also been shown to be involved in IBD pathophysiology. He hopes to ultimately achieve additional results through his research and demonstrate whether fat cells actively participate in the events taking place in the colonic lumen during IBD. As a post-doctoral fellow at Harvard, Dr. Karagiannides received a three-year Fellowship Award from the Crohn's and Colitis Foundation of America to investigate the SP-mediated involvement of mesenteric fat tissue in the development of IBD. He joined UCLA in July of 2007 as an assistant researcher and a member of the Center of Inflammatory Bowel Disease at the Division of Digestive Diseases and was recently awarded a two-year Broad Medical Research Program grant to investigate the affects of obesity in colitis-associated changes in the intestine and mesenteric adipose tissue. Dr. Karagiannidis has been publishing his work in high quality journals such as Proceedings of the National Academy of Sciences, Journal of Biological Chemistry, Gastroenterology, and American Journal of Physiology. Dr. Karagiannides' work is also consistently presented during the Digestive Disease Week meetings including Posters of Distinction.

Jason Kutch, PhD
Assistant Professor, Division of Biokinesiology and Physical Therapy, USC; Oppenheimer Center for Neurobiology of Stress, UCLA

Jason J. Kutch, PhD, is an assistant professor in the Division of Biokinesiology and Physical Therapy at the University of Southern California. He teaches neuroscience in the USC Doctor of Physical Therapy program, and is the director of the Applied Mathematical Physiology Laboratory (AMPL) at USC. He is also a board member of the International Pelvic Pain Society.

Dr. Kutch’s work focuses on revealing neural mechanisms of pelvic floor muscle control, engineering non-invasive systems to study human motor function, and better understanding neuromuscular disorders. He is a co-investigator in the NIH-funded Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, with a particular focus on understanding brain network mechanisms of altered pelvic floor muscle control in individuals with chronic pelvic pain.

Muriel Larauche, PhD
Assistant Researcher, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Muriel Larauche is Assistant Researcher in the laboratory of Dr. Yvette Taché at UCLA David Geffen School of Medicine, Division of Digestive Diseases and the Center for Neurobiology of Stress. Dr. Larauche obtained her doctorate in Pharmacology and Digestive Pathophysiology from University Paul Sabatier, Toulouse, France in 2003 and was also awarded an NIH Gastroenterology Training Grant (Kirschstein-NRSA) in 2006. Dr. Larauche takes a multidisciplinary approach to her research and has a strong background in animal models of stress and visceral pain. Currently her work is focused towards understanding the mechanisms underlying stress-induced alterations of visceral sensitivity both at the central and peripheral level utilizing a combination of functional, behavioral, electrophysiological and pharmacological techniques. Her research interests include the pathophysiology of irritable bowel syndrome (IBS), brain-gut axis interactions and sex differences in stress-

induced alterations of gut epithelial, motor and sensory functions. Dr. Larauche has served as reviewer of multiple journals and as ad hoc reviewer for the Austrian Science Fund, the Health Research Board Ireland and the American Gastroenterological Association Annual Meeting. She is author and co-author of 27 articles and several abstracts presented at national and international conferences. Dr. Larauche is a member of the Editorial Board of Neurogastroenterology and Motility and of the World Journal of Gastrointestinal Pathophysiology. She is also a member of The American Gastroenterological Association, the American Neurogastroenterology and Motility Society / Functional Brain Gut Research Group and the Organization for the Study of Sex Differences.

Emeran Mayer, MD, PhD
Director, Oppenheimer Center for Neurobiology of Stress; Co-Director, CURE: Digestive Diseases Research Center; Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Mayer has a career long interest in clinical and neurobiological aspects of how the digestive system and the nervous system interact in health and disease. His work has been continuously supported by grants from the National Institutes of Health for the past 30 years. He has published over 300 peer reviewed articles (average H index 88), including 90 chapters and reviews, co-edited four books, and organized several interdisciplinary symposia in the area of visceral pain and mind body interactions. He has made seminal contributions to the characterization of physiologic alterations in patients with various chronic pain disorders, such as irritable bowel syndrome (IBS), as well as on pharmacological and non-pharmacological treatment approaches to these conditions. He is principal investigator on several grants from the National Institutes of Health including a NIDDK/ORWH funded center grant on sex-related differences in brain gut interactions, a NIDDK funded consortium grant (Multidisciplinary Approaches to Pelvic Pain, MAPP) in which he also heads a multisite neuroimaging core, and on a NIDDK funded RO1 grant on the role of the immune system and the gut microbiome on brain signatures. His research efforts during the past few years have focused on several new areas of brain gut interactions, in particular on the role of the gut microbiota and their metabolites in influencing brain structure and function, and associated behavior, on the role of the brain in the pathophysiology of inflammatory bowel disorders and in obesity.

Jeffrey Mogil, PhD
Professor, Department of Psychology and Alan Edwards Centre for Research on Pain, McGill University

Jeffrey S. Mogil is currently the E.P. Taylor Professor of Pain Studies and the Canada Research Chair in the Genetics of Pain. Dr. Mogil has made seminal contributions to the field of pain genetics and is the author of many major reviews of the subject, including an edited book, *The Genetics of Pain* (IASP Press, 2004). He is also a recognized authority in the fields of sex differences in pain and analgesia, and pain testing methods in the laboratory mouse. Dr. Mogil is the author of over 170 journal articles and book chapters since 1992, and has given over 230 invited lectures in that same period. He is the recipient of numerous awards, including the Neal E. Miller New Investigator Award from the Academy of Behavioral Medicine Research, the John C. Liebeskind Early Career Scholar Award from the American Pain Society, the Patrick D. Wall Young Investigator Award from the International Association for the Study of Pain, the Early Career Award from the Canadian Pain Society, the SGV Award from the Swiss Laboratory Animal Science Association, and the Frederick W.L. Kerr Basic Science Research Award from the American Pain Society. He currently serves as a Section Editor (Neurobiology) at the journal, Pain, and a Councilor at IASP, and was the chair of the Scientific Program Committee of the *13th World Congress on Pain*.

Bruce Naliboff, PhD
Research Professor, Departments of Medicine and Psychiatry and Biobehavioral Sciences; Director, Pain Research Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Naliboff received his PhD in Clinical Psychology from Bowling Green State University in Ohio and interned at the UCLA Neuropsychiatric Institute. During his tenure at UCLA and the VA he has served as senior psychologist in the UCLA and VA Pain Management programs and Health Psychology Consultation services as well as a VA Career Scientist. Dr. Naliboff's VA and NIH funded research has focused on psychophysiological mechanisms of stress and pain and includes studies of stress effects on the immune system, glucose regulation in diabetes, and cardiovascular variables. In the area of pain, he has utilized experimental pain procedures to study perceptual

processes in chronic pain states such as chronic back pain, headache, and visceral pain. He has also studied psychosocial and personality variables in chronic pain and especially their impact on treatment choice and outcome. His work in functional gastrointestinal disorders and irritable bowel syndrome (IBS) include perceptual, autonomic, and brain imaging studies of visceral sensation, and the role of psychosocial variables in the presentation, course and treatment of IBS. A major emphasis of Dr. Naliboff's recent work is the development and evaluation of mind body therapies for both visceral and somatic pain. This includes NIH funded studies of a novel cognitive behavioral therapy for IBS, discovery of brain biomarkers associated with training in mindful meditation for IBS and post-traumatic headache, and pilot studies of Yoga for both visceral and somatic pain. He has served as a consulting editor for numerous scientific publications in psychology and medicine and on national and international committees as a grant reviewer and program consultant.

Claudia Sanmiguel, MD
Director, Ingestive Behavior and Obesity Research Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Claudia Sanmiguel is the Ingestive Behaviors and Obesity Program (IBOP) director at the Oppenheimer Center for Neurobiology of Stress (CNS) and she is a clinical instructor at the UCLA Digestive Diseases Division. She was born in Bogota, Colombia where she studied Medicine at the Pontificia Universidad Javeriana and specialized in Internal Medicine and Gastroenterology. Then she moved to Alberta, Canada where she did research on gastrointestinal motility and the use of artificial pacemakers and stimulators for the treatment of gastrointestinal disorders. She continued her research career at the Cleveland Clinic in Ohio and at the Cedars Sinai Medical Center in Los Angeles, where she explored the use of pacemakers and electrical stimulators for the treatment of obesity and obesity related diabetes mellitus, as well as, studied gastric electromechanical signals related to eating behavior and satiety. As part of pursuing a research career in United States, she completed her residency in Internal Medicine at Cedars-Sinai Medical Center and trained in Gastroenterology at the University of California Los Angeles. She has continued her pursue on understanding the mechanisms that regulate eating behavior in health and in obesity, and the role of the brain in interpreting and regulating those behaviors. She has published several papers in well known GI and bioengineering journals and presented her research results in North American and International meetings. She currently has NIH funding for a study on the role of brain activity and changes in eating behavior in weight loss after bariatric surgery and she is also pursuing increasing our understanding on how some peripheral signals coming from visceral fat and gut microbiome may play a role in obesity and weight loss.

John Sheridan, PhD
Professor, Division of Biosciences; Associate Director, Institute for Behavioral Medicine Research, Ohio State University

Dr. Sheridan's research interest is on regulation of innate and adaptive immunity by the nervous and endocrine systems. The focus is on gene x environment interactions that affect behavior and susceptibility to microbial infection. In a model of social defeat, we found that activation of neuroendocrine pathways resulted in the modulation of inflammatory and behavioral responses. Inflammation was associated with the development of anxiety and depressive-like behaviors. Social defeat-induce modulation of innate immunity was accompanied by the release of glucocorticoid insensitive, bone marrow-derived myeloid cells that over expressed proinflammatory cytokine genes. In extending this research, Dr. Sheridan is interested in the overall effect of repeated social defeat on central and peripheral pathways that influence host inflammation and behavior.

Kirsten Tillisch, MD
Director, Mind Body Research Program - Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Kirsten Tillisch is an Associate Professor of Medicine in the Division of Digestive Diseases at the David Geffen School of Medicine at UCLA and the Chief of Integrative Medicine at the Greater Los Angeles VA. Dr. Tillisch's clinical interests include the promotion of non-pharmacological and integrative therapies for chronic disease and wellness, functional bowel disorders, and chronic pain. Her research interests include brain-gut and microbiome-gut-brain interactions, the effects of non-pharmacological therapies on chronic disease, and pharmacological treatment of irritable bowel syndrome. She is a member of the Rome IV Committee on Functional Abdominal

Pain. She has been an NIH funded researcher since 2006, utilizing neuroimaging techniques to study the physiology of brain gut interactions. She currently studies the central effects of Mindfulness Based Stress Reduction on symptoms of irritable bowel syndrome and post traumatic headache. Her recent research projects also include evaluation of the role of gut microbiota modulation on emotional processing in the brain, and assessment of neurokinin-1 receptor antagonists effects on the gut and brain in irritable bowel syndrome. She directs the Mind Body Program of the Oppenheimer Family Center for Neurobiology of Stress.

Rita Valentino, PhD
Research Professor of Anesthesiology and Critical Care, Children's Hospital of Philadelphia

A goal of my laboratory is to elucidate the mechanisms by which stress leads to psychiatric and medical disorders. To this end, we demonstrated that the stress-related neuropeptide, corticotropin-releasing factor (CRF) targets and alters the activity of brain monoamine systems that are implicated in psychiatric disorders, the locus coeruleus norepinephrine system and the dorsal raphe serotonin system. We are characterizing the enduring effects of repeated stressors on activity of these monoamine systems, identifying the circuits that mediate these long-term effects and assessing their behavioral and cognitive consequences. Because stress-related psychiatric disorders are more prevalent in females we have investigated the molecular basis for this. Our research has shown that CRF receptor signaling is sex-biased in a manner that can account for the increased prevalence of stress-related psychiatric disorders. Stress can have different effects depending on the stage of development and our laboratory is comparing the effects of social stress in male and female juvenile, adolescent and adult animals and uncovering the mechanisms underlying these developmental differences. Finally, another branch of our research is revealing how the brain processes pelvic visceral information and how it uses this information to regulate activity of the viscera. This is relevant to understanding the comorbidity of pelvic visceral and psychiatric disorders.

Elizabeth Videlock, MD
Gastroenterology Fellow, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Elizabeth (Beth) Videlock is a Gastroenterology Fellow at UCLA in her second year. She is in the Specialty Training and Advanced Research (STAR) Program. Her research focuses on the role of stress and early life adversity on irritable bowel syndrome (IBS) and on developing novel biomarkers under the mentorship of Drs. Lin Chang, Charalabous Pothoulakis and Dimitrios Illiopoulos. A a native of Philadelphia, she completed undergrad at Yale University, medical school at UCLA and internship and residency at the Beth Israel Deaconess Medical Center in Boston.

Zhuo Wang, PhD
Assistant Professor of Research, Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, USC

Zhuo Wang is a Research Assistant Professor in psychiatry at USC. He earned his BS degree in Biology at the University of Science and Technology of China, and PhD in Neurobiology at USC. He then received postdoctoral training at the VA Greater Los Angeles Healthcare System and the Center for Neurobiology of Stress at UCLA, before joining USC as a research faculty. Dr. Wang's research focuses on functional brain mapping and functional connectivity analysis in rodent models of visceral pain, with an emphasis on understanding the brain mechanisms underlying sex-related differences, modulation by stress, and pharmacological intervention. His main approach is autoradiographic blood flow mapping in awake, nonrestrained rodents, performed in parallel with other physiological and behavioral measurements.

Abstracts of Posters
Basic and Translational

1.

Identification and Characterization of IBD Associated Exosomal miRNAs: Horizontal Gene Transfer in the Pathophysiology of Intestinal Inflammation

Bakirtzi K, Law, IK, Kalatzi EM, Pothoulakis C

Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA

Background and Aims: The effects of cytokine induced pro-inflammatory signaling on exosome-driven intercellular communication during Inflammatory Bowel Disease (IBD) and vice versa, has never been studied while the available exosome isolation protocols are far from standardized. Our aim was to establish an efficient and reproducible protocol for exosome isolation from body fluids, tissues, cultured cells and cell culture media and identify possible differences in intestine-derived exosomes properties between health and disease (IBD). **Methods:** We used human intestine epithelial cells (NCM460) plus or minus pro-inflammatory cytokine cocktail treatment and their cell culture media and human blood serum from Ulcerative Colitis (UC) or control patients, to establish our exosome isolation protocol. Sucrose density/velocity gradients and western blot analysis (intestinal epithelium cell specific A33 antibody), were used for exosome quantification. MiRNA array analysis was used to identify the miRNA array cargo in IBD (UC) patients versus controls. **Results:** Differential centrifugation of 1,000g (5min), 27,000g (35 min), 280,000g [sucrose velocity (2.5 hours) or density (16 hours) gradients] or 33,000g (35 min, pelleting secreted exosomes) is an efficient and reproducible (p=0.3153) exosome isolation protocol. Pro-inflammatory cytokine signaling induces exosome release from NCM460s (p=0.0057). A33-positive exosomes isolated from human blood serum are significantly increased in UC patients versus controls (p=0.0051). Three miRNAs are significantly increased (p=0.037, 0.004 and 0.016 respectively) in exosomal cargo of UC patient blood serum while four miRNAs and small-RNA unidentified sequences are significantly decreased (p=0.014, 0.049, 0.026 and 0.011 respectively). **Conclusion:** Exosomes can efficiently and reproducibly be isolated from our experimental models using our differential centrifugation protocol. Cytokine signaling *in vitro* and intestinal inflammation *in vivo*, induce release and modify miRNA cargo of intestinal exosomes. A detailed characterization of the miRNA-cargo fingerprint of exosomes released by the inflamed gut may provide with an efficient diagnostic tool and a potential target or targeting vehicle for the resolution of IBD.

Funding: 1 RO-1 DK 47343 Pothoulakis (PI) NIH, NIDDK

2.

Sex Differences in Diurnal Rhythms of Food Intake in Mice Caused by Gonadal Hormones and Complement of Sex Chromosomes

Xuqi Chen[1,2], Lixin Wang[3,4], Dawn Loh[2,5], Christopher Colwell[2,5], Yvette Taché[3,4], Karen Reue[6†], Arthur P. Arnold[1,2†]

[1]Dept Integrative Biology & Physiology,[2]Lab of Neuroendocrinology of the Brain Research Institute,[3]CURE/Digestive Diseases Research Center, and Center for the Neurobiology of Stress, Dept Medicine, Division of Digestive Diseases, [4]VA Greater Los Angeles Healthcare System [5]Dept Psychiatry and Biobehavioral Sciences, [6]Dept Human Genetics and Molecular Biology Institute, UCLA College and David Geffen School of Medicine at UCLA. † Equal contribution

We previously reported that after gonadectomy in adulthood, mice with two X chromosomes gain more weight and body fat than mice with one X chromosome, independent of the gonadal sex of the animal. Here we measured diurnal rhythms of food intake, as well as body weight and composition, while varying three major classes of sex-biasing factors: activational and organizational effects of gonadal hormones, and sex chromosome complement (SCC). Four Core Genotypes (FCG), comprising XX and XY gonadal males and XX and XY gonadal females, were either gonad-intact or gonadectomized (GDX) as adults (2.5 months); food intake was measured second-by-second for 7 days starting 5 weeks later, and body weight and composition were measured for 22 weeks thereafter. Gonadal males weighed more than females. GDX increased body weight / fat of gonadal females, but increased body fat and reduced body weight of males. After GDX, XX mice had greater

body weight and more fat than XY mice. In gonad-intact mice, gonadal males had greater total food intake and more meals than gonadal females during the dark phase, but females had more food intake and meals and larger meals than males during the light phase. GDX reduced overall food intake irrespective of gonad type or SCC, and eliminated differences in feeding between groups with different gonads. Diurnal phase of feeding was influenced by all three sex-biasing variables. Gonad-intact females had earlier onset and acrophase (peak) of feeding relative to males. GDX caused a phase-advance of feeding, especially in XX mice, leading to an earlier onset of feeding in GDX XX vs. XY mice, but earlier acrophase in GDX males relative to females. Gonadal hormones and SCC interact in the control of diurnal rhythms of food intake.

3.
Substance P (SP)-Regulated miR-31-3p Modulates Inflammation in Human Colonic Epithelial Cells

Kai Fang, Ivy Ka Man Law, Aristea Sideri, Hon Wai Koon, Dimitrios Iliopoulos, Charalabos Pothoulakis

Division of Digestive Diseases, Inflammatory Bowel Disease Center, David Geffen School of Medicine at UCLA

Background and Aims: Our previous microarray analysis indicated that miR-31-3p is induced by SP stimulation in human colonic epithelial cells. However, miR-31-3p expression during colitis has never been investigated. Our aim was to analyze the miR-31-3p expression and elucidate the role of miR-31-3p in relation to inflammatory signaling. **Methods:** We performed real time PCR analysis of miR-31-3p expression in human colonic epithelial NCM460 cells overexpressing NK-1R (NCM460 NK1R) following SP stimulation and in NCM460 cells in response to IL6, IL8, TNFα, and IFN-γ stimulation. Cells were transfected with anti-miR-31-3p or anti-miR-control for miR-31-3p for in vitro functional analysis. For colitis models, mouse colon tissues were collected from TNBS-colitis (7 days), DSS-colitis (5 days) and T-cell transfer colitis (4 weeks) models. RNAs from colon tissues from UC patients UC and normal subjects were purchased from Origene. **Results:** SP stimulated miR-31-3p expression in NCM460-NK-1R cells. In NCM460-NK-1R cells pretreated with the C-Jun N-terminal Kinase (JNK) inhibitor SP600125, SP-stimulated miR-31-3p expression was almost normalized. Furthermore, miR-31-3p was up-regulated by IL6, IL8, TNFα, and IFN-γ. MiR-31-3p silencing increased RhoA expression. Conversely, transfection with miR-31-3p mimic decreased the protein level of RhoA in NCM460 cells. MiR-31-3p silencing increased CCL2 and IL6 mRNA expression in NCM460-NK-1R cells in response to SP. Expression of miR-31-5p was increased in TNBS-colitis model, DSS- model, T-cell transfer colitis model, and in colon biopsies from UC patients compared to controls. **Conclusions:** This is the first demonstration that miR-31-3p regulates IL6, CCL2, and RhoA expression in human colonic epithelial cells. Our novel evidence for increased expression of miR-31-3p in human and mouse colitis tissues suggests that this microRNA may represent a novel regulator and/or biomarker for colitis and IBD.

Funding: NIDDK RO-1 DK 47343 (CP) and a CURE: DDRC P30 DK 41301 Pilot and Feasibility study (KF)

4.
Corticotropin-Releasing Hormone Receptor 2-Mediated Mucosal Repair Responses Following Colitis

Jill M. Hoffman, Stavroula Baritaki, Jonathan J. Ruiz, Aristea Sideri, Charalabos Pothoulakis

Center for Inflammatory Bowel Diseases, Medicine, UCLA

Background: IBD is a chronic relapsing inflammatory disorder of the gastrointestinal tract. The corticotropin releasing hormone (CRH) family includes hormones/peptides that affect the function of many organs, including the intestine. Here, we hypothesized that specific modulation of CRHR2 signaling in the colonic mucosa can limit inflammation or promote restoration of the epithelial barrier through stimulation of proliferative, anti-apoptotic and wound healing responses. **Methods:** Mucosal healing following dextran sodium sulfate (DSS) colitis was assessed in male CD-1 mice (n=8/group). Mice were given DSS in their drinking water (4% w/v) for 5 days. On days 6-15, mice were injected daily with vehicle or the CRHR2 antagonist, Astressin 2B. Mice were euthanized on day 15 and colons processed for damage scoring, immunohistochemistry and RT-PCR. CRHR2-overexpressing human colonic epithelial cells (NCM460R2) and scramble negative control cells were stimulated with CRH or the CRHR2- selective ligand Urocortin 2 (Ucn2) to assess cell proliferation and migration in real-time. RNA was extracted and protein lysates processed for RT-PCR and phosphoprotein assays, respectively. A wound healing assay was used to assess repair mechanisms *in vitro*. **Results:** Mice treated with intracolonic Ast2B following DSS had increased disease activity, delayed healing and decreased epithelial cell proliferation compared to vehicle controls. Colons from these mice also showed increased terminal deoxynucleotidyl transferase dUTP nick

end labeling (TUNEL), as well as elevated TNF-α and Fas ligand mRNA levels. Ucn2 or CRH treatment of NCM460-R2 cells increased epithelial cell proliferation and migration in a dose-dependent manner. Both the pro-migratory and proliferative effects of CRHR2 stimulation in NCM460-R2 cells were reversed by pretreatment with Ast2B. Wound healing was accelerated in NCM460-R2 cells following Ucn2 and IL-6 treatment, suggesting advanced healing progression. NCM460-R2 cells had higher STAT3 activity in response to both IL-6 and Ucn2 as compared to EV cells suggesting a role for STAT3 signaling in CRHR2-driven mucosal repair. **Conclusion:** CRHR2 signaling promotes mucosal repair following DSS colitis *in vivo* and in human colonocytes *in vitro*. We suggest that selective CRHR2 activation may provide a targeted approach to enhance mucosal repair following colitis.

5.
Fear Conditioning Leads to an Increase in the Number of PACAP Neurons Expressing cfos within the Basolateral Amygdala

Y. Huang[1], A.K. Rajbhandari[1,2], M.S. Fanselow[1,2], J.A.Waschek[1]

Departments of [1]Psychiatry, [2]Psychology, UCLA

Recent studies indicate the involvement of the pituitary adenylyl cyclase-activating polypeptide (PACAP) and its G protein-coupled receptor PAC1 in the neural circuitry of stress. Post-traumatic stress disorder (PTSD) is reported to occur after exposure to intense traumatic experience and is conceptualized to involve inappropriate control over fear and has recently been genetically linked to the PACAP/PAC1 signaling pathway. Thus, studying the involvement of the PACAP/PAC1 system in regulation of conditioned fear behaviors could help understand the neural mechanisms involved in PTSD. In this study, we sought to investigate the changes in the level of immediate early gene cfos after fear conditioning in PACAP-EGFP mice (mice with Green Fluorescent Protein in PACAP-containing neurons). We hypothesized that acquisition of conditioned fear would alter neuronal activity in PACAP expressing neurons within the basolateral amygdala (BLA), a brain region crucial for mediating conditioned fear behaviors. A group of PACAP-EGFP mice were placed in a context in which they received a 0.65mA, 1-second foot shock after 4 minutes. After 6 consecutive days of this acquisition phase during which freezing levels reached an asymptotic level, half of the mice were tested in a novel context for changes in the level of fear while the other half were left in the home cage as controls. Ninety minutes following the test in the novel context or home cage, all mice were perfused and their brains extracted. Using immunofluorescence procedures, positive cfos and EGFP immunolabeling were analyzed and quantified in the BLA slices. Preliminary cell counting analysis revealed an increase in the number of PACAP neurons expressing cfos in the test group than in the controls, indicating that fear expression may have altered the activity of PACAP neurons within the BLA. These results indicate that the PACAP expressing neurons in the BLA may be involved in the regulation of fear and that targeting this system may be important for understanding the neural circuitry underlying fear dysregulation in anxiety disorders including PTSD. Future studies are needed to understand the specific role of the PACAP/PAC1 system within fear circuitry.

6.
Chronic Fructose Consumption Enhances Cocaine-Seeking in Rats

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Psychostimulants (e.g., cocaine, amphetamine) expose mesolimbic brain structures to large increases in extracellular of dopamine (DA) by impairing the function of dopamine transporters (DATs). With repeated use, such increases in DA transmission become associated with proximate cues (such as drug paraphernalia and specific locations of drug use), cues that can then trigger further drug-seeking and relapse. Interestingly, recent evidence suggests that DAT is positively regulated by insulin, such that potentiating insulin signaling facilitates DAT activity, thereby promoting DA clearance and attenuating DA transmission. Conversely, decreasing insulin signaling, such as during fasting, downregulates DAT activity. This may be particularly relevant to psychostimulant users, whose eating behavior is characterized by periods of drug-induced anorexia followed by eating binges, typically of highly-processed, high-sugar foods. Chronic consumption of diets high in sugars and refined carbohydrates is well known to impair insulin signaling in the periphery (as in Type II diabetes), and recent

evidence suggests this may also occur in neuronal tissue. Given this, we hypothesize that chronically downregulated insulin signaling as a result of repeated fasting may result in sustained downregulation of DAT, thus reducing extracellular DA clearance and reuptake. This may synergize with the effects of psychostimulants to further compromise DAT function, thereby increasing DA transmission, intensifying sensitivity to drug-paired cues, and creating an escalating vicious cycle of increased drug taking. To test this hypothesis, we compared fructose-exposed (15% fructose solution for 11 weeks) with fructose-naïve rats in a Pavlovian-to-instrumental transfer paradigm, a behavioral model of cue-induced motivation for reward, using cocaine as the reward. As predicted, we found an increase in incentive motivation for cocaine reward as a result of fructose exposure. Ongoing studies in our lab are aimed at elucidating how neuronal insulin dysregulation interacts with DA signaling to produce hypersensitivity to drug-paired cues.

7.

Modulation of Visceral Pain by Stress: Dose-Dependent Visceral Analgesia Induced by Central Injections of Corticotropin- Releasing Factor (CRF) in Male Rats

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Background: Brain CRF is the central mediator orchestrating the adaptive stress response. In rodent models of visceral pain, using invasive surgical monitoring of visceromotor response (VMR) to colorectal distension (CRD) by chronic implantation of EMG electrodes, exposure to water avoidance stress (WAS) or intracerebroventricular (ICV) CRF promotes a visceral hyperalgesia. By contrast, central injections of CRF induce stress-related analgesia in somatic pain models. Using a non-invasive method of VMR measurement based on manometry (Larauche et al., AJP 2009), we recently found a visceral analgesia induced by WAS in mice and rats. **Aims:** To determine if ICV CRF could reproduce the analgesic effect of psychological stress on VMR to CRD when monitored non invasively. **Methods:** Ten days before the experiment, adult male Sprague Dawley rats (250-300g, 2/cage, n=6-15) were surgically implanted with an ICV cannula. The VMR to graded phasic CRD (10, 20, 40, 60 mmHg, 20 sec duration, 4 min intervals) was monitored using manometry. A 1st CRD served as baseline, then after 1h of rest, rats were injected ICV with either CRF (30, 100, 300 ng, 1 g and 3 g/rat) or vehicle (saline, 10 l). Five minutes after injection, a 2nd CRD was performed. In another set of experiments, rats were pretreated with the CRF receptor 1 and 2 antagonist, astressinB (30 g/rat) or vehicle (sterile water, 5 l) 15 min before the administration of CRF (300 ng, 5 l). Results were expressed in % of maximal basal VMR. Data were analyzed using 2-way ANOVA and Bonferroni post-hoc test. **Results:** CRF at 30ng did not change the VMR compared to vehicle (n=11). At 100 (n=12) and 300 ng (n=10), CRF injections significantly reduced the VMR at 60mmHg (-36.6±6.8% and -48.7±11.7% respectively, $p<0.001$) compared to baseline. This analgesic effect of CRF disappeared at higher concentrations (1, 3 and 5 g, n=6, 15 and 11, respectively). The analgesic effect of CRF (300 ng) (n=6) was prevented by pretreatment with astressinB (n=9). **Conclusions:** In a non invasive model of visceral pain, CRF ICV injected at low doses (100 and 300 ng) leads to a CRF receptor-mediated visceral analgesia that disappears at higher doses. These results suggest a dual action of brain CRF: a visceral stress analgesia that could be abrogated at a high intensity of stress.

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8.

Continuous Neonatal Chronic Stress Influences Basal Visceral Sensitivity in a Sex-Dependent Manner in Adult Wistar Rats

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Background: The neonatal period is a critical time window that is malleable and sensitive to environmental stress. Preclinically, neonatal maternal separation (3h/day) predisposes rodents to anxiety and visceral hypersensitivity to colorectal distension (CRD) when monitored using electromyography as adults. By contrast, neonatal short handling (NSH, 15 min) reduces anxiety and stress behaviors but limited data is available

regarding its impact on basal visceral pain. Early life adverse events contribute to the development of stress-sensitive disorders such as irritable bowel syndrome (IBS) with higher occurrence in females. The limited bedding stress (LBS) model has recently been validated as a model of maternal neglect and abuse in rodents, but its influence on visceral sensitivity in adult rats has not been characterized non invasively. **Aims:** To determine the influence of LBS and NSH on the basal visceromotor response (VMR) to CRD in adult rats when monitored using intracolonic manometry. **Methods:** Time-pregnant Wistar females (E15, Harlan) were used. On postnatal day 2 (PND 2), litters were culled to 12 pups with equal ratio of males/females. Dams were then housed either on wood shaving bedding with 1 paper towel (control and NSH) or in LBS conditions with ½ paper towel placed onto wire bottom flooring. Control and LBS pups were undisturbed for 7 days. NSH pups were separated from the dam 15 min/day. On day 10, all dams and pups were returned to wood shaving until weaned on PND 21. In adult rats (9-14 weeks old), the VMR to graded phasic CRD (10, 20, 40, 60 mmHg, 20 sec, 4 min intervals) was monitored. Results expressed in AUC/min were analyzed using 2-way ANOVA and Bonferroni post-hoc test. **Results:** Control (n=7), NSH (n=8) and LBS (n=8) female rats presented similar VMR to all CRD pressures. In contrast, LBS (n=10) or NSH (n=11) male rats exhibited a decrease in their VMR at 40 mmHg compared to control male rats (n=11) (VMR: 16.0±4.2 and 19.1±3.1 vs 39.9±7.5 AUC/min, $p<0.05$, respectively). In all groups, female rats showed a higher VMR to CRD than males that was restricted to 60 mmHg in controls ($p<0.01$), but present at both 40 and 60 mmHg in LBS ($p<0.05$ and $p<0.0001$) and NSH ($p<0.05$ and $p<0.001$) animals. **Conclusions:** Using manometry to monitor visceral sensitivity to CRD, we found that early life stress in the form of neonatal LBS or NSH induces a visceral hyposensitivity at noxious pressures of CRD in adult Wistar male rats. In contrast, in adult Wistar cycling females, neither LBS nor NSH alters the nociceptive responses to CRD. These findings suggest that early life events affect the visceral pain response of rodents in a sex-dependent manner. Further studies assessing the impact of those changes on the visceral response to chronic stress during adulthood are warranted.

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9.

The Trans-Golgi Network Protein Aftiphilin Is Involved in Regulation of Intestinal Epithelial Permeability in Colonic Epithelial Cells

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Background and Aims: Aftiphilin (AFTPH) is localized in the trans-golgi network (TGN) and is involved in intracellular trafficking. We have recently found that AFTPH expression is downregulated in colonic epithelial cells in TNBS-induced mouse colitis and patients with ulcerative colitis (Law et al, Gut 2014). However, the role of AFTPH in epithelial cell signaling and colitis are unknown. Since epithelial cell permeability is an important feature of colitis and is related to TGN function, we examined the hypothesis that AFTPH may regulate epithelial cell polarity and permeability during colitis. **Methods:** AFTPH gene-silencing was performed by transfection of small interfering RNA (siRNA) against AFTPH (si-AFTPH) to human NCM460 colonic epithelial cells, while AFTPH overexpression *in vitro* was by achieved by transduction of lentivirus-expressing AFTPH. Global gene regulation by AFTPH gene silencing in these cells was evaluated using microarray analysis (array type: U133 +2.0). Cellular localization of E-cadherin (CDH1) and tight junction protein ZO1 in NCM460 cells was examined by immunocytochemistry (ICC). Epithelial cell permeability was studied using Dextran, Alexa Fluor® 680 (10 kMW, Life Technologies) and trans-epithelial electric resistance (TEER) was measured with the Millicell ERS-2 (Millipore). **Results:** Microarray analysis showed that AFTPH gene silencing in NCM460 cells downregulated expression of genes involved in epithelial cell adhesion signaling (E-catherin and β-catenin among others). AFTPH gene-silencing also reduced the sensitivity to contact inhibition in NCM460 cells. In NCM460 cell during the growth arrest state, AFTPH gene-silencing downregulated ZO-1 protein expression (ICC and Western blot) in cell junctions, while CDH1 showed increased perinuclear localization (ICC). Knock down of AFTPH in NCM460 cells reduced TEER by 34.3%, and increased dextran permeability ($p<0.05$), while lentiviral AFTPH overexpression reduced permeability ($p<0.05$).**Conclusions:** Our results indicate that gene silencing of AFTPH in human colonocytes increased epithelial permeability, possibly by regulating expression and localization of genes related to epithelial cell adhesion signaling. These are the first results suggesting that AFTPH may be a new gene regulating intestinal epithelial permeability.

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10.

Constitutive Activity of μ-Opioid Receptors Suppresses Hyperalgesia in Complete Freund's Adjuvant-Induced Latent Sensitization

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Latent Sensitization (LS) is a rodent model of pain that reproduces key features of chronic pain in humans: it lasts indefinitely, is sensitive to stress and involves μ-opioid receptors (MORs) and NMDA receptors. LS is characterized by a period of hyperalgesia followed by remission during which hyperalgesia can be temporarily reinstated by naltrexone, a MOR inverse agonist (Corder et al., 2013, Science 341:1394). This suggests that the remission phase of LS is not a return to a normal analgesic state but is rather a suppression of hyperalgesia by MORs. This could be the result of ligand-dependent or ligand-independent (constitutive) MOR signaling. We have used multiple experimental approaches to examine these possibilities. Mice and rats were injected in one hind paw with complete Freund's adjuvant (CFA) and developed an expected hypersensitivity to mechanical stimulation, which resolved to a 'remission' pain state after 3 weeks. The hyperalgesic state can be reinstated for ~2 hr by naltrexone. First, we measured opioid release in the spinal cord of rats during the remission phase by assessing MOR internalization in the presence of peptidase inhibitors. No MOR neurons with internalization (0-1 %) were found in the L4, T10 and C2 spinal cord segments, indicating that there was no opioid release. In contrast, acute nociceptive stimuli do induce MOR internalization in the spinal cord (Chen & Marvizon, Neuroscience 161:157, 2009). Second, LS was induced in mice lacking the genes encoding the primary endogenous MOR ligands, pro-enkephalin and pro-opiomelanocortin. Mice lacking either of these peptides showed similar CFA-induced hyperalgesia, remission and naltrexone reinstatement as their wild type littermates. This indicates that enkephalins or endorphins are not necessary for the continued activation of MORs during LS remission. We next assessed constitutive MOR signaling. Depolarization reversal of voltage-gated CaV channel inhibition, assessed by whole cell patch-clamp recordings of acutely isolated dorsal root ganglion neurons, revealed a tonic inhibition of these channels, a sign of MOR constitutive activity (Walwyn et al., J. Neurosci. 27:5092, 2007). We also assessed conditioned place aversion to naltrexone, an indicator of MOR constitutive activity (Shoblock and Maidment, Neuropsychopharm. 31:171-7) and found that LS mice showed greater aversion to naltrexone than naïve mice. These results strongly suggest that the remission of hyperalgesia following chronic inflammatory pain is not a result of continual opioid peptide release but caused by ligand-independent, constitutive MOR activity.

11.

μ-Opioid Receptor Knock-Out Mice Only Partially Recover from Hyperalgesia in Latent Sensitization – Contribution of α_{2A} Adrenergic and δ-Opioid Receptors to Pain Remission

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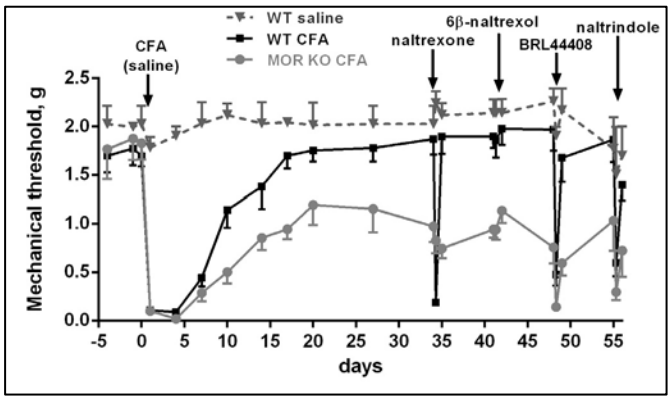
Latent Sensitization (LS) is a chronic pain model consisting of a period of hyperalgesia followed by a period of remission, during which hyperalgesia can be temporarily reinstated by opioid antagonists like naltrexone (Corder et al., 2013, Science 341:1394). Suppression of hyperalgesia during the remission phase of LS is thought to be mediated by the continued activation of μ-opioid receptors (MORs). To test this hypothesis, we studied LS induced by hind paw injection of complete Freund's adjuvant (CFA, 5 μl) in MOR knock-out (MOR -/-) and wild type (WT) mice. As a control, a group of WT mice received saline in the paw instead of CFA. CFA-injected WT and MOR -/- mice, but not saline-injected mice, developed hypersensitivity of the injected paw to mechanical stimulation (von Frey hairs) (Figure). After 20 days, paw sensitivity of the WT mice returned to baseline and was similar to saline-injected mice. In contrast, paw sensitivity of the MOR -/- mice recovered to ~50% of baseline and remained at that level for up to 56 days after the CFA injection. Naltrexone (3 mg/kg, s.c.) reinstated hyperalgesia in the CFA-injected WT mice but had no effect on the MOR -/- mice or in the saline-injected mice. The MOR neutral antagonist 6β-naltrexol



(10 mg/kg, s.c.) had no effect on any of the three groups of mice. The fact that the inverse agonist naltrexone, but not the neutral antagonist 6β-naltrexol, produced reinstatement in the WT mice supports the idea that the suppression of hyperalgesia is due to MOR constitutive activity and not to opioid release. Next, we determined whether δ-opioid receptors (DORs) or α2A adrenergic receptors mediated the partial recovery from hyperalgesia in the MOR -/- mice. The selective α2A receptor antagonist BRL44408 (1 mg/kg, s.c.) and the DOR antagonist naltrindole (3 mg/kg, s.c.) reinstated hyperalgesia in the CFA-injected WT and MOR -/- mice, but had no effect on the saline-injected mice. In conclusion, during the remission phase of LS, hyperalgesia is suppressed by the activation of MORs, but DORs and α2A adrenergic receptors also contribute to this effect.

12.
The Role of Enkephalin Signaling in Dopamine D2-Receptor Containing Neurons in Food Motivation

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Opioid neurotransmission is implicated in processes related to reward and aversion; however, how and where specific opioid peptides are involved in these processes remains unclear. The endogenous opioid peptide enkephalin is found in dopamine receptor 2 expressing neurons that primarily constitute the indirect pathway of the basal ganglia, a circuit with known roles in reward seeking behavior. Given this, two experiments were conducted to examine the role of enkephalin, specifically in these neurons, as it pertains to food reward and aversion. To this end, mice (designated here D2-PENK8) were genetically modified to lack proenkephalin-derived peptides in dopamine D2-receptor expressing neurons. We examined food reward motivation using licking microstructure analysis during consumption of sucrose solution, and the Pavlovian-to-instrumental transfer task, which assesses the ability of reward-paired cues to invigorate reward-seeking. We found that compared to wildtype mice, D2-PENK8 KO mice engaged in significantly fewer bouts of licking for sucrose and attenuated cue-induced reward seeking. Next, we investigated the role of enkephalin in behavioral aversion observed following antagonism of opioid receptors, by examining place conditioning to the malaise-inducing general opioid receptor antagonist naloxone, and the aphagic effects of the general opioid antagonist naltrexone. We found that unlike wildtype mice, D2-PENK8 KO mice are completely insensitive to the conditioned aversive effects of naloxone and the aphagic effects of naltrexone. Finally, we noted that whereas mice with body-wide loss of enkephalin signaling are underweight and resistant to diet-induced obesity, D2-PENK8 mice exhibit normal body weights, at least when maintained on a chow diet, suggesting a dissociation of the opioid-dependent psychological aspects of energy balance from the metabolic aspects. Together, these studies show that endogenous enkephalin signaling in D2-expressing neurons promotes behaviors directed at the unconditioned and conditioned aspects of food, and withdrawing this action renders animals amotivational or dysphoric. Accordingly, aberrant enkephalin signaling in D2 neurons may underlie pathological motivational and hedonic states related to disorders such as overeating.

13.
Premature Gut and Neonatal Stress: High Intestinal Glucocorticoid Responsiveness in Early Life Shapes the Risk of Epithelial Barrier Defect in Response to Maternal Separation

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Background: Glucocorticoids (GCs) contribute to human intestine ontogeny and accelerate gut barrier development in preparation to birth. In comparison, the rat gut is immature at birth, and high intestinal GCs sensitivity during the first two weeks of life resembles that of premature infants. This makes suckling rats a model to investigate postpartum impact of maternal separation (MS)-associated GC release in preterm babies. Our aim was to determine the effects of an episode of MS on epithelial barrier integrity, and whether high intestinal GC sensitivity at birth may shape MS effects in an immature gut. **Results:** A 4h-MS applied once at postnatal day (PND)10 enhanced plasma corticosterone in male and female pups, increased the total *in vivo* intestinal permeability(IP) to oral FITC-Dextran 4 kDa (FD4) immediately after the end of MS (2-fold; $p<0.01$), and induced bacterial translocation (BT) to liver and spleen compared to sham pups. Ussing chamber experiments demonstrated a 2-fold increase of permeability to FD4 in the colon of MS pups ($p<0.01$), but not in the ileum.

Colonic permeability was not only increased for FD4 after MS but also to intact horseradish peroxidase 44kDa demonstrating MS-induced transepithelial passage of high molecular weight macromolecules. *In vivo*, the glucocorticoid receptor (GR) antagonist RU486 or ML7 blockade of myosin light chain kinase controlling epithelial cytoskeleton contraction prevented MS-induced IP increase to FD4 and BT. In addition, the GR agonist dexamethasone dose-dependently mimicked MS-increase of IP to FD4 (ED50 = 0.1mg/kg). In contrast, MS effects on IP and BT were absent at PND20, a model of full-term infant, characterized by a marked drop in IP response to dexamethasone (i.e. no response before 1mg/kg), and decreased GR expression in the colon only compared to PND10 pups. **Conclusion:** These results show that high intestinal GC responsiveness in a rat model of prematurity defines a vulnerable window for a post-delivery MS, evoking immediate disruption of epithelial integrity in the large intestine, and increasing susceptibility to macromolecule passage and bacteremia.

14.

Translocation of Enteric Bacteria, Colonic Dismotility and Altered Behavior in Blast-type Traumatic Brain Injury in Rats

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Background: Traumatic Brain Injury (TBI) is associated with intolerance to enteral feeding in patients) and to upper gut dysfunction both in humans and rodents. Overpressure/blast TBI (bTBI), in addition to the brain, disproportionately affects air filled organs such as the gastrointestinal tract. The impact of TBI in the lower gut is less known. **Aim:** Determine the effect of single or repeated bTBI on enteric bacterial translocation, colonic motility and behavior in rats. **Methods:** Adult, male SD rats were anesthetized and exposed to a single (S-BTI) or repeated (R-BTI, 2 blasts, 2-weeks interval) air overpressure(~25psi, peak pressure, 1.1 msec after onset) to the head in a sealed chamber. Sham controls were anesthetized and placed in the chamber without exposure toblast. Rats were euthanized 24-hr (S-TBI, R-TBI) or 2 weeks (R-TBI) after the last blast and mesenteric lymphnodes (MLNs) of the ileo-cecal region collected. DNA from MLNs was used to sequence the 16S rRNA gene (Illumina MiSeq). Microbial diversity and operational taxonomic unit were analyzed for differences between groups. Colonic contractility was assessed (24-h post last bTBI) using manometry. In separate groups, motor, anxiety and cognitive behaviors were assessed 24-hr and 2 week post last bTBI using gait-dynamics, startle and pre-pulse inhibition responses and learning (water maze). **Results:** The largest microbial alpha diversity was observed between bTBIs (S-BTI and R-BTI) and the sham group. Compared to sham, MLNs from bTBIs have increased Actinomycetales coriobacteriaceae (sham:4.6% vs bTBI:11.6%) and lower Firmicutes (sham:23% vs bTBI:14%) of the total bacterial load. MLNs collected at 2 weeks in the R-BTI group have higher loads of both the Actinomycetales coriobacteriaceae and Firmicutes than those of S-TBI. Colonic motility was reduced post S-TBI and increased post R-TBI. Both S-TBI and R-TBI, compared to sham rats, showed persistent alterations in gait-dynamics, startle and pre-pulse inhibition responses and learning in the water maze that developed fully after the repeated blast. **Conclusion:** bTBI modulates microbial load to intestinal MLNs, alters colonic motility as well as motor, behavior and cognition in rats. Gut function is altered in bTBI and changes in gut function in bTBI may have relevance in the pathophysiology of bTBI.

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15.

Inflammation-Induced Modulation of Adiponectin Receptor 1 (AdipoR1) During Colitis: Adipose Tissue-Intestinal Crosstalk

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Background and Aims: We presented evidence suggesting that the adiponectin-AdipoR1 axis may play a role in the communication between mesenteric preadipocytes and the intestine during IBD. Here, we expanded these studies and examined whether mesenteric whole fat induces inflammatory responses in human colonic epithelial NCM460 cells. The potential intracellular signaling pathways regulating AdipoR1 expression and the role of AdipoR1 in mice with colitis were also investigated. **Methods:** Conditioned medium from mesenteric fat from

Ulcerative colitis (UC), Crohn's disease (CD) and control subjects (n=8-11 individual samples per group) were added to human colonic epithelial NCM460 cell monolayers and cytokine and PPARγ mRNA levels were measured using FlexScript LDA and RT-PCR, respectively. Colonic biopsies of control, UC and CD patients (n=4) were stained for AdipoR1. AdipoR1 mRNA levels in colon tissues from TNBS and vehicle-exposed mice (n=4) were evaluated with RT-PCR. The effect of intracolonic silencing of AdipoR1 (by si- AdipoR1) in the severity (weight, colon length, histologic colitis score) of TNBS-induced colitis (48 hrs) in mice (n=4-6 per group) was also evaluated. **Results:** VEGFA, TGFB2, G-CSF, and IL-8 were increased while CCL4, IFNγ, and IL-5 mRNAs were decreased in colonocytes exposed to UC vs control fat media. IL-8 and IL-12A were increased, while IL-1β, IL-5, IL-15, CCL3 and PDGFA ($p<0.01$) mRNAs were decreased in NCM460 cells exposed to CD vs control fat media. Interestingly, VEGFA, TGFB2, CCL4 and IL-12A levels were different in colonocytes exposed to UC vs CD media. Human colonic biopsies of UC and CD patients and mice with TNBS colitis show higher AdipoR1 levels ($p<0.05$). PPARγ mRNA levels were decreased in colonocytes exposed to media from UC ($p<0.01$) and CD ($p=0.0832$) whole fat media, mirroring the regulation of AdipoR1. Mice with intracolonic AdipoR1 silencing lost more weight and had worse colitis scores ($p<0.05$). **Conclusion:** Media from human mesenteric fat of UC and CD patients induce disease-dependent inflammation-related responses in colonocytes, including changes in AdipoR1 levels that may be related to down regulation of PPARγ, a known regulator of AdipoR1. The exacerbation of colitis in mice after intra-colonic silencing of AdipoR1 suggests a novel protective role for this receptor in the development of colitis and IBD.

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16.

Diet and Cognition in Rats: Comparison of a Refined to an Unrefined Foods Diet on Cognition: Understanding the Role of Diet Quality on tests of Vigilance in Rats

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Highly processed foods, commonly referred to as "junk foods", are increasingly recognized as having negative impacts on health and disease. Little is known, however, about the impact of a highly processed diet on cognition. We report the effects on attention of chronic consumption of a low-quality diet compared to a high-quality diet. Specifically, we investigated the effects of a diet high in refined carbohydrates (e.g., sugar) on adiposity and attention. We hypothesized that the refined-sugar diet, as compared to a control chow diet low in refined carbohydrates, would lead to a significant increase in adiposity despite its low fat content and in specific impairments of performance on a behavioral task that requires sustained attention (vigilance). Female Long Evans rats were placed on either a control diet consisting of unrefined ingredients (CON) or diet consisting of refined and purified ingredients (REF). Both diets were low in overall fat (<13%). After three months on their respective diets, the rats on the REF diet gained significantly more weight than rats on the CON diet, entirely through increased adiposity as determined by echo MRI scans. The effects of these diets on attention were tested by training the rats to press a lever under a briefly-presented light for reinforcement. The light was presented for 1-s at various delays within each trial from the onset of the trial to the onset of the light. Thus, the rat had to maintain vigilance to perform accurately. While both groups of rats were very accurate (about 90% accuracy) with no delay in the onset of the light, REF rats reduced accuracy with increasing delays at a greater rate than did CON rats. The increased error rates in REF rats were due to increased premature responses (impulsivity) and omissions (lapses in attention).

These results suggest that a refined foods diet causes impairments in attention, and thus, suggest that junk food diets consumed by humans can cause obesity and impair cognition.

17.

Novel Ghrelin Agonist HM01 Reverses Postoperative Gastric Ileus (POGI) by Its Dual Prokinetic and Anti-Inflammatory Actions through Activation of Vagal Cholinergic Pathway in Rats

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Background: Abdominal surgery (AS) induces delayed gastric emptying (GE) and is characterized by inhibited muscle contractility and evoked intestinal inflammatory responses. Ghrelin and its agonists stimulate appetite and enhance gastric motility through growth hormone secretagogue receptor 1a (GhsR1a). **Aims:** To determine in rats: 1. the gene expression of gastric GhsR1a and its splicing variant 1b. 2. the activation of cholinergic neurons in the gastric myenteric plexus (MP) and dorsal motor nucleus of the vagus (DMV) by HM01, a novel orally peripheral and brain penetrant ghrelin-receptor agonist. 3. the effects of HM01 on delayed GE and altered expression of cytokines by AS. **Methods:** 1. The gastric corpus (GC) collected from 3 naïve adult male SD rats was separated into the mucosa (M) and submucosa plus muscle layer (S+M) and processed for RT-PCR to amplify full length rat GhsR1a and 1b coding sequences. 2. Adult male SD rats (8-10/group) received pretreatment (-30 min) of IP saline or the peripheral nicotinic blocker hexamethonium (Hexa) (20 mg/kg) followed by IP saline (0.3 ml) or HM01 (6 mg/kg) for 2h. Whole mount preparations of gastric MP and brainstem cryostat sections were processed for Fos immunohistochemistry and double immunostaining of Fos and the peripheral isoform of acetylcholine transferase (pChAT) or common ChAT (cChAT) to mark enteric and central cholinergic neurons respectively. 3. Fasted SD male rats (8/group) received orogastric HM01 or saline and 20 min later AS (laparoscopy and small intestinal manipulation) was performed while sham rats had anesthesia alone. GE was determined and the gastric S+M was processed for qPCR to detect IL-1β, TNFα and IL-10 mRNA at 6 h post AS. **Results:** GhsR1a was detected predominantly in the S+M layer with a 40-fold higher level than in M layer while GhsR1b is 3-fold higher in M than S+M. HM01 increased significantly Fos immunoreactive (IR) cells in MP and DMN (18.1- and 3.0-fold over saline respectively). Hexa reduced HM01-induced increase of Fos expression in the MP by 2-fold ($p<0.001$) but values were still higher than in Hexa/saline group ($p<0.01$) while Hexa did not change Fos expression in DMN. HM01 induced Fos expression in 55% of pChAT IR and 52% of cChAT IR neurons in MP and DMN respectively. At 6 h post AS, IL-1β and TNFα are upregulated by 1.6- and 1.3-fold respectively and GE is delayed to 28% of that of sham group at 6 h post AS, ($p<0.01$). HM01 pretreatment completely abolished AS-induced delayed GE and increased IL-1β and TNFα expression while significantly elevating IL-10 in both sham and AS goups (3.2- and 4.0-fold respectively). **Conclusions:** HM01 displays potent prokinetic and gastric anti-inflammatory actions and prevents delayed GE induced by AS. These actions may be mediated by activating gastric vagal cholinergic pathway via GhsR1a at both central and peripheral sites.

Abstracts of Posters
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18.
Anatomical Properties of Emotion Arousal Regions Are Associated with Early Adverse Life Events and Vary Based on Sex

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Introduction: Neuroimaging studies have shown that alterations in regions of an emotional arousal network (including the amygdala [AMYG], subgenual [sgACC] and anterior cingulate cortex [ACC]) have been associated with a self-reported history of early adverse life events (EALs) (Gupta et al., Psychosomatic Medicine, 2014). The topology of the brain can be quantified using network metrics of centrality that index a brain region's contribution to the network's structural integrity and information flow (Rubinov & Sporns, NeuroImage, 2010). Regions with high *degree* are considered essential for facilitating functional integration. The ability of a region to propagate information across a network of regions is referred to as *local efficiency*. We hypothesized that differences in the degree and clustering coefficients of emotional arousal network regions would be related to reports of EALs in healthy subjects. **Methods:** 46 males and 44 females underwent structural diffusion tensor (DTI) and functional resting state (RS) MRI. Segmentation and regional parcellation of each individual's brain into 165 regions was performed using Freesurfer based on the Destrieux and Harvard-Oxford Atlases. Deterministic tractography using the Runge-Kutta algorithm was performed using TrackVis and provided a measure of relative fiber DTI density between regions. The Functional Conn Toolbox was used to process RS images of each individual. Network metrics (degree, local efficiency) based on DTI and RS connectivity were generated for the emotional arousal brain regions using the Brain Connectivity Toolbox. The Early Traumatic Inventory (ETI) was used to access self-reported history of EALs. The general linear model was applied to test the hypotheses. **Results:** No differences were observed between males and females on ETI total scores (mean ETI=4.36, SD=4.107). *Association between EALs and degree of emotional arousal regions*. Interaction effects were observed between sex and ETI with DTI degree of right sgACC (p=.019) and the left ACC (p=.03). Females but not males had large negative correlation between DTI degree of the right sgACC and ETI (r=-.48, p=.001). On the other hand, males but not females showed strong positive association between DTI degree of ACC connectivity and ETI (r=.35, p=.02). Across sex, ETI was positively associated with DTI degree of left AMYG (p=.038). Association between EALs and local efficiency of emotional arousal regions. For females (r(41)=-.35, p=.02) but not males (r(43) =-.14, p=.35) DTI local efficiency of the mid ACC was negatively associated with ETI. Significant interaction effects were observed between sex and ETI with RS local efficiency of the right sgACC (p=.027). For females (r=.29, p=.06) but not males (r=.12, p=.42) RS local efficiency of the sgACC was negatively correlated with ETI. Across sex, EALs were associated with DTI local efficiency of right sgACC (β= .003, p=.03). **Conclusion:** The network architecture of core emotional arousal network regions was associated with a self-reported history of EALs. Findings indicate that exposure to EALs affects not only the developing brain during childhood and adolescence but these alterations persist into adulthood as seen in this nonclinical sample of healthy men and women. The observed alterations in brain architecture of the emotional arousal network regions may be vulnerability factors for the development of psychiatric disease.

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19.
Patients with Irritable Bowel Syndrome (IBS) Have Reduced Blood Flow in the Prefrontal Cortex

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Background: Irritable Bowel Syndrome (IBS) is a disorder of brain-gut interactions, presenting as recurrent abdominal pain and altered bowel habits. Functional and structural brain alterations in sensorimotor, salience, affective and cortical control regions have been identified. Arterial spin labeling (ASL) is a brain imaging technique to quantitate regional cerebral blood flow (CBF) during the resting state. Based on previous functional imaging studies using evoked pain paradigms, we hypothesize greater CBF flow in affective and sensorimotor regions, and reduced blood flow in prefrontal regions involved in cortico-limbic inhibition. **Aim:** To assess resting CBF differences between IBS subjects and healthy controls (HCs). **Methods:** The study included 29 Rome III positive IBS subjects (11 female) and 30 healthy controls (12 female). The sample was age-matched with a mean age of 30.1 (SD = 9.6) for HCs and 30.8 (SD = 8.5) for IBS. CBF was evaluated using ASL, an imaging technique that utilizes magnetically labeled water as an endogenous tracer to directly measure regional blood flow in the context of functional magnetic resonance imaging. On a 3 Tesla Trio scanner, a Siemens pseudo-arterial spin labeling sequence with 40 unlabeled/labeled image pairs (whole-brain, 3.4x3.4x6 mm voxel size, 24 slices, repetition time 3.6s, echo time 12ms) was implemented. A questionnaire for usual symptom severity (0-20 visual analogue scale) was administered on the day of imaging. Data was preprocessed and analyzed under the general linear model using SPM12 and custom software. Comparisons of interest included sex differences across all subjects with group as a covariate and IBS-control differences with sex as a covariate. **Results:** Mean symptom severity was 9.6 (SD 4.6) and did not differ by sex. Across groups, females showed substantially higher CBF in most brain regions compared to men ($p<0.05$, corrected for multiple comparisons). HCs showed greater CBF compared to IBS subjects in the prefrontal cortex and temporal lobe (set level $p<.001$). IBS subjects had a trend toward greater CBF than HCs in multiple regions, including the cingulate cortex, thalamus, hypothalamus, cerebellar cortex, and precuneus, with an effect size of 5. **Conclusion:** IBS patients show altered CBF at rest relative to HC, with increases in the deeper brain structures, which include regions associated with sensory and affective processing, and decreases in cortical regions, including the prefrontal cortex. Presumably, the altered CBF may impact both brain function and structure. The prominent sex differences support importance of taking sex into consideration in brain imaging studies.

20.
Yoga for Teens with Irritable Bowel Syndrome: Results from a Mixed-Methods Pilot Study

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Irritable bowel syndrome (IBS) is a common, chronic condition associated with incurable pain and altered bowel habits. IBS is particularly pernicious to young patients, who may withdraw from life tasks due to pain, diarrhea and/or fear of symptoms. Emotional stress exacerbates IBS symptoms, and mind-body interventions may be beneficial. In this mixed-methods study of 18 teens aged 14-17 years undertaking a 6-week Iyengar yoga intervention, we aimed to identify sub-groups of treatment responders and to explore differences between responder and nonresponder teens on a range of quantitative outcome and qualitative themes related to yoga impact, goodness of fit, and barriers to treatment. Results revealed half of the teens responded successfully to yoga, defined as a clinically meaningful reduction in abdominal pain. Responders and nonresponders differed on quantitative outcomes, with responders reporting improved IBS symptoms, disability, fatigue, sleep problems, visceral sensitivity and physiologic stress reactivity (HRV), at either levels of significance or trend compared to nonresponders; and qualitative outcomes, with responders reporting generalized benefits early in treatment, and that their parents were supportive and committed to the intervention. Responders and nonresponders alike noted the importance of home practice to achieve maximal, sustained benefit. Overall, our data reveal the need for developmentally sensitive yoga programs that increase the accessibility of yoga for all patients.

21.

Functional and Anatomical Network Metrics are Associated with Longitudinal Symptom Reports in Patients with Interstitial Cystitis/Painful Bladder Syndrome

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Introduction: Interstitial Cystitis/ Pain Bladder Syndrome (IC/PBS) is a chronic pain condition that can produce severe pain in the bladder and pelvic region. Recent evidence suggests alterations in the gray matter volume and resting state connectivity of regions that comprise the somatosensory and salience networks are altered in IC/PBS and these alterations are associated with urgency and pain during bladder filling (Kilpatrick et al., 2014, Kairys et al. 2015, Bargarinao et al. 2014). We hypothesized that the degree and local efficiency of regions comprising the somatosensory and salience networks would represent a central biological marker that can be used to predict longitudinal symptoms. **Methods:** Diffusion tensor images(DTI) from 24 IC/PBS patients (Mean age= 38.07; 11 males) and resting state functional images from 34 IC/PBS patients (Mean age= 36. 19, 11 males) were processed using several semi-automated pipelines and workflows implemented at the Oppenheimer Center for Neurobiology of Stress and the University of Southern California Laboratory of Neuroimaging (LONI). The Brain Connectivity Toolbox (Rubinov, Sporns, 2010) was used to characterize the degree and local efficiency of regions of interest in the salience (anterior insula [INS}, and subregions of the anterior cingulate cortex) and somatosensory (thalamus [THAL], precentral gyrus, postcentral gyrus, central sulcus, postcentral sulcus, precentral sulcus and posterior insula) regions. Pain symptom severity and urinary symptom severity, were assessed every 2 weeks for 1 year using the Genitourinary Pain Index (GUPI) (Clemens et al, 2009). The relationship between the degree and local efficiency of somatosensory and salience region with symptom trajectories were tested using general linear models. r**esults:** *Resting State: Urinary severity* was negatively associated with local efficiency of the left(L) subcentral gyrus and sulcus ((se) -0.15(.06), p=0.03) and positively associated with the L anterior INS (0.30(.11), p=0.01). Similarly, *pain severity* was positively associated with local efficiency of the L anterior INS (0.17(.06), p=0.007) and right(R) putamen (0.29(.10), p=0.008). *DTI: Pain severity* was positively associated with local efficiency of the L precentral gyrus (12.0(4.6), p=0.02) but negatively associated with degree of the L central sulcus (-5.7(2.5), p=0.04),and R posterior INS (6.8(3.2), p=0.046). *Urinary severity* was positively associated with local efficiency of the R precentral gyrus (0.12(.05), p=0.03), R inferior precentral sulcus (0.16(.08), p=0.044), bilateral posterior INS (L: 0.14(.06), p=0.02; R: 0.17(.06), p=0.02) and negatively associated with local efficiency of the bilateral THAL (L: -0.11(.04), p=0.02; R: -0.14(.06), p=0.02). *Urinary severity* was also positively associated with degree of the L putamen (31.2(10.2), p=0.006), R caudate (19.55(7.7), p=0.02), R thalamus (35.4(12.6), p=0.01) and negatively associated with L subcentral gyrus and sulcus (-6.72(3.1), p=0.04) and L inferior precentral sulcus ((4.87)= -11.53, p=0.028). **Conclusions:** Topological properties of the somatosensory and salience networks predict change in pain and urinary severity within IC/PBS patients over time. Future studies in separate IC/PBS patient cohorts will be needed to validate the value of neuroimaging for prediction of IC/PBS symptom change over time.

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22.

Neurological Differences between Female IBS patients and Healthy Controls during Expectation of Safety from Abdominal Pain

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Background: IBS is a common gastrointestinal disorder characterized by chronic abdominal pain, alteration in

bowel habits, and symptom-related anxiety. Previous studies have shown that IBS patients have abnormal brain responses to the expectation of visceral pain. It is unknown whether IBS patients exhibit normal responses to 1) the expectation of a non-visceral threatening stimulus or 2) the presence of a safety condition within the context of a threat paradigm. **Aims**: To identify differences in functional neural activity between IBS patients and healthy controls (HC's) during the expectation of an abdominal shock and during a designated safe period. **Methods:** 24 female IBS patients and 10 female HC's (ages 18-50) were recruited by advertisement. We recorded the blood oxygen level-dependent (BOLD) response to an abdominal threat paradigm using a 3 Tesla Siemens Trio scanner. The paradigm was a jittered block design which included the following conditions: safe (no shock will be delivered), threat (shock may be delivered), and a neutral cross-hair condition. Multivariate partial least squares (PLS) analysis was employed to identify group differences in patterns of brain activity related to being in the "safe" or "threat" conditions. BOLD activity values during the safe condition were extracted from brain regions with the greatest activation in the "threat network", and were then correlated with behavioral measures using SPSS. **Results:** Mean age of the IBS group was 31.5, SD=9.53 and the age of the HC group was 26.1, SD=5.38. PLS identified a differentially activated network that accounted for 34.02% of the variance in the data ($p<0.008$). This network includes the insula, thalamus, and supplementary motor area. These regions are activated during the threat condition in both groups without significant differences ($p<0.05$). However, during the safe condition, these regions are significantly more deactivated in HC's ($p<0.05$). BOLD activity in these regions during the safe condition was found to be positively correlated to IBS behavioral measures. For example, the left anterior insula was correlated with IBS-SSS [r(24)=24, p=0.020] and IBS-NRS scores [r(24)=24, p=0.039], while the left thalamus was correlated with IPIP Neuroticism [r(24)=24, p=0.037], as well as abdominal symptom unpleasantness [r(24)=24, p=0.032]. **Conclusions:** These findings show increased activity of threat circuitry in IBS during a safe condition, suggesting that the safe cue is less effective in this group. Furthermore, the more severe the IBS symptoms, the greater the up-regulation of the threat network during the safe condition. These findings suggest that those with IBS may have abnormalities in the deactivation of the afferent processing network. It is possible that these central alterations play a role in symptoms such as bloating, abdominal pain, and increased sensitivity to visceral sensations.

23.

Gene Expression Profiles in Peripheral Blood Mononuclear Cells (PBMCs) Correlate with Structural and Functional Brain Networks in Chronic Visceral Pain

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Background: IBS is a stress sensitive disorder and conflicting data about associated immune alterations have been reported. Distinct gene expression profiles in PBMCs consistent with increased activity of the SNS have been described in populations under chronic stress ("*conserved transcriptional response to adversity*" [CTRA]). Migration of primed monocytes to the brain can result in regional glia activation and neuroinflammation. Neuroinflammatory changes have been implicated in the etiology of brain alterations in chronic pain. **Aims:** To test two hypotheses: 1) IBS subjects show altered gene expression profiles in PBMCs, consistent with the CTRA pattern, which are correlated with *structural* changes in the salience and emotional arousal networks. 2) Inflammatory gene expression profiles are correlated with *functional* resting state changes in the salience network. **Methods:** 20 IBS and 20 healthy controls (HCs) completed MRI scans. Gene expression profiles in PBMCs were assessed using human transcriptome array-2. Bioinformatic analyses determined: 1. Signal transduction pathway activity and transcription factor-binding motifs in the promotor areas of PBMCs, which were correlated with brain morphometry. 2. Differential expression of PBMCs on functional activity in the salience network. **Results:** 280 gene transcripts were identified showing >10% differential expression across groups (134 genes up-regulated from IBS, and 146 relatively down-regulated). 1. Transcription control pathways were implicated in the observed differences in gene expression, including increased activity of CREB factors (e.g., mediating -adrenergic signaling from the SNS), growth control pathways (the MAPK-responsive transcription factor ELK1), oxidative stress response pathways (NRF2), and pathways involved in growth factor and cytokine signaling (STAT). Transcript origin analyses indicated that IBS up-regulated genes derived predominately from monocytes and dendritic cells. Differential signaling by myeloid lineage transcription factor MZF-1 was positively associated with morphometric changes in salience and central autonomic networks. 2. In IBS, regions of the

salience network were positively correlated with proinflammatory genes (IL6, APOL2), whereas in HCs salience network regions showed negative correlations with anti-inflammatory genes (KRT8, APOA4). **Discussion:** 1. Regional structural changes in the salience and central autonomic networks in IBS are correlated with differences in myelopoetic processes and gene expression in PBMCs, consistent with increased SNS modulation of the peripheral immune system. 2. Regional functional changes in the salience network are correlated with expression of pro inflammatory genes, suggesting that primed monocytes may migrate to the brain, inducing structural and functional changes in brain regions involved in visceral hypersensitivity and increased anxiety.

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24.

Association of Body Mass Index with Anatomical Architecture of Reward Network Regions in Healthy Subjects

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Background: Similarities between brain mechanisms involved in maladaptive obesity-related ingestive behaviors and addictive behaviors have resulted in the concept of food addiction. Alterations in key brain regions of the reward network have been linked to increased ingestive behaviors in obesity. With recent advances in more efficient and computationally intense mathematical algorithms, it has become possible to characterize the architecture of regions in large-scale networks in specific disorders. The most fundamental network measure is *degree* or the connectedness of a particular region to other regions. Regions with high degree are considered essential for maintaining global connectedness. *Clustering coefficient* reflects the fraction of a region's neighbors that are also neighbors with each other and are thought to be key nodes for clusters or modules in the brain. High clustering efficiency is associated with greater efficiency in transferring information between regions. **Aim:** To characterize the association between BMI with differences in degree and clustering coefficients of key regions within the extended reward circuit. **Methods:** 99 healthy, male and female subjects completed structural and diffusion tensor imaging MRI scans. Data processing workflows were created using the USC Laboratory of Neuroimaging Pipeline. Regional parcellation was conducted using Freesurfer based on the Destrieux and Harvard Oxford atlases (resulting in 74 bilateral cortical and 7 subcortical structures, including the cerebellum). Relative fiber density between regions was obtained using deterministic tractography and the Runge-Kutta algorithm. Anatomical network metrics were generated using the Brain Connectivity Toolbox and were constructed from the threshholded correlation matrix between the 165 regions. Controlling for the main effects of age and sex, the general linear model was applied to examine the association between BMI with degree and clustering coefficients of regions comprising the reward network. The interaction between BMI and topology of the regions of interest as moderated by sex were also investigated. Significance was set at $p<.05$ uncorrected. **Results:** There were 57 lean individuals (mean BMI=22.08kg/m^2, sd=1.54, range=18.19-24.4kg/m^2) and 42 overweight/obese individuals (mean BMI=29kg/m^2, sd=3.85, range=25.0-43.6kg/m^2). 1. *Association between BMI and degree of reward regions*. After controlling for age and sex, BMI was positively associated with degree of left thalamus (β=1.14, p=.04), left caudate (β=.67, p=.04), and right nucleus accumbens (β=.83, p=.03). BMI was also negatively associated with degree of the right ventromedial prefrontal cortex (β=-.62, p=.03). 3. *Association between BMI and local clustering coefficient efficiency of extended reward regions*: After controlling for age and sex, BMI was significantly positively associated with local efficiency for the right amygdala (β= .009, p=.02) and left nucleus accumbens (β= .008, p=.04). BMI was also negatively associated with local efficiency of the right anterior insula (β=-.006, p=.01), bilateral ventromedial prefrontal cortex (β=-.005, p=.03; β=-.007, p=05). Interaction effects were not observed for sex and BMI on degree or clustering coefficient measures. **Discussion:** The anatomical network architecture of regions within the reward network are associated with BMI. Findings indicate that higher BMI is associated with more local and regional communication between regions with increased dopamine production, and less information propagation was observed in the cognitive frontal regions. Longitudinal studies will be required to address the question of causality between BMI and network alterations and association with ingestive behavioral patterns.

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Center (Pilot Scanning)

25.
IBS Patients Show Altered Brain Responses During Uncertain, But Not Certain Expectation of Painful Stimulation of the Abdominal Wall

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Background: Irritable bowel syndrome (IBS), a common gastrointestinal pain disorder, is characterized by chronically recurrent abdominal pain and discomfort associated with altered bowel habits. The majority of patients exhibit increased symptom-related worries, a measure of hypervigilance and prediction error about future gastrointestinal symptoms ("catastrophizing"). Many patients also show increased perceptual sensitivity to natural and experimental visceral stimuli, as well as altered brain responses in salience and pain processing regions both during cued expectation and delivery of rectal pain stimuli. **Aims:** We aimed to determine if uncertainty related to expected abdominal pain influences group differences in brain responses between IBS patients and healthy control subjects (HCs) **Methods:** A task-dependent functional magnetic resonance imaging technique was used to investigate the brain responses of 37 healthy controls (HCs; 18 females) and 37 IBS patients (21 females) during three conditions: 1. a cued safe condition 2. a cued expectation of an electric shock to the left lower abdomen 3. an ambiguous condition with no specific cue in which the threat is primarily based on context. The intensity of the abdominal shock stimuli was adjusted to the individual pain threshold. Images were acquired with echo planar sequence on a Siemens 3 Tesla Trio scanner. Individual brain responses for cued anticipation and ambiguous contextual threat were evaluated by contrasting the regressions for the three conditions (2 vs. 1 and 3 vs. 1, respectively). The first level contrast maps were entered into full factorial models for second level group analyses. Age, trait anxiety and depression scores were also modeled as covariates. Statistic significance was achieved with a minimum cluster size of 120 contiguous voxels. **Results:** Female IBS patients had significantly greater anxiety and depression scores compared to female HCs. During contextual threat condition versus safe condition, IBS patients showed greater brain activations in affective (amygdala, ventral anterior insula), sensory (thalamus), and attentional (middle frontal gyrus, including dorsolateral prefrontal cortex) regions, and in the precuneus. These disease-related differences were not related to symptoms of anxiety and depression, and were primarily seen in female subjects. In contrast, no disease-related differences were observed during cued expectation of abdominal threat condition versus safe condition, both groups showed robust threat responses. **Conclusion:** The observed greater engagement of cognitive and emotional brain networks in IBS patients during ambiguous contextual threat of abdominal pain may reflect the propensity of IBS patients to make prediction errors about the likelihood and severity of future abdominal pain ("catastrophizing") primarily under conditions of uncertainty.

26.
Genome-Wide Transcriptional Profiling Demonstrates Differences between Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD) and Healthy Controls

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Background and Aims: Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder which remains difficult to diagnose due to a lack of a diagnostic biomarker, its multifactorial etiology, and overlap of symptoms with organic GI diseases such as IBD. The aim of this study was to identify gene expression differences associated with IBS and identify potential biomarkers that can diagnose IBS and discriminate them from healthy controls (HCs) and disease controls such as ulcerative colitis (UC) and Crohn's disease (CD). **Methods:** Total RNA was isolated from peripheral blood mononuclear cells from patients with Rome III + IBS patients, UC and CD (confirmed by endoscopy and histopathology), and HCs. Gene expression was measured using Affymetrix HTA2.0 arrays, for expression profiling of all transcript isoforms including microRNAs and non-coding RNAs (70,523 transcripts). A 1.5 fold change (FC) and $p<0.05$ were considered significant. Data were

analyzed using Affymetrix Expression Console and R. **Results:** 35 IBS patients (48.5% F; mean age 39.4 yrs, 40% IBS-D, 33% IBS-C, 27% IBS-M), 32 HCs (50% F; mean age 39.4 yrs), 8 UC (50% F; mean age 27.4 yrs) and 4 CD (25% F; mean age 19 yrs). By comparing mRNA profiles of IBS patients with HCs, UC and CD, we identified several transcripts that were deregulated in each disease type. **Figure 1** shows the number of differentially regulated transcripts in various comparisons. IBS vs CD showed the highest number of deregulated transcripts (N=686). **Table 1** shows GO terms, associated genes and p values inferred from functional annotation clustering for all the comparisons. Clustering revealed upregulation of inflammatory genes (e.g., CD38 molecule; TRGC2: T-cell receptor gamma locus; IGHG4: Immunoglobulin heavy constant gamma 4 (G4M marker) for both

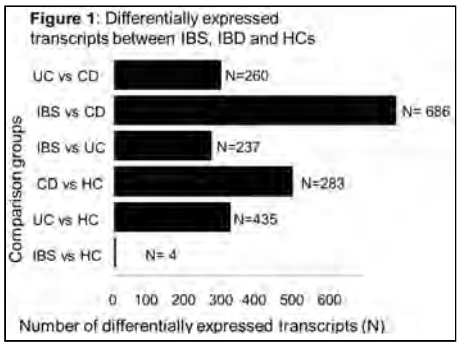

Table 1: Gene ontology (GO) terms associated with IBS vs healthy and disease controls

Groups	GO Term	Gene Count	FDR p value
IBS-UC	Immune Response	16	3.90E-11
IBS-CD	Immune Response	10	3.20E-10
IBS-HC	0 clusters found	-	-
UC-HC	Immune Response	15	1.30E-07
CD-HC	Immune Response	15	9.50E-06
UC-CD	Positive regulation of adaptive immune response	8	1.10E-01

CD and UC compared to IBS. There were 4 transcripts deregulated between IBS and HCs. microRNA miR-4461 was significantly downregulated (FC: -2.2, p=0.006) in IBS compared to HCs. However, at a lower fold change cutoff (FC>1.3), inflammation and defense response associated genes, such as *NFKB1A*, S100 Calcium Binding Protein A12 (*S100A12*), *NCF1B,* were upregulated in IBS patients vs. HCs. miR-27A, which has been reported as a class of adipogenic inhibitors, was upregulated in IBS patients. Most genes that had significantly different expressions in IBS vs. HCs were unannotated. **Conclusions:** Our findings suggest that while inflammatory genes were modestly upregulated in IBS vs. HCs, they were much lower compared to IBD. Interestingly, miR-27, which is upregulated in obesity, is also upregulated in IBS, suggesting that there may be a shared pathophysiologic mechanism. Thus, comparing mRNA profiles of IBS to that of GI disease controls such as IBD and healthy controls may lead to a better understanding of the pathophysiology of IBS and potentially a diagnostic biomarker.

27.

Differentiation of Epileptic and Non-Epileptic Seizures Through Regularized Logistic Regression of Features in Clinical History

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Psychogenic non-epileptic seizures (NES) are understood as physical manifestations of psychological stress, pain and emotion, and are three times more likely in women. These behavioral episodes superficially appear similar to epileptic seizures, but have no electrophysiologic correlate. Early and accurate differentiation between patients with non-epileptic and epileptic seizures (ES) is critical to establish effective treatments, improve quality of life, and reduce the cost of intractable seizures. Hundreds of measures have been shown to differentiate these populations, including sexual abuse, chronic pain and psychiatric conditions. However, the diagnosis remains challenging and questioned by non-epileptologists. We assessed real-world clinical applicability of a large subset of these measures using a data-driven approach in a large population with intractable seizure disorder, based on routine outpatient clinical reports. Methods: All 1,126 consecutive patients (634 ES, 314 NES, 178 mixed/inconclusive) admitted to our adult video-electroencephography epilepsy-monitoring unit (EMU) between 2006 and April 2014. Undergraduate researchers recorded 97 potentially diagnostic measures mentioned in the first sufficiently detailed outpatient neurological report. Multiple imputation of missing data combined with L1-regularized logistic regression estimated a data-driven discriminative score using leave-one-out cross-validation.

Permutation tests estimated empirical null distributions of all reported measures. Results: The area under the receiver-operating curve was 90.1% ($p<0.001$). Of the 97 studied measures, 51 exhibited significant univariate changes (false discovery rate, $p<0.05$) whereas 31 significantly contributed to the multivariate L1-regularized logistic regression score (empirical Wald $p<0.05$). Significance: This quantitative analysis expands our understanding of the combined role historical factors to diagnose seizures. Patients with NES had more multisystem complaints on the review of systems, had more medical and psychiatric comorbidities, and took more medication than patients with ES. Each of these factors negatively affects patients' quality of life, separate from their seizures. Therefore, early identification and treatment of NES is just the beginning of addressing the multiple challenges in this population.

28.

Sex Differences in the Relationship Between Trait Resiliency and the Intrinsic Connectivity of the Salience and Default Mode Networks of the Brain

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Background: Increased resilience is associated with better health outcomes and reduced morbidity in response to injury and homeostatic perturbations. Only recently have neurobiological correlates of resilience been investigated and the potential impact of sex/gender has been largely ignored. **Aims:** To identify possible sex-common and sex-specific correlations between personality traits of resilience and connectivity of the salience network (SN) and the default mode network (DMN). **Methods:** 82 healthy subjects (46 female; 36 male) completed a resting fMRI scan and NEO personality inventory. Independent components analysis was used to identify the SN and DMN. Partial Least Squares was performed to examine sex differences and commonalities in the relationship between intrinsic connectivity and a resilient NEO personality profile. **Results:** Stronger right anterior insula (aINS) connectivity within the SN was associated with increased resilience in both men and women. However, connectivity among DMN sub-networks and between SN and DMN demonstrated mainly sex differences in relationship to resilience. **Conclusions:** While the integrity of the aINS with the SN is important for resilience in both men and women, the results suggest that increased connectivity involving the anterior DMN preferentially benefits women in terms of resilience while increased connectivity involving the posterior DMN preferentially benefits men. These findings may relate to previous literature demonstrating that men and women engage different behavioral strategies to achieve resilience and highlight the importance of considering sex and gender in resilience research.

29.

Neurobiology of Resilience: Alterations of Brain Morphology in Healthy Subjects

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Background: Resilience is defined as the ability to adequately adapt to homeostatic perturbations. Increased resilience is associated with better health outcomes and reduced morbidity in response to psychological and physical stressors. However the biological correlates of resilience have only recently begun to be investigated. Understanding the neural endophenotypes associated with resilience holds promise for the development of pharmacological and psychological interventions targeted at treating or preventing disorders in susceptible individuals or those exposed to high levels of stress, adversity, and trauma. **Aims:** To identify relationships between self-report measures of resilience and specific brain morphology in healthy subjects. **Methods:** Forty-eight healthy subjects (33 female; 15 male), with a mean age of 26.31 years (SD=6.96 years, range = 18-46), completed a structural MRI scan and validated resilience questionnaires (*Connor and Davidson Resilience Scale* [CD-RISC], including the subscales). Segmentation and regional parcellation of the T1-image was performed using Freesurfer on the USC Laboratory of Neuroimaging (LONI) Pipeline (pipeline.loni.usc.edu) generating a

complete set of 165 parcellations for the entire brain. Grey matter volume (GMV), cortical thickness (CT), surface area (SA), and mean curvature (MC) were calculated for each region. Borrowing from animal and human trauma studies, regions of interest within the executive control, emotional arousal, salience, and reward networks were chosen a priori. Bivariate correlations were run between CD-RISC total, CD-RISC subscales, and the behavioral measures and morphological measures. General linear models (GLMs) using specified linear contrasts were used to identify morphological differences between those with high resilience compared to individuals with low resilience. A cutoff score of 80 was applied to the CD-RISC total scores to determine high and low resilience groups, in order to determine a clinical cut off. **Results:** Significant correlations were observed between CD-RISC score and CT of the left suborbital sulcus ($r(46)= 0.443$, $q= 0.004$), CT of left subcentral gyrus and sulci (a subregion of the postcentral gyrus) ($r(46)= -0.333$, $q= 0.042$). The subscales of the CD-RISC were also significantly correlated with regions within the reward, emotional arousal, and somatosensory networks. Linear contrasts in a GLM showed greater GMV ($t(1) = 2.90$, $q= 0.047$) and CT ($t(1) = 0.34$, $q= 0.008$) in the left suborbital sulcus (a subregion of the orbital gyrus) in high resilience subjects compared to subject with low resilience. **Conclusions:** Greater resilience was significantly associated with morphological differences in regions of the reward (suborbital sulcus), emotional arousal (frontomarginal gyrus and sulcus, gyrus rectus) and somatosensory networks (postcentral gyrus, subcentral gyrus, posterior insula, supramarginal gyrus). These data suggest that stress resilience incorporates a broad range of brain networks including those involved in affect, sensation and motivation. Further exploration of these networks should lead to better identification of mechanisms of risk and resilience to stress related disorders.

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30.

Adverse Childhood Experiences are Associated with Irritable Bowel Syndrome and Gastrointestinal Symptom Severity

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Background: Early adverse life events (EALs) have been associated with irritable bowel syndrome (IBS). Various instruments have been used to measure EALs in IBS. The Early Trauma Inventory short form (ETI-SF) measures 27 EAL events in the 4 categories of general trauma, and physical, emotional, and sexual abuse, and produces an ETI score. IBS patients report a higher number of EAL events compared to healthy controls based on the ETI-SF. The Adverse Childhood Events (ACE) has been used in large-scale studies to measure EALs and classifies a subject as having one or more of the EAL categories (prevalence). Higher ACE scores have been shown to be predictive of multiple diseases but has not been used in IBS. **Aim:** 1) To measure EALs in IBS vs. healthy controls using the ACE, 2) To compare ACE and ETI-SF scores in IBS and controls, and 3) To correlate ACE and ETI-SF scores with IBS symptom severity. **Methods:** 131 Rome III positive IBS (76% F, mean age=30 yrs) and 142 controls (61% F, mean age=30 yrs) completed both the ETI-SF and ACE to measure EALs before the age of 18. ACE score (0-8) is based on the number of EAL categories, i.e., general trauma (0-5), physical abuse (0-1), sexual abuse (0-1), emotional abuse (0-1). ETI-SF score was calculated for the 27 EAL items (score 0-27). IBS symptom severity was measured by a 20-point scale (0=none, 20=worst symptoms). Wilcoxon and chi-squared tests were used to compare ETI-SF and ACE scores and the prevalence of EALs by ACE in IBS and controls. Multiple logistic regression was used to adjust these comparisons for age, race and education. **Results:** Based on the ACE, the prevalence of EALs were higher in IBS vs. controls for the combined EAL categories (76% vs. 61%, p=0.010), for general trauma (71% vs. 57%, p=0.017), and for emotional abuse (26% vs. 15%, p=0.024). There was a trend for sexual abuse (20% vs. 11%, p=0.064). Compared to controls, IBS patients had higher total scores for both ACE (2.08 vs. 1.36, p=0.001) and ETI-SF (5.56 vs. 4.25, p=0.040). In addition, both ACE (OR=1.24 [95% CI: 1.15-1.35], p=0.004) and ETI-SF (OR=1.09 [95% CI: 1.06-1.13], p=0.002) scores predicted increased odds of having IBS. ETI-SF scores were significantly higher in subjects who had an EAL as defined by ACE vs. those who did not (Table). ACE score modestly correlated with GI symptom severity in IBS (r=0.19, p=0.031), but ETI-SF score did not (r=0.03, p=0.71). **Conclusion:** ACE and ETI-SF surveys both demonstrated significantly higher EAL scores in IBS patients vs controls. However, ACE appears to be more clinically useful in IBS because it measures the prevalence of EALs, is predictive of having IBS and the score positively correlates with IBS symptom severity.

Table. ETI-SF scores (mean [SD]) in subjects with and without EAL as defined by ACE

	IBS Patients			Controls		
Mean (SD)	+EAL	-EAL	p-value	+EAL	-EAL	p-value
Physical Abuse (0-5)	2.93 (1.33)	1.30 (1.68)	0.001	2.75 (1.48)	1.25 (1.58)	0.002
Sexual Abuse (0-6)	2.72 (2.21)	0.22 (0.70)	<0.001	1.88 (1.20)	0.15 (0.67)	<0.001
Emotional Abuse (0-5)	3.48 (1.99)	1.09 (1.41)	<0.001	2.71 (2.10)	0.61 (1.16)	<0.001

31.

Overweight and Obese Individuals Display Reduced Functional Brain Connectivity between the Reward System and the Prefrontal Cortex

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Background: The nucleus accumbens (NAcc) and the amygdala (AMYG) play a critical role in food-related reward processing and ingestive behavior. Prefrontal cortical control regions are thought to exert a restraining effect on the reward circuit. Resting-state functional MRI has been used to study functional connectivity (FC) in the human brain. **Hypothesis:** 1) Brain regions of the reward system show different FC patterns between obese/overweight (O/O) and lean individuals, and 2) FC of the NAcc and AMYG differ among male and female individuals with normal and high body-mass-index (BMI). **Methods:** 98 healthy subjects, age: 30.6±10.7, were divided into 48 lean subjects (BMI: 24.5 ±3.7; females:25) and 50 O/O subjects (BMI:27.2±5.07, females: 24). Subjects underwent brain fMRI. The individual seed-to-voxel connectivity map for NAc and AMY were created in the CONN fMRI connectivity toolbox. Imaging data was bandpass filtered 0.008-0.08 Hz. 4 mm-smoothed Fisher transformed bivariate correlation maps were implemented in SPM8. A second-level random effects full factorial model specified the four groups as factors. Significant regions were corrected for multiple comparisons at the whole-brain cluster-level using FWE correction at a threshold of $p<0.05$. **Results:** 1. NAcc FC: Lean subjects compared to O/O subjects had enhanced FC with the inferior ventrolateral and dorsomedial prefrontal cortex (PFC), the posterior cingulate cortex and the thalamus. In lean compared to O/O females, the NAcc showed greater FC with inferior ventrolateral and dorsomedial PFC, and posterior cingulate cortex. In lean vs O/O males Nacc had increased FC with inferior ventrolateral PFC, AMYG and with the posterior cingulate cortex (CC) was seen. 2. AMYG FC: Lean subjects displayed increased FC with the dorsolateral PFC, anterior cingulated cortex (ACC), insula, hippocampus, precuneus, and postcentral regions than O/O subjects. Lean compared to O/O females showed greater FC of the AMYG with dorsolateral PFC and precuneus. Lean compared to O/O males showed increased FC of the AMYG with the ACC, insula, hippocampus and precuneus. 3. Within the O/O group, females had greater NAcc FC with the hippocampus than males, and males had enhanced FC with the dorsolateral PFC than females. **Conclusions:** BMI correlated with changes in the NAcc and AMYG functional connectivity. In general, in both male and female subjects, normal BMI was associated with enhanced connectivity of several prefrontal regions with both NAcc and AMYG, compared to high-BMI. These findings suggest a compromised top down control of key reward regions by the PFC in overweight/obese subjects.

32.

Adiposity Is Associated with Alterations within the Brain reward System in Adult Subjects

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Background: Structural and functional brain changes have been identified in obese subjects, but the mechanisms underlying these changes are incompletely understood. Increased cytokine production by visceral adipose tissue (VAT) may play a role in triggering regional inflammatory changes within the brain. **Aims:** We hypothesized that: 1) The morphology of reward network regions differs between obese/overweight [O/O] and lean 2) Morphometric changes are related to VAT and proinflammatory adipokines. **Methods:** 37 adult subjects (age:24.1±6yrs, 26 females) without history of diabetes, neurological, cardiovascular or psychiatric disorders underwent structural brain MRIs. Subjects were divided into 22 lean subjects (BMI: 21.8±1.7) and 15 O/O

subjects (BMI: 29±4.9). Freesurfer analysis yielded 165 regions with 4 gray matter (GM) metrics (volume; cortical thickness; surface area; mean curvature). Adipokines were measured in serum using magnetic bead-based multiplex assay. VAT was measured using DEXA scans. Associations between morphometric measures and adipokines, BMI, waist-hip ratio (WHR), and VAT were explored using Pearson correlations. General linear models were constructed to examine interactions of obesity with adipokines on gray matter changes. **Results:** 1) GM properties were positively correlated with BMI in the insula (INS) and posterior cingulate cortex (CC), and negatively in orbital gyrus (OFG). VAT was positively associated with INS and precentral gyrus GM properties. Increased WHR was related to higher INS grey matter properties and low nucleus accumbens (NAcc) volume. Females tended to have larger INS volumes than men and smaller CC volumes. 2) Measures of adiposity (BMI, VAT and WHR) were negatively correlated with Adiponectin. Pro-inflammatory adipokines were associated with GM changes: a) CMP-1: positive correlations with CC, INS, amygdala (AMYG) and post-central gyrus (PostCG); b) IL-6 and IL-8: negative correlation with INS, and c) TNF-α: positive association with postCG and precuneus. 3) Higher BMI tended to be associated with lower volumes in parahippocampal gyrus (F=5.8, p=0.02), INS (F=3.4, p=0.02) and OFG (F=12.8, p=0.001). Adiponectin was positively associated OFG volumes (F=6.7, p=0.01) and there was an interaction effect between BMI and Adiponectin (F=6.153, p=.019). **Conclusion:** Increased adiposity was associated with lower volumes at parahippocampal gyrus, INS and OFG. Adiponectin, an "anti-inflammatory" adipokine was negatively correlated with obesity and associated with greater OFG volumes. Adipokines correlated with altered morphology in the reward system regions that could lead to abnormal top-down regulation of eating behaviors. Although current findings are enticing for a possible association between an obesity-related pro-inflammatory environment and brain morphometric changes, a larger sample is needed to confirm these associations.

33.
Targeting the Stress Pathway in Cognitive Decline

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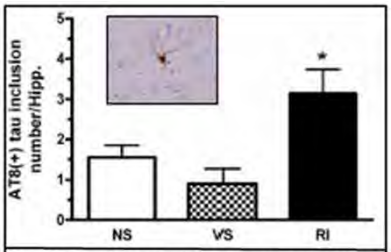

Fig. 1 Chronic stress increases ptau. Reactivity with AT8 antibody specific for ptau increases with chronic stress (RI).

Background: Stress is associated with cognitive decline (Tschanz, *Int Rev Psychiatry* 2013) and increases risk for Alzheimer's disease (AD). Stress-associated corticotropin-releasing factor receptor (CRF-1) stimulation leads to increased phosphorylation of the microtubule protein tau (Rissman, PNAS 2012) and neurofibrillary tangles (Fig. 1, Carroll, *J. Neurosci.* 2011). We target stress by "healthstyle" changes in the "MEND" program (Metabolic enhancement for neurodegeneration; *Bredesen*, Aging 2014) and targeting our Drug Discovery to inhibition of the CRF-1 pathway. **Methods:** Stress-reducing activities such as exercise, meditation, yoga, and improved sleep are part of the MEND program. Ten patients with complaints of cognitive decline have participated in the program. In Drug Discovery, we screened a series of CRF-1 inhibitors in SH-SY5Y cells at 1 M with/without 100 nM CRF. Total tau and ptau were determined by AlphaLISA (Perkin-Elmer). J03 was identified and tested *in vivo* in an AD mouse model by 14-day treatment at 10 mkd. Cognition was assessed by Novel Object Recognition (Bevins, *Nat. Protocol.* 2006); ttau and ptau were determined in brain tissue. **Results:** Nine of ten patients were improved by MEND. Most returned to work. CRF-1 inhibitor J03 decreased ptau and the ptau/ttau ratio both *in vitro* and *in vivo*, and improved cognition. **Conclusions:** Small initial studies with patients complaining of memory deficits, while anecdotal, indicate that stress-reduction has a role in reversing memory impairment. And, our drug studies show interruption of CRF-1 signaling reduces ptau and improves cognition in an AD mouse model. Our goal is to provide therapeutic intervention on the MEND platform of healthstyle support.

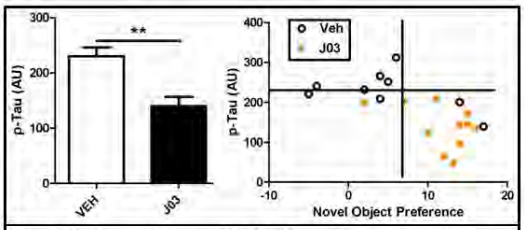

Fig. 2 J03 decreases ptau. CRF-1 inhibitor J03 decreased ptau *in vivo* and decreases in ptau correlated with improved memory.

34.
MRI Scan-Related Subjective Discomfort and Brain Metabolites in OCD Patients and Healthy Controls

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Background: Magnetic resonance spectroscopy (MRS) is used in longitudinal studies of brain physiology in obsessive-compulsive disorder (OCD). However, test-retest reliability of MRS metabolite levels has not been determined in OCD, nor have effects on metabolites of subjective state during the scan *(e.g.*, anxiety or discomfort level) been assessed. **Methods:** We acquired proton MRS from bilateral pregenual anterior cingulate cortex (pACC), anterior middle cingulate cortex (aMCC), and thalamus for the metabolites tNAA, Glu, Glx, Cr, Cho, mI in OCD patients and age-matched healthy controls at baseline and after 4 weeks of no-treatment waitlist. Test-retest reliability was calculated as the intraclass correlation (ICC). Subjective experience with an exit survey consisting of Likert-type scales for items comprising a cognitive anxiety index or physical anxiety index. Group-mean scan-to-scan changes were tested with repeated-measures ANOVA. Correlations between changes in survey indices and changes in brain metabolites were also tested (Pearson). **Results:** Scan-to-scan ICC averaged across metabolites and brain regions was relatively low but did not differ significantly between groups. Controls had significantly less anxiety in the second scan, which correlated negatively with changes of mI, Glu, and Cho in right thalamus (r=-0.59, p<0.05; r=-0.54, p<0.05; r=-0.67, p<0.01, respectively). OCD subjects were similarly anxious during both scans, but thought 33% less about how long the scan was taking for the second scan (p<0.05), which correlated significantly with changes of Glx in thalamus (r=-0.63, p<0.05), mI in left pACC (r=0.72, p<0.05), and Glu in right aMCC (r=-0.63, p<0.05). **Discussion:** Scan-to-scan variability in MRS brain metabolite levels is comparable in OCD subjects and healthy controls. While healthy controls may be less anxious with a repeat MRI scan, OCD subjects may not be, though they may think less about how long the scan takes. Changes in these anxiety-related items correlated with change in neurometabolite concentration, and may reflect neurophysiological changes to anxiety state. This cautions against assumptions in longitudinal studies that scanner environment experience is equivalent between control and patient groups, and calls for additional study to determine if state anxiety presents an additional confound in MRS studies.

35.
The Association of Early Adverse Life Events and Irritable Bowel Syndrome (IBS) Is Amplified by the Presence of Peritraumatic Fear

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Background: Early adverse life events are associated with the diagnosis of irritable bowel syndrome (IBS). The Early Trauma Inventory Self Report-Short Form (ETI-SR), which inventories adverse events before age 18, contains two questions that ask about the impact of the events. One question asks about the presence of emotions of fear, horror or helplessness and the other asks about experiencing an "out-of-body-sensation." Since IBS patients frequently report emotions of fear and helplessness, we hypothesized that an individual's reaction to trauma may be as, if not more, important than the trauma itself in the development and severity of IBS. **Aim:** To compare peritraumatic experiences in IBS patients and healthy controls (HCs). **Methods:** IBS patients were Rome+. Reponses to the items addressing peritraumatic emotions and experiences (Fear, Dissociation) in IBS vs HCs were compared with Chi-square tests. Logistic regression was used to test the ability to predict group membership for IBS vs HCs. Continuous variables were compared with the Mann Whitney test. **Results:** Participants were 368 IBS and 445 HCs (77.7% and 69.4% F) who reported ≥ 1 EAL. ETI-SR scores (total and subscales) were higher in IBS compared to HCs (mean(SD) for total scale: 6.1(5.3) and 3.9(4.0) in IBS and HCs, p<0.0005). Fear and Dissociation were more frequently reported in IBS vs HCs (60.4% vs 36.7%, p<0.0005; 23.7% vs 13.0%, p<0.0005, respectively). Total ETI-SR score predicted IBS status (B=0.095, p<0.0005, $\chi 2$ for model = 66.7, p<0.0005). When Fear and Dissociation were added to the model, its ability to predict IBS was improved, ($\chi 2$ = 86.9, p<0.0005) and Fear was an independent predictor of IBS (B=0.691, p<0.0005,). The odds ratio (95%CI) for IBS in those reporting Fear was 2.0 (95%CI:1.4-2.8) compared to those who did not. Within IBS, Fear was associated with increased mean abdominal pain scores (10.0 vs 8.9, p=0.032) and number of MD visits in the prior year (p=0.021). **Conclusions:** The association of peritraumatic fear with the development of IBS may

be due to sustained effects of an enhanced stress response at the time of the traumatic event. In addition, emotions of fear and helplessness can increase the severity of IBS by amplifying the emotional response to GI symptoms.

36.

Gender Disparities in the Effects of Body Mass Index on Depression and Depressive Episodes in 49 Low- and Middle-Income Countries

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Introduction: Excess body mass index (BMI) has been linked to depression or depressive symptoms in high-income countries. Yet, few studies examined such relations and whether they differed by gender in low-income countries (LICs) versus middle-income countries (MICs), using standardized measurements across countries. This study investigated the associations of BMI with depression and episode of depressive symptoms, and whether such relations differed by gender in LICs versus MICs. **Methods:** We analyzed World Health Survey (2002-2004) data on 145,077 participants from 49 LICs and MICs. Using random-intercept multilevel logistic regressions, we estimated gender-specific adjusted odds ratios and corresponding 95% confidence intervals for the associations of BMI with depression and depressive episode in LICs and MICs separately. **Results:** Being underweight or moderately obese was positively associated with ever being diagnosed with depression in both genders and in LICs and MICs. The relations between BMI and depression were similar in both genders in LICs, but such relations were slightly stronger among females than among males in MICs. Being overweight or mild obese was not or slightly negatively associated with depression among males and females in LICs, but such associations varied in direction by gender in MICs. The relations between BMI and depressive episode followed similar patterns as observed in the relations between BMI and depression, although the strength of the associations tended to be slightly smaller. **Conclusion:** Extreme BMI is associated with depression and depressive episode, more frequently among females than males in MICs. Tackling obesity and depression would benefit from both local and global analyses aimed at intra- and cross-national learning.

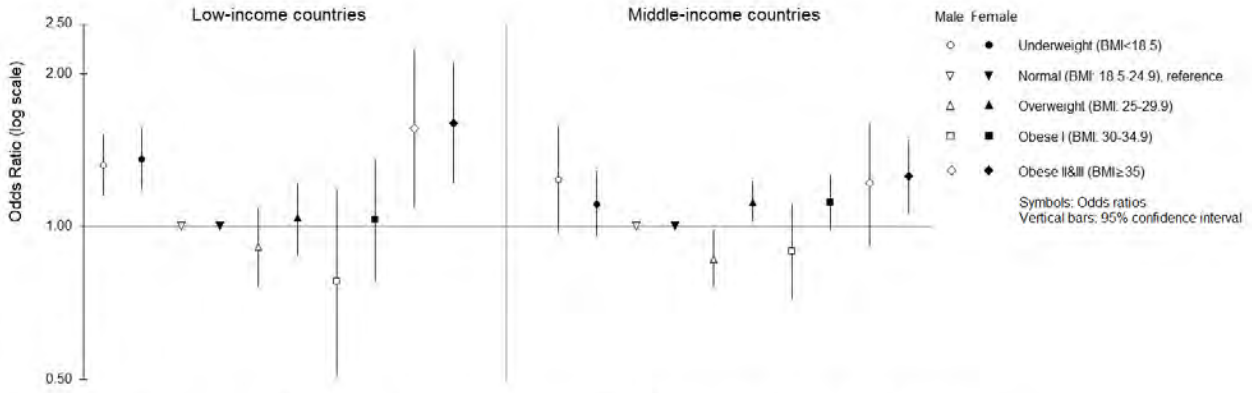

Figure 1. Model-based gender-specific associations between body mass index (BMI) and depression in 49 low- and middle-income countries. Estimates were obtained from the multilevel multivariable regression analysis of the World Health Survey 2002-2004 data (N=145,077).

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Zhuo Wang, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Neonatal Stress from Limited Bedding Elicits Visceral Hyperalgesia and Functional Brain Reorganization in Adult Rats

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

The Department of Medicine is greatly interested in improving the teaching of fellows and all other health professionals. For the instructor named above, please circle the number which indicates the degree to which you believe each item is descriptive of him or her.

	Not at all Descriptive									Very Descriptive	Doesn't Apply
1. Instructor is knowledgeable in the field and has command of the subject.	1	2	3	4	5	6	7	8	9	10	❒
2. Instructor presents material in an analytic way, contracts various points of view and discusses current developments.	1	2	3	4	5	6	7	8	9	10	❒
3. My knowledge of the subject matter increased as a result of this experience.	1	2	3	4	5	6	7	8	9	10	❒
4. Instructor is available, accessible, and meets appointments.	1	2	3	4	5	6	7	8	9	10	❒
5. Instructor enjoys teaching; is enthusiastic about the subject; makes the material exciting.	1	2	3	4	5	6	7	8	9	10	❒
6. Instructor is effective in providing guidance in the technical and intellectual aspects of research.	1	2	3	4	5	6	7	8	9	10	❒
7. Instructor provides feedback.	1	2	3	4	5	6	7	8	9	10	❒
8. Overall rating of this instructor compared with other teachers you have had at UCLA (10 is best).	1	2	3	4	5	6	7	8	9	10	❒

COMMENTS (including suggestions for improvement): _____

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Center for Neurobiology of Stress
CHS 42-210 MC737818

Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Muriel Larauche, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Role of Sex Hormones and Sex Chromosomes in Mechanically-Induced Visceral Hyperalgesia in Mice

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Arpana Gupta, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Sex Differences in Anatomical Connectivity Networks Associated with Obesity

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Iordanis Karagiannidis, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – IBD-Associated Changes in Mesenteric Fat and Their Effects on Experimental Colitis

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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COMMENTS (including suggestions for improvement): _____

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Elizabeth Videlock, MD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Sex Differences in Dysregulation Hypothalamic-Pituitary-Adrenal (HPA) Axis Associated with Irritable Bowel Syndrome and Early Adverse Life Events

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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COMMENTS (including suggestions for improvement): _____

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CHS 42-210 MC737818

Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Jason Kutch, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Unraveling a Brain Interface between Skeletal Muscle Function and the Viscera in Humans

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Rita Valentino, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Sex Biased Cell Signaling

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

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CHS 42-210 MC737818

Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Jeffrey Mogil, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Sex Differences in the Genetic and Cellular Mediation of Pain and Analgesia

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

The Department of Medicine is greatly interested in improving the teaching of fellows and all other health professionals. For the instructor named above, please circle the number which indicates the degree to which you believe each item is descriptive of him or her.

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COMMENTS (including suggestions for improvement): _____

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Kathleen Brady, MD, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Gender Differences In the Relationship Between Stress and Addictions: Clinical Correlates

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

The Department of Medicine is greatly interested in improving the teaching of fellows and all other health professionals. For the instructor named above, please circle the number which indicates the degree to which you believe each item is descriptive of him or her.

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Academic Year 2014-2015
Date 02/27/15

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: John Sheridan, PhD

ACTIVITY: 13th Annual CNS Basic & Translational Science Symposium – Neuroimmune Interactions in Stress

Evaluation submitted by: ❒ Student ❒ Post-doc ❒ Fellow ❒ Other _____

The Department of Medicine is greatly interested in improving the teaching of fellows and all other health professionals. For the instructor named above, please circle the number which indicates the degree to which you believe each item is descriptive of him or her.

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