11th Annual CNS
Basic and Translational Symposium
SYSTEMS BIOLOGICAL APPROACHES TO GUT-BRAIN INTERACTIONS IN HEALTH AND DISEASE – FROM MOLECULAR TO SOCIAL NETWORKS
April 26, 2013
Neuroscience Research Building
Contributors

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Bruce Naliboff, PhD

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Brentwood Biomedical Research Institute
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Morris A. Hazan Family Foundation

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11TH ANNUAL CNS BASIC AND TRANSLATIONAL SCIENCE SYMPOSIUM
SYSTEMS BIOLOGICAL APPROACHES TO GUT-BRAIN INTERACTIONS IN HEALTH AND DISEASE – FROM MOLECULAR TO SOCIAL NETWORKS

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, the Gail and Gerald Oppenheimer Family Foundation and the Morris A. Hazan Family Foundation

Friday, April 26, 2013
NEUROSCIENCE RESEARCH BUILDING AUDITORIUM (NRB 132)

8:00 am – 8:15 am INTRODUCTION

Symposium Chairs: Bruce Naliboff, PhD (Co-Director, Program in Mind-Body Research, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA; VA Greater Los Angeles Healthcare System) and Sylvie Bradesi, PhD (Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, Division of Digestive Diseases, David Geffen School of Medicine at UCLA; VA Greater Los Angeles Healthcare System)

Alan Fogelman, MD
Executive Chair, Department of Medicine, David Geffen School of Medicine at UCLA

SESSION I ADIPOCYTE-RELATED NETWORKS AND SYSTEMS BIOLOGY

Session Chairs: Sylvie Bradesi, PhD and Mete Civelek, PhD (Division of Cardiology, David Geffen School of Medicine at UCLA)

8:15 am – 8:40 am Mesenteric Adipocyte Networks and Gastrointestinal Diseases
(20 minute presentation + 5 minute discussion)
Charalabos Pothoulakis, MD
Director, UCLA Research Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
8:40 am – 8:55 am  Chronic Psychological Stress Regulates Visceral Adipocyte-Mediated Glucose Metabolism and Inflammatory Circuits
(10 minute presentation + 5 minute discussion)
Iordanis Karagiannidis, PhD
Adjunct Assistant Professor, UCLA Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

8:55 am – 9:10 am  The Genetic Regulation of Adipose Tissue Transcript Expression in Humans and Mice
(10 minute presentation + 5 minute discussion)
Mete Civelek, PhD

9:10 am – 9:35 am  Systems Biology Approach to Gastrointestinal Diseases
(20 minute presentation + 5 minute discussion)
Dimitrios Iliopoulos, PhD
Director, Center for Systems Biomedicine, Associate Professor of Medicine, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

SESSION II  SEX DIFFERENCES IN BRAIN NETWORKS
Session Chairs: Andrea Rapkin, MD (Director, UCLA Pelvic Pain Program, Professor, Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA) and Paul Macey, PhD (School of Nursing and Brain Research Institute, UCLA)

9:35 am – 10:00 am  Sex-Related Differences in Structural and Functional Brain Connectivity in Irritable Bowel Syndrome
(20 minute presentation + 5 minute discussion)
Kirsten Tillisch, MD
Director, Neuroimaging Core, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

10:00 am – 10:15 am  Sex Differences in Emotion-Related Cognitive Processes in Irritable Bowel Syndrome and Healthy Control Subjects
(10 minute presentation + 5 minute discussion)
Arpana Gupta, PhD
Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

10:15 am – 10:35 am  COFFEE BREAK

10:35 am – 10:50 am  STATE OF THE CENTER
(15 minute presentation)
Emeran Mayer, MD
Director, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and Co-Director, CURE: Digestive Diseases Research Center, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
SESSION III  SOCIAL NETWORKS

Session Chair: Lin Chang, MD (Director, Center for Neurovisceral Sciences and Women's Health, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

10:50 am – 11:15 am Social Networks Related to Chronic Intestinal Disorders
(20 minute presentation + 5 minute discussion)
Martijn van Oijen, PhD
Associate Director, Quality Initiative Program, VA/UCLA Center for Outcomes Research and Education (CORE), Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:15 am – 12:45 pm LUNCH AND POSTER SESSION

SESSION IV  GENE AND BRAIN NETWORKS

Session Chairs: Jack Van Horn, PhD (Laboratory of Neuro Imaging, Department of Neurology, UCLA) and Jen Labus, PhD (Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

12:45 pm – 1:10 pm Large Scale Brain Networks
(20 minute presentation + 5 minute discussion)
Jack Van Horn, PhD

1:10 pm – 1:25 pm Alterations in Prefrontal-Limbic Activation and Structurally-Linked Functional Connectivity in Chronic Stress-Induced Visceral Hyperalgesia
(10 minute presentation + 5 minute discussion)
Daniel Holschneider, MD
Associate Professor, Keck School of Medicine, Dept. of Psychiatry and the Behavioral Sciences, University of Southern California

1:25 pm – 1:50 pm Systems Biological Approach to Genetics of Complex Diseases
(20 minute presentation + 5 minute discussion)
James Weiss, MD
Chief, Division of Cardiology; Director, Cardiovascular Research Laboratory, David Geffen School of Medicine at UCLA

1:50 pm – 1:55 pm 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
Poster Award

1:55 pm – 2:00 pm Lin Chang, MD
Closing Comments

2:00 pm END OF SYMPOSIUM
Abstracts of Presentations

Symposium Chairs: Bruce Naliboff, PhD (Financial Disclosure: None)
Sylvie Bradesi, PhD (Financial Disclosure: None)

SESSION I: ADIPOCYTE-RELATED NETWORKS AND SYSTEMS BIOLOGY

Chairs: Sylvie Bradesi, PhD (Financial Disclosure: None)
Mete Civelek, PhD (Financial Disclosure: None)

Mesenteric Adipocyte Networks and Gastrointestinal Diseases
Charalabos Pothoulakis, MD
UCLA Research Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Earlier studies have demonstrated that chronic obesity is associated with immune dysregulation reminiscent of low-grade inflammation characterized by increased macrophage infiltration into adipose tissue and increased expression of proinflammatory cytokines from fat cells. These observations stimulated discussion suggesting that adipose tissue may affect the outcome or even the development of diseases in which inflammation plays a central role, including IBD, and IBS. Furthermore, it is also becoming clear that the proinflammatory environment that exists with increased adiposity is favorable for the development of conditions where inflammation represents a central component, such as IBD. Patients with Crohn’s disease have increased abdominal fat and elevated circulating levels of fat-derived cytokines, termed adipokines. In the case of Crohn’s disease the extent of inflammation and histological damage are correlated with the development of a mesenteric fat mass that wraps the intestine, termed ‘creeping fat’, characterized by infiltration of fat depots with immune cells and increased levels of proinflammatory adipokines. Our laboratory has shown that substance P and neurotensin, two neuropeptides that promote intestinal inflammation and IBD-like colitis, are also involved in inflammatory changes in the mesenteric fat depots of mice in colitis models, suggesting their potential involvement in proinflammatory responses in the adipose tissue that may participate in IBD pathogenesis. We also found that these peptides are able to activate pathways linked to obesity and metabolism suggesting a cross talk between inflammatory and metabolic pathways mediated by neuropeptides at the adipocyte level. Recent results also indicate that rats exposed to chronic unpredictable stress show increased mesenteric fat accumulation accompanied by elevated levels of adipokines both in the circulation and the mesenteric fat depots. This new evidence linking neuropeptides, both centrally and peripherally, adipose tissue, colonic responses to stress and inflammation, and metabolic changes and their impact in gastrointestinal pathophysiology in different disease states are discussed in this presentation.

* Financial Disclosure: Research grants from Merck Pharmaceuticals and Optimer Pharmaceuticals

Chronic Psychological Stress Regulates Visceral Adipocyte-Mediated Glucose Metabolism and Inflammatory Circuits
Iordanis Karagiannidis, PhD
UCLA Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, UCLA

Aims/Hypothesis: Chronic psychological stress is a prominent risk factor involved in the pathogenesis of many complex diseases, including major depression, obesity, and type II diabetes. Visceral adipose tissue is a key endocrine organ involved in the regulation of insulin action and an important component in the development of insulin resistance. Here we examined for the first time the changes on visceral adipose tissue physiology and on adipocyte-associated insulin sensitivity and function after chronic psychological stress. Methods: Male rats were subjected to chronic unpredictable stress for 35 days and total body fat was measured. Cytokines and activated intracellular kinase levels were determined using high throughput
multiplex assays. Adipocyte function was assessed via tritiated glucose uptake assay. **Results:** High throughput molecular screening in adipocytes isolated from stressed rats revealed activation of intracellular inflammatory, glucose metabolism and MAPK networks compared to controls, as well as significantly reduced glucose uptake capacity in response to insulin stimulation. Stressed rats showed no weight gain, and their fat/lean mass ratio increased dramatically compared to control animals. Stressed rats had significantly higher mesenteric fat content and epididymal fat pad weight and demonstrated reduced serum glucose clearing capacity following glucose challenge. Alterations in fat depot size were mainly due to changes in adipocyte numbers and not size. **Conclusions/interpretation:** Our study identifies the adipocyte as a key regulator of the effects of chronic stress on insulin resistance, and glucose metabolism, with important ramifications in the pathophysiology of several stress-related disease states.

* Financial Disclosure: None

*The Genetic Regulation of Adipose Tissue Transcript Expression in Humans and Mice*

**Mete Civelek, PhD**  
Division of Cardiology, UCLA

Metabolic syndrome (MetSyn) is a group of metabolic conditions that occur together and promote the development of cardiovascular disease (CVD) and type 2 diabetes. Although various criteria for defining MetSyn exist, disease conditions include abdominal obesity, insulin resistance, elevated serum triglyceride levels, depressed serum high-density lipoprotein (HDL) levels, elevated blood glucose levels and hypertension. The incidence of MetSyn is predicted to increase as obesity has become a worldwide epidemic. This increase may have detrimental effects and may actually reverse the trend of decreasing CVD in the US.

MetSyn involves the complex interplay of hundreds of genes accompanied by interactions with environmental factors and their combined influence on the development of obesity, insulin resistance and inflammatory processes in various tissues. All MetSyn traits are strongly influenced by genetic factors with heritability estimates up to 70%. Our current understanding of the genetics of MetSyn has come from studies of Mendelian traits as well as recent genome-wide association studies (GWAS) in humans. GWAS have identified over 400 loci that are associated with obesity, diabetes, CVD and cardiometabolic traits. However, most of the underlying genes and the related mechanisms remain unknown. Given their firm association with disease risk, novel MetSyn loci provide a solid foundation to unravel disease networks.

We used a systems genetics approach to identify causal genes and pathways underlying GWAS loci by combining data from extensively phenotyped human and mouse cohorts that are part of the Metabolic Syndrome in Men (METSIM) and Hybrid Mouse Diversity Panel (HMDP) studies, respectively. METSIM is one of the largest population based cohorts that have been subjected to extensive clinical exams for detailed cardiometabolic traits. The HMDP is a resource of 100 inbred strains of mice which have also been carefully phenotyped for similar metabolic traits. These resources provide an excellent platform because of the genetic diversity and extensive phenotyping to perform systems genetics analyses and validate the associations of genetic variants with multiple molecular and intermediate traits that play a role in the development of MetSyn across species.

Samples from MetSyn-relevant and metabolically active subcutaneous adipose tissue of 100 HMDP strains and 200 METSIM participants have been collected. Preliminary analyses of mRNA and microRNA (miRNA) expression from these resources have predicted causal genes in 27 GWAS loci for metabolic traits, 8 of which also showed significant associations in mouse adipose tissue. We are currently testing the causal involvement of these genes using gene manipulations *in vitro* and *in vivo*.

* Financial Disclosure: None

*Systems Biology Approach to Gastrointestinal Diseases*

**Dimitrios Iliopoulos, PhD**  
Center for Systems Biomedicine, Division of Digestive Diseases, UCLA

It is known that human gastrointestinal (GI) diseases are multifactorial, and both genetic and environmental factors contribute to their pathogenesis. Although during the last few years there is increasing knowledge
about the molecular mechanisms and signaling pathways involved in the pathogenesis of GI diseases, there is limited progress towards the identification of novel drugs. Systems biology is a revolutionary approach that potentially could contribute to our understanding about the biological complexity of these diseases. Here, we will describe for the first time, a novel systems biology approach that we have developed, in order to characterize these diseases in a genome-wide level and identify the central hubs of disease pathogenesis. Interestingly, this powerful approach has revealed novel transcriptomic and epigenomic circuits that have not been previously implicated in the pathogenesis of these diseases. Furthermore, we will discuss how integration of the different high throughput molecular data could identify novel drug targets by using a “Network-based Chemical Screening” approach. Overall, it becomes more and more evident that system biology approaches could revolutionize biomedical research leading to the identification of novel prognostic and diagnostic tools, together with the development of novel therapeutic approaches.

* Financial Disclosure: None

SESSION II: SEX DIFFERENCES IN BRAIN NETWORKS

Chairs: Andrea Rapkin, MD (Financial Disclosure: None)
Paul Macey, PhD (Financial Disclosure: None)

Sex-Related Differences in Structural and Functional Brain Connectivity in Irritable Bowel Syndrome

Kirsten Tillisch, MD
Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, UCLA

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort, in addition to altered bowel habits. IBS affects both men and women but with a female predominance. Sex differences in symptoms include an increased frequency of the constipation bowel habit in women, though overall severity tends to be similar. In terms of the pathophysiology of the disorder, a dysregulation of the gut-brain axis has been proposed and is supported by numerous studies showing altered brain function, particularly in response to visceral pain tasks. Sex differences in brain structure and function within IBS have been described, but have not been fully elucidated. In this talk an update on sex differences in brain connectivity in terms of structure, as measured by diffusion tensor imaging, and function, as measured in the resting brain, will be described. Additionally, differential features of whole brain networks in men and women with IBS will be presented. The cumulative evidence suggests that while men and women with IBS present with similar basic complaints, differences in the generation of their symptoms exists and is likely to influence their response to pharmacological and non-pharmacological therapy.

* Financial Disclosure: None

Sex Differences in Emotion-Related Cognitive Processes in Irritable Bowel Syndrome and Healthy Control Subjects

Arpana Gupta, PhD
Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, UCLA

Background/Aims: Greater responsiveness of emotional arousal circuits in relation to delivered visceral pain has been implicated as underlying central pain amplification in Irritable Bowel Syndrome (IBS), with females showing greater responses than males. Methods: Functional MRI was used to measure neural responses to an emotion recognition paradigm, using faces expressing negative emotions (fear and anger). Sex and disease differences in the connectivity of affective and modulatory cortical circuits were studied in 47 IBS (27 premenopausal females) and 67 healthy controls (HCs; 38 premenopausal females). Results: Male subjects (IBS+HCs) showed greater overall neural activations than female subjects in prefrontal cortex, insula, and amygdala. Effective connectivity analyses identified major sex and disease related differences in brain connections.
networks related to prefrontal regions, cingulate, insula, and amygdala. Males had stronger connectivity between anterior cingulate subregions, amygdala, and insula, whereas females had stronger connectivity to and from the prefrontal modulatory regions (medial/dorsolateral cortex). **Conclusions:** Male IBS demonstrate greater engagement of cortical and affect related circuits compared to male controls and females, when viewing faces depicting emotions previously shown to elicit greater behavioral and brain responses in male subjects. As previous studies using GI symptom related stimuli in female subjects have demonstrated differences in the engagement of similar brain circuits between IBS subjects and HCs, the current findings suggest that IBS related differences in brain responses are sex and stimulus dependent.

* Financial Disclosure: None

**STATE OF THE CENTER**  
Emeran Mayer, MD  
Director, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, UCLA  
* Financial Disclosure: None

**SESSION III: SOCIAL NETWORKS**

**Chair:** Lin Chang, MD (Financial Disclosure: Research grant from Ironwood Pharmaceuticals; Consultant for Ironwood Pharmaceuticals, Forest Pharmaceuticals, Takeda Pharmaceuticals, Salix Pharmaceuticals, Ferring Pharmaceuticals)

**Social Networks Related to Chronic Intestinal Disorders**  
Martijn van Oijen, PhD  
Quality Initiative Program, VA/UCLA; Center for Outcomes Research and Education (CORE), Division of Digestive Diseases, UCLA

Many initiatives are currently present online for patients, such as disease-specific closed patient communities on Facebook, patientslikeme.com, and open discussions about diseases and their treatment on Twitter. These initiatives provide huge data streams that may be harnessed for research, patient education and clinical care.

IBS is the most common gastrointestinal disorder in the US, costing billions of healthcare dollars and incurs significant decrease in the health related quality of life (HRQoL) of affected patients. Yet only a small fraction of IBS patients seek care, while their symptoms, behaviors, and attitudes outside the clinical setting are largely unquantifiable to physicians and researchers. Social media, such as twitter, has the potential to provide such information, and may serve as a novel strategy to measure patient reported outcomes (PRO) in IBS patients.

* Financial Disclosure: None
SESSION IV: GENE AND BRAIN NETWORKS

**Chairs:** Jack Van Horn, PhD (Financial Disclosure: Research support from Kitware, Inc.)
Jen Labus, PhD (Financial Disclosure: None)

**Large Scale Brain Networks**

**Jack Van Horn, PhD**
Laboratory of Neuro Imaging, Department of Neurology, UCLA

While neuroimaging has long been labeled “brain mapping”, the last several years have seen a remarkable surge in approaches seeking to map large-scale brain networks in vivo. In particular, the availability of diffusion weighted imaging methods now provides the opportunity to map white matter structure and, thereby, creating mappings of cortico-cortico and cortico-subcortico connectivity. These representations enable examination of individual patterns of connectivity, those of population level group averages, as well as facilitate modeling of white matter damage or degeneration. Moreover, connectivity models of the brain often employ graphical and computational abstractions whose relationships to anatomical properties is frequently unresolved. In this presentation I will provide an overview of connectivity modeling methods used to map white matter fiber pathways in the living brain, discuss means for how these networks can be represented, and discuss the use of graph theoretical methods to decompose and characterize network structure. I will illustrate examples of network modeling in healthy subjects as well as those with brain damage. I will conclude with considerations for the modeling of such networks in neuropsychiatric, chronic pain, and other patient samples.

* Financial Disclosure: Research support from Kitware, Inc.

**Alterations in Prefrontal-Limbic Activation and Structurally-Linked Functional Connectivity in Chronic Stress-Induced Visceral Hyperalgesia**

**Daniel Holschneider, MD**
Keck School of Medicine, Department of Psychiatry and the Behavioral Sciences, University of Southern California

Repeated water avoidance stress (WAS) induces sustained visceral hyperalgesia (VH) in rats measured as enhanced visceromotor response to colorectal distension (CRD). This model incorporates two characteristic features of human irritable bowel syndrome (IBS), VH and a prominent role of stress in the onset and exacerbation of IBS symptoms. Little is known regarding central mechanisms underlying the stress-induced VH. Here, we applied an autoradiographic perfusion method to map regional and network-level neural correlates of VH. Adult male rats were exposed to WAS or sham treatment for 1 hour/day for 10 days. The visceromotor response was measured before and after the treatment. Cerebral blood flow (CBF) mapping was performed by intravenous injection of radiotracer ([14C]-iodoantipyrine) while the rat was receiving a 60-mmHg CRD or no distension. Regional CBF-related tissue radioactivity was quantified in autoradiographic images of brain slices and analyzed in 3-dimensionally reconstructed brains with statistical parametric mapping. Compared to sham rats, stressed rats showed VH in association with greater CRD-evoked activation in the insular cortex, amygdala, and hypothalamus, but reduced activation in the prelimbic area (PrL) of prefrontal cortex. We constrained results of seed correlation analysis by known structural connectivity of the PrL to generate structurally linked functional connectivity (SLFC) of the PrL. Dramatic differences in the SLFC of PrL were noted between stressed and sham rats under distension. In particular, sham rats showed negative correlation between the PrL and amygdala, which was absent in stressed rats. The altered pattern of functional brain activation is in general agreement with that observed in IBS patients in human brain imaging studies, providing further support for the face and construct validity of the WAS model for IBS. The absence of prefrontal cortex-amygdala anticorrelation in stressed rats is consistent with the notion that impaired corticolimbic modulation acts as a central mechanism underlying stress-induced VH.

* Financial Disclosure: None
Gene Module Association Studies (GMAS) are a novel approach complementing Genome Wide Association Studies (GWAS) to understand complex diseases by focusing on how genes work together in groups rather than singly. The first step is to characterize phenotypic differences among a genetically diverse population. The second step is to use DNA microarray (or other high throughput) data from the population to construct gene co-expression networks. Co-expression analysis typically groups 20,000 genes into 20-30 modules containing 10’s to 100’s of genes, whose aggregate behavior can be represented by the module’s “eigengene.” The third step is to correlate expression patterns with phenotype, as in GWAS, only applied to eigengenes instead of SNPs. The goal of the GMAS approach is to identify groups of co-regulated genes that explain complex traits from a systems perspective. From an evolutionary standpoint, we hypothesize that variability in eigengene patterns reflects the “good enough solution” concept, that biological systems are sufficiently complex so that many possible combinations of the same elements (in this case eigengenes) can produce an equivalent output, i.e. a “good enough solution” to accomplish normal biological functions. However, when faced with environmental stresses, some “good enough solutions” adapt better than others, explaining individual variability to disease and drug susceptibility. If validated in heart failure, GMAS may imply that common polygenic diseases as well are related much as to group interactions between normal genes, as to multiple gene mutations.

* Financial Disclosure: None
Biosketches of Speakers

Mete Civelek, PhD
Division of Cardiology, David Geffen School of Medicine at UCLA

Mete Civelek is a postdoctoral fellow in the laboratory of Aldons J. Lusis in the Division of Cardiology. His research is focused on elucidating the genetic basis of complex traits that are involved in Metabolic Syndrome. He completed his PhD in Bioengineering at the University of Pennsylvania under the supervision of Peter F. Davies. He studied the heterogeneous phenotype of the arterial endothelium in relation to atherosclerosis. His studies at UCLA are currently being supported by a Ruth L. Kirschstein National Research Service Award.

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

Arpana Gupta completed a PhD degree in Clinical Neuropsychology from the University of Tennessee, Knoxville, followed by an APA accredited internship at Massachusetts General Hospital/Harvard Medical Center. After coming to UCLA in 2010 she joined the neuroimaging and psychophysiological cores at the Center for Neurobiology of Stress in 2012. Her research fuses three lines of research: neuroimaging, genetics, and psychosocial research in order to investigate the neurobiological sequelae of the underlying pathophysiology of disorders with altered interoceptive processing (functional pain disorders and obesity) in diverse individuals. Specifically, she is dedicated to developing and testing models that comprehensively address the interactions between psychosocial (e.g. early adverse life events, adult trauma, resilience, exercise, diet), environmental (socioeconomic status), and biological factors (genes, sex, race) in causing epigenetic changes and in shaping structural and functional brain endophenotypes, as an important step towards providing powerful and sensitive biomarkers to stress-based disorders. Her hope is that such biological readouts with bring to the forefront those disadvantaged groups and individuals who are at increased risk as a result of disadvantaged backgrounds and consequently altered neurobiologies.

Daniel Holschneider, MD
Associate Professor, Keck School of Medicine, Dept. of Psychiatry and the Behavioral Sciences, University of Southern California

Daniel P. Holschneider, MD: Dr. Holschneider is an Associate Professor in the Dept. of Psychiatry & Behavioral Sciences at the University of Southern California. He directs the Laboratory of Vertebrate Functional Brain Mapping whose interest is the brain imaging of animal behaviors as they occur in the nontethered, nonrestrained animal. This emphasis is part of a broader interest in the characterization of the neurobiology, behavior and physiologic function of specific animal models of human behavior and illness.

Dimitrios Iliopoulos, PhD
Director, Center for Systems Biomedicine, Associate Professor of Medicine, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Iliopoulos graduated at 2006 with a Ph.D degree in Cancer Biology from the Integrative Biomedical Science Graduate Program at Ohio State University and then, he performed his postdoctoral fellowship studies in Kevin Struhl’s lab in the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. At 2010, he became an Assistant Professor in the Department of Cancer Immunology & AIDS at Dana-Farber Cancer Institute and in the Department of Microbiology & Immunobiology at Harvard Medical School. Currently, Dr. Iliopoulos is an Associate Professor of Medicine at David Geffen School of Medicine at UCLA and Director of the newly established Center for Systems Biomedicine.
Dr. Iliopoulos has more than 60 publications in top tier scientific journals including Cell, Cancer Cell, Molecular Cell and PNAS. In addition, Dr. Iliopoulos has received several awards, including a prestigious Career Development Award from the American Association for Cancer Research and a Kimmel Scholar Award from the Sidney Kimmel Foundation. In addition, more recently, Dr. Iliopoulos has received several awards/grants (HITI/Helmsley Trust Award, Harvard Digestive Diseases Center Award, Charles H. Hood Foundation Award) for his work on Inflammatory Bowel Diseases. Dr. Iliopoulos has extensive experience with the development and use of high throughput technologies and systems biology approaches. His innovative methodology has revolutionized and expedited the drug discovery process and he is interested in applied these strategies in order to identify novel therapeutic agents against different human gastrointestinal diseases. Dr. Iliopoulos research revealed that metformin, an anti-diabetic drug, targets cancer stem cells and these data led to the initiation of several phase II and phase III clinical trials all over the world, combining chemotherapy together with metformin. Furthermore, Dr. Iliopoulos is a full member of several professional societies, including the International Society for Computational Biology, the American Gastroenterology Association and the American Association for Cancer Research.

Iordanis Karagiannidis, PhD
Assistant Researcher, UCLA Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Karagiannidis received his BS degree in Biology with Honors from the Plymouth State University in 1994 and his Masters degree in Genetics at the College of Life Sciences and Agriculture at the University of New Hampshire in 1998 where he received a stipend towards his training. He completed his Ph.D. at the Department of Pathology and Laboratory Medicine at Boston University School of Medicine in 2004. Upon graduation, Dr. Karagiannidis joined Dr. Pothoulaki’s laboratory at Beth Israel Medical Center in Boston and studied neuropeptide related intestinal inflammation with particular focus on the regulation of substance P receptor expression and proinflammatory substance P signaling in the intestinal mucosa.

He joined the UCLA academic community in August of 2007 along with the group of Dr. Pothoulakis from Beth Israel Medical center at Harvard Medical School. During this period he has produced data that implicate SP signaling in fat tissue with the development of inflammatory changes both in mesenteric adipose and potentially neighboring tissues such as the intestine. In addition, he has demonstrated that SP signaling may affect adipose tissue expansion with potential consequences on the development of obesity and associated metabolic pathologies such as insulin resistance. Since his arrival at UCLA he has expanded his studies to investigate the overall relationship between obesity and intestinal inflammation both as it relates to SP or other obesity-associated molecules (cytokines, adipokines). With respect to SP, he has worked on developing animal models that will enable him to investigate its effects on mesenteric fat depots in vivo and then evaluate potential changes in their overall metabolic responsiveness. In addition he jas initiated animal studies that examine the effects of pre-established obesity on the severity of intestinal inflammation. On the other hand, driven by the changes observed in mesenteric fat depots of CD patients, he is in the process of evaluating the effects of pre-established intestinal inflammation on abdominal fat-associated pathologies such as insulin resistance.

Charalabos Pothoulakis, MD
Director, UCLA Research Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Pothoulakis is the Eli and Edythe Broad Professor of Medicine at the Department of Medicine, and a Professor of Pathology and Laboratory Medicine at UCLA. He is also the Director of the IBD Research Center, and a member and investigator of the Center for the Neurobiology of Stress at the Division of Digestive Diseases at UCLA. He graduated from the Aristotelian University of Thessaloniki Medical School in Greece and he joined the Division of Gastroenterology at Boston University Medical Center as a Research Fellow in Gastroenterology in 1982. After completion of his fellowship he became a faculty member at the Department of Medicine at Boston University School of Medicine. Dr Pothoulakis joined the Division of Gastroenterology at Beth Israel Medical Center, Harvard Medical School in 1996 and became Professor of Medicine in this institution in 2005. In 2003 he established a “Gastrointestinal Neuropeptide Center” in the
Division of Gastroenterology at Beth Israel Deaconess Medical Center that involved a multi-disciplinary approach to study neuropeptide function in the GI tract. During his tenure at Harvard Medical School he has also been a member of the Division of Pediatric Gastroenterology and Nutrition at Massachusetts General Hospital and he was the Director of a NIH Program Project that examined the barrier function of the GI Tract in health and disease. Dr. Pothoulakis' research program is primarily focused on the role of neuropeptides and hormones in several disease states, including Inflammatory Bowel Disease, Clostridium difficile infection, and Irritable Bowel Syndrome. His recent projects also involve the neuropeptide-dependent mechanisms by which communication between the intestinal mucosa and the fat depots affect the pathogenesis of intestinal inflammation. He is an author of over 165 original articles and numerous reviews and book chapters and served in the Editorial Board of several biomedical journals, including Gastroenterology, and American Journal of Physiology. He has also been a member of Hormones, Transmitters, Growth Factors and Receptors, and Inflammatory Bowel Disease Sections of the American Gastroenterological Association. In 2005 Dr. Pothoulakis received a honorary degree from Harvard University and he is the recipient of the “Janssen Award in Basic Research in Gastrointestinal Motility” by the American Gastroenterological Association for his discoveries and insights into the function of gastrointestinal neuropeptides. Dr. Pothoulakis' research projects have been supported by grants from the National Institutes of Health, the Broad Foundation, The Martin Blinder Foundation for Crohn's Disease, and the Knapp Foundation.

Kirsten Tillisch, MD
Director, Neuroimaging Core, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Kirsten Tillisch completed her undergraduate work at the Otis Institute of Parsons School of Design, earning a Bachelor of Fine Arts with Honors. She obtained her medical degree from the David Geffen School of Medicine at UCLA and was elected to the medical honor society Alpha Omega Alpha. She continued on at UCLA to complete her training in internal medicine and gastroenterology, graduating in 2003. Her clinical interests are functional bowel disorders such as irritable bowel syndrome, functional dyspepsia, and cyclic vomiting syndrome. Her research interests include brain-gut interactions, the effects of nonpharmacological therapies on functional gastrointestinal disorders, and pharmacological treatment of irritable bowel syndrome. Her recent research projects include defining resting state brain dysfunction in irritable bowel syndrome patients, evaluating 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 is a member of the Neuroimaging Program of the Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress.

Jack Van Horn, PhD
Laboratory of Neuro Imaging, Department of Neurology, UCLA

Dr. Van Horn is a faculty member in the Laboratory of Neuro Imaging (LONI) and an associate professor of neurology at UCLA. He received his Ph.D. from Department of Psychology at the University of London and holds a masters degree in engineering from the University of Maryland College Park. He was an NIH Intramural Research Training Award (IRTA) recipient, conducting post-doctoral work in PET/MRI neuroimaging of healthy and neuropsychiatric samples. From 2002 to 2006, he designed the fMRI Data Center at Dartmouth College, as well as a high performance neuroimaging, computational, analysis and visualization facility based at Dartmouth College. He is an accomplished author and educator, and is known internationally as an expert in neuroscientific data sharing. His research interests include neuroimaging assessment of traumatic brain injury, investigating neurophysiological human cognition using in vivo neuroimaging techniques such as functional MRI, diffusion tensor imaging, and its relations to other biological systems, and the use of pharmacological manipulations as probes of cognitive and physiological brain networks during fMRI. His work in various aspects of brain imaging is widely published (h-index >30) and he has been featured frequently in the mass media, news outlets, and television. Dr. Van Horn teaches undergraduate neuroanatomy at UCLA as well as a seminar course on human brain imaging using fMRI.
**Martijn van Oijen, PhD**  
Associate Director, Quality Initiative Program, VA/UCLA Center for Outcomes Research and Education (CORE), Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Martijn van Oijen received a dual Master of Science in Biomedical Health Science (epidemiology and health technology assessment) from Radboud University Nijmegen. At Radboud, he also received his PhD in Medicine, based on his thesis titled ‘Balancing Gastrointestinal and Cardiovascular Outcomes in Low-Dose Aspirin Users.’ After completing his PhD, Dr. Van Oijen worked as a post-doc for a nationwide project aiming at developing an IBD research database connecting input from medical records, patient reported outcomes and bio-banking. In 2010, he became assistant professor in GI Epidemiology, department of Gastroenterology and Hepatology, at University Medical Center Utrecht. Dr. Van Oijen was also head of the departmental clinical trial bureau, and supervised a team of PhD students on topics covering the whole disease spectrum of gastroenterology and hepatology.

Dr. Van Oijen has advanced skills in database analysis, cost-effectiveness analysis and epidemiology. He joined UCLA in 2012 and will work on a series of outcomes research as a member of the UCLA/VA Center of Outcomes Research and Education (CORE). He has appointed as the associate director of the Quality Initiative Program aiming at increasing quality of care throughout the division.

**James Weiss, MD**  
Chief, Division of Cardiology; Director, Cardiovascular Research Laboratory, David Geffen School of Medicine at UCLA

James N. Weiss received his undergraduate degree in physics from Hamilton College, and his medical degree and internal medicine training at the University of Pennsylvania School of Medicine. He completed his cardiology fellowship at the University of California, Los Angeles in 1981, including clinical electrophysiology training at the University of Maastricht, the Netherlands. He then joined the faculty at the UCLA School of Medicine, where he was director of Clinical Cardiac Electrophysiology from 1981-1985. He became the first holder of the Chizuko Kawata Endowed Chair in Cardiology in 1993, the Director of the Cardiovascular Research Laboratory in 1997, the Chief of Cardiology in 2001, and is currently Distinguished Professor of Medicine and Physiology. From a background in ion channel biophysics and basic and clinical cardiac electrophysiology, he currently leads an interdisciplinary group which combines mathematical and experimental biology to develop innovative techniques to treat cardiac arrhythmias, to prevent injury from heart attacks and to understand the genetic basis of heart disease using systems biology approaches. He has directed a National Institutes of Health Specialized Center of Research in Sudden Cardiac Death from 1995-2005, since continued as a National Institutes of Health Program Project Grant, and several other grants. He has published over 300 articles and holds memberships in numerous professional organizations, including the American Heart Association, American College of Cardiology, the Heart Rhythm Society, the American Society of Clinical Investigation, and the Association of University Cardiologists.
Abstracts of Posters
Basic and Translational

1. Corticotropin-Releasing Hormone Receptors Activate Inflammatory Pathways in Mesenteric Adipose Tissue

JM Hoffman, C Fink, A Sideri, KM Law, I Karagiannidis, C Pothoulakis

Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, Department of Medicine, UCLA

The corticotropin-releasing hormone (CRH) peptide/receptor family mediates several gastrointestinal responses, including intestinal inflammation. Abdominal adipose tissue hyperplasia is a hallmark of Crohn’s disease, and mounting evidence suggests that adipocyte-derived molecules are involved in intestinal inflammation. Human visceral and subcutaneous adipocytes express Ucn1 and CRH receptors, but expression in mesenteric fat, including adipocytes, has not been evaluated. Here we determined whether CRH peptides and receptors are expressed in mesenteric adipose tissue and isolated preadipocytes and explored the novel hypothesis that adipose tissue CRH signaling is involved in the pathophysiology of colitis. Human mesenteric preadipocytes were isolated from patient surgical specimens and grown in culture. Isolated mesenteric preadipocytes were stimulated (4 h) with CRH or the CRHR2-specific peptide Ucn2. RNA was extracted for qPCR and multiplex gene expression analysis, and cell lysates processed for phosphoprotein assays. qPCR was also performed on mesenteric adipose tissue from mice following acute (48 h) trinitrobenzene sulfonic acid (TNBS) colitis. CRHR1, CRHR2 and Ucn2 mRNA was detected in human preadipocytes and mouse adipose tissue. Stimulation of human preadipocytes with CRH increased mRNA levels of the proinflammatory cytokines and chemokines TNF-α (2.2 fold), IL-8 (1.26 fold), CCL7 (1.94 fold) and CXCL1 (1.95 fold; p<0.05). These effects were inhibited by pretreatment with the CRHR1 antagonist, antalarmin. Ucn2 stimulation of human preadipocytes decreased IL-8 (0.64 fold), CCL7 (0.37 fold) and CXCL1 (0.38 fold; p<0.05), increased the anti-inflammatory factor adiponectin (1.8 fold; p<0.05), and activated the serine/threonine-specific protein kinases Akt, p70S6K, c-Jun and GSK3B. CRHR2 mRNA levels were decreased in TNBS-colitis (0.46 fold; p<0.05). This is the first demonstration of CRH receptors and Ucn2 in human mesenteric preadipocytes, suggesting a local receptor action in adipose tissue function. Activation of CRHR1 and 2 had opposing effects on cytokine expression in these cells. Decreased adipose tissue CRHR2 expression during experimental colitis supports a link between the inflamed intestine and the adjacent fat. We suggest that CRH receptors in mesenteric adipose tissue may participate in the pathophysiology of Inflammatory Bowel Disease.

2. Sex, Strain and Regional Differences in the Colonic Epithelial Response to Repeated Water Avoidance Stress (rWAS)

M Larauche, M Million, Y Taché

Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, David Geffen School of Medicine, UCLA.

Background: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits, and in a subset of patients, by a compromised colonic epithelial barrier function. IBS predominantly affects women, but the underlying mechanisms of this female prevalence remain largely unknown. Stress is known to worsen IBS symptoms. In male rodents, chronic stress increases colonic secretion and paracellular permeability, an event associated with visceral hyperalgesia. Potential sex differences in the colonic epithelial response to stress have not yet been addressed. Aims: To determine the influence of sex on stress-induced alterations of colonic mucosal function in rats. Methods: Male and female Wistar and Wistar-Kyoto rats (7-11 wks) were used. Naive or stressed
(rWAS, 1h/day, 4 days) rats were euthanized 5h after the last stress session. Proximal colon (PC) and distal colon (DC) were collected, stripped from the seromuscular layer and the mucosa was mounted in Ussing chambers containing modified oxygenated Krebs Ringer’s buffer. The conductance (G, reflect of paracellular permeability) and short circuit current (Isc, reflect of transmembrane ion exchanges) were measured. Data were analyzed using unpaired t test. **Results:** In the PC of both Wistar and Wistar-Kyoto females, rWAS increased the Isc (75.9 ± 10.0 vs 26.3 ± 2.1 & 57.6 ± 3.8 vs 38.4 ± 3.3 A/cm², p<0.01, respectively) while it did not affect the Isc in male rats. In the DC, both male and female Wistar rats displayed an increase in Isc following rWAS (79.4 ± 11.5 vs 28.7 ± 2.5 and 79.0 ± 10.2 vs 20.8 ± 1.9 A/cm², p<0.001, respectively), while female Wistar-Kyoto rats showed a decreased Isc (34.6 ± 3.8 vs 51.1 ± 5.7 A/cm², p<0.05) and males no change. Females, but not males of both strains exhibited an increase in G exclusively in the PC following rWAS. **Conclusion:** The data highlight sex, strain and regional differences in rat colonic epithelial function alterations induced by exposure to repeated psychological stress.

Supported by NIH NIDDK K01 DK0888937 (ML) and P50 DK064539.

3. Neutrotensin-Induced Tumor Formation Is Regulated by Neutrotensin Receptor 1 (NTR1)/microRNA-133a-Associated NTR1 Recycling Involving the Negative Regulator Zinc Finger E-Box-Binding Homeobox 1 (ZEB1)

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**Background and Aims:** G protein-coupled receptors (GPCRs) signaling is regulated by receptor endocytosis and recycling. We showed that neutrotensin (NT), via the high affinity neutrotensin receptor 1 (NTR1), mediates intestinal inflammation, cell proliferation and colon cancer. MicroRNAs (miRNAs) are short inhibitory non-coding RNAs involved in different pathophysiological functions at the post-transcriptional level. We recently identified miR-133a and its downstream target, aftiphilin (AFTPH), localized in the trans-golgi network (TGN), as regulators of NTR1 recycling in human colonocytes (DDW2012: Tu1823). Here we examined the mechanism by which NT regulates miR-133a, and correlated miR-133a and AFTPH expression with colon cancer development in mouse xenografts and human colon tissue samples. **Methods:** MiR-133a transcriptional regulation was verified by quantitative PCR, promoter-driven luciferase, promoter site-directed mutagenesis, and chromatin immunoprecipitation (ChiP) assays in human colon epithelial cells overexpressing NTR1 (NCM460-NTR1). The association of miR-133a and AFTPH with tumor growth was examined by tumor colony formation assays and mouse xenografts using SW480 and HCT116 colon cancer cells. **Results:** The genomic sequence of 2000bp upstream to the start of miR-133a was analyzed by transcription binding site prediction software and identified a binding site for zinc finger E-box homeobox 1 (ZEB1, a negative transcriptional regulator). ZEB1 gene silencing in non-stimulated NCM460-NTR1 cells increased miR-133a (3.3±0.6 fold, p<0.05) and reduced AFTPH mRNA (27.2±0.1%, p<0.01). ChiP analysis showed that upon NT exposure ZEB1 was dissociated from the miR-133a promoter (41.0±1.7%, p<0.05 compared to non-stimulated cells). MiR-133a overexpression increased cyclin D1 expression (5.2±0.7 fold, p<0.001) in SW480 colon cancer cells. Blocking NTR1 recycling through AFTPH-localized TGN by Brefeldin A reduced NT-induced tumor colony formation (44.1±1.1%, p<0.05). MiR-133a overexpression and AFTPH gene silencing also promoted tumor growth in vitro (~2.0 fold and ~1.7 fold respectively, p<0.05) and in mouse cancer xenografts (~1.25 fold and ~1.6 fold respectively, p<0.05), while miR-133a knock-down attenuated NT-induced tumor growth (31.6%, p<0.05). MiR-133a mRNA was negatively correlated with AFTPH mRNA in human tumor samples (r= -0.8979, n=42), and well correlated with tumor stage (p<0.01). **Conclusions:** NTR1 signaling modulates miR-133a/AFTPH expression through dissociation of ZEB1 from the miR-133a promoter, which promotes NTR1 recycling. NTR1/miR-133a/AFTPH interactions regulate colonic tumor growth. This is the first study providing evidence for an important role of microRNAs in regulation of GPCR recycling linked to development of colon cancer.

Supported by NIH DK60729 (CP) and the Blinder Research Foundation for Crohn’s Disease (IKML).
4. Mu-Opioid Receptors Switch NMDA Receptors in Primary Afferents to a Non-Functional State

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Introduction: NMDA receptors present in the central terminals of primary afferents elicit substance P release into the dorsal horn, but this requires phosphorylation of their NR2B subunit by a Src family kinase (SFK) (Chen et al., 2010, Neuroscience 166:924). We recently found that in naïve rats these NMDA receptors are in a dephosphorylated, non-functional state. However, in rats with chronic constriction injury (CCI) of the sciatic nerve (a model of neuropathic pain) these NMDA receptors become functional through a signaling cascade involving microglia activation, BDNF release and SFK phosphorylation. After CCI, these NMDA receptors gradually return to a non-functional state during a period of 3-7 days, suggesting that there is a signal leading to their dephosphorylation.

Results: Since mu-opioid receptors (MORs) in primary afferents also activate a SFK, we investigated whether MOR agonists could also turn the NMDA receptors into their functional state. We found the opposite: the MOR agonists DAMGO, morphine and endomorphin-2 abolished NMDA-induced substance P release from rat spinal cord slices (measured as neurokinin 1 receptor internalization). The inhibition by DAMGO was time-dependent, requiring a preincubation of the slices with DAMGO for at least 15 min, whereas DAMGO produced no effect when added together with NMDA. The effect of DAMGO was dose-dependent, with IC50 = 10 nM. The selective MOR antagonist CTAP (10 µM) shifted the dose-response of DAMGO to the right (IC50 = 492 nM, Fig.), confirming the involvement of MORs. However, a similar inhibition of NMDA-induced substance P release was produced by the delta-opioid receptor agonist DPDPE (1 µM), but not by the GABAB receptor agonist baclofen (10 µM). The inhibition by DAMGO was abolished by the protein tyrosine phosphatase inhibitor BVT 948 (10 µM).

Conclusions: This suggests that the MORs present in primary afferent terminals turn these NMDA receptors into a non-functional state by triggering the dephosphorylation of their NR2B subunit by a protein tyrosine phosphatase, reversing the effect of BDNF. This may contribute to the analgesic effect of opioids.

5. CRF Receptor Activation Modulates Rat Colonic Neuronal Tau Phosphorylation: Role of Enteric Tau in the Colonic Motor Response to Stress?

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1CURE: Digestive Diseases Research Center, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, Department of Medicine, UCLA and ²Veterans Affair Greater Los Angeles Healthcare System

Background: Corticotropin releasing factor receptor-1 (CRF1)-overexpression or CRF2 receptor-KO enhances experimental stress or CRF-induced tau (TAU) phosphorylation in the mouse brain (PNAS, 2012: 109(16):6277-82). CRF is the main brain peptide that orchestrates the stress response. CRF is also a key mediator of the gut response to stress. It is however unclear whether stress or CRF affect enteric TAU and whether enteric neuronal TAU modulation impacts gastrointestinal tract functions. Aims: 1) determine the effect of CRF ligands (CRF, Ucn1, Ucn2) on rat primary colonic neuronal tau phosphorylation 2) Assess intestinal tau and CRF2 receptor expression and the colonic response to acute stress in homozygous triple transgenic-AD (3xTg-AD) mice expressing mutant TauP301L, transgenic Swedish mutant human amyloid precursor protein (APPswe) and knock-in mutant presenilin-1 (PS1M146V). Methods: Rat colonic myenteric primary neurons were incubated with CRF, Ucn1 and Ucn2 (10 or 100 nM) and phospho-TAU probed by western blot. 3xTg-AD mice and wild-type (WT) mice (~14 months old) were exposed to a 60-minute novel environment stress and fecal pellet output (FPO) monitored. Ileum (ILE), proximal-colon (PC) and distal-colon (DC) tissues were collected from WT and 3xTg-AD mice. RNA extracts were analyzed for Tau, APP (human), CRF2, and GAPDH expression by RT-PCR. Total and phospho-MAPT were determined by western blotting. Results: Ucn1 and Ucn2 suppressed pTAU in the rat primary distal colonic myenteric neurons while CRF did not. The 3xTg-AD mice exhibited a 60.7±6.5% increase in cumulative FPO compared to WT mice at 60 min time point. TAU mRNA was significantly elevated in ILE (400%), PC (140%), DC (100%) compared with WT
mice. The Tau primer used in this study detected both the mouse and human forms. 3xTG-AD, but not WT mice, expressed APP (hAPP) mRNA. CRF2 mRNA expression showed a 10.0% increase in ILE and a 20.4% decrease in DC of 3xTG-AD mice compared to WT mice. **Conclusions:** 1) The modulation of colonic myenteric TAU phophorylation by CRF peptides 2) the altered colonic motor response to stress in the 3xTg-AD mice that express human mutant TAU, APP and PSEN1 transgenes in the intestine and 3) the modulation of colonic CRF2 receptor mRNA profile in these mice, suggest a possible interplay between myenteric TAU and CRF-signaling in the colonic response to stress.

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6. **Effects of Substance P on Pro- and Anti-Inflammatory Reponses of Human Mesenteric Preadipocytes Isolated from IBD Patients**

**A Sideri, ¹K Bakirtzi, ²R Arsenescu, ³P Fleshner, ²DQ Shih, ¹I Karagiannides, ³C Pothoulakis**

**¹Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA; ²Ohio State University IBD Center, Department of Internal Medicine, Division of Gastroenterology, Hepatology & Nutrition, Wexner Medical Center, OSU; ³F. Widjaja Foundation, Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California**

**Background and Aims:** Substance P (SP) is a neuropeptide found in various cell types, commonly linked with inflammatory processes. We and others have demonstrated the potential involvement of substance P in different stages of Inflammatory Bowel Disease (IBD) pathophysiology. Previous work on animal models of colitis (TNBS), as well as data from patients with IBD, show up-regulation of NK-1R (high affinity SP receptor) in the involved enteric epithelium. We also demonstrated up-regulation of NK-1R in mesenteric adipose tissue of mice with TNBS colitis. Here, we used primary human mesenteric preadipocytes from control and IBD patients to examine the expression patterns of the receptors for SP (NK-1R, NK-R2 and NK-R3), as well as cytokine responses to substance P exposure. **Methods:** During intra-abdominal operations, human mesenteric adipose tissue was collected from control (colon cancer), UC and CD patients (n=10-11 per group). Preadipocytes were isolated and cultured. When reached 80% confluence, cells were exposed to 10-7 M substance P for 8hrs and supernatants and RNA were collected for measurements. Protein levels of cytokines in cell supernatants were determined using the Bioplex 3D suspension array system (Bio-Rad). mRNA levels of NK-1R, and other NK-Rs were estimated with qPCR. Inflammatory molecule mRNA expression was evaluated with Luminex inflammatory panels (FlexScript LDA). **Results:** UC preadipocytes had higher NK-1R, while those from CD had higher NK-R1 and NK-R2 mRNA levels, compared to control (p value<0.05). NK-R3 was undetectable in all groups. At the mRNA level, we observed both common and differential responses to SP stimulation between UC and CD preadipocytes. PDGFA and IL-12b increased in both patient groups after SP exposure, compared to control. IL-1b, IL-2, IL-10, IL-15, IL-17A, CXCL10, CCL2, CCL5 were increased and IL-4 decreased only in UC preadipocytes, while CSF1 was increased and IL-7 decreased only in CD preadipocytes after SP stimulation, compared to control (p<0.05). Of the 27 cytokines tested in the supernatants in response to SP stimulation, IL-1b, IL-2, IL-9, IL-15, IL-17a and MIP-1b were significantly increased in both UC and CD, Basic FGF was increased only in UC, VEGF, IL-13, IL-12p50, IL-10 were decreased in UC and Eotaxin with MIP-1a were decreased only in CD, compared to control (p<0.05). **Conclusions:** Human mesenteric preadipocytes are a SP responsive cell population representing an active source of cytokines, possibly contributing to the pro and anti-inflammatory milieu during IBD. The different responses between the UC and CD preadipocytes indicate a disease dependant response-signature to SP.

Supported by NIH P50 DK064539 (CP & IK), DK047343, DK060729 (CP), The Broad Foundation (BMRP) (IK, RA), and the Blinder Research Foundation for Crohn’s Disease (AS)
7. Preadipocyte-Specific Effects on Human Colonocyte Proinflammatory Responses Are Obesity and IBD-Dependent

**A Sideri, 1K Bakirtzi, 2R Arsenescu, 3P Fleshner, 3DQ Shih, 1C Pothoulakis, 1I Karagiannides**

**Inflammatory Bowel Disease Center, Division of Digestive Diseases, David Geffen School of Medicine, UCLA; 2Ohio State University IBD Center, Department of Internal Medicine, Division of Gastroenterology, Hepatology & Nutrition, Wexner Medical Center, OSU; 3F. Widjaja Foundation, Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California**

**Background and Aims:** The incidence of Inflammatory Bowel Diseases (IBD) is increasing rapidly, while obesity contributes to the development of various pathological conditions and affects disease outcome, including IBD. We and others have demonstrated changes in mesenteric fat depots of mice during experimental colitis and patients with Crohn’s Disease (CD). Despite the anatomical proximity between the mesenteric adipose tissue and intestine, the precise role of adipose tissue in the pathophysiology of IBD has yet to be elucidated. Here we compared the secretion profiles of preadipocytes isolated from IBD, obese, and control human subjects and examined their effects on intestinal epithelial cells expression patterns. **Methods:** Human mesenteric adipose tissue was collected during surgery from control, obese, UC and CD patients (n=6-9 per group). Preadipocytes were isolated from fat depots. When cells reached 80% confluence (24 hrs), supernatants, RNA, and total protein were collected. Cytokine levels in cell supernatants were determined using the Bioplex 3D suspension array system (Bio-Rad). Preadipocyte supernatants were also applied on cultures of human colonic NCM-460 cells for 24hs and RNA and protein were collected. Inflammatory molecule mRNA expression and activation of intracellular kinases were evaluated with Luminex inflammatory panels (FlexScript LDA), and phospho-protein multiplex panels, respectively. **Results:** Preadipocytes isolated from IBD patients demonstrated differential mediator secretion patterns compared to preadipocytes from control and obese patients. Of the 42 proinflammatory cytokines and growth factors tested, IL-7/IL-8/Gro/MCP3/VEGF/PDGF-AA showed statistically significant differences between control, obese and IBD preadipocytes (p<0.05). Notably, there were significant differences in mediator secretion between preadipocytes isolated from UC and CD patients, in particular VEGF and PDGF (p<0.01 for both). NCM-460 cells had distinct GSK-3, AKT kinase activation (p<0.05 for both) and cytokine mRNA expression patterns of TNF, IL-2, IL-3, IL-17, VEGF, MIP-1β, MIP-3, RANTES (p<0.05) following exposure to preadipocyte supernatants from all three pathological conditions compared to controls. **Conclusions:** Our data suggest the existence of preadipocyte-disease-dependent mediators contributing to the generation of differential colonocyte responses. Together with reports indicating altered levels of several adipokines during IBD, our results provide the first direct evidence for the importance of adipose tissue homeostasis during obesity in determining the outcome of IBD.

Supported by NIH P50 DK064539 (CP & IK), DK047343, DK060729 (CP), The Broad Foundation (BMRP) (IK, RA), and the Blinder Research Foundation for Crohn’s Disease (AS)

8. **Effect of Ghrelin Agonist, Anamorelin on Feeding, Meal Structure and Body Weight in Alpha-Synuclein Over-Expressing Mice**

**L Wang, 1C Pietra, 2H Liang, 3SR Northrup, 4MF Chesselet, 4Y Taché**

**CURE, Division of Digestive Diseases, UCLA; 2Helsinn SA, Lugano, Switzerland; 3Helsinn Therapeutics (U.S.), Inc., Bridgewater, NJ, USS; 4Neurobiology and Neurology, UCLA**

**Background:** Body weight (BW) loss is common in PD patients, with an incidence of 39-73% related to the disease severity. We reported previously that the mouse model overexpressing human wild type alpha-synuclein under a neuronal promoter, Thy1 (Thy1- Syn mice) reproduces several non-motor symptoms of PD including BW loss. Ghrelin is an orexigenic hormone produced by the gastric mucosa endocrine cells, and it increases BW gain. **Aim:** To investigate whether daily food intake and the diurnal meal pattern are altered in Thy1-aSyn mice and whether a ghrelin agonist can reverse the alterations and BW change. **Methods:** Male Thy1-aSyn mice and wild type (WT) littermates (4-5 and 8-9 months old) were monitored for basal daily food
intake for 5-7 days and meal pattern in an automated episodic food intake monitoring system (BioDAQ). The ghrelin agonist, anamorelin (10 mg/kg) or saline (3 ml/kg) was injected ip at the early light phase either acutely or daily for 7 days, and food intake, meal pattern and BW were monitored. **Results:** Thy1-aSyn and WT mice (4-5 months old) did not have significant difference in BW (32.2±1.5 vs 31.2±0.7 g). However, Thy1-aSyn compared with WT mice had lower basal 24 h food intake (2.9±0.3 vs 3.8±0.2 g, p<0.05), which was more prominent during the dark phase (2.3±0.2 vs 3.2±0.2 g, p<0.05) and associated with a reduced meal duration (237.2±31.6 vs 346.8±33.1 min, p=0.05). Thy1-aSyn mice at 8-9 months old had lower BW than WT (36.9±3.0 vs 40.9±1.0 g, p<0.05), and displayed similar alterations in basal food intake and meal pattern as those in younger mice. In 8-9 months old mice, anamorelin daily treatment for 1 week increased BW gain in Thy1-aSyn but not WT mice (3.0±0.7% vs -1.2±1.2%, p<0.05) associated with an increase in food intake and change in meal pattern. Analysis of 8-h meal pattern after anamorelin treatment in the light phase showed that Thy1-aSyn had increased food intake, number of bouts, meal frequency and meal duration compared to vehicle, similarly as in WT mice (Table 1). **Conclusions:** Thy1-aSyn mice showed a reduced BW as aging that could be related to a reduced food intake and altered meal structures. The BW gain induced by anamorelin in Thy1-aSyn mice suggests that a ghrelin agonist may have potential to curtail weight loss in PD patients.

**Table 1.** Meal structure alterations induced by ip anamorelin (Ana, 10 mg/kg) in Thy1-aSyn (n=8) and WT (n=7) mice for the 8-h period post ip injection. *: p<0.05 vs saline.

<table>
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<th>Genotype</th>
<th>ip</th>
<th>Food intake (g)</th>
<th>Bouts (number)</th>
<th>Meal size (g)</th>
<th>Meal frequency</th>
<th>meal time (%)</th>
<th>Meal time (min)</th>
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</thead>
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<td>WT</td>
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<td>0.21±0.09</td>
<td>7.6±2.3</td>
<td>0.09±0.03</td>
<td>1.7±0.4</td>
<td>1.9±0.7</td>
<td>26.7±10.0</td>
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<td>WT</td>
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<td>0.94±0.12*</td>
<td>13.3±1.9</td>
<td>0.27±0.04*</td>
<td>3.6±0.4</td>
<td>6.2±1.1*</td>
<td>89.3±16.0*</td>
</tr>
<tr>
<td>Thy1-aSyn</td>
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<td>5.1±1.8</td>
<td>0.13±0.05</td>
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<td>2.0±0.8</td>
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<td>Thy1-aSyn</td>
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Supported by the Michael J. Fox Foundation and NIHDKK 41303 (animal core)

9. **Role of Central-Peripheral Interaction of Cardiac Nerve System in Modulation of Ventricular Electrophysiology in a Porcine Model**

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**Background:** Enhanced cardiac sympathetic tone has been associated with ventricular arrhythmias and sudden cardiac death. Dynamic interactions between different levels of neural control are essential to the maintenance of regional cardiac function. If such interactions are disrupted, effective control of regional cardiac electrical indices are compromised, leading to arrhythmogenesis. **Aim:** The purpose of this study is to investigate the role of central-peripheral interaction of cardiac nerve system in modulation of ventricular electrophysiology. **Methods:** Female Yorkshire pigs (n=5) underwent surgical exposure of the heart and left stellate ganglion (LSG) through thoracotomy. Dorsal roots of the spinal cord were also exposed through laminectomy. A 56-electrode sock was placed over the ventricles to record epicardial electrograms. Animals underwent LSG stimulation in intact, and after dorsal root transaction (DRTx). Activation recovery intervals (ARIs) as surrogate of action potential were measured at each electrode before and during LSG stimulation. **Results:**
With intact roots, LSG stimulation resulted in significant global ARI shortening by 12.9% (p<0.05). In response to partial DRTx at T1-T2, mean global ARI shortened by 7.2% with increased dispersion. Moreover, in response to LSG stimulation, ARI was further decreased and its electrical dispersion correspondingly increased. **Conclusion:** Our results deafferentation of high thoracic spinal cord increases potential ventricular arrhythmogenesis. This finding provides insight into the mechanism underlying the beneficial effects of neuromodulation therapy in reducing ventricular arrhythmias.

10.
Corticotropin-Releasing Factor (CRF)-Proopiomelanocortin (POMC)-β-Endorphin (END) System in the Rat Colon: Expression, Regulation and Implication in the Local Modulation of Visceral Pain

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Visceral pain is a cardinal symptom in irritable bowel syndrome (IBS) that drives illness severity more than other motor symptoms. IBS patients have compromised engagement of the inhibitory descending pain modulation systems under conditions of heterotypic stimulus while healthy subjects respond with a decreased visceral pain to rectal distension. In the colon, abundant endings of visceral afferent neurons are present in the mucosal epithelium, serosa, muscles, and myenteric ganglia, from where the initial noxious impulses are generated to travel towards relay stations in the spinal cord and the brain. END is a potent analgesic exclusively derived from POMC by the activation of CRF via CRF1 receptor (CRF1) and cleavage by prohormone convertases (PC1 or PC2). Aim of this study is to establish a CRF-POMC-END system in the rat colon and to explore its role in the local antinociceptive mechanism. The gene expression of CRF1 isoforms, POMC, PC1 and PC2 was assessed using RT-PCR in the colon collected from 2 naïve adult male SD rats. Immunostaining for POMC and END was performed in the colonic tissue sections and whole mount preparations of enteric plexus. The regulation of colonic POMC gene by CRF (10 μg/kg, ip, 1h, n=6) was detected by real time quantitative PCR. Rats (5-7/group) were subjected to repeated water avoidance stress (rWAS) (1 h daily 10 days) or no stress. The visceromotor response (VMR) to colorectal distension (CRD) was assessed on days 0 (baseline) and 11 (24 h) after rWAS. In the rat colon, transcripts of CRF1 wild type 1a and splice variants 1c, 1f and 1o were detected. In addition, we identified two novel splice variants, named 1a-2 which is lacking three bases encoding K-111 in exon 5 and 1p with deleted exon 7. Transcripts of POMC, PC1 and PC2 were detected in both proximal and distal colon. The immunoreactivity for POMC and END was located in cells scattered in the lamina propria, and neurons of the submucosal and myenteric plexus in both proximal and distal segments. CRF significantly up-regulated POMC mRNA level by 2.5 fold compared with vehicle group in the proximal colon. rWAS vs control group decreased VMR to CRD (p< 0.05) and up-regulated POMC mRNA expression in the proximal colon (p<0.05). Both changes displayed a significant correlation (rP=0.601, p=0.036). These data indicate the existence of a local CRF-POMC-END system in the colon and the upregulation of POMC by CRF and rWAS which may have functional significance in locally modulating the visceral pain response under stress conditions.
Abstracts of Posters
Clinical

11. Rapid Infrared Microscopy (IRMS) for Differential Diagnosis of Interstitial Cystitis/Bladder Pain Syndrome

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Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic pain syndrome that affects up to seven million American women. Current diagnostic procedures are invasive and uncomfortable. We previously have used IRMS to differentiate IC/BPS patients from healthy subjects and patients with overactive bladder or incontinence. In the present study, we tested the ability of IRMS to differentiate IC/BPS from fibromyalgia (FM), a related chronic pain syndrome, and from rheumatoid arthritis (RA), a chronic inflammatory disorder. Under IRB approval, blood samples were collected from women classified as IC/BPS (n=20), FM (n=30) or RA (n=15). IR spectra were collected using IRMS, and compared using principle components analysis. IRMS correctly differentiated patients in all groups with 100% accuracy (Figure 1a). Differentiation was greatest based on spectral bands in the 1560cm⁻¹ range, which is associated with primary amines (Figure 1b).

These results support the use of IRMS to differentiate patients with IC/BPS from those with other chronic pain or inflammatory syndromes. The accuracy and simplicity of the test may make it useful for earlier diagnosis of these syndromes.

12. Effect of Satiety Hormone Analog, Exenatide on Resting State Brain Activity in Lean vs Obese Women

K Coveleskie, L Kilpatrick, C Ashe-McNalley, J Stains, L Connolly, EA Mayer

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Background: Exenatide is a clinically used analogue of the satiety hormone GLP-1. GLP-1 increases after bariatric surgery and is hypothesized to be involved in successful weight loss following this surgery. Potential drug-induced changes in the brain have largely been unexplored. Aims: To investigate the potential effect of Exenatide on intrinsic oscillations of the resting brains of healthy lean and obese women using a resting state analysis technique aimed at characterizing shifts in patterns of regional frequency power. Based on previous frequency analyses and the literature on GLP-1 and satiety, we hypothesized the drug to show an altered pattern of frequency band power in regions associated with hunger and satiety and that this pattern would be

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altered in the obese woman. **Methods:** Resting state scans were taken of 19 healthy female subjects (10 lean, 9 obese) using a Siemens Allegra 3T MRI scanner after at least 8 hours of fasting. In a two-day double-blind crossover design, ten minute scans during which the subject was asked to lay quietly with their eyes closed but not fall asleep were run before, 10 min. and 30 min. after the subcutaneous injection of 5ug of Exenatide or saline placebo. Normalized fractional amplitude of lower frequency fluctuations (fALFF) maps were created for frequency bands in .073-.198hz (Slow-3), .027-.073hz(slow-4), and .01-.027 (slow-5) ranges. A flexible factorial design in SPM8 was used to test for changes in the relative distribution of frequency power among these bands in regions of interest (ROIs) using type I error rate of 5%. Regions were chosen based on their association with hunger (incl. insula, hypothalamus, anterior cingulate) and satiety (prefrontal cortices (PFC)) and were deemed significant at a corrected significance of p<0.001 and a cluster threshold of 4. **Results:** At pre-infusion baseline, obese subjects displayed a frequency power distribution shifted towards lower frequencies in left medial prefrontal cortices (DMPFC, pACC, VMPFC) and striatal (Nuc Accumbens, Putamen) regions. Across all subjects (Obese and Lean), drug infusion (vs placebo) was associated with a shift in the frequency power distribution of the right dorsomedial prefrontal cortex towards lower frequencies. In general, lean subjects displayed a greater response to drug in terms of significant changes in regional frequency power distribution. Drug infusion compared to placebo was associated with a shift in the frequency distribution towards higher frequencies in left lateral prefrontal cortices (VLPFC, DLPFC) and towards lower frequencies in left anterior cingulate (pACC) to a significantly greater extent in lean subjects than in obese subjects. **Discussion:** Changes in the frequency power distribution in brain regions associated with hunger and satiety were observed as a result of Exenatide administration. These shifts differed in the obese versus the lean groups, suggesting a differential effect of the drug on the brain of obese individuals.

13. **Corticotropin Releasing Hormone Receptor 1 (CRH-R1) Polymorphisms Are Predictive of Irritable Bowel Syndrome (IBS) Status**

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**Background:** IBS is a stress-sensitive disorder associated with chronic abdominal pain and altered bowel habits. Alterations in corticotropin releasing hormone (CRH) stress response pathways have been implicated in the pathophysiology of IBS. The association of single nucleotide polymorphisms (SNPs) of the CRH-1 receptor (CRH-R1) gene with IBS has only been evaluated in one, relatively small study, however, the presence of major alleles of these SNPs appear to be protective for psychiatric and other stress-related conditions. **Aims:** 1) To perform an association analysis between CRH-R1 SNPs in IBS vs. healthy control subjects (HCs) and 2) To determine if these SNPs are associated with GI and non-GI characteristics. **Methods:** In male and female Rome III positive IBS patients and HCs, three SNPs of the CRH-R1 gene (rs7209436, rs110402, and rs242924) were genotyped. GI symptom severity, Visceral Sensitivity Index [VSI]), early life trauma, anxiety and depression symptoms were measured. Logistic regressions were used to predict IBS status from each CRH-R1 SNP in three models while controlling for race. The association of haplotypes with IBS status was evaluated. In order to mitigate multiple comparisons, we used the WGCNA (weighted gene co-expression network analysis) to define clusters of clinical traits within IBS. We tested associations between individual traits within the most clinically relevant cluster and the CRH-R1 SNPs. **Results:** 277 IBS patients (mean age 30.3 yrs) and 382 HCs (mean age 36.4 yrs) were studied. Age and race were significantly different between IBS and HCs (both p<0.001). Using an additive model approach, all 3 CRH SNPs were significantly associated with IBS status. However, only rs110402 remained significant after controlling for race, i.e., IBS patients had less of the major allele (A) compared to HCs (A:A 24% vs. 41%; A:G 48% vs. 40%, G:G 29% vs. 20%, p=0.023). Similarly, the haplotype TAT, which was comprised of major alleles, was less common in IBS vs. HCs (p<0.001). Within IBS, there were 15 traits in the clinically relevant cluster and only VSI correlated with all 3 SNPs (β=-3.4 to -3.0, p=0.02-0.05). **Conclusion:** The presence of the major alleles in the CRH SNPs is associated with less GI anxiety and is protective against having IBS. Further studies are needed to determine the physiologic and clinical significance of having the minor allele of the CRH-R1 SNPs in IBS.
14. Early Adverse Life Events: Impact on Sex Differences in the Salience Intrinsic Network Connectivity in Irritable Bowel Syndrome

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Introduction: Early adverse life (EAL) events have been linked to increased risk for the pathophysiology associated with irritable bowel syndrome (IBS), which is a primary functional gastrointestinal disorder mainly prevalent in women. Prior research has characterized sex-based differences related to functional and structural changes in IBS in order to identify the sex-based etiology of IBS. However, a detailed understanding of resting state brain networks associated with alterations in pain perception has yet to be conducted among IBS, and this is crucial especially as at present little is known about potential alterations of the networks and brain imprints in IBS patients, and how these connectivity networks are altered in association with important covariate and behavioral measures such as EALs and sex. Aims: We used “resting state” functional magnetic resonance imaging to investigate the impact of EAL on the integrity of resting state networks in male and female IBS patients and healthy controls (HCs). Methods: Resting state functional scans were obtained in a large sample of 168 subjects, 58 IBS (30 female) and 110 HCs (72 female). Group independent component analysis (gICA) was performed to extract the identified components and subject maps created for each component, which were then entered into partial least square (PLS) multivariate analyses to examine how the distribution of intrinsic connectivity networks (ICNs) correlated with EALs in IBS compared to HCs in the context of elucidating sex differences. Singular value decomposition (SVD) was employed in order to extract latent variables (LVs) representing the EAL related behavioral profiles that accounted for the maximum amount of covariance with the imaging data. Results: One-way ANOVAs indicated that IBS subjects had higher levels of EALs compared to HCs. Two of the identified resting state networks, the Salience/Executive Control (SAL) and Cerebellar (CELL) networks, displayed significant LVs relating EAL measures to within-network intrinsic connectivity as identified by the PLS analysis. Conclusions: Intrinsic connectivity networks are altered in IBS compared to HC in the context of early adverse life trauma. While EALs modified connectivity in the salience/executive control network to a similar extent in male and female IBS patients; male IBS patients demonstrated additional EAL-related alteration in the cerebellar network. Consistent with other research, these results suggest that an increased exposure to trauma and pain in male IBS compared to female IBS may be associated with altered connectivity integrity with increasing levels of early life adversity.

15. NR3C1 and IL-1 β Polymorphisms Interact with Early Life Trauma in Healthy Controls and Patients with Irritable Bowel Syndrome

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Background: Neuroplastic gray matter (GM) brain changes have been reported in many chronic pain syndromes, including irritable bowel syndrome (IBS). Female IBS patients have demonstrated reductions in cortical thickness (CT) in the left sgACC when compared to female HC subjects. Although these GM variations have been linked to clinical symptoms they are not necessarily dependent on the presence of a chronic pain condition or ongoing nociceptive input, but may be determined by genetic or epigenetic factors. Therefore the investigation of gene-environment interactions are important in demonstrating increased vulnerability for disease, and associating these interactions with specific brain endophenotypes will lead to an increased understanding of the underlying etiology and pathophysiology of IBS. Aims: To examine the influence of environmental (EALs) and gene [glucocorticoids (NR3C1) and proinflammatory cytokines (IL-1β polymorphisms)] interactions in influencing cortical thickness (CT) in the subgenual anterior cingulate cortex.
(sgACC) in premenopausal female IBS patients and HC subjects. **Methods:** 2 SNPs of the NR3C1 gene (rs33389, rs2963155), and 2 SNPs of the IL-1β gene (rs1143634, rs16944), were genotyped. Subjects completed structural MRI scans and the cortical thickness of the right and left sgACC were computed. General linear models (GLM) were constructed to examine the main and interactive effects of genetic variation with EAL, and diagnosis on CT in left and right sgACC, while controlling for race, age and total brain volume. **Results:** 210 female subjects (73 IBS and 107 HCs) were studied. Increased number of copies of the most common NR3C1 haplotype (CA) was associated with increased cortical thickness in the left sgACC and increased number of copies of the least common haplotype (TG) was associated with decreased cortical thickness in the left sgACC. A significant gene-gene-environment interaction was found for the left sgACC (NR3C1*IL-1β rs1143634*EAL) and a significant gene-gene-environment-diagnosis interaction was found for the right sgACC (NR3C1*IL-1β rs16944*EAL*Dx). **Conclusion:** Since GC receptor binding regulates the ability of NF-κB to bind to DNA and enhance cytokine gene transcription; which, in its pro-inflammatory state, is associated with susceptibility to stress and IBS diagnosis, suggests the need to investigate these relationships in order to get a better understanding of the underlying pathophysiology of these interactions in IBS. Our study found support for these interactions, specifically with influence on the CT in the sgACC, which is a region that mediates pain responses to environmental stresses.

16. **Differences in Resting-State BOLD Oscillation Signals Between Healthy and IBS Subjects**

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**Background:** Regional alterations of blood oxygen level dependent (BOLD) signals have been identified in patients with Irritable Bowel Syndrome (IBS), and sex-related differences in brain responses to visceral distension and its anticipation have been reported in both healthy control subjects (HCs) and IBS patients. We used the fractional Amplitude of Low Frequency Fluctuation (fALFF) method to characterize differences in the resting state activity of the brain in HCs and IBS, and to identify sex related differences. **Aims:** To test the following hypotheses: 1) Disease related differences in frequency fluctuations exist in brain regions of sensorimotor and of emotional arousal/salience networks. 2) Sex-related differences in oscillatory dynamics exist in emotional and interoceptive regions. **Methods:** We measured brain resting state activity (Siemens 3 Tesla Trio and Allegra MRI scanner) in 76 female HCs, 42 male HC, 29 male IBS and 31 female IBS subjects. SPM8 was employed to preprocess and analyze the imaging data using the general linear model and a region of interest analysis. Main effects for four subject groups (male HC, female, HC, male IBS, female IBS), three frequency bands (LF, MF, and HF), and the interaction between groups and bands was performed using a flexible factorial design. Results were considered significant at p<.05, using family wise error correction. **Results:** The main findings of the study were: 1) Female patients compared to female HCs showed greater frequency power oscillation skewed toward HF in AMYG and aINS. 2) Significant sex related differences were also seen within the HC and IBS groups: Within the HCs, female subjects showed greater frequency power distribution skewed toward HF in AMYG and HIPP. Within the IBS group, female patients (compared to males) showed similar patterns as the observed sex differences within the HCs in regions of an emotional arousal circuit (AMYG and HIPP), in addition to greater skew toward HF in all insular subregions. The relative frequency power distribution for sensorimotor cortical regions in female patients was more significantly skewed toward LF compared to male patients. **Conclusions:** Our findings demonstrate that women compared to men, regardless of disease show greater oscillations toward HF in regions of an emotional arousal/salience brain circuit. In female patients, disease related differences are only seen when sex is taking into account.

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17. Impaired Cerebral and Peripheral Vascular Responses to the Valsalva with Hypertension in OSA

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**Introduction:** Obstructive sleep apnea (OSA) is an independent risk factor for hypertension, which likely leads to the high incidence of cardiovascular morbidity and mortality in the sleep disorder. Hypertension in OSA is difficult to treat, which may be due to neural injury in autonomic areas, resulting in impaired central sympathetic and parasympathetic regulation, with consequences for vascular control. We assessed whether hypertensive OSA patients showed greater autonomic impairment than normotensive patients with heart rate (HR) and insular cortex functional magnetic resonance imaging (fMRI) responses to an autonomic challenge.

**Methods:** We studied 30 recently-diagnosed, untreated, moderate-to-severe OSA patients and 59 healthy control subjects, with no history of mental illness. Based on a blood pressure threshold of 140/90 mmHg, we classified 10 OSA subjects as hypertensive (age 50.5±8.0, AHI 46.3±25.2, 3 female) and 20 subjects as normotensive (age 46.6±9.0, AHI 40.3±18.5, 3 female). All controls were normotensive (age 46.7±8.8, 22 female). We measured fMRI and HR signals while subjects performed four Valsalva maneuvers, an 18 s forcible exhalation against a closed glottis, which normally elicits large transient blood pressure and HR changes. Neural responses were calculated from fMRI signals in the insular cortex, as identified from anatomical scans. We assessed between-group differences by repeated-measures ANOVA. Results: Group differences (p < 0.05) in HR appeared, with normotensive OSA showing smaller increases than controls, and a further reduced response emerging in the hypertensive OSA. Insular fMRI responses were altered in hypertensive OSA relative to the other groups. All groups showed signal decreases in the first 4 s, but only the hypertensive OSA failed to return to baseline during the strain period (4-18 s). At 6-10 s after release, the hypertensive OSA showed an exaggerated overshoot before returning to baseline. The differences were most pronounced in anterior insular regions. Conclusion: Hypertensive OSA patients show reductions in the magnitude of heart rate responses, and a time lag in undampened neural responses to a strong autonomic stimulus. The source of the impaired regulation likely includes neural injury in autonomic regulatory brain regions, including the insular cortex. The findings suggest a limitation in dynamic range of cardiovascular responses available to hypertensive OSA patients, which may contribute to further pathology and difficult-to-treat hypertension associated with OSA.

18. Sex Differences in Pontine Structure as Measured with Magnetic Resonance Imaging

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Male and female brains differ in regional structure; the tissue characteristics of areas showing sex-related variations, other than volume, are unclear; whether the differences extend to children is also unknown. The pons, a structure contributing to gender-dependent behaviors such as mood, has lower volume in females over males. To investigate the nature of these differences, we assessed structural measures in samples of healthy males and females, one adult (F N = 22; mean age ± std 49.5 ± 8.3 yrs; M N = 39; age 46.0 ± 9.2) and one pediatric (F N = 10; age 15.5 ± 1.4; M N = 15; age 15.6 ± 1.2). We performed diffusion tensor imaging (4 repeats, 12 directions) and T2/proton density weighted imaging in a 3 Tesla MRI scanner, and calculated whole-brain “maps” of mean diffusivity (MD; decreases with compact structure and cells), fractional anisotropy (FA; increases with enhanced tissue organization, e.g., grouping of axons), and T2-relaxation time (T2; increases with greater water content). Values of FA, MD and T2 from the pons were compared between sexes using ANCOVA with age as a covariate. Models with a second covariate of total intracranial volume (TIV) were also estimated. Adults: Females showed lower FA in the pons compared with males (F 0.388 ± 0.032, M 0.411 ± 0.022, p = 0.003), and MD was lower in males (F 0.00135 ± 0.00015 mm²/s, M 0.00127 ± 0.00009 mm²/s, p = 0.01). However, T2 values did not significantly differ between groups (F 159.8 ± 15.6 ms,
M 160.8 ± 14.6 ms, p = 0.7). Pediatric: No pontine sex differences emerged on FA (F 0.293 ± 0.024, M 0.312 ± 0.018, p = 0.9), MD (F 0.00110 ± 0.00007 mm²/s, M 0.00107 ± 0.00007 mm²/s, p = 0.3), or T2 (F 123.5 ± 17.9 ms, M 122.5 ± 11.1 ms, p = 0.4). Age was insignificant, other than for pediatric FA (p = 0.002), and TIV was not significant in any pediatric or adult model. The adult FA findings suggest that males have more fiber organization (more parallel or tightly-packed axons) than females. The MD and T2 findings suggest local tissue organization differences between sexes, but no difference in water content. Since no sex differences appeared in pediatric subjects, the changes may result from developmental processes. However, the smaller number of pediatric subjects, as well as developmental and technical factors, limits direct comparisons. Differing brain sizes between males and females are unlikely to contribute to the findings, as TIV was not a significant term. The smaller pontine volumes in adult females are accompanied by altered fiber and other tissue organization. The processes underlying the structural differences are unclear, but the findings impact mixed-gender imaging studies, and may contribute to sex differences in behaviors.

19.
Female and Male Heart Rate Responses to Autonomic Challenges in Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is accompanied by brain injury and dysfunction in autonomic regulatory regions. That injury may impair dynamic regulation of the vasculature and contribute to other syndrome pathologies, including exaggerated or unresponsive sympathetic tone. Characterizing cardiovascular responses to autonomic challenges may provide insights into processes underlying impairments, and since the extent of brain injury is enhanced in females over males, such assessment should be partitioned by sex.

The objective was to assess OSA heart rate responses versus healthy controls’ to autonomic challenges, using a two-group comparative design, and, separately, characterize female and male patterns.

We studied 94 subjects, with newly-diagnosed, untreated OSA groups of 6 female (age mean±std: 52.1±8.1 years) and 31 male (54.3±8.4 years) patients, and 20 female (50.5±8.1 years) and 37 male (45.6±9.2 years) controls.

We measured instantaneous heart rate with pulse oximetry during cold pressor, hand grip, and Valsalva maneuver challenges.

All challenges changed heart rate, with significant differences between OSA and control groups (repeated measures ANOVA, p<0.05). OSA females showed greater differences in magnitude and response timing, relative to their healthy counterparts and OSA males. Indices reflecting differences included, by group (female OSA/Control, male OSA/control): for cold pressor, lower initial increase (9.5/7.3, 7.6/3.7 bpm), OSA delay to 1st peak (2.5 s females/0.9 s males), slower mid-challenge rate-of-increase (-0.11/0.09, 0.03/0.06 bpm/s); for hand grip, lower initial peak (2.6/4.6, 5.3/6.0 bpm), less sustained elevation during strain (area-under-curve 13.7/27/35.1/46.3 bpm*s); for Valsalva maneuver, lower Valsalva ratio (1.14/1.30, 1.29/1.34), lower phase II rate-of-increase (0.62/1.25, 1.23/1.34 bpm/s), and OSA delayed phase II peak (0.68 s females/1.31 s males).

Heart rate responses were lower amplitude, delayed in onset, and slower to change in OSA patients over healthy controls, and impairments were more pronounced in females. The dysfunctions likely developed from neural injury in the syndrome, and suggest autonomic deficiencies that may contribute to further tissue and functional pathology.
20.  
Association of Abdominal Fat with Resting State Low Frequency Brain Activity in Human Subjects


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Background: Obesity is a major health problem worldwide. Even though the body mass index (BMI) is commonly used to define obesity, waist circumference (WC) correlates better with abdominal fat and metabolic syndrome than BMI. Brain imaging studies in humans have shown differences in brain activity between lean and obese subjects, including alterations in reward network activity. Still, data is very scarce on the relationship between obesity and resting state networks (RSN) of the brain. A recent study assessing functional connectivity within RSNs in lean and obese subjects, showed increased connectivity in the precuneus/posterior cingulate cortex and reduced brain activity in the right anterior cingulate (ACC) and insular cortices in the obese.

Aims: To investigate correlations between WC and intrinsic low frequency oscillations (indexed by regional low-frequency power (ALFF) signal in resting state functional MRI), in lean and obese subjects in brain regions involved with hunger/satiety feelings, and with the reward system.

Methods: Resting state brain scans (10 min, during fasting state) from 75 subjects (31 healthy controls, 44 patients with mild chronic GI symptoms, 27 males), with mean age of 29±8.5y and mean WC of 86±12.2cm in the Center’s extensive brain image repository were analyzed. Normalized ALFF maps were created for frequency band in 0.01-0.08Hz range. A factorial design in SPM8 was applied to test for frequency power among ROIs. Multiple regression analysis was applied to control for age and diagnosis. Data shown as mean±SD

Results: ALFF analysis showed significant correlations between WC and intrinsic brain oscillatory frequency in insula, ventral tegmental area, prefrontal cortex, and ventral diencephalon. When controlling for diagnosis (healthy vs GI symptoms), WC continued to be associated with brain activity in the insula and prefrontal cortex, and new areas were demonstrated at the ACC and orbitofrontal cortex.

Conclusions: To our knowledge this is first study to assess the relationship between a measure of abdominal fat and the pattern of spontaneous oscillation frequency in the human brain. We found that higher WCs are associated with spontaneous brain activity in areas involved in the reward and homeostatic systems. The mechanisms underlying these brain alterations, including the possible role of genetic and epigenetic factors remain to be determined.

21. How Do Dementia Behaviors Cluster? Identifying Behavioral Clustering Relationship to Cortisol

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Behavioral symptoms in persons with dementia (BSD), such as yelling, wandering, and restlessness, are extremely challenging to elders, their clinicians and caregivers. Progress in developing and refining tailored interventions to address BSD has been hampered by the ability to detect and characterize complex recurrent patterns and the relationship to altered circadian rhythm. The purpose of this study was to develop a measurement method to more precisely characterize the relationships between BSD and circadian rhythm. Using the modified Agitated Behavior Rating Scale (mABRS) (low, moderate or high intensity), we coded the BSD of 60 participants over a 4-day period. Data were analyzed using pattern recognition software (THEME). We categorized THEME patterns of high intensity behaviors into clinically significant escalation/de-escalation categories. Factor analysis identified clusters of these behavior categories. We used correlation and chi-square tests to test the association between identified factors, age, gender and cortisol (an index for circadian rhythm). Cortisol was categorized as normal or abnormal. Factors 1 and 2 explained 12 – 16% of the variance. Participants with normal cortisol rhythm exhibited higher vocalization when staff or residents were present (Factor 3) than those with abnormal cortisol (p < 0.05). Older age was correlated with less pacing and screaming in the presence of staff (p < 0.1). Men exhibited increased intensity pacing and searching (Factor 8) compared to women (p<0.05). Relating clusters of behavior to participant characteristics using innovative analysis identifies those most likely to
exhibit BSD. The contribution of stress reactivity to these behaviors, indexed by 12-hour cortisol profiles is intriguing. Predicting persons at risk for manifesting disturbing behavioral clusters will assist the use of interventions that can be specifically refined and timed.
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