12th Annual CNS
Basic and Translational Symposium

BRINGING THE BRAIN BACK INTO MEDICINE: FROM GUT MICROBES TO BEHAVIORAL INTERVENTIONS

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

February 28, 2014
UCLA Neuroscience Research Building

Contributors

Symposium Chairs

Lin Chang, MD

Muriel Larauche, PhD

Sponsors

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Program

12TH ANNUAL CNS BASIC AND TRANSLATIONAL SCIENCE SYMPOSIUM

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

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

Friday, February 28, 2014

NEUROSCIENCE RESEARCH BUILDING AUDITORIUM (NRB 132)

8:30 am – 8:45 am	**INTRODUCTION**
	Symposium Chairs: **Lin Chang, MD (**Director, Functional GI Disorders Program - Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress Division of Digestive Diseases, David Geffen School of Medicine at UCLA) and **Muriel Larauche, PhD** (Assistant Researcher, Division of Digestive Diseases, David Geffen Department of Medicine at UCLA)
	Judy Gasson, PhD Senior Associate Dean for Research David Geffen School of Medicine, UCLA
8:45 am – 9:00 am	**STATE OF THE CENTER** **Emeran Mayer, MD** Director, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress; Co-Director, CURE: Digestive Diseases Research Center; Division of Digestive Diseases, David Geffen School of Medicine at UCLA
SESSION I	Session Chairs: **Lin Chang, MD** and **Muriel Larauche, PhD**
9:00 am – 9:45 am	**RESEARCH PROGRAMS OF THE CENTER** (Program highlights and future direction: each 10 minutes + 5 minutes Q&A)
9:00 am – 9:15 am	NEUROCARDIOLOGY PROGRAM **Marmar Vaseghi, MD**
9:15 am – 9:30 am	INGESTIVE BEHAVIOR AND OBESITY RESEARCH PROGRAM **Claudia Sanmiguel, MD**

9:30 am – 9:45 am	PAIN RESEARCH PROGRAM	**Bruce Naliboff, PhD**
9:45 am – 10:00 am	**COFFEE BREAK**	
10:00 am – 10:45 am		
10:00 am – 10:15 am	MIND BODY RESEARCH PROGRAM	**Kirsten Tillisch, MD**
10:15 am – 10:30 am	ENTERIC NEUROSCIENCE PROGRAM	**Emeran Mayer, MD**
10:30 am – 10:45 am	FUNCTIONAL GI DISORDERS PROGRAM	**Lin Chang, MD**

SESSION II

Session Chairs: Million Mulugeta, DVM, PhD (Adjunct Professor, Division of Digestive Diseases, David Geffen School of Medicine at UCLA) and **Andrea Rapkin, MD** (Director, UCLA Pelvic Pain Program, Professor, Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA)

10:45 am – 12:15 pm   **DATA BLITZ – RESEARCH HIGHLIGHTS**
(6 presentations, 1 from each Center Program: each 10 minutes + 5 minutes discussion)

10:45 am – 11:00 am   *Clinical and Mechanistic Updates on Cardiac Decentralization in the Treatment of Ventricular Arrhythmias*
Olujimi Ajijola, MD, PhD
Clinical Instructor in Medicine, UCLA Cardiac Arrhythmia Center

11:00 am – 11:15 am   *Morphological Imaging-Based Brain Signatures Discriminate Obese from Lean Subjects: Examining Central Mechanisms within the Brain*
Arpana Gupta, PhD
Post-Doctoral Scholar, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:15 am – 11:30 am   *Central Alterations in Localized Provoked Vulvodynia*
Jennifer Labus, PhD
Adjunct Associate Professor, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:30 am – 11:45 am   *Irritable Bowel Syndrome Symptoms Are Related to the Resting Brain's Sensorimotor Network*
Michelle Chen, BS
Graduate Student - School of Public Health, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

11:45 am – 12:00 pm   *Structural and Functional Brain Changes in Inflammatory Bowel Diseases*
Emeran Mayer, MD
Director, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress; Co-Director, CURE: Digestive Diseases Research Center; Division of Digestive Diseases, David Geffen School of Medicine at UCLA

12:00 pm – 12:15 pm	*Epigenetic Landscape of Irritable Bowel Syndrome* **Swapna Joshi, PhD** Post-Doctoral Scholar, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
12:15 pm – 1:45 pm	**LUNCH AND POSTER SESSION**
SESSION III	**Session Chair: Charalabos Harry Pothoulakis, MD** (Director, UCLA Research Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)
1:45 pm – 3:15 pm	**STATE OF THE ART LECTURES** (Each 25 minutes + 5 minutes discussion)
1:45 pm – 2:15 pm	*Social Regulation of Human Gene Expression* **Steve Cole, PhD** Professor of Medicine, Department of Hematology-Oncology, UCLA
2:15 pm – 2:45 pm	*Defining and Harnessing the Intestinal Microbiome* **Jonathan Braun, MD, PhD** Co-Director, Jonsson Comprehensive Cancer Center Tumor Immunology Program Area; Professor, Pathology and Laboratory Medicine, UCLA
2:45 pm – 3:15 pm	*Computer-Assisted Cognitive Behavioral Therapy for Anxiety Disorders in Primary Care* **Michelle Craske, PhD** Director, Anxiety Disorders Research Center of UCLA; Professor of Psychology and of Psychiatry and Biobehavioral Sciences, UCLA
3:15 pm – 3:20pm	**POSTER AWARD** **Joseph Pisegna, MD** Chief, Division of Gastroenterology and Hepatology, VA Greater Los Angeles Healthcare System; Professor of Medicine, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
3:20 pm – 3:30 pm	**CLOSING COMMENTS** **Yvette Taché, PhD** Co-Director, Enteric Neuroscience Program – Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress; Director, CURE: Animal Models Core; Professor, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
3:30 pm	**END OF SYMPOSIUM**

Summaries of Presentations

Symposium Chairs: Lin Chang, MD (Financial Disclosure: None)

Muriel Larauche, PhD (Financial Disclosure: Grant support - Sucampo)

SESSION I: RESEARCH PROGRAMS OF THE CENTER

Chairs: Lin Chang, MD

Muriel Larauche, PhD

NEUROCARDIOLOGY PROGRAM
Marmar Vaseghi, MD
Financial Disclosure: None

Mission: With the emerging role of neuro-modulation in the treatment of acute and chronic cardiovascular diseases, the goal of the neurocardiology center is to translate mechanistic insight obtained from neuro-cardiac physiology and pathophysiology into a comprehensive team based integrated approach to neural-based cardiac therapies.

Background and Rationale:
- Cardiovascular diseases, including sudden cardiac death and heart failure, are leading causes of morbidity and mortality in the United States
- The autonomic nervous system plays a key role in the pathogenesis of cardiovascular diseases, including heart failure and arrhythmias
- Extensive neural remodeling involving afferent and efferent neural signaling to the central nervous system occurs in patients with cardiomyopathy
- Neuromodulatory therapies present a new and important avenue of treatment options for cardiovascular diseases

Disease Areas: Ventricular arrhythmias, atrial arrhythmias, cardiomyopathy, hypertension, chronic angina.

INGESTIVE BEHAVIOR AND OBESITY RESEARCH PROGRAM
Claudia Sanmiguel, MD
Financial Disclosure: None

Mission: To advance the understanding of the role of the human brain in the regulation of ingestive behavior in health, obesity and eating disorders through neuroimaging, and psychophysiological approaches

Background and Rationale:
- Disorders of ingestive behavior, including obesity and anorexia nervosa (AN) are common, affect women more than men, and are associated with a high morbidity and mortality
- The control of food intake is one of the most highly adaptive and regulated biological processes, and the high prevalence of disorders in industrialized societies points towards strong environmental factors
- For both obesity and AN, alterations in bidirectional brain gut interactions have been proposed as plausible disease models

Disease Areas: Obesity, Eating Disorders

PAIN RESEARCH PROGRAM
Bruce Naliboff, PhD
Financial Disclosure: None

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

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

Example Projects:
- Established first NIH funded repository of brain imaging in chronic pain to identify "brain signatures" (changes in brain structure and function) associated with various chronic pain conditions
- Development of a web based program of cognitive therapy to help patients develop behavioral and stress management skills for pain control
- Identify brain signatures of resilience

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

MIND BODY RESEARCH PROGRAM
Kirsten Tillisch, MD
Financial Disclosure: None

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

Background and Rationale:
- Mind-Body and alternative medicine approaches are increasingly sought out by patients to supplement their traditional health care. While sometimes effective there is little current scientific study in this area or rationale for which treatments to apply to which conditions or patients
- This program applies western science to determine how specific Mind Body and alternative medicine treatments work and how to enhance their effectiveness.

Example Projects:
- An NIH funded study of brain signatures from neuroimaging associated with successfully use of mindfulness meditation for chronic visceral pain
- A study of Yoga training for Veteran's with post traumatic headache

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

ENTERIC NEUROSCIENCE PROGRAM
Emeran Mayer, MD
Financial Disclosure: None

Mission: To characterize the bidirectional interactions between the brain, the gut and the gut microbiome in health and disease, with an emphasis on studying sex related differences

Background and Rationale:
- This NIH funded research program aims to understand how changes in the way the brain and the digestive system talk to each other may be responsible for a wide range of chronic diseases ranging from heartburn, chronic abdominal pain, and inflammatory bowel diseases

- Researchers apply cutting edge technologies to unravel the structure and function of the brain, the immune system and the microorganisms living in our intestine
- The studies will help to more effectively treat many chronic gastrointestinal disorders with pharmacological and non-pharmacological treatments.

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

FUNCTIONAL GI DISORDERS PROGRAM
Lin Chang, MD

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

Background and Rationale:
- Functional GI and motility disorders, such as irritable bowel syndrome (IBS), constipation, dyspepsia, gastroparesis and chronic abdominal pain are the most commonly diagnosed GI conditions in clinical practices
- Patient care is provided at the UCLA Digestive Health and Nutrition Clinic where patients can be seen by a multidisciplinary team of dedicated physicians, nurses, and a dietitian who specialize in GI disorders and apply a holistic approach designed to bring a broader and more in-depth dimension to patient care. The physicians are internationally renowned experts in the science, diagnosis and treatment of brain-gut disorders
- The research program will use cutting edge scientific techniques to identify biologic markers to diagnose and predict treatment response in patients with functional GI disorders, including IBS.

Disease Areas: Irritable Bowel Syndrome, Constipation, Cyclic Vomiting Syndrome, Dyspepsia, Gastroparesis, Bowel Incontinence

SESSION II: DATA BLITZ – RESEARCH HIGHLIGHTS

Chairs: Million Mulugeta, DVM, PhD (Financial Disclosure: None)
          Andrea Rapkin, MD (Financial Disclosure: None)

Clinical and Mechanistic Updates on Cardiac Decentralization in the Treatment of Ventricular Arrhythmias
Olujimi Ajijola, MD PhD
Clinical Instructor in Medicine, UCLA Cardiac Arrhythmia Center
Financial Disclosure: None

The clinical and basic/translational divisions of the neurocardiology group have studied in parallel, the clinical use of neuro-modulation in the treatment cardiovascular arrhythmias, and in animal models, the mechanisms by which neuro-modulation imparts antiarrhythmic benefits. Our findings over the past 12-months are summarized as follows: *Clinical* – Bilateral cardiac sympathetic denervation (BCSD), the surgical resection of the majority of efferent cardiac sympathetic input was demonstrated to impart significant intermediate- to long-term antiarrhythmic benefit over unilateral cardiac sympathetic denervation[1]. The anesthetic considerations[2] for this procedure, as well as the synergistic use of this therapy with comprehensive psychiatric treatment[3] were also detailed in two separate publications. The adjunctive benefit of renal denervation[4] added to contemporary medical and catheter-based interventions in attenuating arrhythmias in patients was also described in part by the clinical neurocardiology group. *Basic/Translation* – Following studies characterizing the myocardial effects of efferent cardiac sympathetic activation (left and right stellate ganglia stimulation) in a porcine model, which demonstrated distinct and overlapping regions of left and right sided efferent sympathetic input to the heart[5, 6], the effects of myocardial infarction on global functional sympathetic innervation were examined. These studies demonstrated that focal myocardial injury results in global heterogeneity of functional cardiac electrophysiologic responses to efferent cardiac sympathetic activation, creating myocardial substrates at high risk of ventricular arrhythmogenesis[7].

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Morphological Imaging-Based Brain Signatures Discriminate Obese from Lean Subjects: Examining Central Mechanisms within the Brain

Arpana Gupta, PhD
Post-Doctoral Scholar, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
Financial Disclosure: None

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

Behavioral and neuroimaging based observations have identified similarities between brain mechanisms involved in maladaptive obesity-related ingestive behaviors and addictive behaviors, resulting in the concept of food addiction. These studies offer some insight into the fact that structural brain alterations in key regions of the extended reward network may be linked to increased food related behaviors in obesity.

We propose that data driven multivariate pattern analysis/recognition methods allow for the ability to classify and identify obesity related brain alterations in key structures of the reward network. The advantage of using these advanced mathematical machine-learning approaches is that they are model free, and have the ability to make good predictions using small samples and when there is high collinearity among the predictors. I will show examples of the use of these novel and powerful data driven analyses in how morphological brain signatures (e.g. volume, mean curvature, surface area, cortical thickness) discriminate individuals with high BMI from those with low BMI. These classification algorithms based on the morphometry of regional brain structure alone can identify specific targets for future mechanistic studies and treatments aimed at abnormal ingestive behavior and obesity.

Central Alterations in Localized Provoked Vulvodynia

Jennifer Labus, PhD
Adjunct Associate Professor, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
Financial Disclosure: None

Localized provoked vulvodynia (LPVD) affects approximately 7 to 10% of the female population and is characterized by localized sensitivity of the vulva that is provoked (e.g., tampon use and intercourse). The biological etiology of LPVD is unknown. LPVD is comorbid with other chronic pain disorders such as irritable bowel syndrome and fibromyalgia. Investigation of central processes in LPVD are sparse but suggest 1) dysregulation of endogenous pain modulatory systems, 2) altered sensory innervation 3) enhancement of pain due to attention and /or 4) central sensitization. Dr Labus will discuss recent findings suggesting resting state and morphometric alterations in LPVD compared to healthy controls and a positive disease control group, irritable bowel syndrome.

Irritable Bowel Syndrome Symptoms Are Related to the Resting Brain's Sensorimotor Network

Michelle Chen, BS
Graduate Student, School of Public Health and Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
Financial Disclosure: None

Abdominal pain and/or discomfort is a universal symptom in irritable bowel syndrome (IBS). Altered function of the brain's pain processing pathways have been identified in IBS during task related functional imaging studies, however less is known about the impact of IBS on the resting brain. A sensorimotor network is identifiable in large scale resting brain studies using independent components analysis. This network has been associated with both painful and non-painful sensory tasks and thus may be relevant in chronic pain states, including IBS. The aims of this study are to demonstrate the relationship between IBS symptoms and sensorimotor resting state network (SM-RSN) function and to assess the effect of successful mind-body interventions (IBS directed hypnosis or educational classes) on the SM-RSN.

Structural and Functional Brain Changes in Inflammatory Bowel Diseases

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

Patients with chronic inflammatory disorders including inflammatory bowel diseases and rheumatoid arthritis have a greater prevalence of anxiety and depression, and stressful life events play a role in symptom flares. Treatment with TNF alpha antibodies is often accompanied by an immediate therapeutic effect, in the absence of any changes in disease activity, pointing towards a central effect. In rodent models, chronic peripheral inflammation has been shown to cause neuroinflammatory changes in the brain. In this pilot study, we aimed to use structural and resting state functional brain imaging to identify disease related brain signatures. Cortical thickness was assessed in ulcerative colitis (UC), and two control groups (irritable bowel syndrome [IBS] and healthy control subjects [Hc]). UC subjects showed greater cortical thickness in the anterior cingulate cortex and in primary somatosensory cortex compared with both IBS and HCs. Compared with HCs, UC subjects showed lower cortical thickness in orbitofrontal cortex and in primary interoceptive regions (mid and posterior insula), while IBS subjects showed lower cortical thickness in the anterior INS, an association area receiving cognitive, affective and interoceptive input. Strong correlations between thickness in the orbitofrontal cortex and post central gyrus with symptom duration were only observed in UC subjects. The findings from this pilot study clearly demonstrate that chronic inflammation of the gut is associated with neuroplastic changes in sensory as well as in prefrontal brain regions, and these brain changes were correlated with symptom duration, suggesting a possible role of chronic inflammatory signaling to the brain. Future studies in larger samples combined with assessment of peripheral profiles of inflammatory mediators will be required to further characterize the relationship between gut inflammation, brain structure and function, and associated behavioral changes.

Epigenetic Landscape of Irritable Bowel Syndrome

Swapna Joshi, PhD
Post-Doctoral Researcher, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA
Financial Disclosure: None

Irritable bowel syndrome (IBS) is functional gastro intestinal, stress-sensitive disorder associated with alterations in brain-gut interactions. DNA methylation of cytosine residues is an essential epigenetic modification in mammalian cells. It is a leading candidate biological pathway linking gene-environment interactions to long-term behavioral development, particularly in complex disorders. However, there are no studies that have investigated the role of DNA methylation in IBS. We compared global DNA methylation profiles of PBMCs from 12 IBS patients (mean[±sd] age=39.8±3.4 yrs, 58% F, 25% IBS-C 50% IBS-D, 25% IBS-M) with 12 HCs (mean[±sd] age=39.8±3.8 yrs, 58% F), using Illumina HM450 array, which interrogates DNA methylation status of > 450,000 CpG sites and >99% of all genes. DNA methylation levels were compared between IBS and healthy controls (HCs), and between the IBS bowel habit subtypes using Wilcoxon rank-sum test. Using the criteria of a mean methylation difference ≥ 15% and $p < 0.05$, 29 probes were different between IBS and HCs, 81 probes were

different between IBS-C vs. IBS-D, 39 between IBS-C vs. HCs, and 26 between IBS-D vs. HCs (total of 175 probes for 128 genes). We performed gene ontology (GO) analysis to identify common functions associated with the group of genes. These genes were identified to be associated with GO term 'neuropeptide hormone', defined as "any peptide hormone that acts in the central nervous system".

This finding is consistent with the large body of evidence that supports the unifying theme that symptoms of IBS result from dysregulation of the "brain-gut axis", which describes the bidirectional communication between the enteric, autonomic and central nervous systems. Six genes corresponding to 10 probes with the lowest p values and highest methylation group differences were Synphilin-1 *(SNCAIP),* SCO-spondin (*SSPO*), RING finger protein 39 (*RNF39*) and Tubulin Polymerization Promoting (*TPPP*), glutathione S transferases mu class (*GSTM1*, *GSTM5*). All 10 probes were hyper-methylated in IBS compared to HCs. We analyzed the expression of these genes to test whether these genes were epigenetically silenced. We found an inverse correlation between DNA methylation and gene expression levels for *GSTM5*. In conclusion, our analysis showed for the first time, that differences in DNA methylation patterns exist between IBS and HCs and that epigenetics might play an important role in regulation of gene expression associated with the pathogenesis of IBS.

SESSION III: STATE OF THE ART LECTURES

Chair: Charalabos Harry Pothoulakis, MD (Financial Disclosure: None)

Social Regulation of Human Gene Expression
Steve Cole, PhD
Professor of Medicine, Department of Hematology-Oncology, UCLA
Financial Disclosure: None

Relationships between genes and social behavior have historically been viewed as a one-way street, with genes in control. Recent analyses have challenged this view by discovering broad alterations in the expression of human genes as a function of differing socio-environmental conditions. This talk summarizes the developing field of social genomics, and its efforts to identify the types of genes subject to social regulation, the biological signaling pathways mediating those effects, and the genetic polymorphisms that moderate socio-environmental influences on human gene expression. This approach provides a concrete molecular perspective on how external social conditions interact with our genes to shape the functional characteristics of our bodies, and alter our future biological and behavioral responses based on our personal transcriptional histories.

Defining and Harnessing the Intestinal Microbiome
Jonathan Braun, MD, PhD
Co-Director, Jonsson Comprehensive Cancer Center Tumor Immunology Program Area; Professor, Pathology and Laboratory Medicine, UCLA
Financial Disclosure: None

The fabulous abundance and diversity of the microorganisms inhabiting the human intestine is a wonder and challenge for research and clinical integration. This talk is a report surveying the analytic and conceptual frontier. First, I will summarize the major "settled" facts about the composition of the intestinal microbiota, and its relation to stages of life, genetics, and diet. Second, I will summarize key analytic tools in place to monitor the microbiome. Third, I'll describe the strongest links of the microbiome to physiologic and disease states, and some of the proposed mechanisms. Finally, I'll present the opportunities and challenges for modifying the microbiome.

Computer-Assisted Cognitive Behavioral Therapy for Anxiety Disorders in Primary Care
Michelle Craske, PhD
Director, Anxiety Disorders Research Center of UCLA; Professor of Psychology and of Psychiatry and Biobehavioral Sciences, UCLA
Financial Disclosure: None

Anxiety disorders are highly common and yet often poorly treated in primary care. The CALM study evaluated the effectiveness of (a) cognitive behavioral therapy, psychotropic medication recommendations, or both compared to (b) treatment as usual, for anxiety disorders in primary care. Cognitive behavioral therapy for multiple anxiety disorders was computer/internet assisted, in order to increase fidelity of CBT in the hands of novice clinicians. Computer-assisted CBT and its effects will be presented. In addition, methods for training novice clinicians in computer-assisted CBT, the acceptability of the program, and the role of therapist adherence/competency in treatment outcomes will be described. Also, the role of ethnicity, income, and age as moderators of outcome will be presented. Finally, the role of engagement in CBT and self efficacy and outcome expectancy as mediators or treatment outcomes will be described.

About the Speakers

Olujimi Ajijola, MD, PhD
Clinical Instructor in Medicine, UCLA Cardiac Arrhythmia Center

Dr. Ajijola completed his undergraduate degree with distinction at the University of Virginia in biology. He received his medical degree from Duke University School of Medicine, during which the National Institutes of Health and Howard Hughes Medical Institute awarded him medical research fellowships, and a medical studies scholarship. He completed a residency in Internal Medicine at Massachusetts General Hospital/Harvard Medical School, and a cardiology fellowship at the University of California Los Angeles - Specialty Training and Research (STAR) program. He completed a PhD in Molecular, Cellular, and Integrative Physiology. Upon completing his cardiology and PhD training, he joined the UCLA Cardiac Arrhythmia Center as a Clinical Instructor in January 2013.

His research interests are in understanding the neural basis of ventricular arrhythmias in normal and abnormal hearts. He studies how nerves remodel within and outside of the heart after cardiac injury, and how this process contributes to abnormal electrical rhythms. He also studies electrical propagation through damaged regions of the heart using electrical mapping techniques.

Clinically, his interests are in using modulation of the sympathetic nervous system to treat patients with severe arrhythmias. He is actively involved in developing novel approaches to treating arrhythmias in patients. Dr. Ajijola will be completing clinical training in cardiac electrophysiology in July 2014.

He holds memberships in several professional organizations including the American heart Association, Heart Rhythm Society, and the American College of Cardiology. He also serves as a peer-reviewer for journals in cardiology and electrophysiology, and serves on the editorial board of the journal of electrocardiography.

Jonathan Braun, MD, PhD
Co-Director, Jonsson Comprehensive Cancer Center Tumor Immunology Program Area; Professor, Pathology and Laboratory Medicine, UCLA

Jonathan Braun, MD, PhD is a physician-researcher devoted to the roles of the immune system in resistance and susceptibility to inflammatory bowel disease and cancer. He is a professor and chair of Pathology and Lab Medicine at the David Geffen School of Medicine at UCLA. A native of Cleveland, Ohio, Dr. Braun was raised in Los Angeles, where he focused on violin performance. He was an undergraduate at Stanford University (BS, chemistry and biology), and did his MD and PhD studies at Harvard Medical School with Emil Unanue. After residency in Pathology at Brigham and Women's Hospital, and a postdoctoral fellowship with David Baltimore at the Whitehead Institute, he joined the faculty at the UCLA School of Medicine in 1985. Through an integrated approach of molecular microbial ecology and metaproteomic and metabolite analysis, and human genetics, his research centers on the biology of mucosal interaction of host immunity with the local microbial community, and its impact on chronic mucosal inflammatory disease and cancer. He has published more than 140 primary research studies, 14 issued patents, and co-founded three biopharma companies. His recent national service includes Chair of the National Scientific Advisory Committee of the Crohn's and Colitis Foundation, and President of the Federation of Clinical Immunology Societies. He still plays violin when possible.

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

Lin Chang, MD, is a Professor of Medicine in the Department of Medicine, Division of Digestive Diseases, at the David Geffen School of Medicine at UCLA. She serves as the Co-Director of the Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress at the David Geffen School of Medicine at UCLA. This center is an interdisciplinary research and education organization, dedicated to the study of brain-body interactions in health and disease. She serves as Program Director of the UCLA Gastroenterology Fellowship Program and Director of the Digestive Health and Nutrition Clinic at UCLA. Dr. Chang's clinical expertise is in functional gastrointestinal disorders which include irritable bowel syndrome (IBS), chronic constipation, and functional dyspepsia. She is a funded NIH-investigator studying the central and peripheral mechanisms underlying IBS. Specifically, her

research is focused on the pathophysiology of IBS related to stress, sex differences, and epigenetic modifications and the treatment of IBS.

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

Michelle Chen, BS
Graduate Student - School of Public Health, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Michelle Chen is a first year graduate student in the Masters in Public Health program at the UCLA Fielding School of Public Health concentrating in Health Policy and Management. She received her bachelor degree in Psychobiology at UCLA. Under the guidance of Dr. Kirsten Tillisch, she is a Graduate Student Researcher in the UCLA Center for Neurobiology of Stress.

Steve Cole, PhD
Professor of Medicine, Department of Hematology-Oncology, UCLA

Steven W Cole is a Professor of Medicine in the Division of Hematology-Oncology at the David Geffen School of Medicine at UCLA. His research analyzes the pathways by which social and environmental factors influence the activity of the human genome, as well as viral and tumor genomes. He pioneered the filed of human social genomics, and he provides strategic consulting in this area as Director of the UCLA Social Genomics Core Laboratory and as a consultant to the Institute of Medicine, the National Cancer Institute, the National Institute of Aging, the Santa Fe Institute, and the MacArthur Foundation, among others. He received his PhD from Stanford University in 1993 and completed two post-doctoral fellowships at UCLA before his appointment to its School of Medicine in 1998. He is an elected Fellow of the AAAS, recipient of Stanford University's Centennial Teaching Award, and a member of the Jonsson Comprehensive Cancer Center, the Norman Cousins Center, the UCLA AIDS Institute, and the UCLA Molecular Biology Institute. His laboratory specializes in developing new bioinformatics strategies for mapping the pathways through which social and environmental conditions influence gene expression in inflammation, infectious diseases such as HIV-1, and breast and ovarian cancers.

Michelle Craske, PhD
Director, Anxiety Disorders Research Center of UCLA; Professor of Psychology and of Psychiatry and Biobehavioral Sciences, UCLA

Michelle G Craske, PhD, is Professor of Psychology, Psychiatry and Biobehavioral Sciences and the Director of the Anxiety Disorders Research Center at the University of California, Los Angeles. She has published extensively in the area of fear and anxiety disorders. In addition to many research articles, she has written academic books on the topics of the etiology and treatment of anxiety disorders, gender differences in anxiety, translation from the basic science of fear learning to the understanding and treating of phobias, and principles and practice of cognitive behavioral therapy, as well as several self-help books and therapist guides. In addition, she has been the recipient of National Institute of Mental Health funding since 1993 for research projects pertaining to risk factors for anxiety disorders and depression among children and adolescents, the cognitive and physiological aspects of anxiety and panic attacks, neural mediators of behavioral treatments for anxiety disorders, fear extinction mechanisms of exposure therapy, implementation of treatments for anxiety and related disorders, and constructs of positive valence and negative valence underlying anxiety and depression. She was associate editor for the Journal of Abnormal Psychology, and is presently associate editor for Behaviour Research and Therapy and Psychological Bulletin, as well as a scientific board member for the Anxiety and Depression Association of America. She was a member of the DSM-IV Anxiety Disorders Work Group and the DSM-5 Anxiety, Obsessive Compulsive Spectrum, Posttraumatic, and Dissociative Disorders Work Group (Chair, Anxiety Disorders

Subworkgroup). She is also a member of the APA Clinical Treatment Guidelines Advisory Steering Committee. Dr. Craske has given invited keynote addresses at many international conferences and frequently is invited to present training workshops on the most recent advances in the cognitive–behavioral treatment for anxiety disorders. She is currently a professor in the Department of Psychology and Department of Psychiatry and Biobehavioral Sciences, UCLA, and director of the UCLA Anxiety Disorders Research Center. Dr. Craske received her BA Hons from the University of Tasmania and her PhD from the University of British Columbia.

Judy Gasson, PhD
Senior Associate Dean for Research, David Geffen School of Medicine, UCLA

Judith C Gasson, a professor of biological chemistry and medicine, became director of UCLA?s Jonsson Comprehensive Cancer Center on September 15, 1995. A molecular biologist, Gasson is responsible for one of only 39 institutions nationwide designated as comprehensive cancer centers by the National Cancer Institute. In addition to her administrative duties, Gasson also is a gifted scientist. She was instrumental in purifying for the first time a hormone-like substance that increases the speed of bone marrow cell reproduction. That substance, called GM-CSF, is used to help prevent infections in cancer patients, and to allow patients to tolerate more chemotherapy and radiation than had previously been possible. In 2005, Gasson was named a co-director of the UCLA Institute of Stem Cell Biology and Medicine and she recently testified before a key Senate subcommittee on the promise of stem cell research in cancer. Gasson also serves as a board member for the American Association for Cancer Research. She earned a bachelor's degree in microbiology from Colorado State University and a doctorate in physiology at the University of Colorado. Gasson did post doctoral work at the Salk Institute in La Jolla. In 1983, she left the Salk Institute to join UCLA's Jonsson Cancer Center, which comprises more than 240 researchers and clinicians engaged in research, prevention, detection, control, treatment and education. One of the nation's largest comprehensive cancer centers, the Jonsson center is dedicated to promoting research and translating the results into leading-edge clinical studies. In July 2005, the Jonsson Cancer Center was named the best cancer center in the western United States by US News & World Report, a ranking it has held for six consecutive years.

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

Dr. Gupta received her PhD degree in Clinical Neuropsychology from the University of Tennessee, Knoxville and completed her APA accredited clinical internship at Massachusetts General Hospital/Harvard Medical Center, 2010. Consequently she came to University of California, Los Angeles for her postdoctoral research training, and in 2012, she joined the Neuroimaging and Ingestive Behavior and Obesity Programs at the Oppenheimer Family Center for Neurobiology of Stress. Her research examines the influence of brain, genetics, and psychosocial factors in the underlying pathophysiology of disorders with altered interoceptive processing (obesity and functional pain disorders). As an important step towards providing powerful and sensitive biomarkers for obesity and pain disorders, Dr Gupta is dedicated to developing and testing biopsychosocial 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 brain structure and function. Her hope is that such biological readouts will bring to the forefront those groups and individuals who are at increased risk as a result of disadvantaged backgrounds and consequently altered neurobiologies.

Swapna Joshi, PhD
Post-Doctoral Scholar, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Joshi received her PhD from Center for Cellular and Molecular Biology, India. Her previous work in the USC epigenome center at University of Southern California was focused on bioinformatics and big data analysis in various cancers including breast, renal and pancreatic carcinoma. She analyzed DNA methylation data for breast and renal carcinoma data for 'The Cancer Genome Atlas' consortium projects and integrated data from various molecular platforms such as mRNA expression, miRNA, mutation, copy number and protein expression to get a big picture on the molecular events associated with the disease. These findings were published in *Nature,* where

she was one of the lead authors responsible for the epigenetic analyses. Additionally, her work on ethnic differences in the pattern and consequences of obesity identified molecular pathways that might be driving differential fat deposition between African Americans and Hispanics. Her current work is focused on molecular mechanisms of irritable bowel syndrome (IBS). Specifically, she is interested in deciphering epigenetic mechanisms of regulation of gene expression in IBS. As DNA methylation is a leading mechanism linking gene-environment interactions to long-term behavioral development, particularly in complex disorders, she is interested in studying the DNA methylation patterns associated with IBS. She has published more than 20 articles in peer-reviewed high impact journals.

Jennifer Labus, PhD
Adjunct Associate Professor, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Jennifer S Labus is an investigator and Co-director for the Neuroimaging Core in the Oppenheimer Family Center for Neurobiology of Stress at the University of California, Los Angeles. Dr. Labus graduated from Ohio University in 2013 with a PhD in Clinical Psychology and specializations in health psychology and quantitative statistics. Her research is focused on the interface of stress, pain and emotions and its influence on the role of dysregulation in the pathophysiology of common chronic pain disorders. She has unique expertise in applying advanced statistical and computational technologies to analyze multimodal imaging data. Dr. Labus's current focus lies in applying network modeling techniques such as graph theoretical analysis and multivariate pattern analysis, to integrate anatomical, structural and functional brain imaging, genetics, and clinical data to identify central endophenotypes of stress-sensitive chronic pain disorders, which will help advance new treatments. She has been the recipient of a K08 Career Development award, "Effective connectivity of central response in irritable bowel disorder", from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as well as a R03 award examining the role of altered attention and emotional arousal networks in IBS. Recently, acting as lead Co-Primary investigator she was awarded R01 funding by the National Institute of Childhood Health and Human Development (NICHD) to use brain imaging data, along with genetic, physiological and biological data, to extensively phenotype women with vulvodynia. Dr. Labus is a co-investigator on several NIH funded grants, international research collaborations, and is actively involved in mentoring graduate students and postdoctoral fellows. As a result of her work she was awarded the Master's Award in Gastroenterology in 2010 for her outstanding achievements in Basic and Clinical Digestive Sciences. Dr. Labus was recipient of the American College of Neuropsychopharmacolgy Travel Award in 2013.

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

Muriel Larauche obtained her doctorate in Pharmacology and Digestive Pathophysiology from the University Paul Sabatier, Toulouse, France in 2003. From 2003 to 2009, she held two postdoctoral positions under the respective tutelage of Dr Emeran Mayer and Dr Yvette Taché at the University of California, Los Angeles. In 2009, she got recruited by the Division of Digestive Diseases, Department of Medicine UCLA where she currently holds an Assistant Researcher position. She is an Associate Member of the CURE: Digestive Disease Research Center, Los Angeles and of the Specialized Center for Research (SCOR) for Neurovisceral Sciences and Women's Health in the Center for Neurobiology of Stress at UCLA where she also serves as Executive Board Member.

Dr Larauche has had several NIH and pharmaceutical grants for research. She is currently NIH funded (PI) to study mechanisms behind stress-related visceral sensitivity and epithelial function alterations, with an emphasis on the role of sex differences. Dr Larauche takes a multidisciplinary approach to her research and has a strong background in animal models of stress and visceral pain. Her research interests include the pathophysiology of irritable bowel syndrome (IBS), brain-gut axis interaction and sex differences in stress-induced alterations of gut epithelial, motor and sensory functions. She is author and co-author of 24 articles, 3 book chapters and several abstracts presented at national and international conferences. She has trained several undergraduate and post doctoral fellows. Dr Larauche is currently serving as member of the editorial board of Neurogastroenterology and Motility journal and World Journal of Gastrointestinal Pathophysiology. She is also a member of several scientific societies among which the American Gastroenterological Association, the American Neurogastroenterology and Motility Society and the Organization for the Study of Sex Differences. She served as member of the abstract review committee of sections of AGA for DDW and as ad hoc reviewer for the Austrian Science Fund, the Health

Research Board Ireland and the Agence Nationale pour la Recherche. She serves as a regular reviewer to several scientific journals in the fields of Neurogastroenterology, Sex Differences and Pain.

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

Dr. Mayer has a career long interest in clinical and neurobiological aspects of how the digestive system and the nervous system interact in health and disease, and his work has been continuously supported by several NIH grants. He has published over 300 peer reviewed articles (average H index 76), including 90 chapters and reviews, co-edited four books, and organized several interdisciplinary symposia in the area of visceral pain and mind body interactions. He has made seminal contributions to the characterization of physiologic alterations in patients with various chronic pain disorders, such as irritable bowel syndrome (IBS), as well as on pharmacological and non-pharmacological treatment approaches to these conditions. He is principal investigator on several grants from the National Institutes of Health including a NIDDK/ORWH funded center grant on sex-related differences in brain gut interactions, a NIDDK funded consortium grant (Multidisciplinary Approaches to Pelvic Pain, MAPP) in which he also heads a multisite neuroimaging core, and on a NIDDK funded RO1 grant on the role of the immune system and the gut microbiome on brain signatures. His research efforts during the past few years have focused on several new areas of brain gut interactions, in particular on the role of the gut microbiota and their metabolites in influencing brain structure and function, and associated behavior, and on the role of food addiction in obesity.

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

Dr. Naliboff received his PhD in Clinical Psychology from Bowling Green State University in Ohio and interned at the UCLA Neuropsychiatric Institute. During his tenure at UCLA and the VA he has served as senior psychologist in the UCLA and VA Pain Management programs and Health Psychology Consultation services as well as a VA Career Scientist. Dr. Naliboff's VA and NIH funded research has focused on psychophysiological mechanisms of stress and pain and includes studies of stress effects on the immune system, glucose regulation in diabetes, and cardiovascular variables. In the area of pain, he has utilized experimental pain procedures to study perceptual processes in chronic pain states such as chronic back pain, headache, and visceral pain. He has also studied psychosocial and personality variables in chronic pain and especially their impact on treatment choice and outcome. His work in functional gastrointestinal disorders and irritable bowel syndrome (IBS) include perceptual, autonomic, and brain imaging studies of visceral sensation, and the role of psychosocial variables in the presentation, course and treatment of IBS. A major emphasis of Dr. Naliboff's recent work is the development and evaluation of mind body therapies for both visceral and somatic pain. This includes NIH funded studies of a novel cognitive behavioral therapy for IBS, discovery of brain biomarkers associated with training in mindful meditation for IBS and post-traumatic headache, and pilot studies of Yoga for both visceral and somatic pain. He has served as a consulting editor for numerous scientific publications in psychology and medicine and on national and international committees as a grant reviewer and program consultant.

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

Dr. Pisegna is a recognized expert in the diagnosis and management of neuroendocrine tumors and acid peptic disorders. His research and clinical interests are focused on the molecular pharmacology of gastrointestinal hormones and he has lectured extensively in this area. Dr. Pisegna joined the UCLA faculty in 1996. He was previously Clinical Associate and Staff Physician at the Digestive Diseases Branch, National Institutes of Health. Dr. Pisegna completed his internal medicine training at the University of Miami/Jackson Memorial Hospital and gastroenterology fellowship at the Combined Georgetown University, Washington VA Hospital, D.C. General Hospital and National Institutes of Health. Dr. Pisegna is a member of the American Gastroenterological

Association, American College of Gastroenterology and American Society of Gastrointestinal Endoscopy. He is a Diplomate, National Board of Medical Examiners and the American Board Internal Medicine. Dr. Pisegna is chief of gastroenterology and hepatology at the VA Greater Los Angeles Healthcare System.

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

Claudia Sanmiguel is a current Fellow at the UCLA Digestive Diseases Division. She was born in Bogota, Colombia where she studied Medicine at the Pontificia Universidad Javeriana. Then she moved to Alberta, Canada where she did research on gastrointestinal motility and the use of artificial pacemakers and stimulators for the treatment of gastrointestinal disorders. Also, she was a research fellow at the Cleveland Clinic in Ohio, where she continued to do research on the use of pacemakers and electrical stimulation of the stomach for the treatment of obesity and obesity related diabetes mellitus, as well as, research in gastric electromechanical signals related to eating behavior and satiety. She continued this work at Cedars Sinai Medical Center in Los Angeles. Then, she decided to continue her medical education in USA. She did her residency in Internal Medicine at Cedars-Sinai Medical Center and now she is about to finish her training in Gastroenterology at the University of California Los Angeles. She has continued her pursue her understanding the mechanisms that regulate eating behavior in health and disease, namely obesity, and the role of the brain in interpreting and regulating those behaviors. She has published several papers in well known GI and bioengineering journals and presented her research results in North American and International meetings. She currently has NIH funding for a study on the role of brain activity and changes in eating behavior in weight loss after bariatric surgery.

Yvette Taché, PhD
Co-Director, Enteric Neuroscience Program – Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress; Director, CURE: Animal Models Core; Professor, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Dr. Taché obtained her PhD in experimental medicine and surgery from the University of Montréal, Montréal, Canada and pursued her postdoctoral training at the Salk Institute, La Jolla, California. In 1982, she joined the Division of Digestive Diseases, Department of Medicine at UCLA, where she is presently co-director of the UCLA Center of Neurobiology of Stress and Director of the Animal core, Digestive Diseases Research Center. Her laboratories conduct experimental research focused on brain-gut interactions of stress-related underlying mechanisms of gut motor dysfunction, visceral pain and postoperative ileus through funding of the National Institute of Health (NIHDDK) ,Veteran Administration (VA) Merit Award and Fox Foundation. She is the recipient of NIHDDK MERIT Award, the Distinguished Research Award in Gastrointestinal Physiology from the American Physiological Society, the Janssen Award for Basic Research in Gastrointestinal Motility, VA Research Career Scientist Award and the Outstanding American Gastroenterology Association Women in Sciences. She served on NIHDDK and VA grant review panels.

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

Dr. Kirsten Tillisch is an Associate Professor of Medicine in the Division of Digestive Diseases at the David Geffen School of Medicine at UCLA and the Chief of Integrative Medicine at the Greater Los Angeles VA. Dr. Tillisch's clinical interests include the promotion of non-pharmacological and integrative therapies for chronic disease and wellness, functional bowel disorders, and chronic pain. Her research interests include brain-gut and microbiome-gut-brain interactions, the effects of non-pharmacological therapies on chronic disease, and pharmacological treatment of irritable bowel syndrome. She is a member of the Rome IV Committee on Functional Abdominal Pain.   She has been an NIH funded researcher since 2006, utilizing neuroimaging techniques to study the physiology of brain gut interactions. She currently studies the central effects of Mindfulness Based Stress Reduction on symptoms of irritable bowel syndrome and post traumatic headache. Her recent research projects also include evaluation of the role of gut microbiota modulation on emotional processing in the brain, and assessment of neurokinin-1 receptor antagonists effects on the gut and brain in irritable bowel syndrome. She directs the Neuroimaging Program of the Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress.

Marmar Vaseghi, MD
Assistant Professor of Medicine; Director, Clinical and Translational Research - UCLA Cardiac Arrhythmia Center

Marmar Vaseghi an assistant professor of medicine and electrophysiologist as well as the director of clinical and translational research at the UCLA Cardiac Arrhythmia Center. Her research focuses on the effects of the autonomic nervous system on ventricular arrhythmias including post infarction, as well as neural remodeling involving cardiac and extra cardiac neural structures. She uses a combination of electrical mapping and imaging modalities in addition to immunohistochemistry to assess the physiological and patholophysiologic changes and effects of the sympathetic and parasympathetic nervous system on the myocardium in normal hearts and cardiomyopathy. In addition, she studies and is an investigator in clinical trials evaluating neuromdulatory therapies, such as bilateral cervicothoracic sympathectomy, as treatment option in patients with ventricular tachycardias. She is the recipient of National American Heart Association Fellow to Faculty Transition Award as well as co-investigator on NIH funded grants. She received her B.S. in biomedical engineering from Northwestern University and M.D. from Stanford University School of Medicine. She subsequently trained in internal medicine, cardiology, and electrophysiology at UCLA. She received her Masters in Clinical Research from the Biomathematics department as part of the Specialty Training and Advanced Research Program (STAR) at UCLA.

Abstracts of Posters
Basic and Translational

1.

Food Quality and Motivation: A Refined Low-Fat Diet Induces Obesity and Impairs Performance on a Progressive Ratio Schedule of Instrumental Lever Pressing in Rats

Aaron. P Blaisdell, Yan Lam Matthew Lau, Ekatherina Telminova, Boyang Fan, Hwee Cheei Lim, Cynthia D Fast, Dennis Garlick

Comparative Cognition Laboratory, Department of Psychology, UCLA

Highly processed and refined foods, commonly referred to as "junk foods", are increasingly recognized as having negative impacts on health and disease. Little is known, however, about the impact of a highly processed foods diet on cognition. Four experiments investigated the effect of a refined diet on body weight and motivation to perform instrumental lever pressing by rats. We placed one group of rats on a purified, refined foods diet (REF, Research Diets D12450B) while another group of rats were maintained on a relatively unrefined, whole foods control diet (CON, LabDiets 5001). After three months on their respective diets, the rats on the REF gained significantly more weight than rats on the CON diet, largely through increased adiposity. Rats received two sessions of instrumental lever pressing on a Progressive Ratio 3 (PR3) followed by two sessions on a PR5 schedule of reinforcement. In a PR schedule, sucrose solution (Experiments 1 and 3) or water (Experiment 2) was delivered only after completing an additional 3 (PR3) or 5 (PR5) lever presses relative to how many presses were required to earn the previous reinforcer. For example, a PR3 schedule results in delivery of reinforcement after 3 lever presses, then 6, than 9, and so on until the end of the session. PR schedules provide a very sensitive assay for motivation due to the fact that the less the motivation to work, the earlier the subject will "give up" and stop lever pressing. REF rats made significantly fewer lever presses, and exhibited dramatically lower breaking points than CON rats, for both sucrose and water reinforcement. Switching the rats' diet for 9 days (Experiment 4) had no effect on these measures. These results suggest that a refined foods diet produces a chronic reduction in motivation for instrumental performance in rats, and thus, have implications for an association between obesity and motivation.

2.

Role of Corticotropin-Releasing Hormone 2 in Mucosal Healing During Colitis

JM Hoffman, S Baritaki, JJ Ruiz, A Sideri, C Pothoulakis

Division of Digestive Diseases, UCLA.

Objective: Inflammatory Bowel Disease (IBD) is a chronic relapsing disorder that involves a defective mucosal epithelium. Corticotropin-releasing hormone (CRH) signaling affects the function of many organs, including the intestine. Activation of CRH receptor 2 (CRHR2) promotes inflammation during acute colitis but enhances mucosal repair during chronic colitis. Our aims were to 1) investigate whether modulation of CRHR2 signaling in the colonic mucosa could alter inflammation and/or restoration of the epithelial barrier and 2) test the hypothesis that IL-6/STAT3 activity in intestinal epithelial cells mediates CRHR2-dependent mucosal healing. **Methods:** Mice were treated with dextran sodium sulfate (DSS) in their drinking water (4% w/v) for 5 days. On days 6-15, mice were injected with vehicle or the CRHR2 antagonist, Astressin 2B (Ast2B; 30 μg/kg, i.p). Mice were euthanized on day 10, 13 or 15 and colons scored for histological damage and apoptosis by TUNEL staining. CRHR2-overexpressing human colonic epithelial cells (NCM460R2) and scramble negative control (EV) cells were stimulated with CRH, the CRHR2-selective ligand Urocortin 2 (Ucn2) and/or IL-6. RNA was extracted for qPCR for targets of IL-6/STAT3 signaling and wound healing pathways. Protein lysates were processed for phosphoprotein assays. A wound healing assay was used to assess healing in vitro. **Results:** Mice treated with Ast2B following DSS had more severe colitis, delayed healing and increased epithelial cell apoptosis compared to controls. Stimulation of NCM460R2 cells with IL-6 and Ucn2 increased STAT3 activity as compared to EV cells. Activation of ERK and Akt was detected in NCM460R2 cells following CRH or Ucn2. Wound healing was accelerated in NCM460R2 cells treated with IL-6 and Ucn2 as compared to EV cells. Expression of genes

promoting inflammation and re-epithelialization, STAT3 activators and downstream targets were all elevated in NCM460R2 cells following Ucn2 and IL-6, suggesting advanced healing progression. **Conclusion:** CRHR2 signaling promotes wound healing following DSS colitis in vivo and in human colonocytes in vitro. CRHR2 stimulation activates STAT3 and the upstream Raf/MEK/ERK1/2 and PI3K/Akt survival pathways, as well as genes involved in wound healing. Collectively, this suggests that CRHR2 activation promotes mucosal healing through a novel IL-6/STAT3 dependent pathway.

3.
Dipsogenic and Orexigenic Effects of Somatostatin Analogues and Cortistatin in Rats

Hiroshi Karasawa[1], Seiichi Yakabi[1], Lixin Wang[1], Jean Rivier[2], Yvette Taché[1]

[1]CURE Digestive Disease Research Center, David Geffen School of Medicin at UCLA; [2]Peptide Biology Laboratories, Salk Institute, La Jolla, CA

Background: Somatostatin (SST) is a pleiotropic neuropeptide exerting its actions through interaction with five distinct receptors sst_{1-5}. Intracerebroventricular (icv) injection of SST analogues induces orexigenic and dipsogenic effects. The orexigenic effect is shown to be mediated by sst_2 receptor. Cortistatin (CST), a neuropeptide that is encoded by a distinct gene, has structural similarity to SST and activates sst_{1-5} receptors. The effect of CST on food and water intake is not known. **Aim:** To characterize the orexigenic and dipsogenic effects of SST analogues and CST and examine whether their actions are linked with the orexin pathways. **Methods:** SST-14, CST-14, stable pan-SST agonist, ODT8-SST, selective sst_2 agonist , selective sst_2 antagonist , and selective orexin 1 receptor antagonist were injected icv to male SD rats chronically implanted with an icv guide cannula. Peptides were dissolved in saline and the selective orexin 1 receptor antagonist was dissolved in 100% dimethylsulfoxide. Water and food intake were monitored either concomitantly or separately in non-fasted and non-water deprived rats after icv injection (10 µL). **Results:** ODT8-SST, SST-14 or CST-14 (all 1 µg/rat, icv) significantly increased the first 10 min and 1 hr cumulative water intake (3.3/8.5, 4.9/5.6, and 4.0/4.8 mL/rat, respectively) compared to vehicle (0.8/2.3 mL/rat). The selective sst_2 agonist (1 µg/rat, icv) had no effect for the first 10 min while increasing the 1-hr cumulative water intake (0.7/7.2 mL/rat). The sst_2 selective antagonist (1 µg/rat, icv) significantly inhibited ODT8-SST- and CST-induced dipsogenic effect by 73%/68% and 66%/87%, respectively (1.5/4.0 and 1.9/2.6 mL/rat in 10 min/1 h), while the antagonist alone had no effect (0.7/1.7 mL/rat). Interestingly, SST-14 and CST-14 did not increase food intake even at a higher dose (3 µg/rat, icv) while ODT8-SST (1 µg/rat) showed orexigenic effect as we reported previously. Pretreatment of selective orexin 1 receptor antagonist (16 µg/rat, icv) completely blocked the orexigenic effect of ODT8-SST. **Conclusions:** SST and CST act in the brain to induce prominent dipsogenic effect dissociated from food intake and that effect is mediated at least partly by sst_2 receptor. Orexin system is possibly involved in orexigenic effect of stable pan-SST agonist, ODT8-SST via SST receptor activation.

4.
The CIC-2 Chloride Channel Agonist, Lubiprostone, Prevents Ileal Epithelial Permeability Alterations in a Murine Model of Diarrhea-Predominant Irritable Bowel Syndrome

Ganna Tolstanova[1-3], **Muriel Larauche**[1,2], Pu-Qing Yuan[1,2], Yvette Taché[1,2]

[1]Medicine, UCLA, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and CURE: Digestive Diseases Research Center, David Geffen School of Medicine at UCLA; [2]VA Greater Los Angeles Healthcare System; [3]ESC "institute of Biology" Kiev National Taras Shevchenko University, Kiev, Ukraine

Irritable bowel syndrome (IBS) is characterized by altered bowel habits and abdominal pain. Throughout their gut, patients with diarrhea-predominant IBS (IBS-D) exhibit increased permeability linked to downregulation and redistribution of several tight junction (TJ) proteins. Stress exacerbates IBS symptoms and increases intestinal permeability in both human and rodents. Corticotropin-releasing factor (CRF) via its CRF_1 receptor is a key player in the stress-related alterations of gut function. We previously established that peripheral injection of cortagine, a selective CRF_1 agonist, recapitulates IBS-D cardinal symptoms in rodents. Recent evidence suggests that lubiprostone, an agonist of the ClC-2 chloride channel approved to treat IBS with constipation, promotes repair of barrier properties. We aimed to assess whether an acute therapeutic treatment with lubiprostone could prevent the cortagine-induced alterations of murine ileal epithelial barrier. Female Balb/c mice (8-9 weeks, n=3-9)

received cortagine (30 µg/kg, 0.2 ml) intraperitoneally and 30 min later lubiprostone (3, 10 or 30 µg/kg) or vehicle (MCT, medium-chain triglyceride) *per os* (PO, 100 µl). Mice were euthanized 1, 2 and 4h after MCT and 2h after lubiprostone. Segments of ileum were collected for qPCR assays and *in vitro* permeability studies in Ussing chambers. After seromuscular stripping, mounting of tissue in the chambers and stabilization for 45 min, the short-circuit current (Isc), transepithelial electrical resistance (TER) and mucosal-to-serosal flux of 4 kDa-FITC dextran (FD4) were recorded as indices of intestinal epithelial barrier function. Cortagine increased FD4 ileal flux at 1h and 2h post-injection (0.20 ± 0.03 and 0.14 ± 0.05 respectively vs 0.08 ± 0.01 nmol/min/cm2 for vehicle, p<0.001 and p<0.05 respectively, one-way ANOVA, Dunnett's test), but did not affect the TER or Isc. Lubiprostone (30 µg/kg) prevented the cortagine-induced increase in ileal epithelial permeability (0.08 ± 0.04 vs 0.14 ± 0.05 nmol/min/cm2, p<0.05, unpaired t test) while lower doses had no effect. Lubiprostone increased the ileal Isc similarly at all doses, but did not affect the TER in cortagine-treated mice. In MCT-treated mice, cortagine did not affect TJ proteins gene expression, but exhibited a trend to increase IL1β and IL6 expression. Lubiprostone restored the basal levels of IL1β and IL6 and up-regulated occludin and JAM-A expression. These results support a protective role of lubiprostone (30 µg/kg PO) in a mouse model of IBS-D like symptoms with increased ileal epithelial permeability, and may represent a potential new therapeutic venue for IBS-D patients.

5.
Repeated Water Avoidance Stress Induces Sex and Regional-Dependent Alterations in Rats Colonic Epithelial Function

M Larauche[1, 2], G Tolstanova[1, 2], M Biraud[1, 2], M Million[1, 2], Y Taché[1, 2]

[1]*Medicine, UCLA, Oppenheimer Family Center for Neurobiology of Stress and CURE:Digestive Diseases Research Center, David Geffen School of Medicine at UCLA;* [2]*VA Greater Los Angeles Healthcare System*

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. Studies limited to male rodents showed that chronic stress increases colonic secretion and paracellular permeability, the latter being associated with visceral hyperalgesia. **Aim:** To establish potential sex differences in the colonic epithelial response to repeated water avoidance stress (rWAS). **Methods:** Male and female Wistar rats (7-11 wks, n=4/group) naïve or exposed to rWAS (1 h/day, 4 days) were euthanized 5 h 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) and short circuit current (Isc) were measured and the mucosal-to-serosal flux of 4 kDa-FITC dextran (FD4) was recorded as an index of intestinal epithelial barrier function. Data are mean ± SEM, with 2-3 tissues averaged per rat, and were analyzed using unpaired *t* test. **Results:** In the pC, rWAS increased the Isc in female rats (75.9±16.0 vs 26.0±1.3 µA/cm^2, p<0.05) while having no effect on Isc in males (45.0±15.3 vs 33.7±4.7 µA/cm^2, p>0.05). In the dC, both male and female rats displayed an increase in Isc following rWAS (60.8±9.2 vs 28.7±3.6 µA/cm^2, p<0.05 and 79.0±11.5 vs 20.0±2.9 µA/cm^2, p<0.01, respectively). Females, but not males exhibited an increase in G exclusively in the pC following rWAS (16.3±1.1 vs 11.8±1.2 mS/cm^2, p<0.05). In dC, G was not affected by rWAS in either sex. The FD4 flux was increased in both pC (3.2 ± 0.2 vs 0.8 ± 0.2 nmol/h/cm^2, p<0.001 and 2.9 ± 0.3 vs 2.0 ± 0.4 nmol/h/cm^2, p=0.0506, respectively) and dC (2.2 ± 0.3 vs 0.9 ± 0.3 nmol/h/cm^2 and 2.7 ± 0.3 vs 1.3 ± 0.2 nmol/h/cm^2, respectively, p<0.05 each) of male and female rats. **Conclusions:** Female rats exhibit an increased susceptibility to develop epithelial function disturbances in pC during repeated psychological stress compared to male rats. This altered colonic response may contribute to the greater prevalence of IBS symptoms in women.

6.

Colonic MicroRNA-133α Promotes Neurotensin-Associated Proinflammatory Responses in Human Colonocytes and Experimental Colitis

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Background and Aims: MicroRNAs (miRNAs) are short non-coding RNAs involved in different pathophysiological functions at the post-transcriptional level. Neurotensin (NTS)/neurotensin receptor 1 (NTSR1) interactions mediate intestinal inflammation and proliferation *in vitro* and *in vivo*. We have recently shown that NTS exposure to NTSR1-expressing human colonic NCM460 epithelial cells (NCM460-NTSR1) induces differential expression of miRNAs (Gastroenterology 2011;141:1749) and NTS-modulated miR-133α expression regulates the expression of its downstream target aftiphilin (AFPTH) (CURE2013). Here we elucidated the mechanism by which miR-133α regulates NTS signaling *in vitro*, and studied the functional consequences of this response in colitis. **Methods:** NTS/miR-133α -regulated proinflammatory cytokine production in NCM460-NTSR1 cells and colon tissues was examined by qPCR and Bio-Plex Pro Human Cytokine Assay. Acute colonic inflammation was induced by intracolonic administration of TNBS (5 mg/kg, 48 h). Expression of miR-133α in the colon was inhibited by intracolonic administration of anti-sense (as)-miR-133α (2 doses, every two days) before TNBS treatment. The degree of inflammation was evaluated on distal colon segments stained with H&E. **Results:** MiR-133α overexpression in NCM460-NTSR1 cells increased transcription of IL-8, IL-1β and TNF-α, while its knock-down attenuated NTS-induced IL-8 and IL-6 transcription ($P<0.01$). Bio-plex cytokine assays showed that NTS/miR-133α/AFTPH interactions are directly involved in the production of IL-1β ($P<0.05$). MiR-133α knock-down in mouse colon reduced colonic cxcl1, lcn2 and TNF-α expression ($P<0.05$) and neutrophil infiltration ($P<0.05$) in response to intracolonic TNBS administration. MiR-133α levels we increased (15-times, p<0.0001) during TNBS-induced colitis. MiR-133α knock-down in vivo also improved mucosal integrity ($P<0.05$) and overall histological score ($P<0.05$), supported by increased expression of the colonic epithelial cell marker, krt20 ($P<0.01$). Importantly, AFTPH transcription levels were significantly lower (P=0.0104) while miR-133α levels were up-regulated in colon tissues from patients with ulcerative colitis (n=22), compared to control tissues (n-21). **Conclusions:** miR-133α/AFTPH interactions regulate NTS-stimulated proinflammatory response in human colonic epithelial cells. Silencing of miR-133α in the colon reduces cytokine expression and histologic damage and inflammation in mouse colitis. These results suggest that miR-133α/AFTPH interactions promote NTS-induced proinflammatory responses in the colonic mucosa. Targeting of miR-133α in the colon may represent a novel form for treatment in Inflammatory Bowel Disease.

7.

NMDA Receptors in Primary Afferents Are Potentiated by BDNF Released by Microglia during the Induction of Neuropathic Pain

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We previously found that BDNF induces the activating phosphorylation of the NR2B subunit of NMDA receptors in primary afferents, increasing NMDA-induced neurokinin-1 receptor (NK1R) internalization, a measure of substance P release. Since spinal cord microglia release BDNF during the onset of neuropathic pain, we hypothesized that these NMDA receptors become potentiated after nerve injury. To confirm this, we gave rats chronic constriction injury (CCI) of the sciatic nerve and intrathecal NMDA (10 nmol, with 10 nmol D-Ser) at various times thereafter. Measures of hind paw withdrawal to von Frey hairs confirmed that allodynia developed during the first two days after CCI. Ipsilaterally to CCI, there was a marked increase in NMDA-induced NK1R internalization that peaked 6 hr after CCI and lasted 3 days. Contralaterally, NK1R internalization increased in days 2 and 3 to values similar to the ipsilateral side. Intrathecal saline after CCI or intrathecal NMDA after sham surgery resulted in negligible NK1R internalization, showing that substance P release required both NMDA

receptor activation and nerve injury. To investigate the signals involved in NMDA receptor potentiation, rats were given microglia inhibitors (200 nmol minocycline, 1 nmol fluorocitrate or 10 μg propentofylline), the BDNF scavenger trkB-Fc (10 μg), the trkB antagonist ANA-12 (100 nmol), the Src family kinase inhibitor PP2 (10 nmol) or saline. These compounds were injected intrathecally twice: immediately after CCI and 3 hr later; followed by intrathecal NMDA 6 hr after CCI. All of the compounds inhibited NMDA-induced NK1R internalization. We also determined whether activation of microglia with lipopolysaccharide (LPS) increases NMDA- induced NK1R internalization. We gave rats intrathecal LPS (2 μg) or saline twice, 24 hr apart; and NMDA or saline 6 hr after the second injection. LPS induced microglia activation, measured as staining for the microglia marker Iba-1 in the central dorsal horn. NK1R internalization was high when NMDA was given after LPS, but not when NMDA was given after saline, when LPS was followed by saline, or in the saline-saline controls. NMDA-induced NK1R internalization peaked 6 hr after LPS and disappeared by 24 hr. The increase in NMDA-induced NK1R internalization produced by LPS was decreased by trkB receptor antagonist ANA-12, the BDNF scavenger trkB-Fc or the Src family kinase inhibitor PP2. Therefore, NMDA receptors in primary afferent terminals are potentiated during the induction of neuropathic pain as the result of BDNF release from microglia, activation of trkB receptors and phosphorylation of the NR2B subunit by a Src family kinase.
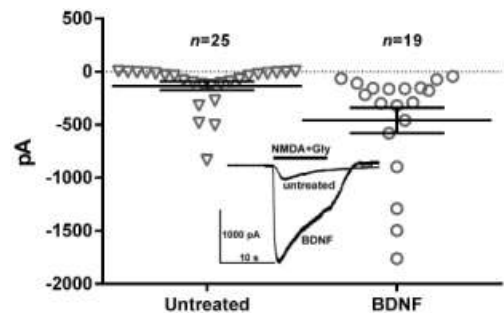
8.

BDNF Increases NMDA Receptor Currents in Primary Afferent Neurons by Inducing Phosphorylation of Tyr[1472] of the NR2B Subunit

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NMDA receptors are present in the central and peripheral terminals of primary afferent neurons. Previously, we found that the ability of NMDA to induce substance P release from the central terminals of primary afferents was markedly increased by BDNF. Using dorsal root ganglion (DRG) neurons from adult rats cultured for 2-3 days, we investigated whether BDNF increased NMDA receptor currents, and induced the phosphorylation in Tyr1[472] of the NR2B subunit, which is known to increase NMDA receptor activity. Prior to whole cell patch- clamp recording, DRG neurons were left untreated or were pre-treated with BDNF (30 ng/ml) for 1-2 hr. Once the cells had stabilized at a holding potential of -70 mV, NMDA (250 μM) and glycine (10 μM) were applied for 10 s by pressure ejection and the peak current measured. BDNF increased the NMDA/Gly induced inward current from -149 ± 45 pA to -459 ± 119 pA (p = 0.0168, t-test, Figure). There was also an increase in the number of cells that responded to NMDA/Gly above 50 pA: untreated, 50%, n = 25; BDNF, 95%, n = 19 (p = 0.001, Fisher's exact test). There was no difference in the size of the cells recorded as assessed from cell capacitance (untreated: 41 ± 4 pF, BDNF: 49 ± 5 pF). To determine if BDNF increases tyrosine phosphorylation of the NR2B subunit, cultured DRG neurons were left untreated or treated with 20 ng/ml BDNF for 1 hr, then harvested and protein extracts prepared for electrophoresis. Western blots were first probed with an antibody to phospho-Tyr[1472]-NR2B, then stripped and reprobed with antibodies to total NR2B and ß-actin. Although there was NR2B phosphorylation in control cultures, BDNF caused a 2.1 ± 0.4-fold increase in phospho-NR2B (p < 0.008; t-test). Therefore, BDNF increases NMDA receptor currents in primary afferents by inducing the phosphorylation of Tyr[1472] of the NR2B subunit. In related experiments that measured NMDA-induced substance P release, we found that this phosphorylation is mediated by activation of trkB receptors and a Src family kinase. The potentiation of NMDA receptors in primary afferents by BDNF may contribute to neuropathic/chronic pain.

9.

Low Brain Penetrant Cannabinoid Receptor Agonists for the Treatment of Cisplatin Induced Peripheral Neuropathy

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Painful peripheral neuropathy as a consequence of cancer chemotherapy is a severe and dose limiting side effect associated with the use of antineoplastic agents such as cisplatin, taxanes and vinca alkaloids. Current medications for pain alleviation often lack efficacy and exhibit undesirable side effects. Preclinical studies have demonstrated the analgesic effectiveness of cannabinoids (CB) in the treatment of chemotherapy induced peripheral neuropathy (CIPN). A major impediment to the widespread use of CB based analgesics is their central nervous system (CNS) mediated psychotropic side effects which can potentially be circumvented by the development of low brain penetrant cannabinoid receptor (CBR) agonists. We recently succeed in the development of several such compounds which exhibited potent effects in alleviating chronic inflammatory and neuropathic pain symptoms without CNS side effects (Spigelman et al, 4th International Congress on Neuropathic Pain, 2013). Here we examined one of these compounds (DouleuRx) for effectiveness in alleviating the painful symptoms of mechanical and cold allodynia in a rat model of CIPN. Oral administration of DouleuRx dose-dependently suppressed mechanical and cold allodynia symptoms with complete symptom suppression at 3 mg/kg. Daily oral administration at 1 mg/kg consecutively for two weeks resulted in similar daily suppression of mechanical allodynia implicating little, if any, tolerance development. Intraplantar injection (0.25 mg/kg) completely suppressed CIPN symptoms, suggesting peripheral sensory nerve terminals as the main sites of anti-allodynic action. DouleuRx co-administration with specific CB1R or CB2R blockers revealed mainly CB1R contribution to its analgesic effects. CNS side effects assays compared the brain permeant CB1R agonist HU-210 at doses that alleviate neuropathy symptoms to DouleuRx and vehicle. While HU-210 exhibited strong CNS side effects at systemic doses that relieve neuropathy symptoms, DouleuRx showed complete lack of side effects in the assays that test for catalepsy, hypothermia and motor incoordination. The potency, peripheral selectivity, in vivo efficacy, and absence of CNS side effects of this novel class of CBR agonists point to their potential as a viable treatment for CIPN.

10.

Corticotropin-Releasing Factor (CRF) Peptides Modulates Rat Colonic Neuronal Tau Phosphorylation: Differential Role of CRF Receptors

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Background: Stress or Corticotropin releasing factor (CRF) causes tau (TAU) phosphorylation in the mouse brain, along with altered behavioral responses, though CRF_1 receptor activation (PNAS, 2012: 109(16):6277-82). The gastrointestinal tract secretomotor response is highly modulated by stress and CRF. Whether CRF affects enteric TAU and whether enteric neuronal TAU modulation plays role in the gastrointestinal tract responses to stress or CRF are not known. **Aim:** determine the effects of selective activation of CRF receptors on rat colon myneteric (RCM) and dorsal root ganglia (DRG) primary neurons TAU activation 2) the colonic motor response of Tau-overexpressing (Tau-OE) mice to acute stress. **Methods:** RCM and L6-S1 DRG primary neurons were treated with non-selective CRF_1 and $_2$ receptor agonists (CRF, urocortin 1 (Ucn1)) or selective CRF_2 receptor agonist (Ucn2) for 30 min (10 or 100 nM) and pTAU probed by western blot. Rat colon sections were processed for immunostaining of Tau. Human TauP[301L] overexpressing and wild-type (WT) mice were exposed to 1-hour novel environment stress and cumulative Fecal Pellet Output (FPO) at 5, 15, 30, 45 and 60 min was monitored. The overexpression of human Tau in the Tau-OE mice was confirmed by western blotting. **Results:** Rat colon primary myenteric neurons (RCPMN) have abundant Tau. RCPMN have constitutively active pTau that is suppressed by selective CRF_2 receptor activation but not by the non-selective CRF receptor ligand, CRF

increased pTau in rat DRG primary neurons while Ucn2 did not. Compared to WT, Tau-OE mice have 2-4X increased total Tau mRNA and pTAU; have increased defecation (>60%) response to mild novel environment stress and display altered ileal and colonic CRF_2 receptor expression. **Conclusion:** Selective activation of CRF_2 receptors in RCPMN suppresses Tau-phosphorylation. Similarly CRF but not Ucn2 induce pTau in rat L6-S1 DRG primary neurons. The differential effect of CRF receptors on rat colon myenteric and DRG neurons TAU coupled with the altered colonic motor response to stress in the mice that express phospho TAU in the intestine suggest that stress or CRF-induced colonic sensorimotor responses may involve modulation of TAU activity in the spinal and colonic neurons.

11.
Corticosterone Is Necessary but Not Sufficient to Drive AMPA Receptor Changes in the Amygdala that Support Stress-Enhanced Fear Learning

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Severe stress strongly potentiates future learning. These experiments assessed the contributions of corticosterone (CORT) on basolateral amygdala (BLA) glutamatergic receptor changes in stress-enhanced fear learning (SEFL). First, the CORT synthesis inhibitor metyrapone was administered before 15 shocks in context A. Animals were given 1 shock in a novel context and tested for freezing. Results show that prior stress with 15 shocks enhanced conditioning to the single shock context, indicating SEFL, and metyrapone administration before this stress blocked SEFL. CORT was then co-administered with metyrapone prior to stress to determine if metyrapone specifically acts via CORT. Pre-stress CORT injections rescued the freezing response from the drug; however, CORT without stress did not produce SEFL. Next, the BLA was inactivated with muscimol before or after stress to determine its role in SEFL. Inactivation before but not after stress eliminated SEFL. Then, western blots of BLA tissue were done to analyze glutamatergic receptor subunit changes in shocked- and metyrapone-treated rats. BLA expression of the AMPA receptor subunit, glutamate receptor 1 (GluA1), was significantly increased in shocked rats versus controls, but this increase was attenuated with metyrapone. Lastly, intra-BLA infusions of the AMPA receptor antagonist, NBQX, were administered after the stress to determine if AMPA receptor blockade prevented the sensitized fear response. NBQX attenuated freezing, which was rescued 24 hours later when the drug was no longer on board. These data indicate that both CORT and BLA activity are necessary for SEFL initiation. Moreover, SEFL expression requires CORT-dependent increased GluA1 expression in the BLA.

12.
IBD-Associated Effects of Fat-Derived Mediators in the Regulation of Adiponectin Receptor 1 (AdipoR1) in Human Colonocytes

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Background: In patients with Inflammatory Bowel Disease (IBD) [Ulcerative Colitis (UC) and Crohn's Disease (CD)], the affected intestine is in immediate proximity to the intra-abdominal fat depots. Inflamed adipose tissue wrapping around intestinal lesions in CD (creeping fat) is well documented during surgery. Adiponectin is implicated in the induction of morphological changes in "creeping fat" adipocytes, while its levels are increased in the serum of IBD patients. In previous reports we have demonstrated differential mediator release from preadipocytes isolated from IBD patients compared to controls and the capacity of these mediators to induce disease-dependent responses in human colonocytes. Our goal here was to investigate the patterns of adipokines

from whole fat of IBD patients compared to controls and evaluate the effects of these mediators on colonocyte responses. **Methods:** Mesenteric fat from CD and UC patients and non-IBD patients (controls), (n=8-11 patients/group), males and females, were used for the determination of adipokine release levels. For controls fat tissue resected during gynecological and adenocarcinoma operations or vascular surgeries were used. Preadipocytes and mature adipocytes were also isolated and used for our studies. Total protein and RNA were isolated for measurements of adipokine protein release and receptor mRNA expression. In addition, culture media were collected from preadipocytes and whole mesenteric fat tissue and added to cultured human NCM460 colonocytes. RNA was collected after 24 hrs for AdipoR expression measurements. **Results:** We show a disease-dependent release of adipokines from the mesenteric fat tissue of IBD patients compared to controls. In particular we observed significant increases in the release of adiponectin, leptin, TNFα, and IL-1β in UC (p<0.05) and of adiponectin, TNFα, IL-1β and IL-8 in CD (p<0.05) patient samples while resistin release was decreased only in CD patient samples (p=0.068). This is in agreement with studies showing increased circulating levels of the majority of these adipokines in IBD. Adiponectin receptor (AdipoR1 & R2) mRNA expression was decreased in the mesenteric fat of both UC and CD patients compared to controls, while they were significantly increased in colonic biopsies of IBD patients. AdipoR1 levels decrease significantly after exposure of human colonocytes to conditioned media from mesenteric fat isolated from IBD patients. **Conclusion:** Our data support the concept of IBD-type specific changes in adipokine release from mesenteric fat. We also demonstrate a differential IBD-associated regulation of adiponectin receptors in the fat and the intestine, supporting a role of adipose tissue-derived mediators in this response.

13.

Vasoactive Intestinal Peptide Is Involved in Intraperitoneal Corticotropin-Releasing Factor Induced Diarrhea in Rats

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Background: Most of the patients with irritable bowel syndrome (IBS) experience sudden diarrhea but the mechanism is not clear. Stress contributes to IBS, and corticotropin-releasing factor (CRF) plays a role as shown by intraperitoneal (IP) CRF induces rapid onset of defecation and diarrhea in rats. Recent reports indicate that IBS patients have higher circulating levels of vasoactive intestinal peptide (VIP) that can influence intestinal secretory function. **Aim**: To investigate whether VIP mediates IP CRF stimulatory effect on defecation and diarrhea. **Methods**: In male SD rats, the VIP antagonist, [4Cl-D-Phe[6],Leu[17]]VIP or vehicle was injected IP at same time as IP CRF or vehicle. Fecal pellet output and diarrhea were monitored every 15 min for 1 h, then the terminal ileum and proximal colon were collected for whole mount preparations, which were processed for double immunolabeling of Fos and VIP. Another cohort of rats was sacrificed at 15 min after IP CRF or vehicle. Plasma and ileum levels of VIP were measured. **Results:** Compared with vehicle+vehicle, vehicle+CRF stimulated fecal output by 2.7 folds and induced diarrhea with a rapid onset (15 min). The VIP antagonist completely prevented the fecal output and occurrence of diarrhea. CRF increased Fos expression in the submucosal plexus of the terminal ileum (2.1±0.4 vs. 0.1±0.0 cells/ganglion in vehicle,, p<0.01) and myenteric plexus of the proximal colon (17.5±2.4 vs. 0.4±0.3 cells/ganglion in vehicle, p<0.01) with few Fos neurons in the ileal myenteric and proximal colon submucosal plexus. Fos expression induced by CRF was co-localized in VIP positive neurons (92.2%) in the ileum submucosal plexus, but not in the proximal colon myenteric plexus. The VIP antagonist inhibited Fos induction by CRF in both the ileal submucosal plexus and the proximal colon myenteric plexus. The Fos-positive cells in the ileal submucosal plexus were highly correlated to diarrhea and pellets as well. There was no significant difference in VIP levels in the plasma and in the terminal ileum between CRF and vehicle at 15 min post injection. **Conclusions**: Activation of VIP containing submucosal neurons in the ileum by IP CRF plays an important role in CRF-induced diarrhea and increase in fecal output. The therapeutic application in stress-related onset of diarrhea in IBS patients warrants further investigation.

14.

Abdominal Surgery Induced Gastric Ileus and Activation of M1 Macrophages in the Gastric Myenteric Plexus: Prevention by Central Vagal Activation in Rats

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Background: The inflammation induced by abdominal surgery (AS) and its role in ileus have been reported so far mainly in the intestine while rarely studied in the stomach. Resident macrophages within the intestinal muscularis contribute to both the initiation and the resolution of inflammation through activations of M1 and M2 phenotypes secreting pro- and anti-inflammatory cytokines respectively. Central vagal stimulation induced by intracisternal (ic) injection of a stable thyrotropin-releasing hormone analog, RX-77368 activates gastric myenteric neurons and prevents postoperative gastric ileus (POGI) in rats. **Aims:** To investigate whether AS induces gastric inflammation by altering the activation states of macrophages in the myenteric plexus (MP) and whether central vagal stimulation prevents this response. **Methods:** Fasted SD male rats (271-293g, 5-7/group) received ic injection of RX77368 (50 ng/rat) or vehicle (saline). 1 h later, AS consisting of a midline celiotomy, 5 min cecum palpation and 8 min small intestinal manipulation was performed while control rats (sham group) received anesthesia alone. Gastric emptying (GE) was measured and the gastric corpus was harvested at 6 h post AS. Whole-mount preparations of muscularis externa (ME) and longitudinal muscle/MP (LMMP) were prepared for myeloperoxidase (MPO) staining and double immunostaining of MHCII (a marker for M1)/CD206 and CD163 (markers for M2), CD163/peripheral acetylcholine transferase (pChAT, a marker for enteric cholinergic neurons) and Cuprolinic blue (a neuronal conterstaining). Real time PCR was carried out to detect the expression of pChAT, vesicular acetylcholine transporter (VAChT), IL-1β, TNFα and IL-10 in the submucosal plus muscle layer (S+M). **Results:** M1 and M2 macrophages were labeled distinctively by marker antibodies in LMMP of sham rats. M1 was distributed on or around ganglia in a highly variable or patchy pattern while M2 often outlined the perimeter of ganglia and its processes were closed and conformed to the surface of the cholinergic neurons. AS induced a significant increase in the number of M1 cells (2.2-fold) and the gene expression of IL1β and TNFα (1.6- and 1.3-fold respectively) along with a significant infiltration of neutrophils labeled by MPO in the ME (9.5-fold) and delayed GE to 28% of that of sham group at 6 h post AS. Ic RX77368 significantly upregulated pChAT and VAChT gene expression in the S+M, abolished the above increases and prevented the delayed GE induced by AS. No significant changes were observed in M2 cell number and IL-10 expression after AS or ic RX77368. **Conclusions:** AS increases M1 macrophage and expression of proinflammatory cytokines leading to inflammation in the gastric LMMP and delayed GE. Central vagal activation prevents POGI probably through its anti-inflammatory action by deactivation of M1 macrophages in the gastric MP.

Abstracts of Posters
Clinical

15.

Sexual and Gender Identity Disorder as a Risk Factor for Diabetes Mellitus Type 2

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A recent study demonstrated that diabetes screening is not cost-effective in the general population[1], but roughly 25% of US diabetics were undiagnosed as of 2011. Diabetes can be prevented in high-risk individuals and reverted in recently diagnosed diabetics, with interventions such as weight loss and lifestyle changes[2] [3,4,5]. This makes targeted diabetes screening an issue not just of treatment, but also of prevention.

Many risk factors are well-established in diabetes, such as hypertension, obesity, and age[6]. Although the relationship between sexual orientation, gender, and weight has been investigated[7], the role of sexual identity with diabetes has not. Diabetes risk scores assess risk using a limited number of covariates, but the electronic health record (EHR) has now allowed novel identification of diabetes risk factors because of the breadth of information it contains.

Using EHRs from an unselected population of US patients in a cross-sectional study (n=9,948) from 1,137 practice sites, we used logistic regression to predict current diabetes mellitus type 2 (DM2) status with an EHR model (medication history, co-morbidities, laboratory tests and transcripts). We compared this to a restricted model (BMI, age, smoking, gender, and hypertension) as a reference standard using a Chi-square test.

Using a patient's medical history for predicting DM2 status was superior to using basic covariates alone (p<0.005) on the general population. In additional to traditional risk factors, we identified increased risk for diabetes associated with sexual and gender identity disorders (ICD9 302.X) (p<0.005). This risk factor was significant while holding constant the effect of age, gender, BMI and all other covariates.

The association of sexual and gender identity with diabetes could be due to many factors, such as hormonal treatment or stress. More research is needed to understand this relationship in this previously unidentified at-risk population. Furthermore, this also suggests that the transgender community could benefit from targeted screening. The EHR's ability to nominate novel risk factors for DM2 that could lead to better understanding of the disease and its comorbidities, and could help dissociate the contributing roles of gender and gender identity in metabolic syndrome.

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16.

A Fronto-Insular Based Intrinsic Brain Network Is Associated with the Tellegan Absorption Scale

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Background: The Tellegan Absorption Scale (TAS) is a commonly used questionnaire to assess the personality trait of absorption. The neural correlates of absorption are not known. In a sample of women with chronic visceral pain (irritable bowel syndrome, IBS), we assessed the role of absorption in resting state brain connectivity. We hypothesized that absorption may be related to a fronto-insular based brain network, which has been shown to be involved in executive function, affective, and interoceptive processes. In addition, we assessed the role of absorption in the severity of IBS symptoms. **Aims:** 1) To demonstrate the relationship between absorption and the fronto-insular resting state network (FI-RSN) function. **Methods:** 30 female Rome III positive IBS subjects were referred by primary care physicians in the area of Linkoping University Hospital, Sweden. Absorption was measured using the Tellegan Absorption Scale (TAS). IBS symptoms were measured using the IBS symptom severity score (IBS-SSS). Subjects underwent a 10-minute resting fMRI on a 1.5 Tesla scanner. Data was preprocessed and smoothed using a 5mm Gaussian kernel using SPM8. GIFT v2.0a was used to perform the independent components analysis with the Infomax algorithm. The component correlating to the fronto-insular network was identified using visual inspection and the template from Laird et al(1). Multiple regressions were implemented in SPM8 using the FI-RSN maps and TAS scores to perform brain-absorption correlations. **Results:** The 30 subjects scored an average of 16.17 on the TAS (SD=8.35). The FIRSN was well correlated to the Laird template (R= 0.4569). While TAS did not correlate with IBS-SSS, regions within the FI-RSN correlated significantly with both IBS-SSS and TAS scores. IBS-SSS showed a significant correlation to FI-RSN in the anterior cingulate cortex at 0, 28, 24 (T=3.41, p<.001, k=35261 , Z= 12.38). TAS showed a significant correlation to the FI-RSN in the anterior insula at 34, 12, 6 (T=3.41, p=0.026, k=8, Z=3.99) and the thalamus at 20, -18, 10 (T=3.41, p=0.048, k=8, Z=3.79). **Conclusions:** Absorption shows strong correlations with multiple regions of the fronto-insular brain network, suggesting that this trait reflects aspects of the central integrative processing of interoceptive function. Absorption does not appear to play a role in the severity of IBS symptoms.

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17.

Altered Resting State and Functional Connectivity between the Nucleus Accumbens and Reward-based Regions in Overweight and Obese Women

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Background and Aims: Neuroimaging studies in obese subjects have identified abnormal activation of central reward circuits, including the nucleus accumbens (NAcc), by food related stimuli. We aimed to examine if subjects with elevated body mass index (BMI) show structural, and resting state functional and connectivity alterations within regions of the central reward network, in the absence of any food stimulus.
Methods: 50 healthy, premenopausal women, 19 overweight and obese (high BMI=26-38 kg/m^2) and 31 lean (BMI=19-25 kg/m^2) were studied. Structural and resting state functional scans were collected using a Siemens Allegra 3T magnetic resonance imaging (MRI) scanner. Group differences were examined in grey matter volume (GMV) of the NAcc, oscillation dynamics of intrinsic brain activity, and functional connectivity of the NAcc to regions within the reward network. **Results:** GMV of left NAcc was significantly greater in the high BMI group than in the lean group (p=0.031). Altered frequency distributions were observed in women with high BMI compared to lean in the left NAcc, right and left anterior cingulate cortex (ACC) and ventro-medial prefrontal cortex (vmPFC). Compared to lean, high BMI individuals had greater connectivity of the left NAcc with left and right ACC and right

vmPFC in specific frequency bands. **Conclusions:** Overweight and obese women show regional alterations in spontaneous resting state oscillations of key regions of the central reward system, increased connectivity between these regions, and increased GMV in the left NAcc. This is the first demonstration of reward network alterations in obese subjects in the absence of food related stimuli, and may represent a biomarker of obesity.

18.
Iyengar Yoga for Adolescents and Young Adults with Irritable Bowel Syndrome (IBS): A Randomized Waitlist Study

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Irritable bowel syndrome (IBS) is a chronic, disabling condition that greatly compromises patient functioning. The primary aim of this study was to assess the impact of a 6-week twice/week Iyengar yoga (IY) program on IBS symptoms in adolescents and young adults (YA) with IBS compared to a usual-care waitlist control group. Assessments of symptoms, global improvement, pain, health-related quality of life, psychological distress, functional disability, fatigue and sleep were collected pre and post treatment. Weekly ratings of pain, IBS symptoms and global improvement were also recorded until 2 month follow-up. A total of 51 participants completed the intervention (yoga = 29; usual-care waitlist = 22). Baseline attrition was 24%. On average, the yoga group attended 75% of classes. Analyses were divided by age-group. Relative to controls, adolescents (14-17 years) assigned to yoga reported significantly improved physical functioning while YA (18-26 years) assigned to yoga reported significantly improved IBS symptoms, global improvement, disability, psychological distress, sleep quality, and fatigue. Although abdominal pain intensity did not statistically improve, 30% of adolescents and 46% of YA reported a minimally clinically significant reduction in pain following yoga, and one third of YA reported clinically significant levels of global symptom improvement. Analysis of the uncontrolled effects and maintenance of treatment effects for adolescents revealed global improvement immediately post-yoga that was not maintained at follow-up and for YA, improvements in global improvement, worst pain, constipation, and nausea; only global improvement, worst pain and nausea maintained at the 2 month follow-up. The findings suggest that a brief IY intervention is a feasible and safe adjunctive treatment for young people with IBS, leading to benefits in a number of IBS specific and general functioning domains for YA. The age-specific results suggest that yoga interventions may be most fruitful when developmentally tailored.

19.
Omega-3 Fatty Acids and Vitamin D3 In Vitro and Smartfish Drink In Vivo Attenuate Inflammation and Improve Amyloid-Beta Phagocytosis in Patients with Alzheimer Disease

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Background: Alzheimer disease (AD) patients have abnormal phagocytosis of Aβ 1-42, which is improved by docosahexaenoic acid (DHA) in vitro. DHA and eicosapentaenoic acid (EPA) are the precursors of the anti-inflammatory lipid mediators resolvins and maresins that participate in the resolution of inflammation. Resolvins and maresins are produced in vivo through transcellular synthesis by macrophages. **Objective:** To clarify the mechanisms of omega3 supplementation in the immune system of AD patients. **Methods: (a)** Daily supplementation of AD patients with Smartfish drink (200 ml) providing per day: 1,000 mg EPA and 1,000 mg DHA (stabilized against oxidation by botanical additives (pomegranate, chookberry and transresveratrol)), 10 μg vitamin D3, 3.8 mg vitamin E, and other components (150 kcal). **(b)** Testing of phagocytosis of Aβ1-42 by primary macrophages of AD and ALS patients and controls. **(c)** RT PCR mRNA analysis of inflammatory gene transcription in PBMCs. **(d)** ELISA of cytokines in the blood. **Results: In vitro results -** Peripheral blood-derived macrophages of AD patients are almost universally defective in phagocytosis of Aβ 1-42. RvD1 promotes Aβ1-42 phagocytosis by signaling through chemokine receptor 32. Inflammatory gene (such as IL1α/β) transcription in AD patients classified in Group 1 is low but it is high in patients classified in Group 2. RvD1 up regulates IL1α/β in Group 1 patients, whereas it down regulates IL1α/β in Group 2 patients. **In vivo results -** Nutritional supplementation with Smartfish drink corrected defective Aβ 1-42 phagocytosis in Group 1 AD patients. In Group

1 (low inflammatory transcription), IL1α/β and other gene transcription was increased during Smartfish supplementation. In Group 2 (high inflammatory transcription), IL1α/β and most other inflammatory gene transcription was decreased during Smartfish supplementation. Antiinflammatory lipid mediators produced by macrophages were increased during supplementation. **Conclusions:** Omega 3 fatty acids improve the clearance of Abeta by macrophages of AD patients in vitro and also in vivo when added as nutritional supplements in form of the Smartfish drink. Nutritional supplementation of patients with Alzheimer disease with the Smartfish drink may improve the immune system of AD patients.

20.
Morphological Imaging-Based Brain Signatures Discriminate Overweight from Lean Subjects: Examining Central Mechanisms within the Reward Network

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Background: Behavioral and neuroimaging based observations have identified similarities between brain mechanisms involved in maladaptive obesity-related ingestive behaviors and addictive behaviors, resulting in the concept of food addiction. These studies have demonstrated that structural alterations in key regions of an extended reward network are linked to increased food related behaviors in obesity. **Aim:** To apply multivariate pattern analysis/recognition methods from machine-based learning approaches to identify obesity related structural alterations. **Hypothesis:** Data driven morphological brain signatures can discriminate overweight from lean healthy control subjects. **Methods:** Structural brain images were obtained from 325 male and female healthy control subjects (159 overweight subjects). The UCLA Laboratory of Neuroimaging (LONI) pipeline was used for image preprocessing, volumetric, shape analysis, and cortical thickness analysis using the LONI probabilistic brain atlas (LBPA 40) and the ICBM (International Consortium for Brain Mapping) atlas, yielding 56 regions. For each cortical region, measures of gray matter (GM) morphometry (volume, mean curvature, surface area and cortical thickness) were computed. Each subjects' structural values were entered as a data matrix into a Sparse Partial Least Square-Discrimination Analysis (sPLS-DA) to examine whether the morphological measures can distinguish overweight from lean individuals. **Results:** The classification algorithm indicated that two multivariate brain signatures comprising 20 regions each achieved 76% accuracy in discriminating overweight from lean individuals (*Figure 1*), based on 10 fold cross-validation performed 10 times. Both signatures were primarily comprised of GM reductions in hippocampus, parietal (precuneus, postcentral gyrus), and temporal regions, and GM increases in insular, brainstem, frontal and occipital regions in overweight compared to lean. The two signatures accounted for 68% of the variance in the data set, with the first component explaining 63% of the variance and the second component explaining 5% of the variance. Binary classification measures included sensitivity at 76%, specificity at 92%, negative predictive value at 86%, and positive predictive value at 85%. **Conclusions:** 1. Obesity and overweight in healthy subjects are associated with structural brain changes. 2. Classification algorithms based on the morphometry of regional brain structure alone can identify specific targets for future mechanistic studies and treatments aimed at abnormal ingestive behavior and obesity.

21.
The Resting Brain in Localized Provoked Vulvodynia (LPVD)

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Background: Localized provoked vulvodynia (LPVD) affects approximately 7 to 10% of the female population and is characterized by localized sensitivity of the vulvar vestibule that is provoked by genital contact (e.g., intercourse and tampon use). The biological etiology of LPVD is unknown. LPVD is often comorbid with other chronic pain disorders such as irritable bowel syndrome and fibromyalgia. Investigation of central processes in

LPVD are sparse but suggest altered central sensory processing and modulation, including central sensitization, dysregulation of endogenous pain modulatory systems, and attentional enhancement of pain perception. **Aim:** 1. To determine alterations in resting state (RS) networks in LPVD compared to healthy controls (HCs) in sensorimotor and executive control/saliency networks. 2. To identify group differences in these RS networks between LPVD, healthy controls (HCs), and a disease control group (irritable bowel syndrome, IBS). **Methods:** Functional magnetic resonance (fMRI) imaging during the resting state was conducted in a sample of 87 age-matched premenopausal females (29 LPVD: mean=30.31 yrs, sd= 6.79; 29 HCs: mean=30.31 yrs, sd=6.80; 29 IBS: mean=30.31 yrs, sd=6.95). Group independent component analysis (gICA) in GIFT 2.0c was performed to investigate group differences in functional connectivity of resting state networks involved in sensorimotor and executive control/salience networks. Controlling for age, resting state activity of regions showing group differences were correlated with clinical (measures of vulvar muscle tenderness, self-report of pain), and behavioral variables (anxiety, depression, pain catastrophizing (PCS), and pain duration). **Results:** *Sensorimotor Network*: In LPVD compared to HCs and IBS, bilateral supplementary motor area (SMA) had greater connectivity in the sensorimotor network. Also left precentral gyrus (PreCG; primary motor cortex) had greater connectivity in LPVD compared to IBS but not HCs. *Executive Control/Salience Network*: Compared to HCs and IBS, LPVD had greater connectivity of the basal ganglia regions (caudate and globus pallidus), and less connectivity of cortical modulatory areas (BA 9, medial OFC) in the executive control/salience network. *Correlations with Clinical and Behavioral Measures:* SMA showed moderate correlation with pain not related to intercourse r(25)=.45, p=.012; and to total muscle tenderness r(25)=-.50, p=.009. PreCG correlated moderately with several behavioral variables including anxiety, depression, and PCS (r's>.40, p<.05). Furthermore, resting state activity in the pallidum was correlated with pain duration, r(25)=-0.36, p=0.06 and depression r(25)=.46, p=.02) and there was a trend for the correlation in the left putamen with total muscle tenderness r(25)=.38, p=.05. **Conclusions:** These resting state findings in LPVD are consistent with previously reported connectivity alterations in the same two brain networks in chronic pain conditions often comorbid with LPVD. The greater connectivity of the basal ganglia with in the executive control/ salience network of LPVD is consistent with previously reported structural and white matter alterations in these regions in subjects with chronic visceral pain. The greater connectivity of bilateral SMA may be related to the tonic contractions of pelvic floor muscles often noted on clinical examination in women affected with LPVD.

22.

Patients with Irritable Bowel Syndrome Show Sex Related Differences in Resting-State Functional Connectivity

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Background: Resting-state functional MRI has been widely used to investigate intrinsic brain connectivity in healthy and patient populations, including those with chronic pain. The dorsal anterior insula cortex (daINS) is a major cognitive hub in the saliency network. Sex-related differences in the brain frequency power distribution of aINS have recently been reported in irritable bowel syndrome (IBS), a disorder more prevalent in women (Hong et al, 2013). However, the daINS functional connectivity of sex differences in IBS has not been investigated. **Aims:** 1. To characterize the intrinsic connectivity of daINS between age-matched female and male patients with IBS and healthy controls (HCs). 2. To examine the possible sex and disease related alterations in the functional connectivity of daINS. **Methods:** 48 Rome III positive IBS patients (24 males) and 48 age-matched HCs (24 males) were recruited. Images were acquired with echo planar sequence on a Siemens 3 Tesla Trio scanner. The daINS was manually delineated based on Destrieux Atlas. The individual seed-to-voxel connectivity map was created in the CONN fMRI connectivity toolbox. The component-based noise correction method was used to remove confounds and head movement. Imaging data was bandpass filtered 0.008-0.08 Hz. 4 mm-smoothed Fisher transformed bivariate correlation maps were implemented in SPM8. A second-level random effects full factorial model specified the four groups as factors. Regions considered significant were corrected for multiple comparisons at a combination of p<0.005 for voxel level and a minimum cluster size of 30 contiguous voxels. **Results:** In the *left* hemisphere, male IBS had increased positive daINS connectivity to medial and dorsal medial prefrontal regions when compared to female IBS. Contrarily, female IBS had stronger negative daINS connectivity to precuneus when compared to male IBS. These regions were comprised within the default mode and executive

networks. Male IBS also showed increased positive connectivity between daINS and dorsal posterior INS compared to female IBS. In the *right* hemisphere, male IBS also showed greater daINS connectivity to medial prefrontal regions and dorsal posterior INS compared to female IBS. Significantly positive correlation was observed between insular connectivity to dorsal medial prefrontal area and Visceral Sensitivity Index in male IBS. There were no significant differences between IBS subjects and HCs when males and females were combined in each group. **Conclusion:** In the absence of any stimulus, IBS subjects showed sex-specific alterations in functional connectivity between daINS and medial prefrontal brain regions, consistent with differences in the executive/saliency network between male and female patients. These findings are also consistent with previous observations from evoked brain responses of greater prefrontal involvement in male IBS patients.

23.
Global DNA Methylation Analysis of Irritable Bowel Syndrome Patients Compared to Healthy Controls

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Background and Aims: Despite a growing consensus about the role of altered brain gut interactions in the pathophysiology of irritable bowel syndrome (IBS), there is little understanding about underlying molecular mechanisms. Complex interactions between host and environment can influence gene expression mediated by epigenetic mechanisms, such as DNA methylation. In an exploratory analysis, we aimed to identify differentially methylated genes between IBS patients and healthy controls (HCs) and between various IBS bowel habit subtypes. **Methods:** We compared global DNA methylation profiles of peripheral blood mononuclear cells from 12 IBS patients (mean[±sd] age=39.8±3.4 yrs, 58 % F, 25% IBS-Constipation [IBS-C], 50% IBS-Diarrhea [IBS-D], 25% Mixed [IBS-M]) with 12 HCs (mean[±sd] age=39.8±3.8 yrs, 58% F), using Illumina HM450 array, which interrogates DNA methylation status of > 450,000 CpG sites and > 99% of all genes. DNA methylation values were compared between IBS and HCs, and between various bowel habits using Wilcoxon rank-sum test. Multiple testing corrections were not applied initially, due to limited power; however, we assumed 5% genes to be significant by chance. Gene ontology (GO) signature was analyzed to identify the common function term associated with a gene list, using DAVID bioinformatics tool (http://david.abcc.ncifcrf.gov/). **Results:** Using the criteria of a mean methylation difference ≥ 15% and p<0.05, 29 probes were different between IBS and HCs, 81 probes were different between IBS-C vs. IBS-D, 39 between IBS-C vs. HCs, and 26 between IBS-D vs. HCs (total of 175 probes for 128 genes). Six genes corresponding to 10 probes (Table 1) with the lowest p values and highest methylation group differences were Synphilin-1 (SNCAIP), SCO-spondin (SSPO), RING finger protein 39 (RNF39) and Tubulin Polymerization Promoting (TPPP), glutathione S transferases mu class (GSTM1, GSTM5). All 10 probes were hypermethylated in IBS. Four out of 6 genes, SNCAIP, SSPO, RNF39 and TPP3, were associated with neuronal function. GSTM enzymes play a role in the detoxification of environmental toxins and products of oxidative stress. GO analysis of 128 significant genes showed a significant enrichment of GO term "neuropeptide hormone activity" (defined as "any peptide hormone that acts in the central nervous system") (p=0.004,

Table1: Location and DNA methylation values of 10 selected probes

Probe_ID	Gene	Mean DNA methylation % HCs	Mean DNA methylation %IBS	Mean DNA methylation % IBS-C	Mean DNA methylation % IBS -D	P-value
cg00867835%	SSPO	51	69	63	73	<0.005$
cg07382347%	RNF39	27	36	71	27	<0.05$
cg10930308%	RNF39	29	36	71	24	<0.05$
cg10950028%	GSTM1	23	47	62	48	<0.005$
cg11680055#	GSTM1	17	36	55	37	<0.01$
cg12858902#	GSTM5	24	43	55	44	<0.001
cg20803293#	GSTM5	25	52	69	53	<0.001
cg21036194%	SNCAIP	47	87	88	86	<0.001
Cg22879098%	TPPP	35	49	44	52	<0.001
cg24467349#	GSTM5	35	58	64	59	<0.001

$Significant difference by bowel habit subtype; #Promoter probes; %Gene body probes

FDR=5.4). **Conclusions:** Although there were fewer overall differences in DNA methylation between IBS patients and HCs, there were marked differences by bowel habit subtypes. These findings warrant replication in a larger cohort and assessment of expression levels; however, our data suggests that epigenetic modifications play a role in IBS, and that IBS-C and IBS-D have different pathophysiologic mechanisms that involve oxidative stress and neuropeptide hormonal activity within the brain-gut axis.

24.

Morphological Brain Differences in Healthy Control Subjects with and without Family History of Pain/Psychiatric Disorders

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Background: Patients with chronic pain conditions (including Irritable Bowel Syndrome) show regional structural brain changes, including the prefrontal cortex, basal ganglia, insula, and anterior cingulate cortex. In most studies, healthy controls (HCs) are not categorized based on their family history (FH) of disease, and those with a positive FH are usually included in the healthy control group. If brain endophenotypes of these disorders are present in asymptomatic relatives, inclusion of control subjects with a positive FH may obscure group differences. **Aims:** 1) To determine structural brain differences between HCs with and without a FH of chronic pain or psychiatric disorders. 2) To determine sex-related differences between these groups. **Methods:** Structural brain images were obtained from 142 HCs (62 males, 80 females; Mean age=31.1 yrs, sd=11.1). Subjects reported either presence or absence of family history of pain, and/or psychiatric symptoms (+Hx Pain, N=38, -Hx Pain, N=103; +Hx Psych, N=49; -Hx Psych, N=93). The UCLA Laboratory of Neuroimaging (LONI) pipeline was used for image preprocessing, volumetric, surface area, mean curvature, and cortical thickness analysis. The brain structures were parcellated into 165 regions, including 7 subcortical regions using the Destrieux and the Harvard-Oxford atlases. Group and sex differences were investigated using linear contrasts in a general linear model (GLM), while controlling for age, total cortex volume, and acquisition protocol. **Results:** There were no statistically significant structural differences between HCs with or without a positive FH. However, significant sex differences were observed in both HC groups. *In HCs with a positive FH for pain*, males showed significantly greater within-group differences in the surface area of the right superior precentral sulcus (p=.014) compared to females. In HCs with a negative FH for pain, males showed significantly greater structural within-group differences in the left pallidum (p=0.034), insular subregions (p<.001- p=.049), subregions of the pre and postcentral gyrus (p=.019-p=.049), anterior cingulate cortex (ACC) regions (p=.015 - p=.043), and in the PFC regions (p=.03 - p=.04) compared to females. *In HCs with a positive FH for psychiatric disorders*, males again showed significantly greater within-group differences in the surface area of the left superior circular INS (p=.049) compared to females. In HCs with a negative FH, males also showed significantly greater within-group structural differences in the left pallidum (p=0.008), insular subregions (p=.002- p=.025), subregions of the pre and postcentral gyrus (p=.004-p=.036), ACC regions (p=.002- p=.024), and in prefrontal regions (p=.023 - p=.036) compared to females. **Conclusions:** Although no structural group differences were observed between those HC subjects with a family history of pain/psychiatric disorders and those without, we observed sex-related differences between these two groups. These findings provide validity for the inclusion of HCs in neuroimaging studies regardless of their family histories. The observed patterns of sex related differences in the two HC groups warrant further exploration.

25.
Alterations in Resting State Oscillations and Connectivity within Sensory and Motor Networks in Women with Interstitial Cystitis/Painful Bladder Syndrome

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Purpose: The pathophysiology of interstitial cystitis/painful bladder syndrome (IC/PBS) remains incompletely understood, but is thought to involve a central disturbance in the processing of pain and viscerosensory signals. We aimed to identify differences in brain activity and connectivity between female IC/PBS patients and healthy controls in order to advance clinical phenotyping and treatment efforts for IC/PBS. **Materials and Methods:** We examined oscillation dynamics of intrinsic brain activity in a large sample of well-phenotyped female IC/PBS patients and female healthy controls collected during a 10-minute resting fMRI scan as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network project. The BOLD signal was transformed to the frequency domain and relative power was computed for multiple frequency bands. **Results:** The results demonstrated altered frequency distributions in viscerosensory (post insula), somatosensory (postcentral gyrus) and motor regions (anterior paracentral lobule, medial and ventral supplementary motor area (SMA). Additionally, anterior paracentral lobule, medial SMA and ventral SMA all demonstrated increased functional connectivity to the midbrain (red nucleus) and cerebellum. This increased functional connectivity was greatest in patients reporting pain during bladder filling. **Conclusions:** These findings suggest that women with IC/PBS have a sensorimotor component to their pathology involving an alteration in the intrinsic oscillations and connectivity within a cortico-cerebellar network previously associated with urinary bladder function.

26.
Corticotropin Releasing Hormone Receptor 1 and Progesterone Receptor Gene Polymorphisms Interact with Early Life Trauma to Shape Hippocampal Volume

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Background: The hippocampus plays an important inhibitory role on central stress circuits, and its transcriptome and morphology are modified by early stressful life events. **Aims:** To examine the influence of gene-early environment interactions in influencing hippocampal volumes in male and female subjects with and without a diagnosis of irritable bowel syndrome (IBS). **Methods:** 122 IBS patients (91 female) and 205 HCs (female 164), completed structural MRI scans for which the volumes of the right and left hippocampus were computed. Subjects were genotyped for 14 SNPs of 6 HPA/HPG-related genes. Following basic association analyses, haplotypes from two genes (CRHR1 and PGR)were examined for association with hippocampal volume in a linear regression model testing for main effects of genotype, sex, diagnosis, early adverse life events (EALs) as well as interactions between genotype and EAL with sex and diagnosis. **Results:** Significant interactions between gene, sex and EALs were seen for PGR and CRH-R1 haplotypes with the right hippocampus, and for PGR with the left hippocampus. Regardless of disease, smaller hippocampal volumes in males with higher ETI scores were associated with PGR minor alleles and with CRH-R1 major alleles, while no such interactions were seen in female

subjects. PGR and CRHR1 haplotypes also demonstrated significant association with IBS, with the most common haplotype occurring less frequently in IBS. **Conclusion:** Significant sex-related differences in the interactions between early life adversity and genetic polymorphisms on hippocampal volumes were observed. Deleterious interactions between EAL and PGR/CRHR1 haplotype, were only seen in male subjects, regardless of disease.

27.

Diffuse Tensor Imaging-Based Brain Signatures Accurately Discriminate a Functional Pain from Health: Examining Central Mechanisms in Visceral Pain

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Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort associated with a change in stool frequency. The prevalence rate of this functional disorder is 10-15% in North America and Europe. IBS is comorbid with other functional somatic syndromes including fibromyalgia, chronic fatigue syndrome, chronic headache, temporal mandibular disorder, and chronic pelvic pain. The pathophysiology of IBS is incompletely understood, however evidence strongly suggests dysregulation of the brain-gut axis and the involvement of both central and peripheral mechanisms. **Aim:** Application multivariate pattern analysis/recognition methods from machine-based learning to analyze large-scale neuroimaging-based structural and anatomical connectivity data to provide new mechanistic insights into IBS. **Hypothesis:** Structural and anatomical brain signatures can discriminate IBS patients from healthy controls. **Methods:** Structural and diffusion tensor imaging (DTI) brain images were obtained from 48 controls (25 F) and 46 IBS (25 F). Segmentation and regional parcellation was performed using Freesurfer on the UCLA Laboratory of Neuroimaging pipeline using the Destrieux atlas and 7 subcortical regions yielding 165 regions. For each cortical region measures of gray matter morphometry (volume, mean curvature, surface area and cortical thickness) were computed. Deterministic tractography using the Runge-Kutta algorithm was then performed using TrackVis to provide a measure of relative fiber density between regions (Irimia et al, NeuroImage, 2012). Each subjects connectivity matrices were concatenated and entered as the data matrix into a sparse Partial Least Square-Discrimination Analysis (Le Cao et al, Bioinformatics, 2011). **Results:** DTI-based classifier with two components/brain signatures comprising 55 connectivities each achieved greater than 90% accuracy in discriminating IBS from controls based on 10 fold cross-validation performed 10 times and leave-one-out cross validation. Both signatures were primarily comprised by insular, cingulate, frontal, and subcortical (amygdala, brainstem, basal ganglia, thalamus) connectivity. The two signatures accounted for 69% of the variance in the data set (Component 1, 60%, Component 2, 9%). Binary classification measures including sensitivity, specificity, negative predictive value, and positive predictive value were satifactory. Classification based on gray matter morphometry was less impressive yielding classification accuracy of 78%. **Conclusions:** The regions identified as having altered connectivity in IBS have also shown difference in HC-IBS comparisons of resting state and task based function and morphometry. Results suggest classification algorithms based DTI-based connectivity can be used to identify specific central targets for further pathophysiological investigations targeting treatment of IBS.

28.

Grey Matter Alterations in Medial Prefrontal Cortex Show Negative Associations with Subjective Reports of Worry in IBS Patients

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Background: A hallmark of IBS patients is the presence of "worry", a state of anxiety or uncertainty about actual or potential problems. While this feature has been dismissed as purely psychological, neurobiological mechanisms related to IBS pathophysiology may be involved. The medial prefrontal cortex (mPFC) plays a major

role in emotion regulation and alterations in the structure, function and connectivity of mPFC with amygdala, insula and nucleus accumbens have been implicated in the pathophysiology of anxiety disorders (Kim et al, 2011) and in chronic pain (Baliki et al, 2012). **Aim:** To determine if self-report of "worry" is associated with structural alteration in bilateral middle frontal gyrus as indexed by volume, surface area, cortical thickness and mean curvature. **Methods:** Structural brain images were obtained from 22 right handed female IBS patients (mean age = 40 y(SD=15) beginning a non-pharmacological treatment trial. All Rome III subtypes were represented (Constipation=4, Diarrhea=8, Mixed= 9, and Unspecified=1). Segmentation and regional parcellation was performed using Freesurfer on the UCLA Laboratory of Neuroimaging pipeline using the Destrieux atlas. Partial correlations controlling for age were used to determine the association between the abbreviated Penn State Worry Questionnaire(PSWQ-A), a self-report measure of cognitions associated with anxiety, with morphometry of the middle frontal sulci and gyri and the gyrus rectus (ventral medial prefrontal cortex, Brodmann area 11). Significance was only considered after correcting for the number of tests (N=4) for each region and hemisphere using false discovery rate (q<.05). **Results:** Average score on the PSWQ-A was 28.14 (SD=6.67). Analyses indicated significant

Table. Catecholaminergic SNPS

Gene	SNP
COMT (catechol-o-methyltransferase)	rs4680 (nonsynonymous)
COMT (catechol-o-methyltransferase)	rs6269
COMT (catechol-o-methyltransferase)	rs174697
Adrenergic-beta2 receptor (ADRA-B2)	rs1432622
Adrenergic-beta2 receptor (ADRA-B2)	rs2400707
Adrenergic-beta2 receptor (ADRA-B2)	rs1042717
Adrenergic-beta2 receptor (ADRA-B2)	rs1042713 (nonsynonymous)
Alpha-1D adrenergic receptor (ADRA-1D)	rs1556832
Alpha-1D adrenergic receptor (ADRA-1D)	rs946188
ANKK1 (ankyrin repeat and kinase domain containing 1)	rs1800497
Dopamine receptor D3 (DRD3)	rs6280

negative associations between the volume of the right middle frontal gyrus, r(19)-.57, p=.008, q=.03, and the right gyrus rectus, r=-.55, p=.009, q=.03. Trends for an association with the PSWQ-A were also seen in this small sample for the surface area of the right middle frontal gyrus, r= -.41, p=.07, surface area of the right gyrus rectus, r=-.45, p=.04, and mean curvature, an index of gyrification, of the right and left middle frontal sulci, r=.40, p=.07 and r=.48, p=.03. **Conclusions:** These findings implicate a role of prefrontal brain regions (including the medial and ventromedial PFC) in the generation of worry symptoms in IBS patients, consistent with an alteration in effectiveness of this brain region in corticolimbic inhibition. They are consistent with previous reports in anxiety and other chronic pain disorders. The mechanisms underlying these structural changes deserve further study.

29.
Catecholaminergic Genetic Polymorphisms are Associated with Autonomic Nervous System (ANS) Function in Irritable Bowel Syndrome

Alexa Orand, Wendy Shih, Tiffany Ju, Angela P Presson, Nuwanthi Heendeniya, Emeran A Mayer, Bruce Naliboff and Lin Chang

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

Background: Alterations in autonomic function, including an imbalance between sympathetic and vagal activity have been implicated in the complex pathophysiology of IBS. Genetic and epigenetic (including early adverse life events [EAL]) factors are likely to contribute to these alterations. However, there is limited data on the role of catecholaminergic single nucleotide polymorphisms (SNPs) in irritable bowel syndrome (IBS).
Aims: To determine if catecholaminergic SNPs are associated with: 1) a diagnosis of IBS with or without taking the interaction with EALs into account, 2) gastrointestinal (GI) or psychological symptoms, and 3) ANS function.
Methods: Salivary samples for DNA and symptom and EAL questionnaires were obtained in IBS patients and healthy controls (HCs). 11 catecholaminergic SNPS were genotyped (see Table). Factor analysis was used to define clusters of clinical traits within the IBS group. ANS measures of baseline average skin conductance level (sympathetic tone) and heart rate variability (HRV) ratio of low frequency to high frequency power (LF/HF; a measure of sympathetic/vagal balance) were obtained in a subset of subjects. The dominant genetic model (one or more copies of the minor allele vs. no copies) was found to be optimal for testing associations of SNPs with IBS status and ANS function. Logistic regressions were used to predict IBS status from each SNP, evaluate their interactions with EAL in predicting IBS status, and to evaluate correlations with clinical traits and ANS measures. P value <0.05 was considered significant. **Results:** 278 IBS patients (mean age 30.3 yrs, 73.2% F) and 381 HCs (mean age 36.4 yrs, 75.2% F) were studied. Of these subjects, 161 IBS and 176 HCs had baseline ANS data. *1)*

IBS diagnosis: There was no difference in SNP frequency between IBS and HCs for the 11 SNPs. However, individuals who were dominant (i.e., at least one copy of the minor allele) for COMT SNP rs174697 had a higher likelihood of having IBS if they had an increased emotional abuse score (p=0.041). The adrenergic receptor SNPs, ADRA-β2 rs1042717 was associated with increased likelihood of having IBS in those with an increased sexual abuse score (p=0.039). *2) Symptoms:* The ANKK1 SNP rs1800497 (involved in dopamine synthesis) was significantly associated with psychological symptoms (p= 0.045), and ADRA-1D SNP rs1556832 was associated with GI symptom severity (p=0.010). *3) ANS function*: Dominance for COMT SNP rs4680 was associated with a decrease in skin conductance level (p= 0.044) and decreases in sympathetic/vagal balance (p=0.015). The ANKK1 SNP rs1800497 was associated with increases in sympathetic/vagal balance (p=0.038). **Conclusion:** By interacting with early adversity, catecholaminergic gene SNPs may predispose individuals to IBS by affecting ANS function and responsiveness, thus leading to dysregulation in brain-gut interactions.

30.

Relationships among Dysmenorrhea, Laboratory Pain, Somatization, and Anxiety in Healthy Girls and Girls with Chronic Pain

Laura A Payne[1], Andrea J Rapkin[2], Laura C Seidman[1], Kirsten C Lung[1], Lonnie K Zeltzer[1], Jennie CI Tsao[1]

[1]*Department of Pediatrics, David Geffen School of Medicine at UCLA;* [2]*Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA*

Painful menstruation, known as dysmenorrhea, is a chronic and disabling condition affecting up to 90% of women and adolescent girls. Despite this high prevalence, very little is known about potential factors that may share a relationship with menstrual pain. Research has demonstrated elevated pain responses in adult women with dysmenorrhea compared to controls, and studies have also suggested a relationship between dysmenorrhea and anxiety in adults. However, much less is known about these relationships in adolescents. We aimed to explore relationships among self-reported menstrual pain ratings, somatization, pain-related anxiety, and acute laboratory pain in a sample of menstruating adolescents with and without a chronic pain condition. Participants were 65 menstruating girls, ages 10-17 (34 healthy, mean age 15.14 years; 31 chronic pain, mean age 16.01 years), who reported having had period cramps. During a laboratory session, all participants completed questionnaires and laboratory pain tasks involving cold and pressure pain. Menstrual pain (without medication) was rated on a 0 (none) to 10 (extreme) scale. Girls with ratings of "4" and above were classified as having dysmenorrhea. Results indicated a higher proportion of participants with chronic pain were classified with dysmenorrhea (87.1%), as compared to those without chronic pain (61.8%), $\chi2 > 1$, $p < .05$, and were more likely to be taking hormones or birth control for menstrual pain (38.7%) compared to healthy girls (0%), $\chi2 > 1$, $p < .05$. After controlling for age, healthy girls' ratings of menstrual pain were significantly positively correlated with cold and pressure lab pain intensity and somatization (r's = .58, .41, & .36, respectively; ps < .05). Menstrual pain ratings in girls with chronic pain were significantly correlated with pain catastrophizing, pain anxiety, anxiety sensitivity, and total anxiety (r's = .59, .61, .44 & .45, respectively; ps < .05). These data suggest healthy girls' menstrual pain appears related to acute pain intensity and somatic symptoms, whereas menstrual pain in girls with chronic pain is related to psychological aspects of pain. The findings underscore the importance of assessing behavioral and psychosocial variables in girls with dysmenorrhea and addressing anxiety and related constructs in interventions.

31.

Autonomic Modulation in Functional Gastrointestinal Disorders: An Integrative East-West Approach

Andrew Shubov and Lawrence Taw

UCLA Center for East-West Medicine

A 52 year old male with a history of functional dyspepsia was referred to us with a complaint of postprandial burning epigastric pain associated with reflux and abdominal distention. He had an abdominal gunshot wound 21 years ago resulting in chronic constipation from neurogenic bowel and neurogenic bladder requiring ileal conduit and self-catheterization. Medications included levothyroxine, polyethylene glycol and omeprazole. Despite medical management resulting in daily bowel movements, he still suffered from incomplete rectal emptying and

persistent abdominal pain. Prior workup including esophagogastroduodenoscopy, colonoscopy and computed tomography of the abdomen and pelvis was unremarkable.

Physical examination was notable for palpable trigger points of the upper back and neck regions. He received biweekly treatments incorporating acupuncture as well as lidocaine trigger point injections to the bilateral trapezius and cervical musculature. After four visits he experienced improvement of his abdominal pain and resolution of his constipation but was then lost to follow up for two months. He returned to our clinic with recurrence of his presenting symptoms. At this point myofascial release of the upper back and neck was added to the treatment regimen. After 5 additional biweekly visits, he experienced complete resolution of his abdominal pain and constipation, and furthermore was able to discontinue his omeprazole and polyethylene glycol with no subsequent relapse.

This is a case report of a patient with functional dyspepsia and chronic constipation treated successfully with an integrative approach incorporating acupuncture, trigger point injections and myofascial release. His symptoms are consistent with an underlying defect in his visceral parasympathetic tone, and interestingly, much of the science behind acupuncture and myofascial release point to restoration of parasympathetic tone as a mechanism of action. Here we describe a case of gastrointestinal dysmotility and autonomic dysfunction refractory to pharmacotherapy that was successfully treated with an integrative therapeutic approach.

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Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Olujimi Ajijola MD PhD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Clinical and Mechanistic Updates on Cardiac Decentralization in the Treatment of Ventricular Arrhythmias</u>

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

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

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

COMMENTS (including suggestions for improvement): _____

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Signature of Evaluator*: _____

* The Department accepts only signed evaluations as valid. However, please note that prior to sharing evaluation with instructor, signature is removed.

Please return to: Fornessa Randal
c/o Gail & Gerald Oppenheimer Family
Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: Arpana Gupta, PhD

ACTIVITY: 12th Annual CNS Basic & Translational Science Symposium – Morphological Imaging-Based Brain Signatures Discriminate Obese from Lean Subjects: Examining Central Mechanisms within the Brain

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

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7. Instructor provides feedback.	1 2 3 4 5 6 7 8 9 10	❏
8. Overall rating of this instructor compared with other teachers you have had at UCLA (10 is best).	1 2 3 4 5 6 7 8 9 10	❏

COMMENTS (including suggestions for improvement): _____

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Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Jennifer Labus, PhD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Central Alterations in Localized Provoked Vulvodynia</u>

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

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COMMENTS (including suggestions for improvement): _____

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Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Michelle Chen, BS</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Irritable Bowel Syndrome Symptoms Are Related to the Resting Brain's Sensorimotor Network</u>

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

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COMMENTS (including suggestions for improvement): _____

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Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Emeran Mayer, MD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Structural and Functional Brain Changes in Inflammatory Bowel Diseases</u>

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

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COMMENTS (including suggestions for improvement): _____

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Signature of Evaluator*: _____

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c/o Gail & Gerald Oppenheimer Family
Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Swapna Joshi, PhD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Epigenetic Landscape of Irritable Bowel Syndrome</u>

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

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COMMENTS (including suggestions for improvement): _____

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Signature of Evaluator*: _____

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Please return to: Fornessa Randal
c/o Gail & Gerald Oppenheimer Family
Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Steve W. Cole, PhD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Social Regulation of Human Gene Expression</u>

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

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

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COMMENTS (including suggestions for improvement): _____

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Signature of Evaluator*: _____

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c/o Gail & Gerald Oppenheimer Family
Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Jonathan Braun, MD, PhD</u>
ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Defining and Harnessing the Intestinal Microbiome</u>

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

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

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5. Instructor enjoys teaching; is enthusiastic about the subject; makes the material exciting.	1 2 3 4 5 6 7 8 9 10			❏
6. Instructor is effective in providing guidance in the technical and intellectual aspects of research.	1 2 3 4 5 6 7 8 9 10			❏
7. Instructor provides feedback.	1 2 3 4 5 6 7 8 9 10			❏
8. Overall rating of this instructor compared with other teachers you have had at UCLA (10 is best).	1 2 3 4 5 6 7 8 9 10			❏

COMMENTS (including suggestions for improvement): _____

_____

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Signature of Evaluator*: _____

* The Department accepts only signed evaluations as valid. However, please note that prior to sharing evaluation with instructor, signature is removed.

Please return to: Fornessa Randal
c/o Gail & Gerald Oppenheimer Family
Center for Neurobiology of Stress
CHS 42-210 MC737818

Evaluation of Non-Clinical Teaching Activities

INSTRUCTOR: <u>Michelle Craske, PhD</u>

ACTIVITY: <u>12th Annual CNS Basic & Translational Science Symposium – Computer-Assisted Cognitive Behavioral Therapy for Anxiety Disorders in Primary Care</u>

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

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

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

COMMENTS (including suggestions for improvement): _____

_____

_____

_____

_____

Signature of Evaluator*: _____

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