GCC
Health Psychology and Behavioral Medicine
March 1, 2019

BioScience Research Collaborative Auditorium
6500 Main St.
Houston, Texas

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES
The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC training programs currently focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Neuroengineering and Pharmacological Sciences. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences, and currently include Antimicrobial Resistance, Nanox, Mental Health, Chemical Genomics, Translational Pain Research, Theoretical and Computational Neuroscience, Alcohol and Addiction Research, Regenerative Medicine, Translational Imaging and Cellular and Molecular Biophysics. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, and the Institute of Biosciences and Technology of Texas A&M Health Science Center.

Gulfcoastconsortia.org
8:30  Breakfast and poster set up

9:00  Welcoming remarks

9:10  Keynote: Social Regulation of Human Gene Expression
      Steve Cole, University of California Los Angeles

**Session 1: Anhedonia/Depression**
Convener: Fernanda Laezza, University of Texas Medical Branch

10:00  Retinoic Acid Signaling: Novel Targets for Depression-related Behavior
       Tom Green, University of Texas Medical Branch

10:20  Deep Brain Stimulation of the Medial Forebrain Bundle: Significant Responses in Treatment Resistant Depression
       Albert Fenoy, University of Texas Health Science Center

10:40  Selected Abstract: A Neurophysiological Measure of Reward Sensitivity and its Limited Association with Anhedonia in Psychiatrically Healthy Adolescents and Young Adults
       David Frank, MD Anderson

10:55  Break

11:15  Workgroup Breakout Sessions (Event Space)
       Biological Psychiatry
       Drug Discovery
       Health Psychology
       Cross-institutional Research Registry

12:00-1:15  Lunch and poster session (Event Space)
(Poster presenters need to stand at poster from 12:30-1:15)

**Session 2 Trauma**
Convener: Robert Dantzer, M.D. Anderson Cancer Center

1:20  Project Heart: Biobehavioral mechanisms underlying grief and ghosts of relationships past
      Chris Fagundes, Rice University

1:40  The Neurobiological Embedding of Early Life Stress and Trauma: Mechanistic Pathways Underlying Mental Health Risk and Resiliency
      Johanna Bick, University of Houston
2:00  Wellness for Warriors: Developing A Veterans Self-Guided Behavioral Health Workbook With Stakeholders  
Jennifer Bryan, Baylor College of Medicine

Session 3: Pain and Chronic Illness
Convener: Chris Fagundes, Rice University

2:15  Curable Schizophrenia: Autoimmune Psychosis  
Joseph Masdeu, Houston Methodist

2:35  Resolution of pain and depression: a key role for the immune system  
Annemiek Kavelaars, MD Anderson

2:55  Bio-behavioral regulation of plasma IL-18, a novel therapeutic target in nociceptive pain states  
Alan Prossin, University of Texas Health Science Center

3:15  Effects of the Pyrethroid Insecticide Deltamethrin on Rodent Medium Spiny Neurons of the Nucleus Accumbens Following Acute and Early-Life Exposure  
Cynthia Tapia, University of Texas Medical Branch

3:30  Networking and Coffee Break

4:00  Keck Seminar Keynote: Lovesick: How Couples’ Relationships Influence Health  
Janice Kiecolt-Glaser, OSU

5:00  Reception
Speaker Abstracts
(In order of appearance)

Steve Cole, PhD
Professor, Psychiatry & Biobehavioral Sciences and Medicine
University of California Los Angeles
Social Regulation of Human Gene Expression

Steven Cole is a Professor of Psychiatry & Biobehavioral Sciences and Medicine in the Division of Hematology-Oncology at the David Geffen School of Medicine at UCLA. His research utilizes molecular genetics and computational bioinformatics to map 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 field of human social genomics, and serves as Director of the UCLA Social Genomics Core Laboratory.

Abstract:
Research in human social genomics has begun to map the molecular pathways by which social, psychological, and other environmental processes regulate the function of the human genome and thereby influence physiology, development, and health. As research in this area enters its second decade, the field is yielding new insights into the molecular underpinnings of thriving and resilience, in addition to its historical focus on psychosocial determinants of disease. This talk summarizes the state of the field and its role in understanding the molecular pathways through which mind and body interact to create a whole human life.
Dr. Green studies the molecular determinants of behavior relating to mental health and addiction using rodent models. The focus of the laboratory is to identify novel targets for successful pharmacotherapeutic development. Workflows include discovery-based target identification to in vitro validation to in vivo validation of novel targets. Dr. Green has used an environmental enrichment paradigm to develop novel hypotheses for mental health and addiction, including a tonic-phasic model of deltaFosB action, an inoculation stress hypothesis of environmental enrichment, and a regionally-enhanced gene expression focus. Novel targets in the retinoic acid signaling pathway are being explored for depression and addiction-related behavior.

Abstract: Previous research in rodent preclinical models identified environmental enrichment as a protective factor for depression-related behavior. Our recent transcriptomics data suggests that retinoic acid signaling in the nucleus accumbens might be a mediating factor of this protective phenotype, and analysis of the Allen Brain Atlas confirms retinoic acid signaling components are enriched in the shell of the nucleus accumbens. To provide causal evidence, we developed a viral vector that, when injected into the nucleus accumbens shell, increases retinoic acid signaling. This vector produces a depressant-like phenotype in rats. Inversely, a vector that blocks one aspect of retinoic acid signaling produces an antidepressant-like phenotype. Electrophysiological data further suggest retinoic acid signaling in the nucleus accumbens shell may be mediating the protective phenotype from environmental enrichment. Current studies are evaluating the best targets for therapeutic development.
Abstract:

Introduction: Deep brain stimulation (DBS) to the superolateral branch of the medial forebrain bundle (MFB) has been reported to be effective in rapidly improving treatment resistant depression (TRD). This report is an update to our recently published results (Fenoy et al., 2018).

Methods: In this analysis of an ongoing study, we assessed the efficacy of MFB-DBS in a cohort of eight TRD patients over a 52-week period using improvement on the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome measure. Implanted patients entered a 4-week single-blinded sham stimulation period prior to stimulation initiation.

Results: Upon stimulation at target intraoperatively, responders reported immediate increases in energy and motivation. There was a significant mean change in mood during the 4 week sham stimulation phase (34% mean MADRS reduction, p = 0.03), but no significant difference upon stimulation initiation at 1 week relative to end sham. However, the difference in MADRS score between baseline and 2 weeks of active stimulation was significant (mean change = 17 pts, 49% reduction, p < 0.001). One patient withdrew from study participation. At 26 weeks, 6 of 7 remaining patients have >50% improvement of MADRS (mean improvement = 24 pts, 73% reduction, p = 0.001). At 52 weeks, 6 of remaining 7 patients continue to have >50% decrease in MADRS scores relative to baseline. 3 patients are currently active in the study and have not completed all assessments. One patient failed to respond. Evaluation of modulated fiber tracts reveals significant common frontal connectivity to the target region in all responders.

Conclusion: This study of MFB-DBS confirms rapid anti-depressant effects are observed with stimulation, as reported by Schlaepfer et al. (2013). Although the insertional response itself is significant, the effect becomes more pronounced with time after stimulation onset.
Dr. Frank received his B.S. in Psychology at U.C. San Diego and his Ph.D. in Neuroscience at the University of Georgia. Broadly, he is focused on leveraging neuroimaging techniques, such as fMRI and EEG, to determine the neuropsychological underpinnings of unhealthy behavior, such as smoking and overeating. In particular, Dr. Frank is interested in how environmental cues shape behavior and determining how executive control mechanisms can be leveraged to counteract maladaptive decision making. The goal of this research is to allow for precision medicine through the development of tailored individual treatment for compulsive behaviors.

Abstract:
Background: Anhedonia, the attenuated ability to enjoy pleasurable stimuli, characterizes multiple mood disorders. In adolescents, anhedonia is associated with enhanced depression severity and longer time to remission. Given its clinical relevance, understanding the neurophysiological mechanisms underlying anhedonia is extremely significant as it can contribute to the improvement of diagnostic procedures and clinical interventions.

Hypothesis: We hypothesize that individuals with reduced reward sensitivity, as measured by their performance on a reward signal detection task, will report greater anhedonia scores on the Snaith-Hamilton Pleasure Scale (SHAPS) and exhibit a less negative FRN to reward feedback stimuli delivered during the reward signal detection task.

Methods: Here, we measured event-related potentials in 116 adolescents and young adults engaged in a signal detection task designed to objectively characterize the anhedonic phenotype.

Results: In line with previous studies, the behavioral results showed that approximately 35% of the sample did not develop a response bias towards the more frequently rewarded stimuli (a sign of low hedonic capacity). The event-related potentials (ERPs) evoked by the reward feedback stimuli delivered during the task showed that individuals that did not develop a response bias had less cortical positivity at Fz from 224 ms to 316 ms post feedback onset compared to those that developed a response bias during the task. However, further analyses showed that this between groups difference was relatively weak, as it disappeared when we controlled for response-locked ERPs. Furthermore, the response bias observed in the signal detection task was not strongly associated with self-reported ratings of hedonic capacity.

Conclusions: We conclude that even though the signal detection task may be used as a reward sensitivity measure in neurotypical adolescents and young adults, this task may only be able to detect clinically significant levels of anhedonia in this particular population.
Working in the area of psychoneuroimmunology, Dr. Fagundes uses theories and methods from social/personality, developmental, and applied psychology to examine how stress “gets under the skin” to impact diseases of older adulthood such as cardiovascular disease, cancer, and cognitive decline. He is also interested in how the immune system regulates neuronal function in ways that influence mood and behavior. His theoretical work has focused on the adoption of attachment theory to understand physical health trajectories, particularly in relation to how attachment security can buffer the negative consequences of current and past life stressors. He has authored more than 90 articles and book chapters. The goal of his current funded work is to understand how attachment insecurity in the context of losing a spouse impacts inflammation, an immune marker that is prognostic for cardiovascular disease, type II diabetes, arthritis, osteoporosis, Alzheimer’s disease, and some cancers. With a team of collaborators, he is also developing theoretically based interventions to improve the negative physical health consequences of stressful contexts. The National Institute of Health (NIH) funds most of his research; Dr. Fagundes has also been the primary mentor on several NIH training grants. He was named a “Rising Star” by the Association of Psychological Science. He was the recipient of the Robert Ader New Investigator Award from the Psychoneuroimmunology Research Society, the Neal E. Miller New Investigator Award from the Academy of Behavioral Medicine Research, and the Excellence in Health Psychology Research Award by an Early Career Professional from Division 38 of the American Psychological Association.

Abstract:
One-third of the population age sixty-five and older is considered a widowed person. Compared with non-bereaved adults, older spousal bereaved adults have a greater occurrence of somatic symptom, illness, heart attack and stroke, medical service usage, new illnesses, worsened illnesses, poorer health ratings, depression, and mortality. Excess mortality among those who are widowed is highest immediately after the loss, but bereaved individuals remain at heightened risk well after their first year of being widowed. In this talk, we will present work showing that those who have been widowed have greater autonomic and immune dysregulation compared with age-matched controls. We will then present data showing that bereaved older adults who experience grief above a clinical cut-score have higher levels of inflammation compared with those who are below this threshold. While bereavement promotes adverse health outcomes, not everyone responds to the loss of a spouse in the same way. Specifically, researchers have used the “kindling” hypothesis to understand the ways child abuse and neglect promotes stress sensitivity and physiological reactivity later in life. In the final part of this talk, we will present data showing that early life abuse and neglect impacts mental health and biomarkers of physical health among older bereaved adults. We will also discuss other important factors that play an important role in the physical and mental health outcomes of the spousally bereaved.
Dr. Johanna Bick is an assistant professor in the department of psychology at the University of Houston. She received a PhD in Clinical Psychology with a developmental emphasis from the University of Delaware in 2011. She then completed postdoctoral fellowships at the Yale Child Study Center and Boston Children’s Hospital/Harvard Medical School. Dr. Bick’s research program examines how early adverse experiences, including institutional rearing, poverty, and maltreatment, shape neurodevelopment in ways that increase risk for emotional and cognitive problems. She also studies how early intervention can mitigate neural and behavioral consequences associated with early adverse exposures.

Abstract:
Exposure to early adversity, including extreme stress and trauma, has long been linked to increased risk for emotion and behavior problems and associated mental health disorders. Emerging work points to alterations in stress physiology and affective neural systems as mechanisms explaining ongoing risk. In this talk, I will review evidence for the neurobiological impact of various early traumatic and adverse experiences from two studies: one involving children reared in maltreating contexts and the second involving follow up assessments of infants born to mothers traumatically affected by Hurricane Harvey. Findings from these studies point to the impact of these adverse exposures on the early developing brain and behavior, and underscore the need for early intervention and prevention to mitigate ongoing risk.
Abstract: Background There is a vast evidence base for the mental and physical health benefits of brief positive psychology interventions. These interventions are ideal for self-help as they are often brief (e.g., recalling three good things that happened in one’s day) and do not require guidance from a health care professional. However, these self-help resources tend to be designed for, marketed to, and utilized by affluent, white women. Currently, there is limited self-guided material with positive psychology interventions centered towards the Veteran population, despite the potential to benefit greatly from such resources. Veterans are typically at higher risk for mental and substance use disorders than the general population. Moreover, many Veterans wanting to improve their quality of life may not seek help due to a culture of self-reliance and social stigma, thus, a Veteran-centric self-guided workbook could be a welcomed resource.

Hypothesis/Goals The goal of this study was to create a self-guided workbook comprised of evidence-based interventions and exercises targeted at the Veteran population in conjunction with Veteran stakeholders.

Methods We created an evidence-based self-guided workbook that provides Veterans with a wide array of easy to use activities that incorporate these interventions; the workbook does not require the guidance of a professional and can be done at one’s own pace. Then, the workbook was presented to a diverse (age, gender, race, ethnicity, military branch, and rank) focus group of Veteran stakeholders (n=8) for feedback on cultural appropriateness, usability, and acceptability.

Results Veteran stakeholders were supportive of the idea of improving wellness through the use of a workbook and thought the content would be well received in the community after changes in images and phrasing were made. A large consensus from the group was that it was unclear that the manual was for a Veteran population instead of a civilian population, specifically from the pictures and passive language. Suggested changes included pictures related to the military and use of direct language. In addition, emphasis was given to refer to other resources such as the Veterans Affairs online self-guided cognitive behavioral therapy for insomnia (CBT-I) and volunteer opportunities with national Veteran organizations such as the Mission Continues. Dissemination opportunities with Veteran service organizations were also discussed.

Conclusion This is the first step in creating culturally appropriate self-help specifically for the Veteran population. Veterans reported high levels of interest and need in their underserved community. Such materials place priority not only on the mental health problems that Veterans face, but also on sustaining well-being, and can be utilized without the guidance of a health care professional or while waiting to access care.
Joseph C. Masdeu, MD, PhD leads the Nantz National Alzheimer Center and Neuroimaging at the Houston Methodist Neurological and Research Institutes and is a professor of Neurology at the Weill Medical College of Cornell University. He completed residencies in Psychiatry (Spain) and Neurology (Chicago Medical School), and a fellowship in Neuropathology at the Brigham and Women’s Hospital of Harvard Medical School. He has been a professor of neurology at the Albert Einstein College of Medicine, in New York, and Chairman of Neurology at the New York Medical College. He is the author of 147 peer-reviewed papers, 61 book chapters, and of seven books, including “Localization in Clinical Neurology,” now in its 7th edition. He is chairman of the Neuroimaging Research Group of the World Federation of Neurology. He has been a director of the American Academy of Neurology and president of the American Society of Neuroimaging, as well as Editor-in-Chief of the Journal of Neuroimaging.

While a scientist at the Intramural Research Program of the NIMH, from 2008-2014, he examined patients with schizophrenia and became interested in the autoimmune etiology of some cases. He has published 3 papers on this topic.

Abstract:
A consensus exists that schizophrenic-type psychosis, including many cases of bipolar disease, is not a single disease, but the final pathway of a variety of still unknown neurobiological derangements (Morris et al. 2011). An autoimmune etiology for selected patients with idiopathic psychosis is likely because inflammation-related genes are up-regulated in brain tissue of patients with psychosis (Saetre et al. 2007, Fillman et al. 2013), several of the leading risk genes associated with schizophrenia in genome-wide association studies code for proteins critical for immunity (Schizophrenia Working Group of the Psychiatric Genomics 2014) and a recently discovered synaptic autoimmune brain disease targeting the N-acetyl methyl D-aspartate receptor (NMDAR), known to be downregulated in schizophrenia (Moghaddam 2003), courses with psychotic manifestations (Dalmau et al. 2008, Kayser et al. 2014, Dalmau et al. 2018). Responsible anti-synaptic antibodies have been detected in cerebrospinal fluid (CSF) and, often, in serum as well (Gresa-Arribas et al. 2014).

However, using current methodology (Dalmau et al. 2008) anti-NMDAR IgG antibodies in the sera of patients with schizophrenia have very seldom been detected by us (Masdeu et al. 2012), or others (de Witte et al. 2015, van Mierlo et al. 2015, Schou et al. 2016). This is logical because the methods currently used, screening with rat brain or cell constructs, are likely to miss antibodies against human synaptic receptors, more evolved than in the rat, or human native receptors, molded by post-transcriptional changes (Masdeu 2017). At Houston Methodist we are developing a more sensitive method and are about to start a proof-of-concept clinical trial.
Dr. Annemieke Kavelaars, Professor, Laboratories of Neuroimmunology, Department of Symptom Research, M.D. Anderson Cancer Center, Houston TX trained in Neuroimmunology at the University Medical Center Utrecht in the Netherlands, where she continued her work until moving to M.D. Anderson Cancer Center in 2012. She started her career investigating production of opioid peptides by the immune system. She developed a broad interest in neuroimmunology and performed studies on adrenergic regulation of immune function and the role of G protein coupled receptor kinases (GRK) in autoimmunity. Her work on GRK expanded into the role of GRK2 in the transition from acute to chronic pain. She is currently focusing on the role of neuroimmune interactions in the resolution of pain. Dr. Kavelaars has published more than 245 papers, has served as associate editor of Brain, Behavior, and Immunity, and was president of the Psychoneuroimmunology Research Society and is currently chairing the GCC translational pain consortium.

Abstract:
Chronic pain and depression often co-occur indicating that common mechanisms may be involved. There is ample evidence for a role of microglial activation in the central nervous system and local production of pro-inflammatory cytokines in the development of pain and depression-like behavior in rodent models. Therefore, it has been proposed that suppression of inflammation may be sufficient to promote resolution of pain and depression. Our recent data indicate that this may not be sufficient. Specifically, we demonstrated that resolution of inflammatory pain and of chemotherapy-induced peripheral neuropathy critically depend on the activity of T lymphocytes and an endogenous IL-10 signaling pathway. Mice deficient in T cells or IL-10 show a markedly delayed recovery in models of transient pain. Similarly, we demonstrated that resolution of depression-like behavior in response to intraperitoneal administration of LPS is dependent on T lymphocytes and IL-10 signaling at the level of the meninges of the brain. We also showed that T lymphocytes can be educated to more efficiently promote resolution of neuropathic pain. Collectively, our findings indicate that suppression of pro-inflammation may suppress pain and depression-like behavior, but is likely not sufficient to promote resolution of these comorbidities.
Alan Prossin, MBBS
Assistant Professor, U Psychiatry and Behavioral Sciences
University of Texas Health Science Center

Bio-behavioral Regulation of Plasma IL-18, a Novel Therapeutic Target in Nociceptive Pain States

Alan Prossin in on a mission to develop innovative research paradigms that facilitate translation of basic animal model research to novel treatment target and bio-signature discovery in human pain states. Trained as a psychiatrist, engineer, and psychoneuroimmunology researcher, for the past 5 years he has been leading an independent research program that uses molecular brain imaging with positron emission tomography to develop innovative, non-invasive ways of probing neuroimmune interactions underlying depression and pain states in-vivo in humans. He collaborates widely by sharing his research approach with both internal and external colleagues whose research covers a wide range of illness (traumatic brain injury, stroke, psychological trauma, maladaptive grief, coronary artery disease, acute and chronic post-operative pain). His work has been supported directly and indirectly by various federal (NIH, DOD, SAMHSA), foundation (BBRF, PARTNERS, NY Life), and institutional (UT Health, UofM Comprehensive Depression Center) funds. He has authored or co-authored various peer-reviewed manuscripts in highly regarded journals in his field.

Abstract: To curb the current opioid epidemic, novel, non-opioid analgesic alternatives are sorely needed and discovery of novel treatment targets is an essential first step. However, wide inter-individual bio-behavioral variance underlying the human pain experience often complicates target discovery in human pain states. Understanding how human bio-behavioral factors impact potent, non-opioid pain factors will enhance mechanistic understanding of pain variance factors while facilitating discovery of novel treatment targets. Evidence suggests psychosocial stress and negative affective states can have a profound impact on potent pro-nociceptive IL-1 family cytokines previously shown to facilitate emergence and persistence of nociceptive and neuropathic pain states as well as emergence of opioid tolerance and morphine hyperalgesia. Recently, we provided evidence of prominent interactions between these bio-behavioral factors and potent endogenous opioid analgesic mechanisms underlying the human experience of acute nociceptive pain. Subsequent investigations in our lab also reveal prominent neuroimmune interactions underlying powerful physical and emotional effects of placebo. This work shows that expectation-based behavioral interventions (i.e. placebo) (known for potent analgesic effects) can dramatically modulate potent pro-nociceptive IL-1 family cytokines and underlying interactions with endogenous opioid receptor activity, subsequently reducing sensitivity to a standardized nociceptive pain challenge. Taken together, this work is providing novel insight into molecular mechanisms underlying relationships between mind and body that are particularly relevant to the human acute nociceptive pain experience. The work also suggests novel leads for development of novel, non-opioid, bio-behavioral analgesic targets, a pre-requisite to combating the devastating impact of the current opioid epidemic.
Cynthia Tapia
Doctoral Candidate, Pharmacology and Toxicology Graduate Program
University of Texas Medical Branch at Galveston
Effects of the Pyrethroid Insecticide Deltamethrin on Rodent Medium Spiny Neurons of the
Nucleus Accumbens Following Acute and Early-Life Exposure

Cynthia Tapia is a doctoral candidate at the University of Texas Medical Branch in the Pharmacology and Toxicology Graduate Program. Her interest in neurotoxicology began at St. Edward’s University as a Ronald E. McNair Scholar where she conducted undergraduate research on a neonicotinoid insecticide. She received a B.S. in Biology before beginning her graduate school training as a UTMB Presidential Scholar under the guidance of Drs. Fernanda Laezza and Thomas Green. As an NIEHS Environmental Toxicology T32 pre-doctoral fellow, her current research investigates the cellular and circuitry mechanisms through which commonly encountered environmental neurotoxins, like pesticides, increase the risk of mental health disorders. Through her research, she aims to provide lasting contributions to the field of environmental neurotoxicology and improve risk mitigation and policy for especially vulnerable populations.

Abstract:
Background: Deltamethrin (DM), a pyrethroid insecticide in wide use, delays the inactivation of voltage gated sodium (Nav) channels essential for neuronal transmission. A correlation between levels of pyrethroid metabolites in urine and ADHD diagnosis in children has been illustrated through epidemiological studies. In rats, exposure to DM results in behavioral phenotypes that mimic aspects of ADHD and are associated with the dopaminergic (DA) reward pathway in the nucleus accumbens (NAc). Dysregulation of DA medium spiny neurons (MSNs) in the NAc is thought to play a critical role in neuropsychiatric disorders like ADHD, anxiety, and depression. The Nav 1.6 channel, critical in synaptic transmission, is abundant in the MSNs.

Goal: Here, we investigate the mechanism of MSNs dysfunction due to both acute and developmental DM exposure.

Methods: For the acute model, rodent brain slices containing the NAc were incubated in 10uM DM. Using whole-cell patch clamp electrophysiology, we assessed changes to intrinsic excitability of MSNs. For the early-life exposure model, pregnant female B6 mice were exposed to 3.0 mg/kg of DM throughout pregnancy and lactation. Then, male mice litter-mates from post-natal day ~30 were used for subsequent experiments. We employed whole-cell patch-clamp electrophysiology in coronal brain slices to monitor changes in NAc MSNs firing due to developmental DM exposure.

Results and Conclusions: Following acute exposure, an increase in the instantaneous firing frequency and the total number of action potentials and a decrease in the peak amplitude was observed at multiple injected current steps (n=7-8, data was normal with equal variance, two-sample t-test, p<0.05). Following early-life exposure, a decrease in the total number of action potentials and instantaneous firing frequency was observed (n=7-12, data was normal with equal variance, two-sample t-test, p<0.05). These studies will advance our knowledge of the toxic activity of DM in the developing brain and help assess risk exposure in the human population and potential increased vulnerability to substance use disorders.
Janice Kiecolt-Glaser, PhD, the Director of the Ohio State Institute for Behavioral Medicine Research, also holds the title of Distinguished University Professor as well as the S. Robert Davis Endowed Chair in the Ohio State College of Medicine. A clinical psychologist who works in the area of psychoneuroimmunology, she has published more than 250 articles, chapters, and books, most in collaboration with Ronald Glaser. Their studies have demonstrated important health consequences of stress, including slower wound healing and impaired vaccine responses; they have also shown that chronic stress substantially accelerates inflammation which has been linked with many age-related diseases. In addition, her programmatic work has focused on how close personal relationships influence immune and endocrine function, and health. Her recent work has shown that stress and depression dysregulate energy metabolism following high-fat meals, promoting weight gain. Most notable among her honors is her elected membership in the National Academy of Medicine. She has also received the American Psychological Association’s Award for Scientific Contributions to Psychology, the Lifetime Achievement Award from the Academy of Behavioral Medicine Research, and the American Psychosomatic Society’s Distinguished Scientist Award for career contributions. A Fellow in the American Association for the Advancement of Science, she has served on the editorial boards of 11 journals. Her research has been supported by a series of NIH grants, including a MERIT award.

Abstract:

Unhappy intimate partner relationships take a toll on mental and physical health, elevating the risk for many disorders including depression, cardiovascular disease, metabolic syndrome, and diabetes. Relationship distress impacts key physiological systems implicated in each of these disorders, including the sympathetic and parasympathetic branches of the autonomic nervous system, the immune system’s inflammatory response, and the gut microbiota. The multiple stresses of a troubled relationship are depressogenic, and the development of a mood disorder sets the stage for psychological and biological vulnerability. Depression provides a central pathway to immune dysregulation, inflammation, and poor health. Sleep and obesity can simultaneously feed off depression as they fuel its fires. In addition, the strong mutual influences that the members of a couple have on each other’s mental and physical health trajectories provides a new way to view the health implications of couples’ convergence or interdependence. Partner similarities in health behaviors, gene expression, immune profiles and the gut microbiota offer new ways to consider the health advantages and risks of marriage and divorce, providing new perspectives on couples’ interdependence, as well as new directions for research.
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Background. Pregnancy prompts significant life changes, particularly in one’s relationships. Close relationships are often in focus during pregnancy as friends, family, and particularly partners, are involved providing care and/or support. In general social relationships have been shown to predict adverse health problems via changes in immune factors. Cytokines play a role in both maintaining and terminating normal pregnancy. Enhanced expression of proinflammatory cytokines, particularly interleukin (IL)-6, is implicated in preterm birth. Indeed, vaginal IL-6 has the greatest sensitivity of candidate cytokines to detect preterm birth. Socioeconomic factors are also relevant such that those who are low socioeconomic status (SES) have lower infant birth weights than those who are higher SES. However, there is little work identifying specific risk factors in the Hispanic population. This study aimed to identify whether marital status influenced the odds of adverse birth outcomes for Hispanic women.

Hypothesis/Goals. This study investigated the relationship between marital status and birth outcomes among Hispanic women. We hypothesized that women who were unmarried would have, on average, lower birth weight than married, Hispanic women. We also predicted that among those who were unmarried, those with higher levels of vaginal IL-6 would have greater odds of preterm birth than unmarried women with lower vaginal IL-6.

Methods. We utilized a sample of 421 Hispanic women in Texas assessed between 2008-2011 as part of a larger study examining biological and psychosocial factors associated with low birth weight and preterm birth. Participants were between 22-24 weeks gestation when they completed the questionnaire portion of the study. We also examined how vaginal inflammation might affect these relationships in a subset of 109 women.

Results. We ran a multiple linear regression predicting birth weight (assessed continuously in grams), which included age, income, maternal depressive symptoms, viral infections, acculturative stress, and pre-pregnancy BMI ($F(9, 411) = 2.12, p = .027$). Specifically, being married predicted 128 additional grams in birthweight ($p = .037$), which were not explained by socioeconomic factors or depressive symptoms. Next, we used a logistic regression to assess odds of preterm birth. There was a reliable interaction between being married and vaginal IL-6 ($OR = 0.47, 95\% CI [0.47, 0.47], p = .038$). Simple effects coefficients revealed that marital status changed the relationship between vaginal IL-6 and preterm birth such that unmarried women with higher vaginal levels of IL-6 have higher odds of preterm delivery ($OR = 1.92, 95\% CI [0.47, 0.47], p = .038$). Among married women, there was no relationship between vaginal IL-6 and preterm birth ($p > .4$).

Conclusions. We demonstrated the importance of marital status when assessing one’s risk for adverse birth outcomes. Although vaginal inflammation reliably predicts preterm birth in many studies, there exist discrepancies. The present study contributes to the broader literature by demonstrating how a protective, psychosocial factor changes the relationship between vaginal inflammation and preterm birth.

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Inflammation reduces incentive motivation but increases behavioral contrast

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Background

Major depressive disorder is one of the most prevalent mental health disorders affecting over 16 million adults in USA. Currently available antidepressant drugs have limited efficacy. The development of novel therapies is limited by our understanding of the pathophysiology of the disorder. Several clinical and preclinical studies indicate that inflammation is involved in the development of depressive symptoms, with a predominance of somatic symptoms (e.g., fatigue, decreased motivation and reduced appetite). We have previously shown that inflammation is able not only to reduce incentive motivation but also to increase responding to the most salient stimulus in a situation of motivational competition.

Hypothesis

With the current investigation we wanted to determine whether inflammation can enhance responding to changes in expected value of an incentive stimulus.

Methods

Experiments used adult male C57BL6/J mice maintained on a 12 h light/dark cycle. To assess incentive motivation, mice were trained on a progressive ratio (PR) schedule of \( PR = 5e^{(R \times 0.2)} - 5 \), where \( R \) equals the number of rewards earned plus one. The final ratio completed (breakpoint) was assessed at the earlier of 5 min without nose pokes or 45 min. After a stable performance, mice were treated with PBS or lipopolysaccharide (LPS) 0.5 mg/kg by intraperitoneal (ip) injection and tested 24 h later. To assess the reward prediction error, mice trained to nosepoke on a fixed ratio 10 (10 nose pokes for 1 chocolate pellet) schedule were treated with PBS or 1 mg/kg of LPS by ip injection and were tested 24 h later. On the test day, chocolate pellets (C) were replaced by grain pellets (G) for half of the mice (C-G) while the other half continued receiving chocolate pellet (C-C).

Results

The assessment of incentive motivation shows that mice treated with LPS had a lower breakpoint in the PR task when compared to PBS-treated mice (\( p<0.05 \); Fig. 1A). In the negative prediction error test, PBS-injected mice decreased their responding when switched to grain pellets (C-G PBS vs C-C PBS, \( p<0.001 \); Fig. 1B). LPS had no effect on mice that received chocolate pellet on the testing day (C-C LPS vs C-C PBS) but decreased further responding in mice switched to grain (C-G LPS vs C-G PBS, \( p<0.05 \)).

Conclusions

LPS induced motivational deficits is characterized by a decreased incentive motivation suggesting a reduced willingness to work for a reward, but with an increased sensitivity to a downshift in expected hedonic value.

Acknowledgments

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**Fig. 1** – Effect of LPS on (A) incentive motivation and (B) negative prediction error and. Data are expressed as mean ± standard error of the mean. (A) *\( p<0.05 \) compared to PBS (n=8 mice/group). (B) **\( p<0.001 \) compared to C-C saline, ++\( p<0.01 \) compared to C-G saline, ^^^\( p<0.001 \) compared to C-C LPS (n=8-10 mice/group).
Association Between Depression and Inflammation Among Bereaved Adults Chen,

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Abstract

Background. Spousal bereavement is a highly stressful life event associated with an increased mortality risk due to cardiovascular disease (CVD). Work from our team and others has documented that inflammation is a key mechanism that underlies this link. Of course, not every bereaved individual is at the same risk.

Hypothesis/Goals. In this study, we sought to determine if bereaved individuals who reported more depressive symptoms show elevations in inflammation in comparison to bereaved individuals with less depressive symptoms.

Methods. We examined the relationship between inflammation and depressive symptoms in 100 bereaved participants. Inflammation was measured using in vitro stimulated cytokine secretion by T cells due to the variability of blood serum levels of cytokines. Cytokines that were measured included IL-2, IL-6, IL-17A, IFN-γ, and TNF-α.

Results. After controlling for standard confounds, bereaved individuals with more depressive symptoms exhibited greater elevations in pro-inflammatory cytokines compared with those who reported less depressive symptoms. Specifically, depression was associated with higher levels of the pro-inflammatory cytokines IL-6 (unstandardized beta = .028, p = .020), TNF-alpha (unstandardized beta = .031, p = .010), and IFN-gamma (unstandardized beta = .038, p = .009). Depression did not significantly predict IL17-A, IL-2, or any other chemokines (CCL2, CCL5, CXCL10).

Conclusions. Given that, on average, these bereaved individuals reported very high levels of depressive symptoms, it is novel that a gradient increase in depression could be identified. Thus, this study provides evidence that those bereaved individuals who are most depressed may be at highest risk for cardiovascular complications among widows/widowers.

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Role of the Glycogen Synthase Kinase 3 Pathway in the Pathophysiology of Schizophrenia

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Background: The mechanisms underlying schizophrenia (SZ), one of the most severe and debilitating mental health disorders, are not well understood. Studies and clinical evidence suggest that multiple environmental and genomic risk factors contribute to the risk of developing SZ. As such, preclinical animal models do not fully recapitulate the complexity of the disease and can be only used to characterize specific endophenotypes associated with disease presentation. Integrative translational approaches that include in vitro models and fine-tuned human genetic studies are therefore necessary to elucidate the contribution of these genomic risk factors to endophenotypes of SZ. Emerging evidence indicates that dysregulation of the protein kinase B (AKT)/glycogen synthase kinase 3β (GSK3β) pathway is a risk factor for SZ. As such, there is a need to understand the molecular targets of this pathway that directly affect neuronal excitability. We have previously shown that GSK3β regulates the complex assembly and protein:protein interactions (PPI) within the voltage-gated sodium (NaV) channel complex at the axon initial segment (AIS), the molecular determinant of neuronal excitability.

Hypothesis: Based on this premise we hypothesized that dysfunction of the GSK3/AKT pathway could lead to disruption of PPI of the AIS and excitability that could recapitulate molecular endophenotypes of SZ.

Methods: Using the split-luciferase in-cell assay we have reconstituted the PPI complex between neurofascin, an important AIS cell adhesion molecule, and voltage-gated sodium (Nav) channels and found that this interaction is increased by increasing the level of active GSK3. We also integrated genomic and functional studies in neurons differentiated from induced pluripotent stem cells (iPSCs) from a small, homogeneous population with SZ.

Results: We have found a decrease in the mRNA level of GSK3β in SZ patients (p<.05, n=11, T-test with Welch’s Corrections) compared to controls. We also identified a missense mutation in the NFASC protein associated with the disease in a combined cohort including patients from the NIMH Human Brain Collection Core (p<.01, n= 424, 1-sample test of proportions). We are currently evaluating whether changes associated with SZ and GSK3β distribution and intensity of neurofascin and Nav channels could be identified in neurons derived from patient iPSCs compared to unaffected relatives, which may underlie changes in intrinsic excitability that have previously been linked to SZ.

Conclusions: Overall, these studies might help elucidate new endophenotypes associated with SZ due to a dysregulation in the GSK3 pathway that could lead to a biological based classification of the disease and future targeted therapeutics.

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Toll-Like Receptor 4 signaling is critical for Lewis Lung Carcinoma (LLC)-induced fatigue-like behavior and metabolic alterations

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Background
Cancer-related fatigue is one of the most common and disruptive symptoms reported by cancer patients. It often presents prior to diagnosis, and this pre-treatment fatigue is one of the best predictors of fatigue during and after treatment. We currently have no FDA approved treatments for fatigue because of our poor understanding of its pathophysiology. Our ongoing work suggests that it is mediated by inefficient metabolic processes. In the current investigation, we sought to determine if signaling through Toll-Like Receptor 4 (TLR4) is involved in the development of fatigue-like behavior and metabolic changes in an inflammatory tumor model. We selected the Lewis Lung Carcinoma (LLC) murine model as it is known to be highly inflammatory.

Goal
The goal of this study is to determine if, in an inflammatory tumor model, blocking TLR4 signaling through the use of knockout mice will attenuate fatigue-like behavior and prevent tumor-induced metabolism alterations thought to underlie fatigue.

Methods
C57BL/6J and tlr4−/− mice (n=6-9 per group) were single housed and provided access to a running wheel in their home cage. After 10 days of wheel exposure and stabilization of voluntary wheel running mice were injected with 1 x 10^6 LLC cells in the right flank. We measured daily total number of rotations of the wheel per night and food consumption and body weights weekly. Animals were euthanized and tissues were collected 22 days post-tumor injection. Liver and brain gene expression was measured by qRT-PCR.

Results
WT and tlr4−/− mice displayed similar tumor growth. Tumor bearing mice engaged in less voluntary wheel running than controls by day 20 days post-tumor injection, this effect was prevented in the tumor-bearing tlr4−/− mice (Figure 1). Further, the WT tumor-bearing mice showed elevated Il-1β mRNA expression in the brain and evidence of liver metabolic dysregulation as indicated by increased mRNA levels of mct1, mct4, ldha, hk1, hk2, pkm1, pkm2, ucp2, and ucp3 (all p<0.05), these changes were not observed in tlr4−/− mice (Fig. 2).

Conclusions
Signaling through TLR4 is involved in the development of fatigue-like behavior and metabolic alterations in an inflammatory model of cancer. The exact ligand responsible for activating TLR4 remains to be identified but could be tumor-derived HMGB1.

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Discovery of HKP Compounds as New Drug Candidates for Chemotherapy-induced Chronic Neuropathic Pain

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Background
Many chemotherapy agents, including taxanes (paclitaxel [PAC], docetaxel), vinca alkaloids (vincristine, vinblastine), platinum compounds (cisplatin, oxaliplatin), and proteasome inhibitors (bortezomib), produce neuropathic pain in cancer patients and survivors. This chemotherapy-induced chronic neuropathic pain (CINP) is a dose-limiting adverse effect. Present, nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen), anticonvulsants (gabapentin, pregabalin), and antidepressants (amitriptyline, nortriptyline) have only modest analgesic effects at best for CINP.

Hypothesis/Goals
The goals is to find potent new drugs for chronic neuropathic pain.

Methods
For the PAC-induced chronic neuropathic pain (PINP), PAC (2 mg/kg) was intraperitoneally injected to male adult Sprague-Dawley rat on days 0, 2, 4, and 6 (total 8 mg/kg). The pain behavioral testing was measured with a set of von Frey filaments and then 50% mechanical threshold was calculated. The level of phosphorylated NFĸB, TNF-α, and IL-1β in the dorsal root ganglia was measured by Western blotting. HKP compounds (HKP-16, 17) was suspended in 0.5% methylcellulose in distilled water and their orally administered single or multiple to PINP rats after fully developed pain.

Results
HKP-16 or 17 significantly increased the mechanical threshold at doses of 10, 30, and 100 mg/kg by single oral administration on PINP rats. The 100-mg/kg dose of HKP-16 or 17 significantly increased the mechanical threshold up to more than 10 g at 2 h after single oral administration without sedation. The multiple oral administrations (twice daily for 4 days) of HKP-16 or 17 (30 mg/kg) also significantly increased the mechanical threshold for 4 days without sedation. In contrast, the 100-mg/kg of gabapentin as a reference drug did not significantly increase the mechanical threshold. In addition, the mechanisms of action of HKP-16 and 17 decreased PAC-induced inflammatory mediators (phosphorylated NFĸB, TNF-α, IL-1β). Furthermore, the median lethal dose of HKP-16 or 17 was more than 1 g/kg in rats by single oral administration.

Conclusions
HKP-16 and 17 showed potent analgesic effects on PINP rats by single or multiple oral administrations without sedation effect. Their mechanisms of action was to decrease the inflammatory mediators. They also had wide safety margins. Therefore, HKP-16 and 17 are new drug candidates for CINP.

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An Effort Expenditure Perspective In Cancer-Related Fatigue

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Background: Fatigue is a common and debilitating side effect of cancer and cancer treatment that can persist until well after cancer-treatment cessation. To date, cancer-related fatigue remains poorly understood, partly because it is usually characterized by patient-reported outcomes. As patient-reports are inherently subjective, behavioral correlates of the symptom of fatigue are needed to increase our understanding of the symptom.

Goals/Hypothesis: We focused on incentive motivation, the amount of effort one is willing to engage in order to obtain a reward, as potential behavioral correlate of fatigue. We hypothesized that patients undergoing cancer therapy and post-treatment survivors with higher fatigue but no depression would display decreased effort expenditure with intact reward sensitivity.

Methods: The Effort Expenditure for Reward Task (EEfRT) was used to assess incentive motivation in cancer patients (n=47; n=17 undergoing treatment for current disease and n=30 post-treatment survivors with no evidence for disease). The EEfRT is a validated computerized task contrasting high effort/high reward and low effort/low reward choices under different probabilities of success. Patient-reported fatigue, negative and positive affect, and biomarkers of inflammation were also assessed.

Results: Contrary to our expectations, higher patient-reported fatigue was related to higher effort expenditure. As we observed an interaction of fatigue with patient status, exploratory models were computed for patients and survivors separately. These analyses indicated that the effects of fatigue on effort expenditure were predominantly seen in post-treatment survivors. In patients still undergoing treatment, fatigue was associated with lower effort expenditure but only in the most favorable reward condition. Higher negative affect and plasma concentrations of pro-inflammatory biomarkers were also associated with higher effort expenditure and these effects also were seen predominantly in survivors. Positive affect was associated with lower effort expenditure.

Conclusions: The association between higher fatigue and higher effort expenditure was primarily driven by cancer survivors in whom both fatigue and negative affect were associated with higher effort expenditure. These findings are tentatively interpreted to suggest that a tendency to invest more effort despite feeling fatigued is a vulnerability for developing chronic fatigue. Inflammation and negative affect might contribute to fatigue in some survivors through this effort investment pathway.

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Attachment Anxiety, but Not Avoidance, is Associated with Greater Inflammation and Poorer Mental and Physical Health among Bereaved Spouses

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Background. Throughout the lifespan, social relationships play a key role in emotional and physiological regulation. Attachment theory provides a valuable framework for understanding how interpersonal relationships contribute to the development of one’s capacities to cope with loss experiences. How an individual relates to others, reflected by their attachment style, affects their ability to overcome stress, particularly in the context of social loss. The degree to which an individual is high in attachment anxiety or avoidance, reflects unhealthy relationship patterns, which may influence adjustment to losing a spouse.

Hypothesis/Goals. This study investigated the relationship between attachment style and poor loss adjustment, operationalized as greater levels of inflammation and poor mental and physical health. We hypothesized that among those who had recently lost a spouse, individuals high in anxious attachment would exhibit an elevated proinflammatory state and report worse mental and physical health, compared to less anxious individuals. Given the discrepancies in the literature between attachment avoidance and loss adjustment, it was unclear whether individuals high in attachment avoidance would demonstrate a similar pattern of negative health outcomes; thus, we explored the relationship between these variables.

Methods. One hundred recently bereaved participants (\(M = 84.74\) days since spouse’s passing, \(SD = 18.17\)) completed a series of questionnaires and underwent a single stick blood draw. Attachment variables were measured using the Experiences in Close Relationships – Relationship Structures Questionnaire. To measure the reactivity of the monocytes to challenge, we treated whole blood to induce cytokine/chemokine production; the outcome of this process reflects cellular immunity, which is a superior biomarker compared to peripheral levels of pro-inflammatory cytokines. Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF\(\alpha\)), and Chemokine ligand 4 (CCL4) were chosen for investigation because they were higher among bereaved individuals compared to healthy age-matched controls, in a preliminary analysis.

Results. Covariates included sleep quality, comorbidities, physical activity, age, sex, alcohol use, statin use, and the time since their spouse’s passing. Anxious attachment was associated with monocyte stimulated IL-6 and CCL4, but not TNF\(\alpha\); those high in anxious attachment also reported poorer mental and physical health compared to those low in anxious attachment. Although avoidant attachment was not significantly associated with circulating levels of inflammation, participants high in avoidance reported significantly better mental and physical health compared to those low in avoidance.

Conclusions. Our results complement recent work showing a relationship between high attachment anxiety and biologically relevant health outcomes, and fill in a gap in the literature by assessing this relationship among bereaved spouses, whose loss adjustment may be impacted by relationship factors.

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Microglia are dispensable in two preclinical models of tumor-induced fatigue.

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Background
Cancer-related fatigue (CRF) greatly contributes to decreased quality of life in patients diagnosed with cancer. Present in roughly 20% of patients at the time of diagnosis, CRF only increases in prevalence and severity throughout the course of treatment, often persisting through survivorship. A lack of FDA-approved treatments is likely due in part to an incomplete mechanistic understanding of CRF. Much of the literature implicates changes in inflammatory signaling in the development of CRF. Macrophages and microglia, their CNS counterparts, are some of the fundamental cellular drivers of the body’s inflammatory response. Recent pharmacological advances have provided the opportunity for deeper investigation of these cells’ roles in pathology by allowing for their conditional depletion. By applying these tools in rodents, we can begin to answer questions regarding the inflammatory mechanisms of CRF.

Goal
The purpose of this study was to determine the differential effects of a murine model of human papillomavirus-positive head and neck cancer (mEER) and Lewis Lung Carcinoma (LLC) tumors on wheel-running as mediated by macrophage/microglia activity using a macrophage/microglia-depleting drug, PLX5622, administered in chow.

Methods
Male C57 wild type mice (n=32) were divided into the following groups: control diet saline (C-S; n=6), control diet mEER (C-M; n=5), control diet LLC (C-L; n=5), PLX5622 diet saline (P-S; n=6), PLX5622 diet mEER (P-M; n=5), and PLX5622 diet LLC (P-L; n=5). Animals were then placed on either the experimental or control diets while group-housed (4 animals per cage). After 10 days on the assigned diet, animals were single housed with running wheels. Body and food weights were recorded twice each week throughout the study. At week 3 of feeding, animals were injected with either saline, 1 mil cells LLC, or 0.5 mil cells mEER. Animals were euthanized on day 21 post-tumor injection and tissues (blood/plasma, liver, spleen, tumor) were collected for analysis by qRT-PCR.

Results
Depletion of macrophages and microglia was confirmed by qRT-PCR analysis of CxC3CR1, CSFRI, and CD11b gene expression. Both mEER and LLC tumors induced deficits in nightly wheel-running behavior. There were no differences in nightly wheel running between diet groups. IL-6 expression was increased in the brains of C-M mice, but not in any other group. PLX5622 treatment decreased expression of IL-6, IL-1β, and TNF-α in the livers and IL-1β and TNF-α in the tumors of tumor-bearing mice.

Conclusions
Pharmacological depletion of macrophages and microglia is sufficient to reduce tumor induced inflammation in the models studied. However, this manipulation is unable to rescue tumor-induced fatigue behavior in mice. Further research is needed to determine the exact mechanisms of cancer-related fatigue as mediated by alterations in inflammatory signaling.

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Oral Administration of Leucine Ameliorates Effects of Lipopolysaccharide Induced Depression

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Background
Previous studies by our lab have shown that intraperitoneal (IP) administration of the amino acid leucine decreases lipopolysaccharide (LPS) induced depressive like behaviors in mice. Leucine acts on the L-Type Amino Acid Transporter 1 (LAT1), which is critical for blood to brain transport of kynurenine, a precursor to neurotoxic metabolites formed in the brain during inflammation. Our study aims to understand if a similar benefit can be obtained orally, since this would be a more clinically relevant route of administration.

Hypothesis
We hypothesize oral administration of leucine will prevent LPS-induced depressive behavior in mice by competing with kynurenine for LAT1 and preventing kynurenine from being transported into the brain.

Methods
26 CD1 male mice (10-12 weeks) were housed individually in standard shoebox cages with a 12/12-h modified dark-light cycle. Food and water were available ad libitum. Mice were handled 3 days before testing. LPS (E. coli serotype 0127:B8; Sigma, St Louis, MO) was administered IP at a dose of 0.83 mg/kg followed immediately by oral gavage of leucine (L6914, Sigma) at a dose of 0.76 mmol/kg. Leucine was re-administered at the same dose 6 h later. Mice were randomly allocated into treatment groups: Saline + Water (n = 8); LPS + Water (n = 9); LPS + Leucine (n = 9). The alleviating effect of leucine on LPS-induced depression-like behavior was measured by duration of sniffing of female urine (female urine sniffing test, FUST) completed at 22 h post-LPS and duration of immobility in the forced swim test (FST) completed at 23 h post-LPS. Blood and brain samples were collected at the end of the experiment. Brain and plasma kynurenine levels were measured by ELISA kits (K3728, Immundiagnostik AG; ISE-2227, Immunosmol).

Results
LPS administration significantly decreased female urine sniffing behavior in the FUST when compared to the control mice (p < 0.05), however, administering leucine significantly recovered the behavior (p < 0.01). Similarly, LPS administration significantly increased immobility time when compared to the control mice (p < 0.0001), and, leucine administration significantly recovered performance (p < 0.005). Tissue analysis indicated that leucine mitigated LPS-induced increases in brain kynurenine, although; this effect did not reach statistical significance.

Conclusions
The oral administration of leucine ameliorates LPS-induced behavioral deficits in mice. Ongoing studies are further investigating the mechanism of action.

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Ajinomoto-Tokyo, Japan. University of Texas MD Anderson Cancer Center-Houston, Texas.
Preliminary Results of an Investigation of Attitudes, Social Norms, and Behavioral Control Factors Influencing Cervical Cancer Screening in Hispanic Americans

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Background: Hispanic women bear higher rates of cervical cancer than non-Hispanic women. Additionally, the cancer is typically discovered at a later stage and leads to greater rates of fatality. This may be due to a lack of cervical cancer screening within this population, as Hispanic women endorse lower rates of cervical cancer screening than those of non-Hispanic ethnicity. Previous lines of research have investigated the impact of embarrassment, cultural factors, self-efficacy, and health literacy on cervical screening behaviors, but little research has integrated these influences into a cohesive framework, and none has done so in a nationally representative sample of Hispanic women. Thus, the current study seeks to examine the utility of the Theory of Planned Behavior (TPB) to predict cervical cancer screening in a representative sample of US Hispanic women.

Hypothesis/Goals: The TPB postulates that attitudes, social norms, and perceived behavioral control predict behavioral intention. We hypothesized that culturally tailored indices of attitudes (medical embarrassment), social norms (marianismo beliefs; acculturation), and perceived behavioral control factors (cervical cancer screening self-efficacy; health literacy) will predict cervical cancer screening intentions among US Hispanic women.

Methods: 93 Hispanic women between the ages of 23-65 currently residing in the US were recruited from Amazon Mechanical Turk and answered all study measures via Qualtrics. Measures for the study included Medical Embarrassment Questionnaire, English subscales of the Abbreviated Multidimensional Acculturation Scale, Marianismo Beliefs Scale, Cancer Health Literacy Questionnaire-30, and Cervical Cancer Self-Efficacy Scale, questions concerning their intentions and plan to receive cervical cancer screening (Roncancio et al., 2013), and questions concerning past cervical cancer screening behavior.

Results: A linear regression was conducted to determine the relative predictive value of each of the 5 indices described above, covarying for past screening behavior. The overall model fit was good (p=0.003), and explained 42 percent of the variance in screening intention. However, only cervical cancer self-efficacy was significantly predictive of cervical cancer screening intention (β=0.009, p=0.002).

Conclusions: Cervical cancer screening self-efficacy may be an important predictor of cervical cancer screening intentions among US Hispanic women. This is congruent with previous research stating that perceived behavioral control is the most important predictive factor of health behavior. The Theory of Planned Behavior is a succinct model that elucidates reasons for the lower rates of cervical cancer screening at the personal, cultural, and societal level.
The Prospective Influence of Inflammation and Childhood Trauma on Future Depressive Symptomology Among Bereaved Spouses

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Background. Major life stressors often precede depression onset, with the distress of interpersonal loss being especially associated with the emotional distress characteristic of depression. According to the social signal transduction theory of depression, social stressors are biologically “converted” to create an internal environment that promotes inflammation and depression pathogenesis. Though inflammation is not a necessary determinant of depression onset, many people with depression present an elevated inflammatory profile. We aimed to examine the prospective associations between inflammation on depressive symptoms in the spousally bereaved population, as risk for depression is high during the first year after loss compared to non-bereaved adults.

Hypothesis. This study examined the relationship between inflammation and depression across two time points and also investigated what factors make inflammation more likely to be followed by depression. We hypothesized that among bereaved spouses, inflammatory levels at 3 months post-loss (V1) would predict depressive symptoms at 6 months post-loss (V2), such that elevated inflammatory levels at V1 would predict the maintenance or increase of depressive symptoms at V2. We also hypothesized that childhood trauma would moderate the associations between inflammation at V1 and depression at V3.

Methods. Ninety-eight spousally bereaved individuals were evaluated at 3 months post-loss (M = 84.74 days since spousal loss, SD = 18.17) and 6 months post-loss (M = 196.21, SD = 13.94). At both visits, blood was collected in the morning to control for diurnal variation. Participants completed self-report questionnaires including the Center for Epidemiological Studies in Depression Scale and Childhood Trauma Questionnaire. LPS-stimulated T cell-derived proinflammatory cytokines were evaluated including IL-6, TNF-α, and IFN-γ. The following covariates were included in analyses: age, sex, BMI, days since passing, comorbidities, smoking use, and statin use.

Results. Inflammation at 3 months post-loss (V1) predicted depressive symptoms at 6 months post-loss (V3); bereaved individuals with elevated levels of IL-6, TNF-α, and IFN-γ also exhibited greater depressive symptoms. Childhood trauma moderated the association between inflammation at V1 and depression at V3; individuals with greater childhood trauma and elevated levels of IL-6, TNF-α, and IFN-γ exhibited greater depressive symptoms compared to individuals with elevated inflammation but less childhood trauma.

Conclusions. Our work integrates current knowledge on depression, early life adversity, and bereavement by demonstrating the prospective influence of inflammation and childhood trauma on future depressive symptomology. We provide support for theories on stress-induced depression in which inflammation and major life stressors play an integral mechanistic role in the pathophysiology of depression.

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