Seventh Annual Meeting Of The Organization For The Study Of Sex Differences

OSSD 2013

April 25-27, 2013
Sheraton Lincoln Harbor
Weehawken, NJ
USA
Welcome to **OSSD 2013**, the 7th annual meeting of the Organization for the Study of Sex Differences! Under the capable leadership of the chair, Kevin Beck, UMDNJ - New Jersey Medical School, and co-chair, DeLisa Fairweather, Johns Hopkins University, the OSSD Program Committee has put together a spectacular program with an outstanding line-up of basic and clinical scientists. This meeting will also introduce you to a terrific crop of up-and-coming researchers in the field of sex differences, who will present their work in the Elizabeth Young New Investigator Symposium and in the two planned poster sessions. OSSD's mission is to promote research in, and knowledge of, sex and gender differences in biology and medicine. Our first priority is to hold high-quality annual meetings. We fully expect OSSD 2013 to meet that goal and to generate the same level of inspiring cross-discipline interaction as did the previous meetings.

OSSD's official journal, *Biology of Sex Differences* (BSD), celebrated its second anniversary in early November of last year. Under the excellent stewardship of editor-in-chief, Art Arnold, and with the assistance of an internationally acclaimed editorial board, the journal did great last year: the total number of articles published more than doubled, the total number of accessions nearly quadrupled, and the number of articles that got the designation 'highly accessed' climbed five-fold, as did the number of citations. The journal keeps publishing stimulating primary research and review papers in a rich variety of biological and medical sub-disciplines. These papers are freely available on the web and several of them have circulated extensively in news media, drawing a lot of attention. If you haven’t done so already, consider BSD for publishing your best work on sex differences in biology and medicine.

Finally, I would like to thank the Society for Women’s Health Research for its generous financial as well as administrative support in founding OSSD and in shepherding it through its initial six years. This past year was the first year that OSSD operated independently of SWHR. I would like to express my deep gratitude to the members of OSSD Council and the Executive Board for their tireless efforts that made this all possible.

Geert J. de Vries Ph.D.
President of the OSSD
Professor of Neuroscience
Neuroscience Institute
Georgia State University
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<tr>
<td>7:30 am – 8:30 am</td>
<td>Breakfast (provided)</td>
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<td>8:00 am – 12:00 pm</td>
<td>Workshop: “Sex Differences 101”: Biological Basics of Biomarkers</td>
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<td>12:00 pm – 1:00 pm</td>
<td>Free Time</td>
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<td>1:00 pm – 1:15 pm</td>
<td>Welcome and Introductions</td>
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<td>OSSD President: Geert de Vries PhD</td>
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<td>OSSD 2013 Program Chair: Kevin Beck PhD</td>
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<td>1:15 pm – 2:15 pm</td>
<td>Keynote Address</td>
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<td>Sex, Stress, and the Brain: From Serendipity to Clinical Relevance</td>
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<td>Bruce McEwen PhD</td>
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<td>2:15 pm – 3:15 pm</td>
<td>Elizabeth Young New Investigator Symposium</td>
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<td>3:15 pm – 3:30 pm</td>
<td>Break (provided)</td>
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<td>3:30 pm – 5:30 pm</td>
<td>Presidential Symposium</td>
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<td>Sex Differences in Autism</td>
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<td>Chairs: Rosanna Weksberg MD/PhD &amp; Peter Szatmari MD</td>
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<td>5:30 pm – 8:00 pm</td>
<td>Poster Session 1</td>
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<td>8:00 pm – 10:00 pm</td>
<td>Welcoming Session</td>
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**Friday, April 26, 2013**

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<td>7:30 am – 8:30 am</td>
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<tr>
<td>8:15 am – 10:15 am</td>
<td>Symposium I</td>
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<tr>
<td></td>
<td>Diverse Roles of Gonadal Hormones in the Pathology and Treatment of</td>
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<td>Epilepsy in Men and Women</td>
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<td>Chair: Helen Scharfman PhD</td>
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<td>10:15 am – 10:30 am</td>
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<td>10:30 am – 12:30 pm</td>
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<td>Psychoimmunology of Mental Illness (in memory of S. Zalcman)</td>
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<td>Chairs: Kevin Beck PhD &amp; Gretchen Neigh PhD</td>
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<td>12:30 pm – 2:30 pm</td>
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<td>2:30 pm – 4:30 pm</td>
<td>Symposium V</td>
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<td>Clinical Considerations of Sex and Gender in Clinical Practice:</td>
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<td>Promise, Potential, and Pitfalls</td>
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<td>Chair: Marjorie Jenkins MD</td>
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<td>Symposium II</td>
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<td>Infections and Heart Disease</td>
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<td>Chair: Sally Huber PhD</td>
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<td>Symposium IV</td>
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<td>Sex Differences in Cardiac Arrhythmias</td>
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<td>Chair: Glenna Bett PhD</td>
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<td>Symposium VI</td>
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<td>Sex and Gender in Cardiovascular-renal Physiology and Pathology</td>
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<td>Chair: Jane Recklehoff PhD</td>
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<td>7:30 am – 8:30 am</td>
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<td>8:15 am – 10:15 am</td>
<td>Symposium VII</td>
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<td>Pain Management in Cancer</td>
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<td>Chair: Karen Berkley PhD</td>
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<td>10:15 am – 10:30 am</td>
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<td>10:30 am – 12:30 pm</td>
<td>Symposium IX</td>
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<td>Causes and Consequences of Sex Differences in Multiple Sclerosis</td>
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<tr>
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<td>Plenary Symposium XI</td>
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<td>Centers for Sex Difference Research</td>
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<td>Chair: Janine Clayton MD</td>
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<td>4:30 pm – 5:30 pm</td>
<td>Capstone Lecture</td>
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<td>Gender and Genetics of Sexual Development</td>
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<td>Eric Vilain MD/PhD</td>
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<td>5:30 pm – 6:30 pm</td>
<td>General OSSD Membership Meeting</td>
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<td>7:00 pm – 9:00 pm</td>
<td>OSSD Awards Dinner</td>
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ELIZABETH YOUNG NEW INVESTIGATOR SYMPOSIUM

Sienmi Du (University of California, Los Angeles, CA)
Di K. Nguyen (University of Washington, Seattle, WA)
Amutha Selvamani (Texas A&M Health Sciences Center, College Station, TX)
Marianne L. Seney (University of Pittsburgh, Pittsburgh, PA)
Michael V. Lombardo (University of Cambridge, Cambridge, UK)

NIH-SPONSORED TRAVEL AWARDS

Tuck Ngun (University of California, Los Angeles, CA)
Nicole T. Nowak-Saenz (University of Wisconsin, Milwaukee, WI)
Tychele Turner (Johns Hopkins University School of Medicine, Baltimore, MD)
Jill M. Weathington (Georgia State University, Atlanta, GA)
Shayna Williams-Burris (University of California, Los Angeles, CA)
Lauren Wright (McMaster University, Hamilton, ON)
Arthur P. Arnold, PhD, is Distinguished Professor of Integrative Biology & Physiology at UCLA. He is the Editor-in-Chief of Biology of Sex Differences, the official journal of the OSSD. For many years he has studied gonadal hormone effects on brain sexual differentiation, and now focuses on novel mouse models that allow one to detect the physiological and disease-related effects of sex chromosome complement (XX vs. XY). Dr. Arnold was Inaugural President of the Society of Behavioral Neuroendocrinology in 1997-1999, and is fellow of the John Simon Guggenheim Memorial Foundation and the American Association for the Advancement of Science.

Jill N. Barnes, PhD, is a Research Fellow in Anesthesiology and an Assistant Professor of Physiology in the College of Medicine, Mayo Clinic. She grew up in Quincy, Michigan and attended the University of Michigan, Ann Arbor, MI where she worked in Dr. Jeffrey Horowitz’s Substrate Metabolism laboratory. Jill then moved to the University of Texas at Austin and received her Master’s and Ph.D. under the direction of Hirofumi Tanaka, Ph.D in the Cardiovascular Aging Research Laboratory. She then came to Mayo Clinic to work in Dr. Michael Joyner’s Human and Integrative Physiology as a postdoctoral fellow. Her research interests include: cardiovascular regulation in humans; control of cerebral blood flow; and mechanisms of central arterial stiffness, and how these change in aging men and women. Her work at Mayo Clinic was supported by an individual fellowship awards from the National Institute of Aging at NIH.

Kevin D. Beck, PhD, received his B.A. in Psychology from La Salle University, his M.A. in Developmental Psychology from Teachers College, Columbia University, and his Ph.D. in Biopsychology from the City University of New York. He conducted post-doctoral training in Neuroscience at the University of Medicine and Dentistry of New Jersey (UMDNJ). He now holds the position of Research Physiologist at the VA New Jersey Health Care System and holds the position of Associate Professor at UMDNJ – New Jersey Medical School. His research spans from basic experimental psychology to behavioral neuroscience to psychoneuroimmunology, with a fundamental focus of understanding individual differences in susceptibility to develop stress-related disorders and illness. Human studies and animal experimentation in his lab have been specifically developed to elucidate neural mechanisms underlying anxiety vulnerability, depression, and unexplained illness. His research has been funded by the U.S. Department of Veterans Affairs and the U.S. Department of Defense.

Karen J. Berkley, PhD is Emeritus Professor in Neuroscience / Psychology, Florida State University, Tallahassee, FL. She received her BA in Biology in 1963 from Brown University and her PhD in 1968 from the University of Washington in Physiology / Biophysics. She has published ~150 scientific articles/chapters/book, served on the editorial boards of ten scientific journals, was a councilor for the International Association for the Study of Pain and the Society for...
Neuroscience, and is currently a councilor for the Organization for the Study of Sex Differences. She served on three committees of the USA National Academy of Sciences, including “Exploring the Biological Contributions to Human Health. Does Sex Matter?” Her research has addressed central and peripheral neural mechanisms of pelvic pain for more than 47 years, with a recent focus on endometriosis. She is also involved in translational issues concerning mechanisms of co-existing chronic pain conditions, women’s health, and sex/gender differences in pain.

Glenna C.L. Bett, PhD, is Vice-chair for Research in the Department of Gynecology-Obstetrics, and Deputy Director of the Institute for Research and Education on Women and Gender (IREWG) at the University at Buffalo, Buffalo, NY. Dr. Bett studied Physics at the University of Oxford, UK, where she subsequently continued for her PhD (DPhil) in Physiology. Dr. Bett has used her quantitative and analytical training in Physics as a basis to develop an expertise in electrophysiology, ion channel biophysics, and mathematical modeling of cellular excitability. Her research has been funded by the NIH, AHA, the March of Dimes, the Simons Foundation, and the Bill and Melinda Gates Foundation. She is Co-chair of the Cardiac Electrophysiology AHA study section and has served as a grant reviewer for the NIH and other foundations. She serves on the editorial board of several journals. In addition to studying the electrical profile of the uterus, Dr. Bett is interested in the sex differences in the electrical profiles, and she has a particular focus on the interplay between genetic and environmental factors that alter ion channel function and result in sex dependent cardiac and neurological development and dysfunction.

Lori Blauwet, MD, is an Assistant Professor of Medicine and a Senior Associate Consultant in the Cardiovascular Diseases Division at Mayo Clinic, Rochester, Minnesota. Her clinical and research interests include heart disease in women, peripartum cardiomyopathy, myocarditis and echocardiography. She has a keen interest in sex differences in cardiovascular disease and is currently collaborating with Dr. DeLisa Fairweather on several translational clinical research projects to investigate the mechanistic basis for these sex differences and their therapeutic implications.

Arapinda Chakravarti, PhD, is Director, Center for Complex Disease Genomics and Professor of Medicine, Pediatrics, Molecular Biology & Genetics, and Biostatistics at the Johns Hopkins University School of Medicine and the Bloomberg School of Public Health. He is the 2008 President of the American Society of Human Genetics, a member of the US National Academy’s Institute of Medicine and an Honorary Fellow of the Indian Academy of Sciences. He has been a key participant and architect of the Human Genome, HapMap and 1000 Genomes project. His research is aimed at genome-scale analysis of humans and computational analysis of gene variation and function to understand the molecular genetic basis of human disease. He received his doctoral degree in human genetics from the University of Texas Health Science Center in Houston and continued postdoctoral training at the University of Washington in Seattle. He started his faculty career at the University of Pittsburgh (1980 – 1993), was the James H. Jewell Professor of Genetics at Case Western Reserve University (1994-2000), and the inaugural Director and Henry J. Knott Professor of the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins (2000-2007). He is currently the founding Director of the Center for Complex Disease Genomics at Johns Hopkins. Dr.
Chakravarti is one of the founding Editors-in-Chief of Genome Research and Annual Reviews of Genomics & Human Genetics, and serves on the Advisory and Editorial Boards of numerous international journals, boards, academic societies, the US NIH and biotechnology companies.

Janine Austin Clayton, MD, is the Director of the Office of Research on Women's Health, National Institutes of Health (NIH), and Associate Director for Research on Women's Health, NIH, in the NIH Office of the Director. She is the author of over 80 scientific publications, journal articles, and book chapters. A board certified ophthalmologist, Dr. Clayton's research interests include autoimmune ocular diseases and the role of sex and gender in health and disease. Dr. Clayton received her undergraduate degree from the Johns Hopkins University, her medical degree from Howard University College of Medicine, and completed a residency in ophthalmology at the Medical College of Virginia, followed by fellowship training at both the Wilmer Eye Institute at Johns Hopkins Hospital and at NEI. Dr. Clayton has been an attending physician and clinical investigator in cornea and uveitis at the NEI since 1996, conducting research on inflammatory diseases of the anterior segment. Dr. Clayton is a Fellow of the New York Academy of Medicine, and currently serves on the FDA Advisory Panel for Ophthalmic Devices; the medical and scientific advisory board of Tissue Banks International; and the editorial board of The Ocular Surface. She was selected as a Silver Fellow by the Association for Research in Vision and Ophthalmology and is a recipient of the Senior Achievement Award from the American Academy of Ophthalmology. She co-chairs the NIH Working Group on Women in Biomedical Careers with the NIH Director.

Michael Coronado, PhD, earned a Bachelor of Sciences degree in Biochemistry from the University of California, Riverside where he conducted undergraduate research identifying xenoestrogens that feminized fish living near the Los Angeles CA outfall. After graduation, Michael transitioned from studying ecology to human health by pursuing a PhD in Environmental Health Sciences at the Johns Hopkins Bloomberg School of Public Health where he investigated the role of sex differences in inflammatory heart disease. Currently, Michael is a Postdoctoral Research Fellow at Stanford University in the Department of Pediatric Cardiology. Under the mentorship of Dr. Daniel Bernstein, Michael is investigating the role of mitochondria in the development of heart failure and the role of sex in mitochondrial sensitivity to reactive oxygen species.

Madeleine Cunningham, PhD, received her PhD in 1973 at University of Tennessee Health Sciences Center-Memphis in Microbiology and Immunology. She studied for 3 years as a postdoctoral fellow in Protein Studies at the Oklahoma Medical Research Foundation in Oklahoma City. Following her postdoctoral fellowship, she accepted a position at the University of Oklahoma Health Sciences Center, where she is now the Director of the NIAID supported Immunology Training Program at the University of Oklahoma Health Sciences Center. Research in Dr. Cunningham's laboratory investigates molecular mimicry, autoimmunity and infection in inflammatory heart diseases and in behavioral and movement disorders. Studies in myocarditis currently are supported by the National Heart Lung and Blood Institute and are focused on a 5 year longitudinal study. She is also funded by the Lyme Disease Association, and the National Institute of Mental Health Bench to Bedside Grant, which is to investigate autoantibodies in pediatric autoimmune neuropsychiatric
disorder. Dr. Cunningham has served many years on review panels at the NIH and on the National Research Committee at the American Heart Association. She represented the United States in the US-Indo Vaccine Action Program. She was elected an AAAS fellow and ASM fellow, and received a National Heart Lung and Blood Institute Research Career Development Award and Merit Award.

Edwin A. Deitch, MD, is Professor of Surgery at New Jersey Medical School. His clinical and research fields of interest have included abdominal surgery, burns, trauma and critical care. He has been named as “Best Doctor in the US”, “Best Doctor in New Jersey” and “Best Doctor in New York” for over a decade. He has served on the board of many national societies, on multiple NIH committees and has been elected President of four national Surgical Societies. Additionally, he has also received 4 national awards for his clinical and research activities and has received more than $18.8 million (direct and indirect) in NIH and federal funding. He has published more than 350 original articles and three books and has served as Visiting Professor at more than 75 Universities and Medical Schools in the US and Canada and has been an invited speaker at 69 national conferences and 40 international conferences.

Christine Distetche, PhD, is a professor in the Department of Pathology with an adjunct appointment in Medical Genetics at the University of Washington. Her laboratory has considerable expertise in research on the regulation of the X chromosome and has a strong interest in understanding sex differences. The long term goal is to study the molecular mechanisms of regulation of X-linked genes in relation to sex and dosage of the X chromosome. Unique resources and productive collaborations have been developed in the laboratory to follow gene expression and epigenetic modifications of the mouse and human X chromosomes using next-generation sequencing. Notably, the laboratory has used RNA-seq to establish complete expression profiles of each X chromosome. She has been an active member of the Council of the Organization for the Study of Sex Differences.

Alice Dreger, PhD, is Professor of Clinical Medical Humanities and Bioethics at Northwestern University’s Feinberg School of Medicine. She is author of Hermaphrodites and the Medical Invention of Sex and One of Us: Conjoined Twins and the Future of Normal (both with Harvard University Press). She is a regular contributor to the Health section of The Atlantic and has also written for The New York Times, the Washington Post, the Wall Street Journal, and the Chicago Tribune. She served as board chair of the Intersex Society of North America (ISNA) for five years. In 2011, UTNE Reader named her a visionary for her work on intersex, and TED released her talk on intersex in the “Sex, Secrets, & Love Online” Netflix compilation. Her essay, “Lavish Dwarf Entertainment,” was chosen for Norton’s 2009 annual anthology of Best Creative Non-Fiction. Her forthcoming book is on scientific controversies over human identity.

Shannon Dunn, PhD, started as a scientist in 2009 after conducting post-doctoral research at Stanford University in the laboratory of Dr. Lawrence Steinman. She currently leads a research program that focuses on various risk factors for the development of T cell-mediated autoimmune diseases such as multiple sclerosis (MS). Currently, she is exploring the role of sex in autoimmunity development focusing on the animal model of MS, called EAE. She is interested in the underlying reasons for why female T cells proliferate more
robustly and secrete higher levels of T helper 1 associated cytokines as compared to male T cells. She is also exploring possible roles for peroxisome proliferator-activated receptors in the suppression of T cell activation. She holds operating grants from CIHR and MS Society of Canada to conduct this research.

DeLisa Fairweather, PhD, FAHA, completed her PhD at the University of Western Australia in Perth, Western Australia on cytomegalovirus-induced myocarditis in 2000. While conducting her Postdoctoral Fellowship in the lab of Dr. Noel Rose she developed a new autoimmune model of coxsackievirus B3-induced myocarditis, which displays marked sex differences that closely resemble clinical disease. She took this model to her own lab at Johns Hopkins University in 2005, where she is currently studying how sex steroids regulate the inflammatory response to infection leading to chronic cardiovascular disease.

Paul Farquhar-Smith, PhD, has been a Consultant in Pain, Anaesthetics and Intensive Care for over 10 years and is a Fellow of the Faculty of Pain of the Royal College of Anaesthetists and a Fellow of the Faculty of Intensive Care Medicine. He works in chronic cancer pain in liaison with palliative care, offering invasive analgesic techniques. A major interest is pain in cancer survivors such as chronic pain after surgery and chemotherapy-induced neuropathic pain. He has written in reference textbooks and in the British Pain Society guidelines for cancer pain and has lectured nationally and internationally on the subject. He is currently section editor of *Current Opinion in Supportive and Palliative Care* and is co-chair of the British Pain Society and the Association for Palliative Medicine joint working group in Pain in Cancer Patients. He is currently investigating bortezomib-induced neuropathy and looking at chronic pain after different types of reconstructive surgery for breast cancer.

Jeffrey P. Henderson, MD PhD, is Assistant Professor of Medicine and Molecular Microbiology at the Center for Women's Infectious Disease Research (cWIDR) at Washington University in St. Louis. Following undergraduate study at the University of Wisconsin, he studied medicine and completed thesis research with Jay W Heinecke at Washington University. As an infectious diseases fellow and ORWH BIRCWH scholar he studied urinary tract infection (UTI) pathophysiology with Scott Hultgren. Dr. Henderson's laboratory focuses on multidisciplinary studies of Gram negative infections. Diagnostic and therapeutic discovery efforts in the lab aim to better understand how host and pathogen-specific interactions influence clinical outcomes. The Henderson laboratory makes extensive use of mass spectrometry in both human and mechanistic biochemical studies to identify relevant interactions between secondary metabolites, metal ions, and host proteins. As a SCOR investigator, he is focused on identifying biochemical sex differences influencing UTI susceptibility.

Sally Huber, PhD, obtained a Ph.D. in Immunology from Duke University with Dr. Bernard Amos in 1975; was a postdoctoral fellow at Stanford University from 1975 to 1978 and a Research Associate in Pathology with Dr. Jack Woodruff from 1975 to 1981. Since 1981 she has been in the Department of Pathology at the University of Vermont where she currently holds the rank of Professor. She investigates the mechanisms of virus induction of autoimmunity to cardiac antigens using a mouse model of coxsackievirus B3 myocarditis. Work has concentrated on how the initial interaction of the virus infection with the innate immune response determines whether
autoimmunity develops; and how sex chromosome complement and sex hormones impact innate immune responses to infection. These studies have resulted in over 160 publications since 1981.

Meredith Hullar, PhD, is a microbiologist at FHCRC. She received her Ph.D. from Harvard University in 2000. Her research interests include the role of the microbiome and diet in human health. Her research focuses on how the gut microbiome metabolizes dietary constituents and alters exposures that may influence health outcomes related to cancer. She uses a combination of dietary interventions and cross-sectional human population designs to study changes in the microbial community composition and functional genes associated with health outcomes. More specifically, she is interested in the role of the gut microbiome in obesity, the metabolism of phytochemicals by microbiota, and intermediary mechanisms of inflammation modulated by the gut microbiome.

Marjorie R Jenkins, MD FACP, is a Professor of Medicine and Associate Dean for Women in Science at Texas Tech University Health Sciences Center. Her career focus is the cultivation of multidisciplinary research and education efforts in sex and gender-based medicine (SGBM) and through these efforts, the promotion of personalized care for men and women. She served as the Founding Executive Director and currently as Director and Chief Scientific Officer of the Laura W. Bush Institute for Women’s Health (LWBIWH). She serves nationally in a variety of roles, such as an executive council member of the Sex and Gender Women’s Health Collaborative, a member of the Women’s Health Task Force of the National Board of Medical Examiners, a founding board member for the Academy of Women’s Health, an expert panel member for the Health Resources and Services Organization (HRSA) Women’s Health Curricula: Report on Interprofessional Collaboration Across the Health Professions and co-chair for the NASA Decadal Review in Sex and Gender Reproduction Workgroup.

Lisa Kilpatrick, PhD, received B.A.s in Cognitive Science and Mathematics from the University of CA, Los Angeles and received her Ph.D. in Biological Sciences from the University of CA, Irvine. Dr. Kilpatrick is part of the neuroimaging and psychophysiology cores at the University of CA Los Angeles Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress. Her research focuses on the altered central nervous system processes in functional pain disorders such as Irritable Bowel Syndrome (IBS) and in other patient populations thought to have altered interoceptive processing such as obesity. She is dedicated to exploring sex differences in nervous system processes as an important step towards tailoring therapies to individual neurobiologies. Current projects include sex-gene interactions in IBS and the effect of satiety signals on resting state activity in lean and obese women.

Sabra L. Klein, PhD, received her B.A. in Psychology from Randolph-Macon College, her M.S. from the University of Georgia in Biological Psychology, and her Ph.D. in Behavioral Neuroscience from Johns Hopkins University. She did postdoctoral training at the Johns Hopkins Bloomberg School of Public Health in Molecular Microbiology and Immunology where she is now an Assistant Professor. Dr. Klein is a leading expert on sex differences in susceptibility to infection and currently has over 80 peer-reviewed publications. She has authored several book chapters and has edited a book entitled Sex Hormones and Immunity to Infection. Dr. Klein’s research examines the impact of hormones on immune responses
Working with viruses, including influenza viruses, her research indicates that females typically mount more robust immune responses than males, which can be beneficial for clearance of viruses, but also can be detrimental by causing immune-mediated pathology. She has further demonstrated that females mount higher adaptive immune responses following vaccination against influenza, which leads to greater cross-protection in females than males. Her research has been supported by grants from the National Institute of Allergy and Infectious Diseases, the National Science Foundation, and the National Foundation for Infectious Diseases. In 2010, she won the Society for Women’s Health Research Medtronic Award for Science Contributions.

**Wendy Kohrt, PhD.** is a Professor of Medicine in the Division of Geriatric Medicine at the University of Colorado – Anschutz Medical Campus. She is the Director of Research for Geriatric Medicine and the Director of the Energy Balance Core Laboratory for the Nutrition and Obesity Research Center. One focus of Dr. Kohrt’s research is on age-related changes in metabolism and sex steroids, with an emphasis on understanding changes that are triggered by the menopausal transition in women. Her intervention studies involving exercise, weight loss, and hormone therapy are directed at learning more about the mechanisms for menopause-related changes in body composition and fat distribution. Dr. Kohrt has been continuously funded by the NIH as a principal investigator for 23 years and has over 175 original and solicited research publications. She is the principal investigator for a Department of Defense Investigator-initiated research grant, two NIH R01 grants, one NIH R21 grant, and the Colorado Specialized Center of Research on Sex Differences.

**Janine LaSalle, PhD.** is a Professor of Microbiology and Immunology at the University of California, Davis, with memberships in the Genome Center, and the MIND Institute. Dr. LaSalle serves as Chair of the Genetics Graduate Group at UC Davis. Dr. LaSalle also serves on the editorial board of the journals *Human Molecular Genetics, Molecular Autism, and OA Autism* and is on the Scientific Advisory boards of the International Rett Syndrome Foundation and the Dup15q Alliance. The research focus in Dr. LaSalle’s laboratory is on epigenetics of neurodevelopmental disorders, including autism, Rett, Prader-Willi, Angelman, and Dup15q syndromes. Dr. LaSalle’s laboratory uses genomic and epigenetic technologies to investigate the role of DNA methylation and MeCP2 in the pathogenesis of Rett syndrome and autism spectrum disorders. Dr. LaSalle’s lab has more recently been taking integrative genetic and epigenomic approaches to investigate to role of persistent organic pollutants such as flame retardant PBDEs and long lived PCBs in mouse models and human postmortem brain samples.

**Neil J. MacLusky, PhD,** is Professor and Chair of the Department of Biomedical Sciences at the University of Guelph in Ontario, Canada. He received his PhD from the University of London, and then moved to the Rockefeller University where he was a postdoctoral fellow with Bruce McEwen. Over the last thirty years, he has held faculty positions at University of London, Yale University, McGill University and the University of Toronto. He moved to Guelph to take up his current position in September 2005, after five years at Columbia University in New York. Dr. MacLusky’s research interests focus on the mechanisms involved in hormone action in the brain. Author or co-author of more than 200 scientific papers, he was Associate Editor of the...
Pauline M. Maki, PhD, is a Professor of Psychiatry and Psychology at the University of Illinois at Chicago. In this role, she also serves as Director of Women's Mental Health Research, Associate Director of the Center for Research on Women and Gender, and Program Director of the K12 BIRCWH program (Building Interdisciplinary Research Careers in Women's Health). Dr. Maki received her Ph.D. in Experimental Psychology from The University of Minnesota, Twin Cities in 1994, and completed postdoctoral training at Johns Hopkins University School of Medicine (1994-1996), and at the National Institute of Aging, through the NIA National Research Council Fellowship (1996-1999). Following this training, Dr. Maki was a tenure-track investigator in the NIA Laboratory of Personality and Cognition, until she joined the UIC faculty in 2002. She has a longstanding interest in the effects of sex hormones and phytoestrogens on cognition, brain function, and psychological wellbeing in young, midlife and elderly women. For the past 15 years, she has led a program of NIH-funded research on the role of sex steroid hormones on cognition, mood, brain function, and stress responsivity.

Anna L. Marsland, PhD RN, is an Associate Professor of Psychology at the University of Pittsburgh. She is Director of the Behavioral Immunology Laboratory and an accomplished psychoneuroimmunology researcher who has conducted and published a programmatic series of investigations exploring relationships among stress, immunity and physical illness. Her work shows that stress is associated with a number of immune processes, including activation of inflammatory pathways, which are known to increase risk for acute and chronic physical disease. In addition to her laboratory-based research, she studies the psychological and physical benefits of stress management interventions. She offers extensive clinical and basic science skills in evidence-based intervention, psychoneuroimmunology, and the physical health sequelae of acute and chronic stress.

Emeran A. Mayer, MD, is director of the Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress in the Division of Digestive Diseases and co-director of the CURE: Digestive Diseases Research Center. A member of the faculty at the University of California-Los Angeles' Division of Gastroenterology since 1982, Dr. Mayer played a key role in the development of this clinical and translational research program in digestive diseases and brain gut interactions, and served as founding chair of UCLA's Collaborative Centers for Integrative Medicine. Dr. Mayer has served as an editorial board member of several high-impact digestive disease journals, and as Associate Editor of Gastroenterology. He has written 200 original, peer-reviewed publications, 90 reviews and book chapters in the leading textbooks on pain and medicine, and edited 3 books. Dr. Mayer received the Janssen Award for Outstanding Achievements in Gastroenterology in 2001, the Basic Scientist Research Award from the Functional Brain Gut Research group, and the Senior Basic Scientist Award from the International Foundation for Functional GI Disorders (IFFGD) in 2009. Dr. Mayer earned his M.D./Ph.D. summa cum laude at the Ludwig Maximilian University in Munich, completed internal medicine residencies in Munich at the University Hospital Center, Grosshadern and in Vancouver, B.C. at Vancouver General Hospital, and completed fellowship training in gastroenterology at the UCLA-VA Wadsworth Training Program.
Bruce S. McEwen, PhD, is Professor and Head of the Laboratory of Neuroendocrinology at The Rockefeller University. He is a member of the National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences and was President of the Society for Neuroscience in 1997-98. As a neuroscientist, McEwen studies brain plasticity mediated by hormones in relation to brain sexual differentiation and adult brain function. He is a member of the National Scientific Council on the Developing Child which focuses on healthy brain development. He is the co-author of 2 books for general audiences.

Virginia M. Miller, PhD, is Professor of Surgery and Physiology in the College of Medicine, Mayo Clinic. A native of Pittsburgh, PA she attended college at Slippery Rock University, Slippery Rock, PA before going to Missouri to earn her Ph.D. in physiology from the University of Missouri in Columbia, MO. She has held professional positions at the University of Virginia and the University of Delaware before coming to the Mayo Clinic. She received her Master’s of Business Administration from the Carlson School of Management at the University of Minnesota.

Dr. Miller served as director for the Office of Women’s Health at Mayo from 2001-2005. Her research for the last 25 years has focused on how estrogen affects the heart and blood vessels. She is the principal investigator for Mayo Clinic’s Specialized Center of Research on Sex Differences and Research Director of the Mayo Clinic training program Building Interdisciplinary Careers in Women’s Health. She served as the principal investigator of the Mayo Clinic site for the Kronos Early Estrogen Prevention Study. She has authored over 200 original publications and reviews. In addition to service on various grant review panels and editorial boards for scientific journals, she has served as a member of the governing council for the American Physiological Society (APS) and as President of the Organization for the Study of Sex Differences (OSSD).

Gretchen N. Neigh, PhD, is a behavioral neuroendocrinologist at Emory University. Dr. Neigh received her B.A. in Biology from Washington & Jefferson College, her Ph.D. from the Ohio State University, and conducted her postdoctoral training at Emory University. Dr. Neigh’s work focuses on the neurobiological mechanisms of depression comorbid with systemic disease. The work in the Neigh lab puts particular emphasis on the role of alterations in stress responsivity in the manifestation of depression. Given that the stress response is an organism-wide event, Dr. Neigh’s work includes assessment of the interactions of sex steroids, the cardiovascular system, and the immune system in the manifestation of stress-induced depression. Dr. Neigh’s work has been funded by the American Heart Association, the Brain & Behavior Research Foundation, the International AIDS Society, the National Institute of Neurological Disorders and Stroke, and the National Institute of Mental Health.

Ann O’Mara, PhD RN, is Head of Palliative Research in the Division of Cancer Prevention at the National Cancer Institute. She manages a portfolio of symptom management and palliative and end-of-life care research projects, which are primarily focused on the common morbidities associated with cancer and its treatment. Dr. O’Mara has conducted research in the field of end of life care, as well in the area of educating nurses and physicians about palliative care. Dr. O’Mara received her Bachelor of Science in Nursing from the University at Buffalo, the State University of New York, her Master of Science in Nursing from the Catholic University of
America, and her PhD from the University of Maryland, College Park.

Randall L. Rasmusson, PhD is Professor of Physiology and Biophysics and Biomedical Engineering at the University at Buffalo, Buffalo, NY. Dr Rasmusson obtained his BS and MS in Electrical Engineering and Computer Science from Rice University, then his PhD in Physiology from Duke University. He is a member of the editorial board of the Biophysical Journal and a former member of the editorial board of Circulation Research. He has received numerous grants from public and private foundations including the NIH, NSF, AHA, Whittaker Foundation, Simons Foundation and Bill and Melinda Gates Foundation. Dr. Rasmusson’s research interests focus on developing the theory and models necessary to apply engineering principles to cellular electrophysiology and biophysics and to extend this theory to the design of therapy. His particular area of specialization is in the electrophysiology and pharmacology of ion channels. Dr. Rasmusson is Director of the Center for Cellular and Systems Electrophysiology, which has a unique integration and not only carries out the wet lab experiments but also performs quantitative analysis and develops mathematical models of cellular electrophysiological problems. His current research interests involve examination of ion channel gating biophysics, development of structurally related Markov models, and integration of these models into models of cellular and multicellular electrical activity.

Jane Reckelhoff, PhD, is currently Professor of Physiology and Biophysics and Director of the Women’s Health Research Center at the University of Mississippi Medical Center in Jackson. She received a B.S. degree from the College of William and Mary, in Williamsburg, VA, in Chemistry, and a Ph.D. in Biochemistry from Medical College of Virginia/Virginia Commonwealth University, in Richmond. Dr. Reckelhoff did a postdoctoral fellowship in Physiology with Dr. George DeMartino at Texas Southwestern Medical School in Dallas and another one in Physiology with Dr. Chris Baylis at West Virginia University in Morgantown, before coming to the University of Mississippi Medical Center as an assistant professor. Dr. Reckelhoff’s research focuses on the mechanisms responsible for the sex differences in blood pressure control and renal disease, postmenopausal hypertension, and polycystic ovary syndrome. She received the Harry Goldblatt Award in Cardiovascular Research, from the Council for High Blood Pressure Research and the Young Scholar Award, from the American Society of Hypertension/Monarch Pharmaceuticals, both in 2000. In 2011 Dr. Reckelhoff received the Lewis K. Dahl Award for Hypertension Research from the Council for High Blood Pressure Research. Her research has been continuously funded by the National Institutes of Health since 1998. She currently holds two RO1s and has a project on a PO1 as principal investigator.

Michael Rogawski, MD PhD, received his doctorates from Yale University and then trained in Neurology at Johns Hopkins University. He established his laboratory at the National Institutes of Health, where he played a central role in epilepsy research, and received numerous awards for his research in neurological therapeutics. One of his major contributions has been to clarify the actions of neurosteroids at GABA receptors and address their role as potential anticonvulsants. Currently his major clinical interests are in epilepsy and headache, and his research focuses on the cellular and molecular mechanisms of ion channels and anticonvulsants. He has a prolific publication record, mentored numerous investigators, and is recognized throughout the world for his outstanding editorial
abilities and dedicated service to clinical and basic research endeavors in pharmacology and neurological disease. He currently is Chair of Neurology of University California at Davis.

Michael Ryan, PhD, received his Ph.D. from the State University of New York at Buffalo. He conducted postdoctoral work at the University of Iowa and subsequently joined the Department of Physiology at the University of Mississippi Medical Center where he holds the rank of Associate Professor. His research program is focused on understanding mechanisms that promote the development of hypertension. He is currently utilizing an experimental model of the autoimmune disorder systemic lupus erythematosus to examine the link between immune system activation, estrogens and renal changes that promote hypertension.

Guy Salama, PhD, is Professor of Medicine at the University of Pittsburgh. Dr Salama trained in Solid State Physics (with Nobel Laureate Dr. Alan Heeger) and optics at the Johnson Research Foundation (Dr. Britton Chance). His thesis work in the Physiology Department (Dr. Martin Morad) propelled him into the field of electrophysiology and optical mapping. As a postdoctoral fellow, Dr. Salama worked with Dr. Antonio Scarpa on sarcoplasmic reticulum Ca2+ transport, ionic fluxes and membrane potential changes. Dr. Salama has made numerous major contributions to optical mapping techniques in heart and video imaging of the visual cortex. His group developed simultaneous optical mapping of voltage and calcium in the heart which is now routinely used in numerous labs. Dr Salama’s group has made significant strides in understanding sex-differences in arrhythmias elicited by bradycardia and LQT types 1-3, including elucidating the molecular mechanisms underlying genomic regulation of cardiac ion channel expression by estrogen and showing that the upregulation of ICaL and INCX promotes Torsade de Pointes.

Stephan Sanders, MD, is a pediatric physician scientist who works on the genetic cause of autism. His research in Dr. State’s laboratory at Yale University uses next-generation sequencing and microarray technology to identify the genes that are disrupted in autism. Using the Simons Simplex Collection, a series of autism cases enrolled with the view to understanding the role of de novo mutation in autism, he has shown that de novo copy number variants (CNVs) and de novo loss of function mutations are associated with autism. Furthermore by looking for mutations within the same locus he has demonstrated that duplications at 7q11.23 and the gene SCN2A can contribute towards causing autism.

Jennifer Sasser, PhD, is an Assistant Professor of Pharmacology and Toxicology and a member of the Women’s Health Research Center at the University of Mississippi Medical Center in Jackson. She received a BChE from the Georgia Institute of Technology in chemical engineering and a Ph.D. in Biomedical Science from the Medical College of Georgia. Dr. Sasser then completed a postdoctoral fellowship in Renal Physiology with Dr. Chris Baylis at the University of Florida. Dr. Sasser’s research focuses on hypertensive kidney disease and hypertension in pregnancy, specifically focusing on the protective effects of relaxin in hypertension. She has received New Investigator Awards from the American Heart Association and the American Physiological Society. Her research has been funded by the American Heart Association and the PhRMA Foundation, and she currently holds a K01 from the NIDDK.
Helen Scharfman, PhD, is a Professor in the Departments of Psychiatry, Physiology & Neuroscience at New York University Langone Medical Center and is a Senior Research Scientist in the Center for Dementia Research at The Nathan Kline Institute for Psychiatric Research. Dr. Scharfman obtained her doctoral degree in Pharmacology at the Uniformed Services University of the Health Sciences, Bethesda, MD, and conducted postdoctoral training at the University of Washington in Seattle and the State University of New York at Stony Brook. Her laboratory focuses on the cellular and systems neurobiology of hippocampal circuits and their relevance to diseases such as epilepsy and Alzheimer’s disease. How these mechanisms differ in males and females is a major interest. The laboratory has produced over 100 peer-reviewed articles and edited or co-edited 8 books or issues in scientific journals. She has served as an advisory board member to numerous domestic and international organizations and editor or reviewer for many neuroscience journals as well as The National Institutes of Health.

School in Dallas with the MD degree in 1984. Subsequently, he was an internal medicine intern, resident, and endocrinology fellow at the University of Oklahoma Health Sciences Center and a postdoctoral fellow in immunology at the Oklahoma Medical Research Foundation. He joined the faculty at OUHSC in the Department of Medicine and the Arthritis & Immunology Program at OMRF in 1991. His research concentrates on the immunology, genetics and endocrinology of systemic lupus erythematosus and Sjögren’s syndrome. He has had continuous funding by the National Institutes of Health since 1991, publishing over 225 scientific articles. He was an NIH Fogarty International Fellow at the Universidad Autónoma de Madrid in 1998. In May 2008 he was appointed Associate Dean for Clinical & Translational Research in the College of Medicine at OUHSC. He is the co-Director of the History of Medicine Enrichment course for second year medical students. He has served in predominately Spanish-speaking free clinics in Oklahoma City since his second year of residency in 1985-1986.

Pharmacology from Albany Medical College. Dr. Sullivan then moved to the Medical College of Georgia for her postdoctoral training in Vascular Biology. She is now an Assistant Professor in Experimental Medicine in the Department of Medicine at Georgia Regents University. Her research is focused on understanding the molecular mechanisms regulating blood pressure control under both physiological and pathophysiological conditions in males and females. Her work has been funded by the American Heart Association and the NIH.

Peter Szatmari, MD, is Chief of the Child and Youth Mental Health Collaborative at the Centre for Addiction and Mental Health and the Hospital for Sick Children in Toronto, as well as Director of the Division of Child and Adolescent Psychiatry at the University of Toronto. Dr. Szatmari, will hold the newly-endowed Patsy and Jamie Anderson Chair in Child and Youth Mental Health. He has worked in the field of autism spectrum disorder for over thirty years and has published extensively on longitudinal studies that attempt to identify clinically useful subtypes of ASD and on genetic studies attempting to identify key susceptibility genes. He has

R. Hal Scofield, MD, received a BA in Chemistry from Texas A&M University in 1980, and graduated from the University of Texas Southwestern Medical

Jennifer C. Sullivan, PhD, received her B.S in biology from the State University of NY at Geneseo and both her M.S. and PhD in Cardiovascular

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been editor of several important journals in the field of child and adolescent psychiatry and has consulted to government agencies in Canada, the USA and the UK. He is the author of the book "A Mind Apart; Understanding Autism and Asperger Syndrome".

Veena Taneja, PhD, is an Associate Professor in the Department of Immunology with a joint appointment in the Division of Rheumatology at Mayo Clinic. She is a member of the Mayo Clinic Cancer Center Immunology and Immunotherapy Program. Dr. Taneja has received numerous awards and honors for her work. She also serves on the Editorial Advisory Board for two journals in the field of rheumatology. Research in her laboratory is focused on understanding the interaction between genetic and environmental factors that can modulate immune response in autoimmune diseases with special emphasis on sex-bias in Rheumatoid arthritis and Myocarditis. Her laboratory is investigating the basis for individualized medicine and a need for treatment to be based on sex of the patient. Her research is currently funded by the National Institute of Allergy and Infectious Disease, the Department of Defense and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Kim Templeton, MD, is Professor of orthopedic surgery at the University of Kansas Medical Center in Kansas City. She has been the orthopedic residency program director for the past several years, while also serving on the Graduate Medical Education executive committee. Dr. Templeton was the first McCann Professor for Women in Medicine and Science. Dr. Templeton is currently the president of the US Bone and Joint Initiative, a non-profit organization of over 100 organizations whose mission is to improve bone and joint health in the United States through research, education, and advocacy. Dr. Templeton is also president of the American College of Women’s Health Physicians (ACWHP) and serves on the Board of Directors of the American Medical Women's Association (AMWA). She serves on the executive committee of the Women’s Health Working Group, a collaborative effort of the ACWHP and AMWA, whose mission is to improve the translation of research into sex- and gender-based differences into clinical practice through education and evaluation. She is leading an effort to review sex- and gender-based content of the United States Medical Licensing Examinations. Dr. Templeton is an invited founding board member of the newly created Academy of Women’s Health.

Cory Teuscher, PhD, received his Ph.D. in Pathology/Immunology at the University of New Mexico in 1982. He has been on the faculty at The University of Pennsylvania School of Medicine, Brigham Young University, and University of Illinois at Champaign-Urbana. He is currently Professor of Medicine and Pathology at the University of Vermont. The research in his laboratory utilizes forward genetics in animal models to identify genes underlying quantitative trait variation in genetically controlled responses relevant to human health and disease.

Eric Vilain, MD, PhD, earned his M.D. from the Paris Children’s Hospital Necker, his Ph.D. from the Pasteur Institute in Paris, France, then completed a post-doctoral fellowship in Medical Genetics at the University of California, Los Angeles. He is Professor of Human Genetics, Pediatrics and Urology in the David Geffen School of Medicine at UCLA, the Chief of Medical Genetics in the Department of Pediatrics, the Director of the UCLA Center for Gender-Based Biology and the Director of the Institute for
Society and Genetics. His laboratory explores the genetics of sexual development, focusing on the molecular mechanisms of gonad development, as well as on the genetic determinants of brain sexual differentiation. He has identified a large number of mutations in sex-determining genes, developed animal models with atypical sexual development, and identified genes differentially expressed between male and female fetal mouse brains. His laboratory currently investigates the genetics of Disorders of Sex Development (DSD or intersexuality), the outcomes of patients with DSD as part of a large DSD Translational Research Network, and the genetics of sexual orientation and gender identity. His research program has been continuously supported by several grants from the NIH, and he has published extensively in the field of sexual development. He is a Fellow of the American College of Medical Genetics, and a member of numerous professional committees, including those related to the care of individuals with Disorders of Sex Development.

Rosanna Weksberg, MD PhD, is a Professor of Pediatrics and Medical Genetics at the Hospital for Sick Children and the University of Toronto. She has worked on human imprinting disorders and growth-related conditions since 1995, and has published extensively in this area. Dr. Weksberg’s current research focuses on the epigenetic basis of normal human development and the identification of epigenetic alterations associated with human disease, especially in growth and neurodevelopmental disorders. Key areas of research in the lab involve the characterization of the effects on the epigenotype of genetic variation including sex differences and of environmental exposures such as assisted reproduction and therapeutic agents. Dr. Weksberg is funded by CIHR and NSERC. She is a Founding Member of the Organization for the Study of Sex Differences and was on the Organizing Committee for their Annual Conferences in 2007-2009. Dr. Weksberg is an Associate Editor for the American Journal of Medical Genetics and an Editor for Frontiers in Epigenomics.

Jun Xu, PhD, is an Assistant Professor in the Department of Integrative Physiology and Neuroscience, Washington State University, where he studies epigenetic chromatin remodeling in brain development and behavior. He was trained by people who share a similar interest in the study of gender differences (Nancy Forger, Art Arnold, and Christine Disteche). Living now in the picturesque Palouse Prairie, he enjoys a variety of outdoor activities.
PRE-CONFERENCE WORKSHOP: SEX DIFFERENCES 101: FROM BIOLOGICAL BASICS TO BIOMARKERS

APRIL 25, 2013: 8:00 - 12:00

Chair: DeLisa Fairweather PhD (Johns Hopkins University), Co-Chair Virginia Miller PhD (Mayo Clinic)

Introduction and Goals

Virginia Miller PhD (Departments of Surgery and Physiology and Biomedical Engineering, Mayo Clinic)

Animal Models and Experimental Design for Studying Sex Differences

Art Arnold PhD (Department of Integrative Biology & Physiology, University of California – Los Angeles)

Studying Sex Differences in the Clinic:
Obstacles and Opportunities

Lori A. Blauwet MD (Department of Medicine, Mayo Clinic)

Experiences with Translational Studies: Human to Animal and Back Again

DeLisa Fairweather PhD (Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University) and Lori Blauwet MD (Department of Medicine, Mayo Clinic)

Policy: a Tool for Translating Research

Michael Coronado PhD (Department of Pediatrics, Stanford University)
Sex, Stress and the Brain: From Serendipity to Clinical Relevance

Bruce McEwen PhD (Laboratory of Neuroendocrinology, The Rockefeller University)

Sex and stress hormones act upon neural targets throughout the brain and influence many aspects of brain function and behavior. Investigations of hormone action in brain have revealed that the adult brain is much more resilient and adaptable than previously believed, and that adaptive structural plasticity involves growth and shrinkage of dendritic trees, turnover of synapses and neurogenesis in the dentate gyrus of the hippocampal formation. Sex and stress hormones mediate adaptive structural plasticity, which has been extensively investigated in hippocampus as well as in prefrontal cortex, amygdala and nigrostriatal and mesolimbic systems. Sex and stress hormones exert their effects on brain structural remodeling through both classical genomic, as well as non-genomic mechanisms and do so in collaboration with neurotransmitters and other intra- and extracellular mediators. This will be illustrated for estrogen actions on synapse formation in the hippocampus and for stress-induced remodelling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex. The influence of early developmental events such as early life stress and brain sexual differentiation will be noted along with the interactions between sex hormones and the effects of stress on the brain. Because hormones influence so many aspects of brain structure and function and because hormone secretion is governed by the cognitive and emotional brain, the role of brain plasticity and hormone action must be considered in understanding virtually every aspect of brain and body resilience and vulnerability to disease. Supported by NIH Grants MH41256 and 5P01 AG16765.

Elizabeth Young New Investigator Symposium

April 25, 2013: 2:15 – 3:15

Sex Chromosome Complement Affects the CNS Neurodegenerative Response to Injury

Sienmi Du MS (Department of Neurology, Laboratory of Neuroendocrinology, and Department of Integrative Biology and Physiology, University of California at Los Angeles)

Sex Chromosomes and Sexual Dimorphism of Human Transcriptomes

Di K Nguyen PhD (Department of Pathology, University of Washington)

Sex Differences in Stroke-Induced Circulating MicroRNA: A Strategy for Identifying Therapeutic Targets

Amutha Selvamani PhD (Texas A&M Health Science Center, Department of Neuroscience and Experimental Therapeutics, Women’s Health in Neuroscience Program)

The Role of Genetic Sex in Affect Regulation and Expression of GABA-Related Genes Across Species

Marianne L. Seney PhD (Department of Psychiatry and Translational Neuroscience Program, University of Pittsburgh)

Elevated Fetal Steroidogenic Activity in Autism

Michael V. Lombardo PhD (Autism Research Centre, Department of Psychiatry, University of Cambridge)
Presidential Symposium: Sex Differences in Autism (Sponsored by Autism Speaks)

April 25, 2013: 3:30 – 5:30

Chairs: Rosanna Weksberg MD/PhD (University of Toronto) & Peter Szatmari MD (McMaster University)

The Genetic Epidemiology of Sex Differences in Autism Spectrum Disorders (ASD)

Peter Szatmari MD (Department of Pediatrics, McMaster University)

It is well known that boys outnumber girls among ASD children by a ratio of about 4 to 1. However, the explanation of this phenomenon is not known. It is possible that girls with ASD are ascertained less frequently than boys due to some kind of ascertainment or diagnostic bias. Another possibility is that there is some factor (genetic, epigenetic or environmental) that protects girls from developing the disorder given the same risk factors as boys. This presentation will bring together data from a variety of family studies suggesting that the “true” sex ratio in ASD is closer to unity than 4 to 1. There is also evidence from high risk families that genetic factors may moderate the phenotype in girls and even protect girls from developing ASD in the first place. Identifying those protective factors should be a high priority for translational studies.

Testing Genetic Etiologies of Sex Differences in Disease Incidence

Arivinda Chakravarti PhD (Departments of Medicine, Pediatrics, and Molecular Biology and Genetics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University)

Sex-differences in the incidence and prevalence of human disease is ubiquitous and arises from a variety of biological and social factors. The dominant biological hypothesis for sex differences is the action of hormones on host processes. However, this cannot be universally proven since the effects of hormones (androgens, estrogens) and chromosome constitution (XY, XX) are completely confounded. In other words, experimental evidence that disassociates these two effects needs to be considered. Disease incidence from Mendelian X-linked mutations is one compelling example of a non-hormonal sex-difference but there are other genetic arguments. This talk will outline various biological and genetic hypotheses leading to sex-differences in traits and how they can be distinguished using human and animal model studies.

Evidence for Sex Bias Etiologies in Exome and Copy Number Variation (CNV) Data

Stephan Sanders MD (Yale University)

The predominance of male cases is amongst the most striking, consistent, and unexplained observations in autism spectrum disorder (ASD). Epidemiological studies aim to infer differences in the distribution of all genetic risk factors between the sexes by considering the rate of ASD in the population. A complementary approach is to directly assess the distribution of known genetic risk factors between the sexes by considering the rate of ASD in the population. A complementary approach is to directly assess the distribution of known genetic risk factors between the sexes. Advances in genomics have facilitated the identification of numerous ASD risk factors, including de novo copy number variants (CNVs, including 16p11.2) and de novo loss of function mutations (e.g. SCN2A). This talk will outline how the rate of these ASD risk loci varies between males and females and consider whether these observations support organizational, activational, or sex chromosome theories of sexual dimorphism in ASD prevalence.
Epigenetic Sex Differences from Environmental Exposures Relevant to Autism Spectrum Disorders

Janine LaSalle PhD (Medical Microbiology & Immunology, Genome Center, M.I.N.D. Institute, University of California - Davis)

Epigenetic mechanisms, such as DNA methylation, are responsive to environmental influences and can have long-lasting consequences. Autism spectrum disorders (ASD) have complex neurodevelopmental origins whereby both genetic and environmental factors are implicated. Rett syndrome is an X-linked ASD caused by mutations in the epigenetic factor methyl-CpG binding protein 2 (MECP2).

The widespread use of persistent organic polybrominated diphenyl ethers (PBDEs) as commercial flame-retardants has raised concern about potential long-lived effects on human health. This study was designed to reduce the complexity in a controlled experimental system by examining the effects of perinatal exposure to PBDE on both sexes in a genetically and epigenetically susceptible mouse model. A truncation mutant mouse model (Mecp2^{308/}) with social behavioral defects is a useful mouse model for examining environmental modifying factors. To test potential genetic, epigenetic, and environmental interactions relevant to social and cognitive behaviors, a daily perinatal low-dose BDE-47 exposure was performed on Mecp2^{208/} dams bred to wild-type C57Bl/6J males. Perinatal BDE-47 exposure negatively impacted fertility of Mecp2^{208/} dams and preweaning weights of female pups.

Global hypomethylation of brain DNA was observed specifically in BDE-47 exposed female offspring and correlated with reduced sociability in a genotype-independent manner. A reversing interaction of Mecp2 genotype on BDE-47 exposure was observed in a short-term memory test of social novelty that correlated with increased Dnmt3a levels specifically in BDE-47 exposed Mecp2^{208/} mice. In contrast, a compounding BDE-47*Mecp2 interaction was observed in a test of spatial learning and long-term memory. These results suggest that genetic and environmental interactions on the developing brain are complex and involve sexual dimorphism, epigenetic dysregulation, compensatory molecular mechanisms, and specific behavioral deficits.

This work was supported by NIH R01ES015171, 2R01HD041462, ARRA stimulus funds 3R01ES015171-04S1, T32002321, and the NIEHS/EPA Center for Children’s Environmental Health PO1 ES11269, the U.S. Environmental Protection Agency through the Science to Achieve Results (STAR) program award numbers R833292 and R829388.

Symposium I:
April 26, 2013: 8:15 – 10:15

Diverse Roles of Gonadal Hormones in the Pathology and Treatment of Epilepsy in Men and Women

Chair: Helen Scharfman PhD (NYU Langone Medical Ctr.)

Neurosteroids as Drug Targets in Epilepsy

Michael Rogawski MD PhD (Department of Neurology, University of California, Davis School of Medicine)

Women and men with epilepsy exhibit fluctuations in seizure susceptibility that may be related to alterations in neurosteroid levels. Women often experience seizure clustering that conforms to the menstrual cycle (commonly known as catamenial epilepsy). In women and men, stress or relief from stress may cause clustering, whereas hypogonadism in men may exacerbate seizures. The neurosteroids implicated in these situations are allopregnanolone, a metabolite of progesterone; tetrahydrodeoxycorticosterone, derived from the adrenal steroid deoxycorticosterone; and the
testosterone metabolites 5α-androstane-3α,17β-diol, androsterone and etiocholanolone. Neurosteroids are synthesized within the brain, predominantly in principal (excitatory) neurons, and also in peripheral tissues. Their actions on seizures are not believed to be due to interactions with cytosolic steroid hormone receptors. Rather, they enhance the action of GABA on inhibitory GABA_A receptors including nonsynaptic δ subunit-containing GABA_A receptors that mediate tonic inhibition of neurons. GABA_A receptor positive modulatory neurosteroids confer seizure protection in diverse animal models. Withdrawal of endogenous neurosteroids may be a key factor in seizure exacerbation, suggest that neurosteroid replacement with natural or synthetic neurosteroids could be a treatment approach. I will discuss promising clinical trials with ganaxolone, the synthetic 3β-methyl analog of allopregnanolone; preliminary human data demonstrate it to be an efficacious and safe treatment for partial seizures in both women and men, although it may be of particular utility in women. Recently, my laboratory has received FDA approval to investigate allopregnanolone in clinical trials. Emerging understanding of the role of neurosteroids in epilepsy and an appreciation of the differences in the physiology of neurosteroids in women and men provide opportunities to optimize therapy for both sexes.

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**The Role of Gonadal and Brain Synthesis of Estrogen and Androgen in Regulating Brain Structure and Function**

**Neil MacLusky PhD** (Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph)

The fact that circulating gonadal steroids are converted to locally-active metabolites in the brain has been known for more than 40 years. For much of that time, the effects of these metabolites were considered primarily in terms of their potential actions on cell nuclear receptor systems. Over the last decade, it has become clear that androgen synthesis and metabolism in the brain is also involved in directly modulating glial and neuronal plasticity, thereby controlling the activity of sexually differentiated neural pathways. In addition to the role of 5alpha reduction in the generation of active metabolites that affect GABA_A receptor function, local androgen conversion to estrogen can also directly modulate synaptic activity, particularly responses involving glutamate receptor signaling. Thus, in the brain, gonadal steroids play a multifunctional role, acting as both signaling molecules mediating responses to changes in the secretory activity of peripheral endocrine organs, and as neuromodulators rapidly regulating local neurotransmitter function.

**Mechanisms Underlying Differences in Brain Excitability in Men and Women and Their Relevance to Epilepsy**

**Helen Scharfman PhD** (Departments of Child and Adolescent Psychiatry, Physiology and Neuroscience, and Psychiatry, NYU Langone Medical Ctr.)

Sex differences in brain excitability have relevance not only to epilepsy, but also many other diseases where hyperexcitability has been suggested to play a critical role. Nevertheless, many aspects of sex differences in excitibility are not well understood – and some are even contested. We have used the normal adult male and female rodent to understand sex differences in excitibility more clearly, and focused on hippocampus, where the regulation of normal excitability is critical to normal cognitive function, as well as several epilepsy syndromes. Our data suggest that there are robust differences in male and female excitability in normal hippocampus of adult rats. Thus, slices from adult female rats exhibit increased excitability when examined on proestrus or estrous morning of their ovarian cycle whereas adult males do not exhibit increased excitability. However, males exhibit a similar type of altered excitability as female rats, if they are gonadectomized. A primary mechanism underlying...
hyperexcitability in both female and males is upregulation of the neurotrophin brain-derived neurotrophic factor (BDNF) in glutamatergic pathways, and actions of BDNF at TrkB receptors on the glutamatergic nerve terminals. BDNF protein levels are increased by 17b-estradiol in the adult female and appear to be tonically suppressed by testosterone in the male. The collective data suggest that normally hippocampal excitability waxes and wanes in adult females and males as BDNF levels rise and fall, but for different reasons that are sex-dependent. These data help explain several aspects about normal sex differences in adult hippocampal function. They also address sex differences in a type of epilepsy that involves the hippocampus, temporal lobe epilepsy.

Symposium II:

April 26, 2013: 8:15 – 10:15

Infections and heart disease

Chair: Sally A. Huber PhD (University of Vermont)

Sex Differences in Viral Myocarditis: The Mouse Model and What It Tells Us

DeLisa Fairweather PhD (Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University)

Cardiovascular disease (CVD) is the leading cause of death in men and women worldwide. Hypertension excluded, CVD occurs more frequently in men than women yet the reasons for this are not well understood. Using an autoimmune mouse model of viral-induced cardiac inflammation, or myocarditis, we have identified serum and cardiac genes/biomarkers that drive disease in males. We have been able to confirm that these biomarkers are elevated in men with myocarditis and dilated cardiomyopathy. Our research indicates that the inflammatory response to viral infection is entirely different when “read” in the context of androgen or estrogen signaling (i.e. androgen or estrogen response elements). We have found that testosterone alters regulation of the inflammatory response resulting in a damaging inflammatory response in males that leads to cardiac remodeling and heart failure. Understanding the mechanistic differences in how men and women develop CVD and heart failure is critical to develop more effective therapies.

Decreased T Regulatory Cells, Increased Th17 Cells and Proinflammatory Cytokine Responses Correlate with Impaired Cardiac Function in Human Myocarditis

Madeleine W. Cunningham PhD (Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center)

Despite many animal models of autoimmune myocarditis and dilated cardiomyopathy, the contribution of T cells in the progression and immunopathogenesis of human myocarditis is not as well defined. Animal models have suggested that reduction of T regulatory (Treg) cells and proinflammatory immune responses may lead to autoimmune myocarditis and subsequent cardiomyopathy. We tested the hypothesis that Treg cells would be decreased and Th17 cells would be increased creating a proinflammatory environment in human myocarditis/DCM (n=23). As detected by FACS analysis, CD4+FOXP3+CD25+ Treg cells were significantly decreased and Th17 cell percentages were increased in myocarditis/DCM compared to healthy subjects. The Th17/Treg ratio was significantly altered (p=0.04) in myocarditis/DCM compared to normals. Indicative of a pro-inflammatory response and associated with the Th17 subset, IL-6 (p=0.0004) and IL-23 (p<0.0001) were elevated in serum in myocarditis/DCM and may account
for significantly altered Th17/Treg cell ratios in disease. Stimulation of PBMCs (CD14+ monocytes) from myocarditis/DCM produced significantly higher pro-inflammatory cytokine levels of TGF-β1 (p<0.0001) and IL-6 (p<0.0001) compared to normals. In 60% of myocarditis/DCM subjects, reduced Treg cells correlated with increased TGF-β1 and IL-6 responses by PBMCs/monocytes. TGF-β1 was significantly higher in males than in females with myocarditis. In our myocarditis/DCM group, increased serum IL-6 correlated (r=-0.53) with decreased left ventricular ejection fraction (LVEF) and decreased heart function. In addition, elevated Th17 cells were associated with left heart failure (p<0.05). Our data suggest that reduced T regulatory cells, higher Th17 cells and elevated IL-6/TGFβ1 may play important roles in the pathogenesis of human myocarditis/DCM.

Funding: NIH-R01HL56267; American Heart Association Pre-doctoral Fellowship and NIH-T32AI007633

Sex-Specific Issues in Progression of Cardiovascular Disease: Results from the Kronos Early Estrogen Prevention Study (KEEPS)

Virginia Miller PhD (Departments of Surgery and Physiology and Biomedical Engineering, Mayo Clinic)

Cardiovascular disease remains the number one killer of women. Menopause is a sex-specific shift in the hormonal milieu that increases a women’s risk for cardiovascular disease. Data from many observational and epidemiological studies provide evidence that women who use hormone treatments early in menopause have reduced all cause cardiovascular mortality. By implication, these data suggest that use of menopausal hormone treatments (MHT) may slow progression of arterial disease. This hypothesis was tested in the prospective randomized, double blinded trial, the Kronos Early Estrogen Prevention Study (KEEPS). Women who were within 6-12 months of menopause were randomized to either placebo patch and pill, oral conjugated equine estrogen or transdermal 17β-estradiol each with pulsed progesterone for 4 years. The primary outcome was carotid intimal medial thickening with secondary outcomes of coronary calcification, blood inflammatory profile, menopausal symptoms and cognition. Results of this trial as reported at the North American Menopause Society will be summarized as well as potential mechanisms of how MHT alter components of the vascular system that may explain the vascular outcomes.

Symposium III:
April 26, 2013: 10:30 – 12:30

Psychoimmunology of Mental Illness (in Memory of Steve Zalcman)

Chairs: Kevin Beck PhD (University of Medicine & Dentistry of NJ/ VA New Jersey Health Care System) & Gretchen Neigh PhD (Emory University)

Suppression of Sensory Reactivity by Cytokines: An Unexplored Mechanism of Behavioral Depression in Females

Kevin Beck PhD (Stress & Motivated Behavior Institute, Department of Neurology & Neurosciences, UMDNJ – New Jersey Medical School; Neurobehavioral Research Laboratory, VA New Jersey Health Care System)

Stress causes sex-specific behavioral and physiological changes in mammals. Our theory is that the differences in the prevalence of stress-related mental disorders in men versus women can be attributed to these sex differences in how stress affects male and female physiology. Under different stressor models, our laboratory has shown male and female rats exhibit sex-
specific changes in startle reactivity following stressor exposure; males tend to exhibit increased startle reactivity and females decreased startle reactivity. In examining potential mechanisms for this sex-specific effect of stressor exposure on startle reactivity, the peripheral immune response, specifically interleukin (IL)-1β, was found to decrease startle reactivity in a similar manner as certain stressors. This effect of IL-1β is ovarian hormone dependent and is more or less robust in rats strains that exhibit greater stress-induced pro-inflammatory signaling versus anti-inflammatory (glucocorticoid) signaling. Subsequent work has tried to determine if IL-1β reduces startle reactivity in females via subsequent peripheral immune signaling cascades, as well as determine which brain areas are involved in dampening startle reactivity.

Expression of HIV-1 Causes Depressive-Like Behaviors and Decreased Cell Genesis in the Dentate Gyrus of Adolescent Female Rats: Role of Non-Viral Neuroinflammation

Gretchen Neigh PhD (Departments of Psychiatry and Behavioral Sciences and Physiology, Emory University School of Medicine)

The HIV-positive adolescent population experiences an elevated rate of clinical depression, and HIV associated depression accelerates cognitive impairment. Clinical depression has been linked to morphological changes in the brain and increased activity of the inflammatory system. This study used adolescent HIV-1 transgenic rats (HIV-tg), that display related immune-immune response alterations and pathologies, to test the hypothesis that developmental expression of HIV-1-related proteins induces a depressive-like phenotype that parallels a decrease in hippocampal cell proliferation and an increase in pro-inflammatory cytokine activity. Consistent with the hypothesis, HIV-tg rats exhibit depressive-like behaviors, decreased levels of cell proliferation in the hippocampus, and elevated expression of CCl2 in the hippocampus. Importantly, these data support a biological basis for the co-morbid manifestation of depression in HIV-positive patients under conditions devoid of stress or other psychosocial factors which could account for the manifestation of HIV-related depression.

Gender Differences in Stimulated Cytokine Production Following Acute Psychological Stress

Anna Marsland PhD RN (Behavioral Immunology Laboratory, Department of Psychology, University of Pittsburgh)

Individuals differ in the magnitude of inflammatory response to acute psychological stress. Gender may contribute to this variation. We examined lipopolysaccharide-induced production of the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α in response to an evaluative speech task among healthy midlife men (n=28) and women (n=34). Results showed an increase in production of cytokines from pre- to 30 min. post-stress, with no gender differences in the magnitude of this effect. Men showed a significant decrease in cytokine production from pre- to immediately post-stress, whereas women showed no change across this period. These differences were related to menopausal status, with postmenopausal women displaying greater increases in cytokines production across this period than men. Results support increased inflammatory response to acute stress, with gender differences in the patterning of stress-related cytokine activity. Increased immune reactivity among post-menopausal women may contribute to increased susceptibility to inflammatory disease.
Symposium IV:
April 26, 2013: 10:30 – 12:30
Sex Differences in Cardiac Arrhythmias
Chair: Glenna Bett PhD (University of Buffalo)

Sex Differences in Arrhythmia Susceptibility: Drugs, Subunits, and Systems

Glenna Bett PhD (Department of Gynecology – Obstetrics, School of Medicine and Biomedical Sciences, University of Buffalo)

Women have a longer baseline QTc than men, and are at higher risk for long QT syndrome (LQTS). LQTS is characterized by sudden syncopal attacks, seizures, and even sudden death. LQTS is associated with a particularly dangerous form of abnormal electrical activity, or polymorphic ventricular tachycardia, called Torsade de Pointes (TdP). TdP is a particularly dangerous arrhythmia, and can lead to ventricular fibrillation and sudden death. Both drug-induced and genetically inherited long QT syndrome can result in TdP. Women are at much greater risk (60-75%) than men of suffering the potentially fatal side effect of TdP. In addition, sex is an important risk factor in individuals with genetically-based long QT syndromes: Genetic LQTS is present in 1 in 5,000 individuals, with adult women being more susceptible to cardiac events than men. Thus, the problem of arrhythmia susceptibility in women is a major health problem. Progress in addressing this important women’s health problem is hampered by a lack of understanding of the mechanisms responsible for the differences in the electrical susceptibility to LQTS. The current paradigm maintains that the longer natural QTc of post-pubertal women is the basis for this susceptibility. However, this fails to account for the observation that even though QTc does not appear to vary during the menstrual cycle, there are cyclical changes in susceptibility to paroxysmal supraventricular tachycardia, and changes in the ability of drugs to prolong QTc. Although basal QTc does not change, the balance and kinetics of repolarizing currents does change during the menstrual cycle. This change alters the dynamic properties of repolarization as well as the cardiac pharmacological profile. Understanding the molecular mechanisms for this cycle-dependent change in electrical activity will help improve our understanding of the molecular basis of arrhythmogenesis and the relationship between hormonal signaling and QT prolongation.

Mapping Sex Differences in the Spatial Heterogeneity of Cardiac Electrophysiology

Guy Salama PhD (Department of Medicine, University of Pittsburgh)

Post-pubertal women have longer rate-corrected QTc intervals than men and are two times more likely to be afflicted by a form of polymorphic ventricular arrhythmia known as TdP (torsade de Pointes). TdP caused by the suppression of the fast component of the delayed rectifying K+ current, Ik, results in repolarization delay and QT prolongation, called Long QT type 2 (LQT2). Congenital forms of LQT2 caused by mutations that result in a ‘loss-of-function’ of Ik are rare but drug—induced LQT2 remains a serious public health problem because the channel protein encoded by hERG is highly promiscuous and numerous pharmaceutical agents targeting a broad range of diseases can have lethal off-target cardiac effects. Sex and age differences in the propensity to LQT2 have been attributed to a reduced ‘repolarization reserve’ in females and is not confined to humans female rabbits, as female rabbits, dogs and guinea pigs have longer action potential durations than males. The molecular basis for this difference has long been attributed to reduced levels of hERG expression but recent studies from our group in female hearts has discovered that estrogen (0.3-1nM) upregulates voltage-gated L-type Ca2+ channels and Na/Ca exchanger (NCX) to increase their currents, Ical and INCX, respectively. In isolated myocytes from the base of female hearts, estrogen acts via a genomic mechanism requiring 24-48
hours to increase levels of message, protein and current densities. Excessive prolongation of the action potential changes the balance of $I_{\text{Ca,L}}$ and $I_{\text{NCX}}$ and Ca$^{2+}$ fluxes that signal excitation and contraction in the heart. Most importantly action potential prolongation may lead to sarcoplasmic reticulum (SR) Ca$^{2+}$ overload and leakage of Ca$^{2+}$ through the ryanodine receptors, which then reactivates the L-type Ca$^{2+}$ channels out of phase causing ectopic beats. SR Ca$^{2+}$ release during the action potential plateau activated the forward mode of NCX and the consequent Na$^+$ influx results in early after-depolarizations (EADs) and TdP. Spatially, EADs originate from the base of the ventricles and may propagate into other regions of the heart, disturbing organized progression of activation and repolarization. This situation can initiate a self-sustaining rapid reentrant excitation with a frequency much greater than the natural heart rate, resulting in tachycardia. We have explored the heterogeneity of cardiac ion channels using proteomics, optical mapping, and electrophysiology. We found heterogeneous expression in currents and exchangers which affect cellular calcium dynamics. Our animal work was confirmed in tissue from healthy adult human hearts. The observed differences were sex-related as it did not occur in the hearts of adult men, as well as age-dependent as it was not manifested in postmenopausal women.

**Pregnancy: Sex Dependent Reversible Hypertrophy and Action Potential Prolongation**

**Randall L. Rasmusson PhD (Center for Cellular and Systems Electrophysiology, University of Buffalo)**

Pregnancy is a unique and complex physiological condition that puts numerous stresses on the heart. Cardiac output must adapt to the increased circulating maternal blood mass, changes in fetal demands, and the demands of the uteroplacental circulation. In pregnancy, the heart undergoes reversible physiologic eccentric hypertrophy, secondary to an increased plasma volume and cardiac output. On a short-term basis, the strength and duration of cardiac muscle contraction is modulated by the behavior and relative magnitudes of the currents which underlie the cardiac action potential, and the subsequent ability of the cell to sequester calcium in the sarcoplasmic reticulum or extrude it through sarcolemmal pathways. All of these functions are controlled by the membrane potential and most importantly, the shape and duration of the action potential. Thus, it may not seem surprising that cardiac repolarization is prolonged in pregnancy. However, the adaptation to the increased demands placed on the heart may come with some trade-offs. Action potential prolongation and its clinical phenotype, long QT syndrome, are generally thought to be proarrhythmic. Not surprisingly, PVCs and PACs are more common in pregnancy and the likelihood of having an arrhythmia is higher in pregnancy. The cardiac action potential (AP) arises from the complex interplay of numerous non-linear time-dependent currents. Given the diversity and complexity of the interaction of these currents, mathematical modeling provides a uniquely useful tool to explore the consequence of electrical remodeling on the cellular level. This is particularly true when trying to determine effects and consequences in the intracellular calcium handling dynamics. We have previously developed a comprehensive mathematical model of the mouse cardiac myocyte, in which each current has been assigned a putative molecular basis. This makes the mathematical model suitable for matching with molecular data on changes in expression levels, as was previously done for a neonatal mouse ventricular action potential. We used quantitative analysis of mRNA expression to alter our model of the mouse ventricular myocyte to develop a model of the pregnant mouse myocyte. Understanding the molecular basis and electrophysiological consequences of changes in expression of ion channels in pregnancy is key to understanding characteristic of cardiac repolarization as well as response to pharmacological interventions, and arrhythmogenic potential.
Symposium V:
April 26, 2013: 2:30 – 4:30
Clinical Considerations of Sex and Gender in Clinical Practice: Promise, Potential, and Pitfalls
Chair: Marjorie Jenkins MD (Texas Tech Health Sciences University)

"Sexxing" of Diseases Matters in Caring for the Aging Patient
Marjorie Jenkins MD (Laura W. Bush Institute for Women’s Health, Texas Tech Health Sciences University)

Cardiovascular disease is the signature clinical entity for sex and gender differences. However, over the past two decades scientific research in many other areas of aging have revealed pronounced sex and gender differences with resulting clinical implications. This presentation will further clarify the two terms of sex and gender in relation to patient care and provide real-world examples of applying sex and gender evidence within clinical practice to improve the care for both men and women. In addition, there will be a brief review of sex and gender knowledge gaps which provide opportunities for expanding translational and clinical research platforms.

Sex- and Gender-Based Differences in Osteoarthritis
Kim Templeton MD (Department of Orthopedics, University of Kansas Medical Center)

As with most musculoskeletal conditions, sex- and gender-based differences are noted in osteoarthritis. These differences are seen in incidence, joints most commonly affected, risk factors, etiology, and responses to treatment. Factors that have been implicated to explain these differences include differences in anatomic alignment, the influence of sex hormones, risk for and response to injury, ligamentous laxity, and available treatment.

Women and Alzheimer’s Disease: What Role does Reproductive Aging Play?
Pauline M. Maki PhD (Departments of Psychiatry and Psychology, University of Illinois at Chicago)

Alzheimer’s disease (AD) is the sixth leading cause of death in the U.S., with approximately 5.4 million individuals currently living with the disease. Of the top 10 leading causes of death in the U.S., only AD shows a significant sex difference in the direction of greater risks to women. There is debate about whether this sex/gender difference is due to the greater longevity of women compared to men, or alternatively, whether women have an increased risk of AD, even after accounting for their greater longevity. This presentation will provide an overview of sex- and gender-related risk factors for AD, with a focus on the role of menopause and estrogen. Overall the data suggest that early menopause is a risk factor for dementia and that use of estrogen therapy early in the menopausal transition but not later may reduce the risk of AD.
Symposium VI:
April 26, 2013: 2:30 – 4:30
Sex and Gender in Cardiovascular-Renal Physiology and Pathophysiology
Chair: Jane Recklehoff PhD (University of Mississippi Medical Center)

Relaxin in Renal Physiology and Disease
Jennifer Sasser PhD (Department of Pharmacology and Toxicology, University of Mississippi Medical Center)

Emerging evidence supports a potential therapeutic role of relaxin in fibrotic diseases including chronic kidney disease. Relaxin is a pleiotropic hormone, best characterized for its role in the reproductive system; however, recent studies have demonstrated a role of relaxin in the cardio-renal system. Both relaxin and its receptor, RXFP1, are expressed in the kidney, and relaxin has been shown to play a role in renal vasodilation, in sodium excretion, and as an anti-fibrotic agent. Together, these findings suggest that the kidney is a target organ of relaxin. Various mechanisms have been implicated in the renal effects of relaxin including increased nitric oxide production, stimulation of matrix metalloproteinases, and inhibition of transforming growth factor beta. As clinical studies on relaxin move forward, a better understanding of its mechanisms of action is required, especially with regard to the hormone’s effects on renal function. This presentation will discuss the functional and structural impacts of relaxin treatment on the kidney, the evidence that relaxin prevents disease progression in several experimental models of kidney disease, and the potential mechanisms that are involved in the therapeutic actions of relaxin.

Immune Regulation of Blood Pressure in Males and Females
Jennifer Sullivan PhD (Department of Medicine, Georgia Regents University)

There is a growing body of evidence supporting a role for T cells in hypertension in male animal models, yet data in females has been lacking. Pro-inflammatory Th17 cells contribute to hypertension, while anti-inflammatory regulatory T cells (Tregs) maintain immune homeostasis and contribute to cardiovascular health in males. We recently published that immune suppression decreases blood pressure in female SHR implicating a role for lymphocytes in blood pressure control in females, yet there remains a scarcity of data on the role of T cells in hypertension in females. This is particularly alarming when women are more likely to develop autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus, both of which have an increased risk of cardiovascular disease. Available data in the literature suggests that females are at greater risk to exhibit a dysfunctional innate immune response, which is mediated by B cells and the production of autoantibodies, however, less is known regarding how females vs. males respond to adaptive immune system activation. We have reported that SHR of both sexes have greater T cell infiltration than normotensive WKY, although female SHR have greater renal Treg infiltration and less Th17 infiltration than males. The differentiation of naïve T cells is dependent in large part, on the local cytokine environment and proximal signals from antigen presenting cells and our data suggests that both of these factors are dependent on sex. My talk will be focused on sex differences in inflammation in hypertension and the implications for blood pressure control.

Mechanisms Responsible for Hypertension and Renal Injury in a Model of Lupus Erythematosus
Michael Ryan PhD (Department of Physiology and Biophysics, University Mississippi Medicine Center)
In contrast to young healthy women, the prevalence of hypertension is markedly increased in young women with the autoimmune disorder systemic lupus erythematosus (SLE). Mortality during SLE is largely due to cardiovascular disease, and hypertension is a major cardiovascular risk factor. Despite this, the underlying mechanisms leading to hypertension during SLE are not well defined. The bias of SLE towards young women, along with evidence that estrogens can promote adaptive immune system activation, suggests a prominent role for estrogens in SLE disease progression. However, the role of estrogens in SLE and SLE associated hypertension remains controversial and unclear. This may be due, in part, to the disparate temporal actions of estrogens on immune system function. For example, estrogens can promote antibody mediated immunity early in disease progression (asymptomatic phase), but have powerful immunosuppressive actions during the symptomatic phase of the disease. These immunosuppressive actions could provide an important protection against the development of hypertension and renal disease in women with SLE. Further complicating our understanding of estrogens role during SLE is clinical data related to the affect of hormone therapy in this patient population. For example, in otherwise healthy postmenopausal women, evidence suggests that hormone therapy increases cardiovascular risk. However, the available clinical data in postmenopausal women with SLE show that hormone therapy does not increase cardiovascular risk, and may even reduce it. This presentation will examine the impact of estrogens on blood pressure control in an experimental model of SLE.  

SPECIAL LECTURE
April 26, 2013: 4:30 – 5:30
The Use of Prenatal Dexamethasone for Congenital Adrenal Hyperplasia
Alice Dreger PhD (Medical Humanities & Bioethics Program, Feinberg School of Medicine, Northwestern University)

This talk will review the history of the use of prenatal dexamethasone as it has been aimed at preventing atypical sex development in females affected by congenital adrenal hyperplasia (CAH). As will be shown, this use has been promoted and enacted in scientifically and ethically problematic ways and raises larger issues of how the population of individuals affected with sex anomalies have often been mistreated in research. The talk will conclude with a discussion of why many adults with various disorders of sex development are justifiably wary of participating in sex difference research, and a discussion of what it might take to create an environment of ethical behavior towards and genuine respect for research participants born with atypical forms of sex.
Symposium VII:
April 27, 2013: 8:15 – 10:15
Pain Management in Cancer
Chair: Karen Berkley (Florida State University)

Mechanisms of Bone Cancer: Sex Differences?
Patrick Mantyh PhD (Department of Pharmacology, University of Arizona)
Patrick Mantyh is a Professor in the Pharmacology Department and the Cancer Center at the University of Arizona. He completed his B.S. in molecular biology and botany at the University of Wisconsin, and his Ph.D. at UC, San Francisco, USA and post-doc in Cambridge, England. He also has a JD with a specialty in patent law. His lab developed the first animal models of cancer pain, pancreatic cancer pain and chemotherapy-induced peripheral neuropathy and has translated this work into several ongoing human clinical trials. Several therapies which the lab did the early preclinical work have been approved by the FDA to treat cancer related pain / disease progression. He has received numerous national and international awards for this work. The current focus of his lab is developing an understanding of the mechanisms that drive malignant and non-malignant skeletal disease and pain and translating these findings into human clinical trials.

Cancer Pain, Palliative Care, and Quality of Life: Sex Differences?
Ann O'Mara PhD RN (Community Clinical Oncology Program, Division of Cancer Prevention, National Cancer Institute)
Palliative care is often misunderstood to mean end of life or hospice care. To the contrary, palliative care, within the context of cancer care, is a package of services offered to patients from the time of diagnosis and throughout the course of the illness. Palliative care is also more than cancer pain management because of the array of symptoms and quality of life issues cancer patients experience during and following treatment, as well as at the end of life. Many factors contribute to the prevalence and severity of these symptoms and health related quality of life decrements, among them stage and type of disease, treatment regimens, age, gender, and access to care.

In this presentation, participants will gain an understanding of what constitutes palliative care, the common symptoms and quality of life issues that patients face during and following cancer treatment. During the discussion, gender differences in cancer-related physical symptoms (nausea, vomiting, pain, insomnia) and health related quality of life issues will be highlighted. A review of several recent studies that have examined gender differences will be presented.

Cancer Chemotherapy and Pain: Sex Differences?
Paul Farquhar-Smith PhD (Royal Marsden Hospital)
Chemotherapy induced peripheral neuropathy (CIPN) occurs after many types of anti-cancer therapies and is a major cause of pain and adverse symptoms in cancer survivors. The pattern, severity and natural history of CIPN depend on the causative agent which is in turn dependent upon the type of cancer the patient has. Assessment is problematic and there are few data on effective treatments of CIPN. It is unsurprising that there is little discussion of sex differences in CIPN in the existing literature. However, CIPN is a type of neuropathic pain and there is a growing body of evidence indicating genetic susceptibilities including sex differences that are risk factors for the development and maintenance of certain types of neuropathic pain. This talk will investigate epidemiological, scientific and clinical aspects of CIPN to establish the evidence base or the feasibility that sex differences occur in this under
diagnosed, under recognized yet growing clinical problem.

Symposium VIII:
April 27, 2013: 8:15 – 10:15
Sex Differences in Gene Expression
Chair: Christine Distech PhD (University of Washington)

X-Chromosome Aneuploidies Explain the Sex-Bias of Lupus and Sjögren’s Syndrome

R. Hal Scofield MD (Section of Endocrinology and Diabetes, College of Medicine, University of Oklahoma Health Sciences Center)

Women are at least 8 times more likely to have systemic lupus erythematosus (SLE) and 14 times more likely to have Sjögren’s syndrome (SS) when compared to men. We hypothesize that this is a consequence of a gene dose effect from the X chromosome. Chromosome X aneuploidies were found using array based genotyping of single nucleotide polymorphisms (SNP) and confirmed by karyotyping, FISH, and/or quantitative PCR. Among 316 men with SLE, 7 had 47,XXY and 1 had 46,XX. The rate of Klinefelter’s syndrome (47,XXY) was statistically different from that found in control men and from the known prevalence in the population. The 46,XX man had an sry gene, which encodes the testes determining factor, on an X chromosome as a result of an abnormal crossover during meiosis. In the case of 46,XX, 1 of 316 was statistically different from the known population prevalence of 1 in ~20,000 live male births. We calculate that the prevalence of SLE among 47,XXY men is the same as among women. 47,XXX was found in 9 of 2,137 SLE and in 6 of 1,483 Sjögren’s syndrome patients, but in 2 of the 2,898 control women (OR=6.1, 95% CI 1.3-28.3, P<0.0001; and OR=5.9, 95% CI 1.2-29.1, P<0.0001; respectively). The SLE patients with 47,XXX developed the disease on average ~13 years earlier than other women (23±2 years old vs. 35±5 years old; P=0.044, Mann-Whitney U test). Sex chromosome aneuploidies are found in excess among both men and women with SLE or Sjögren’s syndrome. These results support the hypothesis that the X chromosome dose contributes to the sex-bias of SLE and Sjögren’s syndrome, independently of circulating sex hormones or phenotypic sex.

Mouse Models for an X-Linked Intellectual Disability Syndrome

Jun Xu PhD (Department of Integrative Physiology and Neuroscience, Washington State University)

Many diseases affect women and men differently due in part to dimorphic gene expression. Kdm5c, an X-linked chromatin modifying enzyme, is expressed more highly in females than males because of incomplete X inactivation. Being a histone demethylase, it regulates chromatin modifications and gene transcription. When mutated, it causes neuropsychiatric symptoms such as intellectual disability, aggression, seizure, and delayed language development.

These symptoms are recapitulated in the Kdm5c knockout mice which, compared to wild type littermates, are more aggressive, less social, and suffer from cognitive deficits such as impaired memory formation in fear conditioning and Morris water maze. Gene misregulation is evident: synaptic plasticity genes, for instance, are down-regulated in these mice in the amygdala when fear memory is consolidated.

These phenotypes could be attributed to its role in the developing and/or adult brain. To test, Kdm5c was transiently knocked down in adult mice in the hippocampus using small interference RNA. These mice were then tested for object recognition and they performed poorly. Expression array indicated an upregulation of GABAergic genes in these mice; at the promoters of these up-regulated genes, higher levels of...
histone methylation were detected. By blocking the up-regulation of the GABAergic genes, we were able to rescue the object recognition phenotype, suggesting that the cognitive effect of Kdm5c is possibly mediated by these GABAergic genes.

In sum, Kdm5c and other X-linked chromatin enzymes likely make contributions to the sex differences in mental health and disease.

The X and Y Chromosomes both Contribute to Fundamental Sex Differences in Metabolism and Obesity

Art Arnold PhD (Department of Integrative Biology & Physiology, University of California – Los Angeles)

Men and women differ in the distribution of body fat and susceptibility to cardiometabolic diseases. We have recently used mice with unusual sex chromosomes to discover that the number and type of sex chromosomes has important effects on metabolism, not mediated by gonadal secretions. In general, in adult gonadectomized mice, a second X chromosome dramatically increases body weight and adiposity, so that XX mice are heavier and have greater body fat than mice with one X chromosome. Eating a high fat diet leads to dramatically greater accumulation of triglycerides in the liver of XX mice relative to XY, and hyperinsulinemia. The greater adiposity is associated with higher levels of daytime feeding in XX mice, relative to XY. In some mouse strains, the effect of a second X chromosome is mimicked by the effect of a Y chromosome, so that both XX and XY mice have greater body weight and percent body fat, than mice with one X chromosome. The similar effects of X and Y chromosomes points to a small number of paralogous X-Y genes on the two sex chromosomes, which likely cause the effects. The effects of sex chromosome complement are modified by the effects of gonadal hormones, so that each factor blunts the effect of the other. The effects of sex chromosome complement are surprisingly large, and represent a novel source of sex-biasing factors in the metabolome.

Symposium IX:
April 27, 2013: 10:30 – 12:30

Causes and Consequences of Sex Differences in Multiple Sclerosis

Chairs: R. Hal Scofield MD (University of Oklahoma Health Sciences Center) and Sabra Klein PhD (Bloomberg School of Public Health, Johns Hopkins University)

Molecular Mechanisms of Androgen-Dependent Protection in Rodent Models of Multiple Sclerosis

Shannon Dunn PhD (University Health Network and Women’s College Research Institute; Department of Immunology, University of Toronto)

For reasons that remain unclear, the incidence of MS is higher in women as compared to men. A higher female to male sex ratio is also apparent in other autoimmune diseases that have a clear underlying T cell-mediated pathology and manifest during adulthood. Our studies in the mouse model of MS, experimental autoimmune encephalomyelitis (EAE), have suggested that one of the reasons for this sex disparity is because androgens protect males from developing autoimmunity. We found that male T cells that develop in a state associated with low androgen levels are more “feminine” in nature and proliferate more robustly and produce higher levels of Th1 cytokines. We have also discovered that androgens dampen T helper 1 responses through the upregulation of a protective nuclear receptor called peroxisome proliferator-activated receptor (PPAR) alpha in T cells.
In addition to male sex hormones, we have identified that female pubertal factors independently regulate autoimmune risk. Post-pubertal female mice are more susceptible to EAE development than age-matched pre-pubertal controls. This increased EAE susceptibility in post-pubertal females relates to an enhanced ability of antigen presenting cells to prime myelin-reactive T cells. These findings thus shed light on epidemiological evidence that an earlier age of puberty is a risk factor for MS in women, but not men. This talk will provide “our take” on the major factors that are play in the sex-specific regulation of MS risk.

Funding: CIHR and MS Society of Canada

The Y Chromosome as a Regulatory Element Shaping Immune Cell Transcriptomes and Susceptibility to Autoimmune Disease

Cory Teuscher PhD (Departments of Medicine and Pathology, College of Medicine, University of Vermont)

Understanding the DNA elements that constitute and control the regulatory genome is critical for the appropriate therapeutic management of complex diseases. Here, using chromosome Y (ChrY) consomic mouse strains on the C57BL/6J background, we show that susceptibility to two diverse animal models of autoimmune disease, including experimental allergic encephalomyelitis (EAE) and experimental myocarditis, correlates with the natural variation in copy number of Sly and Rbmy1a1 multicopy ChrY genes. In the B6 background, ChrY possesses gene regulatory properties that impact both genome-wide gene expression and the presence of alternative splice variants in pathogenic CD4+ T cells. Using an SJL/J ChrY consomic strain, we discovered an autosome-by-ChrY preference in gene regulation specific to macrophages, the immune cell subset underlying the EAE sexual dimorphism in SJL mice. Importantly, in both genetic backgrounds, an inverse correlation exists between the number of Sly and Rbmy1a1 ChrY gene copies and the number of significantly upregulated genes in immune cells, thereby supporting the copy number variation of Sly and Rbmy1a1 as the ChrY genetic element exerting regulatory properties. Moreover, in humans, an analysis of the CD4+ T cell transcriptome from male multiple sclerosis patients versus healthy controls provides further evidence for an evolutionarily conserved mechanism of gene regulation by ChrY. Thus, these data establish ChrY as a member of the regulatory genome in mammals due to its ability to regulate gene expression and alternative splicing in immune cells linked to disease.

Neuromodulators of Multiple Sclerosis and Psychiatric Illness: The Roles of Sex, Stress, and Hormones

Deborah Walder PhD (Department of Psychology, City University of New York – Brooklyn College).

Multiple Sclerosis (MS; an autoimmune, demyelinating disease) and schizophrenia (a psychiatric disorder) are chronic, debilitating illnesses marked by sex differences with respect to prevalence/incidence and/or symptomatology, which is likely accounted for (in part) by a role of sex hormones. Moreover, there are complex interactions among a range of genetic (e.g., neureglin-1), environmental and neurohormonal susceptibility factors that mutually underlie these illnesses. Interestingly, immunological hypotheses have gained increasing attention in contemporary conceptualizations of schizophrenia, in light of rising prevalence of autoimmune diseases and infections in parents of offspring with schizophrenia. In turn, high prevalence of comorbid psychiatric symptoms (psychosis, depression, mania, anxiety) is well documented in MS. Though speculative, considered together with evidence of shared neuroanatomic features (white matter abnormalities) and the demonstrated role of cytokines in myelination, the aforementioned findings bolster the possibility of (at least some) shared neural mechanisms underlying pathogenesis of schizophrenia and multiple sclerosis. Implications for understanding these illnesses from a neurodevelopmental perspective, with consideration of the modulatory role of sex related factors, will be discussed.
Gut Injury and Multiple Organ Dysfunction Syndrome: Modulation by Sex and Sex Hormones

Edwin Deitch MD (Department of Surgery, UMDNJ – New Jersey Medical School)

Today the multiple organ failure syndrome (MODS) is one of the leading causes of ICU deaths and is particular important in younger individuals who have experienced major trauma or have severe sepsis. Yet, due to an incomplete knowledge of the basic biology that initiates or potentiates its development, the mortality rate of these patients remains high and the treatment options remain largely supportive. Thus, basic studies into the biology of MODS is an area of active interest and one of the major hypotheses being experimentally-studied to explain the early development of sepsis and MODS is the gut hypothesis MODS. Our studies in this area have indicated that gut-derived MODS is due to the stressed gut liberating pro-inflammatory and tissue injurious factors into the intestinal lymph which induce a MODS like condition when they reach the systemic circulation. We have termed this phenomenon the ‘gut-lymph hypothesis of MODS’. One of the unique aspects of this research has been the observation that the susceptibility to trauma-hemorrhagic shock-induced sepsis and MODS is reduced by female sex hormones and hormonally-intact female animals are largely resistant to trauma-shock-induced MODS. This resistance appears to be at many levels and through several different pathways. While much remains to be learned, these preclinical studies are supported by the majority of studies investigating the role of gender in ICU patients after major trauma or with severe sepsis, where survival is improved in females as opposed to males.

Sex Differences in Gut Microbiome and Risk for Rheumatoid Arthritis

Veena Taneja PhD (Department of Immunology and Rheumatology, Mayo Clinic)

Rheumatoid arthritis (RA) is an autoimmune disease that leads to destruction of joints. Predisposition to RA is associated with the presence of HLA-DRB1*0401 while *0402 provides resistance. An infectious etiology of RA is supported by the presence of certain gut bacterial DNA in synovial fluids of patients. To understand the role of gut bacteria in susceptibility to arthritis, we generated HLA transgenic mice carrying DRB1*0401 and *0402 genes but lacking endogenous class II genes. DRB1*0401 mice develop arthritis that mimics human RA in the presence of autoantibodies and sex-bias. DRB1*0402 mice are resistant to arthritis. We tested if an arthritis-susceptible genotype may be associated with the presence or absence of specific gut bacteria by sequencing the microbiome community structure of HLA transgenic mice. Our data showed dynamic age and sex driven gut microbiome in *0402 mice while *0401 mice lost age and sex differences in their gut microbiome. Dysbiosis in gut microbiome of *0401 mice is associated with an altered age and sex dependent gut permeability with a higher Th17 expression in the guts of *0401 mice compared to *0402 mice. These findings imply that interaction between HLA genes and gut microbiome may influence systemic immune environment in sex-biased manner. We are determining if RA patients show sex-bias in the presence of specific gut bacteria that can be used as biomarker(s). Despite the known sex-bias of RA, current therapeutic guidelines make no distinction based on patient’s sex. Modulation of the gut microbiota is an attractive approach to treat autoimmune diseases.
Human Gut Microbiome and Nutrition

Meredith Hullar PhD (J Lampe Studies and Public Health Sciences, Hutchinson Cancer Research Center)

The gut microbial community is tightly associated with host metabolism and provides a mechanistic link to exposures that influence human health. Diet composition is one of the primary determinants of the bacterial community in the human gastrointestinal tract. There is significant interaction between diet and the gut microbiome wherein the composition of the bacterial community can influence the production of specific metabolites from dietary components, and, conversely, the prevailing dietary pattern can encourage dominance of specific bacterial communities. The recent characterization of bacterial enterotypes, based on molecular analyses of the GMC, suggests that networks of microbial species have redundant metabolic pathways which provide about 10% of the host nutrition by the metabolism of diet. In addition, microbial metabolism of dietary constituents provides a myriad of molecules which interact with host pathways during normal homeostasis and/or inflammatory processes. Mechanisms by which the gut microbiome influences human metabolism and subsequent disease risk include: regulation of energy uptake from diet, interaction with signaling molecules involved in host metabolism, modification of gut permeability, and sub-chronic inflammation, a hallmark of obesity-related diseases. These pathways give insight into the multiple ways through which the gut microbiome may influence health and disease risk.

Symposium XI:

April 27, 2013: 2:30 – 4:30

Centers for Sex Difference Research

Chair: Janine Clayton MD (National Institutes of Health: Office of Research on Women’s Health)

Sex Hormone Regulation of Bioenergetics

Wendy Kohrt PhD (Division of Geriatric Medicine, University of Colorado School of Medicine)

The newly established Specialized Center of Research (SCOR) on Sex Differences at the University of Colorado School of Medicine is focused on Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function. The lecture will cover the following topics: 1) Existing evidence from preclinical research will be presented to demonstrate that sex hormones influence bioenergetics through the regulation of spontaneous physical activity and metabolic rate. Sex differences in the phenotypic response to the loss of gonadal function will be discussed; 2) Preliminary evidence that sex hormones have similar effects on bioenergetics in humans will be presented; and 3) The approach for investigating the gonadal regulation of bioenergetics in women under the new SCOR will be presented.

Chronic Pain and the Brain – Do Sex Differences Matter?

Emeran A. Mayer, MD (Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

The majority of chronic pain conditions, including irritable bowel syndrome, chronic pelvic pain and fibromyalgia are more prevalent in women. Even though differences in health care seeking behavior contribute to this increased
prevalence, population based samples, and results from experimental pain testing support the concept of biological differences in pain perception and modulation. A series of neuroimaging studies performed by our center as part of the SCOR program, have identified both structural and functional sex related differences in patients with irritable bowel syndrome. These differences include greater female responsiveness of emotional arousal circuits during aversive visceral distension, and the expectation of such distension, differences in the dominant frequency of regional intrinsic oscillations of the brain, differences in white matter integrity, and differences in grey matter volume and cortical thickness. When viewed together, these findings suggest that the subjective pain experience may be generated by sex specific brain mechanisms, and that the effectiveness of therapies targeted at these mechanisms may differ between male and female patients.

**Sex Differences in Cerebrovascular Function: Are Women Protected?**

**Jill N. Barnes PhD** (Department of Anesthesiology, Department of Physiology and Biomedical Engineering, Mayo Clinic)

Brain blood flow and microvascular responses decrease with aging, and recent data suggests sex differences in cerebrovascular regulation exist. Young women reportedly have higher cerebrovascular function compared with young men; and older women have superior autoregulatory capacity compared with age-matched men. In addition, we have previously shown that age-related differences in cerebrovascular function (or cerebrovascular reactivity) are abolished by cyclooxygenase inhibition, suggesting that these age-associated changes are mediated by prostaglandins. Yet, it is unknown how sex and age interact in response to the stress of cyclooxygenase inhibition. We further examined cerebrovascular function in young men (YM), young women (YW), older men (OM), and older women (OW) before (CON) and during cyclooxygenase (COX) inhibition via indomethacin. There was no age by sex interaction in cerebrovascular function. However, when accounting for the changes in mean arterial pressure during hypercapnia, there was an age by sex interaction in cerebrovascular conductance index (CVCi). During COX inhibition, there was also an age by sex interaction for the ∆CVCi Slope with YM having a greater slope compared with both YW (0.72 ± 0.15 vs. 0.27 ± 0.13 AU; p<0.01) and OM (0.26 ± 0.18 AU; p<0.01). Our results suggest that sex differences exist in the cerebrovascular response to hypercapnia with and without COX inhibition and that the effect of age is different in women compared to men. Therefore, it is possible that women have a greater risk for cerebrovascular dysfunction. This talk will further discuss these issues and future research questions.

**Sex Differences, Metabolomes, and Urinary Tract Infections**

**Jeffrey Henderson MD PhD** (Center for Women's Infectious Disease Research (cWIDR), Washington University)

Urinary tract infections (UTI) are among the most common human bacterial infectious diseases and exhibit well-known sex differences, with a dramatically higher prevalence among adult females than adult males. From adolescence to adulthood, approximately half of U.S. females will have experienced at least one UTI episode; in contrast, male UTI incidence increases in late adulthood. This SCOR uses interdisciplinary approaches to explore UTI pathophysiology across the lifespan and between sexes. The basis for sex differences in UTI susceptibility has classically been attributed to anatomic factors such as urethral length and presence of a colonized vaginal mucosa. However recent advances in metabolomic analyses are now identifying sex-associated biochemical differences that may also contribute to female UTI susceptibility. Combined with microbiological studies, a picture is emerging of key chemical interactions between humans and bacteria with the potential to define new therapeutic and prophylactic strategies for millions of patients each year.
Human sexual orientation, one's preference for male or female sexual partners, is the largest sex difference in behavior. It is a largely stable behavioral trait with a strong genetic component. As such it is an interesting model for brain sexual differentiation. Yet its biological mechanisms are poorly understood, and to date traditional linkage studies have not yielded any candidate genes. Furthermore, large scale whole genome linkage studies have failed to identify genes for sexual preference in humans.

We will discuss several scientific approaches to decipher the biological bases of this behavior. We will focus the discussion on the interaction between genes and environment. For instance, we will discuss how twin studies could be used to identify novel genes related to complex human behavior, and how epigenetic variations could influence sex differences in sexual behavior.
SESSION 1

April 25, 2013: 5:30 – 8:00

Poster ID: 101
Divergent developmental programming and lifelong trajectories may provide sex-specific cues for dietary alleviation: Nutrition, transcriptomics, epigenetics and sexual dimorphism

Author list: Linda Attig¹, Qihan Wu¹, Alexandre Vigé², Anne Gabory¹, Florence Jaffrezi³, Denis Laloë³, Luc Jouneau¹, Jean-Philippe Jais⁴, and Claudine Junien¹,²,³


Abstract: The 'Developmental Origins of Adult Health and Disease' (DOHaD) concept states that environmental conditions during mammalian development can have lasting effects on cell fate and physiology, thereby influencing the susceptibility to deleterious environments leading to a higher risk of diseases in adulthood. We compared offsprings born either to lean or to obese and diabetic mothers. Both type of mothers were fed a CD during the periconceptional/gestation/lactation period. When the mothers were obese, we observed a pronounced sex-specific shift from susceptibility to resistance to a high-fat diet (HFD), in the female offspring only. Using a custom-built mouse expression microchip for the liver and RT-qPCR for muscle and adipose tissue highlighted that adaptive processes in mice born to obese mothers were associated in the liver, with an enhancement of pathways protecting against steatosis, the recruitment of unexpected neurotransmission-related genes, and the modulation of a vast imprinted gene network. Affymetrix microarrays and locus-specific epigenetic analyses by bisulphite-pyrosequencing and ChIP PCR emphasized the hitherto unsuspected role of the Lepr gene in peripheral leptin-resistance and its liver specificity. Global DNA methylation (LUMA technique) and several histone marks (western blotting, ChIP-PCR) as well as the expression of 15 genes for chromatin-modifying enzymes supported the response and adaptation to HFD, in a generation- and tissue-specific manner. The main factors that best characterized (statistical PCA and BGA analyses) the separation between the sexes and/or generations were: 1) Lepr, Trdmt1, DNA methylation, Kdm4a, and Mecp2 CD; 2) Dnmt3b, and Kdm4a, and Trdmt1, and Mecp2 and hepatosteatosis under a HFD. Unravelling epigenetic mechanisms and marks during key developmental periods and their evolution with diet, lifestyle and time, will provide science-based markers and targets for intervention and recommendations before pregnancy in both parents.

These studies were supported by the Fondation Coeur et Artères (FCA N° 05-T4), and Contrat Cadre d’Aide au Projet d’Innovation Stratégique Industrielle "IT-Diab" OSEO-ISI (18/12/2008).

Poster ID: 102
Placental gene expression and epigenetic patterns highlight sex- and diet-specific programming trajectories

Author list: Anne Gabory¹, Laure Ferry¹, Luc Jouneau¹, Alexandre Vigé², Sylvain Mayeur³, Linda Attig¹, Jean Lesage³, Didier Vieau³, Jean-Philippe Jais⁴, and Claudine Junien¹,⁵

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Hôpital Necker-Enfants Malades, U781, 149 rue de Sèvres, 75015 Paris, France

Abstract: Maternal obesity and malnutrition can alter fetal nutrient provision and predispose the offspring to develop metabolic syndrome - a vicious cycle leading to transmission to subsequent generation(s), with differences in response of placental functions and susceptibility to diseases later in life according to the sex of the individual. Placental weight and shape at term are correlated with the development of metabolic diseases in adulthood in humans in a sex-dependent manner. This implies important epigenetic changes, however the epigenetics of placental development in DOHaD studies is poorly documented, particularly concerning overnutrition. We used histology, microarrays analysis and epigenetic techniques to investigate sexual dimorphism both under a control diet (CD) and a high fat diet (HFD) during mouse placental development. We showed for the first time that not only the gene sets but also their biological functions affected by the HFD differed markedly between the two sexes. Remarkably, genes of the epigenetic machinery as well as global DNA methylation level also showed sexual dimorphism. Imprinted genes expression was altered, with locus-specific changes in DNA methylation. Given the abundance of X-linked genes involved in placentogenesis, and the early unequal gene expression by the sex chromosomes between males and females, the role of X- and Y-chromosome-linked genes, and especially the X/Y pairs of paralogs (i.e. Kdm5c/5d) were of particular interest. These genes giving rise to the sex-specific epigenetic marks may account for the peculiar placenta-specific epigenetics processes and landscapes. Thus, these findings demonstrate a striking sexual dimorphism in programming trajectories under basal conditions, and in response to the same environmental challenge. Explaining the sex-specific causal epigenetic variables and how males versus females respond and adapt to environmental perturbations should help physicians and patients anticipate disease susceptibility.

These studies were funded by the Fondation Coeur et Artères (FCA N° 05-T4), the Institut Benjamin Delessert, and the Agence Nationale pour la Recherche (ANR 06-PNRA-022-01).

Poster ID: 103
Sex differences in circadian rhythms of food intake in mice caused by gonadal hormones and complement of sex chromosomes

Author List: Xuqi Chen, MD¹, Lixin Wang MD²,Yvette Taché PhD²,Karen Reue, PhD²*, and Arthur P. Arnold, PhD¹*

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Abstract: We have used the “Four Core Genotypes” C57BL/6 mice (FCG) to study sex differences in body weight, adiposity, and metabolic syndrome traits. These mice are XX and XY gonadal males and XX and XY gonadal females. We previously reported that mice with two X chromosomes, relative to mice with one X chromosome, experience a dramatic increase in body weight and body fat after gonadectomy (GDX) in adulthood, irrespective of their gonadal sex. The higher body weight of XX compared to XY mice does not develop if mice are pair-fed, indicating that the body weight difference is due, at least in part, to increased food intake in XX mice. We hypothesized that XX and XY mice have distinct eating patterns, and performed in-depth analysis of feeding parameters in GDX FCG mice using the BioDAQ automated system, which measures food intake continuously second-by-second. The analysis of meal size and frequency during several days of housing in the BioDAQ chambers revealed differences between GDX XX and XY mice in circadian rhythms of eating behavior. Under basal conditions, XX mice showed significantly increased total food intake (larger meal size but not frequency) during the light but not dark phase, with XX mice consuming 30% of their daily food during the light period compared to 21% for XY mice (p < 0.05). These results raise the possibility of altered satiety response in XX mice. In addition, a single overnight fast had profound and prolonged effects on meal pattern for 12 days afterwards, such that gonadal females ate larger and more frequent meals than gonadal males during the dark phase, but gonadal males ate larger and more frequent meals during the light
phase. The circadian pattern of food intake in gonadally intact FCG mice was significantly different than in the GDX mice described above. Gonadal females had larger meal size (p=0.02) and number (p=0.00008), than gonadal male mice during the light phase, but gonadal males had larger meal size (p=0.002), meal number (p=0.0002) and spent more time on meals (p=0.003) than gonadal females during the dark phase. One night of food deprivation abolished the distinct sex differences in meal patterns, after which the circadian pattern did not return to normal over the next 13 days. Our results point to complex interactions of gonadal hormones and sex chromosome complement in the control of circadian patterns of food intake, which likely contribute to observed sex differences in body weight and adiposity.

These studies were supported by R01 DK83561 to APA, XC, and KR; P01 HL90553 to KR; R01 NS043196 to APA, and P30 DK41301 to YT.

Poster ID: 104

Sex specific changes in the activity of histone acetyltransferases and histone deacetylases in the cerebral cortex during aging

Author List: Nioka Chisholm, PhD and Farida Sohrabji, PhD

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Abstract: Although several sex differences have been identified in disease development and normal aging, sexual dimorphisms in age-related epigenetic changes are poorly understood, and midlife changes associated with reproductive senescence menopause are even less well studied. Our previous studies indicate that growth factor production, neuroinflammatory responses and post stroke recovery are all impaired in middle-aged females as compared to young females. Middle-aged males however, appear to be similar to their younger counterparts on these measures. The extent of histone acetylation plays an important role in transcriptional changes associated with aging. The level of acetylation, in turn, is modulated in part by histone acetyltransferases (HATs) and deacetylases (HDACs). In the present study, HAT and HDAC activity was measured in the cerebral cortex of adult (6 month) and middle-aged (11+ month) male and female Sprague Dawley rats. Middle-aged females were further characterized as reproductive senescent by vaginal cytology. In the first study, we examined general activity of HDAC and HAT using an ELISA assay. Aging significantly increased general HAT activity in male, but not female, rats (p <.001). In fact, middle-aged male rats had 5-fold greater HAT activity than young males and age matched females. In contrast, general HDAC activity was decreased in both middle-aged males and females (p <.04). To determine the specific HDACs that are altered during aging, we focused on HDAC6. In agreement with overall HDAC activity levels, the amount of HDAC6 is decreased during aging in both males and females. Histone acetylation homeostasis is crucial for cell function and our data suggest that reduction in HDAC activity in aging males and females is countered by elevated HAT activity in aging males but not aging females, consistent with the hypothesis that the aging endocrine environment may predispose females to more severe adverse outcomes following age or neurologic disease.

Supported by NIH/ES020276 to FS

Poster ID: 105

Background and methods of the GENDER ATTENTION study: an Italian observational study to evaluate the influence of gender and hormonal profile on side effects’ incidence in plaque psoriasis patients treated with cyclosporine

Author list: D. Colombo M.D.¹, G. Banfi M.D.², N. Cassano M.D.³, A. Graziottin M.D.⁴, G. Vena M.D.⁵, G. Bellia⁶ on behalf of the GENDER ATTENTION Study Group

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Organization for the Study of Sex Differences (OSSD)
Abstract: Nowadays it is known that clinical study results about women are assimilated to data obtained on men. Thus, the interest in gender medicine has become increasing in order to personalize the treatments on woman physiology. The primary aim of the study is to describe the side effects’ incidence rate between genders and in relation to the estrogenic status (fertile or menopause) and the hormonal profile (cortisol, dehydroepiandrosterone sulfate, free and total testosterone, FSH, LH) on a sample of Italian patients with psoriasis treated with cyclosporine. GENDER ATTENTION is an Italian observational, cohort prospective, multicenter study. It involves 50 dermatology public sites and it was planned to enroll 1200 plaque psoriasis patients aged ≥ 18 years, who started any cyclosporine cycle. Patients will be followed up to cycle end (i.e. from 2 to 6 months). Four patient cohorts were planned with a ratio female:male of 2:1: 400 fertile women and 200 age-matched men, 400 menopausal women and 200 age-matched men. One blood sampling was obtained. Enrolment started on May 2011 and ended on December 2012, recruiting 970 patients, 402 males and 568 females. Follow-up visits are ongoing and will end on July 2013. GENDER ATTENTION study results will allow us to evaluate treatment safety according to gender and estrogenic/hormonal status. Preliminary results about baseline characteristics will be available within the congress date.

Funding: the study was sponsored by Novartis.

Poster ID: 106
Sex Chromosome Complement Affects The CNS Neurodegenerative Response To Injury

Author List: Sienmi Du Ph.D. Candidate¹,²,³, Noriko Itoh M.S.¹, Arthur P. Arnold Ph.D.²,³, and Rhonda R. Voskuhl M.D.¹,²

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Abstract: Women are more susceptible to multiple sclerosis and have more robust immune responses than men. However, men with MS tend to demonstrate a more progressive disease course than women, suggesting a disconnect between the severity of an immune attack and the CNS response to a given immune attack. We have previously shown in a multiple sclerosis model, experimental autoimmune encephalomyelitis, that autoantigen-sensitized XX lymph node cells, compared with XY, are more encephalitogenic. These studies demonstrated an effect of sex chromosomes in the induction of immune responses, but did not address a potential role of sex chromosomes in the CNS response to immune-mediated injury. Here, we examined this possibility using XX versus XY bone marrow chimeras reconstituted with a common immune system of one sex chromosomal type. We show that EAE mice with XY sex chromosome complement in the CNS, compared with XX, demonstrate greater clinical disease severity with more neuropathology in spinal cord and cerebellum. Our results suggest that sex chromosome effects on neurodegeneration in the CNS (XY>XX) may run counter to effects on immune responses (XX>XY). These results may provide insight into why there is greater disease susceptibility in women but faster disability progression in men.

This study was funded by National Institutes of Health grants R21 NS071210 and K24 NS062117 to R.R.V., as well as by the Conrad Hilton Foundation, the Jack Skirball Foundation, and the Sherak Family Foundation.

Poster ID: 107
Ovarian hormones differentially regulate the levels of phosphorylated cofilin (p-cofilin) in the amygdala of female rats

Author List: Sarah L Ferri, MA¹ and Loretta M Flanagan-Cato, PhD¹,²

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Abstract: Many female behaviors vary across the ovarian hormone cycle, including food and water intake, locomotor activity and emotional processing. To mediate these behavioral fluctuations, estradiol and progesterone actions prompt structural and neurochemical changes in various brain areas. Regions of the amygdala, namely the central and basolateral nuclei, contribute to emotional learning and stress responses, respectively. These regions also express estrogen receptors and exhibit ovarian hormone-dependent plasticity. Our laboratory has recently described ovarian hormone-dependent changes in the AMPA-type glutamate receptor subunit GluR2, but not GluR1, in the central and basolateral regions of the amygdala. Although this result suggests that dendritic remodeling is associated with a change in glutamate signaling, the causal relation direction remains unclear. Dendrite remodeling requires changes in actin polymerization, which is dependent on the phosphorylation state of the actin-associated protein coflin. Here, we investigate whether or not ovarian hormones alter the levels of p-cofilin in the central and basolateral amygdala. Ovariectomized female rats were treated with vehicle, estradiol, or estradiol plus progesterone. Four or 72 hours after initial estradiol treatment, the rats were killed by perfusion. Brain sections were immunohistochemically labeled for p-cofilin. Digital photomicrographs of the amygdala were analyzed for optical density using NIH ImageJ. In the central nucleus of the amygdala, but not in the basolateral nucleus, estradiol reduced p-cofilin levels at four hours, but not at 72 hours after estradiol alone or estradiol plus progesterone. This result suggests that estradiol treatment rapidly alters actin polymerization in the central nucleus of the amygdala. Additional studies are needed to determine the time course of estradiol-induced changes in dendrite structure, glutamate receptor subunit composition, and amygdala-mediated behaviors.

Poster ID: 108
The Y chromosome as a regulatory element shaping immune cell transcriptomes and susceptibility to autoimmune disease

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Abstract: Sex-specific differences affect many aspects of immune system physiology and although these differences may arise from multiple mechanisms, including differential effects of sex hormones, there is increasing evidence that genetic differences in the Y chromosome (ChrY) can influence immune-mediated diseases. In Drosophila, natural polymorphic variation in ChrY can influence the epigenetic regulation of autosomal and X chromosome gene expression, thereby epigenetically regulating phenotypic differences in males. Therefore, we hypothesized that the previously observed ChrY-mediated differences in susceptibility to two diverse animal models of autoimmune disease, including experimental allergic encephalomyelitis (EAE) and experimental mycarditis, is the result of an evolutionarily conserved mechanism of genom-wide gene regulation by ChrY. Using ChrY consomic mouse strains on the C57BL/6J background, we show that susceptibility to autoimmune disease correlates with the natural variation in copy number of Sly and Rbmy1a1 multicopy ChrY genes. In the B6 background, ChrY possesses gene regulatory properties that impact both genome-wide gene expression and the presence of alternative splice variants in pathogenic CD4+ T cells. Using an SJL/J ChrY consomic strain, we discovered an autosome-by-ChrY preference in gene regulation specific to macrophages, the immune cell subset underlying the EAE sexual dimorphism in SJL mice. Importantly, in both genetic backgrounds, an inverse correlation exists between the number of Sly and Rbmy1a1 ChrY gene copies and the number of significantly upregulated genes in immune cells, thereby supporting the copy number variation of Sly and Rbmy1a1 as the ChrY genetic element exerting regulatory properties. Thus, these data establish the mammalian ChrY as a member of the regulatory genome in mammals due to its ability to regulate gene expression and alternative splicing in immune cells linked to disease.
This work was funded by NIH Grants NS061014 (CT and EPB), AI45666 (CT and SAH), HL108371 (SAH); Myocarditis Foundation Research Fellowship Grant (LKC)

Poster ID: 109
Sex differences in dendritic architecture in the CA¹ area of the dorsal hippocampus of prepubertal rats

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Abstract: Learning strategies used by rats to solve navigational tasks are influenced by both sex and age. While adult male rats often prefer a hippocampus-associated place strategy to solve cognitive tasks, we found that prepubertal males are biased toward a striatum-associated stimulus-response strategy on a dual-solution water maze task. In contrast, the strategy preference of adult female rats has been linked to their hormonal state while prepubertal females more frequently prefer to use a place strategy. In our behavioral experiments, females and males are tested at 28 days of age, well before the onset of puberty when the activational effects of gonadal hormones are minimal. Therefore, sex differences in learning strategy expressed prior to puberty may result primarily from earlier organizational events. Indeed, we found that prepubertal females treated with testosterone during the critical organizational period shortly after birth were biased toward a stimulus-response strategy similar to vehicle-treated prepubertal males while vehicle-treated prepubertal females were biased toward a place strategy. Taken together, our findings suggest the early postnatal hormone environment establishes a sex difference in learning strategy preference prior to the onset of puberty. Recently, we tested the hypothesis that the sex difference in prepubertal learning strategy preference is linked to sex differences in brain structure. We examined the arborization of dendrites on the apical portion of pyramidal neurons in the CA1 area of the dorsal hippocampus in male and female rats at 28 days of age, mirroring the age at which we find differences in strategy preference. Prepubertal females expressed a significantly greater number of segments and a greater mean length of apical segments when compared to males of the same age. Our results support the hypothesis that the tendency of prepubertal female rats to prefer a hippocampus-associated place strategy is linked to a more complex dendritic arbor in the CA1 region of the female hippocampus compared to males. This sex difference in dendritic arborization could be the result of the sex difference in early hormone conditions and/or a sex difference in the trajectory of hippocampal development because female rats reach puberty almost a full week before males at 36 versus 42 days of age.

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Poster ID: 110
Sex differences in mossy fiber synaptic transmission and synaptic plasticity depend on opioid receptors

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Abstract: It has been suggested that hippocampal synaptic plasticity, including short- and long-term potentiation (PTP, LTP), plays a central role in hippocampal-dependent learning and memory. LTP may also be responsible for “pathological plasticity” in disorders like addiction, where the hippocampus may be involved in controlling memory of the pleasurable experience. The hippocampal mossy fiber (MF) pathway may be particularly important because it contains high levels of opioid peptides and receptors. Opioid peptide expression in MFs is influenced by sex and the estrous cycle; thus sex differences in addiction could be related to sex differences in MFs. To address this hypothesis, we asked if there were opioid-dependent sex differences in MF physiology, using hippocampal slices from adult male and female rats. The results showed sex differences in MF basal transmission, PTP and LTP: male rats had greater field EPSP slopes and paired-pulse facilitation than female rats. Slices from female proestrous rats showed...
(prepared at the time of the estrous cycle where levels of serum 17β-estradiol were highest) had greater PTP and LTP than other female rats or male rats. Acute exposure of slices to naloxone, a nonspecific opioid receptor antagonist, blocked sex differences in most measures of MF transmission and plasticity. Selective opioid receptor antagonists, naltrindole and CTOP, implicated delta and mu receptors. The results suggest that sex differences exist in the physiological responses of the MF pathway of the adult rat, presumably reflecting sex differences in levels of opioid peptides and mu and delta opioid receptors. Estrous cycle-dependent changes also were revealed, and are consistent with reports of increased hippocampal transmission and synaptic plasticity in response to elevated serum levels of 17β-estradiol. We suggest that the sex- and estrous cycle-dependence of MF transmission may contribute to sex- and estrous cycle-dependent differences in addictive behavior.

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**Poster ID: 111**

**Differences in Resting-State BOLD Oscillation Signals between Healthy and IBS Subjects**

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**Abstract:** Background. Regional alterations of blood oxygen level dependent (BOLD) signals have been identified in patients with Irritable Bowel Syndrome (IBS), and sex-related differences in brain responses to visceral distension and its anticipation have been reported in both healthy control subjects (HCs) and IBS patients. Aims. To test the following hypotheses: 1) Disease related differences in frequency fluctuations exist in brain regions of sensorimotor and of emotional arousal/salience networks. 2) Sex-related differences in oscillatory dynamics exist in emotional and cortical modulatory regions.

Methods. We measured brain resting state activity by using the fractional Amplitude of Low Frequency Fluctuation (fALFF) method in 76 female HCs, 42 male HC, 29 male IBS and 1 female IBS subjects. SPM8 was employed to preprocess and analyze the imaging data using the general linear model and a region of interest analysis. Main effects for four subject groups (male HC, female, HC, male IBS, female IBS), three frequency bands (LF, MF, and HF), and the interaction between groups and bands was performed using a flexible factorial design.

Results. 1. Female subjects in both HC and IBS groups showed greater HF power in affective and paralimbic regions compared to male HC and male IBS subjects, respectively. 2. Compared to male IBS, female patients showed greater LF power of sensorimotor regions, while compared to male HCs, females HCs had less LF power in sensorimotor regions. 3. Male IBS showed less HF power and more LF power in the insula, while female IBS showed greater amplitude of HF in the anterior insula and amygdala, compared to their respective controls. Conclusions. Our findings demonstrate that women compared to men, regardless of disease show greater HF oscillations in regions of an emotional arousal/salience brain circuit. In female patients, disease related differences are only seen when sex is taken into account.

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**Poster ID: 112**

**HPA Genes Show Sex-Specific Interactions with Early Life Trauma Influencing Hippocampal Volume in Healthy Controls and Patients with Irritable Bowel Syndrome (IBS)**

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**Abstract:** Genes regulating the effects of stress via the HPA axis have been implicated in the physiological and
pathological regulation of stress reactivity as being mediated by release of hypothalamic corticotrophin releasing hormone (CRH). HPA activity is modulated by sex hormones progesterone and estrogen. HPA axis hyperactivity may be a function of psychosocial stressors such as early adverse life events (EALs) and may show sex-specific effects on emotional arousal circuitry in the brain. The hippocampus is a major component of the emotional arousal system whose morphology and gene expression is modified by EALs. We aimed to examine gene-environment interactions on hippocampal volumes in male and female IBS patients and HCs. Polymorphisms in HPA-related genes were examined for effects on hippocampal volumes and interactions with early life trauma (ETI), sex, and diagnosis. 122 IBS patients (91 female) and 205 HCs (female 164) were studied. SNPs of CRHR1 (rs7209436, rs110402, and rs242924), and PGR (rs1042838, rs10895068) were genotyped. Subjects completed structural MRIs scans and the volumes of the right and left hippocampus were computed. Superloci were created using Mendel software and were analyzed in a linear regression model controlling for age, race, and total brain volume. Significant Sex x Gene x ETI interactions were seen for PGR and CRH-R1 superloci with the right hippocampus and for PGR with the left hippocampus. For males with PGR minor alleles, higher ETI was associated with smaller right and left hippocampal volumes, while no effect was seen in females. For males with CRH-R1 major alleles, higher ETI was associated with smaller right hippocampal volume. Sex differences in interactions between EALs and polymorphisms in genes modulating the CRH system were demonstrated for volume of the hippocampus, a region involved in emotional arousal. Specifically, PGR and CRH-R1 demonstrated male-specific effects of ETI on hippocampal volume. The results highlight the importance of considering sex in examining gene-environment effects in IBS.

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**Abstract:** There are sex differences in the adolescent development of the prefrontal cortex of both rats and humans (Geidd et al, 1999; Markham et al, 2007). At the cellular level, our laboratory has found that female rats show a greater loss of neurons in the medial prefrontal cortex (mPFC) than males during the adolescent period. Additionally, the loss of neurons occurs in both the outer (layers 2/3) and inner layers (layers 5/6) of the female mPFC whereas males only lose neurons in the outer layers. This creates an adult sex difference in the overall number of neurons in the mPFC (males > females). Sex differences also appear after puberty in the number of glia in the rat prefrontal cortex (Markham et al, 2007). To investigate the role of pubertal hormones in the formation of sex differences during puberty, the current study removed the gonads in both female and male rats prior to puberty (postnatal day 20-22). Same-sex littermates that received sham surgery were used as a control group to measure the specific effects of pubertal hormones. The total number of neurons and glia in the mPFC were stereologically quantified using software from Microbrightfield Inc. Results revealed that castrating males prior to puberty did not alter neuron or glia number in the mPFC in any layer. In contrast, females without ovaries had more neurons and glia than intact females in layers 5/6 but not in layers 2/3. These data indicate that pubertal androgens do not affect the number of neurons in the mPFC; however, the ovarian steroids play a role in the decrease in the number of neurons and glia in layers 5/6 seen during adolescence.

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**Poster ID: 114**

**Sex, strain and regional differences in the colonic epithelial response to repeated water avoidance stress (rWAS)**

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**Abstract:** Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits, and in a subset of patients, by a compromised colonic epithelial barrier function. IBS predominantly affects women, but the underlying mechanisms of this female prevalence remain largely unknown. Stress is known to worsen IBS symptoms. In male rodents, chronic stress increases colonic secretion and paracellular permeability, an event associated with visceral hyperalgesia. Potential sex differences in the colonic epithelial response to stress have not yet been addressed. In this study, the effect of stress on colonic mucosal function was determined in male and female Wistar and Wistar-Kyoto rats (7-11 wks). Naïve or stressed (rWAS, 1h/day, 4 days) rats were euthanized 5h after the last stress session. Proximal colon (PC) and distal colon (DC) were collected, stripped from the seromuscular layer and the mucosa was mounted in Ussing chambers containing modified oxygenated Krebs Ringer’s buffer. The conductance (G, paracellular permeability) and short circuit current (Isc, transmembrane ion exchanges) were measured. Data were analyzed using unpaired t test. In the PC of both Wistar and Wistar-Kyoto females, rWAS increased the Isc (75.9±10.0 vs 26.3±2.1 & 57.6±3.8 vs 38.4±3.3 μA/cm², p<0.01, respectively) while it did not affect the Isc in male rats. In the DC, both male and female Wistar rats displayed an increase in Isc following rWAS (79.4±1 1.5 vs 28.7±2.5 and 79.0±10.2 vs 20.8± 1.9 μA/cm², p<0.001, respectively), while female Wistar-Kyoto rats showed a decreased Isc (34.6 ± 3.8 vs 5 1.1 ± 5.7 μA/cm², p<0.05) and males no change. Females, but not males of both strains exhibited an increase in G exclusively in the PC following rWAS. The data highlight sex, strain and regional differences in rat colonic epithelial function alterations induced by exposure to repeated psychological stress.

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**Poster ID: 115**

**Epigenetics and Lupus: Ethnic and Sex Differences**

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**Abstract:** Systemic lupus erythematosus is a multifactorial autoimmune disease that affects women at a 9:1 ratio when compared to men. In addition, women of specific ethnic groups, such as African Americans, Hispanic/Latinos, Asia and Native American, have a higher incidence when compared to European Americans. Pathogenesis of lupus remains unknown; however, emerging data are beginning to show that aberrant epigenetic mechanisms may play a central role in its onset and progression. Our laboratory and others have shown global hypomethylation in PMBCs, altered DNMTs and increases in specific histone deacetylases from lupus patients compared to age-matched non-lupus patients, as well as hypermethylation of specific genes. Ethnic and sex differences were also noted in the above biomarkers. In addition, using a cytokine production DNA methylation PCR array to detect specific promoter methylation profiles, two significant genes were detected in the lupus samples. This study showed that Foxp3 promoter had an increased methylation profile compared to age-matched non-lupus patients. Increased methylation of this gene suggests inactivation of Foxp3 through hypermethylation. Foxp3 is an essential transcription factor for regulatory T-cells (Tregs) and are considered the guardians of peripheral tolerance. Decreased expression of Foxp3 gene has been noted in other autoimmune diseases, such as rheumatoid arthritis. Another gene that was significant in the lupus samples was the ELANE gene. The ELANE gene promoter showed a decrease in per cent methylation, indicating activation of that gene (hypomethylation). This gene codes for a protein called neutrophil elastase and is known to play a role in inflammation. Using expression profiler arrays, three genes showed significantly expression. The gene profile expression arrays revealed significant increase in expression of IL-18 (p<0.013), TNFSF13B (BlyS) (p<0.017) and FASLG (p<0.026). We also showed decrease in Foxp3 expression, which correlated to our methylation profile, suggesting its regulation is through epigenetic mechanisms. We also observed overexpression of microRNA 146a. These studies suggest through several signal pathways may be regulated by epigenetic mechanisms, which may play an important role in lupus onset and progression.

This study was funded by a grant from the FDA-Office of Women’s Health, awarded to B.D. Lyn-Cook.
Is Migraine a Different Disease in Women? New Evidence on Sex related Differences in Migraine Brain

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Abstract: Migraine is about three times more prevalent in women compared to men. The mechanisms underlying this difference in prevalence are still poorly understood. The aim of this study was to understand the structural and functional mechanisms underlying sex related brain differences in migraine. Two cohorts of opposite sex, age-matched migraineurs (N=11 each) along with age- and sex-matched healthy controls (N=11 each) were recruited to the study. Migraineurs met the ICHD-II classification criteria for migraine and had suffered from migraine for 3 years or longer. Imaging was carried out on a 3T Trio MR scanner. Subjects underwent both structural and functional brain imaging using Blood Oxygen Level Dependant (BOLD) contrast while a thermal stimulus (3 noxious stimuli at pain threshold +1oC) was applied to the dorsum of the hand (on the migraine dominant side). The imaging data were processed to determine sex related differences in pain response as well as subtle cortical and subcortical structural differences. There were three major findings in this study: (i) Disease related structural changes in insula, and precuneus regions that were specific to women migraineurs; and (ii) Disease related structural changes in parahippocampal gyrus that were specific to male migraineurs; (iii) Functional changes in response to noxious heat showed more pronounced responses in female migraineurs in regions involved in emotional processing such as the amygdala, and parahippocampus that was consistent with increased measures of pain unpleasantness. Significant differences in cortical thickness were observed in various regions of the brain. Specifically, morphometric measures revealed thickening in the posterior insula and precuneus in female migraineurs versus male migraineurs and healthy controls of both sexes. Furthermore, evaluation of functional responses to heat in the migraine groups indicated concurrent differential functional differences in male and female migraineurs that was consistent with a specific pattern of functional connectivity of these two regions with the rest of the brain. The results support the notion of a ‘sex phenotype’ in migraine and the fact that brain is affected differentially in women compared to men.

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Gender Differences in a Stable Outpatient Population of Inner-City Kidney Transplant Recipients (KTR’s): Women have lower iPTH & Hemoglobin, but Higher Vitamin D & BMI

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Abstract: Most studies of KTR’s make the assumption that men (M) and women (W) have similar characteristics. We studied 194 randomly selected pts attending outpatient transplant clinic in a cross sectional design, comparing values in routinely observed parameters for M and W. There were 34 (17.5%) Caucasians, 148 (76.3%) Blacks & 12 (6.2%) other race, with 116 (59.7%) men. W were post-menopausal. By Chi Squared analysis, there was no difference in number of pts with diabetes or hypertension, type of immunosuppression, including pts on mycophenolate mofetil (MMF), treatment with calcium, Vit D or analogues, or race. By t-test, there was no difference in age (M: 56.4 ± 1.0 vs W:56.2 ± 1.5 yrs), months since transplant (M:75.4±5.5 vs W:65.3±5.0), Ca++ (M: 9.23±0.07 vs. W:9.53±0.08), PO4 (M:3.2±0.07 vs W:3.3±0.08), Mg++, albumin, total cholesterol, eGFR by MDRD calculation (M:55.9±2.3 vs W:54.5±2.6), prot/creat ratio (M:0.68±0.1 vs W:0.58±0.14), W had lower hemoglobin (W:11.8 ±0.17 vs M:13.1± 0.22, p<0.0001), creatinine (W: 1.6 ±0.11 vs M: 1.99± 0.09, p<0.05), and iPTH (W: 150.6 ±13.8 vs M: 201.0 ±14.8, p<0.05) but higher 25-OH vitamin D (W: 24.3± 1.22 vs M: 20.9 ± 1.05, p<0.05) and BMI (W: 30.7 ±0.7 vs M: 27.8 ±0.7, p =0.004). We conclude in our population: 1. Women have lower creatinine and higher BMI but similar
eGFR, suggesting that they have higher fat mass. 2. Despite post-menopausal status and no increased use of MMF or difference in eGFR, women have lower hgb values, which may be due to androgen effects in M. 3. Despite no difference in reported intake of Vitamin D, women have higher Vit D levels and lower iPTH. It is possible that they are using more OTC vitamins or have increased intake of vitamin D fortified foods. There was no difference in Ca++ or PO4 values. 4. It will be important to further clarify gender differences in KTR’s, as body composition and baseline measurements may be different and response to therapy may differ as well.

**Poster ID: 118**

**Survival advantage in female patients with congenital adrenal hyperplasia: Adrenal androgen precursors are playing a role?**

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**Abstract:** Congenital Adrenal Hyperplasia (CAH) is an autosomal recessively inherited metabolic disorder caused by the impairment of cortisol production and excess androgen production. Androgen excess leads to ambiguous genitalia in female fetuses and hence they are diagnosed early in life. CAH diagnosis may be missed in newborn boys unless salt wasting is detected. Most prevalence studies noticed a female preponderance. However neonatal screening has shown less disparity in the gender ratio. One of the speculations regarding this is that girls may have early diagnosis because of genital ambiguity. The aim of our study was to assess neonatal deaths in families with CAH children. This study was approved by AIIMS ethics committee. We had taken the detailed medical history including genital appearance, hirsutism status and three generational family pedigrees from 5 families where one or more children were diagnosed to have CAH from the cohort of sixty two (56 females & 6 males) CAH patients. Twelve were found to have salt wasting (SW) CAH. Among them, 11 were (91.7%) females and one (8.3%) was male. Informed consent was taken from the patients/parents before collecting the blood samples for molecular analysis. Genotyping was done by PCR and RFLP method to find out the underlying mutations of CYP21A2 gene. The highest frequency was found to be the stop codon mutation on exon 8, p.Q318X (37.50%) followed by Intron 2 (12.50 %) and Δ 8-bp (12.50%). There were 21 children born out of 5 families. Among them, 6 were normal (4 boys & 2 girls), 6 were affected (4 girls & 2 boys) and nine died (7 boys & 2 girls) during infancy due to diarrhea and vomiting. In this small cohort there were more neonatal deaths among boys. We suspect these children may also have undiagnosed CAH. It is possible that boys with CAH may go undiagnosed as there are markers / indicators (like genital ambiguity in girls). It is also possible that the androgen excess may give a survival advantage for girls. This study was funded by Department of Biotechnology (Ref.N0.BT/PR7205/Med/12/277/06), Government of India.

**Poster ID: 119**

**The effects of parity on dendritic spines in the prefrontal cortex and hippocampus of the female rat**

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**Abstract:** Studies show that female rats that experience multiple bouts of pregnancy, birth, and pup rearing (multiparity) show better cognitive function than virgin (nulliparous) rats. There is also evidence that parity may have long-term effects on cognition and plasticity, which may lead to enhanced spatial and non-spatial memory performance in old age. The current study examined whether multiparity led to changes in the dendritic spine density of neurons in the prefrontal cortex (PFC) and CA1 hippocampus (HIPP) in aged female rats. Young nulliparous p(Y-NULL; n=8), middle-aged nulliparous (M-NULL; n=10), and middle-aged multiparous (M-MULT; pn=8) rat groups were used. We hypothesized that the M-NULL group would have lower pPFC and CA1 HIPP spine density compared to the other groups with no differences between the M-MULT and Y-NULL groups. The object recognition (OR) and object placement (OP)
tasks were administered to all groups. No differences were found in the OR task but in the OP task, the M-NULL rats were significantly impaired as compared to the Y-NULL females, while MMULT females did not differ from either group. Upon completion of the behavioral tasks, Golgi impregnation was used for brain tissue analysis. Although no significant differences were found between PFC basal spine density (F=0.196, p=0.82), M-NULL rats had lower PFC apical spine density (F=5.43, p<0.05) as well as lower CA1 HIPP apical (F=20.9, p<0.01) and basal (F=11.8, p<0.01) spine density than compared to the Y-NULL and M-MULT groups. No significant differences were observed between the Y-NULL and M-MULT groups in PFC basal, CA1 HIPP apical, and CA1 HIPP basal spine density. No significant differences were observed between the Y-NULL and M-MULT groups in PFC basal, CA1 HIPP apical, and CA1 HIPP basal spine density. Results suggest that the extension of PFC and CA1 HIPP dendrites' capacity for hormonal-dependent plasticity into older age has positive implications for the attenuation of age-related cognitive declines.

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Poster ID: 120
Sex differences in formalin-evoked primary afferent release of substance P

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Abstract: Accumulating evidence has indicated the presence of sex differences to pain and noiception in humans and animals. Occurrence of certain chronic pain conditions is more prevalent in women than in men. Similar to the findings in humans, female rats have a greater nociceptive sensitivity in behavioral models of mononeuropathy, inflammatory, and tonic pain conditions as compared to male rats. Therefore, we sought to determine whether sex differences are observed in nociception evoked primary afferent excitation by assessing substance P release after intraplantar administration of formalin. In our studies, gonadally intact or gonadectomized male and female rats were administered intraplantar formalin (5%). Animals were sacrificed at either 5min or 30min post formalin injection, representing phase 1 and 2 of the formalin response, respectively. Spinal cords were removed and processed for immunofluorescent staining of neurokinin 1 receptors (NK1r). NK1r internalization in lamina 1 neurons was used as a measure of primary afferent substance P release. Preliminary analysis of our data suggest that administration of formalin evoked similar amounts of NK1r internalization 5min after formalin in male and female rats regardless of gonadal status. However, intact females exhibited significantly higher NK1r internalization 30min post formalin as compared to intact males. This difference was sensitive to changes in gonadal hormone levels, as ovariectomy reduced the NK1r internalization as compared to intact females; whereas castration did not produce a notable difference in NK1r internalization as compared to intact male rats. These findings suggest sex differences in primary afferent excitation during a time period that is believed to correspond to a state of hyperalgesia and central sensitization in the formalin model.

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Poster ID: 121
The effects of perinatal testosterone exposure on DNA methylation in the brain are late-emerging and dynamic

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Abstract: Sexual differentiation of the rodent brain is driven mainly by the actions of gonadal hormones, primarily testosterone (T) and estradiol. Perinatal exposure to T can have long-lasting and irreversible consequences on brain anatomy. These have been termed organizational effects, and lead to masculinization of certain brain regions, including those that control sexually dimorphic traits. The molecular mechanisms underlying these effects are still poorly understood. We hypothesized that perinatal T exposure will affect DNA methylation patterns in the bed nucleus of the stria terminalis/preoptic area (BNST/POA) and that this exposure contributes to the establishment of sex differences in the methylome. We established genome-wide methylation profiles for male (XY), female (XX), and females treated with T at birth (XX+T) at two time points. The first was postnatal day 4 (PN4), which is within the window for T’s organizational effects, and the second was PN60 (i.e. adulthood, to evaluate the longer term effects of T). Our approach was validated by the finding that the majority of X chromosome CG sites differing between XX and XY mice at PN60 were hypermethylated in XX animals, consistent with X chromosome inactivation. The short-term effect of T exposure was relatively modest: 45 genes were differentially methylated between XX and XX+T. However, by PN60, this number had grown dramatically and the methylation status of 760 genes was influenced by T. Unexpectedly, few of the genes affected by T at PN4 were the same as those affected at PN60. Furthermore, the masculinization of sexually dimorphic CG sites in XX+T was greater at PN60 than at PN4. Taken together, this data suggests that the organizational effect of T on the BNST/POA in terms of DNA methylation is late-emerging and dynamic. Organization by T may occur via early programming on relatively few genes and that this small initial effect sets up the brain to respond in a particular fashion to later developmental events.

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humans we used the cantharidin blister model in healthy volunteers. Similar to rodents, neutrophil influx into the blister was substantially less in women than men and was directly correlated with blister CXCL6, the human orthologue of rodent Cxcl5. Thus, our study reveals a novel concept that equivalent stimuli may induce distinct and opposing inflammatory signals in males and females. Moreover, we demonstrate that Cxcl5/CXCL6 is an essential regulator of neutrophil trafficking and its disparate regulation in males and females underlies sexual dimorphism in acute inflammatory responses.

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Poster ID: 123
Biological sex affects the neurobiology of autism

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Abstract: Since autism was first recognized, males with autism have disproportionately skewed research. Females with autism have been relatively overlooked, and have generally been assumed to have the same underlying neurobiology as males with autism. Growing evidence suggests that this is an oversimplification that risks obscuring the biological base of autism. This study seeks to answer two questions about how autism is modulated by biological sex: (1) Is the neuroanatomy of autism different in males and females? (2) Does the neuroanatomy of autism fit predictions from the ‘extreme male brain’ (EMB) theory of autism, in males and/or in females? Neuroanatomical features derived from voxel-based morphometry were compared in a sample of equal-sized high-functioning male and female adults with and without autism (N=120, N=30/group). The first question was investigated using a 2x2 factorial design, and by spatial overlap analyses of the neuroanatomy of autism in males and females. The second question was tested via spatial overlap analyses of specific patterns predicted by the EMB theory. We found that the neuroanatomy of autism differed between adult males and females, evidenced by minimal spatial overlap (not different from that occurred by under random condition) in both gray and white matter, and substantially large white matter regions showing significant sex-by-diagnosis interactions in the 2x2 factorial design. Furthermore, atypical brain areas in females with autism substantially and non-randomly (P < 0.001) overlapped with areas that were sexually dimorphic in neurotypical controls in both gray and white matter, suggesting neural ‘masculinization’. This was not seen in males with autism. How differences in neuroanatomy relate to the similarities in cognition between males and females with autism remains to be understood. Future research should stratify by biological sex to reduce heterogeneity and to provide greater insight into the neurobiology of autism.

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Abstract: Klinefelter Syndrome (KS; caused by the karyotype 47, XXY) is characterized by low testosterone, high LH and FSH, infertility, decreased muscle mass, cognitive impairment, and increased rates of health problems such as obesity, diabetes, lupus, osteoporosis, and breast cancer. In humans with KS, low testosterone levels are always confounded with sex chromosome complement, making it difficult to attribute KS symptoms to hormonal vs. genetic mechanisms. We hypothesized that many of the syndromic features of KS are caused by direct genetic effects rather than low testosterone. To test this hypothesis we used a new mouse model for the study of KS, the Sex Chromosome Trisomy model (SCT), which makes it possible to dissect these contributing factors by separating gonadal sex from sex chromosome complement. The SCT model allows for within-litter comparison of XX, XY, XXY, and XYY mice, each genotype possessing either testes or ovaries. We tested several metabolic phenotypes as well as social recognition and motor function. We found that the SCT mouse model recapitulates aspects of the metabolic phenotype seen in KS; XXY mice had increased body weight, increased body fat, and increased visceral fat relative to subcutaneous fat. The results provide strong evidence that these traits are the result of direct sex chromosome effects, because they do not require the presence of testes and occur in both gonadal males and females. We also show that the sex chromosome effects persist after adult gonadectomy and testosterone replacement therapy. XXY mice did not have impaired social recognition or motor function, XYY male mice performed worse on motor tests compared to other groups.

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Poster ID: 125
Vitamin D receptor signaling reduces inflammation in female mice with myocarditis, but increases inflammation in males: implications for translation studies

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Abstract: An estimated 1 billion people worldwide have deficient or insufficient levels of vitamin D (VitD), while roughly 25% of individuals in the US are reported to have inadequate VitD levels. Considerable evidence indicates that VitD deficiency is associated with an increased risk of cardiovascular disease (CVD), yet it remains unclear whether low VitD is simply a biomarker of CVD or has a true pathologic role. The role of VitD deficiency in the pathogenesis of inflammatory myocarditis is unknown. Myocarditis has an increased prevalence and severity in men compared to women. When we examined VitD levels in myocarditis patients, we found that only 20% of myocarditis patients had low VitD levels (<19 ng/mL). Surprisingly, high VitD levels only protected women but not men with myocarditis from heart failure measured as %EF. When we examined VitD receptor (VDR) deficient mice in a mouse model of viral myocarditis, we found that VDR-/− females had increased myocarditis (p = 0.007) while males had decreased disease (p = 0.006), confirming translational findings. We found that VDR-/− males had significantly reduced proinflammatory IFN-γ and IL-1β and increased profibrotic IL-17A, but no significant differences were found in females for these cytokines. Comparison of microarray data during myocarditis to published VitD response element genes revealed around 200 genes associated with proinflammatory (e.g. caspase-1) and profibrotic (e.g. TGF-β1, MMP) responses increased in male mice. Female VDR-/− hearts had increased CD45, CD3, TLR4 and Casp-1 while male hearts had increased Foxp3 by qRT-PCR. Our findings in mice indicate that VitD/VDR reduces myocarditis in females, but increases inflammation in males. These findings provide a mechanism for how low VitD levels in men could
increase myocarditis.

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Poster ID: 126
The Pregnancy-Associated Hormones, Estriol and Progesterone, Have Differential Effects on the Outcome of Influenza A Virus Infection in C57BL/6 Female Mice

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Abstract: Pregnancy is a known risk factor for severe disease outcome following Influenza A virus (FluA) infections during seasonal epidemics and during pandemics (e.g., the 2009 H1N1 pandemic). During the third trimester of pregnancy, the immune response is shifted away from inflammatory responses and toward an anti-inflammatory state to support healthy fetal development and production of sex steroids by the placenta, notably estriol (E3) and progesterone (P4), is high. To determine if third trimester levels of E3 and P4 affect the outcome of FluA infection, young adult female C57BL/6 mice (8-10 weeks of age) were ovariectomized and treated with exogenous pellets of E3 (5mg), P4 (15mg), E3 + P4, or placebo, infected with a lethal dose of a mouse-adapted FluA virus, and morbidity and mortality, as well as pulmonary viral loads, cytokine production, and T cell activity were measured. Treatment with E3 increased morbidity and mortality following FluA infection and skewed pulmonary Th1/Th2 cytokine responses by reducing TNF-α and IFN-γ and increasing IL-4 concentrations as compared to placebo-treated mice. In contrast, treatment with P4 significantly reduced morbidity and mortality from FluA and increased production of the regulatory cytokine, TGF-β. Finally, coadministration of E3 and P4 reversed the protective effects of P4 alone on the outcome of FluA infection and significantly increased production of both IL-6 and TGF-β. The changes in cytokine profiles in response to E3 and P4 suggest that these hormones alter the activity of distinct CD4 T cell populations. Because none of the hormonal manipulations affected viral replication, our data suggest that these steroid hormones affect the outcome of FluA by altering host immune responses during infection. Pregnancy is a unique hormonal and immunological state experienced by female mammals and whether the changes in hormone concentrations explain how pregnancy affects the outcome of influenza in females requires consideration.

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Poster ID: 127
Elevated fetal steroidogenic activity in autism

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Abstract: Autism affects males more than females and the influence of steroid hormones on early fetal brain development may be a prominent early biological risk factor. Combining samples from the Danish Historic Birth Cohort with diagnostic information from the Danish Psychiatric Central Register, we examined all amniotic fluid samples of individuals born between 1993-1999 (population n = 19,677) and identified all male individuals who later received ICD-10 diagnoses of childhood autism (n=41), Asperger Syndrome (n=29), or PDD-NOS (n=58). Using liquid chromatography mass spectrometry we assayed concentration levels of Δ4 sex steroids (progesterone, 17α-hydroxy-progesterone, androstenedione, and testosterone) and cortisol. By
comparing these hormones in males who later developed autism to matched typically-developing Controls (n=217), we were able to test directly for the first time whether such steroid hormones are elevated in fetal development of cases with a clinical diagnosis of autism. Principal components analysis (PCA) on hormone concentration levels revealed that one primary factor loading equally onto all measured steroids, accounted for approximately 50% of the variation in the data. Only this latent ‘steroidogenic’ component was significantly different between-groups ($F(1,343) = 11.18$, $p=0.0009$, Cohen’s $d = 0.37$), with elevations apparent in autism relative to typically-developing controls. Elevations were similar across all hormones and ICD-10 subgroups. These results suggest atypical fetal hormonal environmental factors are important in the early development of autism. Testing the specificity of elevated steroidogenic activity in autism relative to other neurodevelopmental conditions with skewed sex ratios will be an important next step. Elevated steroidogenic activity may be an important epigenetic fetal programming mechanism that interacts with many other important pathophysiological factors in the early development of autism.

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**Poster ID: 128**

**The effect of bisphenol A exposure in a multibehavior model of rat migraine**

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**Abstract:** Migraine is a debilitating neurological condition which can be accompanied by nausea, photo- and phonophobia and is aggravated by routine activities. Clinical studies have demonstrated that migraine is experienced by women three times more frequently than men. While the mechanism behind this sex-difference is not well understood, estrogen has been implicated to play a role. Studies have established the presence of estrogen receptors in trigeminal pain receptors, and have revealed the ability of estrogen to modulate pain sensitization through activation of nociceptive pathways. Xenoestrogens are chemicals found in the environment that exhibit estrogen-like activity. Bisphenol A (BPA) is one of the most ubiquitous and pervasive of these chemicals and over 90% of the American population is known to have BPA in their bodies. Studies have demonstrated that BPA can mimic natural estrogen, binding to and activating estrogen receptors. Currently, the consequences of BPA exposure in migraine pathogenesis have not been studied. Therefore, it is hypothesized that BPA exposure leads to an increase in migraine intensity and duration through activation of estrogen receptors and downstream nociceptive pathways. This study employs a multibehavior model of migraine in rat with behavior experiments modeled after the International Headache Classification (ICHD-2). Total locomotor activity, photo- and phonophobia, evoked grooming and startle reflex are monitored following BPA exposure and migraine induction via a cranial cannula implant. Preliminary studies have established that rats exposed to BPA demonstrate significantly higher migraine-like symptoms as compared to rats without BPA exposure (decreased locomotion, etc.). Further studies to investigate changes in estrogen and pain-related genes are currently in progress. Overall, these results indicate that exposure to BPA can alter pain sensitization and migraine intensity and demonstrate an important need to better understand how migraine pathogenesis evolves and is altered by exposure to BPA.

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**Poster ID: 129**

**Differential regulation of specific BDNF exons by sex and steroid treatment in the mouse dorsal hippocampus**

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**Abstract:** In adults, the neurotrophin BDNF can
modulate synaptic plasticity and memory. The BDNF gene is complex with at least nine non-coding exons with individual promoter regions and a coding exon, which codes for pro-BDNF. Activity-dependent regulation of specific BDNF exons is implicated in the spatial and temporal control of cellular responses that mediate physiological and behavioral outcomes. Reports of BDNF regulation by steroids along with sex differences in both synaptic plasticity and memory suggest that differential regulation of BDNF transcription in males and females may underlie these dimorphisms. We compared gonadectomized (GDX) male and female C57Bl6 mice following 48 hours of estradiol (5 ug estradiol benzoate (EB) in sesame oil) or Vehicle (oil alone) administration. Dorsal hippocampal mRNA was isolated and processed for real time RT-PCR with primers for BDNF exons 1-6, 9 and coding region. Results were compared using the standard curve method and significant differences determined by student’s T-test. In GDX male and female mice expression of exon 9, the coding region of BDNF was similar regardless of steroid treatment. Vehicle treated males showed higher expression of exon 3 than females while exon 5 expression was higher in females than males. In GDX males EB increased exon 3 expression. In females, EB had no effect on exon 5 or any other exon. Interestingly, expression of the BDNF receptor TrkB was higher in males than females and was unaffected by estradiol. While this sub-chronic estradiol treatment had modest effects on BDNF transcription, the effects of acute or chronic administration may differ and are currently under investigation. The complexity BDNF transcription continues to grow; both traditional promoters along with epigenetic modifications likely contribute to both differential baseline and activity or environmental activation of BDNF transcription in males and females.

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Poster ID: 130
Decoupling sexually dimorphic development of the mouse external genitalia and brain in a single individual

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Abstract: A nationwide inpatient survey identified Congenital Penile Anomalies (CPA) affect 1 in 125 newborn boys. The etiology of CPA is largely unknown, although exposure to endocrine disrupting chemicals (EDCs) is suspected to play a role. We hypothesized that disrupting androgen receptor (AR) signaling during embryonic development can lead to CPA. Little is known about the genetic targets of AR or the cellular mechanisms by which AR masculinizes male external genitalia. We used mouse genetics to conditionally delete AR at specific stages from specific tissue compartments of the developing genitalia. We find that disrupting AR at different times causes different genital malformations to arise. Loss of AR from discrete tissue compartments alters the expression of gene known to control genital development. Analysis of cellular processes controlled by these pathways links the disruption of AR to defective morphogenesis of the penis. Because of the systemic nature of steroid hormones and exogenous mimics, disruption of sex steroid pathways during a critical developmental period could alter other organs in patients with CPA. During normal development, the brain is masculinized by neonatal testosterone that is converted to estrogen by aromatase. We hypothesized that prenatal exposure to anti-androgenic or estrogenic EDCs could alter development of sexually dimorphic brain nuclei. Behavioral analysis of adult mice that were exposed to AR antagonists or estrogenic chemicals as embryos reveals that sexual behavior is hypermasculinized. Immunohistochemical and morphometric analysis of sexually dimorphic brain nuclei shows that exposed mice develop significantly larger nuclei. At the cellular and molecular levels, we find that prenatal exposure increases the number of aromatase-expressing neurons in both prenatal and postnatal mice. Taken together, our results demonstrate that prenatal anti-AR feminizes external genitalia, but hyper-masculinizes brain development and sexual behavior.

Poster ID: 131
Sex differences in brain-derived neurotrophic factor (BDNF) expression in the early postnatal hippocampus of the rat

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Abstract: The hippocampus is an important regulator of spatial learning and stress reactivity, both of which differ between the sexes. Dysfunction of the hippocampus is critically involved in many disorders that exhibit a sex bias in prevalence or age of onset, including anxiety and depression, schizophrenia, autism, and temporal lobe epilepsy. Because many of these disorders have origins early in life, characterization of sex differences in the developing hippocampus is crucial for understanding their etiology. We previously reported significantly higher rates of neurogenesis during the first week of life in the male Sprague-Dawley rat compared to female littermates (Bowers et al., 2010), and this sex difference is gone by the second week of life. Here, we describe a similar sex difference in the expression of BDNF, where males had higher levels in the CA1 and dentate gyrus compared to females during the first week of life but not the second week. BDNF expression in both sexes was altered by estradiol signaling and differentially regulated among hippocampal subregions. Estradiol also increases neurogenesis in the neonatal female hippocampus. The parallels in both the sex difference and hormonal modulation of neurogenesis and BDNF levels in the developing hippocampus suggest a causal relationship. Given the well-characterized effects of BDNF on neuronal development, future studies exploring the functional consequences of differentiated hippocampal BDNF expression between the sexes may inform our understanding of gender-biased neurodevelopmental disorders.

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Poster ID: 132
Male breast cancer: a rare but peculiar disease

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Abstract: Male breast cancer consists of 1% of all breast cancers and it accounts for the 1% of male deaths for all malignancies. The presence of any mass in a male breast does not suggest the possibility of a cancer because of gender bias: the diagnosis is later than in women (6ms-2ys vs 3ms), the stadiation is more advanced (40% at III-IV), the prognosis at the same stage is worse and the treatments are often only palliative. The aim is to focus on the biological and clinical sex differences in breast cancer, to support a correct approach in men. In line with this aim, the CDM undertook a review of literature about the disease, organized formative events and provided publications on its website. Male breast cancer presents peculiar aspects compared with the female one: more frequent familiarity (20%vs10%), exclusive BRCA2 mutations (F 80% BRCA1), more frequent PTEN (50%vs25%) and HER2/neu mutations (95%vs30%), a greater expression of steroid receptors (85%vs35%), a major incidence of ulceration (3 1.6%vs1 1.1%), arm edema (7.4%vs2.4%), lymphonodal (16%vs7.9%) and fascia (36.7%vs20.3%) involvement, less incidence of breast edema (5.3%vs22.3%) and blood discharge (3.7%vs10.4%), the presence of atypical metastasis (choroid, nasal, sinusal) and paraneoplastic forms (esophtalm). Hormonal therapy is less efficient: tamoxifen represents the gold standard, but causes more side effects. Aromathase inhibitors reduce less the tumor mass (50%vs85%). Fulvestrant and novel agents targeting prolactin and androgen receptors seem to be effective in men. The low incidence of male breast cancer does not make it an incorrectly-treated disease: it is necessary to surpass gender blindness for improving outcomes. It is important to look at conditions of iperestrogenism in men: diet, obesity, sedentarily, smoke, alcohol, gynecomasty, anabolic steroid, and environment. We propose to keep under clinical surveillance men with relatives previously treated for breast cancer, not only women.

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Poster ID: 133
Antisense oligonucleotides injected in a sexually dimorphic nucleus of the MPOA temporarily blocks male sex behavior in the Syrian hamster

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Abstract: Male-typical behavior, in virtually all vertebrate species, is dependent on testosterone; without it males of most species will not mate or engage in any sexual behaviors. Conversely, replacing testosterone in a castrated animal will result in the recovery of motivation and sex behaviors over time. Though this effect is well characterized, the specific mechanism by which testosterone treatment recovers sexual behaviors remains unknown. The medial preoptic area was demonstrated to be a key site in the regulation of sex behavior by steroids in virtually every vertebrate species studied using lesions, stimulation, and site-specific steroid implantation. A specific sub-region of the MPOA, the magnocellular subdivision of the medial preoptic nucleus, the MPN mag, is a sexually dimorphic region of the hamster brain that has a high concentration of steroid receptors, and appears to play a critical and specific role in male sex behavior. A model for the function of the MPOA has been developed by which glutamate from the medial amygdala is received by NMDA receptors in the MPOA triggering NO production and in turn DA release into the MPOA. Central to this model is the notion that nNOS and NMDA are held in close proximity to each other by PSD-95 to couple the activity of glutamate to the release of NO and DA. In the absence of testosterone, NO is not produced, DA is not released, and mating behaviors do not occur. To test the hypothesis that PSD-95 physically and functionally links glutamate reception by NMDA receptors to the release of NO by nNOS and that this connection is critical for male sex behavior, antisense oligonucleotides to PSD-95 were injected bilaterally into the MPOA at the site of the MPN mag, and sex behavior was subsequently tested 24 hours and three weeks after the injection. Antisense oligonucleotides, but not missense oligonucleotides, were effective in preventing the execution of male sex behavior 24 hours after the injection, but not three weeks after the injection. These results suggest that by blocking the production of PSD-95 in the MPOA at the MPN mag, NMDA receptors are not able to activate nNOS to produce NO and cause DA to be released into the MPOA. Furthermore, these results are consistent with a specific deactivation of the MPN mag, as sex behaviors (mounting, intromission, and ejaculation) but not motivational behaviors (anogenital investigation) were temporarily eliminated.

Poster ID: 134
The role of genetic sex in affect regulation and expression of GABA-related genes across species

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Abstract: Major depressive disorder (MDD) is an illness of altered emotion regulation with higher risk in women. Our group recently reported that MDD patients have reduced markers of GABA interneurons (somatostatin (SST) and GABA synthesizing enzymes glutamate decarboxylase 1 (GAD1) and GAD2) in the subgenual anterior cingulate cortex, a hub in the corticolimbic emotion regulation network. These findings were more robust in females. Female MDD prevalence is higher across hormonal states, indicating that biological differences other than activational effects of circulating hormones, place women at higher risk. Developmental organizational effects of hormones and genetic sex also establish brain sexual dimorphism, prompting the hypothesis that elevated female vulnerability to MDD may originate in part from the differential organization of key brain structures early in life. We investigated the contribution of sex-related factors to adult anxiety-like behaviors and frontal cortex expression of GABA markers in the Four Core Genotypes mice, in which genetic and gonadal sex are decoupled. We show that genetic male sex increases anxiety-like behaviors as well as SST, GAD1, and GAD2 gene expression. In an expression QTL study in human BA11 and BA47, we found that, in the general population, genetic polymorphisms on the X-chromosome influence expression of SST, GAD1, GAD2 in this exploratory study. These genes are not located on the X-chromosome, suggesting X-chromosome encoded upstream common regulators. From the same human dataset, we selected GABA signaling-related genes (e.g. GABA receptor subunits, interneurons markers) and created a weighted gene co-expression network. SST, GAD1, and GAD2 display highly correlated expression patterns, even in the context of other GABA-related genes, supporting shared regulation. These convergent mouse-human results suggest that genetic sex regulates...
anxiety-like behavior, potentially through X-chromosome mediated changes in GABA microcircuitry.

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Poster ID: 135
Sex-specific analysis reveals delta catenin as an autism gene

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Abstract: We focused autism gene discovery on individuals with the highest genetic liability, female-enriched multiplex families (FEMFs), which are rare autism families with at least 2 affected females. Unrelated, affected females (n=13) from FEMFs were exome sequenced, tested for rare, highly conserved missense, nonsense, and canonical splice site changes, and subsequently compared to controls. This test revealed 18 new candidate autism genes of which one (CTNND2) was chosen for extensive follow-up. The mutations identified, G34S and R713C, were predicted to create a new phosphorylation site and affect protein-protein binding, respectively. Subsequently, we sought additional variants by sequencing the exons of CTNND2 in 361 affected females and identified 5 new missense variants (G275C, R454H, T862M, P189L, P224L). Exome sequencing in the Simons Simplex Collection yielded another change (Q507P: S>4). At the level of CNVs, 12 were identified in patients with 58% overlapping exons, as compared to 6% in controls (p=0.0005). To further explore the role of CTNND2 in autism, we performed expression and functional studies. By examining 24 human tissues we identified the highest expression to be in fetal brain indicating its importance in development. Examination of expression data across human development (Allen Brain Atlas) yielded a number of autism genes (notably the female-specific autism genes: MECP2 and CDKL5) highly correlated in expression with delta-catenin. By morpholino-based knock-down of ctnnd2 in zebrafish at 1day post-fertilization we observed a significant convergence-extension phenotype that could be rescued by wild type human CTNND2 but not by the autism variants. Finally, functional analysis by over-expression of wild type and autism CTNND2 alleles in rat primary hippocampal neurons revealed that the G34S and R713C mutations are dominant negative and loss of function respectively. Thus, CTNND2 is a novel autism gene.

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Poster ID: 136
Null mutation in the vasopressin gene eliminates sex differences in the development of social play in rats

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Abstract: Play fighting is the most prominent social behavior in juvenile mammals. While it is typically reported that males play fight more than females, we have found that this male-biased sex difference depends on testing conditions and age of participants. For example, female Wistar rats begin playing earlier than their male littermates resulting in a “reversed” sex difference (females > males) around weaning. We also found that during this peri-weaning period, vasopressin mRNA in the bed nucleus of the stria terminalis (BNST) of males is higher than that of females, declines as play emerges, and correlates negatively with play. Based on these findings we proposed that inhibition derived from
elevated BNST vasopressin expression delays play onset in males. The Brattleboro rat provides a unique tool to test this hypothesis. Homozygous (Hom) Brattleboro rats contain a point mutation in the vasopressin gene that blocks vasopressin synthesis. We predicted that sex differences in play development would be absent in Hom rats. Preliminary data indicate that similar to Wistar rats, play fighting in wildtype Long Evans rats emerges earlier in females than in males leading to higher levels of play in females at 21 days of age. Consistent with our hypothesis, this sex difference was absent in Hom rats. The sex difference was also absent in heterozygous (Het) rats indicating loss of function in one allele, which results in a partial vasopressin-deficiency, is sufficient to eliminate the sex difference in play onset. Counter to our hypothesis however, the absence of this sex difference was due to a decrease in the play of Hom and Het females rather than an increase in males. This suggests that vasopressin acts to stimulate play in females, perhaps via vasopressinergic systems originating outside the BNST. These data demonstrate that the earlier onset of play fighting in females is not restricted to the Wistar strain and requires two functional copies of the vasopressin gene.

This study was funded by NIMH grant MH047538 to GJD

Poster ID: 137
Sex Differences in Processing of Early Life Stress and Corticotropin-Releasing Factor Receptor Expression

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Abstract: Women are twice as likely to develop stress-related mood disorders such as anxiety and depression than men and the underlying reason for this sex difference is unknown. Because early adverse experiences increase susceptibility to mood disorders in adulthood, females may be uniquely susceptible to early adversity. We have developed an animal model of child abuse termed juvenile social subjugation (JSS) whereby juvenile male and female rats are subjugated by an aggressive adult male for 10 min daily for 10 days. Here, we report results that collectively show that JSS induces a mood disorder-like state in females but not males, and that the neural substrates that process JSS are sexually dimorphic. JSS increased adult anxiety- and depression-like behavior and physiology in females but not males. To test whether juvenile males and females process JSS differently, we examined the number of neurons immunopositive for Fos, a marker of neural activation, in the amygdala after a single episode of JSS. Fos expression was sex-specific in the medial amygdala but not in the central nucleus of the amygdala. We next examined corticotropin-releasing factor (CRF) receptors, which mediate stress responses and may underlie the sex-specific response of the medial amygdala to JSS. CRF1 receptors generally initiate stress responses while CRF2 receptors have been known to diminish them. We measured CRF1 and CRF2 receptor binding in the amygdala of juvenile and adult, male and female rats. CRF1 binding was greater in adult females than in males while CRF2 binding was greater in adult males than in females. This reciprocal pattern of CRF receptor binding in the amygdala may provide a critical substrate for the increased susceptibility of females and/or the greater resiliency of males to early life stress. Together, these data point to the medial amygdala as an important brain region for the sex-specific effects of JSS on mood disorder-like behavior.

This study was funded by a Brains and Behavior seed grant to BMC.

Poster ID: 138
A review of the differences in symptom profiles and co-occurring conditions between males and females with Autism Spectrum Disorders

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Abstract: Autism spectrum disorders (ASDs) are over four times more prevalent in males compared to females. The purpose of this review is to describe current literature regarding sex differences among persons with ASDs. Females with ASDs are more likely to have
intellectual disability, co-occurring epilepsy, and mood disorders than males with ASDs, while males with ASDs present with more repetitive behaviors, restrictive interests, and attention to detail than females with ASDs. Other traits, such as social-communication deficits, are not significantly different between the sexes or differences are not consistent across studies. Further research is needed to better understand why sex differences in certain ASD traits exist and how this understanding contributes to dialogue about the etiologies and treatment of ASDs.

Poster ID: 139
Neuropeptide levels associated with sex differences in the effect of alcohol on social bonding behavior

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Abstract: Alcohol abuse and alcoholism are widespread problems known to have different physical and social repercussions in men and women. In the socially monogamous prairie vole (Microtus ochrogaster), we found that alcohol self-administration during cohabitation facilitated partner preference in females, but inhibited the preference for the partner in males. Here we hypothesized that alcohol intake during bond formation would affect levels of neuropeptide known to be involved in alcohol intake and bond formation, in specific brain regions in a sex-specific manner. Adult male and female prairie voles were paired for 24 hours, and had continuous access either to water or to water and 10% ethanol in tap water. Immediately after, the voles were euthanized by CO2 inhalation and brains were removed and preserved for immunohistochemistry (IHC). Floating sections of 14 different brain regions underwent IHC for visualization of oxytocin (OT), vasopressin (VP), corticotropin-releasing factor (CRF), neuropeptide Y (NPY), urocortin-1 (Ucn), or the transcription factor cFos. The number or density of immuno-positive cells and/or fibers were counted and compared across treatment groups and sex by ANOVA, and significant interactions between sex and alcohol are reported here. There were no significant interactions between sex and alcohol for OT- or VP. There were significant interactions for the effects of sex and alcohol on NPY fiber density in the medial amygdala, Fos levels in the arcuate nucleus, as well as in the centrally-projecting Edinger-Westphal nucleus. CRF fiber density was lower in alcohol drinking voles in the bed nucleus of the stria terminalis, and there is a known sex difference in the number of CRF type 2 receptors in this region in prairie voles. These data provide evidence that alcohol affects a number of different neuropeptide systems in a sex-dependent manner, and in particular, these regions are all relevant for stress and anxiety related behavior. This work was supported by NIH AA019793 to AER and AA020136 to AMJA.

Poster ID: 140
Sex differences in neuroinflammation in a neurodevelopmental animal model of schizophrenia: An autoradiographic study

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Abstract: A major risk factor for schizophrenia (SCZ) is maternal infection during pregnancy, and extensive animal research seeks to explore the long-term neural and behavioral effects of immune-mediated disruption of early brain development. In the prenatal polyriboinosinic–polyribocytidilic acid (polyI:C) animal model of SCZ, a single injection of pregnant rats with the viral mimic polyI:C, induces a wide spectrum of SCZ-relevant behavioral and brain abnormalities in the adult offspring. The present study was designed to test for the presence and regional distribution of neuroinflammation in adult male and female offspring of polyI:C treated dams by examining the regional levels of TSPO, a molecular biomarker for microglial activation. Ten male and ten female offspring of polyI:C treated dams were sacrificed in adulthood (post natal day 95). TSPO labeling of brain sections with [3H]PK11195 was followed by quantitative autoradiographic measurement of specific binding. In male offspring, prenatal polyI:C was found to be associated with significant elevations in TSPO.
binding, indicative of microgliosis, in two cortical regions (frontal and occipital) as well as several dorsal hippocampal subfields (dentate gyrus, CA1 and CA3) relative to vehicle. A more restricted neuroinflammatory response was observed in female offspring, in which there was increased [³H]PK11195 binding only in the occipital cortex and ventral hippocampus. This difference complements previously reported sex differences in brain structural and behavioral trajectories following prenatal polyI:C, whereby female offspring were less affected than male offspring, and resonates with the clinical picture of later onset and milder disease course of SCZ in women. The findings in both sexes also support a role for neuroinflammation in cortex and hippocampus in the deleterious effects of prenatal poly-I:C administration and in SCZ.

Poster ID: 141
Mechanisms for sex dimorphic cellular sensitivity

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Abstract: Many diseases are more severe in one sex than the other. Although hormones explain some of the difference, other factors may also be in play. Understanding why cells behave differently according to their sex can help to correctly diagnose and treat disease. Using a mouse cell model we show for the first time that an individual cell has a defined sex and thus will behave differently when exposed to stresses such as alcohol, chemotherapeutic agents, or viral infection. We find that this difference in cellular behavior derives from genetic control that we can manipulate. Knowing that the response of an individual cell within an organism can depend on its sex is relevant to addressing the same diseases in men and women.

This work was funded in part by the NIH (MARC_USAR) grant 2T34GM07038, 1R15Al094351-01, and NIH R03 awarded to Zahra Zakeri.

Poster ID: 142
Genetic Control of a Sexually Dimorphic Chemosensory Behavior

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Abstract: Sex-specific modulation of neural circuits is thought to occur across the animal kingdom. However, little is known about the mechanisms by which the genetic sex of the nervous system itself alters neural properties to regulate behavior. The nematode C. elegans, with its simple nervous system and well-studied genetic sex-determination mechanisms, provides an ideal opportunity to address this issue. Previous work in this organism has demonstrated that adult males are potently attracted by hermaphrodite-derived pheromones called ascarosides. In contrast, hermaphrodites and larval males are indifferent to these compounds. Because the master C. elegans sexual regulator tra-1 acts cell-autonomously, we are able to genetically manipulate tra-1 function in specific tissues to generate sexually mosaic animals. We have found that pan-neural “masculinization” of the nervous system is sufficient to generate robust ascaroside attraction in hermaphrodites, while pan-neural “feminization” abolishes male ascaroside attraction. Using more restricted manipulations, we have found that the effects of genetic sex on the pheromone attraction circuit are distributed, as the sexual state of both sensory neurons and certain interneurons is important for wild-type behavior. We have also taken a candidate approach to identify genes required for male pheromone response. These studies have identified three regulatory components—serotonin signaling, PDF neuropeptide signaling, and a conserved DMRT transcription factor—that may act downstream of genetic sex to modulate neural function. Using the powerful tools available in this system, we aim to determine how these or other similar mechanisms are regulated by genetic sex, and how they alter neural circuit function to regulate behavior. Because the C. elegans nervous system employs regulatory mechanisms used across the animal kingdom, these studies should provide insight into the genetic regulation of mammalian neural circuit function.
SESSION 2
April 26, 2013: 5:30 – 8:00

Poster ID: 201
Stroke in Women with Signs and Symptoms of Ischemia Undergoing Coronary Angiography: the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Abstract: Prior WISE study has demonstrated adverse cardiac event rates including stroke in women with signs and symptoms of ischemia but no obstructive coronary artery disease (CAD). We validated stroke in WISE subjects enrolled and followed in a single center between 1998-2008. Three physicians independently reviewed charts. A core lab determined if there was obstructive CAD (≥50%), nonobstructive CAD (≥20 and <50%), and no CAD (<20% luminal stenosis) in epicardial coronary arteries. Among the 240 subjects enrolled, 61 dropped out/lost to follow-up, and 19 died, leaving 160 available with 5 year follow-up. Overall, 14 subjects reported stroke (8.75%). Among these 14 subjects, 9 had available medical records to review (53%), and 7 (78%) were confirmed. Stroke rate was similarly between nonobstructive and obstructive CAD. In obstructive CAD group 5.26 % had stroke. In nonobstructive CAD (20-49%) 4.52% had stroke. In group with no CAD 1. 76% had stroke.

Among women with signs and symptoms of ischemia undergoing coronary angiography for suspected ischemia, confirmed stroke was relatively frequent, including relatively high rates in subjects with no obstructive CAD. Future study should include mechanistic studies and intervention trials aimed at reducing stroke in this population.
other day for 15 sessions. Avoidance performance of female rats was generally superior to males; WKYs were superior to SDs. Moreover, female SD and male WKY were roughly equivalent. Female sex and behaviorally inhibited temperament were confirmed as risk factors in faster acquisition of avoidance behavior. The lack of immediate reinforcement slowed acquisition of male SD rats to the point that they achieved a rate of 50% by the last block of training. All over groups were somewhat slowed, but still achieved up to 80% asymptotic performance without immediate reinforcement strongly supports avoidance of shock (expectancy) as the motivation for lever presses.

Supported by Stress and Motivated Behavior Institute (SMBI), U.S. Department of Veterans Affairs I01BX000218 to KDB and I01BX007080 to KCHP.

Poster ID: 203
Mechanism by which neonatal testosterone exposure mediates sex differences in impulsivity in prepubertal rats

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Abstract: Neonatal testosterone (T) through its conversion to estradiol (E) masculinizes many hypothalamic-mediated behaviors. Less is known regarding neonatal T’s role in behaviors dependent upon other brain areas. We have previously demonstrated that prepubertal male rats display increased impulsivity compared to females during a delay-based impulsive choice task dependent upon the prefrontal cortex (PFC). In this task, rats are given the choice between an immediate small food reward and a delayed large food reward. Impulsive choice is defined as selection of the immediate small food reward. The goal of the current study was to determine if neonatal T exposure, either through direct activation of androgen receptors or activation of estrogen receptors via its conversion to E, mediates this sex difference in impulsive choice. In a first experiment, prepubertal females treated with testosterone propionate on days 1 and 2 post birth made significantly more impulsive choices than vehicle-treated females and their performance was indistinguishable from that of vehicle-treated males. Because T can be aromatized into E, this organizational effect could result from activation of either androgen or estrogen receptors. In a second experiment, prepubertal females treated on days 1 and 2 post birth with estradiol benzoate (activating only estrogen receptors), females treated with the non-aromatizable androgen dihydrotestosterone benzoate (activating only androgen receptors), and males treated with the aromatase inhibitor formestane, which blocks the conversion of T to E (activating only androgen receptors), all made significantly more impulsive choices than vehicle-treated females and their performance was indistinguishable from that of vehicle-treated males. These findings are the first to extend neonatal T’s role to PFC-dependent behavior and to demonstrate that neonatal activation of either estrogen or androgen receptor is sufficient to masculinize impulsivity in prepubertal rats.

This work was supported by the National Science Foundation under Grant No. 0951008 and NIH RO1 AG041374 to JMD.

Poster ID: 204
Effects of Parity on Anxiety and Memory

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Abstract: The experience of motherhood, pregnancy, birth and neonatal care, is associated with neural and behavioral changes in women and animal models. Female rats undergoing multiple bouts of motherhood (multi-parous females) have been shown to have a dampened HPA stress response reduced anxiety, better performance on spatial memory tasks and possibly changes in hormone levels associated with memory and stress as compared to age matched females who have not given birth. Moreover, some of these changes are maintained into old age. Thus, parous rats may provide a unique, physiological model in which to investigate neural and hormonal factors that may contribute to a decrease in compromised function during aging. In the current study, we investigated whether parity influences performance on spatial and recognition memory tasks, anxiety, and oxytocin levels. Performance on memory
tasks was assessed using object recognition and object placement. Corticosterone levels and the Elevated Plus Maze (EPM) were used to assess anxiety levels. Oxytocin levels were assessed from blood serum. It is hypothesized that performance of the retired breeders on the memory tasks would be more similar to young virgin females than to age-matched virgin females, they would have increased oxytocin levels and decreased behaviors indicative of anxiety, all possible indicators of better aging due to the experiences of motherhood. Multi-parous females performed significantly better in the spatial memory task as compared to the other groups where F (2,19)=5.7, p<.013. There were no significant differences between groups in corticosterone levels or on EPM. No significant differences in oxytocin levels were found between groups, although levels were high across all groups. Given the data from this experiment it would seem that parity does indeed have some positive ability to attenuate the effects of cognitive aging in females.

RISE Grant GM 060665 CUNY Collaborative GRANT and RCMI Grant RR03037

Poster ID: 205
Women are less prepared than men to resolve conflicts with same-sex peers

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Abstract: Across primate species, the more gregarious sex generally reconciles conflicts with unrelated individuals more frequently. This occurs presumably because the survival and reproductive benefits of the relationship are more likely to outweigh the costs for the more gregarious sex. Based on research demonstrating that human females are more critical than males of same-sex peers, we hypothesized that human females would be less willing than males to prepare to reconcile a conflict with a same-sex peer. To investigate the hypothesis, we studied 40 women and 40 men individually in a laboratory where they responded to computerized instructions. In the first phase of the experiment, participants relaxed. In the second phase, participants were asked to recall an incident in which a same-sex close friend had argued with them and physically hit them. In the final phase, participants enacted an actual response to the conflict by either confronting the friend or discussing the event with a third party, both of whom were represented by a same-sex experimenter. Heart rate was measured continuously, and cortisol was measured at the end of each phase through saliva collection. Participants also recorded their levels of anger, predictions regarding how long their anger would take to dissipate, and the length of time until they would reconcile with their friend. Whereas women and men reported similar levels of anger, women reported their anger would take significantly longer to dissipate, and they would reconcile less rapidly. Further, during both the confrontation and the third party discussion, women’s heart rates temporarily increased more than men’s did. In contrast, men’s cortisol concentrations increased more than women’s during their actual reactions, suggesting greater energetic investment in conflict resolution. Results suggest that women experience higher immediate fear and lower willingness to invest in repairing a conflict with a same-sex peer.

This study was funded by a Faculty Grant from Emmanuel College to JFB.

Poster ID: 206
Female Bias in Rhox6 and 9 Regulation by the Histone Demethylase KDM6A

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Abstract: The Rhox cluster on the mouse X chromosome contains reproduction-related homeobox genes expressed in a sexually dimorphic manner. We report that two members of the Rhox cluster, Rhox6 and 9, are regulated by de-methylation of histone H3 at lysine 27 by KDM6A, a histone demethylase with female-biased expression. Consistent with other homeobox genes, Rhox6 and 9 are in bivalent domains prior to embryonic
stem cell differentiation and thus poised for activation. In female mouse ES cells KDM6A is specifically recruited to Rhox6 and 9 for gene activation, a process inhibited by Kdm6a knockdown in a dose-dependent manner. In contrast, KDM6A occupancy at Rhox6 and 9 is low in male ES cells and knockdown has no effect on expression. ES cell differentiation into cell types where Rhox6 and 9 are no longer expressed is associated with loss of KDM6A binding. However, in mouse ovary where Rhox6 and 9 remain highly expressed, KDM6A occupancy strongly correlates with expression. Our study implicates Kdm6a, a gene that escapes X inactivation, in the sex-specific regulation of genes important in reproduction, suggesting that KDM6A may play a role in the etiology of developmental and reproduction related effects of X chromosome anomalies.

This work was supported by a fellowship from the National Institutes of Health (HD060402) to J.B., and by a grant (GM046883) from the National Institutes of Health to C.D.

Poster ID: 207
The SWHR ISIS Networks: A Collaborative Model for Conducting Sex-based Research

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Abstract: The Society for Women’s Health Research (SWHR) has established a collaborative research network model for Interdisciplinary Studies in Sex-differences (ISIS) to address cross-cutting research questions that address biological sex differences at all levels (genetic, cellular, tissue and organism). These sex-differences have an impact on disease etiology, onset, progression, and treatment, and identifying them has the potential to revolutionize the way in which we understand health and disease for both men and women.

The SWHR ISIS Network model facilitates the rapid exchange of data, hypotheses, and research approaches among investigators, and leads to the application of novel, multi-disciplinary and translational strategies for the study of sex-based biology. The SWHR ISIS Networks bring together investigators from diverse disciplines to think, discuss, debate and ultimately plan and conduct network-driven pilot studies. Each Network addresses a specific but wide-ranging research question. The products developed by the Networks include papers, books, presentations, conferences, databases, e-content, and pilot data suitable for applications for funding larger studies. This poster describes the process, timelines and accomplishments of five successful SWHR ISIS Networks on sex-based biology.

The SWHR ISIS Networks are funded by philanthropic donors, industry, or foundations.

Poster ID: 208
Survival and re-admission of patients with heart failure. Is there gender-based gap?

Author list: D. Giedrimiene¹,², F. Zaeem¹, J. Radojevic¹, J. Gluck¹, and D. Wencker¹,²

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Abstract: Heart failure is a chronic and progressive condition that has been characterized by frequent hospital admissions and high mortality rates on an annual basis. The overall prevalence of heart failure is similar in both men and women. However, there can be a difference in the survival based on gender, and some clinical studies show that fewer than 15% women survive more than 8-12 years. The purpose of the study was to evaluate whether there are any differences in the management and treatment outcomes in patients with chronic heart failure treated at a single tertiary center related Outpatient Clinic.

The data analysis was based on the follow-up of patients who had multiple daily treatment sessions at the Outpatient Clinic-Infusion Center for HF that were primarily treated with intravenous diuretic infusions. The records of 84 patients (31 females and 53 males) with more than 400 visits during a 2.5 year period were used. These patients were followed for 12 months in order to assess the frequency of re-hospitalizations and their rate of survival. The mean age of this group was 68.9±13.4 years without a significant difference in gender.

The study demonstrated that survival in this population during 12 months was 73 (86.9%), and was significantly lower in females than males: 26 (76.2%) vs 47 (88.7%) accordingly; p =0.045). The rate of re-hospitalizations at
30 days was 13 (15.5%), but males had significantly higher -10 (18.9%) rates of re-hospitalization than females - 3 (9.7%); p =0.02 1. The re-hospitalization rates at 6 months have reached 35 (4 1. 7%), and almost a half of males – 26 (49.1%) have been readmitted to hospital vs only 9 (29.0%) of females (p < 0.05). At 12 months of follow-up the re-hospitalization rates have reached 51 (60.7%), and more than a half of males – 40 (75.5%) have been readmitted to hospital vs only 11 (35.5%) of females (p < 0.012). Based on these findings our conclusions are that gender based gap is significant in regards of re-hospitalization rates and shows that significantly more men are re-hospitalized at 30 days, 6 months and 12 months of follow up as it is compared to re-hospitalization rates of females. As a possible outcome of this females (who have lower re-hospitalization rates) have a significantly higher mortality at 12 months of follow up as compared to males.

Poster ID: 209
Gender-based difference in the utilization of implantable cardioverter-defibrillators in patients with chronic heart failure

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Abstract: Recent literature suggests that heart failure may be a different entity in women than men. Clinical studies have also noted that some gender differences exist in the use of implantable cardioverter-defibrillators (ICDs). The purpose of the study was to examine if there is gender-based gap in the use of ICD’s for primary or secondary prevention in patients with chronic heart failure (HF) treated at a single tertiary center related Outpatient Clinic. The data analysis included the records of more than 400 visits during 2.5 year period. There were 84 patients (31 females and 53 males) who had multiple daily treatment sessions at the Outpatient Clinic-Infusion Center; primarily for HF and treated with intravenous diuretic infusions. Primary disorders, co-morbidities, arrhythmias, including atrial fibrillation (AFib), and reasons for ICD implantations were evaluated. The mean age of the study participants was 68.9±13.4 years. There was no significant difference in gender (mean age was 69.2±13.3 in females vs 68.7±13.5 in males; p =0.12). Ejection fraction (EF) was found to be higher in females than males (4 1. 2±18.6% and 36.5±17.8%, accordingly), however the finding of reduced systolic function (EF≤35%) was similar in both gender groups. The results of study showed that coronary artery disease (CAD) and hypertension were the most common causes of HF in men and women, but CAD was less frequently identified in women than men. Diabetes mellitus and thyroid disease was found at the same frequency in both gender groups. However, renal disease was more prevalent in males. The frequency of arrhythmias (including AFib), was similar in both gender groups: 22 (4 1. 5%) – in males vs 13 (4 1. 9%) – in females; p =0.16. Comparison of ICD implantation cases between gender groups showed that significantly more males had the ICD implanted then females: 27(50.9%) vs 7(22.6%); p = 0.016. ICD implantation rates for primary prevention were significantly higher in males than females: 18/53 (33.9%) vs 6/31(19.6%); p = 0.05, and similar findings were obtained in the case of ICD implantation for secondary prevention: 8/53 (15.1%) - in males vs 2/31 (6.5%) - in females; p = 0.012. In conclusion, there are gender based differences that exist in the utilization of ICDs. Despite very similar rates of arrhythmias occurrence in both genders men receive more ICD implantations for primary or secondary prevention than women.

Poster ID: 210
Sex differences in ambulatory activity after acute administration of cocaine, methamphetamine, and cannabinoids

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Abstract: Aims: Accumulating evidence suggests that sex-specific differences are present at all stages of the addiction process, including induction, maintenance, and relapse. Our lab has recently shown that female rats’ psychomotor responses to cocaine are more robust and longer lasting than male rats’. We hypothesized that,
regardless of the drug treatment (cocaine, methamphetamine, or WIN-55, a selective cannabinoid agonist), behavioral responses to the drug treatment will be sexually dimorphic. To this end, locomotor activity in male and female Fisher rats was measured after acute administration of cocaine (30 mg/kg, i.p.), methamphetamine (3 mg/kg, i.p.), WIN-55 (0.15 mg/kg i.p.), DMSO or saline. Preliminary results show sex differences in behavioral responses only after administration of cocaine and methamphetamine. Specifically, females have more robust behavioral responses than males to both psychostimulants. However, there was no difference in locomotor behavior between males and females in rats administered WIN-55. This study provides evidence of sex differences in psychomotor activity in response to psychostimulant drugs such as cocaine and methamphetamine, and these sex differences are not observed in response to types of drugs, such as marijuana.

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Poster ID: 211
Inadequate cardio-respiratory adaptation of male lambs following preterm birth

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Abstract: After preterm birth, male infants have a greater incidence of respiratory insufficiency than females. Our objective was to compare the cardio-respiratory adaptation in males and females for 8h after preterm birth, using an ovine model of preterm birth in which fewer males survive than females. Male (n=6) and female (n=8) fetal sheep underwent aseptic surgery at ~125 days of gestation (DG; term ~147DG) for the implantation of catheters and an intrapleural balloon. Ewes were given betamethasone (5.7mg i.m.) at 131DG. At 133DG (0.9 of term), lambs were delivered, anaesthetized, via Caesarean section. Arterial and intrapleural pressures were recorded continuously in spontaneously breathing lambs for 8h and arterial blood was taken to measure blood gases and metabolites. At 8h, lambs were euthanized and static lung compliance was measured. Bronchoalveolar lavage fluid (BALF) was collected for analysis of total protein concentration and surfactant phospholipid composition. Lung tissue was collected for analysis of relative surfactant protein (SP)-A, -B, -C and -D mRNA levels. At 6-8h after preterm birth, males had significantly lower arterial pH, glucose and lactate, and higher PaCO2 compared to females; mean arterial pressure was not different. Inspiratory effort was greater in males than in females at 8h (p<0.05) and static lung compliance at 8h was 24% lower in males than in females (p<0.05). Relative SP gene expression in lung tissue was not different between sexes. We conclude that respiratory adaptation to preterm birth is less effective in males than females. Male lambs have less compliant lungs than females, which is the likely cause of the greater inspiratory effort, CO2 retention and acidemia. The lower lung compliance of males could be due to sex differences in surfactant phospholipid composition.

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Poster ID: 212
Sex Chromosomes and Sexual Dimorphism of Human Transcriptomes

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Abstract: Genes with unique functions and sex-specific advantages accrued on the X and Y chromosomes by various evolutionary mechanisms. X-linked recessive mutations that increase male-fitness but are potentially disadvantageous to females are more easily fixed than autosomal mutations because of X hemizygosity in males and random X inactivation in females. Mutations that enhance female-specific fitness are also preferentially selected because the X chromosome spends 2/3 of its time in females. In addition, up to 25% of human X-linked genes appear to escape X-inactivation in contrast to about 3% in mouse. However, only a limited number of tissues, cell lines, and individuals have been assayed. Our overarching goal is to explore the sexual dimorphic
expression of X-linked, Y-linked and autosomal genes in a wide range of human tissues, including during developmental stages from fetal to adulthood. I have analyzed genome-wide gene expression based on more than 500 RNA-seq datasets sexed samples and 7000 sexed expression arrays in 65 human tissues. I reanalyzed only expression arrays and RNA-seq datasets from disease-free individuals deposited in public databases (GEO, Array Express, Allen Institute). I used global normalization to compare arrays from each individual and across tissues for arrays, and RPKM for RNA-seq datasets. A standard two-tailed with unequal variance student-t test with step-down Benjamini-Hockberg correction at 5% FDR was applied throughout to assess any genes with at least 1.2 fold expression difference between the sexes. I selected only tissues with at least 15 individuals per tissue and similar number of female and male individuals with the exception of RNA-seq datasets. I found that genes located within the human pseudoautosomal region (PAR1) had significantly higher expression in male versus female tissues, notably in brain. In contrast, genes that escape X inactivation located outside the PAR had significantly higher, but rarely doubled, expression in females compared to males, in a tissue-specific manner. Such female-specific bias was particularly pronounced in the gyrus and the cortical regions of the brain, in the skin, in CD4 positive blood cells, and in reproductive organs. The female bias was most pronounced for genes known to escape X inactivation but was also seen for other X-linked genes suggesting that these genes may escape silencing in specific tissues. Many genes with higher expression in female brain have been previously implicated in X-linked intellectual disability, suggesting that they play important roles in neurological functions. Moreover, the number of X-linked genes that displayed sex-specific differences in expression in some regions of the brain, most notably in the neocortex, was higher in human compared to chimpanzee and macaque. I also found that the extent of sexual dimorphism in the brain transcriptome differed between fetal stages and adulthood.

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women in disease population ≥ 0.80. Conclusions. Women’s participation in the pivotal trials for NMEs approved between 2010-2012 averaged 47%. In 2001, Government Accounting Office (GAO) reported an average of 55% female participation in larger-scale trials for drugs approved between 1998 and 2000. The frequency of analysis for the sex effects on both safety and efficacy has improved significantly since the 2001 GAO report of 72%. The majority of NDAs had a study population that was representative of sex distribution for the intended patient population.

Poster ID: 214
Sex Differences in Motivated Learning Have Consequences for Neurogenesis

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Abstract: Numerous studies report that males and females can perform differently on various learning tasks (for review, Dalla & Shors, 2009). For example, females tend to outperform males during training with both delay or trace eyeblink conditioning. Interestingly, females that are stressed prior to training learn very much better after stress (Wood and Shors, 1998). In the present study we examined performance of male and female rats while learning a gross motor skill in which animals must learn to maintain their balance on an accelerating rotating rod (the accelerating rotarod). During training, many animals step off the rod. To increase motivation to stay on the rod, cold water was placed below the rod. We termed this condition “motirod” training because animals remain on the rod for longer periods of time in the presence of the water. Based on the studies with eyeblink conditioning, it was hypothesized that males would outperform females. To test this hypothesis, male and female adult Sprague-Dawley rats were trained on either the standard accelerating rotarod or the accelerating motirod for four trials per day on four consecutive days. Latency to fall from the rod (in seconds) was recorded. Surprisingly, females learned much better with the addition of the motivating feature, whereas males were unaffected. In addition to these behaviors, we examined the effect of learning on the survival of new neurons in the hippocampus. Many previous studies report that learning rescues adult-born hippocampal dentate gyrus neurons from death (Gould et al, 1999, & Waddell & Shors, 2008), including training with the accelerating version of the rotarod (Curlik et al, 2012). Consistent with their performance, females that learned well under the motivating condition retained significantly more of the new cells than did males, in which there was no difference between groups in terms of their behavior or cell number. These data indicate that sex differences in motor skill learning can arise from sex differences in motivation and these differences can determine how many new cells survive in the adult hippocampus.

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Poster ID: 215
Effects of mild stress on fear extinction and relevant brain structures in female rats

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Abstract: Women are twice as likely as men to develop stress related disorders, such as post-traumatic stress disorder (PTSD), but the neurobiological factors underlying this discrepancy are mostly unknown. Results from human imaging studies implicate three brain regions to be abnormal in PTSD patients: the hippocampus, medial prefrontal cortex (mPFC), and the amygdala. In animals, these regions are critically involved in fear conditioning, extinction learning and retrieval. Studies with male rodents have shown that stress exposure can impair extinction retrieval. However, it has yet to be determined how stress affects behavior in the fear condition/extinction paradigm in females. The goal of this study was to investigate the effects of mild stress on fear extinction, as well as effects on relevant brain structures and regions. We show that mild, intermittent heat stress impairs fear extinction and extinction retrieval in female rats, without interfering with fear acquisition. We used immunocytochemistry and retrograde labeling to investigate neuronal activity after extinction recall in the mPFC overall, and in mPFC neurons projecting to the...
basolateral amygdala specifically. The results show regional specific differences in mPFC activity between stressed animals and control. To analyze dendritic spine morphology and density in the hippocampus, hippocampal CA3 pyramidal cells were microinjected with Lucifer Yellow, allowing for visualization of dendritic spines with confocal microscopy. We did not find any differences in spine morphology or density between stressed animals and controls. Our results show that even mild stress has a great impact on behavior in the fear conditioning/extinction paradigm in female rats. Further, the results suggest that stress exposure affects mPFC activity in a region specific manner, while having no effect on hippocampal spine morphology and density.

This study was funded by Rebecca Shansky’s start-up grant.

Poster ID: 216
Neurovascular Function in Women with Uterine Leiomyomas: A Proposed Study

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Abstract: Uterine leiomyomata (fibroids) is a condition that commonly affects women of reproductive age. Fibroids are accompanied by a number of adverse effects, such as pelvic pressure and pain, heavy menstrual bleeding, and miscarriage; and removal of the benign tumors is the most common reason for hysterectomy in the United States. Evidence has shown that there is a correlation between fibroids and hypertension; however, the mechanism link between the two diseases is poorly understood. Therefore, the goal of this proposed project is to obtain further information about the relationship between fibroids and blood pressure. To do this, we will perform detailed physiological phenotyping of the determinants of blood pressure including muscle sympathetic nerve activity (MSNA), baroreceptor reflex sensitivity (BRS), and vascular function in women diagnosed with fibroids. MSNA will be studied and BRS will be evaluated during sympathoexcitatory maneuvers, which will include the modified Oxford technique and the cold pressor test.

Arterial tonometry will be used to measure vascular stiffness. Endothelial response to vasodilatory and vasoconstricting agents will be assessed using venous occlusion plethysmography. We hypothesize that women with uterine fibroids will have increased MSNA, reduced BRS, and compromised vascular function in comparison to healthy controls without fibroids. The results of this study will provide important information on the cardiovascular state of women with fibroids and will help us to better understand blood pressure regulation in this condition.

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Poster ID: 217
Creating a Sex and Gender-Based Healthcare Curricular Thread: The Tech Triad Model

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Abstract: A growing body of scientific knowledge on sex and gender differences related to health focuses on all levels of human function. Sex-based biology has made a significant impact on expanding knowledge of sex differences into the delivery of care and demands that medical students are prepared to provide healthcare that is sensitive to both men and women. This will be accomplished through integration of sex and gender-based evidence in healthcare professional education. Texas Tech University Health Sciences Center is undertaking the development of a longitudinal 4-year curricular thread in Sex and Gender-Based Medicine (SGBM). Features of the curriculum include enhanced lecture content on gender differences and small-group activities in the preclinical years. This content will focus on gender differences across the lifecycle as well as differences in manifestations and processes of pathology and treatment. In addition the Schools of Pharmacy and Nursing have entered Phase 1 of this curricular thread development with launch of their Student Scholar Audit of
current curricular content and thus future SGBM Curriculum development will be approached in an interprofessional manner. Through the development of Tech Triad Teams consisting of basic scientists, clinicians and students evidence-based sex and gender medicine will be taught in a clinical problem-based learning web format through interactive modules. Among the innovations of the curriculum is the development of a web-based CME series for faculty, “Y Does X Make a Difference” which will address gender issues in diagnosis, prognosis, and treatment of major and most common health issues and a student knowledge attitudes and awareness instrument. This poster provides a roadmap for integration of sex and gender medicine including national resources, unique learning activities and evaluation strategies, and provides opportunities for peer institutions to collaborate.

Poster ID: 218
Building Infrastructure to Integrate Sex and Gender into Healthcare Education

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Abstract: Background: Sex and gender affect health independently, as well as interactively. Over the past twenty years, much scientific evidence demonstrates unequivocally that women and men vary down to each cell. Sex differences in disease prevention and management should be recognized and applied to provide optimal care for everyone.
Objectives The Sex and Gender Women’s Health Collaborative (SGWHC) is the first and only digital resource dedicated solely to sex and gender evidence based research and education http://sgwhc.org. Historically, sex and gender health information has been fragmented and difficult to access. This impacts medical education and, ultimately, patient care. To address this, the SGWHC is advocating for universal integration of a culturally competent, sex- and gender-based approach to medical education and training. At SGWHC.org, medical students, nurse practitioners/nurses, and allied health faculty and providers have open access to the single largest online collection of sex and gender curricula resources. This evolving content aims to foster sex and gender sensitivity in health education, training and practice to deliver optimal care for all.

Results: To date, the SGWHC 14 official collaborating organizations. The oversight committee for this initiative includes a multidisciplinary group of gender-specific medicine experts. The digital library has 49 folders, more than 300 documents, including journal articles, curricula, PowerPoint presentations, and other teaching materials. This work will also highlight national climate in this area through reporting of student awareness and interest in sex and gender differences curricula and student knowledge of sex and gender in specific disease processes. Conclusions The efforts of the SGWHC are building the infrastructure that is vital to addressing gaps at all levels - research, education and clinical practice - to advance the integration of sex- and gender-specific medicine from the bench to the bedside.

Poster ID: 219
Chronic stress effects on depression and anxiety: Development of a gender-based translational model for depression

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Abstract: Depression is a widespread disorder, and the lifetime prevalence of depressive or anxiety disorders in women is approximately twice that of men. Yet, current treatments are based on research and clinical trials conducted mainly in male subjects. Thus, there is a compelling need for new treatments and for sex to be considered in this translational research. Since most episodes of major depression are preceded by stressful life events and are often associated with altered levels of cortisol, stress models are useful for depression research. In the current study, 2 cohorts of Sprague-Dawley rats, 8 males and 12 females each, served as control or received daily restraint stress (6 h/day) for 21 days. It was hypothesized that stressed females would
become affected earlier than males and/or show greater symptomology. Anhedonia was measured using the sucrose preference test on days 7, 14 and 21, and anxiety was measured on the elevated plus maze on day 22. In Cohort 1, females (M=9.25) exhibited less anxiety with more open arm entries than males (M=6.50) on the EPM test, p < 0.01, but no stress effects were found. There was a significant stress effect on depression with stressed rats of both sexes showing less preference for sucrose than water (sucrose/sucrose + H2O; M=0.84) than the control group (M=0.93), p < 0.04). Thus, this restraint regimen led to depressive-like behavior, but the effect does not appear to be sexually differentiated. In a second cohort, no behavioral changes were found, but it appears that these subjects may have been stressed due to housing with Cohort I during stress and disruptions due to Hurricane Sandy. Current work is measuring corticosterone levels and neural changes in both cohorts to determine possible stress effects. In conclusion, our preliminary results suggest that restraint stress may be useful in developing a gender based model of depression.

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Poster ID: 220
Depression and cardiovascular disease in women: does this comorbidity have an immunological basis? A Theoretical Synthesis

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Abstract: Clinical reports have established an inherent comorbidity between depression and the development of cardiovascular disease (CVD). Furthermore, this comorbidity seems to be more amplified in women than in men. To further investigate this comorbidity, an analysis and synthesis was performed on relevant literature. The Web of Science database was accessed using the keywords: cardiovascular disease, inflammation, depression, and sex differences. The initial search returned 6866 results. This synthesis examines 51 studies (1997 to date). 34 of the studies are based on human populations, and 17 focus on animal models. All 34 of the human studies report chronic elevations of proinflammatory cytokines with this comorbidity. Animal models suggest the mechanisms for this elevation: excess inflammation leads to HPA axis hyperactivity, depletion of 5-HT centrally, and elevation peripherally, and upregulation of angiotensin II, all of which are known factors in the development of depression and CVD. Six studies localize this systemic inflammation to a global deficiency in CD4+CD25+FOXP3 regulatory T cells. Additionally, 7 studies indicate that 17-B estradiol and progesterone modulate cytokine secretion in both humans and animals. This may partially explain the sex differences with this comorbidity. Animal models provide a mechanistic explanation of immune crosstalk between the neuroendocrine and cardiovascular systems. Within human literature, the sex differences of this comorbidity are well established, but the mechanisms remain unclear. Regulatory T cells and hormonal immune modulation need to be examined to fill this gap.

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Poster ID: 221
Stress-induced suppression of learning in females: Dissociating the contribution of prelimbic and infralimbic cortices

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Abstract: Women are nearly twice as likely as men to suffer from depression, which may be indicative of a greater vulnerability to stress in females than males (Tolin & Foa, 2006). A profound sex difference in the response to stress is also observed in laboratory animals. Acute stress exposure disrupts associative learning in female rats but enhances learning in male rats (Wood & Shors, 1998). These sex differences in response to stress are mediated by different brain regions. For example, neuronal activity in the medial prefrontal cortex (mPFC) during the stressor is necessary to modify learning in females but not to modify learning in...
males (Maeng et al., 2010). The medial prefrontal cortex can be divided into different subregions: the prelimbic (PL) and the infralimbic (IL). There are structural and functional differences between the two areas. For instance, the prelimbic cortex projects more heavily to limbic structures such as the basolateral amygdala; in contrast, the infralimbic cortex projects more to sites involved in visceromotor processes (Vertes, 2004). Because the stress effect on learning in females relies on communication between the mPFC and the basolateral amygdala (Maeng et al., 2010), it was hypothesized that neural activity within the PL during the stressor would be critically involved, whereas neural activity within the IL would not be necessary to impair learning in females. To test this hypothesis, the PL or IL subregion of the mPFC in adult female rats was bilaterally inactivated with GABA-A agonist muscimol. The animals were then exposed to inescapable swim stress or left unstressed. One day later, all subjects were trained with delay eyelink conditioning for four consecutive days. Interestingly, females without neuronal activity in the PL during the stressor were able to learn well. This response was different from that in females in which IL activity was suppressed; these females did not learn well after the stressor. These data suggest that stress exposure critically engages the prelimbic, but not infralimbic, subregion of the mPFC to suppress learning in females. The prelimbic area may be especially responsive to stress in women who develop depression triggered by stressful life events.

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Poster ID: 222
Neurobiological study of the increased incidence of hypertension in menopause

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Abstract: The incidence of hypertension in women increases following menopause. In mice, infusion of angiotensin (AngII; 600ng/kg/min for 2 wks) induces hypertension in 2 mo (young) males but not in age-matched females. However, AngII significantly increases blood pressure in 18 mo (aged) females. This parallels reproductive hormone changes: at 2 mo estrogens (E) fluctuate regularly every 4-5 days, whereas at 18 mo persistent estrus/diestrus with low E is seen. These changes could influence receptor trafficking in central cardiovascular circuits and contribute to hypertension. In particular, neurons in the hypothalamic paraventricular nucleus (PVN) that project to the spinal cord and regulate sympathetic tone express estrogen receptor beta (ERb). NMDA receptors are crucial in enhancing sympathoexcitation from PVN neurons in hypertension. Using immunoelectron microscopy, we analyzed NMDA receptor NR1 subunit density/trafficking in PVN dendrites of transgenic mice expressing enhanced green fluorescent protein (EGFP) in ERb-expressing cells to evaluate the hypothesis that differential changes occur in NR1 density/trafficking following menopause in response to a hypertensive challenge. AngII or saline were infused in young females, young males, and aged females. Young females showed higher baseline total NR1 density than aged females and young males, and higher cytoplasmic NR1 density than age-matched males. Total NR1 density was decreased in young females but increased in aged females by AngII. Finally, AngII increased NR1 density near to the plasma membrane in young males. These findings show sex differences at the post-synaptic level in NR1 trafficking in response to AngII infusion. They also show changes in baseline NR1 density after menopause, and differential responses to AngII infusion before and after menopause in ERb-containing PVN neurons that may account for the increased susceptibility to hypertension after menopause.

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The association between the serotonin transporter polymorphism (5-HTTLPR) and late-onset obsessive-compulsive disorder: a meta-analysis

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Abstract: The serotonin transporter polymorphism has been implicated in obsessive compulsive disorder (OCD). However, molecular genetic association studies have yielded inconsistent results. Variation may be due to lack of OCD subtype classification or failure to acknowledge the polymorphism’s triallelic nature. The goal of this review was to investigate the association of the S-allele of the serotonin transporter polymorphism with late-onset (LO) OCD. A total of 116 studies were initially found but only 10 studies with sufficient information to compute odds ratios (ORs) were suitable for review. A total of 1868 participants with OCD and their 5-HTTLPR allele status were examined. The primary outcome measures were allele frequency and OCD diagnosis or presence of obsessive-compulsive symptoms. A full meta-analysis was completed comparing the L- and S-alleles in OCD. Moreover, a secondary meta-analysis stratified by sex was conducted for S- versus L-allele frequency. In the main meta-analysis, LOOCD was not associated with the S-allele of the 5-HTTLPR polymorphism \[Z=0.62, p=0.53\]. However, when stratified based on sex, there was a sex-specific relationship. There was a significant association between the S-allele and OCD status in females \[Z=1.93, p=0.05\] but this relationship was not seen in males \[Z=0.43, p=0.67\]. LO OCD in females only was significantly associated with the S-allele. This provides further support for subtype classification of this heterogeneous disorder. Future studies should examine sex differences and OCD age-of-onset. In particular, vigor needs to be placed on the polymorphism’s triallelic nature and emphasis on the influence of female reproductive milestones.

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Investigating the role of sex chromosome complement in cerebral ischemia

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Abstract: Stroke is the fourth leading cause of death in United States and the major cause of long-term disability. Epidemiological studies have demonstrated sex differences in stroke risk. Women have a lower stroke incidence relative to men until an advanced age, when stroke rates rise dramatically and surpass that of men. To date, most studies have focused on the role of gonadal hormones in shaping this sexual dimorphism. Since the sex chromosome complement differs in men and women, this may be one of the underlying etiologies of these sex differences. The objective of this study was to investigate the role of sex chromosomal complement in the etiology of stroke. We used the four core genotype (FCG) mouse model (C57BL6) to examine the chromosomal contribution to stroke sensitivity in the transient middle cerebral artery occlusion (MCAO) model. In the FCG mice, Sry, the testis determining gene has been deleted from the Y chromosome and inserted on an autosome. The four groups of mice derived by a cross between an XX female and XY-Sry male can be compared to uncouple the influence of sex chromosomes or gonadal hormones on stroke outcome. A 90 minute MCAO was performed and infarct volumes were analyzed by using cresyl violet staining 72 hours later. The mean total hemispheric infarct volume in XYM (47.1±3.5%) and XXM (40.9±2.3%) was higher than XYF (30.1±5.6%) and X XF mice (31.4±4.3%). Overall, there was a significant main effect of sex, \(p<0.05\). This phenotype could have been either due to the protective effects of estrogen in female mice or detrimental effects of testosterone/Sry in males. To remove the effects of gonadal hormones on ischemic sensitivity, we gonadectomized FCG mice and subjected them to MCAO. We found that the mean total hemispheric infarct volumes in gonadectomized females increased, X XF (46.4±3.5%), XYF (49.7±2.3); while in gonadectomized males the infarct volumes were not significantly different from the intact gonadal state, XXM (42.4±3.4%); XYM (47.6±4.3%). We conclude that...
the sex differences seen in ischemic stroke are primarily due to the protective effects of estradiol in females.

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Poster ID: 225
Gender differences in stress reactivity and dissociation in depersonalization disorder

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Abstract: Depersonalization disorder (DPD) is a psychiatric disorder marked by feelings of detachment from one’s mental processes or body. The precipitating factor for DPD onset is typically a major psychological stressor. DPD patients show higher cortisol levels than control groups, and salivary cortisol is positively correlated with depersonalization severity. However, in response to the Trier Social Stress Test (TSST), severity of dissociation has been shown to be inversely related to the cortisol surge under stress. In the current study 10 DPD patients (4 women; 6 men) and 15 normal controls (5 women; 10 men) underwent the TSST after basal levels of alexithymia (the inability to understand or describe one’s feelings) were assessed. Saliva was collected and transient dissociation and subjective stress were measured before, directly following, and at 20 minutes and 40 minutes post-TSST. To control for cortisol reactivity across the menstrual cycle, all women were in the follicular stage or post-menopausal. Compared to the control group, the DPD group was more alexithymic. Although the control group demonstrated an increase in subjective stress directly following the TSST and decreased stress at 20 minutes and 40 minutes post-TSST, there were no changes in subjective stress levels for the DPD group. For men, the DPD group showed higher cortisol directly following the TSST and more dissociation before and 40 minutes post-TSST than the control group. However, for women, the groups did not differ in cortisol or dissociation levels at any time points. These results suggest that although the TSST induces physiological stress in both groups, alexithymia may interfere with the DPD group’s ability to identify and interpret their level of stress. In addition, although depersonalized men show elevated cortisol after stress and elevated dissociation before and after stress, depersonalized women in the follicular stage do not. Thus, gender differences should be considered in DPD studies.

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Poster ID: 226
Acute estradiol treatment affects the salience of cocaine cues

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Abstract: Cue reactivity and exposure to cues are important factors in continued drug use and relapse to former patterns of drug use. Previous research demonstrates that women are more responsive to cues associated with drug reward than males. A growing body of literature supports a role for estradiol as one of the mechanisms underlying sex differences in the behavioral response to drugs of abuse. However, little is known about the influence of acute (versus sustained) elevations in levels of estradiol on drug conditioned behaviors. Thus, the aim of the present study was to evaluate the influence of an acute increase in systemic estradiol on the expression of cocaine-induced conditioned place preference (CPP). Adult ovariectomized Long Evans rats were conditioned with one of four doses of cocaine (2.5, 5, 10, or 15mg/kg) for six days and preference for each dose tested 24 hours after the last conditioning session during a Preference Test. Thirty minutes prior to the Preference Test, all rats received a subcutaneous injection of 5μg 17β-Estradiol 3 benzoate dissolved in 0.1mL of peanut oil (PO) or peanut oil alone (PO) and the expression of cocaine-induced CPP was evaluated. PO treated rats expressed CPP to all but the lowest conditioning dose of cocaine (2.5, 5, 10, or 15mg/kg) for six days and preference for each dose tested 24 hours after the last conditioning session during a Preference Test. Thirty minutes prior to the Preference Test, all rats received a subcutaneous injection of 5μg 17β-Estradiol 3 benzoate dissolved in 0.1mL of peanut oil (EB) or peanut oil alone (PO) and the expression of cocaine-induced CPP was evaluated. PO treated rats expressed CPP to all but the lowest conditioning dose of cocaine (5, 10, 15mg/kg; p<0.05), while EB treated rats expressed CPP only at the moderate and high cocaine conditioning doses (10, 15mg/kg; p<0.05). Further, CPP for PO treated rats was significantly higher than for EB treated rats (p<0.05) when conditioned with 10mg/kg of cocaine, however CPP scores were equivalent between the
groups when rats were conditioned with 15mg/kg of cocaine. Together, these data indicate that acute elevations in estradiol may facilitate or inhibit conditioned responses to cocaine’s secondary rewards.

This study was funded by a young investigator award from the Brain & Behavior Foundation (formerly NARSAD) and a grant from the UT Arlington Research Enhancement Program to LIP.

Poster ID: 227
Contributions of sex, testosterone, and androgen receptor CAG repeat number to virtual Morris water maze performance

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Abstract: Men tend to excel on tests of wayfinding, whether tested in real-world or computerized environments. One example of such a computerized environment is the virtual Morris water task (vMWT), modeled after the traditional rodent spatial learning and memory test. The male advantage typically found on tests of navigation and other spatial abilities such as the mental rotation of 3D objects has been approached for decades from the perspective that androgens contribute to this sex difference. To date, evidence to support the notion that androgens affect spatial cognition in healthy young individuals is balanced by evidence to the contrary. The present study sought to clarify the association between testosterone and spatial performance by extending our measurements of androgenicity to include both measures of circulating testosterone as well as an androgen receptor-specific marker. The aims of this study were to assess the effects of sex, testosterone, and androgen receptor CAG repeat number on spatial performance in a group of healthy young men and women. Participants completed a battery of paper-and-pencil cognitive tests as well as a computerized/virtual Morris Water Task (vMWT). The hypothesis that men would outperform women on spatial measures was largely supported. Results indicate that number of CAG repeats may interact with circulating testosterone to impact vMWT performance differently for men and women.

This study was funded by the departmental startup funds of Dr. Scott Moffat.

Poster ID: 228
Dopamine D1 receptor modulation of fear extinction retrieval in male and female rats

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Abstract: Women are twice as likely as men to develop Post-Traumatic Stress Disorder (PTSD), but the neurobiological factors underlying this discrepancy are mostly unknown. PTSD symptoms indicate a dysfunction of the projection from the medial prefrontal cortex (mPFC) to the amygdala. The infralimbic cortex (IL) in the rodent PFC is known to mediate the memory of extinguished fear through the basolateral amygdala (BLA). High estrogen levels during extinction learning have been shown to facilitate extinction retrieval in females. Further, estrogen is known to influence dopaminergic transmission throughout the brain, which is important given that dopamine influences PFC function. The aim of this project is to explore dopamine-estrogen interactions in extinction retrieval. Male and female rats underwent a 3-day fear conditioning, extinction learning, and extinction retrieval paradigm. Fear was measured as freezing during tone presentation. All animals were given an i.p. injection of D1 agonist SKF-38393, or vehicle before extinction learning. Females were divided into two groups according to estrus cycle phase during extinction learning: low estrogen (estrus, metestrus, diestrus [EMD]) and high estrogen (proestrus [P]). In those who received vehicle, P females demonstrated enhanced extinction retrieval compared to EMD females. Drug administration reversed this effect, enhancing extinction retrieval in EMD females and impairing extinction retrieval in P females. Drug administration had no effect on male behavior. All animals received a retrograde tracer injection into the BLA in order to look at activation of BLA-projecting IL neurons after extinction retrieval. Immunohistochemistry for Fluorogold and cFos was carried out on IL-containing sections of tissue to measure the degree of recruitment in this circuit. We found layer- and estrogen-dependent effects that correlate with
observed behavior, which suggest that dopamine and estrogen likely interact to modulate PFC function. This study was supported by Dr. Shansky’s startup fund.

Poster ID: 229
Sex differences in stroke-induced circulating microRNA: a strategy for identifying therapeutic targets

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Abstract: In stroke studies, young females show consistently smaller infarct volumes as compared to males, while ovariectomy abolishes this sex difference. Furthermore, acyclic middle-aged females also display more severe infarction as compared to young, normally cycling females. The present study investigated sex differences in molecular markers, specifically microRNA, with a view to discovering sex-specific neuroprotective mechanisms as well as therapeutic targets for stroke. Since the pathophysiology of stroke is influenced by local events as well as the systemic immune response, we focused on circulating miRNA, which are shed from diverse sources such as endothelium, leukocytes and brain and detectable in virtually all body fluids. Young (5-6 months) male and young and middle-aged female (9-11 months) Sprague Dawley rats (n=6/grp) were subject to vasoconstrictive MCAo. A saphenous blood draw was obtained at 2d post stroke and animals were terminated at 5d post stroke for infarct analysis. Total RNA was isolated from serum and serum miRNAs were amplified using Exiqon SYBR Green Universal RT in conjunction with Exiqon focus panels. Each focus panel contained 168 LNA microRNA primer sets that focus on serum/plasma relevant human microRNAs and 7 reference microRNAs. Samples were compared using t-test, with Benjamini-Hochberg corrections for false discovery rate. Infarct volumes were significantly smaller in young females (0.12) as compared to young males (0.58), and middle-aged females (0.48) (p<0.05). C-miRNA profiles indicated that a small cohort (7 of 168) had sex specific expression. Furthermore, only 2 of these, mir18a and miR151-5p were elevated in middle-aged females and males as compared to young females. In view of the evidence that mir18a attenuates DNA repair and miR151-5p affects growth factor and ion transporters, these miRNA may regulate infarct severity, and thus present viable therapeutic targets.

This study was supported by NIH NS074895 to FS.

Poster ID: 230
Harm avoidant personality and female sex facilitate avoidance behavior on a computer-based paradigm

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Abstract: Avoidance behavior is a predominant symptom in all anxiety disorders. The propensity to acquire and express such behavior may be an important vulnerability factor contributing to the pathogenesis of clinical anxiety. Our understanding of how avoidance behaviors are exhibited by humans would be facilitated by the development of appropriate research protocols and tasks. Here, we developed a computer-based task to study avoidance learning that was modeled after a previously published task by Molet et al. (2006). In addition to the option to prevent (avoid) the aversive event, we included an option to escape that enables the termination of the aversive event after its initiation. This modification allows us to observe the transition from escape to avoidance behavior, a recognized feature of many anxiety disorders that parallels animal avoidance paradigms. In this study we examined potential relationships between escape/avoidance behavior and several anxiety vulnerabilities, including sex. Results show that while nearly all participants exhibited escape responses, only about two thirds made an avoidance
response. Harm avoidant personality, which is indicative of inhibited behavior that avoids punishment and novelty, was associated with facilitated aversive associative learning and shorter escape periods. Females demonstrated longer avoidance periods. This work is the first to develop a computer-based paradigm that operationalizes escape/avoidance behavior and demonstrates differential associations with known vulnerability factors for the development of clinical anxiety.

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Poster ID: 231
Depressive symptoms in late pregnancy are associated with a systemic pro-inflammatory cytokine profile

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Abstract: Major depressive disorder (MDD) is associated with adverse perinatal outcomes and poor infant health and development, however the underlying mechanisms for these associations remain largely unknown. Research consistently links MDD with systemic inflammation yet, to date, studies examining this relationship during pregnancy are equivocal. We sought to examine this relationship in a sample of pregnant, physically healthy women in the third trimester of pregnancy. Seventy-four pregnant women free of psychotropic medication were assessed at a mean of 34.5±2.6 weeks of gestation for medical conditions and psychiatric symptoms. Depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS). Serum concentrations of pro- and anti-inflammatory cytokines (IL-1β, IL-4, IL-5, IL-6, IL-10, TNF-α, IFN-γ) were quantified using a Multiplex immunoassay. Subjects screening positive for current depression (EPDS≥12, n=14) had significantly lower IL-10 levels (t=−2.47, df=68, p=0.016) and a significantly higher TNF-α/IL-10 ratio (t=2.37, df=68, p=0.021) compared to those screening negative for depression (n=56). Regression analyses controlling for age, gestational week, number of previous pregnancies, and time of blood sampling did not alter the results. No associations were observed between depression status and other cytokines. Depressive symptoms in late pregnancy are associated with higher pro- to anti-inflammatory cytokine ratio. To our knowledge, this is the first study to identify IL-10 as a potential marker for depressive symptoms during late pregnancy.

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Poster ID: 232
Changes in hypertension susceptibility and hypothalamus in a mouse model of menopause

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Abstract: After menopause, hypertension and cardiovascular risk increase in women. A comparable sex-related blood pressure reversal is observed with slow-pressor Angiotensin II (AngII; 600 ng/kg/min) infusion. The hypothalamic paraventricular nucleus (PVN) is importantly involved in regulating sympathetic output. In males, slow-pressor administration of AngII: 1) increases Reactive Oxygen Species (ROS) production in the PVN and 2) traffics p47phox, the critical subunit for ROS production, to the plasma membrane of PVN dendrites that lack Arginine Vasopressin (AVP) (Coleman et al., JN 2013). We hypothesized that the hypertensive
response and p47phox trafficking in “postmenopausal” mice following slow pressor AngII administration would resemble males. To generate “post-menopausal” mice female C57BL/6 mice 50 days old were injected i.p. with 130 mg/kg vinlycyclohexene diepoxide (VCD) or vehicle (VEH) (0.5% DMSO in sesame oil) for 15 days. This regimen selectively accelerates the loss of preantral ovarian follicles and produces gradual ovarian cessation (“postmenopause”) within 129 days (Van Kempen et al., BR 2011). Alzet osmotic minipumps (0.25 μl/hr) were filled with AngII or saline and implanted in “postmenopausal” mice for 14 days. Blood pressure was measured via tail cuff plethysmography. The brains were perfusion-fixed and processed for dual immunoelectron microscopy for p47phox and AVP in the PVN. In “postmenopausal” females, Slow-pressor AngII: 1) induced hypertension resembling that of males; 2) showed no increase in density of p47phox silver-intensified gold (SIG) on the plasmalemma in either AVP or non-AVP containing dendrites. Sex differences in the Renal Angiotensin System (RAS) or in ROS production/signaling may account for altered susceptibility to hypertension in women.

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Poster ID: 233
The impact of postpartum depression on the brain response to smiling infant faces in new mothers

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Abstract: Postpartum depression (PPD) impairs responsive, sensitive parenting, elements that have implications for child development, even after the mother’s depression remits. To date, few studies that have investigated the neural bases of PPD. Two studies have found that, compared to mothers without PPD, mothers with PPD demonstrate reduced amygdala (AMY) response to negatively valenced word probes and negative faces (Silverman et al., 2007; Moses-Kolko et al., 2010). While this work is promising, it is important to consider the neural response of mothers specifically to infant stimuli as much of the disorder centers on this dyad. Using fMRI and block design, we investigated the neural response to smiling own infant faces (OWN) and smiling unfamiliar infant pictures (UNF), in mothers with PPD (n=32) and without PPD (n=25), as determined by structured clinical interview based on DSM-IV-TR criteria. We used a whole brain approach using ordinary least squares, simple mixed effects-group analyses. Preliminary results indicate that mothers without PPD, compared to mothers with PPD, show greater BOLD-response for OWN versus UNF bilaterally in the anterior insula, left AMY and frontal pole. Mothers with PPD, compared to mothers without PPD, show greater BOLD-response for OWN versus UNF in the anterior cingulate cortex and bilateral posterior insula. Analysis of how BOLD-response in these regions relates to self-report measures of maternal mood, early experiences and attitudes are still being undertaken. These early findings are consistent with previous work from our laboratory which demonstrated that non-PPD mothers show greater BOLD response in the left AMY when viewing positive pictures of their own compared to an unfamiliar infant (Barrett et al., 2011). Results are also consistent with the literature suggesting there may be differences in AMY functioning in PPD versus non-PPD mothers. These findings are unique, however, as they examine brain response to infant stimuli, specifically.

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Poster ID: 234
Recurrent angina hospitalization rates in women with signs and symptoms of ischemia but no obstructive coronary artery disease: Findings from the Women’s Ischemia Syndrome Evaluation (WISE)

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Abstract: Recurrent hospitalization is prevalent in women with signs and symptoms of ischemia and no obstructive coronary artery disease (CAD). Diagnostic and therapeutic advances may have impacted this rate. We hypothesized that rates of angina hospitalization stratified by early and later time periods may have changed given these advances. We evaluated 551 WISE women enrolled from 1998-2003 for a median of 6 years. We estimated event rates by Kaplan-Meier Method. Univariate analysis and multivariable Cox proportional hazard models were developed for prediction of angina hospitalization. Mean age was 56 ± 11, 56% had hypertension (HTN), 46% dyslipidemia, 51% were smokers, 10% had prior myocardial infarction and 39% had mild-moderate CAD (20-49% stenosis). We found that over 6 years 28% of women were hospitalized for angina, at a constant rate (15% over early 3 years; 13% over later 3 years, p=ns). HTN, dyslipidemia, mild-moderate CAD, use of nitrates, statins, and angiotensin converting enzyme inhibitors (ACE-I) were univariate predictors of angina hospitalization. Adjusted hazard ratios for angina hospitalization were significant for use of nitrates 2.58 (95% confidence interval, 1.80-3.69, p<0.001), statins 1.80 (1.20-2.70, p=0.004) and ACE-I 1.81 (1.22-2.68, p=0.003). We concluded that among women with signs and symptoms of ischemia but no obstructive CAD, angina hospitalization remained constant over 6 years despite medical advances. Clinical trials aimed at reducing angina hospitalization rates in these patients are needed.

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Poster ID: 235
The perils of affirmative action for women – “token jobs”

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Abstract: In Austria, various affirmative action plans for women are in force at the country’s largely state-run universities. These include a 40% quota for women for all job categories. This law was naturally the subject of controversy, with a bias being expressed against “token women. There is little willingness to markedly increase the number of women professors, nor are politicians willing to force the issue. On the other hand, quotas are not only mandated by law, but are also subject to a reporting commitment. Professors appointed by the customary process of sending out an international call for applications are appointed under Section 98, Austrian University Organization Act 2002. If current policy for appointing professors is maintained, the 40% quota will not be reached for decades. In order to solve this problem, a new category of professors was created (Section 99): it permits civil servants holding tenure to be switched to the job category "professor," thereby filling the quota. This new “Section 99 professor” was touted at least internally as affirmative action for women. In all reporting commitments, these professors are naturally counted as professors according to Section 98. To remedy the situation of not reaching the quota this new category of professors was instituted. The people recruited here are exclusively women who already have tenure and this new job category is not comparable with Section 98 professors, meaning it contradicts the dictate that the "quota be reached in each and every category." By taking up this position they lose all the privileges they hitherto held as civil servants. Moreover, they are not entitled to resources or staff, not even their workplace is guaranteed. This Section 99 job category guarantees only that they are a "professor" and receive a monthly salary. Our conclusion in this matter is that these are "token jobs" that clearly circumvent affirmative action for women at universities.
Corticosterone Sex Differences in Acute and Chronic Stress

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Abstract: Stress results in a variety of health problems and is especially linked to mental illness. It has been shown that stress effects males and females differently. Currently, women out represent men in depression and anxiety related disorders. Previous studies have focused on male model paradigms for testing, leaving a lack of generalization. Cortisol, or corticosterone in rats, is the main hormone released by the Hypothalamic-Adrenal-Pituitary (HPA) axis during stressful situations. Females have been shown to have higher cortisol levels when experiencing acute stress when compared to males. The current study investigates corticosterone levels resulting from chronic or acute restraint stress. Male and female rats were randomly assigned to stress or control groups within two stress exposures: acute stress (6 hrs/1 day) or chronic stress (6 hrs/21 days). Rats were restrained, not immobilized, in a cylindrical tube constructed of clear Plexiglas cylinder. Following treatment of stress, rats were sacrificed and trunk blood was used for corticosterone assay. Our results indicate significant differences in acute stress (M=50.19) and chronic stress (M=549.86) corticosterone levels p=0.01. In addition results indicate, although not significant, a trending corticosterone sex difference in females (M=85.64) and males (M=19.75) in acute stress p=.059. Our ongoing investigations in the area of acute and chronic stress include spine density analysis and the comparison of estrus cycle to corticosterone levels.

Sex differences in linear and non-linear analysis of human heart rate variability during delay eyeblink conditioning

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Abstract: Gender differences become apparent in delay eyeblink conditioning upon closer investigation of heart rate variability (HRV). In this study, we examined delay eyeblink conditioning in college aged students who completed a battery of self-assessed personality measures that included a behavioral inhibition (AMBI) and anxiety inventory (STAI). The conditioning paradigm comprised of a 500ms conditioned stimulus (CS) co-terminating with a 50ms corneal air-puff unconditional stimulus (US). A session consisted of 3 US-alone, 60 paired CS/US and 20 CS-alone trials with a pseudorandom intertrial interval. Two minute epochs were recorded immediately prior to and after the conditioning session. An array of HRV parameters were derived from linear time/frequency-domain analysis methods as well as non-linear Poincaré plot analysis of the interbeat interval (IBI) time series signal. Linear indices used include standard deviation (SDNN), root mean square successive difference (rMSSD), high frequency (HF) power, low frequency (LF) power, and LF/HF ratio. Non-linear indices were limited to SD1 and SD2 descriptors of the Poincaré plot, which are the standard deviations of dispersions along the centroid line and line of identity respectively. Preliminary results show significantly lower SDNN, rMSSD, SD1, SD2, and HF power values in males when compared to females for both the baseline and post-experiment time periods. Furthermore, males showed a significant increase in overall variability as well as LF/HF ratio and decrease in HF power at the end of the conditioning. The same effect was seen when males and females were grouped by low/high behavioral inhibition; an insufficient group size for high anxious females did not allow for an analysis sorted on trait or state anxiety. Lower variability is typically correlated with higher sympathetic tone. Although neither males nor females differed in learning and showed no heart rate change relative to baseline, changes in HRV parameters suggests a shift in autonomic balance likely driven by an alteration of respiratory sinus arrhythmia.

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Age- and estrogen-dependent effects on cerebrovascular reactivity: shifting from beneficial to detrimental

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Abstract: Although mechanisms underlying the beneficial effects of estrogen on cerebrovascular (CV) function are well known, the age-dependent deleterious effects of estrogen are largely unknown. We hypothesized that age enhances the deleterious effects of estrogen on CV function by altering the role of prostanoids in modulating CV reactivity. Female rats approximating key stages of hormonal aging were studied: pre-menopausal (mature multigravid, MA), and post-menopausal (reproductively senescent, RS). Rats underwent bilateral ovariectomy (OvX) and were subjected to estrogen replacement therapy (OE). Reactivity to VP (10−12−10−7M) was measured in pressurized middle cerebral arteries (%vasoconstriction) using COX-1 (SC560, SC, 1μM) or COX-2 (NS398, NS, 10μM) selective inhibitors. Maximal VP reactivity in MAOvX (63±0.7%) was attenuated in MAOE by 21%; in contrast, reactivity in RSOvX (59± 1. 1%) was enhanced in RSOE by 28%. In MAOvX and RSOvX, SC and NS reduced reactivity similarly. In MAOE, SC reduced reactivity to a greater extent than NS (Δ60% vs Δ33%); however, in RSOE this effect was reversed (Δ59% NS vs Δ39% SC). VP-stimulated release of PGI2 and TXA2 were measured using radioimmunoassay of 6-keto-PGF1α and TxB2 (stable metabolites, pg/mg dry wt/45min). VP-stimulated PGI2 in MAOvX (22,805 ± 3,108) and RSOvX (18,499±1,563) was increased by estrogen in MAOE (+58%) and RSOE (+56%). In contrast, PGI2 in MAOvX (22,805±3,108) and MAOE (35,975±2,133) was reduced by age in both RSOvX (-19%) and RSOE (-20%). VP-stimulated TXA2 in MAOvX (706 ± 97) and RSOvX (644±59) was increased by estrogen in MAOE (+59%) and RSOE (+117%). TXA2 in MAOE (1,124±93) was increased by age in RSOE (+24%) with no difference in MAOvX and RSOvX. These data suggest that estrogen exerts distinct age-dependent effects: protective in young females (decreased constriction, increased dilator prostanoid function), yet deleterious in older females (increased constriction, increased constrictor prostanoid function).

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The relative contributions of COX-1 and COX-2 to vascular biosynthesis of prostacyclin and thromboxane and the role of estrogen in COX regulation

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Abstract: The relative contributions of cyclooxygenase-1 (COX-1) versus COX-2 to vascular biosynthesis of prostacyclin (PGI2) and thromboxane (TxA2) and the role of estrogen in the regulation of COX function were studied in the thoracic aorta of age-matched 14-16 week old female (F) and male (M) Sprague Dawley rats. We hypothesize that COX-1 and COX-2 contribute differentially to the synthesis of PGI2 and TxA2 in the presence of estrogen. Ovary intact (Int-F), ovariectomized (OvX-F) and OvX+estrogen-replaced (OvX+ER-F) rats were studied. Rats were sacrificed 14 days post-op, and 3mm aortic rings were incubated in Krebs-Henseleit-bicarbonate buffer (KHB), containing either vehicle (basal), vasopressin (VP, 10−6 M), VP+SC-560 (SC, selective COX-1 inhibitor, 10−7 M), or VP+NS-398 (NS, selective COX-2 inhibitor, 10−5 M). The KHB was analyzed by specific radioimmunoassays for 6-keto-PGF1α (stable metabolite of PGI2) and TxB2 (stable metabolite of TxA2). Basal PGI2 was similar in M and all F groups (3,240 ± 212 pg/mg dry weight/45 min). VP-stimulated PGI2 in M (5,302 ± 705) and OvX-F (5,195 ± 689) was reduced similarly by SC and NS (61% vs. 58%). VP-stimulated PGI2 in Int-F (11,575 ± 1,162) and OvX+ER-F (12,131 ± 1,041) was reduced significantly more by NS (83%) than by SC (62%). Basal PGI2 was similar in M and all F groups (3,240 ± 212 pg/mg dry weight/45 min). VP-stimulated TXA2 in M (31 ± 7) and OvX-F (45 ± 7) was reduced.
similarly by SC and NS (66% vs. 67%). VP-stimulated TxA2 in Int-F (63 ± 4.6) and OvX-ER-F (68 ± 8) was reduced markedly more by NS (88%) than by SC (68%). In conclusion, these data suggest that: 1) in the absence of estrogen in OvX-F and M, both PGI2 and TxA2 are derived equally from COX-1 and COX-2; and 2) in Int-F and OvX-ER-F, estrogen markedly enhances PGI2 and TxA2 production, primarily by upregulating COX-2 function.

In conclusion, these data suggest that: 1) in the absence of estrogen in OvX-F and M, both PGI2 and TxA2 are derived equally from COX-1 and COX-2; and 2) in Int-F and OvX-ER-F, estrogen markedly enhances PGI2 and TxA2 production, primarily by upregulating COX-2 function.

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**Poster ID: 240**

**Moderate arousal but high risk: Enhanced bradycardia in females to positive images of "equal" arousal**

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**Abstract:** Research examining both clinically anxious and anxiety vulnerable populations place emphasis on patterns of reactivity to environmental cues, particularly those of negative valence. However, such work generally uses highly arousing affective stimuli to induce maximal responsivity, possibly masking more subtle, though equally important, individual differences. The current study was thus designed to examine cardiac responsivity in anxiety vulnerable, behaviorally inhibited (BI) individuals while viewing stimuli of positive, neutral, and negative valence. Thirty images from the International Affective Picture System were chosen to differ significantly across valence while remaining equated on a moderate arousal rating. Participants were prescreened using the Adult Measure of Behavioural Inhibition and randomly assigned to valence group (Pos, Neg, Neu) based on predetermined high and low BI scores. Each group was shown 60 images in their respective valence (30 novel, 30 repeated, pseudorandom order) while heart rate (HR) was recorded. An HR difference score was calculated in beats per minute (BPM) for 6-s during and after image exposure and used as the dependent measure. The results indicate that BI individuals demonstrate enhanced bradycardia to novel images independent of valence, and less habituation during the viewing of repeated images. Additionally, an interesting interaction emerged with respect to sex and image valence, revealing that females had enhanced bradycardia to novel positive images relative to males, both during and after image presentation. This deceleration habituated equally across sex for repeated positive images. Females also showed lower parasympathetic tone (as indexed by lower interbeat-interval variability), and less HR recovery after image termination, which superseded image valence. In sum, these data indicate that enhanced reactivity in anxiety vulnerable, BI individuals may result from enhanced orienting to stimuli across negative, positive and neutral valences. Such reactivity could contribute to behavioral vigilance, and the progression of anxiety pathology. Furthermore, subjective classifications of experimental stimuli do not necessarily represent standardized autonomic reactivity, particularly with regard to sex.

Support for this study was provided by Department of Veterans Affairs Medical Research Funds, the Stress & Motivated Behavior Institute of the New Jersey Medical School.

**Poster ID: 241**

**Sex differences in the antidepressant-like effect of duloxetine in the rat forced swimming test**

**Author List:** Laura Castellanos-Cruz MD, MSc student, Monica Lamas Gregori, PhD & Alonso Fernández-Guasti, PhD; Authors Affiliations: Departament of Pharmacobiology, Centre of Research and Advanced Studies, Mexico City, Mexico.

**Abstract:** Based on the sex differences in response to serotonergic (SER) and noradrenergic (NA) antidepressants, determined by sex and hormonal state, we hypothesized that male rats would respond better than females to the mix SER-NA antidepressant, duloxetine. We used a SER antidepressant, fluoxetine, as a positive control. Since ovarian hormones interact with antidepressants we explored the effect of these drugs in intact (pooled in all phases of the estrous cycle) and ovariectomized (OVX) females. Duloxetine (3.16, 10 and 17.78 mg/kg, sc) and fluoxetine (1.33, 3.16 and 10
mg/kg, sc) were daily administered for 3 and 2 weeks, respectively. Rats were evaluated every week using the forced swimming test, scoring immobility, swimming and climbing. Ambulation and motor coordination were also measured. Results: Without pharmacological treatment males showed higher immobility scores than both groups of females. Intact and OVX females did not differ in their basal immobility. In males and intact females the basal immobility was similar along three weeks, while in OVX rats these levels increased by the third week. In males, the higher duloxetine doses (10 and 17.78 mg/kg) decreased immobility after 1 week, while with the lower dose (3.16 mg/kg) this reduction was observed after 3 weeks. An increased in swimming and climbing accompanied the diminished immobility. In intact females duloxetine at no dose or time produced an antidepressant-like action. In OVX rats only the highest duloxetine dose (17.78 mg/kg) reduced immobility after 3 weeks of treatment. In males all doses of fluoxetine decreased immobility since week 1, while in females this drug lacked an action. The lack of effect of these antidepressants in intact females was not related with the estrous cycle phase. These drug-effects were not accompanied by changes in ambulation or motor coordination. Conclusions: Males responded better than females to the antidepressant-like effects of duloxetine and fluoxetine.

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Poster ID: 242
Control of profibrotic cardiac gene expression by sex and estrogen via a miRNA network

Author List: Vera Regitz-Zagrosek1, Hugo Sanchez Rudenisch1, Ana Queiros1, Claudia Eschen1, Daniela Fliegner1, Georgios Kararigas1, Elke Dworatzek1, Christina Westphal2

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Abstract: In pressure overload, profibrotic gene expression and cardiac fibrosis are more pronounced in males than in females. Sex-specific and estrogen-dependent regulation of microRNAs (miRNAs), such as miR-21, may be a potential mechanism leading to sex differences in fibrosis. Objectives: To analyze the influence of sex, estrogen (E2), and estrogen receptor beta (ERβ) on the expression of miR-21 and to identify additional miRNAs potentially involved in pressure overload-induced cardiac remodeling. Methods and Results: Male and female wild type and ERβ-deficient mice after transverse aortic constriction (TAC), primary isolated cardiomyocytes, rat fibroblasts, and a cardiomyocyte-like cell line were employed to analyze the sex-specific regulation of fibrosis-related miRNAs. We report the sex-specific expression of functionally-related miR-21, -24, -27a, -27b, 106a, -106b and the regulation of their expression by estrogen in a sex-specific manner. All 6 miRNAs are induced after TAC only in left ventricles of male mice. E2 inhibits the expression of these miRNAs in female cardiomyocytes as well as in rat cardiac fibroblasts. Treatment with ERβ agonist mimics the E2 effects. In ERβ-deficient mice were these sex-specific effects abolished. We demonstrate the presence of common functional target sites for these miRNAs on three repressors of the mitogen-activated protein kinase signaling pathway, i.e. Rasa1, Rasa2 and Spry1, that may all lead to cardiac fibrosis. As hypothesized, transfection with miRNA mimics targeting these repressors induced ERK1/2 phosphorylation. Conclusion – implications for further research: Sex differences in the expression of miR-21, miR-24, miR-27a, miR-27b, miR-106a and miR-106b exist and these miRNAs may operate together targeting different negative regulators of the MAPK/ERK pathway. In addition, E2 modulates the expression of these miRNAs in the heart in a sex-specific manner. These findings may help to elucidate sex differences in propensity to heart disease that could eventually benefit both sexes in terms of new therapeutic targets.

Poster ID: 243
Sex-specific effects of peripheral IFN-γ on acoustic startle reactivity in immunosensitive rats: Possible connection to changes in brain serotonin

Author List: Jennifer E. Catuzzi1,2, Ian M. Smith2,3, Tiffany J. Garcia1, Amir Itani1, and Kevin D. Beck1,2,3

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Peripheral cytokines are known to mediate aspect of behavior, and abnormalities in peripheral cytokines have been liked to psychiatric disorders, such as depression. Previously, we have shown that a single systemic (i.p.) injection of IL-1β, a pro-inflammatory cytokine, is capable of specifically reducing acoustic startle responsivity (magnitude) in intact female Sprague Dawley rats, or OVX Sprague Dawley rats treated with progesterone, without significantly altering startle sensitivity (threshold to startle). Immune sensitive Lewis rats have reduced responsivity and sensitivity following the same systemic administration of IL-1β. IL-1β is involved in the Th1 signaling pathway. Therefore, we sought to determine if other members of the Th1 signaling pathway are also capable of similarly altering the acoustic startle reactivity. Interferon gamma (IFN-γ) is a pro-inflammatory cytokine associated with Th1 immunity. Again, we used Lewis rats to test the hypothesis that Th1 signaling, mediated by IFN-γ, is capable of reducing startle responsivity and/or sensitivity. Following a systemic injection of IFN-γ (10mg/rat) a significant reduction was observed in the startle responsivity of female Lewis rats 5 hours post injection; however, a significant effect was not observed in males. No effect was observed on startle sensitivity for either sex. Additional studies will focus on the eluting the mechanism by which IFN-γ reduces startle responsivity by reducing 5-HT levels.

Abstract: Many tyrosine kinases (TKs) responsible for cell growth and/or angiogenesis are inappropriately activated in cancer cells. Therefore, chemotherapeutic TK inhibitors (TKIs) block many of the intracellular signaling pathways associated with cell growth. However, cardiotoxicity is emerging as an important limitation to the success of these compounds. We focused on Sunitinib, a multiple TKI that is representative of currently available drugs and examined its effects in male and female mice. We included consideration of dietary phytoestrogens present in soy, potent TKIs thought to be beneficial in cancer by feeding mice a diet with or without phytoestrogens.

Cardiac function, morphology, and pathological gene expression were significantly altered in females after 28 days of Sunitinib treatment. Reduced function and ventricular dilation were observed in females but not males. Interestingly, functional deficits were greatly exacerbated in female mice fed a phytoestrogen-supplemented diet. Reductions in fractional shortening and ejection fraction were twice that of females fed a phytoestrogen-free diet. These data reveal possible interactions between Sunitinib and phytoestrogens in females that caution against dietary soy supplementation when receiving TKIs.

To consider the role of biological sex, we measured phosphorylation of 39 different TKs in the hearts and in isolated cardiomyocytes. In the hearts of females fed a phytoestrogen-free diet, 28 TKs were inhibited by Sunitinib whereas in males, 17 were inhibited; only 10 were shared. Uniquely inhibited TKs in female cells included five Ephrin receptors that are critical to gap junctions and to cardioprotection after ischemic injury. Comparison with isolated cardiomyocytes suggested indirect cardiac effects via systemic administration. In cells treated with estrogen, 21 and 8 TKs were inhibited in female and male, respectively, suggesting that estrogen alone inhibits TKs and could worsen cardiotoxicity in females.

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Poster ID: 245
**Integrating information: Sex Differences, Gender, Addictions, and Psychoactive Substances**

**Author List:** Jill B. Becker, Ph.D.1*, Beth Glover Reed, Ph.D.2, Michelle L. McClellan, Ph.D.3 and Brian D. Athey, Ph.D.4

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**Abstract:** Addictions are a worldwide problem and finding ways to understand and reduce the cost of addictions is the goal of this project. We will describe our proposed use of an informatics approach to integrate existing knowledge about sex differences and gender in relation to drug use and addictions, including compulsive behaviors related to food intake, gambling, and sexual activity. Patterns of addiction and its definition have varied considerably over time and across men and women. Both the concept of addiction (understood today as chronic, compulsive behaviors) and the rubric of gender (a system of social organization and the behavioral prescriptions believed to follow from biological sex characteristics) are socially constructed, shaped by cultural structures and processes over time.

Researchers in the social and natural sciences have demonstrated that addictions and consequences of addictions differ by biological sex and by gender. Yet both research and policy are shaped by unexamined societal attitudes, and suffer from a failure to be advised by a broad historical perspective.

Our goal is to find new answers to solve the problem of addictions for both men and women. Our multidisciplinary team will relate temporally-organized heterogeneous data and information from current and historical archives of use, abuse, and addictions by gender, including medical, neuroscience, social science, and applied research findings in ways that can be modeled and understood across disciplines to yield un-recognized patterns and relationships in these data. These new insights will add to our understanding of the characteristics of addictions and lead to more informed research questions and interventions for both men and women as well as new research proposals to address gaps in knowledge and new emerging questions. It is also our goal to develop new generally applicable strategies for integrating diverse and transdisciplinary information to generate new knowledge.

This research is funded by grants from the Institute for Research on Women and Gender and the Center for Advancing Research and Solutions for Society, University of Michigan.

Poster ID: 246
**Sex differences and estrous cycle in female rats interact with the effects of fluoxetine treatment on fear extinction**

**Author List:** Kelimer Lebrón-Milad Ph.D.1, Alina Tsareva B.S.1, Nafis Ahmed1, Mohammed R. Milad Ph.D.1

**Author Affiliation:** 1Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

**Abstract:** A common treatment for anxiety disorders is chronic administration of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine. Recent data suggest that SSRIs modulate fear responses after conditioned fear extinction and that gonadal hormones influence fear extinction. Studies investigating the effects of fluoxetine on fear extinction have thus far been conducted on males. In this study we investigated the influence of sex and the estrous cycle on the effects of acute (experiment 1) and chronic (experiment 2) fluoxetine treatment on fear extinction. In experiment 1, rats were conditioned with 7 tone-footshock trials during day 1. On day 2, rats received either fluoxetine (10mg/kg in 0.5mL) or vehicle half an hour prior to Extinction Learning (consisting of 20 tones-no footshock trials). On day 3, extinction memory was assessed during Extinction Recall (15 tone alone trials). In experiment 2, rats were exposed to a similar behavioral protocol, except that fluoxetine and vehicle were administered for 14 consecutive days after conditioning (days 2-15). Extinction Learning and Extinction Recall occurred on days 15 and 16, respectively. Our data showed evidence of sex-organization for the Study of Sex Differences (OSSD)
specific anxiolytic effects of 14-day treatment of fluoxetine while the acute anxiogenic effect of SSRI seems independent of sex effects.

This study was funded by the National Institute of Mental Health Grant 1R01MH097880-001 and institutional funds from the Department of Psychiatry at Massachusetts General Hospital to MRM.

Poster ID: 247
The impact of oral contraceptives use on the neural correlates of fear extinction: A functional MRI study

Author List: Moon jung Hwang Ph.D.1, Edward Pace-Schott Ph.D.1, Kelimer Lebron-Milad Ph.D.1, Rachel Zsido1, and Mohammed R Milad Ph.D.1

Author Affiliations: 1 Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

Abstract: Recent data from rodents and human imaging studies have shown that sex hormones, especially estrogen, modulate the functional reactivity of the fear extinction network, which includes the ventromedial prefrontal cortex (vmPFC), hippocampus, amygdala, and insular cortex. We have shown that naturally cycling women that undergo extinction of conditioned fear at a stage of the menstrual cycle where estrogen is high exhibit significantly better extinction memory relative to women with low estrogen. These findings suggest that estrogen may facilitate extinction memory consolidation. These data also raise an important question: Do oral contraceptives, which are known to manipulate the production of natural estrogen, influence fear extinction? In the present study, we conducted an experiment to assess the effects of oral contraceptives (OC) on the neural correlates of fear extinction in women using functional MRI (fMRI) and a well-established two-day fear conditioning and extinction paradigm. On day 1, women underwent de novo fear conditioning session, immediately followed by an extinction training session. On day 2, women underwent an extinction recall test. All experimental procedures were conducted in the fMRI scanner. Skin conductance responses were collected and used as the index of conditioned fear. Our preliminary data analysis show that when compared to women that underwent extinction in a high estrogen state, OC group exhibited reduced ventromedial prefrontal cortex, hippocampus, and insular cortex activations. Interestingly, no significant between-group differences in the fear extinction network were observed between women that underwent fear extinction in a low-estrogen state and women using OC. These data are consistent with our previously published psychophysiological data showing that women using OC exhibit extinction memory levels comparable to women with low estrogen, both of which are significantly lower than those exhibited by high-estrogen women.

This study was funded by a National Institute of Mental Health (NIMH)1R01MH097880-01 to MRM
OSSD 2013 ANNUAL MEMBERSHIP MEETING

SATURDAY APRIL 27, 2013
5:30 – 6:30 PM BEEKMAN CONFERENCE ROOM

AGENDA

Call to Order by OSSD President (Geert de Vries)

Business Reports:

- Membership (Glenna Bett)
- Nominations/Elections (Peg McCarthy/Geert de Vries)
- Journal: Biology of Sex Differences (Art Arnold)
- Finances (Farida Sohrabji)

New Business

- Selection of OSSD 2014 Site (Geert de Vries)

Open Forum

Adjourn
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**Handbook of Clinical Gender Medicine**

Editors: Schenck-Gustafsson, K. (Stockholm); DeCola, P.R.; Pfaff, D.W.; Pisetsky, D.S. (Durham, N.C.)

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