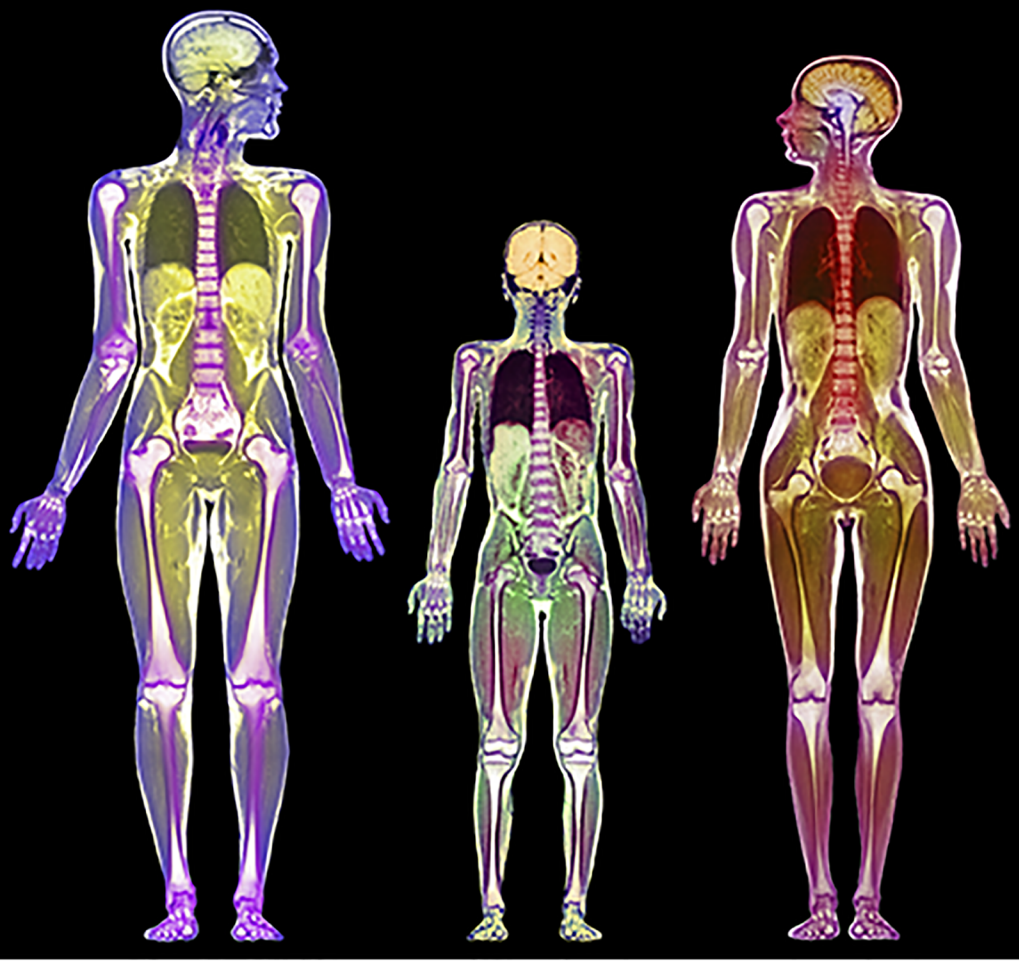
Sex as a Biological Variable Across the Lifespan

12th Annual Meeting

April 30 - May 3, 2018 | Atlanta, GA



SSD

ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES

Founded by the Society for Women's Health Research

Table of Contents

Welcome to Atlanta!

OSSD 2018 is hosted by Georgia State University's *Neuroscience Institute*

We would like to extend a huge THANK YOU to our volunteers!

Top Row: Johnathan Borland, Christopher Searles, Evan Fullerton, Anne Murphy, Jack Whylings, Leah Krevitt

Bottom Row: Laura Cortes, Hannah Harder, Nicole Peters

Not Pictured: Katie Partrick, Anna Rosenhauer, Jennifer Walcott, Niko Rigney

Thank You to Our Sponsors

Thank you to the National Institutes of Health for its generous support of the OSSD 2018 annual meeting.

Funding for this conference was made possible, in part, by 5R13AG056135-02 from National Institute on Aging and the Office of Research for Women's Health, Office of the Director. The views expressed in written conference materials or publications and by speakers or moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Letter from the President

Welcome to OSSD 2018, the 12th annual meeting of the Organization for the Study of Sex Differences!

Once again, sex is at the center of everything. Gender is in the spotlight with the #metoo and #timesup movements, Women's Marches across the world and renewed interest in the Equal Rights Amendment in the US. While focused on gender, these social movements are inextricably linked with the science of sex and its importance to human health. We are now in the third year of implementation of new policies at major research funding agencies in the US, Canada and Europe requiring attention to sex as a biological variable in preclinical and clinical research. The change is beginning to bear fruit in the many new studies coming out revealing surprising and unexpected ways that the biology of males and females differ. At the same time, the push to recognize the importance of gender as a key contributor to health and disease cannot be ignored. At this year's meeting we are giving particular attention to the importance of gender with a panel discussion titled, "Sex Differences and the Google Memo" and in our Capstone Lecture, Dr. Londa Schiebinger's talk, "Gendered Innovations in Health Research, Machine Learning and Robotics". But our overarching emphasis remains on the biology of sex and enhancing the understanding of this key variable to physiology and behavior across the lifespan. As part of our mission to assure the highest level of rigor in our science we also provide you a working lunch on "Efficient and Reproducible Research: An Introduction to the Open Science Framework". Lastly, we seek as always to foster the careers of our trainees with a series of professional and social events to enhance networking and inclusiveness.

The OSSD is a collective of volunteers and would not be able to function without the dedication and tireless effort of so many. The Program Committee was chaired by Dr. Douglas Portman who managed the challenging task of evaluating and ranking a record number of high quality proposals. Together with his committee they have created a broad and balanced program that is sure to provide topics of interest to all attendees throughout the meeting. Our local host is Dr. Anne Murphy (Secretary-elect) who together with her team has worked tirelessly to assure the highest quality venue and organization. Thank them for how seamlessly the meeting is running and know that it is because they thought of every little thing in advance, no matter how small, despite the many other demands on their time and attention. Brittany Osborne collated and organized all the abstracts. Dr. DeLisa Fairweather chaired the Awards Committee and assured that a fair and transparent process was used in the selection of travel awardees, Elizabeth Young Investigators and Florence Haseltine Poster Awardees. Be sure to attend the poster sessions and vote for your favorite on Monday and Tuesday, and don't miss the Young Investigators Symposium on Wednesday afternoon. We also thank the Society for Women's Health Research for their continued support as we move forward together in our shared missions to enhance the health of all people. We also thank the many sponsors for their financial contributions which make this meeting possible. Lastly, it is impossible to exaggerate the invaluable contribution of Dr. Jackie Schwarz who serves as the OSSD's institutional memory, webmaster, grant writer, former secretary and essential ingredient that keeps the gears turning in this complex machine. She is also the PI of our R13 grant from the NIH supported by the National Institute of Aging and the Office for Research on Women's Health of the NIH.

Finally, I thank all of you for attending and making the 2018 OSSD Annual Meeting an exciting and rewarding experience for all.

Margaret M McCarthy, PhD
President – OSSD

Professor and Chair
Department of Pharmacology
University of Maryland School of Medicine
Baltimore MD USA

General Information

OSSD is committed to the support and development of trainees in the field of sex differences research. In accordance with this commitment, we are delighted to offer multiple events and awards for trainees at the 2018 conference.

Trainee Social Hour:
On Tuesday, May 1st, 7:00 PM, a special social hour is offered for trainees at Foxtrot. We will provide appetizers and Foxtrot has a fantastic beverage menu. Post-docs and grad students welcome.

Foxtrot Address: 45 13th Avenue, NE, Atlanta, GA 30309.

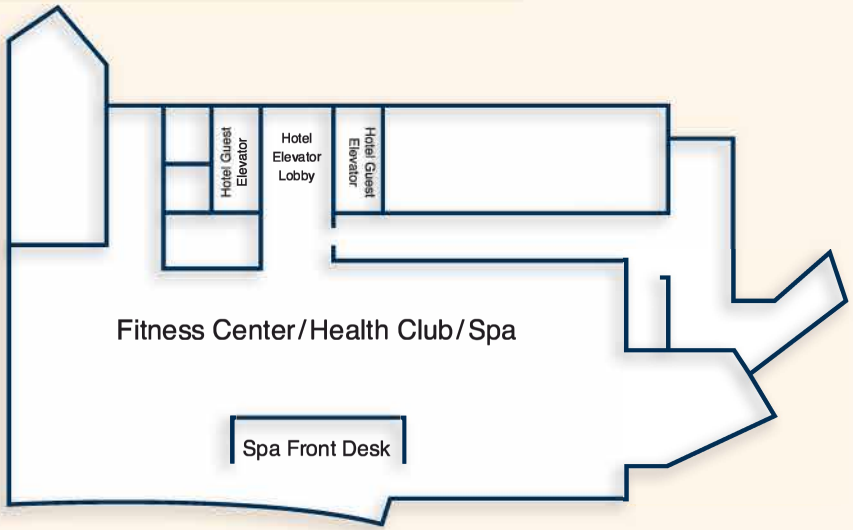
Trainee Mentoring Lunch:
On Wednesday, May 2nd, a mentoring lunch will be offered for trainees featuring five mentors. In order to facilitate in-depth discussions and interactions, attendance at this event will be capped at 35 trainees. Be sure to sign up at the registration desk when you arrive at the conference as attendance will be first come, first served.

We are Live on Social Media!
Use the hashtag **#OSSD2018** throughout the week.
Twitter - @OSSDtweets
Facebook - OSSD - Organization for the Study of Sex Differences

OSSD
ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES
Founded by the Society for Women's Health Research

exhale MINDBODYSPA

Level - 7



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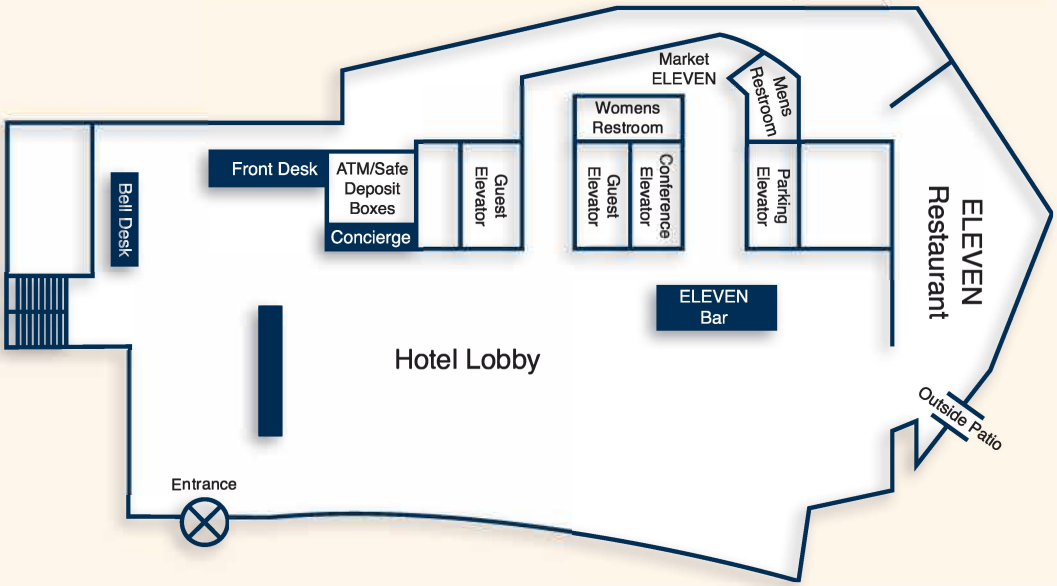
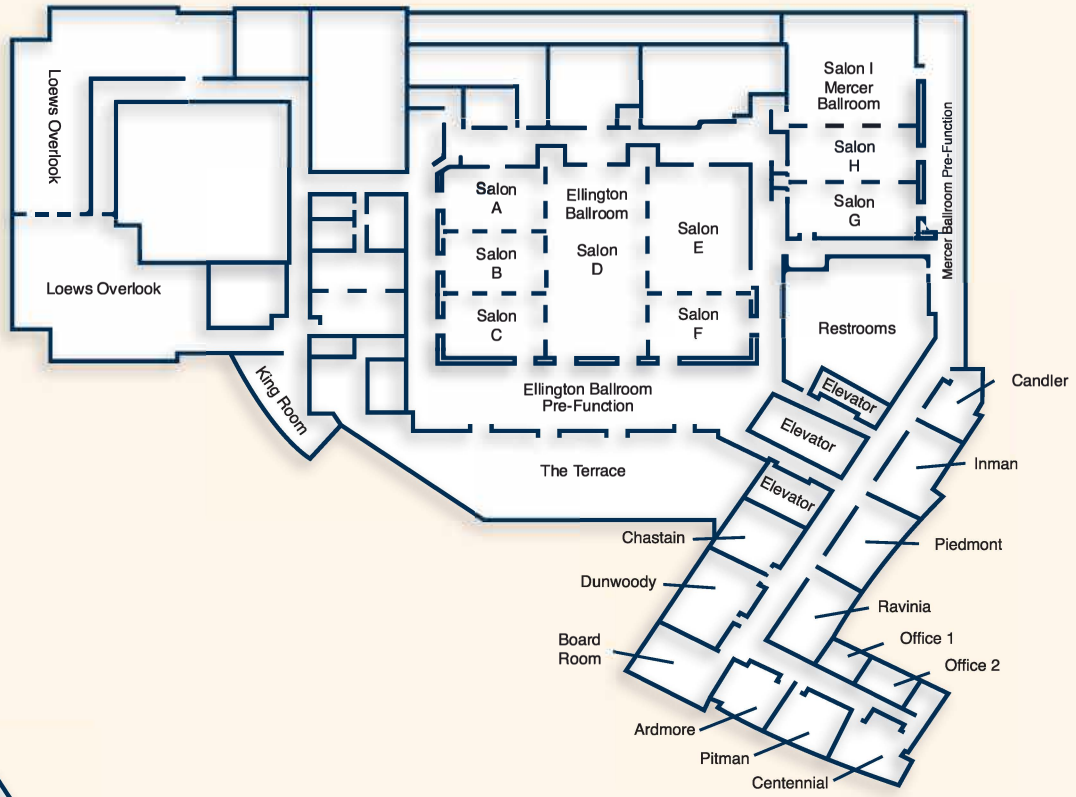
LOEWS Lobby



LOEWS Conference Floor

Level - C (14th Floor)



Loews Atlanta Hotel | 1065 Peachtree Street NE Atlanta, GA 30309 | 404.745.5000

LOEWS
ATLANTA
HOTEL

RESTAURANTS

- ELEVEN (Bar, Market, Restaurant)
- 1 Baraonda Ristorante and Bar
- 2 Campagnolo
- 3 Carolyn's Pizza
- 4 Cucina Asellina
- 5 Deadwood
- 6 Ecco
- 7 Einstein's
- 8 Empire State South
- 9 Escorpion
- 10 Five Napkin Burger
- 11 Flying Biscuit
- 12 Fresh to Order (F20)
- 13 Front Page News
- 14 Goldberg's Bagel Co. & Deli
- 15 Gordon Biersch
- 16 Highland Bakery
- 17 Hudson Grille
- 18 J. Christophers
- 19 Joe's on Juniper
- 20 La Pietra Cucina
- 21 Las Palmeras
- 22 The Lawrence
- 23 Mary Macs Tea Room
- 24 Nan Thai Fine Dining
- 25 The Nook
- 26 Oceanaire Seafood Room
- 27 Park 75
- 28 Pasta da Pulcinella
- 29 Piola
- 30 Proof and Provision
- 31 Ra Sushi Bar
- 32 Ri Ra Irish Pub
- 33 Senior Patron
- 34 Shout
- 35 South City Kitchen
- 36 The Spence
- 37 Spice Market
- 38 Steel
- 39 STK
- 40 Table 1280
- 41 Taco Mac
- 42 Takorea
- 43 Tamarind Seed
- 44 TAP
- 45 Top Flr
- 46 Tin Lizzy's Cantina
- 47 The Varsity
- 48 Veni Vidi Vici
- 49 Vespuccis Pizza n Pasta
- 50 The Vortex Midtown
- 51 Zocalo

POINTS OF INTEREST

- A 14th Street Playhouse
- B Alliance Theatre
- C Atlanta Symphony Orchestra
- D Center for Puppetry Arts
- E Colony Square
- F Federal Reserve
- G Fox Theatre
- H High Museum of Art
- I Margaret Mitchell House
- J Museum of Design

- Loews Hotel
- Bank of America
- CVS
- Marta
- Publix
- Starbucks
- Wells Fargo Bank

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Loews Atlanta Hotel
Saltwood $$ Open Early Daily | 1065 Peachtree Street NE | 404-745-5745 | *Charcuterie, Breakfast, Lunch, Dinner*

Bakeries & Breakfast
Babs Midtown $ Breakfast Daily | 814 Juniper Street NE | 404-541-0888 | *Southern, Local, Breakfast*
Flying Biscuit $ Open Early Daily | 1001 Piedmont Avenue | 404-874-8887 | *Southern, Local, Breakfast*
Highland Bakery $$ Open Early Daily, Breakfast & Lunch, Closed Sunday | 1180 Peachtree Street NE #C | 404-835-3130 | *Bakery*
Joy Cafe $$ Open Early Daily | 1100 Peachtree Street NE | 404-996-1377 | *Breakfast and Lunch*

Bar/Pub, Café, & Deli
Café Intermezzo $$ Open All Day & Late | 1065 Peachtree Street NE | 404-355-0411 | *All Day Breakfast, German Coffee Haus*
Hudson Grille $ Open Daily | 942 Peachtree Street | 404-892-0892 | *Casual Sports Bar & Grille*
Ri Ra Irish Pub $$ Open Daily | 1080 Peachtree Street NE | 404-477-1700 | *Irish Pub*
Taco Mac $ Open Daily | 933 Peachtree Street (Metropolis) | 678-904-7211 | *American Sports Bar*
The Vortex Midtown $ Lunch & Dinner Daily | 878 Peachtree Street | 404-875-1667 | *Classic American*

Casual American
Front Page News $ Open Daily | 1108 Crescent Avenue NE | 404-897-3500 | *Casual Cajun & Creole*
Joe's $ Open Daily | 1049 Juniper Street | 404-875-6634 | *Casual bar food*
TAP $$ Open Daily; Brunch Saturday & Sunday | 1180 Peachtree Street | 404.347.2220 | *American Gastropub*

Ethnic, Fusion & Seasonal
Café Agora $ Lunch & Dinner Daily | 92 Peachtree Place | 404-253-2997 | *Mediterranean*
Ecco $$$ Dinner Daily; Bar & Patio | 40 7th Street NE | 404-347-9555 | *Seasonal European*
Tabla $$ Lunch & Dinner Tuesday – Sunday | 7712th Street NE | 404-464-8571 | *Authentic Indian Meets Modern Gourmet*
Takorea $ Lunch & Dinner Daily | 818 Juniper Street | 404-532-1944 | *Korean Street Food*
Bulla Gastrobar $$ Lunch & Dinner Daily | 6011th St NE | (404) 900-6926 | *Spanish Tapas*

Italian
Campagnolo $$ Dinner Daily & Sun Brunch | 980 Piedmont Ave NE | 404-343-2446 | *Authentic*
Pasta da Pulcinella $$ Lunch & Dinner Daily | 1123 Peachtree Walk | 404-876-1114 | *Casual*
Ribalta $$ Lunch & Dinner Daily | 1080 Peachtree Street NE #9 | 404-249-7019 | *Authentic Neapolitan*
Princi Italia $$ Lunch & Dinner Daily | 77 12th Street | 404-709-2058 | *Casual*

Mexican
Escorpion $$ Lunch & Dinner Daily | 800 Peachtree Street NE | 678-666-5198 | *Mexican Tequila Cantina*
Senor Patron Mexican Restaurant $ Lunch & Dinner Daily | 860 Peachtree Street NE | 404-645-7987 | *Mexican*
Tin Lizzy's Cantina $ Lunch & Dinner Daily | 1136 Crescent Avenue | 404-537-5060 | *Mexican Taqueria*
Zocola $$ Lunch & Dinner Daily | 187 10th Street | 404-249-7576 | *Mexican*
Babalu Tapas and Tacos $$/33 Peachtree Place NE/ 404-900-9595/ *Mexican*

New American
10th & Piedmont $$ Lunch & Dinner Daily; Wkd Brunch | 991 Piedmont Avenue NE | 404.602.5510 | *Sm. Bites, Seasonal Dishes*
The Lawrence $$$ Dinner Daily | 905 Juniper St | 404.961.7177 | *Creative New American*
5Church $$ Dinner Daily | 1197 Peachtree St NE | 404.400.3669 | *Creative New American*

New Southern
Einstein's $$ Lunch & Dinner Daily | 1077 Juniper Street | 404-876-7925 | *Innovative American Cuisine*
Empire State South $$$ Open Early Daily | 999 Peachtree Street NE | 404-541-1105 | *Progressive Southern, Breakfast, Lunch, Dinner*
South City Kitchen $$$ Lunch & Dinner Daily; Sun Brunch | 1144 Crescent Avenue | 404-873-7358 | *New Southern*

Seafood, Steak & Sushi
The Federal $$ Dinner Daily; 1050 Crescent Avenue/ 404-343-3857/ Steakhouse Bistro
Lure Atlanta $$$ Dinner Daily; Bar opens @ 4pm | 1106 Crescent Avenue | 404-817-3650 | *Contemporary Fish House*
Oceanaire Seafood Room $$$ Lunch & Dinner Daily | 1100 Peachtree Street | 404-475-2277 | *Seafood*
Ra Sushi Bar $$ Open Daily | 1080 Peachtree Street NE | 404-267-0114 | *Sushi Bar*
STK $$$ Dinner Daily | 1075 Peachtree Street | 404-793-0144 | *Modern Steakhouse*

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LOEWS HOTELS

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Rockefeller Univ. (Young Investigator; 2 year term)

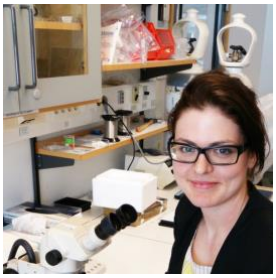
Award Winners

We are pleased to announce the winners of both the new investigator awards and the travel awards for OSSD 2018.

Elizabeth Young New Investigator Awards

Soumya Turaga, PhD student, Cleveland State University
Title: Junction adhesion molecule-A (JAM-A) deficiency drives sex-specific differences in glioblastoma progression via differential responses in the tumor microenvironment

Jonathan VanRyzin, PhD student, University of Maryland School of Medicine
Title: Endocannabinoids program sex differences by inducing microglia phagoptosis of newborn cells in the neonatal rat amygdala



Hilda Ahnstedt, PhD, Postdoc, UT Heath
Title: Sex differences in neutrophil-T cell Immune responses, gut integrity and outcome after ischemic stroke in aged mice

Valeria Raparelli, PhD, Postdoc, Rome, Italy
Title: Impact of sex and gender-related factors on percutaneous coronary intervention in patients with ischemic heart disease: analysis from the EVA study

Travel Awards

- **Jennifer Honeycutt,** PhD, Postdoc, Northeastern University
- **Jordan Marrocco**, PhD, Postdoc, The Rockefeller University
- **Jaekyoon Kim**, PhD student, University of Wisconsin – Milwaukee
- **Emily Mackey**, PhD student, North Carolina State University Center of Veterinary Medicine
- **Philipp Pottmeier**, PhD student, Uppsala University, Sweden
- **Jasmin Sponagel**, PhD student, Washington University in St. Louis
- **Morgan Sherer**, PhD student, University of Delaware
- **Nathalie Fuentes**, PhD student, The Pennsylvania State University College of Medicine
- **Ashley Marquardt**, PhD student, University of Maryland School of Medicine

Keynote Speaker

Dr. Nirao Shah, M.D., Ph.D. is a Professor of Psychiatry and Behavioral Sciences and of Neurobiology at Stanford University. After completing his medical training, Dr. Shah was a graduate student at Caltech, where he identified mechanisms that control differentiation of stem cells that give rise to the peripheral nervous system. For his post-graduate fellowship at Columbia University, Dr. Shah developed genetic approaches to identify neural pathways that regulate social behaviors. In his own laboratory, his research has elaborated on such approaches to identify genes and neurons that control different aspects of social interactions. Dr. Shah's findings have provided insights into how our brains enable social interactions in health, and they are relevant to understanding mechanisms underlying behavioral manifestations of autism, dementia, mood disorders, and PTSD. Dr. Shah was the recipient of a Scholar in Neuroscience award from the Ellison Medical Foundation, an NIH Pioneer Award, and was a NARSAD Young Investigator.

Capstone Speaker

Londa Schiebinger, Ph.D. is the John L. Hinds Professor of History of Science in the History Department at Stanford University and Director of the EU/US Gendered Innovations in Science, Health & Medicine, Engineering, and Environment Project. Professor Schiebinger received her Ph.D. from Harvard University in 1984 and is a leading international authority on gender and science. Over the past thirty years, her work has been devoted to teasing apart three analytically distinct but interlocking pieces of the gender and science puzzle: the history of women's participation in science; gender in the structure of scientific institutions; and the gendering of human knowledge. Dr. Schiebinger has been the recipient of numerous prizes and awards, including the prestigious Alexander von Humboldt Research Prize and John Simon Guggenheim Fellowship. Her research has been supported by the National Science Foundation, National Institutes of Health, National Endowment for the Humanities, Rockefeller Foundation, Fulbright-Hays Commission, Woodrow Wilson Foundation, and Deutscher Akademischer Austauschdienst. She is a member of the American Academy of Arts and Sciences.

MONDAY, APRIL 30

11:00 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*	
1:00 PM – 2:45 PM	**SESSION 1** *(Mercer Salon I)* Sex Differences at the Electrophysiological Level: A Focus on the Limbic System *Chair: Briand*	**SESSION 2** *(Mercer Salon G/H)* Sex Differences in the Pathogenesis of Infectious Diseases *Chairs: Pekosz and Klein*
2:45 PM – 3:00 PM	**COFFEE BREAK** *(Mercer Prefunction)*	
3:00 PM – 4:45 PM	**SESSION 3** *(Mercer Salon I)* Neurocircuitry and Neuroplasticity over the Lifespan: Sex-specific Trajectories Mean Timing is Everything *Chair: Brenhouse*	**SESSION 4** *(Mercer Salon G/H)* Sex-specific Outcomes of Environmental Chemical Exposures *Chair: Meitzen*
5:00 PM – 6:15 PM	**KEYNOTE LECTURE** *(Mercer)* **Nirao Shah, Ph.D., Stanford University** *Molecular and Neural Control of Sexually Dimorphic Behaviors*	
6:15 PM – 8:15 PM	**OPENING RECEPTION and POSTER SESSION 1** *(Overlook West)*	

PROGRAM AT A GLANCE

TUESDAY, MAY 1

8:30 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*	
7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*	
8:30 AM – 10:15 AM	**SESSION 5** *(Mercer Salon I)* Molecular Mechanisms of Sex-dependent Vulnerability to Stress *Chairs: Morrison and Bale*	**SESSION 6** *(Mercer Salon G/H)* Implications of Sex and Gender in Clinical Care *Chair: Becker*
10:15 AM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*	
10:30 AM – 12:15 PM	**SESSION 7** *(Mercer Salon I)* Hormonal Regulation of Behavior and Physiology Across Diverse Species *Chair: Shah*	**SESSION 8** *(Mercer Salon G/H)* *In Silico* Models and Clinical Trials: Innovative Research and Sex and Gender Implications *Chair: Jenkins*
12:15 PM – 1:30 PM	**WORKSHOP LUNCH** *(Mercer)* Aaron Wolen, Ph.D., Virginia Commonwealth University **Efficient and Reproducible Research: An Introduction to the Open Science Framework**	
1:45 PM – 3:30 PM	**SESSION 9** *(Mercer Salon I)* Nuclear Structure and Sex Differences *Chairs: Disteche and Brown*	**SESSION 10** *(Mercer Salon G/H)* Sex Differences in Cerebrovascular Disease: Epidemiology to Epigenetics *Chairs: McCullough and Reeves*
3:30 PM – 3:45 PM	**COFFEE BREAK** *(Mercer Prefunction)*	
3:45 PM – 4:45 PM	**PANEL DISCUSSION** *(Mercer)* Moderator: Lise Eliot, Ph.D., Rosalind Franklin University **Sex Differences and the Google Memo**	
4:45 PM – 6:45 PM	**POSTER SESSION 2** *(Overlook West)*	
7:00 PM	**TRAINEE SOCIAL** *(Foxtrot, 45 13th St. NE)*	

WEDNESDAY, MAY 2

8:30 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*	
7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*	
8:00 AM – 8:30 AM		**OSSD BUSINESS MTG** *(Mercer I)*
8:30 AM – 10:15 AM	**SESSION 11** *(Mercer Salon I)* Sex Steroids, Puberty, and Adolescent Brain Development: A Translational Approach to Understanding Peak Vulnerability to Psychopathology in Adolescence *Chairs: Seney and Ladouceur*	**SESSION 12** *(Mercer Salon G/H)* Statistical Methodologies on Sex Chromosome Association *Chair: Xu*
10:15 AM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*	
10:30 AM – 12:15 PM	**SESSION 13** *(Mercer Salon I)* Sex Differences in Learning and Plasticity *Chairs: Bangasser and Grissom*	**SESSION 14** *(Mercer Salon G/H)* Gender, Sex Hormones, and Lung Inflammation *Chair: Silveyra*
12:15 PM – 1:30 PM	**TRAINEE LUNCH** *(Ravinia) – or, enjoy Atlanta with lunch on your own*	
1:45 PM – 3:30 PM	**SESSION 15** *(Mercer Salon I)* Current Topics in Sex Differences Research I: Genetics and Neuroscience *Chair: Portman*	**SESSION 16** *(Mercer Salon G/H)* Current Topics in Sex Differences Research II: Immunology, Physiology, and Metabolism *Chair: Moeser*
3:30 PM – 3:45 PM	**COFFEE BREAK** *(Mercer Prefunction)*	
3:45 PM – 5:15 PM	**ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM** *(Mercer)*	
5:00 PM – 6:15 PM	**CAPSTONE LECTURE** *(Mercer)* **Londa Schiebinger, Ph.D., Stanford University** *Gendered Innovations in Health Research, Machine Learning, and Robotics*	
6:15 PM – 8:15 PM	**AWARDS RECEPTION** *with heavy hors d'oeuvres (Overlook West)*	

THURSDAY, MAY 3

7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*	
8:30 AM – 10:15 AM	**SESSION 17** *(Mercer Salon I)* Sex Differences in Pain from the Sensory Nerves to the Brain *Chair: Averitt*	**SESSION 18** *(Mercer Salon G/H)* Defining and Measuring Sex and Gender in Clinical Research *Chairs: Pilote and Dreyer*
10:15 AM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*	
10:30 AM – 12:15 PM	**SESSION 19** *(Mercer Salon I)* Endocrine Disruptors: Sex Differences in their Effects During Development *Chair: Juraska*	**SESSION 20** *(Mercer Salon G/H)* Women and Alzheimer's Disease: A Scientific Update from the SWHR Interdisciplinary Panel on Alzheimer's Disease *Chair: Maki*
12:15 PM – 12:30 PM	**CLOSING REMARKS** *(Mercer)*	
END OF MEETING		
12:30 PM – 3:00 PM	**OSSD COUNCIL MEETING** *(Ravinia)*	

MONDAY, APRIL 30

11:00 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*
1:00 PM – 2:45 PM **PARALLEL SESSIONS 1 and 2**	**SESSION 1** *(Mercer Salon I)* **Sex Differences at the Electrophysiological Level: A Focus on the Limbic System** *Chair: Lisa Briand, PhD, Temple University* **Lisa Briand, PhD, Temple University** Sex differences in nucleus accumbens inputs: Basal differences and influence of stress exposure **John Meitzen, PhD, North Carolina State University** Sex differences in medium spiny neuron electrophysiological properties: heterogeneity across striatal regions and evidence for estradiol-dependent sexual differentiation **Dean Kirson, PhD, The Scripps Research Institute** Sex differences in oxytocin effects on CeA GABAergic signaling in alcohol-dependent and naive rats. **Helen Scharfman, PhD, Nathan Kline Institute for Psychiatric Research** Electrophysiological analyses complement and extend the understanding of female and male hippocampus
	SESSION 2 *(Mercer Salon G/H)* **Sex Differences in the Pathogenesis of Infectious Diseases** *Chairs: Andrew Pekosz, PhD, Johns Hopkins Bloomberg School of Public Health and Sabra Klein, PhD, Johns Hopkins Bloomberg School of Public Health* **Theresa Chang, PhD, Rutgers University** Sex differences in innate immune and microbial response and disease progression in simian HIV-infected rhesus macaques **Christopher Robinson, PhD, Indiana University** Sex differences in enteric virus infection **DeLisa Fairweather, PhD, Mayo Clinic** Sex differences in viral-induced myocarditis **Cory Tuescher, PhD, University of Vermont** Genome-wide physical mapping identifies genetic elements contributing to sex differences in susceptibility to IAV infection
2:45 PM – 3:00 PM	**COFFEE BREAK** *(Mercer Prefunction)*

MONDAY, APRIL 30

3:00 PM – 4:45 PM **PARALLEL SESSIONS 3 and 4**	**SESSION 3** *(Mercer Salon I)* **Neurocircuitry and Neuroplasticity over the Lifespan: Sex-specific Trajectories Mean Timing is Everything** *Chair: Heather Brenhouse, PhD, Northeastern University* **Jennifer Honeycutt, PhD, Northeastern University** Too much, too young? Sex-specific differences in corticolimbic innervation following early life stress **Q.D. Walker, PhD, Duke University** Neurocircuitry underlying sex differences in eating disorders **Rebecca Shansky, PhD, Northeastern University** Experience dependent structural plasticity: interactions of circuit and sex **Pavel Osten, PhD, Cold Spring Harbor Laboratory** Brain-wide maps reveal stereotyped cell-type-based cortical architecture and subcortical sexual dimorphism
	SESSION 4 *(Mercer Salon G/H)* **Sex-specific Outcomes of Environmental Chemical Exposures** *Chair: John Meitzen, PhD, North Carolina State University* **Emily Barrett, PhD, Rutgers University** Prenatal exposure to endocrine disrupting chemicals, sex, and neurodevelopment **Heather Stapleton, PhD, Duke University** Sex-Specific Differences in the Accumulation and Thyroid Disrupting Effects of Flame Retardants in the Placenta **Heather Patisaul, PhD, North Carolina State University** Endocrine Disruption of Sexually Dimorphic Neuroendocrine Pathways and Behaviors **Staci Bilbo, PhD, Harvard Medical School** Air Pollution and Maternal Stress produce male-biased adverse outcomes on immune function, stress, and non-reproductive behaviors
5:00 PM – 6:15 PM	**KEYNOTE LECTURE** *(Mercer)* **Nirao Shah, Ph.D., Stanford University** *Molecular and Neural Control of Sexually Dimorphic Behaviors*
6:15 PM – 8:15 PM	**OPENING RECEPTION and POSTER SESSION 1** *(Overlook West)*

TUESDAY, MAY 1

8:30 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*
7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*
8:30 AM – 10:15 AM **PARALLEL SESSIONS 5 and 6**	**SESSION 5** *(Mercer Salon I)* **Molecular Mechanisms of Sex-dependent Vulnerability to Stress** *Chairs: Kathleen E. Morrison, PhD, and Tracy L. Bale, PhD, University of Maryland School of Medicine* **Tanja Jovanovic, PhD, Emory University** Interactions Between ADCYAP1R1 Genotype and Estradiol in Increasing Vulnerability to PTSD **Kevin Bath, PhD, Brown University** Mouse model of sex differences in cognitive outcomes following early life stress **Georgia E. Hodes, PhD, Virginia Tech** Elucidating the contribution of sex differences in the peripheral immune system to stress susceptibility and depression **Kathleen E. Morrison, PhD, University of Maryland School of Medicine** Pubertal stress reprograms the periventricular nucleus and HPA axis responsiveness in a sex-specific manner
	SESSION 6 *(Mercer Salon G/H)* **Implications of Sex and Gender in Clinical Care** *Chair: Bruce Becker, MD, MPH, FACEP, Brown University* **Bruce Becker, MD, MPH, FACEP, Brown University** Women and Men in Pain - sex and gender differences in the presentation and treatment of pain from cradle to grave **Lauren Walter, MD, University of Alabama at Birmingham** Making Medical Education Sex-y: Incorporating Sex and Gender into Acute Care Medicine Curriculum for UME and GME learners **Charles R. Wira III, MD, Yale University** Sex and Gender considerations in the ED for neurovascular emergencies
10:15 PM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*
10:30 AM – 12:15 PM **PARALLEL SESSIONS 7 and 8**	**SESSION 7** *(Mercer Salon I)* **Hormonal Regulation of Behavior and Physiology Across Diverse Species** *Chair: Nirao Shah, PhD, Stanford University* **Deborah Kurrasch, PhD, University of Calgary** Role of hormones in zebrafish and mouse brain development: what does sex have to do with it? **Jing Wang, PhD, University of California, San Diego** Molecular mechanisms of sexually dimorphic sensory neurophysiology in *Drosophila*

TUESDAY, MAY 1

	Kim Huhman, PhD, Georgia State University Sex differences in hypothalamic, pituitary, and gonadal control of agonistic behavior in Syrian hamsters **Kim Wallen, PhD, Emory University** Sex differences in neural and cognitive responses to sexual stimuli: Possible modulation by androgens
	SESSION 8 *(Mercer Salon G/H)* ***In Silico* Models and Clinical Trials: Innovative Research and Sex and Gender Implications** *Chair: Marjorie Jenkins, MD, MEdHP, FACP, U.S. Food and Drug Administration* **Marjorie Jenkins, MD, MEdHP, FACP, U.S. Food and Drug Administration** In Silico Modeling and Virtual Clinical Trials: Opportunities for Advancing Sex Differences and Women's Health **Tina Morrison, PhD, U.S. Food and Drug Administration** Understanding the Potential for In Silico Methods to Advance the Study of Sex Differences **Wendy Wu, PhD, U.S. Food and Drug Administration** Research effort to develop sex-specific in silico models for assessing cardiac safety of new drugs **Aldo Badano, PhD, U.S. Food and Drug Administration** Considerations for using in silico clinical studies for the regulatory evaluation of new imaging products
12:15 PM – 1:30 PM	**WORKSHOP LUNCH** *(Mercer)* Aaron Wolen, Ph.D., Virginia Commonwealth University **Efficient and Reproducible Research:** **An Introduction to the Open Science Framework**
1:45 PM – 3:30 PM **PARALLEL SESSIONS 9 and 10**	**SESSION 9** *(Mercer Salon I)* **Nuclear Structure and Sex Differences** *Chairs: Christine Disteche, PhD, University of Washington, and Carolyn Brown, PhD, University of British Columbia* **Xinxian Deng, PhD, University of Washington** Orientation-dependent Dxz4 contacts shape the 3D structure of the inactive X chromosome **Schahram Akbarian, MD, PhD, Mount Sinai School of Medicine** Neuronal and non-neuronal chromosomal connectomes and epigenomes in adult male and female mouse and human cerebral cortex **Linda Zhou, University of Pennsylvania** 3D-genome reconfiguration in X-linked brain diseases **Andrew Lane, MD, PhD, Dana-Farber Cancer Institute** Why do men get more cancer? Escape from X Inactivation Tumor Suppressor (EXITS) genes in the sex bias of malignancy

TUESDAY, MAY 1

	SESSION 10 *(Mercer Salon G/H)* **Sex Differences in Cerebrovascular Disease: Epidemiology to Epigenetics** *Chairs: Louise McCullough, MD, PhD, UTHealth McGovern Medical School, and Mat Reeves, PhD, Michigan State University* **Virginia Howard, PhD, University of Alabama at Birmingham** What the numbers say: a comparative analysis of stroke epidemiology in women compared to men **Tracy Madsen, MD, Brown University** The Aftermath: Access to Rehabilitation and Sex differences in Stroke Recovery **Stacie Demel, DO, PhD, Michigan State University** Epigenetics and the Second X Chromosome: Back to the Basics of Sex Differences **Mollie McDermott, MD, MS, University of Michigan** Transgender Medicine and Ischemic Stroke
3:30 PM – 3:45 PM	**COFFEE BREAK** *(Mercer Prefunction)*
3:45 PM – 4:45 PM	**PANEL DISCUSSION** *(Mercer)* Moderator: Lise Eliot, Ph.D., Rosalind Franklin University **Sex Differences and the Google Memo** ***Panelists:*** Jill Becker, PhD, University of Michigan Lise Eliot, PhD, Rosalind Franklin University Margaret McCarthy, PhD, University of Maryland Deboleena Roy, PhD, Emory University
4:45 PM – 6:45 PM	**POSTER SESSION 2** *(Overlook West)*
7:00 PM	**TRAINEE SOCIAL** *(Foxtrot, 45 13th St. NE)*

WEDNESDAY, MAY 2

8:30 AM – 5:00 PM	**REGISTRATION** *(Mercer Prefunction)*
7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*
8:00 AM – 8:30 AM	**OSSD BUSINESS MTG** *(Mercer I)*
8:30 AM – 10:15 AM **PARALLEL SESSIONS 11 and 12**	**SESSION 11** *(Mercer Salon I)* **Sex Steroids, Puberty, and Adolescent Brain Development: A Translational Approach to Understanding Peak Vulnerability to Psychopathology in Adolescence** *Chairs: Marianne Seney, PhD, and Cecile Ladouceur, PhD, University of Pittsburgh* **Marianne Seney, PhD, University of Pittsburgh** Developmental origins of sex differences in adult mood **Cecile Ladouceur, PhD, University of Pittsburgh** Sex steroid influences on striatal activation to reward cues in adolescence **Cheryl Sisk, PhD, Michigan State University** Pubertal testosterone programs experience-dependent prefrontal FosB expression and social competence in adulthood **Monique Ernst, MD, PhD, NIMH** Pubertal maturation: intrinsic functional connectivity increased in boys, but decreased in girls, a risk for depression?
	SESSION 12 *(Mercer Salon G/H)* **Statistical Methodologies on Sex Chromosome Association** *Chair: Wei Xu, PhD, Princess Margaret Cancer Centre* **Wei Xu, PhD, Princess Margaret Cancer Centre** A unified partial likelihood approach for X-chromosome association on time to event outcomes **Lei Sun, PhD, University of Toronto** Statistical insights on the association analyses of X chromosome: X-inactivation, confounding, interaction and beyond **Stacey Winham, PhD, Mayo Clinic** An integrative approach to assess X-chromosome inactivation with applications to epithelial ovarian cancer **Osvaldo Espin-Garcia, University of Toronto** X-chromosome Association in Microbiome data
10:15 PM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*

WEDNESDAY, MAY 2

10:30 AM – 12:15 PM **PARALLEL SESSIONS 13 and 14**	**SESSION 13** *(Mercer Salon I)* **Sex Differences in Learning and Plasticity** *Chairs: Debra Bangasser, PhD, Temple University, and Nicola Grissom, PhD, University of Minnesota* **Debra Bangasser, PhD, Temple University** Sex differences in stress regulation of cognition Nicola Grissom, PhD, University of Minnesota **Mechanisms of female resilience to autism-associated genotypes** Erin Calipari, PhD, Vanderbilt University **Enhanced Dopaminergic Function During Estrus Drives Increased Addiction Vulnerability in Females** Mohamed Kabbaj, PhD, Florida State University **Sex differences in ketamine's antidepressant effects**
	SESSION 14 *(Mercer Salon G/H)* **Gender, Sex Hormones, and Lung Inflammation** *Chair: Patricia Silveyra, PhD, Penn State College of Medicine* **Patricia Silveyra, PhD, Penn State College of Medicine** Sex Differences in Lung Response to Environmental Agents **Y.S. Prakash, MD, PhD, Mayo Clinic** Sex Steroid Signaling in the Airway **Dawn Newcomb, PhD, Vanderbilt University** Sex, Gender, and Asthma **Nathalie Fuentes, Penn State College of Medicine** Circulating Sex Hormones as Critical Regulators of the Lung Immune Response
12:15 PM – 1:30 PM	**TRAINEE LUNCH** *(Ravinia)* – or, *enjoy Atlanta with lunch on your own*
1:45 PM – 3:30 PM **PARALLEL SESSIONS 15 and 16**	**SESSION 15** *(Mercer Salon I)* **Current Topics in Sex Differences Research I: Genetics and Neuroscience** *Chair: Douglas Portman, PhD, University of Rochester* **Erica Glasper, PhD, University of Maryland** Neonatal paternal deprivation and stress alter neuroendocrine responses in adult California mice (*Peromyscus californicus*) **Susan Sangha, PhD, Purdue University** Increased reward seeking and lack of conditioned inhibition of fear and fear extinction in female rats

WEDNESDAY, MAY 2

	Nora Engel, PhD, Temple University Vive la difference: zooming in on sex-specific differences in mouse embryonic stem cells **Kristen Pleil, PhD, Cornell University** Sex differences in the function of a limbic circuit driving alcohol drinking and anxiety
	SESSION 16 *(Mercer Salon G/H)* **Current Topics in Sex Diff. Research II: Immunology, Physiology, and Metabolism** *Chair: Adam Moeser, DVM MS PhD, Michigan State University* **Suresh Mishra, PhD, University of Manitoba** Prohibitin: An unexpected role in sex differences in adipose and immune functions **Benoit Chassaing, PhD, Georgia State University** Diet-mediated alterations of the intestinal microbiota: impact on inflammation and behavior **Kristen Zuloaga, PhD, Albany Medical College** Sex Differences in Metabolic, Vascular, and Cognitive Effects of a High Fat Diet **Katelyn Bruno, PhD, Mayo Clinic** Sex Differences in Vitamin D and Urinary Stone Disease **Annie Newell-Fugate, PhD, Texas A&M University** Sexually dimorphic effects of androgens on insulin signaling in white adipose tissue adipocytes
3:30 PM – 3:45 PM	**COFFEE BREAK** *(Mercer Prefunction)*
3:45 PM – 5:15 PM	**ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM** *(Mercer)* **Soumya Turaga, PhD student, Cleveland State University** *Junction adhesion molecule-A (JAM-A) deficiency drives sex-specific differences in glioblastoma progression via differential responses in the tumor microenvironment* **Jonathan VanRyzin, PhD student, University of Maryland School of Medicine** *Endocannabinoids program sex differences by inducing microglia phagoptosis of newborn cells in the neonatal rat amygdala* **Hilda Ahnstedt, PhD, Postdoc, UT Heath** *Sex differences in neutrophil-T cell Immune responses, gut integrity and outcome after ischemic stroke in aged mice* **Valeria Raparelli, PhD, Postdoc, Sapienza University of Rome** *Impact of sex and gender-related factors on percutaneous coronary intervention in patients with ischemic heart disease: analysis from the EVA study*
5:00 PM – 6:15 PM	**CAPSTONE LECTURE** *(Mercer)* **Londa Schiebinger, Ph.D., Stanford University** *Gendered Innovations in Health Research, Machine Learning, and Robotics*
6:15 PM – 8:15 PM	**AWARDS RECEPTION** *(Overlook West) – "Heavy hors d'oeuvres" will be served*

THURSDAY, MAY 3

7:30 AM – 8:30 AM	**BREAKFAST** *(Mercer Prefunction)*
8:30 AM – 10:15 AM **PARALLEL SESSIONS 17 and 18**	**SESSION 17** *(Mercer Salon I)* **Sex Differences in Pain from the Sensory Nerves to the Brain** *Chair: Dayna Loyd Averitt, PhD, Texas Woman's University* **Dayna Loyd Averitt, PhD, Texas Woman's University** The "Painful" Role of Peripheral Serotonin in Females **Greg Dussor, PhD, University of Texas at Dallas** CGRP and prolactin signaling in the meninges produces female-specific migraine-related behavior in rodents **Loren Martin, PhD, University of Toronto** Male-specific conditioned pain sensitivity in mice and humans **Arbi Nazarian, PhD, Western University of Health Sciences** Sexually dimorphic morphine antinociception in the sensory and affective components of pain in rats
	SESSION 18 *(Mercer Salon G/H)* **Defining and Measuring Sex and Gender in Clinical Research** *Chair: Louise Pilote, MD, MPH, PhD, FRCPC, McGill University and Rachel Dreyer, PhD, Yale University* **Londa Schiebinger, PhD, Standford University** Gender as a cultural variable across the lifespan **Valeria Raparelli, PhD, Sapienza University of Rome** European physicians' awareness of the difference between sex and gender: the IMAGINE survey **Louise Pilote, MD MPH PhD FRCPC, McGill University** Measuring Gender in a Cohort of Patients with Premature Acute Coronary Syndrome **Rachel Dreyer, PhD, Yale University** The VIRGO Cohort on Premature Acute Myocardial Infarction. Measuring Sex and Gender: Lessons Learned **Vera Regitz-Zagrosek, MD, PhD, Institute of Gender Medicine** Gender in coronary artery disease and gender in the aging population
10:15 PM – 10:30 AM	**COFFEE BREAK** *(Mercer Prefunction)*
10:30 AM – 12:15 PM **PARALLEL SESSIONS 19 and 20**	**SESSION 19** *(Mercer Salon I)* **Endocrine Disruptors: Sex Differences in their Effects During Development** *Chair: Janice Juraska, PhD, University of Illinois* **Janice Juraska, PhD, University of Illinois** Endocrine disruptor effects during early development and during adolescence on neural structure and cognitive behavior

THURSDAY, MAY 3

	Jodi Flaws, PhD, University of Illinois Sex differences in the effects of phthalate exposure on reproduction **Emilie Rissman, PhD, North Carolina State University** Paternal endocrine disruptor exposure influences behavior in offspring **Rita Strakovsky, PhD, Michigan State University** Sex-specific effects of developmental bisphenol A (BPA) exposure in rats on adiposity and adipose tissue microRNA (miR) expression
	SESSION 20 *(Mercer Salon G/H)* **Women and Alzheimer's Disease: A Scientific Update from the SWHR Interdisciplinary Panel on Alzheimer's Disease** *Chair: Pauline Maki, PhD, University of Illinois at Chicago* **Michelle M. Mielke, PhD, Mayo Clinic** Understanding sex differences in the prevalence, incidence, and risk factors of Alzheimer's disease **Kejal Kantarci, MD, MS, Mayo Clinic** What AD biomarker studies tell us about sex differences in AD **Pauline Maki, PhD, University of Illinois at Chicago** Women, Menopause, and AD: New insights into the intersection between reproductive aging and brain aging **MaryJo LaDu, PhD, University of Illinois at Chicago** Modeling the effect of sex on APOE4-induced AD Risk in transgenic mice
12:15 PM – 12:30 PM	**CLOSING REMARKS** *(Mercer)*

END OF MEETING

Join us next year for the
2nd Joint OSSD/IGM Meeting
Washington Marriott Georgetown
Washington, DC
May 5–8, 2019

12:30 PM – 3:00 PM	**OSSD COUNCIL MEETING** *(Ravinia)*

Speaker Abstracts

Monday, April 30

1:00 PM – 2:45 PM: SESSION 1 *(Mercer Salon I)*

Sex Differences at the Electrophysiological Level: A Focus on the Limbic System *Chair: Lisa Briand, PhD, Temple University*

Lisa Briand, PhD, Temple University
Sex differences in nucleus accubmens inputs: Basal differences and influence of stress exposure

Adolescent social stress puts individuals at increased risk for multiple psychiatric diseases including substance use disorders. However, little is known about how adolescent social isolation alters to brain to make an individual more vulnerable to addiction. The nucleus accumbens plays a central role in the development and expression of addictive behaviors and is influenced by stress exposure. The current studies utilized an adolescent isolation stress model that elicits an increase motivation for cocaine in adulthood to examine the effects of stress on accumbal physiology in both male and female mice. Along with stress-induced alterations, we discovered a number of sex differences that have not been previously described. While female mice exhibit less paired-pulse facilitation than male mice at baseline, adolescent social stress elicits a decrease in facilitation in both male and female mice. As paired-pulse facilitation effects are thought to be mediated by presynaptic alterations, we examined the effect of adolescent social isolation on three inputs to the nucleus accumbens: projections from the prefrontal cortex (PFC), ventral hippocampus (vHIPP) and basolateral amygdala (BLA). Adolescent social isolation decreases paired pulse responses elicited by optical stimulation of both the PFC and vHIPP inputs in female mice. In contrast, male mice exhibit an increase in paired pulse responses elicited by optical stimulation of the PFC and BLA inputs to the accumbens. Furthermore, baseline sex differences in responses following optical stimulation exist. Taken together, we have demonstrated baseline sex differences in presynaptic inputs to the nucleus accumbens. Furthermore, adolescent social isolation influences these inputs in a sex-specific manner. Further work is needed to determine the role of these differences in behavior.

John Meitzen, PhD, North Carolina State University
Sex differences in medium spiny neuron electrophysiological properties: heterogeneity across striatal regions and evidence for estradiol-dependent sexual differentiation

Sex and steroid sex hormones influence how the brain regulates motivated behavior, reward, and sensorimotor function in both normal and pathological contexts. Investigations into the underlying neural mechanisms have targeted the striatal brain regions, including the caudate-putamen, nucleus accumbens core and shell. The output neurons of the striatal regions, the medium spiny neurons (MSNs), exhibit sex differences in electrophysiological properties. Here I will discuss sex differences in rat MSN electrophysiological properties across striatal regions, including evidence for estradiol-mediated sexual differentiation and estrous cycle sensitivity. Importantly, the electrophysiological properties sensitive to sex differ between striatal regions. Thus, despite possessing the same neuron type, striatal regions exhibit heterogeneity in the nature of sex differences in MSN electrophysiological properties. This not only contributes to the sex differences observed in striatal function but highlights the complex and localized nature of sex differences in overall brain function.

Dean Kirson, PhD, The Scripps Research Institute
Sex differences in oxytocin effects on CeA GABAergic signaling in alcohol-dependent and naive rats.

Alcohol use disorders (AUD) are significant public health concerns, characterized by compulsive seeking and consumption of alcohol. AUD have been linked to disruption of brain stress systems, as the transition to dependence recruits these systems leading to the negative affective states seen in withdrawal; the relief of which drives further drinking. The central amygdala (CeA) is an increasingly important brain region as it serves as a neuropeptidergic hub of stress and anxiety processing, and GABA signaling in the CeA is involved in the regulation of alcohol consumption. Both AUD and stress/anxiety disorders have been found to exhibit sex-specific differences among the population. Women are more likely to have an anxiety or mood disorder than men, and men are more likely to abuse alcohol than women. However, women develop addiction more quickly, and are more likely to relapse into repetitive drug use. Oxytocin is a neuropeptide released in response to stress, that has many sexually dimorphic effects in various rodent models. Oxytocin has previously been shown to alter GABA signaling in the CeA of rodents, and administration of oxytocin decreases drinking and blocks alcohol withdrawal symptoms in humans and rodents. However, the mechanism by which oxytocin affects alcohol drinking has not been characterized. We examined the electrophysiological effects of oxytocin and ethanol on CeA GABAergic signaling in both alcohol naïve and chronic intermittent ethanol vapor treated (alcohol dependent) Sprague-Dawley male and female rats. We also used immunohistochemical staining to identify ethanol dependence induced changes in oxytocin expression in male and female rats. We find sexually dimorphic effects of oxytocin on CeA GABA signaling in both naïve and dependent rats as well as sexually dimorphic interactions of oxytocin with ethanol. This research highlights the potential role of oxytocin in the development of targeted therapeutics for the effective treatment of AUD.

Helen Scharfman, PhD, Nathan Kline Institute for Psychiatric Research
Electrophysiological analyses complement and extend the understanding of female and male hippocampus

This presentation will highlight how electrophysiology in hippocampal slices sheds light on sex differences in hippocampus. Area CA3 pyramidal cells and their input from the dentate gyrus, the mossy fiber (MF) pathway, will be a focus. In adult female rats, the neurotrophin brain-derived neurotrophic factor (BDNF) increases in the MFs when serum levels of estradiol are elevated during the estrous cycle. In contrast, ovariectomized females and males exhibit relatively low levels of BDNF protein in the MFs. The functional implications of these sex differences were examined in rat hippocampal slices by recordings of MF synaptic transmission and long-term potentiation (MF LTP). In comparisons of adult females and males, the threshold for MF LTP was correlated with the expression of MF BDNF protein such that MF LTP threshold was low for the proestrous female rats and they had high MF BDNF protein levels. For adult males, there were relatively low levels of MF BDNF protein and MF LTP was rarely elicited. In female rats on diestrus, MF BDNF levels were low and LTP was weak. Interestingly, in male gonadectomized rats the levels of MF BDNF protein rose and MF LTP was increased. MF transmission and MF LTP became sensitive to the BDNF receptor TrkB. These data suggest the intriguing idea that in the adult rat, estrogens increase BDNF and MF LTP in females whereas androgens normally keep MF BDNF expression and MF LTP suppressed in males. Further recordings in the male rat suggest their normal lack of long-term MF plasticity may be compensated by strong individual responses to MF stimuli and strong short-term plasticity. In addition, their normal low levels of MF plasticity may protect them from the hyperexcitability, which was common in proestrous female slices. The results suggest the male has less plasticity but protection from hyperexcitability, whereas the female has heightened plasticity but with the risk of seizure susceptibility.

1:00 PM – 2:45 PM: SESSION 2 *(Mercer Salon G/H)*

Sex Differences in the Pathogenesis of Infectious Diseases *Chairs: Andrew Pekosz, PhD, Johns Hopkins Bloomberg School of Public Health and Sabra Klein, PhD, Johns Hopkins Bloomberg School of Public Health*

Theresa Chang, PhD, Rutgers University
Sex differences in innate immune and microbial response and disease progression in simian HIV- infected rhesus macaques

Sex differences in immune response and disease progression in HIV-infected individuals have been reported but the underlying mechanism remains unclear, in part due to the lack of relevant animal models. We studied mucosal immune and microbial attributes that impact sex disparity in HIV disease progression in a novel nonhuman primate (NHP) model. Rhesus macaques were infected intrarectally with lineage-related subtype C R5 SHIVs. We found that SHIV-infected female rhesus macaques progressed faster to AIDS than males, recapitulating the sex bias in HIV-1 disease in humans. While there were no significant differences in the levels of soluble immune mediators in the rectal mucosa of naïve female and male macaques, there were sex-based differences in rectal gene profiles at the baseline. Analysis of the level of immune mediators longitudinally in infected macaques indicated that the females mounted an earlier and more robust proinflammatory skewed rectal immune response to infection. Moreover, expansion of *Proteobacteria* that increase in other intestinal inflammatory disorders was more pronounced in the rectal mucosa of female than male macaques during acute infection. Expression of genes associated with IFN signaling and IL-22 networks was significantly enriched in the rectal mucosa in infected females but not males. Additionally, there were sex-based differences in expression of genes involved in epithelial remodeling and tight junction as well as in type I IFN pathways in jejunum tissues of SHIV-infected animals at 2 weeks after infection. Our findings indicate that sex differences in innate immune activation and shifts in the gut microbiota could be the drivers of increased disease susceptibility in females. Further studies with this NHP model of HIV infection could lead to innovative research on gender differences, which may have important therapeutic implications for sex-based disease control.

Christopher Robinson, PhD, Indiana University
Sex differences in enteric virus infection

Enteric viruses initiate infection in the complex environment of the mammalian gastrointestinal tract. Intestinal factors that influence enteric viral replication, however, remain unclear. Previously, we developed an oral inoculation model to study intestinal replication of coxsackievirus B3 (CVB3), an enteric virus from the *Picornaviridae* family. Following oral inoculation, we found that male mice supported robust intestinal CVB3 replication and succumbed to CVB3-induced disease, whereas female mice did not. These results mirror the sex bias in CVB3 disease in humans. However, the mechanism for sex-dependent replication in the intestine remains unknown. We hypothesize that sex hormones influence CVB3 replication in the intestine. To investigate this hypothesis, we examined CVB3 replication in castrated and ovariectomized mice. Following oral inoculation, we found that castration of male mice protected against CVB3-induced pathogenesis and significantly reduced CVB3 shedding. Furthermore, while ovariectomy did not enhance CVB3 pathogenesis, ovariectomized female mice shed significantly more CVB3 than surgery-control female mice. Next, we investigated if the estrous cycle in female mice could influence intestinal replication and pathogenesis. We orally inoculated female mice during each of the four stages of the estrous cycle and measured fecal shedding and survival. We found that female mice inoculated during the estrus and proestrus stages shed more CVB3 in the feces than female mice inoculated during metestrus and diestrus. Additionally, female mice inoculated during estrus and proestrus succumbed to CVB3-induced pathogenesis. Overall, these data indicate that sex hormones can influence CVB3 replication in the intestine.

DeLisa Fairweather, PhD, Mayo Clinic
Sex differences in viral-induced myocarditis

Myocarditis is an autoimmune disease that is an important cause of acute and chronic heart failure. Many infectious agents are known to cause myocarditis including viruses, bacteria, and parasites. Infectious causes of myocarditis like Coxsackie B viruses (CVB), CMV, and HIV also cause rheumatic autoimmune diseases and drive the production of rheumatoid factor, an autoantibody directed against other antibodies that leads to immune complex formation. Myocarditis occurs more often in men while rheumatic autoimmune diseases occur more often in women. My lab developed an autoimmune mouse model of myocarditis that closely resembles the disease timecourse and pathology of human disease. Both male and female mice clear virus effectively, but cardiac inflammation is more severe in males who develop fibrosis and progress to dilated cardiomyopathy and chronic heart failure. Men with myocarditis also progress to dilated cardiomyopathy more often than women, have worse recovery, and have an increased need for transplantation compared to women. We found that men with a diagnosis of clinically suspected myocarditis (*n*=328) had significantly higher sera levels of the heart failure biomarker sST2 than women, but only men under age 50. In contrast, sST2 levels were increased in women with myocarditis that were over 50 years of age. Sera sST2 was also significantly higher in male mice with CVB3 myocarditis where levels associated with poor heart function. Gonadectomy with hormone replacement showed that testosterone, but not 17β-estradiol, increased sera sST2 levels in males. Our data emphasize the importance of analyzing inflammatory biomarkers like sST2 according to sex and age.

Cory Tuescher, PhD, University of Vermont
Genome-wide physical mapping identifies genetic elements contributing to sex differences in susceptibility to IAV infection

Seasonal infection with influenza A virus (IAV) is a significant threat to human health. IAV infects ~15% of the world's population annually, resulting in ~1 million deaths each year. Epidemiological evidence from both seasonal outbreaks and pandemics suggests significant sex difference in morbidity and mortality, and provide strong evidence for host genetics as a risk factor in disease susceptibility. Studies in mice have, in general, confirmed the existence of both sex differences and the role of host genetics in IAV susceptibility. For example, genetic studies in the mouse, lead to the identification of *Mx1* (Mx GTPase-1), a type I and III IFN-induced gene with direct IAV activity that is the major determinant of resistance to IAV. In this regard, classical inbred laboratory strains of mice express nonfunctional *Mx1* alleles and are therefore highly susceptible to IAV infection. In contrast, functional *Mx1* alleles segregate among inbred wild-derived strains of mice making them resistant or less susceptible to IAV infection. Additionally, the degree of genetic diversity of inbred wild-derived strains of mice, such as PWD/PhJ (PWD), more accurately models that seen across human populations. Taken together, this suggests that incorporating wild-derived inbred PWD mice into studies on IAV susceptibility may provide novel insight into the genetic control of sex differences associated with IAV infection. Toward this end we are performing genome-wide physical mapping using B6-Chr^{PWD} consomic and conplastic strains of mice, which cover all 19 autosomes, X and Y Chrs, and mitochondrial genome, to identify genetic elements controlling sex differences in susceptibility to IAV.

3:00 PM – 4:45 PM: SESSION 3 *(Mercer Salon I)*

Neurocircuitry and Neuroplasticity over the Lifespan: Sex-specific Trajectories Mean Timing is Everything *Chair: Heather Brenhouse, PhD, Northeastern University*

Jennifer Honeycutt, PhD, Northeastern University
Too much, too young? Sex-specific differences in corticolimbic innervation following early life stress

Early life experiences significantly shape the behavioral and neural trajectory of an organism across development. As such, disruptions during early developmental periods set the course for aberrant brain maturation, which can also be seen in parallel behavioral changes. Indeed, children who have experienced early adversity often exhibit deleterious effects that manifest as maladaptive behaviors, cognitive impairment, and/or increased susceptibility to mental illness, particularly later in development. Increasing evidence in humans with a history of adversity points to a role of atypical corticolimbic circuit development, leading to changes in functional connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC). In rodent models of early adversity via maternal separation (MS) during the postnatal period, comparable neural and behavioral phenotypes are observed, including loss of PFC inhibitory tone and increased anxiety-like behaviors. The neural mechanisms underlying these findings following MS remain unknown, though it is likely that dysfunction is in part driven by precocial BLA innervation of the PFC. To determine the impact of sex and MS on this circuitry, targeted anterograde tracer microinjections into the BLA were performed at key developmental milestones spanning juvenility and adulthood. Labeled axonal fibers from BLA-PFC projecting neurons were quantified within the PFC. We present novel data indicating that MS drives increased BLA innervation of the PFC in a sex- and age-dependent manner, such that juvenile MS female innervation patterns resemble that of their adult control counterparts. This suggests a critical role for early experiences on corticolimbic development and provides putative mechanistic insight into the underlying etiology of adversity-induced vulnerability and resilience.

Q.D. Walker, PhD, Duke University
Neurocircuitry underlying sex differences in eating disorders

Anorexia Nervosa is the leading cause of mortality due to psychiatric causes. No current animal model captures the key characteristics of visceral hypersensitivity, learned food avoidance, adolescent onset and female dominance. The present study used a learned food aversion task to examine these characteristics which could contribute to an understanding of neural mechanisms of eating disorders. Adolescent and adult male and female rats (PN 28-30 or PN 60-62) were habituated with a novel cereal (Cheerios, Ch). They received a novel food (Froot Loops, FL) 24 hours later followed by saline or LiCl (19 mg/kg). Pica was quantitated as a measure of nausea. Rats were allowed to eat FL or another novel cereal, Apple Jacks (AJ) 24 hours after LiCl and cereal intakes (g/kg bw) were quantitated. A separate cohort of animals received saline or LiCl (38 mg/kg) and brains were taken for quantitation of C-fos to assess neuronal activation by LiCl. Results were analyzed by 3 way ANOVA (age x sex x treatment) using NCSS. All experiments were approved by the Duke University IACUC and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals. LiCl caused pica in all groups but most in adult males. All animals showed CFA to FL, but adult males and adolescent females showed most CFA. CFA generalized to a novel food not previously paired with LiCl only in adult females. LiCl induced c-Fos in PVN of the hypothalamus, basolateral amygdala (BLA), insula and prefrontal cortex (PFC). It did so equally in all groups in PVN. In BLA and insula, adults showed more labeling than adolescents, and females exhibited the most labeling. PFC labeling showed the greatest concordance with CFA data: adolescent and adult females showed comparable labeling, while adolescent males showed less. In summary this model demonstrated onset during adolescence, female dominance and conditioned food avoidance. The most robust sex and developmental difference observed was that adult females generalized to foods not previously associated with LiCl. The c-Fos pattern in PFC correlated best with CFA findings, both insula and BLA showed developmental changes. This study suggests that maturation of neural circuits that organize responses to aversive stimuli could play a role in the appearance of food-avoiding eating disorders during adolescence in humans.

Rebecca Shansky, PhD, Northeastern University
Experience dependent structural plasticity: interactions of circuit and sex

The perception of control during a traumatic event can promote resilience against future stress challenges, but the long-term cellular and circuit mechanisms by which this protection is conferred have not been identified. Clinical outcomes after stress exposure differ in men and women, and therefore it is especially important in preclinical research to dissect these processes in both males and females. The "escapable stress" (ES) paradigm, in which experimentally yoked rats either do (ES) or do not ("inescapable stress," IS) have the ability to terminate a tail shock, is a well-established model in which to study the protective effects of stress controllability against future IS exposure, known as behavioral immunization. Past work in male rats has shown that behavioral immunization is mediated by neural projections from the prelimbic area (PL) of the prefrontal cortex to the dorsal raphe nucleus (DRN), and therefore it follows that this circuit might undergo a unique pattern of plasticity in response to ES. Here, we observed behavioral immunization in male rats only, suggesting that stress controllability does not confer protection from IS-related deficits in females. In addition, we also found sex differences in ES- and IS-induced structural plasticity. In males, IS elicited broad, non-specific alterations in PL spine size, while ES elicited PL-DRN circuit-specific spine changes. In contrast, females exhibited broad, non-specific spine enlargement after ES but only minor alterations after IS. Together, these data provide evidence for a circuit-specific mechanism of structural plasticity that could underlie sexual divergence in the protective effects of stress controllability.

Pavel Osten, PhD, Cold Spring Harbor Laboratory
Brain-wide maps reveal stereotyped cell-type-based cortical architecture and subcortical sexual dimorphism

All topics in neuroscience are informed by knowledge of brain cell type anatomy. The distribution and ratios of individual neuronal and glia cell types across the whole brain and the wiring of neuronal cell types into local and long-range circuits underlie the vast diversity of mammalian behaviors, from the simple startle response of defensive behaviors to the complex neuronal computations during cognitive and emotive processing. Here I will describe our work on systematic atlasing of cell-type distribution and morphology in C57BL/6 female and male mouse brain, including establishing novel microscopy methods for rapid imaging of mouse brains at high spatial resolution, computational methods for mapping cell-type distribution and tracing cellular morphologies, computational methods for registering the whole-brain datasets onto the Allen Common Coordinate Framework (CCF) for postnatal day 56 (P56) mouse brain, statistical methods for rigorous analyses of the generated data, and neuroinformatics methods and an online web portal for integrating and disseminating the whole-brain cell type-based anatomical data.

3:00 PM – 4:45 PM: SESSION 4 *(Mercer Salon G/H)*

Sex-specific Outcomes of Environmental Chemical Exposures *Chair: John Meitzen, PhD, North Carolina State University*

Emily Barrett, PhD, Rutgers University
Prenatal exposure to endocrine disrupting chemicals, sex, and neurodevelopment

Exposure to endocrine disrupting chemicals (EDCs) is nearly ubiquitous in the modern world. Many of these chemicals, like phthalates and Bisphenol A (BPA), act on sex steroid and thyroid pathways. They may alter maternal, placental, and/or fetal hormone production, ultimately changing the fetus' endocrine environment. Because thyroid and sex steroid hormones are critical for brain development, in utero EDC exposure may result in long-lasting changes in neurodevelopment. Increasingly, the epidemiological evidence suggests that the effects of EDCs on neurodevelopment differ by sex, with boys typically (but not always) showing greater impairments. In this talk, we discuss findings from several pregnancy cohort studies that measured EDCs in maternal biospecimens collected

during pregnancy and followed the resulting offspring into early-mid childhood to assess neurodevelopment. For example, we have demonstrated that greater BPA exposure in mid-late gestation is associated with problem behaviors (including externalizing behaviors and conduct disorders) in school-age boys, but not girls. Similarly, higher prenatal phthalate metabolite levels were associated with oppositional behavior and conduct problems in boys, but not girls. Results from the same cohort suggest that higher prenatal phthalate exposure is also associated with less masculine play behavior in childhood. More recent findings in two large cohorts suggest that among preschool age boys (but not girls) exposure to certain phthalates in early gestation is associated with language delays. We discuss challenges and limitations of the current work in this field as well as new directions that will help us to better understand how these widespread exposures impact children's neurodevelopment.

Heather Stapleton, PhD, Duke University
Sex-Specific Differences in the Accumulation and Thyroid Disrupting Effects of Flame Retardants in the Placenta

Brominated flame retardants (BFRs) are ubiquitous, persistent contaminants that have been shown to accumulate in human tissues and pass from mom to the fetus through the placenta. One class of BFRs, the polybrominated diphenyl ethers (PBDEs), have a chemical structure that is very similar to endogenous thyroid hormones (THs), and numerous laboratories studies have demonstrated that PBDEs can interfere with thyroid hormone regulation through a variety of different mechanisms. In our previous research, we found that BFRs, including PBDEs, accumulated to significantly higher levels in placenta associated with male infants compared to female infants, despite no differences in maternal serum levels by fetal sex. We also analyzed TH levels in human placental tissues and found that levels were associated with BFRs in placentas in a sex-specific manner. These observations suggest that transporters within the placenta may be facilitating the transfer of BFRs in a sex-specific manner, which may subsequently affect important biological functions of the placenta (e.g. hormone transfer). Here we present and discuss our follow-up studies investigating the transfer of BFRs through the placenta using the Wistar rat as a model and investigating effects on thyroid transporter gene expression in the placenta and fetal growth. This research has significant implications for understanding the full impact of contaminant exposures on placenta function and fetal growth and development. Given that epidemiological studies have observed significant associations between prenatal exposure to BFRs and low birth weight in infants and neurodevelopmental deficits in children, it is critical that these potential mechanisms of action be fully evaluated.

Heather Patisaul, PhD, North Carolina State University
Endocrine Disruption of Sexually Dimorphic Neuroendocrine Pathways and Behaviors

Using a wide variety of rodent species, we have repeatedly shown that developmental exposure to endocrine disrupting chemicals (EDCs), specifically, fire retardants and the plastics component Bisphenol A (BPA), results in a spectrum of neural effects including the loss of behavioral and morphological sexual dimorphisms. Because hormones play such a critical role in sexual differentiation, the brain is particularly vulnerable to EDC exposure, especially during gestation and early life while circuits critical for sexual, social and other complex behaviors are still forming. The myriad of mechanisms by which this disruption occurs, however, remains incompletely understood. Ongoing work in our lab indicates that the placenta may be a critically important but underappreciated target of endocrine disruption, and that sex specific bioaccumulation and disruption of placental function may underlie later in life neural outcomes. Here we focus on Firemaster® 550 (FM 550), a flame retardant mixture applied to foam-based furniture and baby products that has become a ubiquitous contaminant in the home. FM 550 contains two brominated compounds and a mix of organophosphates. We have found that FM 550 is endocrine disrupting, and perinatal exposure can have sex specific effects on exploratory and anxiety-like behavior in rats. We have also found evidence of sex-specific placental FM 550 accumulation and disruption. Ongoing work is revealing that alteration of placental neurotransmitter production could be a mechanism by which FM550 alters neural development and behavior.

Staci Bilbo, PhD, Harvard Medical School
Air Pollution and Maternal Stress produce male-biased adverse outcomes on immune function, stress, and non-reproductive behaviors

The immune system is our interface with the environment, and immune molecules such as cytokines and chemokines and the cells that produce them within the brain, notably microglia, are critical for normal brain development. This recognition has in recent years led to the working hypothesis that inflammatory events during pregnancy or the early postnatal period, e.g. in response to infection, may disrupt the normal developmental trajectory of microglia and consequently their interactions with neurons, thereby contributing to the risk for neurological disorders such as autism spectrum disorder (ASD). This talk will discuss recent findings on the impact of diverse, pervasive environmental challenges, beyond infection, including chemical (e.g. toxins,) and non-chemical social stressors (e.g. maternal stress), and their impact on microglial development and its broad implications for neural pathologies. Moreover, it will emphasize sex differences in microglial development which may underlie the profound sex bias in disorders such as ASD.

KEYNOTE LECTURE *(Mercer)* **Nirao Shah, Ph.D., Stanford University** *Molecular and Neural Control of Sexually Dimorphic Behaviors*
All sexually reproducing animals exhibit instinctual displays of sexually dimorphic behaviors such as mating or territoriality that are sensitive to social context and experience. What neural mechanisms encode such developmentally wired behaviors that are nevertheless modifiable by experience? What mechanisms control longer term changes in behavior such as social attachments? My lab uses mice, flies, and prairie voles to address these questions. Despite their fundamental importance to social interactions in health and psychiatric disorders, the molecular and neural mechanisms underlying sex differences in behaviors remain mysterious. To tackle this long-standing problem, we leverage the fact that sex hormones regulate sexual differentiation of the brain during development and adulthood to control sex-typical behaviors. Thus, identifying sex hormone-responsive neurons and genes should allow us to access the underlying mechanisms. We have used this strategy and developed sensitive genetic reagents to make significant discoveries about how sex hormones regulate neural circuits controlling sex-typical behaviors. We have built upon these findings to identify and link sex hormone-responsive genes and neural pathways to specific sexually dimorphic behaviors. These studies underscore the profound role of gene networks and developmental patterning in controlling the instinctual displays of these social interactions. I will present our findings related to these research directions and also discuss ongoing work on how these can behaviors are profoundly modulated by state-dependent mechanisms.

TUESDAY, MAY 1

8:30 AM – 10:15 AM: SESSION 5 *(Mercer Salon I)*

Molecular Mechanisms of Sex-dependent Vulnerability to Stress *Chairs: Kathleen E. Morrison, PhD, and Tracy L. Bale, PhD, University of Maryland School of Medicine*

Tanja Jovanovic, PhD, Emory University
Interactions Between ADCYAP1R1 Genotype and Estradiol in Increasing Vulnerability to PTSD

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric illness whose prevalence in women is more than twice the rate as men. In addition to higher prevalence rates, women may present with a different symptom profile or be susceptible to sociocultural biases that increase risk; however, there is substantial evidence suggesting that there may be biological underpinnings for the impact of sex on PTSD. Neurobiological phenotypes associated with

vulnerability for PTSD, such as deficits in fear extinction and amygdala over-activation to fearful stimuli, are linked with genotype and sex. Our work with a single nucleotide polymorphism (SNP) in the *ADCYAP1R1* gene, rs2267735, which is located in an estrogen response element, showed that the risk genotype (CC) was associated with increased fear generalization in startle experiments and heightened amygdala response using functional MRI. This same SNP is associated with increased PTSD symptoms in women but not men. These data suggest female-specific genetic risk for biomarkers of fear and anxiety in PTSD. Our research examining fear-potentiated startle in adult women has shown an interaction between estradiol and PTSD diagnosis, such that those with low estradiol and PTSD have deficits in fear extinction. In this study, higher levels of estrogen normalized extinction. These findings are particularly important given that anxiety disorders tend to emerge around puberty, when sex organs begin to release hormones that have effects on brain activity.

Kevin Bath, PhD, Brown University
Mouse model of sex differences in cognitive outcomes following early life stress

Poverty, displacement, and parental stress represent some of the most common and potent sources of early life stress (ELS). Such stress disproportionately impacts females, who are at increased risk for stress-related pathologies that are highly comorbid with cognitive impairment. The mechanisms underlying stress-associated cognitive impairment and enhanced risk of females to stress-associated disorders remain unknown. In a mouse model, we found that ELS is associated with impaired rule reversal learning on an attention task in females, but not males. Impaired performance was associated with decreased expression and density of parvalbumin- (PV) expressing interneurons in orbitofrontal cortex (OFC), but not other common subtypes of interneurons. Optogenetic silencing of PV interneuron activity in the OFC of healthy control mice phenocopied reversal learning deficits observed in ELS female mice. Localization of reversal learning deficits to PV cells in OFC was confirmed by additional optogenetic studies in which neurons of the medial prefrontal cortex (mPFC) were silenced and associated with select deficits in rule shift learning. These sex-, cell type- and region-specific effects show that alterations in PV cell development can be a major driver of sex differences in cognitive dysfunction.

Georgia E. Hodes, PhD, Virginia Tech
Elucidating the contribution of sex differences in the peripheral immune system to stress susceptibility and depression

There is a bi-directional relationship between the immune system and major depressive disorder (MDD). Autoimmune diseases and MDD are more common in women than men. Little is known about mechanisms contributing to the higher incidence of inflammatory and stress related illness in females. Here, we compare sex differences in cytokine profiles for humans with MDD to a stress-based animal model. Serum was sampled from pre-menopausal women and age matched men with a diagnosis of MDD or healthy controls. Cytokine protein levels were detected using multiplex enzyme-linked immunosorbent assays. Sex differences were examined by group effects and by correlation to quick inventory of depressive symptomology (QIDS) scores. In mice, subjects were given a 6- or 28-day course of variable stress. Following 6 days of stress female, but not male mice, express behavior across a test battery that is associated with human symptoms of depression. Both males and females engage in stress susceptible behavior following 28 days of variable stress. In mice, blood was sampled immediately after final stress exposure, one day prior to behavioral testing, in order to examine cytokine levels and behavior in the same subjects. In both humans and mice, we determined that the overall pattern of peripheral cytokine expression in response to MDD/stress was different between the sexes. In humans, women had a more exaggerated immune response to MDD even when cytokines were regulated in the same direction. When male and female data were analyzed separately, 12 cytokines were significantly regulated by depression in women and only 2 were significantly regulated in men. In depressed patients we found that IL-17a and MCP-1 significantly correlated with QIDS scores. Animal studies are ongoing and data that corresponds with human patterns of cytokine expression will be discussed. Overall, these data indicate that women demonstrate a stronger inflammatory dysregulation in response to depression.

Kathleen E. Morrison, PhD, University of Maryland School of Medicine
Pubertal stress reprograms the periventricular nucleus and HPA axis responsiveness in a sex- specific manner

Adverse childhood experiences are one of the greatest predictors for affective disorder presentation for women. As the puberty transition is marked by hormonal changes and ensuing reorganization of the brain and periphery, it may represent a window of vulnerability for adversity to result in long-term programming. Periods of hormonal flux in the female lifespan, including pregnancy, exacerbate the risk for affective disturbances and promote hypothalamic-pituitary-adrenal (HPA) axis dysregulation, a key feature of affective disorders. However, little is understood as to how stress experienced during the pubertal transition alters ongoing brain maturation and its interaction with later-life events, such as pregnancy. We have established a translationally relevant mouse model in which pubertal stress results in a blunted corticosterone response to acute restraint stress only during pregnancy in females, but produces no effect in males. This suggests that HPA programming by pubertal stress in females intersects with the state of pregnancy to expose dysregulation. RNA-Seq analysis of the paraventricular nucleus of the hypothalamus (PVN) during pregnancy implicated stress-induced alterations in the GABA system. As the GABA system is critical in regulating PVN responsiveness and is modulated by allopregnanolone, we hypothesized that the rise in allopregnanolone during pregnancy is responsible for eliciting the HPA axis dysregulation. Pharmacological studies show that allopregnanolone is both necessary to produce the blunted HPA axis response in stressed females and sufficient to recapitulate the blunted HPA axis response in stressed males. Further studies suggest that allopregnanolone is acting via the GABA-A receptor in the PVN. Together, these studies provide novel insight into the mechanisms underlying female-relevant risk factors for stress dysregulation, a central endophenotype of affective disorders.

8:30 AM – 10:15 AM: SESSION 6 *(Mercer Salon G/H)*

Implications of Sex and Gender in Clinical Care *Chair: Bruce Becker, MD, MPH, FACEP, Brown University*

Bruce Becker, MD, MPH, FACEP, Brown University
Women and Men in Pain - sex and gender differences in the presentation and treatment of pain from cradle to grave

Abstract unavailable at time of printing

Lauren Walter, MD, University of Alabama at Birmingham
Making Medical Education Sex-y: Incorporating Sex and Gender into Acute Care Medicine Currciulum for UME and GME learners

The past several decades have resulted in a burgeoning amount of research and advances in sex- and gender-based medicine. With specific regard to acute care and emergency medicine, these advances allow the modern physician to personalize their patient approach and often impact outcome in a lifesaving way. The clinical practice of emergency medicine now demands that we consistently include the application of this evidence-based sex and gender knowledge into bedside practice, considering both a patient's sex as well as their gender as independent variables that may affect a patient's presentation, management, and outcome. Unfortunately, however, standard undergraduate medical (UME) and graduate medical (GME) education models in the U.S. have not yet caught up with the emerging yet important topic of Sex- and Gender-based Medicine (SGBM). This critical gap in medical education, well documented by nationwide medical trainee surveys (Jenkins MR, et al. 2015; Kling JM, et al. 2016) and medical school curricular audits (Miller VM, et al. 2013), results in suboptimal medical training which may ultimately negatively impact patient care. Despite the obvious challenges of curricular change however, ready tools and resources are already available to assist in SGBM integration and ease its incorporation. The training of our future

physicians must evolve to reflect the advancing scientific evidence. These educational 'tools' and resources can the help bridge the curricular gap affecting SGBM, across all medical specialties, including emergency medicine, resulting in real-time personalized healthcare for all.

Charles R. Wira III, MD, Yale University
Sex and Gender considerations in the ED for neurovascular emergencies

Neurovascular emergencies constitute a large number of acute emergency medicine visits (>700,000 per year) and stroke is the 5th leading cause of death in America. Sex- and Gender-specific differences and considerations exist and will be summarized in the pre-hospital and acute phase of care. Additional considerations exist for monitoring risk and managing neurovascular events in pregnancy and the post-partum phase. Implications for changing the clinical practice of Emergency Medicine will be covered as well as a discussion of future Sex- and Gender-based research priorities aimed at improving stroke systems of care.

10:30 AM – 12:15 PM: SESSION 7 *(Mercer Salon I)*

Hormonal Regulation of Behavior and Physiology Across Diverse Species *Chair: Nirao Shah, PhD, Stanford University*

Deborah Kurrasch, PhD, University of Calgary
Role of hormones in zebrafish and mouse brain development: what does sex have to do with it?

Neural progenitor cells (NPCs) of both zebrafish and mice express hormone receptors such as ER and AR during embryonic development, suggesting that hormone signaling plays a key role in early brain formation. Curiously, the expression these receptors in NPCs occur at a timepoint prior to when the gonads have matured to synthesize/secrete sex hormones. This gap in timing raises the intriguing notion that neural progenitors themselves synthesize their own estrogen (and likely testosterone) locally that then mediates specific neurodevelopmental programs. To understand the functional role of sex steroid during embryonic neural development, we employ zebrafish, mice, and isolated NPCs as model systems. First, we asked if exogenous exposure to sex hormones alone and in combination during embryonic development in zebrafish affected overall brain formation. Next, we studied how estrogen and the weak estrogenic contaminant bisphenol A (BPA) would affect the timing and duration of neurogenesis in developing zebrafish and mice, presumably via changing NPC behavior. We also examined the mechanism through which estrogen/BPA would be acting in vivo. Finally, we developed a novel neurosphere assay to isolate NPCs from the developing hypothalamus in mice, a sexually dimorphic brain region, to determine mechanisms driving local estrogen synthesis and changes in NPC behavior. Collectively, our studies illustrate that NPCs are highly sensitive to estrogen and testosterone, and on going work seeks to determine when and how NPCs synthesize local sex hormones.

Jing Wang, PhD, University of California, San Diego
Molecular mechanisms of sexually dimorphic sensory neurophysiology in *Drosophila*

Across animal species, the sex and reproductive status of individuals have profound impacts on their sexual behavior. However, outstanding questions remain unanswered as to how genetic sex and reproductive maturity are coordinated to regulate mating behavior. In *Drosophila*, male fertility increases with age and peaks when flies are around 7 days old. Interestingly, we found that 7-day old males court females more vigorously than their younger counterparts, indicative of an elevated courtship drive. Mechanistically, the elevated courtship behavior of older males arises from their heightened sensitivity to an aphrodisiac pheromone, which is detected by the Or47b olfactory receptor neurons. The age-dependent modulation of Or47b neurophysiology is sexually dimorphic, observed only in males but not females. In addition, we showed that juvenile hormone, a pleiotropic hormone required for

development as well as reproductive maturity in adult flies, is critical for Or47b sensitization. Specifically, treating young males with a juvenile hormone analog markedly enhances their Or47b sensitivity; RNAi knockdown of a juvenile hormone receptor abolishes the age-dependent sensitization. Furthermore, we uncovered that Fru^M, a male-specific transcription factor, instructs the modulation of the courtship-promoting Or47b neurons in males. Inhibiting the expression of Fru^M in male Or47b neurons abolishes their sensitization with age. This age-dependent sensitization of a pheromone sensory neuron may offer a means to coordinate courtship drive with reproductive maturity, thereby maximizing reproductive success. Our findings in *Drosophila* further highlight the evolutionarily conserved interplay between biological sex and reproductive hormones in determining sexually dimorphic neurophysiology.

Kim Huhman, PhD, Georgia State University
Sex differences in hypothalamic, pituitary, and gonadal control of agonistic behavior in Syrian hamsters

Syrian hamsters are an ideal species with which to study potential sex differences in the hormonal mechanisms of agonistic behavior including aggression and dominance as well as defense and submission because, unlike many other rodent species, both sexes readily display agonistic behavior in a variety of contexts. For instance, both male and female hamsters vigorously attack an intruder placed into their home cage. After hamsters have been exposed to a brief social defeat, however, they subsequently display a lack of territorial aggression and instead display only defensive and submissive behavior. This response has been termed conditioned defeat. There are marked sex differences in aggression, in social communication, and in the behavioral response to social defeat, but these sex differences vary depending on the testing procedures. For example, females exhibit little conditioned defeat if they are tested with a freely moving intruder in their home cage, and the response also varies significantly across the four-day estrous cycle. Alternatively, if socially defeated hamsters are tested for social avoidance of a conspecific that is confined in a smaller enclosure within their home cage, there is little to no sex difference in the behavior, and the response of females does not vary across the estrous cycle. The role of hypothalamic-pituitary-gonadal and neurohypophyseal hormones in aggression, social communication, and conditioned defeat in male and female hamsters will be discussed.

Kim Wallen, PhD, Emory University
Sex differences in neural and cognitive responses to sexual stimuli: Possible modulation by androgens

When viewing sexually explicit images (SEI), women have been reported to show less amygdala activation than do men, even though men and women report comparable levels of arousal to the SEI. Additionally, heterosexual men and women differ in the extent that they report exclusive arousal to SEI of their preferred sexual orientation, with men reporting stimulus specificity and women reporting variable patterns of arousal by the sex of the SEI. We investigated whether these sex differences may reflect differences between men and women in their exposure to androgens, by comparing patterns of neural activation and self-reported stimulus specificity in 13 XY heterosexual men, 13 XX heterosexual women, and in 13 XY heterosexual androgen insensitive women (CAIS). fMRI scans were obtained using a 3 T Siemens Tim Trio MRI system while viewing five types of SEI stimuli: (1) heterosexual couples engaged in sexual activity, (2) female nudes, (3) male nudes, (4) female couples engaged in sexual activity, (5) male couples engaged in sexual activity. A sixth control condition showed social interactions between men and women, but without overt sexual content. Using an amygdala region of interest (ROI) approach men showed increased left amygdala activation compared to XX women and both left and right increased amygdala activation compared to women with CAIS. Men showed stimulus specificity to the images, reporting arousal only to heterosexual stimuli, women showed less stimulus specificity than did men. Women with CAIS showed the least stimulus specificity. Women with CAIS do not have functional androgen receptors and thus cannot respond to androgens even though they had functional testes during prenatal development. This suggests that the sex differences in neural activation and stimulus specificity may reflect differences in androgen exposure. Women with CAIS, however, were reared as girls thus social influences on these sex differences in response to SEI cannot be ruled out.

10:30 AM – 12:15 PM: SESSION 8 *(Mercer Salon G/H)*

In Silico Models and Clinical Trials: Innovative Research and Sex and Gender Implications *Chair: Marjorie Jenkins, MD, MEdHP, FACP, U.S. Food and Drug Administration*

Marjorie Jenkins, MD, MEdHP, FACP, U.S. Food and Drug Administration
In Silico Modeling and Virtual Clinical Trials: Opportunities for Advancing Sex Differences and Women's Health
This presentation will provide an overview of the applications of in silico research methods and provide a brief overview of the implications of this model in women's health.

Tina Morrison, PhD, U.S. Food and Drug Administration
Understanding the Potential for In Silico Methods to Advance the Study of Sex Differences

FDA acknowledges the benefits to public health provided by modeling and simulation, such as those in the developing area of in silico clinical trials; in other words, the use of individualized computer simulation in the development and/or regulatory evaluation of medical products, medical device, or medical interventions (Avicenna Roadmap-2016). FDA advocates for their use as one of many research and product development tools because modeling and simulation play a critical role in organizing diverse data sets, exploring alternate study design strategies, identifying subpopulations for therapy, and in some cases, predicting performance, so that safe and effective new therapeutics can advance more efficiently, from preclinical studies through clinical trials to market. FDA routinely advises industry on the use of modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, identify the most relevant patients to study, predict product safety, and evaluate potential adverse event mechanisms. In some cases, in silico clinical trials are used to replace human clinical trials, especially those that are intended to evaluate the risk of drug interactions, or where information from a computer-based model can better inform the performance of a medical device as compared to data collection in a human clinical trial. FDA intends to continue advancing these methodologies and techniques from both a science and regulatory perspective to best take advantage of the benefits for continued product innovation and more rapid introduction of life saving technology to US patients. This presentation will provide an overview of those methodologies and highlight the possibility for in silico clinical trials to be used for evaluating sex differences.

Wendy Wu, PhD, U.S. Food and Drug Administration
Research effort to develop sex-specific in silico models for assessing cardiac safety of new drugs

This presentation will describe the results of the Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative and will discuss how sex-differences (if present) will be used to improve and implement sex-specific models of the human heart cell for regulatory assessment of cardiac safety for new drugs. The CiPA initiative is a novel proposal and a global initiative to assess a new drug's potential to cause Torsade de Pointes (TdP), a potentially fatal abnormal heart rhythm, before the drug is on the market. Under CiPA, drug effects on major cardiac ion channels that underlie the normal cardiac rhythm are integrated using a heart cell model to predict the proarrhythmia propensity of the drug. This presentation will highlight in vitro experiments to uncover sex differences in the activity of major cardiac ion channels and the need for developing male and female cardiac heart cell models for accurate risk prediction.

Aldo Badano, PhD, U.S. Food and Drug Administration
Considerations for using in silico clinical studies for the regulatory evaluation of new imaging products

Clinical trials to evaluate a new imaging technology can be expensive and lengthy, delaying regulatory evaluation and adding significant burden that stifles innovation, affecting patient access to novel, high-quality imaging technologies. In silico imaging holds promise for evaluating the safety and effectiveness of imaging technologies with much less burden than clinical trials. We define in silico imaging as the computer simulation of an entire imaging system

(including source, object, task, and observer components) used for research, development, optimization, technology assessment, and regulatory evaluation of a new technology. In this work, we describe VICTRE (our study of virtual imaging clinical trials for regulatory evaluation) and the considerations for building an entire imaging pipeline in silico including device (physics), patient (anatomy, disease), and image interpretation models for regulatory evaluation using open-source tools. We discuss the potential advantages of using such tools for the examination of differences in device performance across different patient groups and subpopulations.

12:15 PM – 1:30 PM: WORKSHOP LUNCH *(Mercer)*

Aaron Wolen, Ph.D., Virginia Commonwealth University **Efficient and Reproducible Research: An Introduction to the Open Science Framework**

There is widespread agreement that more should be done to improve the computational reproducibility of published research, yet there is a paucity of accessible tools and techniques to help researchers achieve that goal. This workshop will focus on practical steps researchers can take to improve the transparency and reproducibility of their work using the Open Science Framework (OSF), a free project management service developed by the Center for Open Science. We will discuss common practices and technical hurdles that impede reproducibility and how they can be avoided by adopting best practices and using the OSF for developing pre-analysis plans, organizing and documenting projects, managing data, working with collaborators and disseminating materials. Attendees should walk away with an understanding of the OSF's key features and the ability to setup their own OSF project repository.

1:45 PM – 3:30 PM: SESSION 9 *(Mercer Salon I)*

Nuclear Structure and Sex Differences *Chairs: Christine Disteche, PhD, University of Washington, and Carolyn Brown, PhD, University of British Columbia*

Xinxian Deng, PhD, University of Washington
Orientation-dependent Dxz4 contacts shape the 3D structure of the inactive X chromosome

X chromosome inactivation (XCI) is an essential form of mammalian dosage compensation, which silences one of the two X chromosomes in female cells to equalize gene expression between genders. How the XCI is achieved is a central and most puzzling question in biology. It has only been recently appreciated that genome architectures are critical elements of this regulation. Indeed, we and others find that the inactive X chromosome (Xi) has a unique three-dimensional bipartite structure with two superdomains of frequent long-range contacts separated by a boundary or hinge region regulated by the master architectural protein CTCF. Using in situ DNase Hi-C in mouse cells with deletions or inversions within the hinge we show that the conserved macrosatellite repeat locus *Dxz4* within the hinge is sufficient to maintain the bipartite structure and that *Dxz4* orientation controls the distribution of long-range contacts on the Xi. Frequent long-range contacts between *Dxz4* and the telomeric superdomain are either lost after its deletion or shifted to the centromeric superdomain after its inversion. A massive reversal in contact distribution after *Dxz4* inversion is consistent with the reversal of CTCF motif orientation at *Dxz4*. Xi TAD structure is largely unchanged following *Dxz4* deletion or inversion except around the *Dxz4* locus itself and a few localized changes, including the restoration of TADs normally attenuated on the Xi. There is also an increase in chromatin accessibility and CTCF binding after *Dxz4* deletion or inversion, but few changes in gene expression, in accordance with multiple epigenetic mechanisms ensuring X silencing. We propose that *Dxz4* represents a structural platform for frequent long-range contacts with multiple loci in a direction dictated by the orientation of a bank of CTCF motifs at *Dxz4*, which may work as a ratchet to form the distinctive bipartite structure of the condensed Xi.

Schahram Akbarian, MD, PhD, Mount Sinai School of Medicine
Neuronal and non-neuronal chromosomal connectomes and epigenomes in adult male and female mouse and human cerebral cortex

Little is known about sex-specific regulation of chromatin structure and function in differentiated brain cells, including neurons. We have generated a total of 157 reference maps from neuronal, neuronal-depleted and bulk tissue chromatin for two histone marks associated with active promoters and enhancers, H3-trimethyl-lysine 4 (H3K4me3) and H3-acetyl-lysine 27 (H3K27ac), and for two cortical areas from the adult human frontal lobe. Variation across sexes was minimal genome-wide while exerting a strong effect on chrX and chrY linked genes. Regions on chrX and chrY resulted in strong sex-specific clustering on the 4th principal component while male and female brains completely intermixed when the analyses with repeated under exclusion of histone-tagged sequences specific to the X and Y chromosomes. To gain insights into the role of chromatin-associated proteins to maintain epigenomic architectures of the X-chromosome in differentiated brain cells, we study conditional mutant mice with a neuron-specific deletion of *Kmt1e/Setdb1*, encoding a repressive histone H3K9-specific methyltransferase previously shown to moderately affect the inactive X-chromosome in dividing cells. Preliminary evidence indicates that neuronal *Setdb1* deficiency strongly affects X-linked binding of CTCF as a broad regulator of chromosomal architectures and transcription. Therefore, SETDB1 is important for neuronal maintenance of sex-chromosome specific epigenomic architectures.

Linda Zhou, University of Pennsylvania
3D-genome reconfiguration in X-linked brain diseases

More than 25 inherited human disorders are caused by the unstable expansion of repetitive DNA sequences termed short tandem repeats (STRs). A fundamental unresolved question is why some STRs are susceptible to pathologic expansion, whereas thousands of repeat tracts across the human genome are relatively stable. Here, we discover that nearly all disease-associated STRs (daSTRs) are located at boundaries demarcating 3D chromatin domains. We identify a subset of boundaries with markedly higher CpG island density compared to the rest of the genome. daSTRs specifically localize to ultra-high-density CpG island boundaries, suggesting they might be hotspots for epigenetic instability or topological disruption upon STR expansion. Fragile X Syndrome patients exhibit severe boundary disruption and loss of CTCF occupancy in a manner that correlates with the degree of Fmr1 silencing and daSTR length. Our data uncover higher-order chromatin architecture as a new dimension in understanding repeat expansion disorders.

Andrew Lane, MD, PhD, Dana-Farber Cancer Institute
Why do men get more cancer? Escape from X Inactivation Tumor Suppressor (EXITS) genes in the sex bias of malignancy

There is a striking, but poorly understood, male predominance across many cancer types. We hypothesized that sex chromosomes contribute to increased malignancy risk in males (or superior cancer protection in females). Although females have two X chromosomes, one copy is inactivated in all somatic cells. Therefore, acquired mutations in chrX tumor suppressors should be equally likely in male and female cancers because both have only one active copy of each gene vulnerable to a deleterious mutation. However, a small number of genes escape X inactivation in female cells and are expressed from both maternal and paternal alleles. We asked if mutations in tumor suppressor genes that escape X inactivation exhibit gender bias in cancer genomes. These genes could contribute to excess male cancers, as males would require only a single mutation while females would require two. We termed these 'EXITS' genes, for *E*scape from *X* *I*nactivation *T*umor *S*uppressors. To query for EXITS genes in an unbiased manner, we tested for male predominance of chrX loss-of-function (LOF) mutations (single nucleotide variants, insertions/deletions, or copy number loss) in >4100 cancers of 21 types from The Cancer Genome Atlas (TCGA). Six of 783 non-pseudoautosomal region (PAR) chrX genes (*ATRX, CNKSR2, DDX3X, KDM5C, KDM6A,* and *MAGEC3*) more frequently

harbored LOF mutations in males (based on false discovery rate <0.1), compared to zero of 18,055 autosomal and PAR genes in the remaining genome (P<0.0001). *ATRX* was mutated in many cancers but had brain-specific cancer sex bias and escape, suggesting that tissue-restricted EXITS may promote lineage-based sex differences. Sex bias also led to confirmation of tumor suppressor function of a previously uncharacterized cancer gene, *CNKSR2*. We conclude that biallelic expression of EXITS genes in females explains a portion of the reduced cancer incidence compared to males across a variety of tumor types and may contribute to sex differences in cancer biology.

1:45 PM – 3:30 PM: SESSION 10 *(Mercer Salon G/H)*

Sex Differences in Cerberovascular Disease: Epidemiology to Epigenetics *Chairs: Louise McCullough, MD, PhD, UTHealth McGovern Medical School, and Mat Reeves, PhD, Michigan State University*

Virginia Howard, PhD, University of Alabama at Birmingham
What the numbers say: a comparative analysis of stroke epidemiology in women compared to men

Stroke, which is the fifth leading cause of mortality and one of the most common causes of adult-onset disability in the United States, demonstrates important sex differences between men and women that are meaningful both clinically and from a public health standpoint. This talk will serve as an introduction to the session, with a focus on incidence, prevalence, and mortality, and an overview on what is known about potential sex differences in traditional stroke risk factors. Overall, women have a higher lifetime risk of stroke then men. However, in younger- and middle-age groups, age-specific stroke incidence rates are lower in women than men, but in the oldest groups, incidence rates in women are approximately equal or even higher than in men. Similarly, more women die from stroke than men; stroke is the fourth leading cause of death for women and the fifth for men. This higher stroke mortality in women is often attributed to their longer life expectancy. Stroke mortality declined from 2005 to 2015 with a similar decline in age-adjusted stroke mortality by sex: -21.9% in men and -21.5% in women. Data are generally consistent in showing that the association of atrial fibrillation and diabetes with stroke risk is greater for women than men. There does not appear to be a sex difference in the association of systolic blood pressure/hypertension with stroke risk. Limited data are available examining a potential sex difference in the association of heart disease, smoking, and left ventricular hypertrophy on stroke risk. Finally, we will make the audience aware of the lack of epidemiologic data reported by sex-race-age subgroups and other important gaps in knowledge as called out in the first American Stroke Association guidelines (2014) dedicated to stroke risk and prevention in women.

Tracy Madsen, MD, Brown University
The Aftermath: Access to Rehabilitation and Sex differences in Stroke Recovery

Stroke is a leading cause of death and disability for both women and men, but women bear a greater burden of disease due to a higher lifetime risk of stroke (1 in 5 for women vs. 1 in 6 for men), higher mortality from stroke, a higher prevalence of women living with stroke, and worse functional outcomes 90 days after stroke. This session will focus on sex differences in recovery and functional outcomes after brain injury. Data from clinical research have shown that women consistently have more activity limitations following stroke, even after taking into account factors such as pre-stroke functional status, age and co-morbidities. Additionally, preliminary data demonstrate that new interventions including endovascular intervention do not seem to significantly mitigate these sex differences in functional outcomes. Other data suggest that women experience worse quality of life following stroke, though less is known on this topic. Contributors to worse outcomes in women following stroke are likely multifactorial and include differences in brain repair between the sexes, differences in access to rehabilitation, gender differences in factors including social isolation, and differences between women and men in mental health and frailty. This session will conclude with a discussion of future directions for research that are needed to identify sex-specific intervenable factors to improve outcomes for both women and men.

Stacie Demel, DO, PhD, Michigan State University
Epigenetics and the Second X Chromosome: Back to the Basics of Sex Differences

Sex differences are seen in stroke risks, epidemiological measures and clinical outcomes that cannot be fully explained by differences in age or other external factors. Basic science and clinical data indicate that in its most basic form, stroke is a sexually dimorphic disease that stems from differences in genetics, epigenetics and effects of gene by environment interactions. Today, we will review basic science, clinical and epidemiological data that suggests a genetic contribution to sex differences including emerging data on differences in estrogen receptor genotype and their association with cardiovascular disease in men and women. We will also address the gaps in data that are in need of further research.

Mollie McDermott, MD, MS, University of Michigan
Transgender Medicine and Ischemic Stroke

The prevalence of self-identified transgender adults in the United States is estimated to be approximately 0.5% of the population. Some transgender people pursue hormonal therapy and/or gender-affirming surgery to assume secondary sex characteristics consistent with their gender identity. The use of certain hormonal therapies has implications for the prevention of cerebrovascular disease in this population. We will discuss stroke risk factors unique to transmen and transwomen, as well as other aspects of stroke care relevant to this population.

3:45 PM – 4:45 PM: PANEL DISCUSSION *(Mercer)*
Moderator: Lise Eliot, Ph.D., Rosalind Franklin University **Sex Differences and the Google Memo**

Panelists:
Jill Becker, PhD, University of Michigan
Lise Eliot, PhD, Rosalind Franklin University
Margaret McCarthy, PhD, University of Maryland
Deboleena Roy, PhD, Emory University

WEDNESDAY, MAY 2

8:30 AM – 10:15 AM: SESSION 11 *(Mercer Salon I)*
Sex Steroids, Puberty, and Adolescent Brain Development: A Translational Approach to Understanding Peak Vulnerability to Psychopathology in Adolescence *Chairs: Marianne Seney, PhD, and Cecile Ladouceur, PhD, University of Pittsburgh*

Marianne Seney, PhD, University of Pittsburgh
Developmental origins of sex differences in adult mood

Women are two times as likely to have depression compared to men. Studies suggest a developmental origin for mood disorders. Adverse events during early life and through adolescence can increase risk for adult psychopathology. Notably, a developmental process also establishes brain sex differences, as developmental testosterone exposure around the time of birth and through adolescence permanently masculinizes the structure of several brain regions (organizational effects of hormones). We hypothesize that sex differences in exposure to gonadal hormones during critical/sensitive developmental periods cause sex differences in adult mood. We used

adult Four Core Genotypes (FCG) mice (XX females, XY females, XX males, XY males) to examine organizational and sex chromosome complement contributions to adult mood. In adulthood, all mice were gonadectomized (GDX) to remove endogenous sources of gonadal hormones. We assessed mood-related behavior using the novelty suppressed feeding (NSF) test and the social conditioned place preference (CPP) test (a test for social reward). We found that gonadal males had reduced latency to eat in the NSF test. There was no effect of sex chromosome complement and no interaction of sex chromosome complement and gonadal sex on latency to eat. In the social CPP test, gonadal males showed a stronger preference for the social condition compared to gonadal females. There was no effect of sex chromosome complement and no interaction of sex chromosome complement and gonadal sex on social CPP scores. Since all mice were GDX in adulthood, our findings indicate that sex differences in gonadal hormone exposure during critical/sensitive periods of development program adult mood-related behaviors. Together, these results suggest that early life hormonal processes produce sex differences in adult mood. We are currently analyzing RNA-seq data from mood-relevant brain regions to identify genes that are similarly influenced by developmental gonadal sex.

Cecile Ladouceur, PhD, University of Pittsburgh
Sex steroid influences on striatal activation to reward cues in adolescence

Research suggests that changes in the reward circuitry during adolescence may contribute to increased risk for psychiatric disorders. Affective neuroscience research has made progress in understanding the normal development of reward circuitry in adolescence; however, few functional neuroimaging studies have examined the specific influences of pubertal maturation on reward cue processing. Here, we examined how neural activation to reward cues was associated with puberty and levels of pubertal hormones. We hypothesized that striatal activation to reward cues would be positively correlated with pubertal status and pubertal hormones. Seventy-nine adolescents (47 girls; age 11-13) varying in pubertal status underwent an fMRI scan while performing a reward cue processing task. To assess pubertal maturation, we computed composite scores that integrate both self-report measures and Tanner stage to more fully capture adrenal and gonadal hormonal signals of physical development. Pubertal hormones (DHEA, estradiol and testosterone) were measured using salivary assays (3 separate days over a one-month period). Results indicated greater striatal activation and functional connectivity between nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC) to reward cues on this task. Also, girls with higher levels of estradiol showed reduced striatal activation and those with higher levels of estradiol and more advanced in gonadarche showed reduced functional connectivity between NAcc and mPFC when processing reward cues. Findings did not yield any significant associations in boys. Findings suggest that patterns of activation and connectivity in cortico-striatal regions are associated with reward cue processing, particularly in girls. Longitudinal follow-up neuroimaging studies are needed to fully characterize puberty-specific effects on the development of these neural regions and how such changes may contribute to pathways of risk or resilience in adolescence.

Cheryl Sisk, PhD, Michigan State University
Pubertal testosterone programs experience-dependent prefrontal âˆ†FosB expression and social competence in adulthood

Adolescence is associated with increased prevalence of psychiatric disorders that involve dysfunction in social cognition and disproportionately affect males and females. An important component of social cognition is social competence--the ability to make behavioral adaptations with social experience. Here we investigated the contributions of pubertal testosterone and ΔFosB, a transcription factor linked to experience-dependent neural plasticity, to adolescent maturation of social competence. We first compared behavioral adaptations to sexual experience in male Syrian hamsters that were deprived of testosterone during puberty (prepubertal castration; NoT@P) to those of males deprived of testosterone for an equivalent period of time in adulthood (postpubertal castration; T@P). All males received testosterone replacement before repeated sexual behavior testing in adulthood. Both sexual competence, defined as a decrease in ectopic (mis-directed) mounts with sexual experience, and an experience-dependent increase in ΔFosB immunoreactivity in ventromedial prefrontal cortex (vmPFC) were observed

in T@P, but not NoT@P, males. We next found that viral vector-mediated over-expression of ΔFosB in vmPFC of NoT@P males was sufficient to reverse high rates of ectopic mounting and resulted in a T@P behavioral phenotype. Finally, both sexual experience and over-expression of ΔFosB in vmPFC of adult gonad intact males increased the density of immature spines on IL dendrites. Our findings show that pubertal testosterone programs the ability to make behavioral adaptations as a function of social experience, facilitating social competence in adulthood. Findings further suggest a neurobiological mechanism for the organization of social competence: pubertal testosterone permits social experience-dependent upregulation of ΔFosB in the vmPFC, leading to heightened synaptic lability that may be necessary for behavioral adaptations to social experience.

Monique Ernst, MD, PhD, NIMH
Pubertal maturation: intrinsic functional connectivity increased in boys, but decreased in girls, a risk for depression?

Adolescence is marked by the emergence of psychiatric disorders, with a sex disproportionality: female preponderance of internalizing disorders, and male preponderance for externalizing disorders. Resting state fMRI scans from a subset of the large longitudinal cohort of the European IMAGEN consortium were analyzed when all subjects were 14years old. Data processing and analyses were conducted with Analysis of Functional NeuroImages (AFNI). Multiple regression analyses were used to examine the effects and interactions of puberty and sex on anterior and posterior iFC nodes of the default mode network, medial prefrontal cortex (mPFC), pregenual cingulate (pgACC) and posterior congulate (PACC). Individual variability in internalizing symptoms were indexed using the Development and Well-Being Assessment (DAWBA) at time of scan, and 2-year follow-up. Higher puberty level was associated with stronger mPFC- and PCC-iFC in boys, and weaker iFC in girls (sex X puberty interaction). A sex main effect on PCC and pgACC revealed stronger iFC in boys than girls. The main effect of puberty on iFC was not significant. Behaviorally, exploratory analyses indicated negative associations of pgACC-iFC and mPFC-iFC with internalizing symptoms at 2-year follow-up. In other words, the weaker the iFC of pgACC and mPFC was at age 14 years, the more likely participants were to have mood or anxiety (internalizing) symptoms at age 16 years. This study revealed that puberty influences resting state connectivity of regions that have been identified as conferring risk for mood problems in adolescents. Puberty affected mPFC and PCC iFC differently in boys and girls. Additionally, weaker iFC of the pgACC and mPFC at age 14 predicted internalizing symptoms at age 16. Sex and sex-by-puberty effects interactions could underlie the sexually-dimorphic development of mood disorders during adolescence.

8:30 AM – 10:15 AM: SESSION 12 *(Mercer Salon G/H)*

Statistical Methodologies on Sex Chromosome Association *Chair: Wei Xu, PhD, Princess Margaret Cancer Centre*

Wei Xu, PhD, Princess Margaret Cancer Centre
A unified partial likelihood approach for X-chromosome association on time to event outcomes

Currently the X-chromosome has generally been excluded from the majority of GWAS analyses; this is most likely due to the lack of a standardized method in handling X-chromosomal genotype data. Unlike autosomal chromosomes, the expression of X-chromosome undergoes three possible biological processes: X-chromosome inactivation (XCI), escape of the X-chromosome inactivation (XCI-E) and skewed X-chromosome inactivation (XCI-S). To analyze the X-linked genetic association for time to event outcomes with the actual process unknown, we propose a unified approach of maximizing the partial likelihood over all of the potential biological processes. The proposed method can be used to infer the true biological process and derive unbiased estimates of the genetic association parameters. A partial likelihood ratio test statistic is developed to assess the X-chromosome genetic association. Furthermore, if the X-chromosome expression pertains to the XCI-S process, we can infer the correct skewed direction and magnitude of inactivation, which can elucidate significant findings regarding the genetic mechanism. A population-level model and a more general subject-level model have been developed to model the XCI-S process. The model performance of this

novel method is examined via extensive simulation studies. An application is illustrated with implementation of the method on a cancer genomic study with survival outcomes.

Lei Sun, PhD, University of Toronto
Statistical insights on the association analyses of X chromosome: X-inactivation, confounding, interaction and beyond

X-chromosome is often excluded from whole-genome association studies due to a number of complexities. Some are apparent, e.g. sex-specific allele frequencies, sex-genotype interaction, and the choice of (additive or other) genetic models, while others are subtler, e.g. random, skewed or no X-inactivation, and the choice of risk allele. In this work, we aim to consider all these complexities jointly and propose a regression-based association test. We provide theoretical justifications and empirical evidence for its robustness in the presence various aforementioned model uncertainties, as well as for its improved power under certain alternatives as compared with existing approaches.

Stacey Winham, PhD, Mayo Clinic
An integrative approach to assess X-chromosome inactivation with applications to epithelial ovarian cancer

X chromosome inactivation (XCI) randomly silences transcription of one of the two homologous copies of the female X chromosomes to equalize levels of gene expression with males. In particular tissues, some genes are known to escape XCI, and may play a role in women's cancer development. However, this process is understudied due to statistical challenges. We developed a two-stage statistical framework to assess skewed XCI and evaluate gene-level patterns of XCI for an individual sample by integration of RNA sequence, copy number alteration, and genotype data. Our method relies on allele-specific expression (ASE) to directly measure XCI and does not rely on male samples or paired normal tissue for comparison. We applied these methods to data from tumors of 99 ovarian cancer patients. Approximately 10% of genes showed different XCI status (either escaping or being subject to XCI) compared to studies of other tissues. Many of these genes are known tumor suppressors or oncogenes. The process of XCI inherently involves multiple layers of gene regulation, so we further examined the role of XCI in ovarian cancer by incorporating DNA methylation information. We observed strong correlation between *cis* promoter DNA methylation and ASE imbalance ($p=2.0 \times 10^{-10}$). Using both DNA methylation and ASE information, we identified two subgroups of ovarian cancer patients representing those with regulated (N=47) and dysregulated (N=52) XCI. These patient subgroups were associated with expression of *XIST* ($p=0.002$), a known driver of XCI, as well as clinical factors (e.g. age, stage, tumor histology, and extent of residual disease; $p<0.05$). Patients with dysregulated XCI had shorter time to recurrence than those with regulated XCI (HR=2.34, $p=0.001$). We found evidence of a unique ovarian cancer XCI profile, suggesting that XCI may play an important role in ovarian cancer biology, although further studies in paired tumor-normal tissue are needed.

Osvaldo Espin-Garcia, University of Toronto
X-chromosome Association in Microbiome data

Abstract unavailable at time of printing

10:30 AM – 12:15 PM: SESSION 13 *(Mercer Salon I)*

Sex Differences in Learning and Plasticity *Chairs: Debra Bangasser, PhD, Temple University, and Nicola Grissom, PhD, University of Minnesota*

Debra Bangasser, PhD, Temple University
Sex differences in stress regulation of cognition

Patients with schizophrenia and attention deficit hyperactivity disorder (ADHD) have disrupted cognition, an effect that is greater in men than women. These disorders also share stress as a factor associated with symptom onset. Given the link between stress and sex biased disorders with cognitive features, we are exploring how stress and the stress neuropeptide, corticotropin releasing factor (CRF), alter attention and learning in male and female rats. We found that central administration of CRF impairs sustained attention, the ability to monitor situations for intermittent and unpredictable events, in both sexes. However, the magnitude of the attention deficit changed across the estrous cycle of female rats, such that CRF impaired attention when ovarian hormone levels were low, but not when they were high. Males that never have elevated levels of ovarian hormones would never benefit from this protective effect. We are now exploring where CRF is working to modulate sustained attention and the nucleus basalis of Meynert (NBM) within the cholinergic basal forebrain plays a role. Specifically, CRF in the NBM impairs aspects of attention, and males tend to be more affected by this manipulation. A complementary line of work is finding that chronic variable stress also impairs sustained attention in rats, and the effect of this stressor is greater in males than females. Finally, we are testing how CRF can modulate another cholinergic region, the medial septum (MS). CRF in the MS impairs spatial learning, but not recognition learning. This impairment occurs in both sexes, but male rats are more sensitive to this effect. Collectively, these studies suggest that stress and CRF can impair cognition and that males are particularly vulnerable to these effects. Developing a better understanding of mechanisms that promote female resilience to stress-induced cognitive deficits can guide the development of better treatments for stressed patients with schizophrenia and ADHD.

Nicola Grissom, PhD, University of Minnesota
Mechanisms of female resilience to autism-associated genotypes

Neurodevelopmental disorders, such as autism spectrum disorders, are more prevalent in males than females, but the mechanisms of female resilience are not well understood. Dr. Grissom will show evidence that males are more vulnerable to the impact of some autism-associated genoytpes at the level of behavior and molecular mechanisms. She will touch on recent findings from her laboratory demonstrating that females employ different strategies in decision making tasks, which suggest molecular and circuit based mechanisms of female resilience that may be amenable to targeting in males.

Erin Calipari, PhD, Vanderbilt University
Enhanced Dopaminergic Function During Estrus Drives Increased Addiction Vulnerability in Females

Drug addiction is characterized by high levels of drug intake, seeking, and repeated cycles of abstinence and relapse. Even though both males and females become addicted to cocaine, female subjects transition to dependence faster, take more drug, experience more adverse consequences, and have more difficulty remaining abstinent. We demonstrate an estrous cycle-dependent mechanism controlling increased cocaine reward in females. During estrus, ventral tegmental area (VTA) dopamine neuron activity is enhanced and drives post translational modifications at the dopamine transporter (DAT) to increase the ability of cocaine to inhibit its function, an effect mediated by estradiol. The mesolimbic dopamine pathway plays an important role in learning the association between environmental cues and receiving drug. Upregulation of the activity in this pathway during estrus may lead to stronger associations between environmental cues and drug delivery and may influence future drug-taking behavior. Indeed, female mice

conditioned to associate cocaine with contextual cues during estrus have enhanced mesolimbic responses to these cues in the absence of drug. Further, when presented in the presence of drug availability, these cues acted to increase motivated responding and seeking for cocaine. Using chemogenetic approaches, we increase VTA activity to mechanistically link estrous cycle-dependent enhancement of VTA firing to enhanced cocaine affinity at DAT and subsequent reward processing. These data have implications for sexual dimorphism in addiction vulnerability and define a mechanism by which cellular activity results in protein alterations that contribute to dysfunctional learning and reward processing.

Mohamed Kabbaj, PhD, Florida State University
Sex differences in ketamine's antidepressant effects

Current medications for major depression suffer from numerous limitations and take several weeks to improve mood. However, recent clinical studies have shown that a single low-dose injection of ketamine, an N-methyl d-aspartate receptor (NMDAR) antagonist, has rapid antidepressant effects that are observed within hours and are long lasting, even in patients who do not respond well to various other anti-depressants. In this lecture, I will share some of our preclinical findings regarding sex differences in ketamine antidepressant effects and the role of gonadal hormones in these differences. I will also briefly share some of the recent findings surrounding the safety of ketamine as treatment for depression.

1:45 PM – 3:30 PM: SESSION 15 *(Mercer Salon I)*

Current Topics in Sex Differences Research I: Genetics and Neuroscience *Chair: Douglas Portman, PhD, University of Rochester*

Erica Glasper, PhD, University of Maryland
Neonatal paternal deprivation and stress alter neuroendocrine responses in adult California mice (*Peromyscus californicus*)

In human and non-human animals, early-life experiences can significantly alter offspring development. While much of our knowledge of parent-offspring relationships stem from mother-offspring interactions, increasing evidence suggests that interactions with the father are also important and can prevent social, behavioral, and neurological impairments that appear early and have enduring consequences in adulthood. Using a model of paternal deprivation (PD) in the biparental California mouse (*Peromyscus californicus*), we recently demonstrated that PD leads to increased neonatal mortality, decreased locomotion, and increased passive-stress coping behavior during a task of behavioral despair. We also observed a reduction in the survival of newborn cells in the dentate gyrus of the hippocampus in PD female, but not male, adult offspring. Given that numerous factors may inhibit neuronal structure and function, we performed experiments to elucidate potential mechanisms contributing to sex differences in neuroplasticity as a result of PD in the California mice. Basal and stress-induced (acute and chronic) differences in serum corticosterone (CORT) concentrations were assessed in adult offspring that were biparentally-reared or paternally deprived. PD did not alter basal CORT; however, female California mice displayed higher CORT than males. Resolution of stress-induced CORT following an acute saline injection was observed in PD females, but not in PD males. Irrespective of neonatal experience, females demonstrated sustained CORT release following seven days of chronic variable stress (CVS). This effect was only observed in biparentally reared males; PD males were unable to mount an appropriate CORT response to CVS. Together, these findings suggest that stress responsivity following PD is both sexually dimorphic and stressor dependent. The extent to which differential responsivity to PD and adulthood stressors underlie sex-differences in neural and behavioral responses will be discussed.

Susan Sangha, PhD, Purdue University
Increased reward seeking and lack of conditioned inhibition of fear and fear extinction in female rats

Clinical disorders arising from maladaptive emotion regulation present a large burden on society worldwide. Many of these disorders show comorbidity, for example, addiction with anxiety disorders. Cues predicting something aversive elicit avoidance and fear behaviors whereas cues predicting reward elicit approach and reward-seeking behaviors. Cues signifying safety have the power to modulate fear and reward-seeking behaviors by informing the organism whether or not the environment is safe. Thus, safety, fear and reward behaviors, and the circuitries governing these behaviors, are intertwined. The majority of studies on reward and fear processing have been conducted in parallel, investigating the circuitries separately in primarily male subjects. If we hope to understand and treat comorbid disorders resulting from maladaptive emotion regulation increased efforts in investigating how these circuitries integrate their functions to influence behavior is needed in both male and female subjects. We have established in male rats that the amygdalocortical circuit contributes to safety-fear-reward cue discrimination. And, our results comparing males and females show that female rats do not suppress conditioned fear in the presence of the safety cue nor do they learn to extinguish their fear, indicating a failure to regulate fear in 'safe' conditions, and they are more reward responsive during the reward cue compared to males. Since women are more than twice as likely as men to develop emotion dysregulation disorders, this paradigm offers a great opportunity to tease apart the sex differences in neural circuitry that are generating the behavioral sex differences.

Nora Engel, PhD, Temple University
Vive la difference: zooming in on sex-specific differences in mouse embryonic stem cells

Although sexual dimorphisms have historically been attributed to hormonal factors, differences observed at early embryonic stages cannot be accounted for in this way. For example, male embryos in both primates and rodents have a higher growth rate at preimplantation stages, before overt sexual differentiation and exposure to sex hormones. X inactivation, a drastic epigenetic event exclusive to females, affects the embryonic transcriptome and epigenome in a sex-specific manner. Thus, male and female genomes are epigenetically poised for their divergent pathways soon after fertilization. To determine whether there is differential expression at preimplantation stages, we derived male and female mouse embryonic stem (ES) cell lines and performed RNA-sequencing. When XY and XX cell lines were compared, over 1000 coding genes were differentially expressed ($\alpha < 0.01$). A substantial number of these are transcription factors and epigenetic enzymes that are dosage sensitive, indicating that there are regulatory differences between male and female embryos that depend on their chromosomal composition. In addition, we found more than 300 non-coding RNAs that were sex-biased ($\alpha < 0.01$). Strikingly, luciferase assays in male and female ES cells showed sex-specific enhancer activity in response to differential levels of a transcription factor. To determine whether these expression differences translated into epigenomic differences, we conducted focused chromatin immunoprecipitation analyses and observed significant sex-dependent variation in chromatin accessibility in specific genes. Comparison between the transcriptional profiles of XX, XY and 39, XO ES cells yielded information on the dependence of the transcriptome on sex chromosome dosage. Differentiation of the ES cells into cardiomyocytes equalized many expression differences, but others were maintained and new transcriptional biases appeared. We predict that these early molecular dimorphisms explain distinctions in response to environmental signals and foreshadow sex-specific health-related outcomes after birth. Our results will have implications in understanding the developmental origins of disease, will impact disease treatment and stratification and, importantly, may have significance in the field of regenerative medicine.

Kristen Pleil, PhD, Cornell University
Sex differences in the function of a limbic circuit driving alcohol drinking and anxiety

Binge alcohol drinking is a leading risk factor for the development of alcohol use disorder, anxiety, and other stress-related mood disorders. The comorbid expression of these neuropsychiatric diseases is higher in women than men, however the reason for this increased vulnerability is unknown. Female mice binge drink more and have greater basal anxiety than males, and these behaviors are driven by neurons that synthesize the neuropeptide corticotropin-releasing factor (CRF) in the bed nucleus of the stria terminalis (BNST), a sexually-dimorphic limbic brain region. We hypothesized that increased $BNST^{CRF}$ neuronal activity drive binge drinking and stress reactivity, conferring increased risk of comorbid addiction and anxiety disorders in females and increased susceptibility in males following chronic alcohol exposure. Using *ex vivo* slice electrophysiology in CRF-reporter mice, we found that $BNST^{CRF}$ neurons were more likely to be tonically active at baseline in females than males and that repeated binge drinking increased the proportion of active neurons in both sexes. $BNST^{CRF}$ neurons in females also had higher sEPSC frequency and amplitude than those from males, and alcohol drinking increased these measures in males. To investigate the synapse specificity of this increased glutamatergic transmission, we used *ex vivo* optogenetics + slice electrophysiology to map a dense, direct projection of glutamatergic neurons from the paraventricular nucleus of the thalamus (PVT) to $BNST^{CRF}$ neurons, which was larger in females than males and increased in males after alcohol exposure. Altogether, these results suggest that increased glutamatergic drive at PVT→$BNST^{CRF}$ synapses increase $BNST^{CRF}$ neuronal excitability and provide a mechanism for increased drinking and anxiety displayed basally in females and after alcohol exposure in males. Current studies are examining the role of estrogen signaling within this circuit on the neuronal function and plasticity related to these behaviors and neuropsychiatric disease states.

1:45 PM – 3:30 PM: SESSION 16 *(Mercer Salon G/H)*

Current Topics in Sex Diff. Research II: Immunology, Physiology, and Metabolism *Chair: Adam Moeser, PhD, DVM, Michigan State University*

Suresh Mishra, PhD, University of Manitoba
Prohibitin: An unexpected role in sex differences in adipose and immune functions

Sex differences are known to exist in adipose and immune functions in the body, and sex steroid hormones are integral to these differences. However, our knowledge of proteins that mediate such differences is poor. Recently, we have developed two novel transgenic (Tg) mouse models by expressing prohibitin (PHB) or a phospho mutant form of PHB (Y114F-PHB or m-PHB) from the *aP2* gene promoter. Overexpression of PHB in adipocytes was found to induce mitochondrial biogenesis, adipocyte hypertrophy, and increase in adipose tissue mass in a sex-neutral manner. A similar effect of m-PHB on adipocytes was found in m-Mito-Ob mice suggesting that phosphorylation of tyrosine-114 is not required for mitochondria-related adipogenic function of PHB. Of note, PHB-Tg and m-PHB-Tg mice were found to gain weight after puberty. Interestingly, the metabolic phenotype of PHB-Tg and m-PHB-Tg mice revealed a sex dimorphic role of PHB in adipocyte and immune cell functions as only male PHB/m-PHB-Tg mice developed obesity-associated adipose inflammation, impaired glucose homeostasis, and insulin resistance. With aging, a sex-specific metabolic dysregulation in male PHB-Tg mice led to the development of NASH and HCC, suggesting sex differences in adipose-hepatic crosstalk in Mito-Ob mice. Interestingly, metabolic dysregulation in male m-PHB-Tg mice led to the development of lymph node tumors and splenomegaly, revealing an anti-proliferative role of tyrosine-114 in monocytic macrophages and dendritic cells. Female PHB-Tg and m-PHB-Tg mice remained protected from HCC and lymph node tumors despite comparable obesity with their male counterparts. Intriguingly, on a high-fat diet, male m-PHB-Tg mice develop autoimmune insulitis instead of tumors. The development of HCC and lymph node tumors or autoimmune diabetes in a male sex-specific manner suggests a sex dimorphic effect of PHB on adipocyte, monocytic macrophage, and dendritic cell functions, which were not suspected before.

Benoit Chassaing, PhD, Georgia State University
Diet-mediated alterations of the intestinal microbiota: impact on inflammation and behavior

The intestine is a heavily colonized organ, and contain around 10^{14} bacteria from 500-1000 species. When stably maintained, this complex ecosystem is playing important roles for the host, especially calories extraction and immune system maturation. In order to avoid over activation of pro-inflammatory signaling, the host is having many mechanisms to keep this bacterial community at a safe distance, with for example the presence of a thick mucus layer that form a sterile gel at the surface of the intestinal mucosa. Recent works by us and other have revealed that disturbances of the microbiota-host relationship, promoted by genetic or non-genetic factors, can alter intestinal homeostasis and drive chronic low-grade intestinal inflammation, ultimately leading to metabolic disorders. For example, we previously reported that emulsifying agents, a ubiquitous class of food additives used to improve texture and extend shelf life, detrimentally impacts the microbiota, leading to metabolic disorders. As alterations in the gut microbiota can lead to changes in social and anxiety-like behaviors, we investigated here whether emulsifier consumption would affect behavior as well. We confirmed that emulsifier exposure induced adiposity, chronic intestinal inflammation and altered gut microbiota in both male and female mice compared to control animals. Emulsifier consumption altered the microbiota in a sex-dependent manner and increased body weight gain in males but not females. Emulsifier treatment altered anxiety-like and social behaviors, as indicated by reduced time in the center of the open field arena, increased distance travelled in the elevated plus maze, and reduced preference for a novel conspecific mouse in a three-chambered test. Moreover, emulsifier consumption changed expression of neuropeptides associated with anxiety, social, and feeding behaviors. In conclusion, we demonstrated here that emulsifier treatment can alter microbiota composition, physiology, and behavior in a sex-specific manner.

Kristen Zuloaga, PhD, Albany Medical College
Sex Differences in Metabolic, Vascular, and Cognitive Effects of a High Fat Diet

Diabetes causes vascular dysfunction and is a major risk factor for vascular cognitive impairment including dementia (VCID). Diabetic women have increased risk of VCID compared to diabetic men. Data on the effects of prediabetes, which is more prevalent than diabetes, are lacking. Prediabetes can be modeled in mice via long-term high fat (HF) diet. We examined the effect of HF diet on metabolic parameters in juvenile, young adult, and middle-aged male and female mice. Additionally, the middle-aged mice were subjected to unilateral carotid artery occlusion surgery, which causes chronic cerebral hypoperfusion and models VCID. We hypothesized that aged females would lose their protection, relative to males, from the metabolic effects of high fat diet-induced prediabetes. Further, we hypothesized this would cause aged prediabetic females to have increased cognitive deficits in a mouse model of VCID, compared to males. Juvenile, young adult, and middle-aged male and female mice were placed on a HF or control diet. After 3 months, they received a glucose tolerance test and the middle-aged mice received either VCID or sham surgery. Three months later, cognitive function (behavior testing) and blood flow (laser speckle contrast imaging) were assessed. HF diet given to juvenile mice caused a greater increase in body weight and glucose intolerance in males than females. When the diet was initiated in middle aged mice, the opposite occurred and females initially gained more weight and had greater impairments in glucose tolerance. Spatial memory was impaired in VCID males, regardless of diet; however, in females, both HF diet and VCID impaired spatial memory. Our data show that sex differences in the effect of HF diet vary by age of onset and chronic cerebral hypoperfusion impairs spatial recognition and spatial memory in both sexes. Further, prediabetes also appears to increase cognitive deficits to a greater extent in aged females than males.

Katelyn Bruno, PhD, Mayo Clinic
Sex Differences in Vitamin D and Urinary Stone Disease

More men than women develop urinary stones and their prevalence alters in women with menopause suggesting a steroidal influence. In men the incidence of stones is highest during July and August suggesting that environmental factors such as Vitamin D (VitD), a steroid, may affect stone formation. Serum VitD levels are higher in men than women with urinary stones; however, the reason for sex differences in stone formation and type remain unclear. In this study, we examined VitD levels in men and women (n= 18,753) that had no diseases based on a lack of an ICD-9 or ICD-10 code in their electronic medical record. We found that normal, healthy women had significantly higher levels of sera VitD compared to men (p=6x10-6). We then examined whether sex differences existed for key endpoints/data from the Mayo Clinic Urinary Stone Disease (USD) Registry, which has around 1,600 urinary stone patients that are well-phenotyped according to sex, age and stone type. This cohort is 49.4% women and 50.6% men. We are developing a disease severity score, which we will use to correlate to sera VitD levels in patients according to sex, age and race. Future analyses will take into account whether subjects had VitD and calcium supplementation based on data in the medical record. This project begins to explore the mechanism behind the sex differences known to exist in urinary stone disease, which is critically needed to provide improved diagnosis and therapy for this debilitating disease.

Annie Newell-Fugate, PhD, Texas A&M University
Sexually dimorphic effects of androgens on insulin signaling in white adipose tissue adipocytes

Obesity increases the risk for insulin resistance with men, as opposed to women, preferentially developing this sequela. Insulin resistance is extremely severe in obese women with abundant visceral white adipose tissue (VWAT) and in hyperandrogenemic polycystic ovary syndrome patients. The role of androgens in glucose homeostasis is sexually dimorphic, with insulin resistance occurring in hyperandrogenemic females but in hypoandrogenemic males. We hypothesized that androgens decrease expression of transcript abundance and quantities of proteins in the insulin signaling cascade of VWAT adipocytes from females. Subcutaneous WAT (SCWAT) and VWAT were harvested from male rats and female rats in proestrus and cultured, induced adipocytes were treated with: control (C), dihydrotestosterone (DHT 10^{-6} M), estradiol (E2 10^{-6} M), or testosterone + fulvestrant (T+Fulv 10^{-6} M). Cells were evaluated for transcript abundance via qPCR *(Insr, Irs1, Akt2, Foxo1)* and for protein quantity (pAKT/AKT, pFOXO1/FOXO1) via western blotting. *Insr* was upregulated in female SCWAT adipocytes in response to T+Fulv treatment ($p<0.05$). Females had a decreased pAKT/AKT in response to DHT but increased pAKT/AKT in response to T+Fulv in VWAT adipocytes ($p=0.05$). By contrast, females had decreased pFOXO1/FOXO1 in response to DHT and T+Fulv in SCWAT adipocytes ($p<0.05$). Interestingly, males had decreased pAKT/AKT in response to all steroid treatments in VWAT adipocytes ($p<0.0001$) and decreased pFOXO1/FOXO1 in response to T+Fulv in VWAT adipocytes ($p=0.0045$). In conclusion, male SCWAT adipocytes are less sensitive to androgens than female SCWAT adipocytes. Females show decreased phosphorylated protein abundance in VWAT and SCWAT in response to potent androgens, indicating down-regulated insulin signaling. Future studies are necessary to determine why male VWAT adipocytes had decreased pAKT/AKT in response to steroids and how these results affect lipolysis and lipogenesis in WAT of males and females.

3:45 PM – 5:15 PM: ELIZABETH YOUNG NEW INVESTIGATORS SYMPOSIUM *(Mercer)*

Soumya Turaga, PhD student, Cleveland State University
Junction adhesion molecule-A (JAM-A) deficiency drives sex-specific differences in glioblastoma progression via differential responses in the tumor microenvironment

Glioblastoma (GBM) is the most malignant primary brain tumor in adults with poor prognosis. Despite the male preponderance for developing GBM and better outcomes in females, the current treatment paradigms do not account for sex as a biological variable. JAM-A is a tight junction protein that our laboratory found to be important for GBM cancer stem cell growth. To assess its role in the tumor microenvironment JAM-A knockout (KO) mice were injected with mouse glioma cells intracranially and we observed that JAM-A KO mice exhibit differential survival between males and females. While wild-type males experience poorer survival compared to female wild-type mice, this trend is reversed in JAM-A KO mice. Based on these differences, I hypothesize that JAM-A suppresses tumor growth in females and its deficiency in the tumor microenvironment leads to poor outcomes. Since JAM-A is predominantly expressed by the microglia in the brain, analysis of microglia in normal and tumor bearing mice demonstrated significant differences in microglia number and activation status with the female KOs having more activated microglia upon tumor engraftment. Upon qPCR screening of microglia markers that are responsible for sex specific differences in brain pathologies, we identified that an estrogen regulating protein lipocalin2 (LCN2) is highly upregulated in the female JAM-A KO microglia and tumors. Current experimental approaches are aimed at targeting LCN2 and estrogen expression to delineate JAM-A-LCN2-estrogen signaling axis to improve outcomes in a sex-specific manner. Although, tumor cell intrinsic sex-specific differences have been reported, this study is a first to demonstrate that differences in GBM tumor microenvironment drive sexually dimorphic tumor growth. In conclusion, our findings offer a possible explanation for a poorly understood protective effect seen in female gliomas and uncovers important aspects of sex-hormone signaling for optimizing the care of brain tumor patients.

Jonathan VanRyzin, PhD student, University of Maryland School of Medicine *Endocannabinoids program sex differences by inducing microglia phagoptosis of newborn cells in the neonatal rat amygdala*

The amygdala is a sexually dimorphic brain region important for juvenile social play behavior. During neonatal development, the male amygdala contains fewer newborn cells than females. This sex difference inversely correlates to the expression of juvenile social play, a process we previously demonstrated to be the result of a higher developmental endocannabinoid (ECB) tone in the male amygdala (Krebs-Kraft *et al. PNAS* 107(47), 2010). We now report that microglia, the resident immune cells of the brain, are more phagocytic in the amygdala of males during this postnatal window, suggesting a possible mechanism by which ECBs affect the number of newborn cells. Males had more phagocytic microglia between postnatal day 0 and 4 compared to females, mimicing the time course of the elevated ECB tone. Administering testosterone or cannabinoid receptor agonists to female pups masculinized the number of phagocytic microglia and correspondingly decreased the number of newborn cells. Based on these data, *we hypothesized that microglia actively control the number of newborn cells in the postnatal rat amygdala by phagoptosing (targeted phagocytosis of viable cells) newborn cells in an ECB-dependent manner*. Inhibiting phagocytosis increased the number of newborn cells only in males, demonstrating that newborn cells can survive if phagocytic activity is prevented. Moreover, reversing ECB signaling in males and females also reversed their sensitivity to phagocytic block; a higher ECB tone is both necessary and sufficient to drive microglia phagoptosis of newborn cells regardless of the sex or hormonal status of the pup. Together, these data suggest that sex differences in the local environment of the developing amygdala instruct microglia to actively phagoptose newborn cells as a means to produce sex differences in cell genesis with relevance to later life social behavior.

Hilda Ahnstedt, PhD, Postdoc, UT Heath *Sex differences in neutrophil-T cell Immune responses, gut integrity and outcome after ischemic stroke in aged mice*

Stroke is a sexually dimorphic disease. Women suffer from poor functional outcome after stroke, however recent data show that when adjusting for age and pre-stroke function, mortality is higher in men. Immune responses are key determinants of stroke outcome, but less is known in aged animals. This study examined sex differences in immune responses and outcome after stroke in aged mice. We hypothesized that aged male mice have greater post-stroke immune responses and worse outcomes than aged females. C57BL/6 mice (21 months) were subjected to 60 min middle cerebral artery occlusion (n=36-39), or sham surgery (n=18). Neutrophils and T cells were quantified in brain and blood at 24h, 7 days (d) and 15 d post-stroke by flow cytometry. Peripheral effects on gut and spleen, and functional outcomes were assessed at 3, 7 and 15d. Mortality (38% vs 17%, $p<0.05$) and hemorrhagic transformation rates (47% vs 0%) were significantly higher in males vs females. Peripherally, stroke induced greater splenic contraction and gut permeability of FITC-dextran ($p<0.05$) in males compared to females. Stroke induced long-lasting alterations in microbiota β-diversity in males, that was restored by d7 in females. Males had higher levels of MCP-1 and G-CSF at 24h in plasma, and $CD8^+$ T cells in blood at 15d (73±5% vs 52±3%, $p<0.001$). Central effects on the brain included higher neutrophil infiltration at 24h and regulatory T cells at 15 d in males ($p<0.01$). Open-field test showed decreased locomotor activity and higher anxiety levels in males than females at d3 ($p<0.01$). At 7 and 15d these differences were equalized while sticky tape test and hang-wire showed stroke-induced deficits in males and females. In conclusion, aged male mice had higher mortality and hemorrhagic transformation rates after stroke than females. Our data suggest that aged males have an amplified stroke-induced inflammatory response in parallel to greater peripheral effects on gut integrity and spleen size.

Valeria Raparelli, PhD, Postdoc, Sapienza University of Rome *Impact of sex and gender-related factors on percutaneous coronary intervention in patients with ischemic heart disease: analysis from the EVA study*

Ischemic heart diseases (IHD) are not synonymous with obstructive flow-limiting coronary artery disease (CAD), especially in women. Platelet play crucial role in IHD pathogenesis. However, scarce data on sex differences of platelet biomarkers are available. Therefore, we aimed to analyze sex differences in biomarkers of platelet function in patients with IHD according to sex and the coronary anatomy. From the "Endocrine Vascular disease Approach" (EVA) study, we analyzed IHD patients, not on chronic antiplatelet therapy, with available baseline blood samples, clinical and angiographic data. Soluble P selectin (sPs), soluble CD40L (sCD40L), thromboxane B_2 (TxB_2) were measured. A sex stratified biomarkers analysis according to coronary anatomy was performed. No obstructive disease was defined for coronary stenosis <50% in acute myocardial infarction (MINOCA) or stable angina (INOCA). Among one-hundred-ninety-nine patients (mean age 67±11, 37% women), acute coronary syndrome (ACS) was the reason for angiography in 46% cases. Women had more frequently ACS compared to men (54.8 vs 41.3%, p=.001) with no obstructive disease (27% vs 4%, p<.05). Obstructive disease was prevalent in men with stable angina (77% vs 62%, p<.05). Overall, platelet biomarkers were similar between sexes. However, when we stratified by clinical presentation and CAD type, we found statistically significant differences: only women with MINOCA have higher levels of TxB_2 comparing to women with obstructive or INOCA (187±68 vs 125±51 pg/ml, p=.003); women with MINOCA presented also the highest level of sPs (38±18 vs 26±10 ng/ml, p<.05), while no differences were observed in men. Of note, sCD40L level was higher in INOCA women comparing to men (3.2±2.1 vs 1.6±0.5, p=.03). Sex differences in platelet biomarkers exist in IHD. High levels of TxB_2, sPs, sCD40L identified women with no obstructive disease. A differential use of biomarkers might be of help towards a personalized sex-specific management of IHD.

5:00 PM – 6:15 PM: CAPSTONE LECTURE *(Mercer)*

Londa Schiebinger, Ph.D., Stanford University *Gendered Innovations in Health Research, Machine Learning, and Robotics*

How can we harness the creative power of gender analysis for discovery and innovation? In this talk I identify three strategic approaches to gender in research, policy, and practice: 1) "Fix the Numbers of Women" focuses on increasing women's participation; 2) "Fix the Institutions" promotes gender equality in careers through structural change in research organizations; and 3) "Fix the Knowledge" or "Gendered Innovations" stimulates excellence in science and technology by integrating sex and gender analysis into research. This talk focuses on the third approach. I will discuss several case studies, including gender variables in health research, gender and fairness in machine learning, and gender in robotics. To match the global reach of science and technology, Gendered Innovations was developed through a collaboration of over a hundred experts from across the United States, Europe, Canada, and Asia. Major funders for Gendered Innovations include the European Commission, the U.S. National Science Foundation, and Stanford University.

THURSDAY, MAY 3

8:30 AM – 10:15 AM: SESSION 17 *(Mercer Salon I)*

Sex Differences in Pain from the Sensory Nerves to the Brain *Chair: Dayna Loyd Averitt, PhD, Texas Woman's University*

Dayna Loyd Averitt, PhD, Texas Woman's University
The “Painful” Role of Peripheral Serotonin in Females

Currently over 100 million Americans are experiencing chronic pain and 1 in 4 is experiencing craniofacial pain mediated by the trigeminal system, such as migraine and temporomandibular joint disorder pain. Many persistent pain conditions occur predominantly in women making pain a major women’s health issue. One trigeminal pain mechanism that may be under hormonal influence is the peripheral serotonergic system. The neurotransmitter serotonin (5HT) is a proinflammatory and pronociceptive mediator in the periphery. In male rats, 5HT evokes pain via excitatory metabotropic and ionotropic 5HT receptors localized to a subpopulation of trigeminal nociceptors that express the transient receptor potential V1 ion channel (TRPV1), a cation channel activated by capsaicin that initiates pain signaling. While looking for evidence of this mechanism in human nociceptors obtained from extracted tooth pulp of men and women, we discovered that 5HT enhancement of pain signaling was limited to female nociceptors, and especially during the luteal phase of the menstrual cycle. This led us to hypothesize that gonadal hormones modulate serotonergic potentiation of TRPV1-expressing trigeminal sensory neurons. In rats, we found that injection of 5HT into either the rat hindpaw or vibrissal pad evoked greater pain behaviors in females during estrus and proestrus compared to females in diestrus, ovariectomized females, and males. 5HT only enhanced capsaicin-evoked orofacial pain behaviors in females in proestrus. Acute treatment of primary trigeminal sensory neuron cultures with 5HT + 17β-estradiol evoked significantly greater capsaicin-induced proinflammatory peptide release than neurons treated with 5HT + vehicle. This effect was not observed by treatment with membrane-impermeable 17β-estradiol, indicating a role of intracellular estrogen receptors. Together our data reveal a novel peripheral serotonergic pain mechanism in trigeminal sensory neurons that is modulated by gonadal hormones.

Greg Dussor, PhD, University of Texas at Dallas
CGRP and prolactin signaling in the meninges produces female-specific migraine-related behavior in rodents

Migraine is the third most prevalent disease worldwide, the most common neurological disorder, and it is three times more common in women; reasons for the sex difference are not known. Migraine patients have elevated levels of CGRP and attacks can be triggered by CGRP or treated by inhibitors of CGRP signaling. The hormone prolactin (PRL) has also been associated with migraine as levels rise during attacks and PRL-lowering agents have been shown to treat specific types of migraine in humans. The purpose of these studies was to determine whether CGRP and PRL play a differential role between sexes in nociceptive input from the dura mater, an essential event for migraine pain. Using preclinical behavioral models of migraine in both rats and mice, dural application of CGRP produced cutaneous hypersensitivity of the periorbital skin as well as facial grimace; these responses were observed only in females. In females, dural CGRP caused priming; once animals recovered from the initial CGRP-induced behavior, they were sensitized to normally subthreshold stimuli including dural pH 7.0 solution and a systemic nitric oxide (NO) donor (a migraine trigger in humans). In contrast to CGRP, interleukin-6 (IL-6) caused priming in both males and females, indicating that IL-6 responses and priming can be induced in both sexes but that CGRP responses and CGRP-induced priming only occurs in females. Like CGRP, dural application of PRL produced female-specific cutaneous hypersensitivity as well as facial grimace. Interestingly, the response to dural CGRP was blocked by ΔPRL, a PRL receptor antagonist, and the response to dural PRL was blocked by $CGRP_{8-37}$, a CGRP receptor antagonist. Together, these data demonstrate that both dural CGRP and PRL promote female-specific headache behavior and suggest that an interaction between the signaling pathways occurs in females. These dimorphic effects of CGRP and PRL may contribute to the sex differences observed in migraine in humans.

Loren Martin, PhD, University of Toronto
Male-specific conditioned pain sensitivity in mice and humans

Abstract unavailable at time of printing

Arbi Nazarian, PhD, Western University of Health Sciences
Sexually dimorphic morphine antinociception in the sensory and affective components of pain in rats

Sex differences in the antinociceptive effects of morphine have been demonstrated in both acute and chronic pain models in rodents, with males being more sensitive to morphine than females. We have examined sex differences in pain and morphine antinociception in our laboratory at multiple levels. In this presentation, we will demonstrate findings showing sex differences in formalin-evoked primary afferent excitability via internalization of NK1 receptors (measure of SP release), and compare those findings to expression of cFos and pERK in the superficial dorsal horn, demonstrating distinct effect suggesting that primary mechanisms of sex differences may be supraspinal. Moreover, the effects of morphine in the sensory component of formalin- and CFA-evoked pain will be presented along with examination of morphine conditioned place preference in formalin and CFA treated rats. Discussion will primary involve distinction of sex differences and response to morphine between the two components of pain and the effects of pain chronicity and how that impacts morphine antinociception.

8:30 AM – 10:15 AM: SESSION 18 *(Mercer Salon G/H)*

Defining and Measuring Sex and Gender in Clinical Research *Chair: Louise Pilote, MD, MPH, PhD, FRCPC, McGill University and Rachel Dreyer, PhD, Yale University*

Londa Schiebinger, PhD, Stanford University
Gender as a cultural variable across the lifespan

Brief overview and definitions of sex and gender broadly conceived. Current directions in definitions, demographics, and social issues.

Valeria Raparelli, PhD, Sapienza University of Rome
European physicians' awareness of the difference between sex and gender: the IMAGINE survey

Sex and gender shape health status through dynamic interaction, therefore the integration of sex and gender in research and clinical approach is mandatory and it drives towards a personalized medicine and equality in health care. On this basis, the European Federation of Internal Medicine (EFIM) built up the *Internal Medicine and Assessment of Gender differences in Europe* (IMAGINE) working group. The first phase of the IMAGINE framework was conceived to assess the awareness of the Internal Medicine community on sex and gender dimension in approaching clinical and research questions. Therefore, among December 2017 and March 2018, an online short survey was run among European internists clinicians. Briefly, the first 3 questions aim to assess the knowledge on terminology (sex vs. gender) and the awareness of factors specifically related or not to sex and gender dimensions. The fourth question explores the perceived knowledge on sex and gender differences in major diseases within the field of internal medicine. The fifth and sixth questions point out if physicians checked clinical guidelines for the presence of recommendations specifically tailored according to sex and whether they are aware of the low rate of women's enrolment in clinical trials. Finally, the seventh question is targeted to the identification the high-priority topics for internal medicine community in terms of knowledge in a sex- and gender-perspective. Preliminary results of IMAGINE survey (>1000 participants) will be presented.

Louise Pilote, MD MPH PhD FRCPC, McGill University
Measuring Gender in a Cohort of Patients with Premature Acute Coronary Syndrome

Background: There is growing interest in assessing the impact of sex and gender on health outcomes. The distinction between sex and gender is often not clear. Sex is a biologically based construct whereas gender incorporates the effects of social norms and expectations. How gender is measured remains the source of active investigation. In this seminar, we will describe the design of a gender score based on four gender constructs including gender identity, roles, relations and institutionalized gender. Methods: A cohort of 1213 patients aged 55 years or less with acute coronary syndrome filled out a questionnaire pertaining to the four aspects of gender. To group and reduce the number of gender-related variables, we first used a principal component analysis (PCA). To determine which variables were related to gender, we conducted a logistic regression analysis where sex was the dependent variable. Coefficient estimates obtained through the final logistic regression were used to calculate the gender score. Results: Of 26 variables included in the PCA, 6 components were retained and 17 variables explained 70% of the variance. Of these, 7 were found to be significantly associated with sex in the logistic regression. From a score of 0 for gender most related to being a man in our society, to 100 for gender most related to being a woman, the distribution of gender was different between men and women. In men, scores ranged from 0 to 3, 4 to 12 and 13 to 100 and in women from 0 to 43, 49 to 82 and 83 to 100 in women for the first, second and third tertiles respectively. Conclusions: This composite gender score can be used to distinguish the effect of sex and gender on health outcomes. The retained variables may vary from one cohort to another and the gender score distribution will vary with cohort, age, culture and time.

Rachel Dreyer, PhD, Yale University
The VIRGO Cohort on Premature Acute Myocardial Infarction. Measuring Sex and Gender: Lessons Learned

There has been growing public awareness and increasing attention to young women (<55 years) with acute myocardial infarction (AMI) who represent an extreme phenotype in coronary heart disease. Young women presenting with AMI develop coronary disease by different mechanisms and have worse recoveries, with higher risk for morbidity and mortality compared with similarly aged men. One contemporary prospective study has, in particular, informed our recent understanding of outcomes and predictors of outcomes among young women with AMI. The VIRGO study *(Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients)* was a prospective international study to investigate key demographic, clinical, psychosocial, biological, behavioral, and environmental determinants of the prognosis of young women and men with AMI. Findings from the first phase of research in investigating these young patients have emphasized both sex and gender differences in the epidemiology, diagnosis, and management of AMI in young women (when compared with men) across the continuum of care. These results have provided potential targets for interventions to improve their outcomes and clinical course. Accordingly, this seminar will: (1) provide an overview of the VIRGO study rationale, design and methodology; (2) present contemporary results from the VIRGO study in relation to sex *and* gender related factors; (3) discuss lessons learned from measuring sex and gender in prospective cohort studies, including how this work has informed the second phase of research on young women with AMI – with an emphasis on gender.

Vera Regitz-Zagrosek, MD, PhD, Institute of Gender Medicine
Gender in coronary artery disease and gender in the aging population

The relevance of the sociocultural dimension of gender for the development and course of diseases in the older population in particular has been neglected so far. We hypothesized that gender explains differences between women and men in aging.
We therefore initiated a follow-up study of the population-based cohort BASE-II, originally launched to investigate factors of “healthy vs. unhealthy” aging in 2009 to measure the effect of gender. Participants who completed the 1st wave of BASE-II (2009-2014) will be asked for participation in the planned 2nd wave study (2018/19), GendAge. We expect to survey 1,200 participants and collect data on medical, psychosocial and socio-economic conditions and their changes since the first wave. We will calculate a gender score from the 1st and 2nd wave data based on a previously described method (Pilote 2015) using all available gender related variables from our cohort. As proposed by Pilote 2015, we will include these variables into a principal component analysis and thereafter in a stepwise logistic regression to calculate a BASE-II specific gender score that might than be compared with other scores. In parallel, we will calculate the original Gender score published by Pilote (2015).
In this seminar, we will 1) share how we reconstruct this gender score based on the available 1st wave data, 2) investigate how the distribution of our German-specific gender score differs by age and other relevant characteristics, and changes in a longitudinal manner, 3) we will discuss our approach to create a gender construct, specific for this aged healthy German cohort and 4) we will present similar approaches in a German stroke study (Gender PRAISE). The combined efforts will enable us to investigate if and how gender-related factors contained in the gender score are predictors of cardiovascular and metabolic outcomes related to aging and stroke in German women and men.

10:30 AM – 12:15 PM: SESSION 19 *(Mercer Salon I)*

Endocrine Disruptors: Sex Differences in their Effects During Development *Chair: Janice Juraska, PhD, University of Illinois*

Janice Juraska, PhD, University of Illinois
Endocrine disruptor effects during early development and during adolescence on neural structure and cognitive behavior

Because gonadal hormones influence the sexual differentiation of the rodent cerebral cortex during both perinatal and adolescent development, exposure to endocrine disruptors at either of these times may alter the structure and function of the cortex. Here bisphenol A (BPA), which interacts with the estrogen receptor especially Erβ, and an environmentally relevant mixture of phthalates, which have anti-androgenic effects, were investigated. One of these endocrine disruptors was fed to pregnant dams through postnatal day 10 of lactation to examine their offspring. In another experiment, adolescent rats that had not been exposed earlier were fed BPA. In all of the studies, rats were examined in adulthood after months without exposure.
Perinatal BPA exposure resulted in a higher number of neurons in the medial prefrontal cortex (mPFC) in adult males, but not in females, although this result was variable. Additionally, we have evidence that BPA decreased developmental cell death in the pup mPFC. Perinatal BPA exposure also led to less social play during adolescence. Adolescent exposure to BPA resulted in more glia in adult female rats, while adult males had fewer glia. Perinatal exposure to a phthalate mixture, on the other hand, resulted in lower numbers of neurons and synapses in adults of both sexes. There was a dose dependent decrease in adolescent play behavior that was only significant in males. The prior-exposed adult animals of both sexes also performed more poorly on an attentional set shifting task which is a measure of cognitive flexibility that relies in part on the mPFC. Thus BPA tends to affect males more than females at least for these endpoints. This is in contrast to the phthalates which affected both sexes following perinatal exposure.

Jodi Flaws, PhD, University of Illinois
Sex differences in the effects of phthalate exposure on reproduction

Di(2-ethylhexyl) phthalate (DEHP) is used as a plasticizer in consumer products such as toys, food containers, and medical devices. It is also a known endocrine disrupting chemical. However, little is known about whether exposure to DEHP during gestation affects the development and function of the reproductive systems of female and male offspring. Thus, this study tested the hypothesis that gestational exposure to DEHP differentially affects the development and function of the female and male reproductive systems. Pregnant CD-1 mice were orally dosed with corn oil (vehicle control) or DEHP (20 µg/kg/day-750 mg/kg/day) daily from gestation day 10.5 until birth. On postnatal days 1-22 months, some female and male pups from each litter were euthanized, gonads were collected for morphological evaluation of germ cells, and sera were used to measure progesterone, testosterone, and estradiol levels. Some female and male pups were subjected to fertility tests, some female pups were subjected to measurements of estrous cyclicity, and some male pups were subjected to measurements of sperm numbers and morphology. In females, gestational exposure to DEHP reduced germ cell numbers, increased estradiol levels, increased the time females spent in diestrus, reduced female fertility, and caused early onset of reproductive senescence. In males, gestational exposure to DEHP reduced sperm numbers, decreased sperm motility, and increased sperm morphological abnormalities. It also increased estradiol levels, decreased testosterone levels, and caused early reproductive senescence, but not until the males were 16 months old. Interestingly, the effects of gestational exposure to DEHP were more dramatic and occurred at later time-points and different doses in male compared to female offspring. Collectively, these data indicate that gestational exposure to DEHP adversely affects the development and function of the reproductive system, but some of the effects differ by sex.

Emilie Rissman, PhD, North Carolina State University
Paternal endocrine disruptor exposure influences behavior in offspring

Endocrine disrupting compounds (EDC) are manufactured chemicals produced for use in industrial and household items. One of the most abundant and well-known of these is Bisphenol A (BPA), which is now banned in Europe and Canada, and scrutinized by consumers in the US. Thus, manufacturers have started to replace BPA with very similar compounds ("BPA-free"). We performed a dose-response study with one of these BPA-substitutes, bis(4-hydroxyphenyl) methane, abbreviated as BPF. Unlike the majority of EDC experiments in which dams are exposed during pregnancy and offspring are phenotyped here we treated sires only with BPF. Adult CD1 male mice were placed on one of 4 custom diets with either 0, 0.5, 5, or 50 mg/kg BPF incorporated into the diet. Fifty days later mating was conducted and repeated for 4 hours daily until a vaginal plug was noted. Solitary females gave birth and reared pups until weaning (postnatal day 21). Pups were monitored for body weights, food intake, and as adults used either to examine behavior in open field and elevated plus maze, a social recognition task, or a paired social interaction task. Levels of BPF in sires' plasma were measured, they reflected the exposure in food and were in a "human-like" range. Notably, body weight gain of the sires during the BPF-dosed period was affected by BPF exposure, BPF-consuming males gaining less weight than controls. However, the groups did not differ in food intake. To date only a few data have been completely analyzed but preliminary results show that an effect of sires' BPF intake on social interactions in the recognition task is apparent in females, but not in males. Females from sires consuming BPF were less interactive than controls. All behavioral data will be presented at the meeting. This is one of the first studies on BPA substitutes and their effects on behavior.

Rita Strakovsky, PhD, Michigan State University
Sex-specific effects of developmental bisphenol A (BPA) exposure in rats on adiposity and adipose tissue microRNA (miR) expression

Bisphenol A (BPA) is a plasticizer and endocrine disruptor with widespread exposure in pregnant women. Our previous study showed that prenatal BPA exposure in rats increases adulthood adiposity in male but not female offspring. MicroRNAs (miRs) are short non-coding RNAs that post-transcriptionally alter mRNAs. To investigate whether gestational BPA exposure has sexually-dimorphic effects on miRs in adipose tissue of adult rats, pregnant Sprague-Dawley rats were dosed with vehicle (oil) or BPA (100 μg/kg/day) from gestational day 6 until postnatal day (PND) 21. Gonadal adipose tissue from male and female offspring was collected on PND110 and subjected to small RNA-sequencing. 752 known miRs (miRbase v22) were identified. Of these, 64 miRs had a significant BPA by fetal sex interaction ($P < 0.10$, fold change > 1.5). These 64 sexually-dimorphic miRs were predicted ($P < 0.01$, Targetscan) to target 2,021 genes regulating various pathways within biological processes (51 miRs targeting 165 genes), cellular components (46 miRs targeting 174 genes), molecular function (43 miRs targeting 202 genes), nucleus (57 miRs targeting 467 genes), and protein binding (59 miRs targeting 1013 genes). Of these 64 sexually-dimorphic miRs, BPA affected 47 miRs in females but not in males, affected 12 miRs with different magnitude in females vs. males, and had directionally opposing effects on 5 miRs in females vs. males. Pathway analysis using miRPath predicted ($P = 0.001$) that 2 of these 5 miRs (miR-378a-5p and miR-382-5p) targeted 5 genes in the estrogen signaling pathway (*Atf6b, Adcy3, Creb1, Esr2*, and *Hspa2)*. These data suggest that developmental BPA exposure has long-term sexually-dimorphic effects on the expression of miRs predicted to regulate numerous pathways in adipose tissue. Whether these differences mediate observed sex-specific adiposity in females vs. males in response to BPA exposure merits future investigation.

10:30 AM – 12:15 PM: SESSION 20 *(Mercer Salon G/H)*

Women and Alzheimer's Disease: A Scientific Update from the SWHR Interdisciplinary Panel on Alzheimer's Disease *Chair: Pauline Maki, PhD, University of Illinois at Chicago*

Michelle M. Mielke, PhD, Mayo Clinic
Understanding sex differences in the prevalence, incidence, and risk factors of Alzhiemer's disease

Although tremendous strides have been made in Alzheimer's disease (AD) research over the past several years, limited attention has been given to sex and gender differences in AD. This has led to significant knowledge gaps in research and a lack of awareness among the research community on sex and gender differences in AD. This presentation will first discuss and compare the frequency, prevalence, and incidence of AD by sex and how these terms can provide different estimates. In the last few years, several reports have generated misleading headlines stating that women are at greater risk of developing AD compared to men. However, the numbers behind these headlines are not clear. There has also been little discussion about risk factors for AD that may differ between women and men. The goal of this talk is to provide clarity on what the phrase "women are at greater risk" means and to provide a better understanding of the sex and gender differences that can influence the development and progression of AD.

Kejal Kantarci, MD, MS, Mayo Clinic
What AD biomarker studies tell us about sex differences in AD

New neuroimaging and CSF biomarkers show promise in elucidating the influence of sex on Alzheimer's disease (AD) pathophysiology. Recent clinical biomarker studies have informed understanding of the influence of sex on the course of AD from preclinical AD to AD dementia. This presentation will provide an overview of these findings in three distinct categories of validated AD biomarkers: 1) Biomarkers of Aβ deposition, which include decreased CSF Aβ42 and elevated Aβ ligand uptake on PET; 2) Biomarkers of neurofibrillary tangle tau (NFT-tau) pathology, which include elevated CSF phosphorylated tau (p-tau) and elevated NFT-tau ligand uptake on PET; 3) Biomarkers of neurodegeneration which include decreased glucose metabolism on F-18 fluorodeoxyglucose (FDG) PET, structural MRI measures of atrophy in the temporoparietal cortex, and elevated CSF total tau.

Pauline Maki, PhD, University of Illinois at Chicago
Women, Menopause, and AD: New insights into the intersection between reproductive aging and brain aging

The field of Alzheimer's disease (AD) research recognizes the importance of identifying midlife risk factors for AD as a primary means of preventing the disease. However, menopause has received surprisingly little attention as a critical factor that can influence brain aging in women. A rapidly expanding literature demonstrates the importance of considering menopause-related risk factors for AD in women. During the menopausal transition, women report an increase in forgetfulness and show a decline in processing speed and memory for verbal material. Similarly, neuroimaging studies demonstrate menopause-related changes in brain function. These cognitive and brain changes persist after accounting for age and other factors. Decreases in estradiol likely play a prominent role in these cognitive and brain changes; memory performance decreases following oophorectomy and pharmacological suppression of gonadal steroids but is normalized with add-back estrogen. Neuroimaging studies show estrogen-related effects on the hippocampus and prefrontal cortex in midlife women. Vasomotor symptoms (VMS) may also contribute to cognitive difficulties and alterations in brain structure and function in midlife women. There is an association between memory performance and physiological VMS measured with ambulatory skin conductance monitors, and initial evidence that treating physiological VMS results in improvements in memory. In neuroimaging studies physiological VMS are associated with ischemic burden and alterations in brain function, including the function of the hippocampus during active rest and during performance of memory tasks. These effects are not explained by sleep, age, or estradiol

levels. The changes in cognition and brain function that are associated with menopause stage and VMS may represent a sex-specific risk factor for accelerated cognitive aging that may make women more vulnerable to AD pathology.

MaryJo LaDu, PhD, University of Illinois at Chicago
Modeling the effect of sex on APOE4-induced AD Risk in transgenic mice

The ε4 allele of apolipoprotein E (apoE) is the greatest genetic risk factor for Alzheimer's disease (AD) and is associated with accelerated accumulation of both amyloid plaques and soluble oligomeric forms of the amyloid-β peptide (oAβ), likely a proximal neurotoxin. Importantly, female ε4 carriers have a greater lifetime risk for developing AD, an increased rate of cognitive decline and accelerated accumulation of Aβ compared to male ε4 carriers. Data from transgenic mice expressing the human *APOE* genotypes plus familial AD (FAD) mutations allow for the study of sex differences in cognition and AD pathology as a function of *APOE* genotype. We use a unique preclinical mouse model, the EFAD mice, that express the human the *APOE* genotypes plus 5 x FAD mutations. Data from this mouse model demonstrate that sex profoundly influences the *APOE4* genotype-specific effects on AD pathology, including cognition, soluble and deposited Aβ, and neuroinflammation, which was particularly severe in the E4FAD females. This talk will review EFAD mouse data and provide a context for comparing pathology in a preclinical mouse model with diagnosis and/or risk in a human cohort. Understanding these interactions are critical for developing treatment options for female ε4 carriers at a high risk for AD. In addition, interpreting these data, evaluating therapeutics and identifying biomarkers must be grounded in a stratified approach, with both control and AD cohorts by sex within each *APOE* genotype.

Poster Session 1

Monday, April 30, 2018

1. Detection of serotonin receptor and estrogen receptor alpha protein expression in human dental pulp: a potential trigeminal pain mechanism
Sushmitha Ananth, Sukhbir Kaur, M.S., Phillip Kramer, Ph.D., and Dayna L. Averitt, Ph.D.

2. Gray Matter Correlates of Finger Gnosis (Finger Sense) in Children: a VBM Study
Firat Soylu Ph.D., Mona Anchan, and Sharlene D. Newman, Ph.D.

3. "Mainstreaming Gender into Research" means Gender Medicine in the Medical Education
Angelika Bader, Heidi Siller, and Margarethe Hochleitner

4. Understanding immune system sex differences in the healthy human transcriptome
Erika L. Bongen, P.J. Utz, and Purvesh Khatri

5. Sex differences in oxytocin modulation of social reward and social motivation in Syrian hamsters
Johnathan M. Borland M.S., Kymberly Grantham B.S., Kylie O'Laughlin, Lauren Aiani B.S., Kyle J. Frantz Ph.D., H. Elliott Albers Ph.D.

6. Sex-Specific Effects of Testosterone on the Sexually Dimorphic Transcriptome and Epigenome of Embryonic Neural Stem Cells: A Model for Early Hormonal Brain Organization
Matthew S. Bramble, Ph.D., Neerja Vashist, B.S., Hayk Barseghyan, Ph.D., Valerie A. Arboleda, M.D., Ph.D., and Eric Vilain, M.D., Ph.D.

7. Escape from X-chromosome inactivation
Carolyn J. Brown Ph.D., Bradley Balaton B.Sc., Samantha Peeters B.Sc., Andrea Korecki B.Sc., and Elizabeth M. Simpson Ph.D.

8. Sex differences in steroid-sensitive neural projections to the periaqueductal gray: identification of novel pain pathways in female rats
Daisy J. Cantu, Sukhbir Kaur, M.S., Anne Z. Murphy, Ph.D., and Dayna L. Averitt Ph.D.

9. Electrophysiological properties of male and female medium spiny neuron subtypes in the nucleus accumbens core of Drd1a-tdTomato line 6 BAC transgenic mice
Jinyan Cao Ph.D., David Dorris, and John Meitzen Ph.D.

10. Sex and age differences in the metabolic and neural responses to high fat diet
Amy Christensen, Ph.D. and Christian Pike, Ph.D.

11. Role of active demethylation in sexual differentiation of the mouse brain
Carla D. Cisternas Ph.D., Laura R. Cortes B.S., and Nancy G. Forger Ph.D.

12. A Population Level Epidemiological Study of Peripartum Cardiomyopathy in Olmsted County, Minnesota
Erika J. Douglass, MPH, DeLisa Fairweather, Ph.D., and Lori Blauwet, M.D.

13. Sex differences in the blood ethanol concentration profiles of Japanese quail
Shannon E. Eaton B.A., Meredith A. Saunders M.S., Julia E. Jagielo-Miller B.S., Mark A. Prendergast Ph.D., and Chana K. Akins Ph.D.

14. Biological sex affects vaccine efficacy and protection against influenza in mice
Ashley L., Fink Ph.D., Kyrra Engle ScM, and Sabra L. Klein Ph.D.

15. Imaging sex and social status differences in the naked mole-rat
Mariela Faykoo-Martinez HBSc, Lily Qui MSc, Benjamin Darwin HBSc, Jason Lerch Ph.D., and Melissa M. Holmes Ph.D.

16. Role of Circulating Sex Hormones in Compulsive Ethanol Intake
Hannah D. Fulenwider, B.A., Michaela E. Price, Sadie E. Nennig, B.S., Jesse R. Schank, Ph.D.

17. Can transcriptomic profiles be used to predict sex-specific drug metabolism?
James C. Fuscoe, Ph.D., Qiang Shi, Ph.D., Tao Han, Ph.D., Lijun Ren, M.D., James J. Greenhaw, B.S., Joseph Hanig, Ph.D., Richard D. Beger, Ph.D., Lisa M. Pence, Ph.D., Laura K. Schnackenberg, Ph.D., Thomas C. Schmitt, B.S., Varsha G. Desai, Ph.D., Carrie L. Moland, A.A.S., and Vikrant Vijay, Ph.D.

18. Early life stress leads to sex-specific alterations in perineuronal net formation in the developing rat prefrontal cortex
Kelsea R. Gildawie, B.S., Jennifer A. Honeycutt, Ph.D., and Heather C. Brenhouse, Ph.D.

19. The Endocrine Disruptors Bisphenol A (BPA) and BPS increase Myocarditis in Male and Female BALB/c Mice
Anneliese R. Hill, Katelyn A. Bruno, Jessica E. Mathews, Alex Yang, Henry D. Greyer, Frank A. Molina, Ashley J. Scott, J. Augusto Frisancho, Adriana Bucek, Merci S. Greenaway, George M. Cooper, Alexandra C. Coronado, Allison R. Stafford, and DeLisa Fairweather

20. Progesterone efficacy on pain behaviors associated with estrogen in a rat model of persistent temporomandibular joint inflammation
Rebecca S. Hornung, B.A., Will L. Benton, B.S., Sirima Tongkhuya B.S., Lynda Uphouse, Ph.D., and Dayna L. Averitt, Ph.D.

21. High fructose diet impairs learning and alters microglia in adult male, but not female, rats
Molly M. Hyer, Ph.D., Laurel Kovalchick, B.S., Charlie Salome-Sanchez B.S., Samya K. Dyer, B.S., and Gretchen N. Neigh, Ph.D.

22. Impact of sex on gut microbial composition, mucosal immunity and metabolism.
Nyrie Israelian, Alexandra Paun, Ph.D., Alessandra de Paiva Granato, Ph.D., Mark Palmert, M.D., Ph.D., and Jayne S. Danska, Ph.D.

23. Novel Y chromosome long non-coding RNAs expressed in human male CNS during early development
Martin M. Johansson Ph.D., Philipp Pottmeier M.Sc., Pascalina Suciu M.Sc., Tauseef Ahmed M.Sc., Ammar Zaghlool Ph.D., Jonatan Halvardson, Ph.D., Elisabeth Darj M.D., Lars Feuk Prof., Christiane Peuckert, Ph.D., and Elena Jazin Prof.

24. The role of actin polymerization in GPER-mediated hippocampal memory enhancement in female mice
Jaekyoon Kim M.S., Jayson C. Schalk, Wendy A. Koss Ph.D., and Karyn M. Frick, Ph.D.

25. Effects of dorsal hippocampal estradiol treatment and aromatase inhibition on memory consolidation in male mice.
Wendy A. Koss, Ph.D., Rachel L. Gremminger, Sarah M. Philippi and Karyn M. Frick, Ph.D.

26. Developmental and sex differences of GPER1 and ERÎ± expression in the striatum of male and female rats
Amanda A. Krentzel, Ph.D., Ashlyn Johnson, B.S., and John E. Meitzen, Ph.D.

27. Attentional Bias Towards Threat and Trauma Exposure: An Examination of Gender Differences in Children Exposed to Early Life Trauma
Maya Lakshman, Lauren Murphy, Sierra Carter, Abigail Powers, and Tanja Jovanovic

28. Central Immune Alterations in a Gestational Stress Model of Postpartum Depression
Kathryn M. Lenz, Ph.D., Caitlin Post, B.S., Arthur J. Castaneda, B.S., Paul Banta, Lars H. Nelson, B.S., Angela Saulsbury, B.A., Benedetta Leuner, Ph.D.

29. The X-chromosome copy number difference causes the gender disparities in bladder cancer
Satoshi Kaneko and Xue (Sean) Li

30. Sex differences in modulatory effects of 17Î² estradiol on serotonergic neuromodulation of TRPV1 expressing sensory neurons
Sukhbir Kaur Lulla M.S., Cierra Lopez, B.S., Sirima Tongkhuya, B.S., and Dayna L. Averitt, Ph.D.

31. Biological sex influences allergen-induced mast cell activation patterns and severity of anaphylaxis
Emily Mackey, B.S. and Adam J. Moeser, Ph.D., D.V.M.

32. Mercury accumulation and the mercury - PCB - sex interaction in summer flounder
Charles P. Madenjian, Ph.D., Olaf P. Jensen Ph.D., David P. Krabbenhoft Ph.D., John F. DeWild M.S., Jacob M. Ogorek M.S., and Anthony R. Vastano M.S.

33. Sex differences in the effects of paternal deprivation on hippocampal volume and microglia density in the adult California mouse (Peromyscus californicus)
Farrah N. Madison, Sabina Khantsis, Allison Whitaker, and Erica R. Glasper

34. Preliminary results of life persuaded project, a multidisciplinary approach to study BPA and DEHP metabolite exposure and obesity in children: differences between boys and girls in italian population
Dr. F. Maranghi, Dr. S. Tait, Dr. L. Narciso, Dr. R. Tassinari, Dr. C. La Rocca

35. Microglial phagocytosis of newborn cells sculpts the cellular composition of the neonatal rat amygdala in a sex dependent manner
Ashley E. Marquardt B.S., Jonathan W. VanRyzin B.S., and Margaret M. McCarthy Ph.D.

36. A functional investigation of novel Y chromosome encoded long non-coding RNAs expressed in human male CNS during early development
Philipp Pottmeier M.Sc., Christiane Peuckert Ph.D., and Elena Jazin Prof.

37. Sex differences in the consequences of early-life immune activation on the ontogeny of hippocampal-dependent learning and microglia-neural signaling in the juvenile rat brain
Brittany F. Osborne, Sarah B. Beamish, and Jaclyn M. Schwarz, Ph.D.

38. Rat Model of Prenatal Zika Virus Infection
Morgan L. Sherer B.S., Pragyan Khanal B.S., Mark Parcells Ph.D., and Jaclyn M. Schwarz Ph.D.

Poster Session 2

Tuesday, May 1, 2018

1. Sex differences in associations between child abuse victimization, persistent cigarette smoking, and nicotine dependence
Alison L. Cammack, Ph.D., MPH, and Shakira F. Suglia, Sc.D., M.S.

2. Sex-specific behavioral endocrinology of BDNF Val66Met mice maintained on chronic oral corticosterone
Jordan Marrocco Ph.D., Nathan R. Einhorn B.A., Gordon H. Petty B.A., Claire Le Fioch B.A., Ilia N. Karatsoreos Ph.D., Francis S. Lee Ph.D., and Bruce S. McEwen Ph.D.

3. Estrous Cycle Dependent Differences in Female Cocaine Taking and Corresponding Dopamine Terminal Function
Madelyn I Mauterer and Sara R. Jones, Ph.D.

4. Are Sex Differences in the Brain Canalized?
Margaret M. McCarthy, Ph.D.

5. Sex differences and estrous-cycle effects of serotonergic potentiation of capsaicin-evoked orofacial nocifensive behavior
Hanna McDonald, Cierra M.C. Lopez, B.S., Sirima Tongkhuya, B.S., Sukhbir Kaur, M.S., and Dayna L. Averitt, Ph.D.

6. Sex differences in Aging in Healthy Women and Men
Kelly McGill, Paul J. Utz Ph.D., and Purvesh Khatri Ph.D.

7. Sex differences in vitamin D, kidney stones and comorbidities in patients with kidney stone disease
Anna A. Mease, Katelyn A. Bruno, Ph.D., Damian N. Di Florio, Erika J. Douglass MPH, Anneliese R. Hill, Jessica E. Mathews, William E. Haley, M.D., and DeLisa Fairweather, Ph.D.

8. Sex differences in medium spiny neuron electrophysiological properties: heterogeneity across striatal regions and evidence for estradiol-dependent sexual differentiation
John Meitzen, Ph.D.

9. The quandary of gender assignment in 46,XX newborns with classical adrenal hyperplasia and high genital masculinization
Heino F. L. Meyer-Bahlburg Dr. rer. Nat.

10. Biological sex influences gut barrier and neuroimmune developmental trajectories and clinical disease outcomes in a porcine model of early life adversity
Calvin Pohl D.V.M., Julia E. Medland M.S., Emily Mackey B.S., and Adam Moeser M.S. Ph.D., D.V.M.

11. Sex differences in Vitamin D and Cardiovascular Diseases in Systemic Sclerosis Patients
A. Carolina Morales-Lara, Katelyn A. Bruno, Ph.D., and DeLisa Fairweather, Ph.D.

12. Hippocampal cAMP signaling regulates spatial memory deficits in a mouse model of neurodevelopmental disorders in a sex-specific manner
Adele Mossa Ph.D., Marta Zamarbide Ph.D., Molly K. Wilkinson, Heather L. Pond, Adam W. Oaks, Ph.D., and Maria Chiara Manzini Ph.D.

13. Distinct roles of sex chromosomes and developmental timing of establishment of the sex-specific epigenome
Anna K. Naumova, Ph.D., Sanny Moussette, M.S., and Bianca Ho, M.S.

14. Sex Differences in Comorbidities Associated with Fibromyalgia and Hypermobility Syndromes
Rinald Paloka, Nicholas A. Courson, Peter T. Dorsher, M.D., todd D. Rozen, M.D., DeLisa Fairweather, Ph.D., Lynsey A. Seim, M.D., Edsel B. Bittencourt, P.T., Katelyn A. Bruno, Ph.D.

15. Sex differences in IQ and adaptive functioning in long-term adult survivors of pediatric cerebellar brain tumors
Tanya F. Panwala, Tiffany DeVaughn, Michelle E. Fox M.A., Tricia Z. King Ph.D.

16. Sex Differences in Rat Traumatic Stress Responses Recapitulate Sex Differences in Men and Women with PTSD
Apryl E. Pooley Ph.D., S. Marc Breedlove Ph.D., and Cynthia L. Jordan Ph.D.

17. Acute central administration of poly I:C disrupts memory encoding in female but not male mice
Caitlin K. Posillico, M.S., Rosa Garcia-Hernandez, Natalie C. Tronson, Ph.D.

18. Sex and estrous cycle induced differences in medium spiny neuron electrophysiological properties in adult rat nucleus accumbens core
Stephanie B. Proaño, Hannah J. Morris, Lindsey M. Kunz, David M. Dorris, John Meitzen

19. Sex Differences in Platelet Biomarkers and No Obstructive Coronary Artery Disease: Insights from the EVA Study
Valeria Raparelli M.D. Ph.D., Silvia Robuffo M.D., Claudia Tucci Med. Student, Agostino Rossoni Med. Student, Giuseppe Santangelo Med. Student, Roberto Scacciavillani M.D., Giulia Tosti Med. Student, Fabrizio Recchia Med. Student, Giulio Francesco Romiti M.D., Andrea Lenzi M.D., and Stefania Basili M.D.

20. Sex and Gender-Related Differences in Coronary Microvascular Dysfunction: data from the EVA Project
Valeria Raparelli M.D. Ph.D., Ludovica Maria Antonini M.D., Mariateresa Santoliquido Med. Student, Marco Borgi Med. Student, Valeria Spugnardi Med. Student, Maria Virginia Savoia Med. Student, Francesco Morricone Med. Student, Verdiana Santori Med. Student, Giulio Francesco Romiti M.D., Andrea Lenzi M.D., and Stefania Basili M.D.

21. Chronic adolescent stress alters the adult hippocampal transcriptome in a sex-specific manner
Sydney A. Rowson, Mandakh Bekhbat Ph.D., Sean D. Kelly, Zhaohui Qin Ph.D., and Gretchen N. Neigh Ph.D.

22. Gender differences in the access to treatments for substance abuse.
Darlene I. Santiago Ph.D., Chengli Shen M.D., Ph.D., and Douglas Landsittel Ph.D.

23. Sex differences in gray matter volume and behavior across DRD2 allele type during adolescent brain development
Rachel A. Schroeder B.S., Veronica C. Mucciarone B.A., Benson W. Stevens Ph.D., Valerie L. Darcey Ph.D., Emma J. Rose Ph.D., Diana H. Fishbein Ph.D., John W. VanMeter Ph.D.

24. Postnatal androgens masculinize central nervous system myelin
Michael Schumacher Ph.D., Charly Abi Ghanem Ph.D., and Abdel M. Ghoumari Ph.D.

25. Vitamin D deficient diet decreases cardiac function during myocarditis in females
John M. Sousou, Katelyn A. Bruno, Damian N. DiFlorio, Anneliese R. Hill, Jessica E. Mathews, Carolina Morales, Erika J. Douglass, Hewa Rahinduwage, Ilona Petrikovics, Jonathan B. Hoyne, Leslie T. Cooper, and DeLisa Fairweather

26. The PI3K/mTOR pathway contributes to sex differences in glioblastoma
Jasmin Sponagel, Kwanha Yu Ph.D., Joseph Ippolito M.D. Ph.D., Benjamin Deneen Ph.D., Josh B. Rubin M.D. Ph.D.

27. The heterochronic pathway regulates molecular and functional maturation of the male nervous system in C. elegans
Hannah Steinert M.S., and Douglas S. Portman Ph.D.

28. Preliminary evidence that gonadal hormone levels correlate with self-reported pubertal development and internalizing symptoms for African-American boys, but not girls.
A. Stenson, N. Thompson, A. Clifford, B. Bradley, and T. Jovanovic

29. Sex-specific differences in the hazard identification of chemical contaminats and the relevance for risk assessment
Dr. R. Tassinari, Dr. L. Narciso, Dr. C. La Rocca, Dr. S. Tait, Dr. G. Lori, Dr. F. Maranghi

30. Determining the impact of oral hormonal contraceptives on the central nervous system: a large-scale population neuroimaging study.
Caitlin M. Taylor Ph.D., and Emily G. Jacobs Ph.D.

31. Impact of the innate immune variants of the surfactant protein (SP-A) genes, on the susceptibility of mice after Klebsiella pneumoniae infection and sex differences.
Nithyananda Thorenoor, Xuesheng Zhang, Todd M. Umstead, David S. Phelps, and Joanna Floros

32. Estradiol-mediated deficits in fear inhibition can be rescued by zona incerta stimulation
Archana Venkataraman and Brian George Dias

33. B1 cells regulate sex-dependent immune responses to Chlamydia infection
Rachel M Kampen MSc, Cynthia Tram MSc, Melanie Tillman BSc, Nicole Hajjar and Jun Wang Ph.D.

34. The regulation of feeding behavior through the chemoreceptor odr-10 by genetic sex and feeding state in C. elegans
Emily Wexler, Deborah A. Ryan Ph.D. and Doug Portman Ph.D.

35. Estrous Cycle-Dependent Sex Differences in Rat Dorsal Striatal MSN Excitability
Jaime A. Willett B.S., Ashlyn Johnson, Opal Patel, David M. Dorris, and John Meitzen

36. Sex and inhibition: sex-specific differences in the development of the hippocampal GABAergic network
Daniele C. Wolf M.Sc., Nathalie T. Sanon Ph.D., Tarek Shaker M.Sc., Abdul-Rahman Elhassan M.Sc., and Lionel Carmant M.D.

37. Gender difference in association of symptoms and white matter deficits in first episode and drug-naïve schizophrenia
Xiang Yang Zhang, Xiangdong Du, Guangzhong Yin, Bo Cao, Jair C. Soares

38. Gender differences in association of cognitive deficits and low BDNF in first-episode drug-naïve schizophrenia
Xiang Yang Zhang, LiJuan Man, Xiangdong Du, Guangzhong Yin, Bo Cao, Jair C. Soares

ORGANIZATION FOR THE STUDY OF SEX DIFFERENCES

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Washington Marriott Georgetown
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May 5-8, 2019

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IGM President: Alexandra Kautzky-Willer (alexandra.kautzky-willer@meduniwien.ac.at)
Local Host: Kathryn Sandberg (sandberg@georgetown.edu)
Program Committee Chair: Karyn Frick (frickk@uwm.edu)
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14th Annual Meeting
Marina Del Rey Marriott
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May 4-7, 2020

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Local Host: Arbi Nazarian (anazarian@westernu.edu)
Program Committee Chair: Jackie Schwarz (jschwarz@psych.udel.edu)
2020 Symposia Proposals due: **Sept 15, 2019**

Enhancing the knowledge of sex and gender differences by facilitating interdisciplinary communication and collaboration among scientists and clinicians of diverse backgrounds.

Session 14 Wednesday May 2, 2018 10:30 am - 12:30 pm

Gender, Sex Hormones, and Lung Inflammation

Chair: Patricia Silveyra, PhD, Penn State College of Medicine

Title: Sex differences in the lung immune response to environmental agents

Author List: Patricia Silveyra, PhD[1,2]; Nathalie Fuentes, BS[1]; Marvin Nicoleau, BS[1]; Amy Spinelli, PhD[1]; Noe Cabello, BS[1]

Author Affiliations: [1]Department of Pediatrics, [2]Department of Biochemistry and Molecular Biology. Penn State College of Medicine. Hershey, PA 17033

Abstract: Sex differences in respiratory physiology have been identified. Likewise, accumulating evidence suggests that gender affects the incidence, susceptibility, and severity of lung disease. For example, asthma prevalence is higher in boys than girls. This pattern reverses in puberty when the prevalence becomes higher in women than men, and then reverts again to a male-predominant pattern after menopause. In addition, menstrual cycle variations in asthma severity are well established, postmenopausal women receiving hormone replacement therapy have significantly less airway obstruction than those not receiving it, and females with Turner's Syndrome (low circulating estrogen) exhibit increased airway responsiveness that is reduced with estrogen therapy. We hypothesized that circulating levels of sex hormones affect the inflammatory response to environmental agents. We tested our hypothesis in mouse models of acute inflammation (exposure to 2ppm of ozone for 3h) and chronic inflammation (exposure to house dust mite allergens for 5 weeks) by comparing the responses of intact vs. gonadectomized male/female mice. We verified the presence of peri-bronchial inflammation in lung sections, we identified differences in inflammatory gene expression, and in airway reactivity by measuring the sensitivity of animals to contractile agonist challenge using a rodent ventilator. We found significant differences in airway resistance and hyperresponsiveness in males vs. females with both challenges. In both sexes, gonadectomy and hormone replacement affected lung function and expression levels of inflammatory genes. Together, our results indicate that circulating levels of sex hormones affect lung function and prime the lungs for differential inflammatory responses following exposure to environmental agents. This information may help identify mechanisms associated with gender disparities in asthma incidence and severity, and variations of symptoms observed in men and women throughout life.

Funding: This study was funded by NIH grants K01HL133520 and K12HD055882 to Dr. Silveyra

Contact Information: Dr. Patricia Silveyra; Pulmonary, Immunology and Physiology Laboratory, Department of Pediatrics, Penn State College of Medicine; 500 University Drive, H085, Hershey PA 17033. 1-717-531-5605, pzs13@psu.edu

Title: Sex steroid signaling in the airway

Author List: Y.S. Prakash, M.D. Ph.D.[1, 2], and Venkatachalem Sathish, Ph.D.[3]

Author Affiliations: [1]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA; [2]Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA; [3]Department of Pharmacy, North Dakota State University, Fargo, ND, USA

Abstract: Asthma is more common in pre-pubescent males, but increases in women and aging males, highlighting roles for sex steroid effects in airways. A limitation to understanding how sex steroids influence asthmatic airways is their complex, cell- and context-dependent effects. Effects on bronchial epithelium and airway smooth muscle (**ASM**) are relevant, given their roles in modulating airway tone and structure. The focus should probably be on estrogens given increase in asthma among young women and that progesterone does not modulate estrogen effects. Whether and how estrogens are protective or deleterious in asthmatic airway is not clear. Emerging data show that **1)** Human ASM expresses ERα and ERβ; **2)** Estrogens non-genomically reduce ASM intracellular calcium ($[Ca^{2+}]_i$) responses to agonist and increase cAMP, overall aiding bronchodilation. Our data in human ASM show that: **1)** Asthmatic or cytokine-exposed ASM express more ERβ than ERα, suggesting a shift in ER profile; **2)** With inflammation, ERβ functionality is enhanced, and has a suppressive effect on $[Ca^{2+}]_i$, ASM proliferation and fibrosis; **3)** ERα and ERβ signaling diverge in inflamed or asthmatic ASM, with differential effects on cAMP vs. NFκB and p38 MAPK. In mice, estrogens downregulate airway hyperresponsiveness. In models of allergic asthma, ASM ERβ is increased (less so in epithelium), while conversely absence of ERβ results in greater airway thickening, reactivity, and ASM expression of Ca^{2+} regulatory and fibrosis proteins. Conversely, ERβ-specific agonists blunt airway reactivity and remodeling, and ASM expression of fibrosis proteins. Overall, emerging data highlight the need for further research into mechanisms by which estrogens affect the airway, the cell types involved, and specific roles of different receptors. Here, ERβ may take an “anti-inflammatory” role, setting the stage for exploration of ERβ in helping explain conflicting data on estrogens in asthma.

Funding: This study was funded by NIH R01 123494 (Sathish) and R01 HL088029 (Prakash).

Contact Information: Y.S. Prakash, MD, PhD, 4-184 W Jos SMH, Mayo Clinic, Rochester, MN 55905; 1-507-538-9869; Prakash.ys@mayo.edu.

Title: Circulating Sex Hormones as Critical Regulators of the Lung Immune Response

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Abstract: Exposure to ground-level ozone, an oxidative pollutant, causes lung inflammation, which can lead to pulmonary injury and impair lung innate immunity. There is emerging evidence that pulmonary diseases such as asthma affect women disproportionally with a greater degree of severity than men. In addition, most hospitalizations for asthma in women occur during the luteal phase or around the peri-menstrual stage. However, the combined effect of ozone and sex hormones in respiratory mechanics is unclear. Here, we hypothesized that circulating estrogen levels can regulate pulmonary function and lung mechanics following ozone exposure. We performed gonadectomy and hormone replacement (17β-estradiol, 2 weeks) in a group of adult male and female C57BL/6 mice. In control females, the stages of the estrous cycle were monitored by daily by vaginal smear, and confirmed by serum sex hormone levels. We exposed animals to 1 ppm of ozone or filtered air (FA) for 3 hours, and we compared lung function 24h after exposure with a methacholine challenge (MCh; 0 - 50 mg/ml) using the FlexiVent system. We observed significant changes in respiratory parameters (Ers, H, Rrs, R_N, G) in males and females, and in females exposed to ozone at different stages of the estrous cycle, at the two highest MCh concentrations. The pressure-volume curves obtained demonstrated similar MCh concentration-dependent changes. Gonadectomized males exposed to ozone had higher Rrs and Ers than females and males exposed to FA, and treatment with estradiol ameliorated these effects. Surprisingly, female mice in the metestrus and diestrus stages exposed to FA had higher Rrs and Ers values than when compared to the proestrus and estrus stages. Contrarily, exposure to ozone caused a decrease in parameters (Ers, Rrs) during metestrus and diestrus stages, but a slight increase of these in the proestrus and estrus stages. Our results indicate that pulmonary function following ozone exposure can be affected by circulating hormone levels. Future studies examining diseases associated with environmental pollutants should consider the women's menstrual cycle.

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