National Institutes of Health
Turning Discovery Into Health
The Office of Strategic Coordination – The Common Fund and the Office of Research on Women's Health presents:
SEX AS A BIOLOGICAL VARIABLE
October 26-27, 2017
Workshop

ABSTRACTS for POSTER SESSION

*POSTER #1: Sex Differences in the Endocannabinoid System Determines Differences in Juvenile Rough-and-Tumble Play Behavior and Correlating Differences in Phagoptosis by Microglia in the Developing Amygdala

Abstract submitter: Kathryn Jean Argue

Kathryn Jean Argue[1]; Jonathan W. VanRyzin[1]; Margaret M McCarthy[1]

[1]University of Maryland School of Medicine

The amygdala is a sexually dimorphic brain region that is critical for the expression of social behavior. In rats, the medial amygdala mediates the sex difference in juvenile rat play behavior. During early postnatal development, the male amygdala has a higher endocannabinoid (ECB) tone and contains fewer newborn cells than females, which correlates to increased levels of juvenile rough-and-tumble play. Masculinization of the female developing amygdala through agonism of the CB1 and CB2 ECB receptors, decreases the number of newborn cells and increases subsequent juvenile rough-and-tumble play (Krebs-Kraft et al. 2010 and Argue et al. 2017). We now report that the higher ECB tone in males is due to the actions of testosterone. Treating neonatal females with exogenous testosterone was sufficient to increase the ECB tone and juvenile rough-and-tumble play. This testosterone-induced increase in female rough-and-tumble play could be ablated with neonatal administration of CB1 and CB2 receptor antagonists. Additionally, 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. We find that males have more phagocytic microglia between postnatal day 0 and 4, during which time they also have higher ECB tone than females. Increasing ECB tone in female pups by treatment with specific agonists for either CB1 or CB2 receptors increases the number of phagocytic microglia to that of males and results in a corresponding decrease in the number of newborn cells indicated by BrdU labeling. We hypothesize that microglia 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. Masculinizing female pups with testosterone increases the number of phagocytic microglia and decreases the number of BrdU+ cells. Immunohistochemical analysis together with confocal microscopy indicates phagocytic microglia contain markers of DNA as well as newly proliferated cells in their phagocytic cups. To directly implicate microglia phagoptosis we utilized a complement receptor 3 (CR3) function-blocking antibody to inhibit phagocytosis, which increased the number of BrdU+ cells in both males and females. Thus microglia actively control developmental sex differences in cell genesis and this correlates with sex differences in later life social behavior. We are currently investigating whether juvenile rough-and-tumble play behavior can be mediated through direct manipulation of the microglia during the neonatal period.

This poster presentation has also been selected for oral presentation.

POSTER #2: Lateral Habenula-Induced Inhibition of Midbrain Dopamine Neurons in Male and Female Rats

Abstract submitter: P. Leon Brown

P. Leon Brown[1]; Dana Brady[1]

[1]University of Maryland School of Medicine

There are consistent sex differences in the progression from illicit drug use to abuse, potentially due to differences in dopaminergic circuits that mediate reward. Dopamine neurons are transiently inhibited by the lateral habenula, an epithalamic structure activated by aversive stimuli and previously shown to contain estrogen receptors. We test the hypothesis that lateral habenula inhibitory control over dopamine neurons in female rats is reduced relative to males. Preliminary findings demonstrate an elevated baseline firing rate of dopamine neurons in female rats, but no difference in firing regularity or pattern. Although a majority of dopamine neurons are inhibited in both sexes, the duration of inhibition is reduced in female rats. Such dampened inhibitory control may diminish the aversive components of drug use, resulting in increased abuse potential.

POSTER #3: Characterization of Idiopathic Bronchiectasis in Patients with and without Pulmonary Nontuberculous Mycobacterial Disease

Abstract submitter: S. Daniel-Wayman

J. A. Nguyen[1]; S. Daniel-Wayman[1]; D. R. Prevots[1]; J. Adjemian[1]; M. Daniels[2]; C. L. Daley[3]; M. Knowles[2]; K. N. Olivier[1]

[1]National Institutes of Health, [2]University of North Carolina at Chapel Hill, [3]National Jewish Health

Idiopathic bronchiectasis describes abnormal airway widening and stretching without a known cause, leading to mucus build-up, infection, and respiratory complications. Bronchiectasis has been reported more commonly in postmenopausal women with a tall, thin body morphotype and is associated with pectus abnormalities, scoliosis, and nontuberculous mycobacterial (NTM) pulmonary infection. The link between bronchiectasis, gender, and these traits remains unclear.

METHODS: The Genetic Disorders of Mucociliary Clearance Consortium idiopathic bronchiectasis study included 258 idiopathic bronchiectasis patients: 70 women with NTM, 64 women without NTM, 67 men with NTM, and 57 men without NTM. Patient evaluation included a detailed physical examination, chest radiograph, medical history, lung function measurements, and collection of serial respiratory samples.

RESULTS: Men with NTM were significantly older at diagnosis of bronchiectasis (median, IQR, 60, 51-68 years) than men without NTM (46, 24-60 years, $p < 0.001$). While women with NTM were older at diagnosis of bronchiectasis (55, 48-64 years) than women without NTM (45, 26-62 years); this difference was not significant. Scoliosis was significantly more prevalent in men with NTM (45%) than in men without NTM (21%, $p = 0.004$), but no difference was seen among women. Pectus deformities were found in a similar small percentage across all strata.

CONCLUSIONS: This study supports past findings on morphotypic traits in bronchiectasis and NTM patients, including older age of diagnosis, and high incidence of scoliosis and suggests potential differences in these associations based on gender and on the presence or absence of NTM.

POSTER #4: Female and Male Differences in the Human Plasma Metabolome at Baseline and in Response to Insufficient Sleep

Abstract submitter: Christopher Depner

Christopher Depner[1]; Rachel Markwald[1]; Charmion Cruickshank-Quinn[2]; Kevin Quinn[2]; Nichole Reisdorph[2]; Kenneth Wright[2]

[1]University of Colorado Boulder, [2]University of Colorado Anschutz Medical Campus

We previously reported sex differences in energy expenditure, food intake, and weight gain during insufficient sleep. Here, we investigated the plasma metabolome using a cross-over laboratory study (8 females/8 males) consisting of 3 baseline days (9h sleep opportunities) followed by 5 days insufficient (5h sleep opportunities) and adequate sleep (9h sleep opportunities) with *ab libitum* food intake. Across all conditions, 112 metabolites showed sex differences and an additional 209 metabolites showed sex differences during insufficient sleep. For females and males, 28 and 13 metabolites, respectively, were uniquely different during insufficient sleep versus both baseline and adequate sleep. Findings highlight the need to include sex as a variable in metabolomics research and for understanding individual differences in responses to insufficient sleep.

POSTER #5: The Gestational Foundation of Sex Differences in Development and Vulnerability

Abstract submitter: Janet DiPietro

Janet DiPietro[1]; Kristin Voegtline[1]

[1]Johns Hopkins Bloomberg School of Public Health

Despite long-standing interest in the role of sex on human development, the functional consequences of fetal sex on early development are not well understood. Here we explore the gestational origins of sex as a moderator of development. In accordance with the focus of this special issue, we examine evidence for a sex differential in vulnerability to prenatal and perinatal risks. Exposures evaluated include those present in the external environment (e.g., lead, pesticides), those introduced by maternal behaviors (e.g., alcohol, opioid use), and those resulting from an adverse intrauterine environment (e.g., preterm birth). We also provide current knowledge on the degree to which sex differences in fetal neurobehavioral development (i.e., cardiac and motor patterns) are present prior to birth. Also considered are contemporaneous and persistent sex of fetus effects on the pregnant woman. Converging evidence confirms that infant and early childhood developmental outcomes of male fetuses exposed to prenatal and perinatal adversities are more highly impaired than those of female fetuses. In certain circumstances, male fetuses are both more frequently exposed to early adversities and more affected by them when exposed than are female fetuses. The mechanisms through which biological sex imparts vulnerability or protection on the developing nervous system are largely unknown. We consider models that implicate variation in maturation, placental functioning, and the neuroendocrine milieu as potential contributors. Many studies use sex as a control variable,

some analyze and report main effects for sex, but those that report interaction terms for sex are scare. As a result, the true scope of sex differences in vulnerability is unknown.

POSTER #6: Estrous Cycle Differences in Abdominal Sensitivity at Baseline and After Colitis in a Mouse Model of Chronic Visceral Pain

Abstract submitter: Santiago Martinez Gonzalez

Santiago Martinez Gonzalez[1]; Yarimar Carrasquillo[1]

[1]National Institutes of Health

Chronic visceral pain represents a major clinical complaint, with women disproportionately affected. Despite the female prevalence in visceral pain, most preclinical studies in rodents have focused on males due to the potential variability that the estrous cycle stage might add when studying female subjects. As such, systematic evaluation of potential differences between sexes and/or across the estrous cycle in rodent models of visceral pain are warranted. The present study measured abdominal sensitivity using Von Frey filaments in males and in females across the different stages of the estrous cycle at baseline and in the dextran-sodium sulfate (DSS) model of colitis-induced visceral pain. Our results demonstrate that baseline abdominal sensitivity is similar in males and females in estrous and metestrous stages. However, females in the proestrous stage displayed significantly lower abdominal sensitivity than males or females at all other stages, which is consistent with clinical studies. In contrast, females in the diestrous stage displayed significant abdominal hypersensitivity, compared to males or females at all other stages. Following colitis, both male and female subjects exhibited robust referred abdominal hypersensitivity, which was similar in females across the different estrous cycle stages. Altogether, our results demonstrate that the estrous cycle stage is an important biological variable to be considered when studying baseline abdominal sensitivity in females. On the other hand, referred abdominal sensitivity in the DSS model of visceral pain is comparable in females across all stages, suggesting that the estrous cycle stage is not an important biological variable in this model.

POSTER #7: Sex Differences in the Association of Body Mass Index (BMI) with the Anatomical Architecture of Extended Reward Network Regions

Abstract submitter: Arpana Gupta

Arpana Gupta[1]; Emeran A. Mayer[1]; Kareem Hamadani[1]; Mher Alaverdyan[1]; Kirsten Tillisch[1]; Claudia P. Sanmiguel[1]; Jennifer S. Labus[1]

[1]University of California, Los Angeles

Alterations in key brain regions of the extended reward network have been linked to abnormal ingestive behaviors in obesity. Network analysis using graph theory allows the characterization of disease-specific alterations in the architecture of large-scale brain networks. Several measures are used to characterize the connectedness of a particular region to another region, including degree and local efficiency. These measures are associated with greater efficiency in transferring information

between regions.

AIMS: We hypothesized that body mass index (BMI) is associated with differences in degree and local efficiency of key regions comprising the extended reward circuit.

METHODS: White matter was measured in 120 healthy subjects. Regional parcellation was conducted using Freesurfer, and resulted in 74 bilateral cortical and 7 subcortical structures, including the cerebellum. White matter connectivity was estimated using DTI fiber tractography and Runge-Kutta algorithm. Controlling for the main effects of age, the general linear model was applied on connections that measured projections from regions associated with the extended reward network. Customized contrasts were used to assess for disease and sex differences. The resulting p-values were corrected for multiple comparisons. Significance was set at $q<0.05$.

RESULTS: There were 57 lean (34 females), 47 overweight (18 females), and 16 obese (8 females) individuals. *Degree*: BMI was positively associated with degree of left thalamus (β=1.14), left caudate (β=.67), and right nucleus accumbens (β=.83), but negatively associated with right ventromedial prefrontal cortex (β=-.62). There was a significant interaction effect for right dorsolateral prefrontal cortex (β=-1.39) with males and not females; and a significant interaction for right nucleus accumbens (β=-.66). *Local efficiency*: BMI was positively associated with local efficiency for right amygdala (β= .009) and left nucleus accumbens (β=.008), but negatively associated with right anterior insula (β=-.006), and right ventromedial prefrontal cortex (β=-.007), with females but not males. There was a significant interaction for left hippocampus (β=-.005) with males but not females.

DISCUSSION: The anatomical network architecture of regions within the reward network is associated with BMI in both male and female healthy subjects. Higher BMI and being female was associated with more local and regional communication between regions involved in dopamine signaling, and less information propagation was observed in the cognitive frontal regions. In males, the opposite pattern was observed. These findings are consistent with the reward deficiency syndrome hypothesis that suggests lower dopamine levels make them less sensitive to reward stimuli and more prone to food intake in order to compensate for this disorder.

POSTER #8: Sex Differences in Azheimer's disease: Using Optogenetics and Neurochemical Assays to Understand and Rescue Cognitive Decline

Abstract submitter: Holly Hunsberger

Holly Hunsberger[1]; Jennifer Perusini[1]; Christine Denny[1]

[1]Columbia University

Recent evidence from our lab and others suggest that memory retrieval, rather than memory encoding, is impaired in Alzheimer's mice. Our lab previously created the ArcCreER^{T2} mice to permanently tag neurons following learning. We bred this line with the APP/PS1 (an AD model) mouse line and have reported deficits in long-term memory and social memory, which correlated with impaired memory traces in the hippocampus. To rescue this cognitive decline, we used optogenetic stimulation in the hippocampus and were able to recover lost memories in male AD mice. Interestingly, our preliminary data indicate that AD female mice develop memory deficits at an earlier age compared to AD males and that this impairment is comorbid with anxiety-like behavior.

Understanding these different mechanisms can lead to more personalized treatment options for males and females.

POSTER #9: Gender Stratification of the Experience of Violence, Depression, and Immune Function in African American Young Adults

Abstract submitter: Latifa Jackson

Latifa Jackson[1]; Max Shestov[1]; Forough Saadatmand[1]

[1]Howard University

Violence is more prevalent in African American communities than in other American communities. This has impacts not only on criminal justice interventions, but also on the physical and mental health of these communities, including their risk for acquiring life-threatening diseases. While many studies have focused on the effects of violence on African American males, we wanted to understand the relative gender effects of violence. Introducing gender biases associated with exposure to violence, depression, immune function, and risks to HIV/AIDS is an important step in understanding how young women perceive and internalize societal violence directed toward them. We study a cohort of 557 young African American adults aged 18-25 years old (females N=274, males N=283) from the Washington, DC, area with varying experiences of violence exposure. We used sociological, epidemiological, mental health, bioinformatics, and quantitative genetics approaches to build a predictive portrait of the effects of violence on African American health. We find that women are twice as likely to be a victim of sexual, verbal, and gender-based violence as their male counterparts. This is not the case for community-related violence such as that perpetrated by gangs. A cortisol stress response marker is modestly correlated to increased perceived victimization, with women having higher overall concentrations of cortisol. The results suggest that violence may be a contributing factor in negative health outcomes and therefore should be the target of both criminal justice and public health interventions to decrease societal violence and to increase immunological health and mental states.

POSTER #10: Sex Differences in Early Risk Factors for Cocaine Seeking in Adolescence and Adulthood

Abstract submitter: Chloe J. Jordan[1]

[1]National Institutes of Health

Drug abuse before age 14 doubles the likelihood of substance use disorder, yet few studies have focused on identifying risk factors for drug use in young subjects. We screened juvenile male and female rats for (1) sucrose preferences, (2) novelty responses, and (3) working memory, followed by cocaine self-administration starting in early or late adolescence. Stepwise regression revealed sucrose preferences were associated with cocaine seeking in males (R^2=0.54, p<0.01), but not females. In contrast, novelty-induced activity was associated with cocaine seeking in females (R^2=0.48, p<0.02), but not males. Novelty responses also predicted motivation to earn cocaine (R^2= 0.58) and relapse in females (R^2= 0.73, p<0.05). Lastly, poor working memory predicted relapse in

both males (R^2= 0.44) and females (R^2=0.63, p<0.05), suggesting working memory may be a risk factor for both sexes.

POSTER #11: Assessing the Impact of the Knockout Mouse Phenotyping Program (KOMP^2) on the Biomedical Research Enterprise

Abstract submitter: Sheethal Jose

Sheethal Jose[1]; Ya-Ling Li[1]; Christine Change[1]; Rebecca Lenzi[1]; Oleg Mirochnitchenko[1]; Colin Fletcher[1]

[1]National Institutes of Health

KOMP^2 is a Common Fund initiative that aims to generate a resource of mice containing a null ("knockout") mutation in every gene in the mouse genome and to collect phenotype information for 3,000 mouse strains. This resource should enhance the ability of researchers to translate basic genetic research to applications relevant to human health. To study the impact of the KOMP^2 program on the scientific community, we identified more than 1,300 publications that used materials or data from KOMP. A bibliometric analysis of these publications was performed to evaluate the productivity and citation impact. Ultimately, we hope to identify research grants and publications that report findings on previously unexamined genes and measure the impact of KOMP^2.

POSTER #12: Ultrasonographic Median Nerve/Carpal Tunnel Ratio and Female/Male Differences in Carpal Tunnel Syndrome

Abstract submitter: Nanette C. Joyce

Scott Homer[1]; Colleen Anthonisen[2]; Eduard Poltavskiy[2]; Heejung Bang[2]; Michael S. Cronan[2]; Jay J. Han MD[3]; Nanette C. Joyce[2]

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INTRO: Median nerve cross-sectional area (CSA) is commonly measured by ultrasound (US) in carpal tunnel syndrome (CTS). We evaluated whether median nerve/carpal tunnel CSA ratio could be the diagnostic parameter for CTS.

METHODS: Unilateral wrists from 130 electrodiagnostically confirmed CTS cases and 109 sex-matched controls underwent US measurement.

RESULTS: Nerve/tunnel CSA ratio, carpal tunnel and median nerve CSA had significant mean differences between cases and controls (p<0.001). Sex differences occurred for nerve/tunnel ratio, carpal tunnel CSA, and flexor tendon group CSA (p<0.001) but not for mean median nerve CSA (cases and controls).

DISCUSSION: Median nerve CSA was the best predictor for CTS without apparent sex difference. While nerve/tunnel CSA ratio is a suboptimal diagnostic parameter, it provides insight into the pathophysiology of CTS.

POSTER #13: Sex Differences in Response to a Targeted Kyphosis-Specific Exercise Program

Abstract submitter: Wendy B. Katzman

Wendy B. Katzman[1]; Neeta Parimi[2]; Anne Schafer[1,3]; Roger K. Long[1]; Shirley Wong[1]; Amy Gladin[4]; Nancy E. Lane[5]

[1]University of California, San Francisco, [2]San Francisco Coordinating Center, [3]San Francisco Veterans Affairs Medical Center, [4]Kaiser Permanente Northern California, [5]University of California, Davis

Hyperkyphosis, an excessive anterior curvature in the thoracic spine, is associated with reduced health status in older adults. Hyperkyphosis is highly prevalent and more common in older women than men. There is no standard intervention to reduce age-related hyperkyphosis. Sex differences in response to a targeted intervention are not known.

We conducted a waitlist design randomized controlled trial to determine whether a targeted kyphosis specific exercise program improved Cobb angle of kyphosis, and whether the magnitude of change differed between men and women.

One hundred and twelve (112) participants aged ≥60 years with kyphosis ≥40 degrees were randomized to exercise or waitlist control. Group intervention was delivered by a physical therapist for 1 hour twice a week for 3 months. Controls received the intervention after 3 months. Primary outcome was change in Cobb angle measured from standing lateral spine radiographs. Secondary outcomes included change in kyphometer-measured kyphosis, physical function, and quality of life. Groups were combined, and ANOVA was used to test sex by time interaction to evaluate treatment effects in men and women.

Participants (67 women, 45 men) were 70.0±6.2 years with baseline Cobb 55.6±12.1 degrees. There were no between group differences at baseline; however, men had higher kyphometer-measured kyphosis. There was no significant between group difference in change in Cobb after intervention ($p=0.09$), but kyphometer-measured kyphosis differed by 4.8 degrees ($p<0.001$). There was no significant interaction between sex and change in Cobb after intervention ($p=0.67$).

A 3-month targeted exercise program reduced kyphometer but not radiographic-measured kyphosis. Despite sex differences in baseline kyphosis, sex did not affect treatment response.

*POSTER #14: Estrogen Contributes to Sex Differences in M2-Polarization During Asthma

Abstract submitter: Aleksander Keselman

Aleksander Keselman[1]; Jessie X. Fang[1]; Preston White[1]; Nicola Heller[1]

[1]Johns Hopkins University

Asthma exhibits sex differences, affecting mostly boys in childhood and women in adulthood. Alveolar macrophages have emerged as major mediators of allergic lung inflammation. We hypothesized that estrogen enhances the M2 polarization of alveolar macrophages to promote asthma. We found M2-gene expression to be elevated in alveolar and bone-marrow derived macrophages (BMMs) from female mice after challenge with allergen and stimulation with IL-4, respectively. Pretreatment of female BMMs with estrogen receptor ligands enhanced IL-4-induced M2-gene expression. Ovariectomized and LysMCRE ERa flox/floxmice exhibited impaired M2 responses after challenge with OVA. Together these data suggest that sex and hormonal factors contribute to sex differences in macrophage responses during asthma.

This poster presentation has also been selected for oral presentation.

POSTER #15: Sex Commonalities and Differences in Body Mass Index (BMI)-Related Alterations in Intrinsic Brain Activity and Connectivity

Abstract submitter: Lisa A. Kilpatrick

Lisa A. Kilpatrick[1]; Emeran A. Mayer[1]; Jennifer S. Labus[1]; Kirsten Tillisch[1]; Bruce Naliboff[1]; Claudia P. Sanmiguel[1]; Angeles Arpana Gupta[1]

[1]University of California, Los Angeles

We evaluated sex-differences in BMI-related intrinsic activity/connectivity of the brain's reward networks using partial least squares analyses. In both men (n=43) and women (n=43), increased BMI was associated with increased slow-5 activity in left globus pallidus (GP) and substantia nigra. In women only, increased BMI was associated with increased slow-4 activity in right GP and bilateral putamen, and reduced slow-5 connectivity between left GP/putamen and regions involved in emotion and cortical regulation. This sex difference in BMI-related connectivity may be related to observed sex differences in emotional eating and suggests the importance of personalized treatments for obesity that consider the sex of the affected individual.

POSTER #16: Sex Dimorphic Regulation of Osteoprogenitor Progesterone in Bone Stromal Cells

Abstract submitter: Nancy Lane

Alexander Kot[1]; Nancy Lane[1]; Wei Yao[1]; Zhengdong Zhong[1]; Yu-An Evan Lay[1]

[1]University of California, Davis

Increasing peak bone mass is a promising strategy to prevent osteoporosis. A mouse model of progesterone receptor (cPRKO) ablation selectively in mesenchymal stromal cells (MSCs) increased bone mass through a sex-dependent mechanism. Here we employed RNA sequencing analysis to evaluate sex-dependent differences in gene transcription of MSCs of wild type (WT) and cPRKO mice. cPRKO MSCs had marked sex hormone-dependent changes in gene transcription in male mice as compared to WT controls. These transcriptional differences revealed dysregulation in pathways involving immunomodulation, osteoclasts, bone anabolism, extracellular matrix interaction, and matrix interaction. These results identified many potential mechanisms that may explain our observed high bone mass phenotype with sex differences when PR was selectively deleted in the MSCs.

POSTER #17: MicroRNA-19b Acts as a Sex-Dependent Regulatory Hub for Posttraumatic Stress and Chronic Widespread Pain Development Following Trauma Exposure

Abstract submitter: Sarah Linnstaedt

Sarah Linnstaedt[1]; Cathleen Rueckeis[1]; Kyle Riker[1]; Shan Yu[1]; Samuel McLean[1]

[1]University of North Carolina at Chapel Hill

Posttraumatic stress (PTS) and chronic widespread pain (CWP) are frequent co-morbid sequelae of trauma that occur at different rates in men and women. Sex-dependent molecular mediators of PTS and CWP are poorly understood. We examined whether the stress and pain associated microRNA, miR-19b, might contribute to sex-dependent differences in vulnerability to these outcomes. We found a sex-dependent relationship between initial miR-19b expression levels and both PTS development (OR=1.41, p=0.039) and CWP development (OR=1.46, p=0.031) 6 months following motor vehicle collision trauma (n=178). Sex-dependent expression of miR-19b was also observed in two animal models. The potential importance of miR-19b to PTS/CWP pathogenesis is supported by further analyses indicating that miR-19b sex-dependently regulates a number of PTS and CWP associated transcripts.

POSTER #18: Women Experience Greater Chronic Pain Severity Following Major Thermal Burn Injury

Abstract submitter: Matthew Mauck

Matthew Mauck[1]; Christopher Sefton[1]; Samuel McLean[1]

[1]University of North Carolina

Women experience greater chronic pain severity compared to men across a number of chronic pain conditions including widespread pain, chronic abdominal pain, and persistent post-surgical pain. However, no studies have examined sex differences in chronic pain severity following Major Thermal Burn Injury (MThBI), a trauma in which female survivors are known to have worse outcomes. Therefore, we hypothesized that women would experience greater chronic pain severity than men in the aftermath of MThBI. We report the results of an observation cohort study (n=96) that prospectively evaluated chronic pain severity over 1 year following MThBI. These results indicate that women experience a greater burden of chronic pain following MThBI compared to men.

POSTER #19: Sex Differences in Placental Epigenetic Aging

Abstract submitter: Catherine Monk

Catherine Monk [1,2]; Fabien Delahaye[3]; Frances Champagne[4]; Seonjoo Lee, PhD[1]; Tianshu Feng, MA[1]; Ronald Wapner[1]

[1]Columbia University Medical Center, [2]New York State Psychiatric Institute,
[3]Albert Einstein College of Medicine, [4]University of Texas at Austin

The study of prenatal exposures affecting long-term health trajectories has long identified sex differences in illness risk (Braithwaite et al., 2017). Sex differences in the placenta, originating in sex chromosomes, in part undergirds this sex-specific variation (Bale, 2016). Placental DNA methylation (DNAm) is used to calculate epigenetic age, the predicted age by DNAm in relation to the chronological gestational age (GA) at birth; older placental epigenetic age is found in preeclamptic pregnancies (Mayne et al., 2017). Using Mayne's (2017) DNAm approach in two studies of healthy pregnant women (n=192 and n=107) with chronological GA 36-42 and 33-41 weeks we found females versus males had stronger associations between placenta DNAm and chronological GA (.21 versus .11; .39 versus .01). In one sample, maternal education and 1st and 2nd trimester cortisol diurnal slope were inversely associated with placenta DNAm in the males (r=-.27 and r=-.44, r=-.33, all ps<.05) but not females (r=-.13 and r=-.24, r=.06, all ps>.10). Consistent with male vulnerability to preterm birth and early-appearing neurodevelopmental disorders, these data indicate that for women carrying males, lifestyle factors may be associated with placental immaturity relative to birth age, with possible implications for health outcomes.

POSTER #20: Reporting of Sex and Gender in Clinical Trial Protocols and Published Results

Abstract submitter: Thiyagu Rajakannan

Thiyagu Rajakannan[1]; Kevin M. Fain[1]; Rebecca J. Williams[1]; Tony Tse[1]; Deborah A. Zarin[1]

[1]National Institutes of Health

Background: Biomedical research funders and journals have increasingly focused on the importance of assessing and reporting the effect of sex (biological factors) and gender (sociocultural factors) on health outcomes in clinical studies.

Objective: To assess publicly available clinical study protocols and corresponding published studies to analyze how “sex” and “gender” information was incorporated in study design and reported.

Study Design: We identified a convenience sample of 80 articles from *NEJM* and *JAMA* published in 2014/2015 for which full protocols were available online. We searched for and assessed use of the terms “sex” and “gender” in the protocol and corresponding publication.

Results: First, the terms “sex” and “gender” were not defined in any protocol or publication. Second, 40% of trials (32/80) used both terms interchangeably within the protocol; 28 of these used “sex” only and 4 used neither term in the corresponding publication. Third, the term “gender” only was used in 29% (23/80) of protocols, but only one publication used this term.

Our data indicate imprecision in how “sex” and “gender” terms were used in study protocols, suggesting a lack of appreciation among researchers of these distinct concepts. Publications generally used only “sex,” implying that journals enforce specific and consistent terminology when reported. We note the generalizability of these findings may be limited. Also, we did not assess how the constructs were used in the research.

Conclusions: Our study supports the need for continuing efforts to standardize the concepts of “sex” and “gender" and ensure their appropriate use in biomedical research.

POSTER #21: Sex Chromosome Dosage Effects on Gene Expression in Humans

Abstract submitter: Armin Raznahan

Armin Raznahan[1]; Neelroop Parikshak[2]; Judith Ross[3]; Jay Giedd[4], Daniel Geschwind[2]

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A fundamental question in the biology of sex-differences has eluded direct study in humans: how does sex chromosome dosage (SCD) shape genome function? To address this, we developed a systematic map of SCD effects on gene function by analyzing genome-wide expression data in humans with diverse sex chromosome aneuploidies (XO, XXX, XXY, XYY, XXYY). For sex chromosomes, we demonstrate a pattern of obligate dosage sensitivity among evolutionarily preserved X-Y homologs, and revise prevailing theoretical models for SCD compensation by

detecting X-linked genes whose expression increases with decreasing X- and/or Y-chromosome dosage. We further show that SCD-sensitive sex chromosome genes regulate specific co-expression networks of SCD-sensitive autosomal genes with critical cellular functions and a demonstrable potential to mediate previously documented SCD effects on disease. Our findings detail wide-ranging effects of SCD on genome function with implications for human phenotypic variation.

POSTER #22: Dopmine Transporter (DAT1) Gene Variation and Intravenous (IV) Alcohol Self-Administration in Non-Dependent Drinkers: Moderation by Sex

Abstract submitter: Bethany L. Stangl

Bethany L. Stangl[1]; Courtney L. Vaughan[1]; Hui Sun[1]; Melanie L. Schwandt[1]; Falk Lohoff[1]; Vijay A. Ramchandani[1]

[1]National Institutes of Health

Genetic variation in the dopamine transporter (DAT1) has been associated with alcohol dependence. This study aimed to characterize the effect of DAT1 variation and the role of sex differences on self-administration of IV alcohol in 70 non-dependent drinkers.

Results revealed that male 10A homozygotes had greater alcohol self-administration compared to 10A females, while 9A males had lower self-administration than 9A females. Similarly, 10A males felt and wanted more alcohol compared to 10A females, while 9A females had higher subjective responses compared to 9A males.

These findings underscore the critical role of dopamine neurotransmission and the moderating role of sex in the motivation and consumption of alcohol in non-dependent drinkers.

POSTER #23: Sex-Stratified Analysis of Obsessive-Compulsive Disorder Reveals Minor Differences in Genetic Architecture

Abstract submitter: Barbara Stranger

Ekaterina A. Khramtsova[1,6]; Raphael Heldman[2,6]; Eske M. Derks[3,6]; Dongmei Yu[4,6]; Lea K. Davis[5,6]

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Obsessive-compulsive disorder (OCD) exhibits sexual dimorphism in age of onset and clinical presentation. Here, we present the first genome-wide assessment of the sex-specific genetic architecture of OCD. Overall we find evidence for minor differences in the genetic architecture of OCD between the sexes. Specifically, we report that the genetic correlation is high between males and females, and heritability estimates do not differ between the sexes. Despite this, we observed differences in enrichment of functional annotations between variants with very different effects across sexes. This suggests that although we are underpowered to detect these minor differences at the individual variant or gene level, we observe evidence of sexually dimorphic biology underlying risk for OCD. These results hold promise for discoveries in future studies with larger sample sizes.

POSTER #24: Epidemiological and Experimental Evidence for Sex-Dependent Differences in the Outcome of Leishmania Infantum Infection

Abstract submitter: Elizabeth A. Turcotte

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Leishmania infantum causes visceral leishmaniasis (VL) in Brazil. We previously observed that VL is more common in males than females living in endemic neighborhoods, despite similar exposure. Using a larger sample, we document that VL is more common in males than females, but only after puberty. BALB/c and C57BL/6 mouse models confirmed that there is a biological basis for male susceptibility to symptomatic VL, showing higher parasite burdens in males than females. Female C57BL/6 mice generated more antigen-induced cytokines associated with curative responses (IFN-γ, IL-1β). Males expressed higher levels of IL-10 and TNF, which are linked to exacerbated disease. Different parasite lines entered or survived at a higher rate in macrophages of male than female origin. These results suggest that males are inherently more susceptible to L. infantum than females, and that mice are a valid model to study this sex-dependent difference.

POSTER #25: Race and Sex Differences in Maternal Mediated Childhood Obesity (MMCO)

Abstract submitter: ClarLynda Williams-DeVane

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BACKGROUND: Childhood obesity is an epidemic in the United States, creating a medical burden of more than $14 billion a year as of 2010. It is an epidemic that disproportionality effects minorities and those of lower socioeconomic status (SES). While diet and exercise interventions have had limited success, the etiology and complexity of childhood obesity and its disparities are not well understood. To address childhood obesity the Newborn Epigenetic Study (NESt) was initiated to prospectively test the influence of *in utero* environmental exposures on DNA methylation profiles in newborns. However, analyzing DNA methylation data requires the correct classification of obesity status in the child and the associated risk based on maternal body mass index (BMI).

OBJECTIVE: We hypothesize that the relationship between childhood obesity status and maternal BMI classification is both sex and race specific.

METHODS: Here, we calculate race- and sex-specific odds ratios of risk for children in NeST becoming overweight or obesity by age 4. Further, we identify ideal cutoffs for maternal BMI utilizing Receiver Operating Characteristic (ROC) curves.

RESULTS: The odds ratios of obesity risk between Caucasian and African American as well as male and female children are significantly different. Further, the optimal maternal BMI cutoff for the prediction of children becoming overweight or obese by age 4 is significantly different in Caucasian and African American moms.

CONCLUSIONS: Ultimately, this work will lead to better understanding of the maternal influences of childhood obesity and more efficient analysis of DNA methylation data.

POSTER #26: Trajectories of Knee Bone Shape Change Are Associated with Sex and Osteoarthritis

Abstract submitter: Barton L. Wise

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Knee osteoarthritis (OA) is more common in women than men; however, the biological mechanisms for sex difference in knee OA are not well understood. The purpose of the present study was to describe knee bone shape changes over time and to examine whether sex or knee OA are associated with change of bone shape. We outlined distal femur and proximal tibia shape on radiographs of 473 knees chosen without regard to OA status in the Osteoarthritis Initiative at three time points and used group-based trajectory modeling to identify distinctive patterns of bone shape

change for each shape mode. The shapes of the distal femur and proximal tibia changed little over time but did divide into separate trajectory groups largely due to baseline differences that remained consistent across the years. The trajectory subgroups were associated with both sex and knee OA.

POSTER #27: Sex-Dependent, Osteoblast Stage-Specific Effects of Progesterone Receptor on Bone Acquisition

Abstract submitter: Wei Yao

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To define progesterone receptor (PR) in the regulation of sexual dimorphism in bone, we selectively deleted PR at different stages of osteoblast differentiation. We found that mice with PR conditional deletion in early osteoprogenitor cells developed greater trabecular bone volume, greater bone formation, increased number of mesenchymal stem cells, and greater osteogenic potential, particularly in males. PR deficiency during the period of rapid bone growth induced rapid trabecular bone loss in both the wild type and the PRcKO mice in both sexes. No differences in trabecular bone mass was observed when PR was deleted in mature osteoblasts. In conclusion, PR inactivation in early osteoprogenitor cells but not in mature osteoblasts influenced trabecular bone accrual in a sex-dependent manner. PR deletion in osteoblast lineage cells did not affect cortical bone mass.