OSSD 2018 Annual Meeting
"Sex as a Biological Variable Across the Lifespan"
April 30th – May 3rd
Atlanta, GA, USA

POSTER SESSION I: Monday, April 30th 6:15pm – 8:15pm

Poster 1

Title: Detection of serotonin receptor and estrogen receptor alpha protein expression in human dental pulp: a potential trigeminal pain mechanism.

Author List: Sushmitha Ananth[1], Sukhbir Kaur, M.S.[1], Phillip Kramer, Ph.D.[2], and Dayna L. Averitt, Ph.D.[1]

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Abstract: Trigeminal pain is more prevalent in women and often worsens during the luteal phase of the menstrual cycle implicating modulation by gonadal hormones. Serotonin (5HT) is a neurotransmitter that is known to modulate pain via activity at excitatory and inhibitory 5HT receptors located on nociceptors in the periphery. The $5HT_{1B/1D}$, $5HT_{2A}$ and $5HT_{3A}$ receptors have been reported to be involved in trigeminal pain. The $5HT_{1B/1D}$ receptors are inhibitory G protein-coupled and agonists, such as the anti-migraine drug sumatriptan, reduce pain. The $5HT_2$ receptors are excitatory G protein-coupled and the $5HT_3$ receptors are cation-selective ion channels; agonists at both subtypes increase pain. Despite the prevalence of trigeminal pain disorders in females, it is unknown whether gonadal hormones alter the expression of these peripheral 5HT receptors in the human female trigeminal system. As human tooth pulp is densely innervated with trigeminal nociceptors, extracted teeth are a readily available tissue to study trigeminal pain mechanisms in human tissue. We ultimately hypothesize that natural fluctuations in gonadal hormones lead to plasticity in the 5HT receptor system in human dental pulp. To be able to test this hypothesis, we have developed a protocol to detect protein expression in extracted human dental pulp. Teeth were collected from patients who presented at Texas A&M Dentistry who had already elected to have teeth removed. Prior to extraction, demographic data (sex, age, ethnicity, pain medication use, days since last menses) was collected. Here we report methodology for protein extraction and western blot detection of β-actin, nerve fibers, estrogen receptor alpha (ERα), and $5HT_{3A}$ receptor protein expression in human dental pulp. This methodology provides a novel way to detect sex differences and menstrual-cycle effects in a readily-available human tissue innervated by trigeminal nociceptors.

Funding: This research is supported by a Texas Woman's University Chancellor's Research Fellowship awarded to DLA.

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Poster 2

Title: Sex differences in gray matter correlates of finger gnosis (finger sense) in children: a VBM study

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Abstract: Accumulating evidence relates finger gnosis (also called finger sense or finger gnosia), the ability to identify and individuate fingers, to cognitive processing, particularly numerical cognition. Multiple studies have shown that finger gnosis scores correlate with or predict numerical skills in children. In addition, neuropsychological cases as well as magnetic stimulation studies have shown that finger agnosia (defects in finger gnosis) often co-occurs with cognitive impairments, including agraphia and acalculia. However, our knowledge of the structural and functional correlates, and the development of finger gnosis is limited. To expand our understanding of structural brain features that are associated with finger gnosis we conducted a voxel-based morphometry study with 46 7-10-year-old children (23 females, 23 males), where we investigated the correlation between finger gnosis scores and whole-brain gray matter volume (GMV). Correlations between finger gnosis and GMV were found in a set of frontoparietal, striatal, and cerebellar areas. In addition, we found sex differences in how GMV is associated with finger gnosis. While females showed a more distributed and extensive set of frontal and parietal clusters, males showed three striatal and cerebellar clusters. This study provides the first findings on structural brain features that correlate with finger gnosis.

Funding: This work was supported by the Indiana University FRSP grant to SDN, and the LaCrosse Family Business Trust to FS and SDN.

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Poster 3

Title: “Mainstreaming gender into research” means gender medicine in the medical education

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Abstract: Gender Mainstreaming is mandatory within the European Union for state Universities and the health systeme. We think that Gender and Gender Medicine have to be included in all our curricula at the Medical University of Innsbruck, Austria. To get Gender Medicine into medical research it is essential to include it in all curricula offered at medical universities. It must also be included in the core curriculum of all study phases and in all cumulative examinations. So it will become the status quo for all medical students. All instructors are asked to include Gender aspects in their course material and exams and are given a booklet on the subject. Gender Medicine is instructed in the core curriculum twice: in the third semester the fundamentals of Gender Medicine, and in the tenth semester its clinical and research relevance. This material is also covered in the two cumulative exams. Gender Medicine was recently established as a compulsory subject in the PhD-programme. One Gender aspect must be elaborated from the PhD-thesis with subsequent congress presentation or publication of a scientific paper. There is a compulsory course prior to applying for venia docendi.
We started in 2013. Until now more than 150 diploma-theses and 30 PhD-theses were registered on the subject, and 5 poster prizes were awarded at national and international congresses for PhD-Gender-posters. To get Gender and Gender Medicine into medical research they must already be included in the core curriculum if they are to be considered a "normal" subject. Another important factor is to emphasize the usefulness of Gender-Medicine-findings with regard to research possibilities, project applications, grants and resources. We hope that being forced to include Gender aspect in their PhD-theses will help them to get used to it and they will do it also in future projects.

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Poster 4

Title: Understanding immune system sex differences in the healthy human transcriptome

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Abstract: Sex and gender biases in the incidence of autoimmunity and infectious disease imply that women have stronger immune responses. Women are at higher risk of autoimmune diseases, while men are more likely to die of infectious disease. Molecular factors driving this phenomenon may be detectable in the transcriptome, as it reflects immune activation, hormonal regulation, and chromosome status. We performed an immunologically focused investigation of robust transcriptional sex differences across global populations. First, we performed an integrated multi-cohort analysis of 6 cohorts consisting of 447 individuals to identify a 144-gene signature, called the Immune Sex Expression Signature (ISEXS), which is differentially expressed between healthy male and female human adults in the blood across populations. We validated ISEXS in 8 additional cohorts of 361 samples. Second, we examined the role of chromosomal location on ISEXS expression. 75% of ISEXS genes were located on autosomes, indicating that ISEXS is not purely driven by sex chromosomes. We separated ISEXS by chromosomal location and calculated a sex chromosome ISEX score and an autosomal ISEXS score. Both scores separated male and female blood samples in validation cohorts, although the sex chromosome score (validation summary AUC 0.99, 95% CI 0.94-1.0) performed better than autosomal score (validation summary AUC 0.75, 95% CI 0.66-0.82). Interestingly, the chromosome ISEXS score remained constant across the adult life course (18-70 years old), but the autosomal ISEXS score failed to separate males and females older than 45 years of age. Autosomal ISEXS genes include cytotoxic granule associated genes *CTSG, MPO,* and *DEFA1,* which are reduced in females less than 45 years old, but have no transcriptional sex difference in older populations. As a robust gene signature across populations that captures changes with age, ISEXS has applications in understanding why women and men have differential risks of autoimmunity and infection.

Funding: This study was funded by the Gabilan Stanford Graduate Fellowship in Science and Engineering to ELB. Additional funding was provided by the Women and Sex Differences in Medicine (WSDM) Seed Grant to PJU and PK.

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Poster 5

Title: Sex differences in oxytocin modulation of social reward and social motivation in Syrian hamsters

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Abstract: The rewarding and motivating properties of social interaction are a fundamental element in the expression of adaptive social behaviors and the development and maintenance of social relationships. Furthermore, dysfunctions in social reward likely contribute to the etiology of many psychiatric disorders. Because social behavior evolved in response to different selective pressures in males and females, the neurobiological mechanisms mediating social reward are likely sex-dependent, and it seems likely that these sex differences may contribute to sex differences in the prevalence of psychiatric disorders. We have previously shown that activation of oxytocin (OT) receptors in the ventral tegmental area (VTA) is essential for social reward in male Syrian hamsters. However, because the mesolimbic dopamine system and the oxytocin system are sexually differentiated, we hypothesized that OT in the VTA has sex specific effects, and tested this hypothesis using two behavioral assays. With the Conditioned Place Preference (CPP) test and a novel Operant Social Preference (OSP) task, we investigated the role of OT receptors in the VTA on the rewarding and motivating properties of social interactions in male and female hamsters. Both males and females were injected with either OT (9uM), a highly selective OT receptor agonist (23uM) or saline into the VTA just prior to opportunities for social interaction in their non-preferred chambers. Social interaction increased the time spent in the non-preferred chamber in both males and females. OT and a highly selective OT receptor agonist injected in the VTA increased time spent in the social interaction chamber in males, but decreased the time spent in the social interaction chamber in females compared to controls. These data demonstrate that activation of OT receptors in the VTA plays a critical, but different role in modulating the rewarding properties of social interactions in males and females.

Funding: This study was funded by NIH grant MH110212 to HEA and NIH predoctoral fellowship F31MH113367 to JMB

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Poster 6

Title: Sex-specific effects of testosterone on the sexually dimorphic transcriptome and epigenome of embryonic neural stem cells: A model for early hormonal brain organization

Author List: Matthew S. Bramble, Ph.D.[1], Neerja Vashist, B.S[1], Hayk Barseghyan, Ph.D.[1], Valerie A. Arboleda, M.D., Ph.D.[2] and Eric Vilain, M.D., Ph.D.[1]

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Abstract: The mechanisms by which sex differences in the mammalian brain arise are poorly understood, but are influenced by a combination of underlying genetic differences and gonadal hormone exposure. Using a mouse embryonic neural stem cell (eNSC) model to understand early events contributing to sexually dimorphic brain development, we identified novel interactions between chromosomal sex and hormonal exposure that are instrumental to early brain sex differences. RNA-sequencing identified 103 transcripts that were differentially expressed between XX and XY eNSCs at baseline (FDR = 0.10). Treatment with testosterone-propionate (TP) reveals sex-specific gene expression changes, causing 2854 and 792 transcripts to become differentially expressed on XX and XY genetic backgrounds respectively. Within the TP responsive transcripts, there was enrichment for genes which function as epigenetic regulators that affect both histone modifications and DNA methylation patterning. We observed that TP caused a global decrease in 5-methylcytosine abundance in both sexes, a transmissible effect that was maintained in cellular progeny. Additionally, we determined the transcriptional and epigenetic effects of TP were modulated in part by direct androgen signaling via androgen receptor. These findings highlight an unknown component of androgen action on cells within the developmental CNS, and contribute to a novel mechanism of action by which early hormonal organization is initiated and maintained. These findings reveal unique interactions between genetic background and androgen exposure, which has the potential to better explain some of the variations in cognitive outcomes and behavioral differences observed in individuals with congenital adrenal hyperplasia (CAH).

Funding: The majority of funding for this project came from the Neuroendocrinology, Sex Differences and Reproduction training grant (NICHD5T32HD007228) and the DSD Translational Research Network (NICHD 1R01HD068138)

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Poster 7

Title: Escape from X-chromosome inactivation

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Abstract: X-chromosome inactivation (XCI) is the process by which one of the X chromosomes in XX females is silenced, achieving dosage equivalence with XY males. XCI is not complete as 12% of X-linked genes escape XCI in all females and an additional 15% of genes are variable in whether they escape or are subject to XCI. Genes that escape from XCI have expression differences between males and females and therefore may be players in sexually dimorphic disease predispositions. We hypothesize that there are underlying genetic and epigenetic features that allow escape from XCI, and we have approached their identification in two ways. (1) We have examined the ability of human genes to be inactivated when integrated as large transgenes (150-200 kb BACs) onto the mouse X. While the majority of human transgenes are silenced on the mouse inactive X, ongoing expression of the human escape gene *RPS4X* demonstrates that there are intrinsic elements demarcating escape that can be recognized across mammals. Silencing of normally subject genes further suggests retention and recognition of boundary elements between subject and escape regions on the BAC. (2) Examination of variably escaping genes provides a unique opportunity to compare genes that are subject to, or escape from, XCI in the same genomic context. Using a panel of 18 cell lines with skewed XCI we have examined allelic expression and DNA methylation, demonstrating that variable escapees are intermediate in their methylation patterns, which correlate poorly with inactivation status. Extending this study to primary cells using CEEHRC and TwinsUK published datasets confirms intermediate methylation levels for variable escapees despite differences in methylation levels between tissues, and identifies a small but consistent genetic contribution. We do not observe domain-level regulation of variable escape from XCI further implicating promoter-proximal DNA elements allowing expression from the otherwise heterochromatin inactive X.

Funding: This study was funded by a joint Canadian Institutes of Health Research (CIHR) Grant to CJB and EMS.

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Poster 8

Title: Sex differences in steroid-sensitive neural projections to the periaqueductal gray: identification of novel pain pathways in female rats.

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Abstract: The periaqueductal gray (PAG) is a primary pain modulatory center for opioid analgesia. Projections from the PAG to the rostral ventromedial medulla (RVM) and dorsal horn of the spinal cord form a descending circuit that inhibits pain. Females typically require twice the amount of morphine as a male to produce comparable levels of pain relief, and we have previously reported sex differences in the PAG-RVM pathway that contribute to sex differences in morphine analgesia. Previous studies examining projections to the PAG have been conducted exclusively in males. The objective of this study was to delineate neural projections to the PAG in the female rat and determine if they were (1) estrogen-sensitive and (2) activated by persistent inflammatory pain. The retrograde tracer Fluorogold (FG) was injected into the ventrolateral PAG of adult male (n=4) and female (n=4) Sprague Dawley rats. After 10 days, complete Freund's adjuvant (CFA) was injected into the right hind paw. Twenty-four hours later rats were perfused and brain sections were processed by immunohistochemistry for quantification of FG, Fos, and estrogen receptor alpha (ERα). Our data indicate that the amygdala (CeA, MeA), medial preoptic area (MPO), and the hypothalamus (VMN, PVN) project to the PAG in females and are activated by inflammatory pain. We report that while MPO-PAG projections were similar in males and females, inflammatory pain activated the MPO projections neurons to a greater degree in females. Further, the MPO-PAG projections expressed significantly more ERα in females compared to males. Inflammatory pain also resulted in greater activation of the CeA-PAG circuitry, however both males and females showed a comparable number of projections. The MeA projections were similar in males and females, despite males having greater activation of the MeA-PAG pathway. Together, our data suggest that the MPO and the amygdala play a previously unrecognized role in sex differences in pain and analgesia.

Funding: This research was supported by NIH grants DA16272 and AR49555 awarded to AZM and in part by the STC Program of the National Science Foundation under the agreement No. IBN-9876754. This work was also funded in part by TWU Quality Enhancement Program grant awarded to DJC.

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Poster 9

Title: Electrophysiological properties of male and female medium spiny neuron subtypes in the nucleus accumbens core of Drd1a-tdTomato line 6 BAC transgenic mice

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Abstract: The nucleus accumbens core (NAc) is a striatal brain region essential for integrating motivated behavior and reward processing with premotor function. Aspects of these behaviors and associated disorders differ by sex and steroid sex hormone exposure, and research from a number of laboratories has identified multiple sex differences and hormone effects in NAc neural substrate. In rat NAc, excitatory synaptic input onto medium spiny neurons (MSNs) differs between males and females in prepubertal animals and in gonad-intact adults, as evidenced in part by miniature excitatory postsynaptic current (mEPSC) frequency. MSNs are the output neurons of the NAc. MSNs come in subtypes, and it is unknown how the properties of specific MSN subtypes do or do not vary by sex. This is an important knowledge gap, given that MSN subtypes play distinct roles in striatal function, project to different efferent brain regions, and exhibit differences in dopamine receptor expression and neuropeptide content. It is also unknown whether the sex differences detected in rat MSNs extend to mice. Thus, the goal of this study is to test if mEPSC and other electrophysiological properties of MSNs differ by subtype and sex in prepubertal mice. To test this hypothesis we used male and female PND 16-24 Drd1a-tdTomato line 6 BAC transgenic mice on a C57Bl/6 background (Ade et al., 2011), which allows for identification of the Drd1a-positive MSN subtype. We made acute brain slices of the NAc, and performed whole-cell patch clamp recordings of both td-Tomato labeled and unlabeled MSNs, which primarily comprise the Drd2a-positive MSN subtype. We found that mEPSC frequency differed by MSN population, with Drd1a-positive MSNs showing increased mEPSC frequency compared to unlabeled MSNs. Analysis comparing males and females is ongoing, with preliminary results showing sex differences in mEPSC frequency in unlabeled MSNs but not Drd1a-positive MSNs. These findings will provide new insight into sex differences and similarities in NAc MSN subtype properties.

Funding: This work was supported by Army Research Office STIR Award W911NF-15-1-0476 and NIH R01MH109471 to Dr. John Meitzen

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Poster 10

Title: Sex and age differences in the metabolic and neural responses to high fat diet

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Abstract: The metabolic consequences of obesity have been shown to be sexually dimorphic in humans and rodents. Prior research has focused primarily in adulthood, when adult sexually dimorphic characteristics have been established. To begin examining the role of development in the sex differences of obesity, we compared the effects of diet-induced obesity in juvenile versus adult male and female mice. Male and female mice were maintained on either a control or high-fat (HFD) diet initiated at 4 (prepubertal) or 12 (adult) weeks of age. Males and females of both ages showed increased body weight after HFD, although the adult females showed a comparatively lower increase in body mass. Further, body scans show that juvenile and adult females on HFD have less fat mass than males of both ages. Metabolic deficits took longer to arise and were not as advanced in females compared to males of both age groups. Younger females showed metabolic deficits sooner than adult females, but were not as impaired as males. Inflammation in the adipose tissue was greatest in adult males. As has been described previously, adult males show greater hypothalamic inflammation than adult females after HFD. Interestingly, both juvenile males and females show increased hypothalamic inflammation after HFD. NPY neurons, which regulate feeding, reside in the ARH. NPY fiber density was reduced in males and young females after HFD. However, there was no change in the ARH NPY fiber density in adult females. Taken together, these data suggest that while obesogenic diets initiated in prepubertal females yield milder metabolic impairments and inflammation than observed in males, they may increase vulnerability to metabolic dysfunction in female adults, which are otherwise relatively resistant to many HFD-induced outcomes.

Funding: This study was support by NIA T32 AG052374 and NIA AG026572.

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Poster 11

Title: Role of active demethylation in sexual differentiation of the mouse brain.

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Abstract: DNA methylation is an important mechanism for regulating gene expression and has been implicated in sexual differentiation of the brain in rats and mice. Emerging evidence indicates that active DNA demethylation also plays important roles in mammalian brain development, but whether demethylation contributes to neural sex differences is not known. Although DNA methylation (5-methylcytosine; 5mC) was originally considered a stable covalent modification to DNA, it is now clear that ten-eleven translocation (Tet) enzymes can convert 5mC to 5-hydrohymethylcytosine (5hmC). In addition, 5hmC accumulates in gene bodies of activated genes in postmitotic neurons, where it serves as a stable epigenetic mark. The present study explores sex differences and the effect of testosterone on the expression of the Tet enzymes in the mouse brain across development. Newborn mice received testosterone propionate or peanut oil on the day of birth (P0) and P1. Mice were sacrificed at P1, P25 or P60 and the mRNA expression of Tet1, Tet2 and Tet3 was evaluated in the ventromedial hypothalamic region, anterior preoptic region and hippocampus/cortex by quantitative RT-PCR. We find region-specific sex differences, with higher expression of all three Tet enzymes in the ventromedial hypothalamic region of males compared with females. The sex differences are present during development, but not in adulthood (P60). Somewhat surprisingly, neonatal testosterone treatment of females does not alter Tet enzyme expression. We also find that Tet enzyme expression is much higher at P1 than at P25 or P60, suggesting developmental programming of DNA demethylation or an important developmental role for the stable placement of hydroxymethyl marks.

Funding: This study was funded by a seed grant from the Brains & Behavior Program at Georgia State University.

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Poster 12

Title: A population level epidemiological study of peripartum cardiomyopathy in Olmsted County, Minnesota

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Abstract: Conduct an epidemiological study on peripartum cardiomyopathy (PPCM) using the Rochester Epidemiology Project (REP) to estimate incidence and study risk factors, outcomes, and survival. Retrospective cohort study using data from REP abstracted from medical records for females aged 15-55 with a confirmed diagnosis of PPCM between 1970-2014. 49 cases of PPCM were confirmed. The mean age was 28 (range 15-44), 79% were white, 19% of African descent (6/9 were migrants from Africa), and 0.02% American Indian. 46% of the cases were primiparous. Common co-morbidities included mental health conditions (55%), allergies (50%), migraines (44%), and a history of infections (68%) with 47% having an infection during the index pregnancy. Of the 57 infants born to PPCM cases, the sex for 56 was available and showed 57% (*n*=32) were female and 42% (*n*=24) male. 54% of cases were diagnosed with hypertensive disorders of pregnancy with the most common diagnosis being preeclampsia. Mean left ventricular ejection fraction at diagnosis was 32% (range 10-45%). Of 46 patients with follow-up, 43 eventually regained normal cardiac function with an average time to recovery of 14 months (range <1month to >12 years), 2 had continued cardiac dysfunction, and 1 patient died. There were no transplants and no use of cardiac devices. 49 Cases of PPCM were identified from the REP. Previously known risk factors of hypertensive disease of pregnancy and African decent were confirmed while infection during pregnancy, history of mental health diagnosis, migraines, allergies, and sex of the offspring were identified as new potential risk factors requiring further study. The outcomes for women diagnosed with PPCM were better than other studies have shown. However, the study also confirmed worse outcomes in Africa or Africa American cases compared to Whites.

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Poster 13

Title: Sex differences in the blood ethanol concentration profiles of Japanese quail

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Abstract: In humans, females tend to absorb and metabolize ethanol at different rates than males. Specifically, females tend to have higher blood ethanol concentrations (BECs) and as a result. Japanese quail may be an ideal model for studying the effects of ethanol consumption and sex differences. Typically rodents will not freely consume a 20% ethanol solution whereas quail will. Because relatively little research has examined ethanol in quail, there is not much information on BECs in quail nor any information on the resulting metabolism differences between males and females. Developing a working knowledge of the absorption and metabolism rates of ethanol are critical to develop a working model of alcohol use disorder. Therefore, we aimed to document the BEC profile in male and female quail. Male and female quail were gavaged with 3 g/kg of a 20% ethanol solution. Following gavage, blood was collected from the wing vein at 15, 30, 60, 120, and 240 min using heparinized capillary tubes. BECs were determined using an Analox AM1 apparatus. Results showed that male quail absorbed the ethanol quickly and had relatively high BECs within the first 30 min. Female quail had lower BECs 30 min following gavage, however, this difference was not apparent at 60 min following gavage. The clearance rate between males and females also differed, male quail had relatively stable and high BECs for time points between 60 min and 240 min. Female quail, on the other hand, had significantly lower BECs than males at 240 min following gavage. These sex differences could be due to differences in enzymatic activity between the sexes, however, additional research examining hepatic and gastric differences is needed.

Funding: Departmental

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Poster 14

Title: Biological sex affects vaccine efficacy and protection against influenza in mice

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Abstract: Biological sex affects adaptive immune responses, but has not been systemically studied in the context of influenza infection or vaccine efficacy. Infection of mice with 2009 H1N1 induced antibody responses, CD4+ T cell, and CD8+ T cell memory responses that were greater in females than males; both sexes, however, were equally protected against secondary challenge with an H1N1 drift variant virus. To test the hypothesis that greater antibody in females is sufficient for protection against influenza, males and females were immunized with an inactivated H1N1 vaccine that induced predominantly antibody-mediated immunity. Following vaccination, females had greater antibody responses and protection against challenge with an H1N1 drift variant virus than males. Antibody derived from vaccinated females was better at protecting both naïve males and females than antibody derived from males, and this protection was associated with increased antibody specificity and avidity to the H1N1 virus. The expression of *Tlr7*, which is X-linked, was greater in B cells from vaccinated females than males and was associated with higher neutralizing antibody, class switch recombination, and antibody avidity in females. Deletion of *Tlr7* eliminated sex differences in vaccine-induced antibody responses and protection following challenge. Taken together, these data show that greater TLR7-mediated antibody production in females improves the efficacy of vaccination against influenza.

Funding: This work was supported by the NIH/NIAID Center of Excellence in Influenza Research and Surveillance contract HHS N272201400007C

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Poster 15

Title: Imaging sex and social status differences in the naked mole-rat

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Abstract: Neuroanatomical sex differences have been identified in diverse mammalian species, typically seen in reproductively relevant brain regions. The naked mole-rat has an unusual absence of sexual dimorphism in cell number, cell size and regional volume relative to other mammals. These animals live in large colonies consisting of a single reproductively-active female and 1-3 breeding males; other colony members are socially subordinate, prepubertal adults that do not reproductively mature unless they are removed from the suppressive cues of the colony. Previous studies have found that neuroanatomical morphology varies according to social/reproductive status and not sex; reproductively-relevant brain regions are larger in breeders of both sexes compared to subordinates. However, previous work was based on stereological analysis of Nissl-stained brains with limited brain regions examined. In this study, we use a higher throughput approach, high resolution structural magnetic resonance imaging (MRI), to image male and female reproductively-active breeder and reproductively-inactive subordinate naked mole-rats. After correcting for whole-brain volume, we observe a larger volume in brain regions relevant to reproduction and olfaction (e.g. medial amygdala) in breeders. Conversely, regions involved in social reward (e.g. striatum) are larger in subordinates. We also used dual-energy x-ray absorptiometry (DEXA) to image differences in body composition. While breeders, particularly females, were significantly larger in size (measured as fat, bone mineral content and soft tissue in grams), subordinates had a higher percentage of fat while breeding females had a lower percentage of fat. In line with previous findings, status appears to be a better predictor for neuroanatomical differences than sex and gross morphological sex differences emerge with reproduction in naked mole-rats.

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Poster 16

Title: Role of circulating sex hormones in compulsive ethanol intake

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Abstract: Epidemiological data suggest that females may transition from a state of recreational alcohol use to the development of an alcohol use disorder (AUD) more readily than males. According to the DSM-5, a central criterion in AUD diagnoses is compulsive intake, or intake despite negative consequences. To assess this phenomenon in a preclinical model, we employed a quinine-adulteration paradigm using adult male and female C57BL6/J mice. In this assay, subjects are individually housed and provided continuous access two-bottle choice between water and 15% ethanol. After baseline intake is established, the 15% ethanol solution is adulterated with the bitter tastant quinine hydrochloride. Our lab has previously found that females are more aversion-resistant than males, in that they consume higher levels of quinine-adulterated ethanol. To assess whether this sex difference is organizational or activational in nature, we ovariectomized females and compared their behavior to that of intact males and females exposed to the quinine-adulterated ethanol paradigm. The data in this pilot study indicate that ovariectomy attenuates aversion-resistance observed in intact females, suggesting that circulating sex hormones may contribute to the sex difference in aversion-resistant ethanol consumption. Future directions will include estrous cycle monitoring in intact females to assess the role of estrous cycle phase in aversion-resistant intake, as well as Fos immunohistochemistry in intact males and females to identify potential sex differences in neuronal activation of during quinine-adulterated ethanol intake.

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Poster 17

Title: Can transcriptomic profiles be used to predict sex-specific drug metabolism?

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Abstract: Safety assessments of new drug candidates are an important part of the drug development and approval process. Often, possible sex-and/or age-associated susceptibilities are not adequately addressed and better assessment tools are needed. We hypothesized that hepatic transcript profiles of drug metabolism enzymes (DMEs) can be used to predict sex- and/or age-associated differences in drug metabolism, and possible adverse events. Comprehensive hepatic transcript profiles were generated for F344 rats of both sexes at 9 ages, from 2 weeks (pre-weaning) to 104 weeks (elderly). Large differences in the transcript profiles of 29 DMEs/transporters were found between adult males and females (8-52 weeks). Using the Pharmapendium database, 41 drugs were found to be metabolized by 1 or 2 cytochrome P450 (Cyp) enzymes encoded by sexually dimorphic mRNAs, and thus are candidates for evaluation of possible sexually dimorphic metabolism and/or toxicities. Suspension cultures of primary hepatocytes from 3 male and 3 female adult rats (10-13 weeks old) were used to evaluate the metabolism of 7 drugs predicted to have sexually dimorphic metabolism. The sexually dimorphic expression of 4 Cyp genes was verified in the cultured cells during a 2 hr incubation time and was found to be stable and closely matched the in vivo hepatic expression: Cyp2c7, ~4-fold higher expression in females than males; Cyp2c11 and Cyp3a2, >2000-fold higher expression in males than females; and Cyp3a62, ~5-fold higher expression in males than females. The pharmacokinetics of the drug or its metabolite was analyzed by liquid chromatography/tandem mass spectrometry using multiple reaction monitoring. Predicted significant sexually dimorphic metabolism was found for 6 of the 7 drugs, with half-lives 37%- 400% longer in female hepatocytes than in male hepatocytes. Thus, in this rat model, transcript profiles may allow identification of potential sex-related differences in drug metabolism.

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Poster 18

Title: Early life stress leads to sex-specific alterations in perineuronal net formation in the developing rat prefrontal cortex

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Abstract: Early life experiences play a vital role in the development of the brain and its molecular components. Consequently, early life adversity can have detrimental effects on behavioral and neural development, especially in the prefrontal cortex (PFC), a late-maturing region with many subcortical connections involved in emotion regulation. Research demonstrates that the formation of extracellular structures, such as perineuronal nets (PNNs), that enwrap certain neuron subtypes throughout the central nervous system, is essential for proper neurodevelopment. Indeed, PNN formation coincides with the closure of developmental critical periods, potentially playing a role in the emergence of neuropsychiatric disorders. Early life stress via maternal separation (MS) has been seen to have sex-specific effects on expression of parvalbumin, which is expressed in fast spiking GABAergic interneurons that PNNs preferentially surround in the PFC. To determine the impact of MS and sex on PNN density in the PFC, male and female rat pups were separated from their dams for 4 hours per day from postnatal day (P) 2-20. At distinct developmental time points of juvenility (P20), adolescence (P40), and early adulthood (P70), rats were perfused, cryoprotected, and sliced on a freezing microtome to 40 µm slices. Tissue sections containing the prelimbic (PL) and infralimbic (IL) PFC were stained for primary *Wisteria floribunda* agglutinin, a plant lectin that has an affinity for PNNs. A secondary fluorescent marker of streptavidin conjugate 488 was used to visualize PNNs in the PFC. PNNs were then manually counted in the PL and IL, and the density calculated per region. Results demonstrate sex-specific effects of MS on PNN density in the PFC, where females demonstrated a distinct reduction in PNNs following MS. These findings have implications for the role of aberrant PNN development in neural and cognitive dysfunction seen in humans and animals that have experienced early life adversity.

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Poster 19

Title: The Endocrine Disruptors Bisphenol A (BPA) and BPS increase Myocarditis in Male and Female BALB/c Mice

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Abstract: Myocarditis is an inflammatory heart disease that is the leading cause of sudden death in young adults. Sex hormones play a vital role in the development of myocarditis with testosterone driving disease in males. In contrast, estrogen mediates cardioprotection in females. Since myocarditis is influenced by sex hormones, we investigated whether endocrine disruptors (EDs), which interfere with natural hormones, could play a part in the progression of disease. Exposure to BPA or BPS, EDs that bind the estrogen receptor, is found in plastics such as water bottles and food containers. To our knowledge no one has examined the role of EDs like BPA or BPS on myocarditis. We exposed male and female BALB/c mice with EDs for 2 weeks prior to infection with coxsackievirus and harvested during acute myocarditis. We found that clinically relevant doses of BPA increased acute myocarditis in females and males compared to controls. However, only T cells and mast cells were increased in females while males had a global upregulation of inflammation. Interestingly this effect of BPA was only observed in BALB/c and not C57BL/6 mice. We found that BPA activated mast cells, which are more abundant in BALB/c compared to C57BL/6 mice. We also found that BPS, which has replaced BPA in a number of plastics, increased myocarditis in females. We have found that ED exposure is having a significant effect on inflammation during myocarditis suggesting that these chemicals may exacerbate disease in humans.

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Poster 20

Title: Progesterone efficacy on pain behaviors associated with estrogen in a rat model of persistent temporomandibular joint inflammation

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Abstract: Estrogen replacement therapy exacerbates some pain conditions, such as temporomandibular joint disorder (TMD) pain, in postmenopausal women. Progesterone, however, is reported to have anti-inflammatory and antinociceptive properties that may be able to reduce pain. Preclinical studies on the efficacy of progesterone on reducing edema, neuronal loss, and cognitive impairment report a protective effect at 16 mg/kg but whether this is an efficacious dose to reduce estrogen-exacerbated TMD pain is not known. Based on our preliminary data, we hypothesized that pain behaviors induced by estrogen treatment following ovariectomy would be attenuated by treatment with 16 mg/kg and 16 µg/kg but not 16 ng/kg progesterone. Vaginal lavages were performed for 10 consecutive days to ensure female Sprague Dawley rats were cycling normally. Baseline mechanical sensitivity was measured by the von Frey filament method then all rats received a unilateral injection of complete Freund's adjuvant (CFA) into the temporomandibular joint. Twenty-four hours later, mechanical allodynia was confirmed, then all rats were ovariectomized (OVX) or received sham surgery. Two weeks after OVX, rats received one of the following hormone treatment paradigms for 5 days: daily estradiol benzoate (EB; 50 µg/kg), daily EB and progesterone (P; 16 mg, µg, or ng/kg), EB daily and interrupted P given every other day (days 1, 3, 5), daily P, or daily vehicle control. Mechanical allodynia was reassessed one hour following injections on days 1, 3, and 5. CFA evoked significant allodynia that was reversed with ovariectomy and then exacerbated by estrogen treatment. Estrogen-exacerbated TMD pain behaviors were significantly attenuated in rats that received 16 mg/kg or 16 µg/kg progesterone, while no effect was observed with 16 ng/kg. Our data indicate that a low dose of progesterone may reduce the recurrence of TMD pain following estrogen replacement therapy in post-menopausal women.

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Poster 21

Title: High fructose diet impairs learning and alters microglia in adult male, but not female, rats

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Abstract: Fructose consumption in adolescents has increased dramatically since the 1980s and is accompanied by increased incidence of childhood diabetes, metabolic disorder, and obesity. These diseases are associated with deficits in emotional regulation and cognitive processing. Male rats that consume a high fructose diet (HFD) from adolescence into adulthood have dysregulated emotional processing and upregulated neural inflammation, while parallel effects in females are largely unexplored. Heightened neuroinflammation via activated microglia can impair synaptic integrity leading to altered neural function. The current study aimed to determine the extent to which a HFD altered cognition and microglia activation in the hippocampus in males and females. Wister rats were fed either standard chow or a HFD (55% fructose) beginning on postnatal day (PND) 23 and throughout the duration of the study. On PND 80, rats were trained on the Barnes Maze task to assess cognition. There was no effect of diet on initial learning behavior in either sex. However, when required to relearn the task with a new target box, HFD males, but not females, performed significantly worse than chow fed controls ($p<0.05$). These data suggest that the diet-induced impairment in cognitive flexibility – the ability to unlearn something – is sex-dependent. Analysis of structural morphology of microglia has indicated that HFD males have more activated microglia throughout the hippocampus – specifically, shorter and less complex processes ($p<0.05$). These findings suggest that in males, a HFD initiates activation of microglia which likely results in an enhanced inflammatory profile within the male hippocampus. Further investigation of synaptic integrity is ongoing. Taken together, the results from this study suggest that a high fructose diet consumed from adolescence to adulthood disproportionally impairs cognitive function in males and that microglia may contribute to this change in neural function.

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Poster 22

Title: Impact of sex on gut microbial composition, mucosal immunity and metabolism.

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Abstract: The composition of the gut microbiota (Mb) is influenced by both host and environmental factors, and its composition shapes both mucosal and systemic immunity. Previously, our lab showed that sex, and more specifically androgen action, contributes to Mb composition and function, as well as host metabolic phenotypes. However, it remains unclear how chromosomal and hormonal components of sex impact Mb composition, mucosal immunity, and host metabolism. To independently test the contributions of sex chromosome complement (XX or XY) and gonadal sex on Mb composition and mucosal immunity, we used the “four core genotypes” (FCG) mouse model. This model generates XX or XY gonadal females, and XX or XY gonadal males. We performed high-content, single-cell immunophenotyping analyses of the small intestine in parallel with Mb composition analysis in cohorts of pre and post-pubertal FCG mice. Our results show that sex chromosome complement and gonadal hormones affect distinct innate and adaptive immune cell populations in the small intestine. Moreover, these differences in immune cell frequencies were strongly correlated with differentially abundant Mb taxonomic groups between FCG groups. Further, mass spectrometry-based metabolome and bile acid analysis revealed distinct metabolic profiles between FCG groups. These results demonstrate sex chromosomes and hormones contribute to the shaping of the Mb, the intestinal immune system, and host metabolism.

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Poster 23

Title: Novel Y chromosome long non-coding RNAs expressed in human male CNS during early development

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Abstract: Global microarray gene expression analyses demonstrated differences in female and male embryos during neurodevelopment. In particular, before sexual maturation of the gonads, the differences seem to concentrate on the expression of genes encoded on the X and Y chromosomes. To investigate the genome-wide differences in expression during this early developmental window, we combined high resolution RNA sequencing with qPCR to analyse brain samples from human embryos during the first trimester of development. Our results show that the largest biased group consisted of genes encoded on the sex chromosomes and the majority of all differentially expressed genes were male-biased. 10 out of 13 expressed gametolog pairs showed unbalanced gene dosage and as a consequence, a male biased expression. Among X-chromosome genes, three genes had higher expression in female embryos but a balanced gene dosage due to the Y gametolog expression. In addition, we found 6 novel non-annotated long non-coding RNAs on the Y-chromosome with conserved expression patterns in new-born chimpanzee. The tissue specific and time restricted expression of these long non-coding RNAs strongly suggests important functions during central nervous system development in human males.

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Poster 24

Title: The role of actin polymerization in GPER-mediated hippocampal memory enhancement in female mice

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Abstract: We previously reported that dorsal hippocampal (DH) infusion of the G-protein coupled estrogen receptor (GPER) agonist, G-1, mimicked the beneficial effects of 17β-estradiol (E_2) on object recognition and spatial memory consolidation in ovariectomized female mice (Kim et al., 2016, JNeurosci, 33:3309-3321). We also showed that a bilateral DH infusion of E_2 significantly increases dendritic spine density in the DH within 30 minutes (Tuscher et al., 2016, JNeurosci, 36:1483-1489). However, effects of GPER activation on dendritic spine density are unclear. Thus, the present study examined effects on DH dendritic spine density of bilateral DH infusion of G-1. G-1 significantly increased the number of dendritic spines on apical dendrites of CA1 pyramidal neurons in the DH. We next examined cellular mechanisms regulating G-1 induced spinogenesis. Because hippocampal spine remodeling depends on the reorganization of the actin cytoskeleton, we examined the effects of G-1 on the actin-binding protein cofilin, which depolymerizes actin filaments that regulate actin reorganization. G-1 significantly increased phosphorylation of cofilin in the DH 5 and 15 minutes after infusion. Because phosphorylation inactivates cofilin, thereby increasing actin polymerization, these data suggest that activation of GPER may increase dendritic spine morphogenesis through actin polymerization. To verify the importance of actin polymerization in GPER-mediated dendritic spine morphogenesis and hippocampal memory enhancement, we applied an actin polymerization inhibitor, latrunculin A, which prevents de novo actin polymerization and promotes filament disassembly. We found that DH infusion of latrunculin A prevented G-1 from inducing spinogenesis and enhancing object recognition and spatial memory consolidation. Collectively, these data support a critical role of actin polymerization in the GPER-induced regulation of hippocampal function in female mice.

Funding: This study was funded by the University of Wisconsin-Milwaukee College of Letters and Sciences and a UWM Research Foundation Research Growth Initiative grant to KMF.

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Poster 25

Title: Effects of dorsal hippocampal estradiol treatment and aromatase inhibition on memory consolidation in male mice.

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Abstract: In ovariectomized females (OVX), 17β-estradiol (E_2) increases memory consolidation in the object placement (OP) and object recognition (OR) tasks. This enhancement depends on the rapid activation cell signaling cascades involving ERK and PI3K/Akt pathways. The mechanisms through which E_2 may regulate memory consolidation in males is unknown. Here, OVX female and both intact and castrated male mice were infused with vehicle or E_2 directly into the dorsal hippocampus (DH) immediately after training in the object tasks. E_2 enhanced memory consolidation in all groups. To determine if the mechanisms underlying memory enhancements were similar in males, castrated males were infused with vehicle or the ERK phosphorylation inhibitor U0126 into the DH immediately before infusion of vehicle or E_2 into the dorsal third ventricle. Contrary to our hypothesis, U0126 did not block the enhancement of memory by E_2 in males, unlike females. Accordingly, using western blotting to measure relative protein amounts, E_2 did not increase levels of phosphorylated ERK or Akt in the DH of males, whereas both proteins are increased after DH infusion of E_2 in females. However, E_2 did increase the transcription factor CREB in the DH of both male and female mice. To continue investigating the role of E_2 in object and spatial memory, we examined putative sex differences in the effects of aromatase inhibition on memory. Previously, DH infusion of the aromatase inhibitor letrozole disrupts OR and OP memory consolidation in OVX females. In males, DH infusion of letrozole significantly impairs memory in castrated males but not intact males. Together, these studies demonstrate a novel sex difference in the underlying molecular mechanisms of E_2 and that E_2 is necessary for memory consolidation in males, but only in the absence of circulating androgens.

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Poster 26

Title: Developmental and sex differences of GPER1 and ERα expression in the striatum of male and female rats

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Abstract: The striatum comprises multiple subregions instrumental for behaviors and neurological disorders that show sex differences in incidence and function. It has been suggested that estrogens are primarily driving these sex differences. In adult female rodents, striatal regions express nonnuclear estrogen receptors. However, little is known whether estrogen receptor expression varies across the life span of both females and males. This is a critical gap in knowledge because sex-specific estrogen action varies according to developmental stage. We determined how protein expression of two estrogen receptors, GPER1 which is expressed on membranes, and ERα which can be expressed both in the nucleus and in the membrane, changes between males and females at several developmental time points. We collected brains from males and females at ages P3, P20, and adulthood (>P60; N=18) and stained for GPER1 and ERα using immunofluorescence. We used a confocal microscope to take multiple scans throughout the tissue slices in three major regions of the striatum: dorsal striatum, nucleus accumbens core, and nucleus accumbens shell. We also imaged the cingulate cortex and arcuate nucleus of the hypothalamus as positive controls for GPER1 and ERα expression, respectively. We found that GPER1 expression decreased in the dorsal striatum and increased in accumbens core and shell with age, indicating that GPER1 may be regulated differently between the dorsal and ventral subregions before puberty begins. We did not detect robust sex differences in GPER1 expression. For ERα, although expression was very low, we did observe nuclear staining patterns, especially in P3 females. This expression disappeared as animals aged and seemed more pronounced in females compared to males. This study has provided developmental time windows in which to explore changes in estradiol sensitivity across the striatum. Future directions will determine what is driving the differential regulation between region and sex.

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Poster 27

Title: Attentional bias towards threat and trauma exposure: an examination of gender differences in children exposed to early life trauma

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Abstract: A large body of research has shown that both attentional bias and physiological arousal are linked to a range of mood and anxiety disorders, including posttraumatic stress disorder (PTSD). These disorders are more prevalent in females than males, however, the biological mechanisms underlying these sex differences are not well understood. The present study examined the processing of emotional facial stimuli (happy, neutral, and angry) in male and female children who have experienced early life trauma and neighborhood violence, in order to better understand risk factors for PTSD. 31 African American children (16 boys, 15 girls), ages 6-14 (M=9.58 years) completed an eye-tracking task to assess gaze location and duration as well as changes in pupil diameter using an Applied Lab Systems eye-tracker while viewing pairs of emotional and neutral faces. Trauma history was assessed with child report using the Traumatic Events Screening Interview (TESI). Attentional bias towards angry faces was positively correlated with trauma exposure, $r=0.40$, $p=0.05$, and higher in males ($M=0.058+/-0.017$) compared to females ($M=0.002+/-0.010$), ($F(1,30)=7.53$, $p=0.01$). Pupil diameter was much greater when viewing angry compared to neutral faces, ($F(1,30)=20.33$, $p<0.001$), but did not differ by child sex and was not associated with trauma exposure. These results demonstrate that attentional bias towards threatening cues may indicate higher trauma-related risk, especially in young males. On the other hand, sympathetic nervous system activity captured by pupil dilation may be a useful measure of threat-related arousal independent of sex. Our findings indicate that males might have increased vigilance to threat in a dangerous environment. Future directions could include further research into using attentional bias to look at prospective mental health outcomes.

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Poster 28

Title: Central immune alterations in a gestational stress model of postpartum depression

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Abstract: Postpartum depression (PPD) is a major public health problem that is experienced by 15% of new mothers. Despite its prevalence and adverse consequences for women and their children, the causes of PPD remain unclear. To date, research investigating the factors contributing to PPD has largely focused on hormonal fluctuations, although increasing attention has been given to the potential role of the immune system. Immune mediators have only been examined peripherally in depressed mothers and thus little is known about how the brain's immune system is modified in PPD. To address this gap, we used an animal model of PPD based on a well-known risk factor, gestational stress, and evaluated the maternal neuroimmune system focusing on the medial prefrontal cortex (mPFC), a key mood-related brain region implicated in PPD. Pregnant rats were subjected to chronic variable stress from gestation days (GD)7-20 or were unstressed and then sacrificed either one day before (GD21) or one week after (postpartum day 8, PD8) delivery. Brain tissue was collected for qPCR to assess mRNA expression of the pro-inflammatory cytokines interleukin (IL)-1B, interferon (IFN)y, and tumor necrosis factor alpha (TNFa) as well as the growth factor, insulin-like growth factor (IGF)1. Additionally, CD68, integrin alpha M (ITGAM), complement component 3 (C3) and complement component 1 (C1q), markers associated with microglial phagocytosis of synaptic elements, were analyzed. Our results show increased expression of IL-1B and IFNy in the mPFC of gestationally stressed mothers on GD21, suggesting a shift to a pro-inflammatory state. In addition, expression of ITGAM and C1q were increased on GD21 which may further suggest that stress leads to microglia-mediated synaptic remodeling. There was no effect of gestational stress on PD8 for any marker analyzed. Together, these data suggest that gestational stress impacts the maternal neuroimmune system which may contribute to the development of PPD.

Funding: This study was funded by a joint faculty seed grant award from the Ohio State University College of Arts and Sciences to KML and BL.

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Poster 29

Title: The X-chromosome copy number difference causes the gender disparities in bladder cancer

Author List: Satoshi Kaneko[1] and **Xue (Sean) Li**[1]

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Abstract: Men are much more likely than women to develop bladder cancer (BCa) but the underlying cause of this gender disparity remains poorly defined. Using sex-reversed mice, we show that the sex chromosome complement is an independent cause and moreover, amplifies the biasing effects of sex hormones. We also show that the X-linked lysine demethylase 6A (KDM6A) is a sexually dimorphic gene. Wild type but not catalytically-dead KDM6A confers sustained tumor suppressor activity in vitro. Knockout of mouse Kdm6a reduces expression of Cdkn1a and Perp, canonical gene targets of the tumor suppressor p53. Consistently, loss-of-Kdm6a increases BCa risk of female mice; and mutations or reduced expression of human KDM6A predict poor prognosis of female BCa patients. Collectively, the study reveals that the X chromosome protects against BCa among females via a KDM6A-dependent epigenetic mechanism, and further suggests that KDM6A is a prototypical sex-biasing tumor suppressor with both demethylase-dependent and -independent activities.

Funding: This study was funded by NIH/NCI (1R21CA198544, XL).

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Poster 30

Title: Sex differences in modulatory effects of 17β estradiol on serotonergic neuromodulation of TRPV1 expressing sensory neurons

Author List: Sukhbir Kaur Lulla M.S., Cierra Lopez B.S., Sirima Tongkhuya B.S., and Dayna L. Averitt Ph.D.

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Abstract: Trigeminal nerves innervating the orofacial region express the nociceptive transient receptor potential vanilloid-1 (TRPV1) ion channel. TRPV1 activation results in calcium influx and post-synaptic release of proinflammatory mediators, such as calcitonin gene-related peptide (CGRP). The neurotransmitter serotonin (5-hydroxytryptamine, 5HT) acts as a pronociceptive mediator in the periphery that can alter sensory thresholds by binding excitatory 5HT receptors, such as $5HT_{2A}$, that colocalize with and sensitize TRPV1. These studies were done in males; however, pain conditions activating trigeminal neurons are more prevalent in females. This sexual dimorphism may be attributed to fluctuating hormone levels that could influence the peripheral 5HT system and its effects on TRPV1-expressing nociceptors. Our recent studies have found that peripheral 5HT rapidly evokes greater, longer-lasting pain behaviors in female rats during estrus and proestrus. This led us to hypothesize that 17β-estradiol acts through membrane bound receptors to enhance 5HT potentiation of TRPV1-expressing sensory neurons. Rats received pretreatment with $5HT_{2A}$ antagonist or vehicle and 5HT-evoked pain behaviors were measured. Primary neuron cultures were pre-treated with estrogen receptor agonists or vehicle, then stimulated with 5HT and TRPV1 agonist and CGRP release was quantified. Local 5HT levels in the interstitial fluid from inflamed hindpaws were also quantified. We report that the $5HT_{2A}$ antagonist reduced pain behaviors *in vivo* and 17β-estradiol enhanced CGRP release *in vitro*. There was no difference in local 5HT levels during inflammation across the estrous cycle. These data indicate that 5HT evokes pain via $5HT_{2A}$ receptors and estrogen enhances serotonergic potentiation of TRPV1 activity. Together, our data reveal a novel neuromodulatory role of estrogen on 5HT-evoked pain processing, which may provide one mechanism underlying the greater prevalence of trigeminal pain disorders in women.

Funding: This study was supported by TWU Research Enhancement Grants.

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Poster 31

Title: Biological sex influences allergen-induced mast cell activation patterns and severity of anaphylaxis

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Abstract: Highly prevalent and debilitating mast cell (MC)-associated diseases, including allergy, irritable bowel syndrome, and autoimmune disorders exhibit a sex bias with females at increased risk. The mechanisms underlying these sex differences remain poorly understood. Our previous studies utilizing MC-dependent models of IgE-mediated anaphylaxis and psychological stress, demonstrated that female mice exhibited more severe pathophysiology and increased MC mediator release compared with males. The objective of this study was to uncover mechanisms underlying this sexual dimorphism in MC disease. Our hypothesis is that heightened disease in females is due to sex-specific differences in MC activation patterns. To investigate, we performed transcriptional analysis on IgE-DNP allergen-activated male and female bone marrow-derived MCs (BMMCs). Using Ingenuity software (Qiagen, Redwood City, CA), we discovered a similar pattern of activation of canonical pathways between male and female BMMCs after 1h exposure to IgE-DNP. However, many pathways associated with MC activation were upregulated to a greater extent in female BMMCs including sphingosine-1-phosphate signaling (z-score; M:F,1.63:3), leukocyte extravasation (z-score; M:F, 0.73:2.96), NF-κB signaling (z-score; M:F, 1.13-2.53), and chemokine signaling (z-score; M:F, 0.54:2.83). Our analyses also revealed up- and downregulation of pathways that were sex-specific. For example, upon activation, male BMMCs exhibited upregulated pathways of transcriptional repression and downregulated pathways of cell cycle control while female BMMCs exclusively exhibited upregulation of histidine degradation and downregulation of amino acid biosynthesis. Together, these studies reveal new insight into sex differences in MC biology and disease that correlate with the female sex bias in humans. Further elucidating the role of sex in MC activation is likely to provide a novel path for pursuing therapeutic approaches to debilitating MC diseases.

Funding: This study was funded by National Institutes of Health grants NIH R01 HD072968 (to A.J.M.) and NIH F30 OD025354 (to E.M.)

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Poster 32

Title: Mercury accumulation and the mercury – PCB – sex interaction in summer flounder

Author List: Charles P. Madenjian Ph.D.[1], Olaf P. Jensen Ph.D.[2], David P. Krabbenhoft Ph.D.[3], John F. DeWild M.S.[3], Jacob M. Ogorek M.S.[3] & Anthony R. Vastano M.S.[2]

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Abstract: Patterns in the relative differences in contaminant concentrations between the sexes of mature fish may reveal important behavioral and physiological differences between the sexes. We determined whole-fish total mercury (Hg) concentrations in 23 female summer flounder (*Paralichthys dentatus*) and 27 male summer flounder from New Jersey coastal waters. To estimate the change in Hg concentration due to release of eggs at spawning, Hg concentration in the somatic tissue and ovaries of 5 of the 23 female summer flounder were also determined. To ascertain whether most of the Hg in the summer flounder was methylmercury (MeHg), whole-fish MeHg concentrations were determined in all 50 summer flounder. Whole-fish Hg concentrations averaged 113 ng/g for females and 111 ng/g for males. Thus, females were 2% higher in Hg concentration than males, on average, but the difference was not statistically significant. Based on Hg determinations in the somatic tissue and ovaries, we predicted that Hg concentration of females would increase by 3.6%, on average, immediately after spawning due to release of eggs. On average, 92% of the Hg in the summer flounder was MeHg. To determine whether the effect of sex on Hg concentration was significantly different from the effect of sex on polychlorinated biphenyl (PCB) concentration, we paired our Hg determinations with PCB determinations from a previous study, and applied regression analysis. Sex significantly interacted with contaminant type (Hg or PCBs), as males were 43% higher in PCB concentration than females, whereas females were 2% higher in Hg concentration than males. Males eliminating Hg from their bodies at a faster rate than females was a likely explanation for this discrepancy between the two contaminant types. Overall, the Hg and PCB concentrations in the summer flounder were relatively low, and therefore our findings also had implications for continued operation of the summer flounder fishery.

Funding: This study was funded by the U. S. Geological Survey and Rutgers University.

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Poster 33

Title: Sex differences in the effects of paternal deprivation on hippocampal volume and microglia density in the adult California mouse (*Peromyscus californicus*).

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Abstract: Evidence suggests adverse early-life experiences are a risk factor for developing psychiatric disease in adulthood. Likewise, chronic early-life stressors induce neuronal remodeling, resulting in dysfunctional neural circuitry and subsequent psychiatric disease. Maternal deprivation, an animal model for early-life stress, induces deleterious effects on neuroplasticity in the hippocampus; however, less is known about how paternal deprivation modulates hippocampal neuroplasticity in the biparental California mouse (*Peromyscus californicus*). Previous research in our lab has demonstrated that paternal deprivation (PD) facilitates a sex-dependent reduction in dentate gyrus (DG) cell survival in young adult California mice, such that PD reduces survival of newborn cells in female, but not male, offspring. However, mechanisms underlying these sex differences in PD-related cell survival are unknown. In mammals, stress has been shown to modulate immune systems resulting in neuronal damage in higher cortical regions, such as the hippocampus. Moreover, early-life stress dysregulates the function of microglia, resident immune cells of the brain, in the developing hippocampus. The purpose of this study was to investigate to what extent PD results in sex-dependent modifications to microglia in the adult DG. Male and female California mice were born to multiparous breeders and reared by both their mother and father (biparental care) or by their mother alone (i.e., paternal male removed on postnatal day 1). On PND 68, male and female offspring were perfused and immunohistochemistry for the microglial specific marker, Iba1, was performed. Compared to biparentally-reared mice, PD resulted in a reduction in the volume of the DG in both males and females. Interestingly, while the total number of Iba1+ cells in the DG was not altered by sex or rearing, the density of IBA1+ cells was greater among PD females, compared to control females and all males. Taken together, these data suggest that consequences of PD can have lasting effects on structural plasticity of the adult hippocampus. While PD did not result in phenotypic differences in microglia in young adulthood, it is possible that differences in microglial function during development may contribute to the observed changes in hippocampal morphology.

Funding: This study was funded the University of Maryland.

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Poster 34

Title: 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

Author List: Dr. F. Maranghi, Dr. S. Tait, Dr. L. Narciso, Dr. R. Tassinari, Dr. C. La Rocca

Author Affiliations: Center of gender-specific medicine, Istituto Superiore di Sanità Rome Italy

Abstract: Bis(2-ethylhexyl)phthalate (DEHP) and bisphenol A (BPA) are non-persistent environmental contaminants used as plasticizers and recognized as endocrine disruptors (EDs), potentially affecting human health especially childhood, as crucial susceptible phase of development.
LIFE PERSUADED project, funded by the European Commission (LIFE13 ENV/IT/000482), aimed at evaluating children exposure and effects of BPA and DEHP and its metabolites by setting up 1) a biomonitoring study (HBM), to evaluate the Italian background levels in healthy paediatric population, 2) a pilot case-control (CC) study on idiopathic obesity (Ob) to evaluate the association with BPA and DEHP's metabolites exposure, 3) an in vivo animal study using juvenile rodents. Clinical and toxicological biomarkers were measured in serum samples (CC) and contaminant levels in urine samples (CC e HBM). Data on lifestyle, food storage and consumption were collected through a structured questionnaire and a food diary. 1) 1644 eligible children were enrolled. Levels of the sum of DEHP metabolites are higher in girls from Centre of Italy and in boys from South of Italy. Levels are higher in 4-6 years girls from North and South and in boys from North and Centre, whereas boys aged 7-10 have higher levels in South of Italy. BPA levels are higher in the Centre for both sexes but boys aged 4-6 have higher levels in North and Centre. 2) 30 Ob boys and girls, with matched controls were enrolled. BPA levels were higher in girls and leptin serum levels were higher in both girls and boys. 3) See poster Tassinari et. al. Although not persistent BPA and DEHP metabolites have been detected in all enrolled children, internal exposure was different according to residing area and age (lower range), with gender differences. Data evaluation of questionnaires and food diaries is in progress and will be integrated with ED exposure data to provide the determinants to be used in risk assessment.

Funding: Supported by Life PERSUADED project LIFE13 ENV/IT/000482.

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Poster 35

Title: Microglial phagocytosis of newborn cells sculpts the cellular composition of the neonatal rat amygdala in a sex dependent manner

Author List: Ashley E. Marquardt BS[1], Jonathan W. VanRyzin BS[1], and Margaret M. McCarthy Ph.D.[1,2]

Author Affiliations: Program in Neuroscience[1] and Department of Pharmacology[2], University of Maryland School of Medicine, Baltimore, MD, USA.

Abstract: The amygdala, a sexually dimorphic brain region, mediates a conserved male bias in juvenile social play behavior. This sex difference arises as a consequence of the sexual differentiation of the amygdala, in which males exhibit fewer newborn cells shortly after birth. We recently found that microglia, the brain's immune cells, may underlie this process, as microglia are significantly more phagocytic in the male amygdala during this timepoint. To this end, we hypothesized that microglia actively phagocytose newborn cells in the developing amygdala, such that males exhibit fewer newborn cells as a result of having more microglia that are phagocytic. We first measured the diameter of phagocytic cups to characterize the targets of microglial phagocytosis. As the cup sizes suggested that microglia engulf cell bodies, we stained tissue for Iba1, a microglial marker, and NucRed, a DNA binding dye. In both sexes, the majority of cups co-labeled with NucRed, indicating that microglia engulf cells. Further, we found that ~60% of cups colabel with PCNA, a marker of recently divided cells, suggesting that microglia indeed phagocytose newborn cells in the developing amygdala. To explore how this sex difference in phagocytosis, mainly of newborn cells, affects the amygdala's architecture later in life, we used a fate mapping approach. Pups were treated with BrdU on postnatal day 0 (PN0) to PN4 to label newborn cells and sacrificed at PN26. Tissue sections were stained for BrdU and markers of various cell types. In the medial amygdala (MeA), the site of masculinization of play, BrdU+ cells in both sexes predominantly (~80%) colabeled with GFAP. Females had a higher density of BrdU+ cells including a higher density of GFAP+/BrdU+ cells specifically in the posterodorsal MeA. Overall, these data indicate that microglia produce developmental sex differences by phagocytosing newborn cells in the amygdala, sculpting sex differences in neural circuitry with relevance for social play.

Funding: This work was supported by R01MH52716-020 and R01DA0396062-01 to MMM.

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Poster 36

Title: A function investigation of novel Y chromosome encoded long non-coding RNAs expressed in human male CNS during early development

Author List: Philipp Pottmeier M.Sc., Christiane Peuckert Ph.D., Elena Jazin Prof.

Author Affiliations: Uppsala University, Department of Organism Biology, Unit for Evolution and Development, Uppsala, Sweden

Abstract: The prevalence, age of onset, and clinical symptoms of many neuropsychiatric disorders differ substantially between males and females. We hypothesize, that the sexual differentiation of the human brain during development, is a major factor contributing to the difference in susceptibility to neurological disorders between males and females.
The current concept of central nervous system sexual differentiation during development includes, not only the action of gonadal hormones, but also genes encoded on the sex chromosomes. We are investigating whether homologous regions of the X and Y chromosome are involved in the formation of sex differences in the human brain, especially during very early central nervous system development (less than 12 weeks after gestation), before the production of sex hormones by the primordial sex organs. To do this, we use two cell models: a) human embryonic stem cells and b) neuronal stem cells. We investigate gene expression patterns between male and female derived cells after differentiation to mature neurons and glial cells. In addition, marker genes for differentiation, as well as parameters for proliferation, motility and morphology are being measured. We are also using CRISPR/Cas9 knockout, as well as CRISPRa/i genome editing to trace specific neural- and glial-cell lineages, and to investigating the role of novel long non-coding RNAs encoded on the Y chromosome (Y-lncs), previously identified by our group in first trimester human male fetus (manuscript under revision). We have found that these Y-lncs are expressed highest in human males, during early development of the nervous system. Our study will shed light on differences between male and female brain development, and thus sets the basis for advances in one of the most neglected issues in medical science, sex differences.

Funding: This study was funded by the Swedish Research Foundation, grant name: Sex determination factors in the brain encoded in the Y chromosome (Project number K2012-61X-22089-01-3)

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Poster 37

Title: Sex differences in the consequences of early-life immune activation on microglia-neural signaling and the ontogeny of hippocampal-dependent learning in the juvenile rat

Author List: Brittany F. Osborne, Sarah B. Beamish, and Jaclyn M. Schwarz, Ph.D.

Author Affiliations: Department of Psychological and Brain Sciences, University of Delaware, Newark, DE, USA

Abstract: Developmental disorders associated with learning deficits including Autism, ADHD, and pervasive developmental disorders have been linked to early-life immune activation, and most notably, are male-biased in their diagnosis. Microglia are the primary immune cells of the brain and are in constant communication with neurons, thus, activation of microglia can significantly influence the function of surrounding neurons. Recent evidence indicates that microglia-neuron signaling is also necessary for the proper formation of neural circuits that support learning during early brain development. We found that immune activation with lipopolysaccharide (LPS; 100ug/ml/kg) on postnatal day (P) 21 produces sex-dependent deficits in the *emergence* of hippocampal-dependent learning on P24 in rats. Next, we examined gene expression in the hippocampus at 2-, 4-, 8-, and 24-hr following immune activation and determined that there are sex differences in the expression of inflammatory molecules including IL-1β and IL-6 in the hippocampus. Additionally, males, but not females, have a persistent decrease in brain derived neurotrophic factor expression starting 4hr post-LPS that persists until 24hr. Finally, we found that males, but not females, have a significant increase in the expression of C3, an immune molecule that tags synapses for phagocytic elimination, at 24hr. Currently, we are examining whether we can rescue the learning deficits on P24 by treating males and females with the microglia inhibitor minocycline at the time of immune activation. However, we have found a sex difference in the effectiveness of minocycline such that minocycline effectively inhibits microglia in males, but is not as effective in females. The behavioral results following treatment with minocycline will be discussed. Our data suggest that changes in microglia-neural communication may be a mechanism underlying sex differences in the vulnerability to the emergence of developmental learning disorders following early-life immune activation.

Funding: This study was funded by National Institute of Health grant R01MH106553 and a University of Delaware Research Fellowship grant.

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Poster 38

Title: Rat Model of Prenatal Zika Virus Infection.

Author List: Morgan L. Sherer B.S.[1], Pragyan Khanal B.S.[1], Mark Parcells Ph.D.[2], Jaclyn M. Schwarz Ph.D.[1]

Author Affiliations: [1]Department of Psychological and Brain Sciences, University of Delaware, Newark, DE, USA. [2]Department of Animal and Food Sciences, University of Delaware, Newark, DE, USA.

Abstract: Zika virus (ZIKV), a mosquito-borne flavivirus, has been associated with microcephaly and other neurological disorders in infants born to infected mothers. Despite being declared an international emergency by the World Health Organization, comparatively very little is known about the pathogenesis, mechanisms, or behavioral consequences of maternal ZIKV infection in the offspring. Our lab is interested in developing a working animal model to answer some of these questions. Here, we use a rat model of prenatal ZIKV infection to measure the level of infectivity, as well as the rate of viral clearance in both the mother and her pups. We examine various aspects of brain development in pups, including cortical thickness, microglia morphology, apoptosis, and neurogenesis. Given that pregnancy is associated with significant immunomodulation, we are also interested in the role that pregnancy has on the impact of ZIKV infection, therefore we compare viral infectivity between both pregnant and non-pregnant female rats. In this study, we show that prenatal ZIKV infection results in an increase in cell death and reduces hippocampal and cortical volumes in the neonatal rat brain. For the first time, we demonstrate the efficacy and validity of a rat model for maternal ZIKV infection with vertical transmission to the fetus. This model will allow us to 1) better understand the mechanisms underlying ZIKV infection and transmission to the fetus, 2) determine the impact of ZIKV infection on the developing male and female fetal brain, and 3) in the future, measure behavioral deficits and investigate potential sex differences associated with fetal ZIKV infection later in life.

Funding: No specific funding was attributed to this work.

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POSTER SESSION II: Tuesday, May 1st 4:45pm – 6:45pm

Poster 39

Title: Sex differences in associations between child abuse victimization, persistent cigarette smoking, and nicotine dependence

Author List: Alison L. Cammack, Ph.D., MPH[1], Shakira F. Suglia, Sc.D., MS [1]

Author Affiliations: [1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

Abstract: There is evidence child abuse is linked with later smoking, but few studies have examined persistent smoking and nicotine dependence. Further, most of these studies do not consider the potential effect modifying role of sex. This study tested the hypotheses that 1) child abuse is associated with an increased risk of current smoking among ever regular smokers and lifetime history of nicotine dependence and 2) sex modifies these associations. Using data from the National Longitudinal Study of Adolescent to Adult Health, we examined the relationship between retrospectively self-reported child abuse (parent/caregiver perpetrated emotional, physical, and sexual abuse, and non-parent/caregiver perpetrated sexual abuse) and self-reported smoking behaviors in early adulthood (Mean age=29y). Outcomes were current daily smoking among individuals reporting a history of regular smoking at any study wave (persistent smoking; N=3,538) and lifetime history of nicotine dependence via the Fagerstrom scale. We used predicted margins with complex sample weighting to compute risk ratios adjusted for sex, age, other drug use, and socioeconomic status, and used interaction terms to test for effect modification by sex. Non-parent/caregiver sexual abuse by non-physical threat (aRR=1.15,95% CI:1.00-1.33) and physical force (aRR=1.20,95% CI:1.05-1.39) were associated with persistent smoking in men and women, but an association with any abuse by a parent/caregiver was only present among women (aRR=1.14,95% CI:1.05-1.23,p for sex interaction <.001). Most forms of abuse and sums of abuse (aRR for 2+ vs 0 exposures=1.56,95% CI:1.29-1.89) were associated with nicotine dependence in both men and women, and there was no interaction by sex. These data suggest that in a nationally representative sample, child abuse is associated with persistent smoking and nicotine dependence, and women exposed to child abuse by parent/caregivers may be more vulnerable to persistent smoking.

Funding: This study was funded by the National Institutes of Health (R01HL125761 and R01HL125761-04S1) to SFS.

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Poster 40

Title: Sex-specific behavioral endocrinology of BDNF Val66Met mice maintained on chronic oral corticosterone

Author List: Jordan Marrocco Ph.D.[1], Nathan R. Einhorn[1] B.A., Gordon H. Petty B.A.[1], Claire Le Floch B.A.[1], Ilia N. Karatsoreos Ph.D.[2], Francis S. Lee Ph.D.[3], & Bruce S. McEwen Ph.D.[1]

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Abstract: Sex and gender influence a variety of behaviors beyond reproduction, including the response to stress. Overexposure to stress induces chronically elevated cortisol/corticosterone (CORT) levels, leading to allostatic overload and sex-specific susceptibility to psychiatric disorders and metabolic dysfunctions. Little is known about the factors that may aggravate the effects of CORT overexposure, such as genetic variants and biological sex. We investigated the metabolic and behavioral effects of chronic oral CORT in heterozygous BDNF Val66Met (HET-Met) male and female mice, a model of genetic sensitivity to stress. HET-Met and wild-type (WT) mice were treated with CORT (25mg/L) or vehicle in drinking water for 8 weeks. During treatment, a battery of behavioral tests was performed, body weights were recorded weekly, and blood was collected to measure glycaemia. We found that oral CORT did not affect body weight in either sex, but HET-Met females exhibited higher body weight than WT females independently of treatment. Fasting glycaemia was lower in CORT-treated males regardless of genotype, whereas HET-Met females showed reduced fasting glycaemia levels compared to WT females regardless of treatment. Also, CORT-treated mice of either sex, except HET-Met females, displayed lower adrenal gland mass than vehicle-treated mice. Using a Y-maze to assess spatial memory, we showed that CORT corrected cognitive deficit in HET-Met females, but had no effects in males of either genotype. Anxiety- and depressive-like behaviors, referred to as emotional behavior, were tested with the light-dark box and the splash test, respectively. When a z-normalization was applied across complementary measures of emotional behavior, we demonstrated that CORT significantly decreased z-score in HET-Met females but had an opposite effect in WT and HET-Met males. These findings indicate that the chronic oral CORT model highlights sex-specific sensitivity to CORT overexposure that intersects the Met genotype.

Funding: This study was supported by NIH grant MH41256 to B.S.M., and Hope for Depression Research Foundation.

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Poster 41

Title: Female cocaine motivated behavior and dopamine transporter state are dependent on estrous cycle stage

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Abstract: While preclinical cocaine research has focused primarily on male behavior and neurobiology, recent work indicates distinct differences in male versus female cocaine responsivity. In humans, women progress to cocaine dependence faster than men and exhibit greater craving and relapse following abstinence. As in humans, rodent literature suggests males and females have different behavioral responses to cocaine, which appear to be dependent on the estrous cycle. Specifically, female rodents exhibit augmented cocaine taking behaviors, such as increased conditioned place preference and cocaine seeking, during the estrus phase. This increased vulnerability to cocaine use during estrus may be a product of sex and estrous stage specific differences in basal mesolimbic dopamine (DA) system function. This is supported by a recent study showing not only greater activation of ventral tegmental area projections to the nucleus accumbens and cocaine sensitivity at DA terminals during estrus but also increased cocaine preference. We thus sought to determine whether cocaine self-administration behaviors during estrus were related to dopamine transporter (DAT) function. We found that females in estrus exhibited faster acquisition times as well as greater motivation to take cocaine as measured using a threshold self-administration protocol. Using *ex vivo* voltammetry, we found that in both naïve and cocaine treated females, only the DATs of females in estrus showed supersensitivity to cocaine. Furthermore, we found that over the course of multiple estrous cycles, females show greater motivation and augmented cocaine potency at the DAT during each presentation of estrus compared to other stages. This effect was further intensified if an animal's first exposure to cocaine occurred during estrus. These findings are significant because they indicate a neurobiological and potentially pharmacologically targetable vulnerability to cocaine addiction specific to females in estrus.

Funding: This study was funded by R01DA01403 and T32AA007565 (SRJ)

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Poster 42

Title: Are sex differences in the brain canalized?

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Abstract: The term canalization was proposed by Waddington in the 1940's to visually capture the concept of cell fate. Once a particular differentiation canal was entered the path forward was limited and the endpoint inevitable. Subsequently the term canalization has been adopted by evolutionary biologist to explain "species robustness", the phenomenon whereby a species-specific phenotypic trait is maintained within a narrow range despite the constant onslaught of insults that mutate DNA, miss-fold proteins or otherwise push phenotypic boundaries. Phenotypic canals can be maintained in various ways including micro-RNAs, heat-shock proteins and epigenetics. We propose that phenotypic sex differences in the brain are also canalized, which leads to a series of predictions; 1) little overlap between males and females on a sexually differentiated phenotype, 2) variance associated with the phenotypic trait should be small and constant between the sexes, 3) masculinization of females should induce phenotypic changes which follow the above parameters, 4) preventing masculinization in males should induce phenotypic changes which follow the above parameters, and 5) males cannot be "super" masculinized and females cannot be "super" feminized. In order to test these predictions we analyzed 30 papers published from this laboratory from 1996 to 2017 using data generated in rat pups from birth to 1-week-old. Most data were continuous variables but some studies included % responding. Based on this preliminary data, the prediction of little overlap in males and females on structural, protein and biochemical end points holds true and variance is small and equal within males and females. Moreover, masculinization of females induces phenotypic changes which follow the above parameters. Future directions include expanding the analysis to studies from other laboratories and adult animals. Lastly, analysis of behavior, where effects of canalization are predicted to be much less, if at all.

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Poster 43

Title: Sex differences and estrous-cycle effects of serotonergic potentiation of capsaicin-evoked orofacial nocifensive behavior.

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Abstract: Trigeminal pain, such as migraine and temporomandibular joint disorder pain, disproportionately affects women. Despite this prevalence, the biological mechanism(s) underlying this apparent sex difference remains unclear. There is growing evidence that gonadal hormones modulate pain mechanisms. The neurotransmitter serotonin (5HT) acts as a proinflammatory and pronociceptive mediator in the periphery that enhances pain processing and may be subject to modulation by gonadal hormones. We recently reported that peripheral 5HT evokes greater and longer-lasting hyperalgesia in female rats during proestrus and estrus compared to diestrus, males, and ovariectomized (OVX) females. We further found that 5HT evokes orofacial nocifensive behaviors in rats in proestrus and estrus, but not in diestrus, males, or OVX females. As peripheral 5HT receptors are colocalized with the transient receptor potential vanilloid 1 ion channel (TRPV1), a cation channel activated by capsaicin that initiates pain signaling, it is possible that 5HT differentially potentiates TRPV1 activity leading to our observed sex differences and estrous cycle effects. Here we hypothesized that 5HT potentiates capsaicin-evoked orofacial nocifensive behaviors to a greater degree during proestrus and estrus compared to diestrus, males, and OVX females. Adult male, OVX female, or cycling female rats were injected with 5HT + capsaicin (1.5 µg 5HT + 1 µg capsaicin / 50 µl; n=6-8 per group) or capsaicin only (n=6-8 per group) into the vibrissal pad and spontaneous orofacial nocifensive behaviors were scored in 6 min bouts over 30 min. We report that only rats in proestrus exhibited significant spontaneous nocifensive behaviors compared to the capsaicin only group, implicating hormone modulation of 5HT enhancement of TRPV1-evoked pain.

Funding: This research was supported by a Texas Woman's University Research Enhancement Program grant awarded to DLA.

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Poster 44

Title: Sex differences in aging in healthy women and men

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Abstract: Our immune systems are not gender or sex neutral. Women and men have different immune bias towards a stronger or weaker response. The prevalence, severity, and mortality of autoimmune diseases and infectious diseases as well as vaccine response differ among the sexes. The sex differences in immunosenescence or the aging of the immune system are not well understood. We preformed an analysis of peripheral blood samples of women and men of varying ages using a new method, EpiTOF. EpiTOF uses the power of CyTOF to measure epigenetic changes by assessing the difference in expression of histone markers in different immune cell types. We analyzed 24 samples, 12 women and 12 men, 12 old (>65 years) and 12 young (<25 years) in 10 different immune cell types. We determined that aging affects men's immune systems much more strongly than it does women's immune system. Future directions for this research will explore what these changes in histone expression mean for older men's health and how they relate or correlate with the sex bias already seen in different diseases.

Funding: This study was funded by NIH Training Grant, Stanford Graduate Student Fellowship and Stanford Bio-X fellowship.

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Poster 45

Title: Sex differences in vitamin D, kidney stones and comorbidities in patients with kidney stone disease

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Abstract: More men than women develop kidney stones. Vitamin D (VitD) is a critical regulator of calcium that may affect the calcium content of kidney stones. In the United States, 25% of the population has VitD deficiency that is associated with an increased risk of autoimmune and cardiovascular disease. In 18,753 healthy controls (no ICD-9/10 codes in their EMR) from the Mayo Clinic Biobank we found that VitD levels were significantly increased in women vs. men (p=6E-89). In this study, we utilized the Mayo Clinic Urinary Stone Disease Registry, which has around 1,600 kidney stone disease (KSD) patients that are well-phenotyped according to sex, age and stone type. In an initial analysis of 500 KSD patients, the sex difference in VitD levels between men and women was no longer present (p=0.16). However, men with KSD had significantly higher levels of VitD than controls (p=0.01) while women did not (p=0.88). Men with KSD had a greater number of events and larger stones than women and VitD levels correlated with number of events and stone size. When we examined comorbidities associated with KSD from 120 KSD patients we found that 71% had hypertension and 52% dyslipidemia, which occurred more often in men than women (p=0.02 and p=0.0002, respectively). Our preliminary data suggests that VitD may play a role in the pathogenesis of kidney stone formation particularly in men. Understanding the comorbidities associated with kidney stone disease and their relationship to VitD levels may provide further insight into the pathogenesis of disease.

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Poster 46

Title: Sex differences in medium spiny neuron electrophysiological properties: heterogeneity across striatal regions and evidence for estradiol-dependent sexual differentiation

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Abstract: 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.

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Poster 47

Title: The quandary of gender assignment in 46,XX newborns with classical congenital adrenal hyperplasia and high genital masculinization

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Abstract: Prenatal exposure of 46,XX fetuses to excessive androgen levels, as it occurs in classical congenital adrenal hyperplasia (C-CAH), masculinizes genitalia, brain, and behavior to varying degrees (depending on timing and dosage), and, thereby, diminishes the respective sex differences. This constitutes a challenge to binary gender assignment at birth with subsequent endocrine and surgical management and increases the likelihood of later gender dysphoria (Meyer-Bahlburg, 2014). While the Endocrine Society's Clinical Practice Guideline for CAH (Speiser et al., 2010) presumes female assignment of 46,XX newborns with C-CAH, Lee et al. (2010) proposed that male gender assignment be considered (despite resulting infertility) for severely masculinized 46,XX newborns with C-CAH, given (sparse) gender outcome data and the risks of feminizing genital surgery to cosmesis and function. In preparation for the forthcoming guideline update (Speiser et al., 2018), this poster summarizes the current status of the evidence. Under the search term "CAH AND gender", PubMed cited 500 papers published in 2009-2018, which were screened for psychosocial information on male assignment, gender dysphoria, and/or reassignment to male of 46,XX individuals with C-CAH. The resulting 24 papers provide many examples of male assignment, mostly in resource-poor regions, due to delayed clinical presentation and/or male-gender bias. Patient-initiated reassignment from male to female did occur, but rarely, and not at a higher rate than from female to male. Where detailed behavioral data were available, social, sexual, and psychiatric functioning of 46,XX patients with C-CAH living as males were apparently within normal limits. We conclude that the data support a policy of including the male-assignment option in discussions with the parents of 46,XX newborns with C-CAH and high degrees of genital masculinization (Prader stage 4-5), yet systematic comparison studies are still needed.

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Poster 48

Title: Biological sex influences trajectories of gut barrier and neuroimmune development and clinical disease in a porcine model of early life adversity.

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Abstract: Early life adversity (ELA) increases the risk for debilitating and deadly diseases throughout the lifespan. The gastrointestinal (GI) system is highly sensitive to the effects of ELA demonstrated by the large number GI diseases associated with ELA such as irritable bowel syndrome (IBS) and food allergy. A female sex bias exists in many GI diseases linked with ELA but the the mechanisms are poorly understood and translational animal models are lacking. Utilizing a piglet model of ELA induced by early weaning stress (EWS), we investigated the influence of biological sex on clinical and pathophysiologic measures of GI disease in prepubertal (7 weeks of age) and sexually mature (20 weeks of age) pigs. Compared with late-weaned control pigs (LWC), female and male piglets exposed to EWS exhibited chronic, functional diarrhea (EWS 43.6% vs LWC 4.8% of the time with diarrhea, $p<0.0001$), increased intestinal permeability (by 2 fold), and elevated gut mast cell numbers (by ~1.6 fold). Compared with EWS males, EWS female pigs exhibited more frequent and severe episodes of diarrhea (58.8% vs 29.9%, $p=0.0016$) and greater intestinal permeability (by 1-2 fold). Increased mast cell numbers and their enhanced co-localization with neuronal ganglia were observed in both male and female EWS pigs; however, female pigs exhibited greater release of mast cell tryptase upon activation with c48/80 (~1.5 fold increase, $p<0.05$). Both female and male EWS pigs exhibited increased numbers of ileal enteric neurons, compared with respective LWC pigs. EWS females exhibited increased markers of cholinergic nerve activity and function, compared with EWS males. Together, these data show the female pigs exposed to ELA exhibit heightened vulnerability to GI disease compared with males. Sex differences in the GI response to EWS emerge prior to puberty and persist into adulthood which mimics the sex bias and underlying pathophysiology observed in human GI disorders associated with ELA such as IBS.

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Poster 49

Title: Sex differences in Vitamin D and Cardiovascular Diseases in Systemic Sclerosis Patients

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Abstract: Systemic sclerosis (SSc) is a rheumatic autoimmune disease characterized by diffuse vascular injury, immune dysregulation and progressive multisystemic fibrosis. The female to male overall ratio is around 4:1 and has been estimated to be higher in pre-menopausal women compared to post-menopausal women. Approximately one third of SSc deaths are attributed to cardiovascular disease (CVD). Low levels of vitamin D (VitD) have been associated with an increased risk of death from CVD in the general population. VitD deficiency occurs more often in SSc patients compared to healthy controls. But, it remains unclear whether sex differences in VitD levels influence the risk of SSc-associated CVD. In this study, we investigated sex specific association of VitD levels with the risk of CVDs including pulmonary arterial hypertension (PAH), myocardial infarct (MI), coronary artery disease (CAD) and cardiomyopathy (CMP). This retrospective study utilized the Mayo Clinic electronic medical record to examine VitD levels and CVDs in men and women with a diagnosis of SSc by ICD-9/10 codes. In an initial analysis we found a total of 8,376 patients (6,764 women/1,612 men) diagnosed with SSc. 2396 patients have reported VitD levels with 626 having VitD levels below 20 ng/ml (513 women/113 men) of which 271 have a diagnosis of PAH (225 women/46 men) and 243 have a diagnosis of MI, CAD or CMP (184 women/59 men). We found that females with SSc and low VitD levels (<20ng/ml) have a higher risk of PAH alone and MI/CAD/CMP together in comparison to females with SSc and normal VitD levels (≥20ng/ml). Interestingly, we did not find an association between VitD levels and CVDs in males with SSc. Determining whether sex differences exist in sera VitD levels for patients with SSc and whether the levels correlate to CVD is important due to the increased prevalence of VitD deficiency and inconclusive data on the role of VitD in SSc-associated CVD.

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Poster 50

Title: Hippocampal cAMP signaling regulates spatial memory deficits in a mouse model of neurodevelopmental disorders in a sex-specific manner

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Abstract: The molecular mechanisms underlying male bias in neurodevelopmental disorders remain unexplained. In studying *coiled-coil and C-2 domain containing 1A (CC2D1A)*, a gene mutated in intellectual disability (ID) and autism spectrum disorder (ASD), in the mouse, we found that loss of Cc2d1a affects intracellular signaling and behavioral phenotypes in a male-specific manner. CC2D1A is a signaling scaffold that acts as an inhibitor of PDE4D preventing PDE4D activation via PKA and maintaining the intracellular level of cyclic AMP (cAMP). We performed biochemical and behavioral studies in male and female mice to analyze whether PDE4D activation, cAMP levels, learning and memory properties, social interactions, anxiety and hyperactivity were differentially affected. We found that removal of *Cc2d1a* in male mice leads to PDE4D hyperactivity and increased cAMP degradation, resulting in a reduction of CREB activity in male hippocampus associated with hippocampal behavior deficits. *Cc2d1a*-deficient females only show impairments in novel object recognition. We then asked whether reducing PDE4D activity with an inhibitor (GEBR-7b) would restore CREB activity in the hippocampus of *Cc2d1a*-deficient mice and rescue behavioral alterations in males and females. We found that GEBR-7b treatment rescues the hippocampal spatial memory defect specific to male mice. Our results show that CC2D1A regulates cAMP signaling in the hippocampus of male mice leading to male-specific hippocampal-dependent behavior. This promising data suggests that male-specific deficits in particular intracellular signaling pathways may underpin male prevalence in neurodevelopmental disorders.

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Poster 51

Title: Distinct roles of sex chromosomes and developmental timing of establishment of the sex-specific epigenome

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Abstract: Men and women differ in their epigenetic profiles. Sexual dimorphism in DNA methylation levels is found in different human cell types and has been implicated in predisposition to disease, such as psychiatric and autoimmune disorders. To elucidate the mechanisms underlying sex-specific differences in methylation levels in humans, we examined DNA methylation levels at autosomal sex-specific differentially methylated regions (sDMRs) in fibroblast cell lines derived from individuals with different combinations of sex phenotype and sex chromosome complement using pyrosequencing methylation assays. We focused on sDMRs that had higher methylation levels in females and with sex differences conserved across different cell types. Imprinted DMRs were used as controls. SDMR methylation levels were compared in 46,XX females, 46,XY males, sex-reversed 46,XY females, sex-reversed 46,XX males, Turner syndrome patients with monosomy X (45,X) as well as Turner syndrome patients with an isochromosome Xq (46,X,i(Xq)). Our data show that at least 2 loci on the X and at least one locus on the Y chromosome contribute to the sex-specific differences in methylation levels observed at these sDMRs. However, the sex phenotype had no effect on methylation levels at these loci. Next, we asked if the developmental timing of the establishment of sex-specific differences in DNA methylation was similar to that observed for the X-chromosomal genes. We used the DNA methylation data from the Roadmap Epigenomics project and compared the methylation levels in sperm, embryonic stem cells (ESCs), fetal, and adult tissues. We find that, in both XX and XY ESCs, sDMRs are highly methylated, which makes them clearly distinct from both imprinted regions and X-linked loci. In conclusion, several sex chromosome-linked factors contribute to sexual dimorphism in autosomal DNA methylation and developmental timing of sDMR establishment is different from those of X-linked and imprinted regions.

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Poster 52

Title: Sex differences in comorbidities associated with fibromyalgia and hypermobility syndromes

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Abstract: Fibromyalgia is a chronic pain illness estimated to occur in 2% of the population globally with a sex ratio of 9:1 women to men. Previous studies examining comorbidities associated with fibromyalgia found that hypermobile syndromes including hypermobile Ehlers-Danlos Syndrome (hEDS) occur frequently in fibromyalgia patients (4-25x more often). Hypermobile syndromes, including hEDS, are estimated to occur in up to 3.5% of the population. A small cohort of well-characterized hEDS cases found that 89% of patients (*n*=38) were female, a sex ratio similar to fibromyalgia. In spite of the relatively high prevalence of fibromyalgia and hypermobile syndromes in the population, the pathogenesis of disease and reason for the sex difference remains unknown. In this study, we investigated how often 11 common comorbidities occurred in 562 fibromyalgia patients from the Mayo Clinic EMR based on ICD-9/10 codes. Comorbidities included fatigue, migraine, interstitial cystitis, IBS, hypertension, PTSD, central sensitization, hypermobility syndrome, chronic pain, and depression. We found that females with fibromyalgia had more migraines (p=0.0004) and depression (p=0.02) compared to males, whereas males had more fatigue (p=0.03). When we examined comorbidities according to age using age 50 as a surrogate for menopause status, we found that women under 50 had significantly more migraines (p=0.009) and fatigue (p=0.04) while women over 50 had significantly higher hypertension (p=5E-10). Our findings highlight the importance of studying sex and age differences in disease and provide insight on factors that may predispose and/or contribute to chronic pain in fibromyalgia patients. Future studies will expand this study to over 7,000 fibromyalgia and/or hypermobile syndrome/hEDS patients that are available in the Mayo Clinic EMR in order to better understand the mechanism of disease.

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Poster 53

Title: Sex differences in IQ and adaptive functioning in long-term adult survivors of pediatric cerebellar brain tumors

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Abstract: Radiation treatment improves survival following childhood brain tumors but increases the risk for impairments in cognition and independent living skills. Some studies identify females as being at greater risk for cognitive deficits due to radiation, but few identify significant sex differences in adaptive functioning. Adaptive functioning, the ability to perform daily tasks independently, is the culmination of basic cognitive processes. It was hypothesized that females would exhibit poorer IQ scores and independent living skills than males following radiation treatment. The Scales of Independent Behavior-Revised (SIB-R) was used to assess adaptive functioning and the Wechsler Abbreviated Scale of Intelligence (WASI) assessed IQ. SIB-R scores positively correlated with IQ scores. ANOVAs revealed a main effect of radiation on IQ where survivors with radiation had lower IQ scores than survivors without radiation, but there was no main effect of sex. Similarly, ANOVAs for most SIB-R domains showed a similar main effect of radiation on adaptive functioning in that patients displayed better independent living skills if they did not receive radiation, but sex did not have a main effect. There was an interaction between sex and radiation in SIB-R community living skills such that females' community living skills were more negatively impacted by radiation treatment than males'. Compared to other SIB-R domains, community living skills include more advanced skills such as handling money and work skills that may be more impacted by the underlying cognitive deficits traditionally observed in females following radiation. Future studies should assess the degree of adaptive functioning impairment predicted by core cognitive skills (e.g., attention, working memory, processing speed). Identification of critical cognitive processes will allow for targeted interventions to prevent or remediate difficulties in adaptive functioning.

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Poster 54

Title: Sex differences in rat traumatic stress responses recapitulate sex differences in men and women with PTSD

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Abstract: Sex differences in traumatic stress responses are widely reported in clinical studies of post-traumatic stress disorder (PTSD), but the neurobiological basis for this is unknown, largely due to male bias in preclinical research. Using a rodent model of PTSD, single prolonged stress (SPS), we find sex differences described in humans reflected in adult rats. After SPS, males show hyper-responsiveness to subsequent mild stress, as measured by enhanced acoustic startle response and exaggerated negative feedback control of the stress hormone response, two presumed hallmark features of PTSD, but females do not. While these two measures may suggest female resilience to SPS, other measures commonly applied to depression studies (sucrose preference, social interaction) suggest females but not males are affected by SPS and indicate a more depressive-like phenotype for traumatized females. The results reported here further characterize sex differences in response to SPS, with specific attention to measures typically used in depression studies: forced-swim test, marble burying, novelty-induced hypophagia, and high-dose dexamethasone suppression test. Results continue to portray a hyper-responsive phenotype in males and a depressive phenotype in females. Additionally, PTSD is associated with changes in pain sensation/perception, and we find SPS-induced hyperalgesia only in female rats. We propose that the trauma response for female rats recapitulates the female bias in PTSD for internalizing symptoms and major depression in contrast to the externalizing symptoms of males. We conclude that males and females show fundamentally different responses to trauma that do not simply reflect differences in resilience.

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Poster 55

Title: Acute central administration of poly I:C disrupts memory encoding in female but not male mice

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Abstract: Neuroimmune signaling mediates normal cognitive processes such as learning and memory. Dysregulation of the neuroimmune system has been implicated in disorders of memory such as post-traumatic stress disorder and Alzheimer's disease, which have a higher prevalence in women compared with men. Our lab has previously shown sex differences in both the pattern and time course of central cytokine induction following acute peripheral immune stimulation, and sex differences in memory deficits long after a subchronic immune challenge. However, it is important to determine whether sex differences in the acute immune activation state, particularly within the brain, differentially affect mechanisms of learning that may contribute to the sex differences seen in memory impairment. Thus, we first aimed to characterize the effects of central immune activation on physiological and behavioral measures of sickness to determine meaningful time points of the immune response. Second, we aimed to determine the impact of this acute immune activation state on hippocampal-dependent memory tasks in both male and female mice. Polyinosinic:polycytidylic acid (poly I:C) is a viral-like immune stimulant that binds to toll-like receptor 3 expressed on astrocytes, microglia, and neurons, making it a useful tool to study immune activation. Thus, we used intracerebroventricular (ICV) administration of poly I:C (20μg) or sterile saline to stimulate a central immune response in our experiments. First, both males and females showed the greatest weight loss and temperature increases between 4 and 6 hours post-infusion, so we utilized this time frame for future behavioral tasks. Next, we trained males and females on contextual fear conditioning 4 hours after ICV administration of poly I:C and found that female, but not male mice, showed deficits in context fear memory when tested 72 hours later, when the physiological effects of poly I:C were no longer measurable. Finally, to determine how central immune activation affects social-based memory tasks, we analyzed social interaction and social memory behaviors in female mice. We found that social interaction was significantly decreased in female mice 4 hours after poly I:C infusion, indicating that poly I:C disrupts learning about a social conspecific. In a separate cohort of females, ICV administration of poly I:C immediately after social memory training resulted in significantly reduced discrimination between a familiar and novel social mouse. Collectively, these findings suggest that males and females are differentially impacted by central immune activation, with females being more susceptible to the effects of neuroimmune activation on encoding and consolidation of fear- and social-based memories.

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Poster 56

Title: Sex and estrous cycle induced differences in medium spiny neuron electrophysiological properties in adult rat nucleus accumbens core

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Abstract: Naturally occurring hormone cycles in adult female humans and rodents create a dynamic neuroendocrine environment. These cycles include the menstrual cycle in humans, and its counterpart in rodents, the estrous cycle. These hormone fluctuations, along with other influences, induce sex differences in the phenotypes of many behaviors, including those related to reward, motivation, and associated disorders such as depression and addiction. This suggests that the neural substrate instrumental for these behaviors, including the nucleus accumbens core (AcbC), likewise differs between estrous cycle phases. It is unknown if the electrophysiological properties of AcbC output neurons, medium spiny neurons (MSNs), change between estrous cycles phases. This is a critical knowledge gap given that MSN electrophysiological properties determine what information is communicated to AcbC efferent targets. Here we test whether the intrinsic electrophysiological and excitatory synaptic input properties of adult rat AcbC MSNs differs across female estrous cycle and to males. We recorded MSNs using whole cell patch-clamp technique in two experiments: the first using gonad-intact adult males and females in differing phases of the estrous cycle, and the second using gonadectomized males and females wherein estrous cycle was eliminated. MSN intrinsic electrophysiological and excitatory synaptic input properties robustly changed between female estrous cycle phases and males. Differences in MSN electrophysiology disappeared when the estrous cycle was eliminated. These novel findings indicate that AcbC MSN electrophysiological properties change across the estrous cycle, providing a new framework for understanding how biological sex and hormone cyclicity regulate motivated behaviors and other AcbC functions and disorders.

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Poster 57

Title: Impact of sex and gender-related factors on percutaneous coronary intervention in patients with ischemic heart disease: analysis from the EVA study

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Abstract: Improvements in ischemic heart disease (IHD) management have been unbalanced between sexes. Post-procedural coronary microvascular dysfunction (CMD) is one putative reason for worse outcomes in women. Therefore, we aimed to explore sex and gender-sensitive determinants of post-procedural CMD in IHD patients undergoing percutaneous coronary intervention (PCI). Among the original cohort of IHD patients enrolled in the *"Endocrine Vascular disease Approach"* (EVA) Study, those undergoing urgent or elective PCI were included in this analysis. Angiographic indexes of coronary reperfusion [*i.e.* corrected TIMI frame count (cTFC) and myocardial blush grade (MBG)] were assessed before and after stent implantation. Baseline clinical, pharmacological and sociocultural parameters were recorded. Ninety-one subjects undergoing PCI with stent implantation (mean age 68±11 years; 27% women) were analyzed. Indication for angiography was represented by acute coronary syndrome in half cases in both sexes. History of previous PCI with stent implantation was more prevalent in women than men (87% *vs* 62%, p= 0.02); Females were also more frequently retired, widowed, and less adherent to medication therapy (all, p<0.05). The Duke Activity Status Index identified a worse performance status in women compared to men (22±14 *vs* 36±18, p=0.001). Among traditional cardiovascular risk factors, only LDL cholesterol was higher in women compared to men (p=0.011). Better pre-procedural MBG was found in women compared to men (48% *vs* 70% p=0.05). However, despite optimal restoration of epicardial flow, an impaired micro-coronary reperfusion (post-PCI MBG<2) was more frequently observed in women compared to men (32% *vs* 6%, p=0.011). Moreover, in the logistic regression analysis, only female sex was independently associated to post-interventional CMD (OR 4.88, 95% CI 1.26-18.7, p=0.022). In conclusion, female sex is significantly associated with a worse myocardial perfusion after PCI.

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Poster 58

Title: Sex and gender-related differences in coronary microvascular dysfunction: data from the EVA project

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Abstract: Women presenting with myocardial ischemia often have no angiographic evidence of obstructive coronary artery disease (CAD). Coronary microvascular dysfunction (CMD) may play a pivotal role in ischemia, especially in women. The aim of the study was to explore sex- and gender-related determinants of CMD in a real-world cohort of IHD patients. The *"Endocrine Vascular Disease Approach"* (EVA) Study is an ongoing observational study, aimed at assessing sex- and gender-specific interactions between coronary circulation, hormonal status and platelet function. Consecutive IHD patients undergoing urgent or elective angiography with or without percutaneous coronary interventions (PCI) were recruited. CMD was assessed using myocardial blush grade (MBG) and was defined as a MBG<2. Baseline clinical, angiographic, sociocultural data were also recorded. One hundred and sixty-three patients (mean age 67±11 years; 39% women) were included in the analysis. Acute coronary syndrome was the clinical indication for coronary angiography in half of patients in both sexes. History of IHD was more prevalent in men; women were less often smokers and adherent to medication therapy, and were more frequently retired and widowed (p<.05). Median in-hospital stay was longer in females compared to males (9 [6-17] *vs* 7 [4-12] days, p=0.032). CMD and ischemia with no obstructive CAD (INOCA) were more frequently detected in women than in men (48% *vs.* 31% p=.034 and 40% *vs* 25% p=.017, respectively). In logistic regression analysis, only female sex was independently associated to CMD (OR:2.02, 95% CI:1.05-3.88, p=.034). In conclusion, angiographic CMD is commonly found in women, regardless the grade of coronary obstruction, and female sex was significantly and independently associated to CMD. Further analysis of sex-dependent parameters (i.e. hormones and platelet function) on coronary microcirculation will help to clarify the mechanisms underlying this phenomenon.

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Poster 59

Title: Chronic adolescent stress alters the adult hippocampal transcriptome in a sex-specific manner

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Abstract: Adolescence may be a period of particular susceptibility to the harmful effects of chronic stress exposure. Previous work has found that adolescent rats exposed to chronic adolescent stress (CAS) exhibit enhanced depressive-like behaviors and alterations to targeted gene transcription in the hippocampus in a sex-specific manner in adolescence. We hypothesized that CAS impacts hippocampal transcription in a lasting, global, and sex-specific manner in adulthood, and furthermore, that prior exposure to CAS alters the transcriptional response to exposure to a novel acute stressor in adulthood. Male and female rats were exposed to a mixed-modality chronic adolescent stress paradigm consisting of isolation, restraint, and social defeat during mid-adolescence (PND 38-49). In adulthood (PND 94), hippocampal tissue was collected at baseline and 30 minutes following exposure to a novel acute forced swim stressor. The transcriptome was assessed with RNA sequencing. EdgeR was used to assess differential gene expression, and Qiagen Ingenuity Pathway Analysis software was used for pathway analyses. Prior exposure to CAS shifts global gene expression differently in male and female adult rats such that up- and down-regulated genes do not significantly overlap between males and females at baseline ($p>0.05$). Furthermore, prior exposure to CAS alters the transcriptional response following acute stressor exposure in the hippocampus in adulthood in males and females. Together, these data show that CAS alters the hippocampal transcriptional response to novel stressor exposure in a sustained and sex-specific manner. These results highlight that the effects of CAS persist through the lifespan and impact adult responsivity to novel stressor exposures.

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Poster 60

Title: Gender differences in the access to substance use treatments.

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Abstract: Gender differences have been elucidated in the prevalence rates of substance use, treatment access, and outcomes in the US. Further work, however, is needed to understand current perceptions of men and women in terms of access to substance abuse treatments. Such knowledge can then facilitate the development of evidence-based treatments that are better tailored to their specific needs and are more accessible and effective. We hypothesize that by 2015 women still report differences in accessibility and treatment rates compared to men, across ethnic groups. To address this hypothesis, we analyzed the 2015 National Survey on Drug Use and Health (NSDUH) annual census. Data were downloaded through the Substance Abuse and Mental Health Data Archive (SAMSHA) website. Chi-squared tests, accounting for survey weights (in Stata v14) were used to test differences between race (White, Black, Hispanic) and gender (female and male). Females more frequently reported not receiving treatment for the use of alcohol or drug use across all ethnic groups, compared to males ($p<0.001$); they also reported needing treatment less frequently than males (p-value=0.01). However, Black women reported more frequently needing treatment as compared to White or Hispanic women. There was no gender difference in reporting making an effort to receive treatment amongst all races (White, Black and Hispanic). However, gender differences did occur when asked about reasons why the treatment was not received even though an effort was made. Women, as compared to men, more frequently reported lack of transportation ($p=0.053$) and stigma ($p=0.02$) as reasons for not receiving treatment. This analysis demonstrates that men and women still by 2015 have different perceptions and requirements for treatments for the use of substances in terms of accessibility. In order to be accessible and effective, treatments must be tailored to each gender's and ethnicity's needs, with transportation and stigma being two important factors that might limit women accessibility to these treatments.

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Poster 61

Title: Sex differences in gray matter volume and behavior across DRD2 allele type during adolescent brain development

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Abstract: Adolescence is a period of development marked by significant brain and behavioral changes influenced by genetics and sex hormones. One source of variation is the single nucleotide polymorphism (SNP) rs6277 in the dopamine receptor D2 (DRD2) gene. In adults, the C allele is linked to increased risk for Alcohol Use Disorder in men but is inconclusive in women (Padmanabhan & Luna, 2014). Little is known about this SNP and the influence of sex on adolescent neurodevelopment and behavior. We analyzed gray matter volume (GMV) and temporal preference for reward in a community sample of drug and alcohol naïve adolescents (mean age 12.76 +/- 0.74; N = 101; 55 F). GMV was quantified using a T1-weighted MPRAGE (voxel size = $1mm^3$) acquired on a Siemens 3T scanner. Whole brain GMV was assessed via voxel-based morphometry using DARTEL performed in SPM8. A delay discounting task was administered outside of the scanner to measure reward-based planning. Statistical modeling compared groups using a Two-way ANOVA including sex and the DRD2 alleles, T's (T/T combined with T/C) vs. C's (C/C). Significant interactions were found between DRD2 and sex. Greater GMV was found in female T's and male C's when compared to female C's and male T's (589 voxels, p = 0.041, cluster corrected) in the left superior temporal gyrus (peak -46, -19, -1). Given their age, greater GMV implies a developmental delay (Lenroot et al., 2007) in a region involved with reward planning, impulsivity, and goal achievement (FitzGerald et al., 2014; Marsh et al., 2010; Gerlach et al., 2014). The delay discounting task also resulted in a significant sex by DRD2 interaction (p = 0.009), with female T's and male C's indicating a preference for immediate reward. In males, GMV and behavior were significantly correlated (p=0.017). These results suggest that the effect of this DRD2 SNP differs by sex in terms of its effect on brain development and reward planning.

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Poster 62

Title: Postnatal androgens masculinize central nervous system myelin

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Abstract: Sex differences in brain structure are of great interest because the incidence and progress of many neurological disorders differ between males and females. In the central nervous system, myelin is formed by oligodendrocytes. A sexual dimorphism affecting the density of oligodendrocytes and the structure of myelin has been previously reported in adult mice and rats (Cerghet et al. 2006, J. Neurosci. 26:1439). However, a persistent organizational effect of neonatal androgens on myelin appeared unlikely, as oligodendrocyte progenitor cells arise in the rodent brain and begin to differentiate into myelinating oligodendrocytes after the first postnatal week. We establish that sex differences in myelin are already present at postnatal day 10 (P10) using a transgenic mouse line selectively expressing the enhanced green fluorescent protein (EGFP) in the oligodendroglial cell lineage. Furthermore, using gas chromatography coupled to tandem mass spectrometry (GC-MS/MS), we report that brain levels of testosterone and 5α-dihydrotestosterone (5α-DHT), both endogenous agonist ligands of the intracellular androgen receptor (AR), are significantly higher in males when compared with females between postnatal days P0 and P10. We also show persistent effects of postnatal androgens on the density of oligodendrocytes and the structure of the myelin sheaths by postnatal pharmacological treatments. Finally, we demonstrate a key role of brain AR in the structural phenotype of myelin by specifically deleting the receptor in neural cells of the CNS. The role of AR in determining the structure of myelin was further strengthened in genetic male mice with the testicular feminization mutation (Tfm), which lack functional AR. These findings provide new insights into the sexual differentiation of the brain, moving persistent sex differences from neurons to myelin and uncovering new long-lasting effects of postnatal AR signaling (Abi Ghanem et al. 2017, PLoS Genet 13: e1007049).

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Poster 63

Title: Vitamin D deficient diet decreases cardiac function during myocarditis in females

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Abstract: An estimated 1 billion people worldwide have insufficient levels of vitamin D (VitD) increasing their risk for cardiovascular disease (CVD). In this study we examined whether VitD obtained from food alters myocarditis, or inflammation in the heart, using a mouse model. To study the effect of VitD from food we fed female and male mice control (1,500 IU/kg), VitD deficient (0 IU/kg) or VitD supplemented (5,000 IU/kg) food for 5 weeks and examined its effect on circulating VitD levels, myocarditis, cardiac function, and cardiac gene expression. We found that circulating VitD levels were significantly lower in mice fed VitD deficient food than controls and was restored to control levels in supplemented mice. The supplemented VitD levels were lower than expected. Cardiac function was worse in VitD deficient females with a decreased ejection fraction (EF) (p=0.02) and fractional shortening (FS) (p=0.03). We found that heart function (%EF and %FS) correlated with circulating VitD in females, but not in males. Surprisingly, myocarditis was not significantly altered in female mice fed VitD deficient food. But this could be explained by the finding that estrogen receptor-alpha, a hormone receptor known to be altered by VitD/VDR and known to reduce cardiac inflammation in female mice and humans, was increased in females fed a VitD deficient diet (p=0.01). Because the VitD fed to the mice did not produce the estimated circulating VitD levels that it should have, these experiments will be repeated using control (2,200 IU/kg) and supplementation (10,000 IU/kg) food with higher levels of VitD.

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Poster 64

Title: The PI3K/mTOR pathway contributes to sex differences in glioblastoma

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Abstract: Glioblastoma (GBM) is the most common and aggressive brain tumor in adulthood. It occurs more commonly in males but female GBM patients survive significantly longer. In our efforts to identify the mechanisms underlying these differences, we found that EGFR amplification and increased mTOR phosphorylation worsen outcome for male, but not female patients. In order to investigate the contribution of the PI3K/mTOR pathway to sex differences in GBM, we used a murine model of GBM with inactivation of Neurofibromin 1 and p53 function. This model has previously yielded important insights into sexual dimorphism in GBM including a more aggressive growth phenotype of male GBM *in vitro* and *in vivo* and a more resistant drug response phenotype of male GBM. When we activated the pathway in this model through PTEN depletion, we abrogated the sex differences in growth. In a complimentary manner, when we inhibited this pathway with targeted drugs, we increased the sex differences in growth. Thus, we hypothesized that the PI3K/mTOR pathway is sexually dimorphic in GBM. In support of this, we found greater activation of downstream mediators in male GBM cells upon treatment with EGF, insulin or IGF-1. A major mechanism by which the PI3K/mTOR pathway regulates GBM cell growth is through the regulation of glucose metabolism. We performed a metabolic screen of male and female murine GBM cells treated either with insulin or vehicle. Multiple central carbon metabolites, involved in glycolysis, nucleotide metabolism, and the TCA cycle, were significantly different in male and female cells. Together, these data indicate that the PI3K/mTOR pathway and its metabolic targets are sexually dimorphic in GBM. This dimorphism may contribute to sex differences in GBM incidence and outcome and strongly suggests that a sex specific treatment approach will be more effective and beneficial for both male and female GBM patients.

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Poster 65

Title: The heterochronic pathway regulates molecular and functional maturation of the male nervous system in *C. elegans*

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Abstract: Structural and functional remodeling of the nervous system is a pervasive feature of adolescence in many animals. One critical purpose of this is to enable adult-specific sex differences in behaviors. In vertebrates, adolescence is tightly coupled with puberty, whose onset is dependent on activation of the hypothalamic-pituitary-gonadal axis. While it is poorly understood how pubertal onset is timed, a genetically encoded clock originating in the nervous system is thought to have a strong influence on its onset. In fact, polymorphisms in LIN28B and MKRN3 are associated with early onset of puberty in humans. The *C. elegans* homologs of LIN28B and MKRN3, *lin-28* and *lep-2,* respectively, are part of a greater genetic network known as the heterochronic pathway. In *C. elegans*, mutations in this pathway cause either precocious or delayed occurrence of stage-specific events. While several heterochronic genes are conserved, few studies have examined their role in the nervous system. Using a panel of molecular markers, we have investigated whether the heterochronic pathway regulates the onset of sex-specific characteristics of the *C. elegans* nervous system. We found that loss of *lep-2* causes neurons to maintain juvenile-like gene expression, while loss of *lin-28* causes neurons to precociously adopt adult-like gene expression, demonstrating that they time events in the nervous system, similar to their function in vertebrates. Unexpectedly, we found that the mechanisms of heterochronic control may differ between neurons. For example, *lep-2* is critical for the maturation of shared neurons but not male-specific neurons. Consistent with these changes in gene expression, loss of *lep-2* disrupts several adult-specific behaviors. We found that expressing *lep-2* in single neurons is sufficient to rescue their maturation, suggesting the heterochronic pathway acts cell-autonomously. This may indicate that MKRN3 acts cell-autonomously in the hypothalamus to time puberty in vertebrates.

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Poster 66

Title: Preliminary evidence for sex differences in associations between pubertal timing, trauma exposure and community violence in African-American adolescents.

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Abstract: Early puberty has been linked to early life adversity. To date, however, there is limited research on the impact of exposure to trauma and community violence on pubertal timing. We examined relations between pubertal timing, assessed with the Pubertal Development Scale (Petersen et al., 1988), and parent-report of adolescents' 1) experience of traumatic events, measured via the Traumatic Events Screening Inventory (Ippen et al., 2002), and 2) exposure to community violence, measured with the Community Violence Exposure scale (Cooley et al., 1995). Participants were 23 boys and 24 girls from an urban, low-income population with a range of trauma and violence exposure who enrolled in a longitudinal study between the ages of 8 and 13 years (M_{Boys} = 10.1, M_{Girls} = 9.6) and then returned for follow-up assessments 18 months later. We predicted that higher levels of trauma and violence exposure at enrollment would be associated with accelerated pubertal development 18 months later, however, because of sex differences in pubertal timing we tested these associations separately for boys and girls. For boys, when we controlled for age at enrollment, pubertal development was significantly associated with exposure to traumatic events, $r(19) = .61$, $p < .01$, and exposure to community violence, $r(19) = .52$, $p < .05$. For girls, when we controlled for age at baseline, neither trauma nor community violence exposure was significantly associated with pubertal development. These preliminary findings suggest that trauma exposure and community violence may impact pubertal timing differently in boys versus girls.

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Poster 67

Title: Sex-specific differences in the hazard identification of chemical contaminats and the relevance for risk assessment

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Abstract: Sex differences drive the responses to chemicals in females and males. In vivo toxicological studies often evaluate only males, despite the influence of sex on data interpretation. In risk assessment, hazard identification by in vivo tests on laboratory animals of both sexes allows to identify sex-susceptibilities in response to chemicals. Endocrine Disruptors (EDs) are substances altering function(s) of the endocrine system and of priority interest in the study of sex-specific effects. Ethylenethiourea (ETU) is an ED interfering with thyroid hormone biosynthesis. Prenatal oral exposure to ETU at dose levels comparable to human exposure through food, induces – in F1 female rat - alterations of estrogen serum levels and of reproductive system programming with potential effects for fertility. In F1 male rat, effects on testosterone serum levels due to altered hepatic catabolism were present. Nanomaterials are diffused in food and consumer products and, due to physicochemical characteristics, are different from the material with the same chemical composition. Increased gut villus size was present in male rats treated orally with titanium dioxide nanoparticles at 1-2 mg/kg/bw/day (comparable to human exposure through food), whereas female rats showed ovary alterations indicating sex-related effects. The administration of bis(2-ethylhexyl)phthalate (DEHP) and bisphenol A to juvenile male and female rats at dose levels derived from LIFE PERSUADED biomonitoring, showed that DEHP at all dose levels delayed prepurtial separation; no alterations are present in vaginal opening. Leptin and adiponectin serum levels are altered in both sexes. In hazard identification, sex-specific approach is a valuable tool to ensure a reliable risk assessment. In in vivo studies, the use of animals of both sexes allows to better characterize effects and sex-susceptibility potentially leading to reduced number of animals required to obtain sound results.

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Poster 68

Title: Determining the impact of oral hormonal contraceptives on the central nervous system: a large-scale population neuroimaging study.

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Abstract: Oral contraception (OC) is used by >100 million women worldwide. OC use suppresses the endogenous production of sex steroid hormones. Few human studies have investigated the impact of chronic ovarian suppression on brain regions modulated by these hormones. In animal models, estradiol and progesterone act on cortical and subcortical brain regions to alter synaptic morphology. A comprehensive study of the macro-structural brain changes that may result from long-term OC use is long overdue. To that end, we launched a large-scale neuroimaging database at UCSB dedicated to women's health research. By leveraging the activity of the UCSB neuroimaging community, we are pooling standard neuroimaging sequences collected on all Brain Imaging Center participants. We then pair participants' neuroimaging data with a detailed clinical-demographic battery. A core aim of the database is to understand OC's influence on regional brain morphology. We began by asking two questions: Do regional measures of gray matter volume (GMV) differ between current OC users relative to never-users; and does the duration of OC use predict structural difference? In a discovery dataset based on the first 100 database participants (aged 18-33), high-resolution T1 (MPRAGE) scans were analyzed in conjunction with clinical-demographic data. Participants were excluded for previous parity, psychiatric/mood disorder, substance use, or low-quality MPRAGE, yielding a sample of 48 women: 24 current OC users and 24 never-users, matched on age, age of menarche and BMI. Age-matched men (n=27) were included for comparisons by sex. Whole brain analyses (VBM in SPM12, FDR-corrected) revealed greater cerebellar GMV in OC users compared to never-users. Further, duration of OC use (9-84 mos) was positively correlated with greater cerebellar GMV. Finally, sex differences in regional brain volume observed between men and never-users were obscured in OC users. Results are being tested for replication in additional cohorts.

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Poster 69

Title: 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.

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Abstract: Surfactant Protein-A (SP-A) is a major surfactant component and an innate immune molecule. SP-A knockout (KO) mice exhibit reduced survival after infection. Humans have two genes (SFTPA1, SFTPA2) encoding SP-A1 and SP-A2 with several genetic variants identified for each gene. Here, we investigated the effect of hSP-A variants on survival and gene expression profile after *K. pneumoniae (Kp)* infection. We used humanized transgenic (hTG) mice that carried SP-A1 ($6A^2$, $6A^4$), SP-A2 ($1A^0$, $1A^3$) or both variants SP-A1/SP-A2 ($6A^2/1A^0$) and KO. a) These were infected with *Kp* and monitored for survival for 14 days. b) KO mice were treated with SP-A1 or SP-A2 prior to and/or simultaneously with infection and monitored for survival for 14 days. c) Gene expression profiling was performed using SP-A2 ($1A^0$) alveolar macrophages at 6, 18, and 24 h post infection. We found: a) Significant sex difference in survival in all hTG and KO mice, with males exhibiting reduced survival vs females; b) The survival of $6A^2/1A^0$ was greater than all other variants; survival for single gene variants and KO: $1A^0 > 1A^3 > 6A^2 = 6A^4 >$ KO; c) KO mice with SP-A1 or SP-A2 protein exhibited better survival; d) Significant differences were observed between males and females in the expression profile at 6 h vs 18 and 24 h post infection; e) The Ingenuity Pathways Analysis of the top network analysis revealed that males had a higher number of genes related to cell death and survival and signaling, and in females most of the genes were related to tissue morphology, lymphoid tissue structure and development. Our results together indicate that: a) Sex differences in survival exist and that this is gene- and variant-dependent; b) Treatment with hSP-A at or prior to infection improves survival; c) Sex differences in gene expression at the 6 h time point showed most of the genes in males to be involved in cell death and survival. These findings provide insight into the role and importance of innate immune variants of SP-A in survival.

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Poster 70

Title: Estradiol-mediated deficits in fear inhibition can be rescued by zona incerta stimulation.

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Abstract:
The inability to inhibit fear in neutral, non-aversive conditions is associated with a wide range of psychopathological conditions such as post-traumatic stress disorder and generalized anxiety disorder. Women are disproportionately affected by these disorders but the biological basis of this disproportionate incidence remains unclear. Previous research has highlighted that estradiol (E) plays a major role in regulating fear. In line with this literature, we found that high E levels in female mice impair fear inhibition as tested in an auditory fear discrimination task. Next, we performed c-fos studies to identify brain regions specifically involved in modulating fear inhibition but not conditioned fear. Therefore, we examined thalamic/sub-thalamic brain regions outside of the canonical fear-related neuronal networks that monitor threat and emotional valence such as amygdala, PFC, BNST and hippocampus. Interestingly, we found decreased c-fos activation in the zona incerta (ZI) of animals expressing estrogen-mediated impairments in fear inhibition, compared to controls. Furthermore, chemogenetic stimulation of the ZI reversed E-mediated impairments in fear inhibition in females. Additionally, we found that targeted stimulation of E-responsive cells within the ZI was sufficient to restore the ability to inhibit fear in E-treated female mice. Taken together, our data suggest a robust role for ZI in modulating E-mediated fear inhibition. Future studies will be focused towards understanding whether the ZI similarly modulates fear inhibition in males. Moreover, we aim to investigate if and how E acts on the ZI at a cellular level, to effect the observed changes in fear inhibition.

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Poster 71

Title: B1 cells regulate sex-dependent immune responses to *Chlamydia* infection.

Author List: Rachel M Kampen MSc[1,2], Cynthia Tram MSc[1,2], Melanie Tillman BSc[1,2], Nicole Hajjar[1,2] & **Jun Wang Ph.D[1,2,3]**.

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Abstract: *Chlamydia* species are obligate intracellular bacteria that infect epithelium lining ocular, respiratory and genital tract. Compared to men, women are infected more often and have more severe outcomes clinically. However, the biological basis underlying the sex disparity to *Chlamydia* infection is unknown. In this study, we compared host responses in male and female mice following intranasal infection of *Chlamydia muridarum* (Cm). Compared to male mice, female mice lost significantly more body weight and had a higher bacterial burden. Immune profiling showed that males elicited earlier IFN□□responses whereas female mice evolved higher serum antibody production and more IL-10 and IL-13 responses. Interestingly, female mice also had significantly more B1 cells in the lung compared to males. Additional *in vitro* and *in vivo* experiments were conducted to examine the role of B1 cells in host response to *Chlamydia* infection. We demonstrated that females naturally had more B1 cells in the peritoneal cavity compared to males, which had the functional activity of inducing differentiation of IL-10-producing T cells *in vitro*. We further demonstrated that B1 cells migrated to the lung and draining lymph nodes from the peritoneal cavity upon *Cm* infection *in vivo*. Finally, we demonstrated that male mice receiving adoptively transferred B1a cells displayed an increased susceptibility to *Chlamydia* infection, characterized by increased body weight loss and higher bacterial burden in the lung. Collectively, our study demonstrates that sex-specific immune responses occur following *Chlamydia* infection and that these responses are mediated by innate differences in immune regulatory B1 cells.

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Poster 72

Title: The regulation of feeding behavior through the chemoreceptor *odr-10* by genetic sex and feeding state in *C. elegans*

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Abstract: An animal's behavior results from the integration of sensory signals from the environment and internal state. Biological sex is one factor which has a profound effect on animal behavior as the different sexes often need to prioritize different behaviors to maximize fitness. In *C. elegans*, the two sexes, males and hermaphrodites, display sexual dimorphism in feeding behavior; self-fertile hermaphrodites are strongly attracted to food while males are more weakly attracted to food, prioritizing mate searching over feeding. Additionally, food attraction can be modulated by feeding status; well-fed males prioritize mate-searching over feeding, but food-deprived males prioritize feeding until their nutritional needs are met. We have found both sexually dimorphic and feeding state dependent food attraction are mediated in part by regulated expressed of the chemoreceptor *odr-10*, which senses the food-associated odorant diacetyl. We have identified insulin-like signaling and TGFβ signaling as mechanisms that intersect with genetic sex to regulate *odr-10* expression. This regulation of chemoreceptor expression in *C. elegans* provides a tractable model to study how genetic sex is integrated with external sensory signals and other internal state changes to generate plasticity in behavior.

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Poster 73

Title: Estrous cycle-dependent sex differences in rat dorsal striatal MSN excitability

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Abstract: The neuroendocrine environment in which the brain operates is both dynamic and differs by sex. How this unstable neuroendocrine state affects neuron properties has been significantly neglected in neuroscience research. Behavioral data across humans and rodents indicate that natural changes in steroid sex hormone exposure affect sensorimotor and cognitive function in both normal and pathological contexts. These behaviors are critically mediated by the dorsal striatum: a well-conserved constituent of the basal ganglia that is instrumental for forebrain function, various forms of learning, and sensorimotor performance. In the dorsal striatum, medium spiny neurons (MSNs) are the predominant and primary output neurons. As such, MSNs are fundamental components of the circuits which underlie striatal-mediated behaviors. Importantly, MSNs express membrane-associated estrogen receptors and demonstrate estrogen sensitivity. However, the effects of cyclical hormone changes across the estrous cycle on the basic electrophysiological properties of MSNs have not been investigated. Here, I test the hypothesis that dorsal striatal MSN intrinsic excitability is a dynamic property that is modulated in adult females across the estrous cycle via the associated changes in steroid sex hormone levels. I performed whole-cell patch clamp recordings on male, diestrus female, proestrus female, and estrus female MSNs in acute brain slices obtained from adult rat dorsal striatum. Assessment and analysis of the electrophysiological properties is ongoing, with a particular emphasis on intrinsic excitability and miniature excitatory synaptic currents (mEPSC). Preliminary results indicate that the properties that govern cellular excitability differ over the course of the estrous cycle for female MSNs. Additional analysis is needed to further inform these results. Overall, given the estrous-dependent sex differences in the normal and pathological behavioral output of circuits involving the dorsal striatum, understanding the nature of neuroendocrine modulation of MSN function is an important research goal.

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Poster 74

Title: Sex and inhibition: sex-specific differences in the development of the hippocampal GABAergic network

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Abstract: Sexual differentiation of the brain is influenced by testosterone (T) and its metabolites during the perinatal period in males (♂) and females (♀). This period is also critical for GABAergic network maturation and may be involved in T♀ susceptibility to seizures, unlike ♀ that do not develop seizures, as seen in our model of epilepsy (Desgent et al., 2012). Our hypothesis is that T is involved with brain excitability, therefore the present study aims to understand the differential development of the GABAergic network, not only between ♂ and ♀ rats, but also in T♀ and T-insensitive ♂ non-epileptic rats. Expression of the chloride co-transporter KCC2 was evaluated in the hippocampus using Western blot assays at postnatal days 3, 7 and 40 that are ages with different sex-specific GABAergic effects. Preliminary data showed that expression of KCC2 protein increased with age in all sexes and surprisingly was greater in T♀ than in other sexes at P3 ($P=0.01$). To determine the functional consequences of this protein expression levels, spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded in CA1 pyramidal cells and the cumulative probability analysis showed significantly bigger amplitudes events and higher frequency of sIPSCs in ♀ than in ♂ ($P<0.0001$). Interestingly in both variables, T♀ results were in between ♂ and ♀ cumulative probabilities. Morris Water Maze test evaluated hippocampal-dependent spatial memory and showed no difference during the probe test. Despite this, the effects of the absence or presence of circulating T levels (apparition of nipples and testis retraction or increased anogenital distance and absence of vaginal opening) on sexual phenotypes were clear and unequivoqual. Further analysis in the study of the expression of proteins of the GABAergic system and their effect on the physiology and behavior in these sex conditions will make it possible to better understand the sex-specificity of epileptogenesis.

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Poster 75

Title: Gender difference in association of symptoms and white matter deficits in first episode and drug-naïve schizophrenia

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Abstract: Accumulating evidence shows that disruption of white matter (WM) may be involved in the pathophysiology of schizophrenia, even at the onset of psychosis. However, very few studies have explored gender difference in its association with psychopathology in schizophrenia. This study aims to compare gender differences in clinical features and WM abnormalities in first-episode and drug-naïve schizophrenia among Han Chinese inpatients. The WM fractional anisotropy (FA) values of the whole-brain were determined using voxel-based diffusion tensor imaging (DTI) in 39 (16 males and 23 females) first-episode and drug-naïve SCZ patients and 30 healthy controls (13 males and 17 females) matched for gender, age and education. Patient psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Compared with the controls, the patients showed widespread areas of reduced FA, including corpus callosum, brainstem, internal capsule, cingulate and cerebellum (all adjusted $p<0.01$). Further, female patients showed higher FA values in cingulate than male patients ($F=4.92$, $p=0.033$). Multivariate regression analysis showed that for male patients, FA values in corpus callosum were positively associated with the PANSS total (beta=0.785, $t=3.76$, $p=0.002$) and the negative symptom scores (beta=0.494, $t=2.20$, $p=0.044$), while for female patients, FA values in cingulate were negatively associated with the PANSS total (beta=-0.723, $t=-2.26$, $p=0.04$) and positive symptom scores (beta=-0.717, $t=-2.25$, $p=0.041$). Our results indicate gender difference in white matter disconnectivity and its association with psychopathological symptoms in an early stage of schizophrenia onset.

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Poster 76

Title: Gender differences in association of cognitive deficits and low BDNF in first-episode drug-naïve schizophrenia

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Abstract: Gender differences in the cognitive impairments of schizophrenia (SZ) patients have had limited investigation, with ambiguous results. Increasing evidence indicates that brain-derived neurotrophic factor (BDNF) may be related to the pathophysiology of SZ; however, very little research has investigated its association with cognitive deficits or sex differences in first-episode drug-naïve (FEDN) SZ patients. Gender differences in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and serum BDNF were compared between 80 FEDN SZ patients (male/female = 43/37) and 80 healthy controls (male/female = 46/34). The Positive and Negative Syndrome Scale (PANSS) was utilized to assess psychotic symptoms. We found that FEDN SZ patients showed poorer cognitive performance on RBANS total and most of its domain scores than healthy controls, and female patients had significantly lower visuospatial/constructional index score than male patients. The patients had significantly lower BDNF levels than healthy controls, but there was no gender difference in BDNF levels in either patients or healthy controls. For the patients, BDNF was positively associated with visuospatial/constructional, delayed memory and RBANS total scores. Furthermore, these associations only occurred in male but not in female patients. For the healthy controls, there was no gender difference in the association between BDNF and cognition. Our findings demonstrate gender differences in cognitive deficits, as well as in association of cognitive deficits with BDNF in FEDN patients with schizophrenia.

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