

# 2019 Society for Behavioral Neuroendocrinology Annual Meeting

## Poster presentations

The three poster sessions held during the meeting allow for an informal exchange of information and enable networking between established scientists and trainees. All three sessions will be held in the Solarium in the Indiana Memorial Union.

### Poster Session I

Thursday, June 20, 2019, from 4:00pm to 6:00pm

#### P1.1 REGULATION OF ARs IN THE SNB VIA MEMBRANE-INITIATED TESTOSTERONE ACTION

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Classically, estrogens and androgens are known to play a critical role in reproduction across species, and have been studied in this role for some time. We now know steroid hormones influence a vast array of non-reproductive phenomena and can do so through rapid, membrane-initiated signaling. The mechanisms underlying rapid effects have been widely characterized in estrogenic but not androgenic systems. The spinal nucleus of the bulbocavernosus (SNB) is a highly androgen-sensitive neuromuscular system that has been used for decades to study the mechanisms of androgen action. Castration decreases androgen receptor (AR) expression in SNB motoneurons. After castration, testosterone (T) partially upregulates AR within 20 minutes and fully restores AR expression within 2 hours. However, the exact mechanism of this effect is unknown. To determine if a membrane-initiated pathway is responsible for this rapid T-dependent change in ARs, we used T-BSA, a membrane-impermeable form of T. Adult male Long-Evans rats were left gonadally intact or castrated. Castrates were treated with T-BSA and euthanized either 20 mins or 2 hours after T-BSA injection. Spinal cord segments containing the SNB were removed, sectioned, and ARs labeled via immunohistochemistry. Castration resulted in a complete absence of AR-positive motoneurons in the SNB, and T-BSA fully rescued the percentage of AR-positive somata within 2 hours, but failed to significantly increase the percentage of AR-positive motoneuron somata within 20 minutes. These results are the first of our knowledge to demonstrate that testosterone signaling proceeds through a membrane-initiated mechanism in the SNB.

#### P1.2 ROLE OF PREGNANCY HORMONES AND TACTILE STIMULATION ON THE NEURAL RESPONSE TO ANXIETY IN MICE

*Faye Raymond, Imelda Lopez, Mike McCreary, Alex Kowalczyk, Erin Lane, Kimberly D'Anna-Hernandez*

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Past research has shown that lactating dams experience decreased hormonal and behavioral responses to anxiety-like behaviors, when compared to virgin dams. Past research has also shown that lactating dams experience increases in maternal behaviors while virgin dams engage in spontaneous maternal behavior when exposed to pups. The mechanisms behind the relationship between anxiety and maternal behavior is not well understood. As a result, this study aimed to investigate the effects of hormonal changes in pregnancy on anxiety and maternal behavior after a mild stressor compared to sole exposure to pups. Mice were divided either lactating dams, or sensitized virgins (n= 10). Post-natal-day 1-4, virgin mice were sensitized to four donor pups in their home cage for two hours/day. On

the last day, virgins and lactating dams underwent a 15-minute pup retrieval and maternal behavior test. On post-natal-day 5, lactating dams, and sensitized virgins were placed on an elevated zero maze to induce a mild stressor. Maternal behavior was again analyzed for sensitized virgins and lactating dams for 15 minutes immediately after the elevated zero maze.

An independent samples T-Test on IBM SPSS revealed statistically significant differences between lactating dams and sensitized virgins. On average, sensitized virgins were faster to retrieve pups, and spent more time on nest, more time licking and grooming pups, and more time nursing pups.

Maternal anxiety and behavior at work related in lactating dams but not sensitized virgins, thus the circuitry is prompted by more tactile stimulation.

### P1.3 EFFECTS OF ESTRADIOL BEFORE AND AFTER PUBERTY ON THE ANXIETY- AND DEPRESSIVE-LIKE BEHAVIORS OF FEMALE MICE

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Adolescence is a period of rapid growth and development marking the transition from childhood to adulthood. Within the adolescent period, puberty is a developmental milestone in which gonadal hormones increase substantially, culminating in reproductive maturation. While pubertal development is crucial for reproductive development, more recent research suggests that adolescent gonadal hormone exposure is also important for mental health in females. The aim of the current study was to determine the extent to which estradiol mediates anxiety and depressive-related behaviors before and after pubertal development in females. Female C57BL/6 mice were ovariectomized prepubertally or in adulthood and then implanted with either a  $17\beta$ -estradiol or sesame oil filled silastic capsule. One-week post-surgery, anxiety-like behaviors were assessed in the elevated zero maze and open field test, while depressive behavior was measured using the tail suspension test. In the open field, adult females spent significantly more time investigating the center and traveled greater distances than prepubertal females, irrespective of estradiol treatment. Similar effects were observed in the elevated zero maze, with adults investigating the open area of the zero maze for significantly longer durations than prepubertal females. Thus, adults displayed less overall anxiety than prepubertal females. No differences in total time immobile were observed between prepubertal and adult females in the tail suspension test. These data suggest that anxiety-related behavior undergoes significant development during adolescence. Although estradiol played little role in mediating anxiety-related behaviors before puberty or in adulthood, estradiol during puberty may be required for the adult-typical display of anxiety-related behavior.

### P1.4 OXYTOCIN, BROWN ADIPOSE TISSUE, AND THE EXPRESSION OF SOCIAL BEHAVIOR IN MICE

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Oxytocin (OT) plays a central role in a wide range of social and reproductive behaviors. Recent studies highlight that OT is also a critical regulator of metabolism and thermoregulation, including brown adipose tissue (BAT) thermogenesis. Such findings raise questions as to whether effects of OT on social behavior in small mammals such as mice relate in any way to the hormone's thermoregulatory effects. Here, we examined how OT receptor (OTR) inactivation via i.p. injection of L-389,899 affects the expression of social behavior in adult C57BL/6J mice (N = 120; N = 58 males) in the presence of pharmacologically inactivated versus activated BAT. Mice were provided a 10-min social interaction test with an unfamiliar, same-sex partner, and videos later scored for an exhaustive set of social and non-social behaviors. We hypothesized that OT and BAT would act synergistically to influence social behavior, with at least some of the social effects of OT dependent upon OT's thermal effects via BAT. Results from linear

mixed effects models indicate main effects of OT on frequency and duration of a number of pro-social behaviors, including social approach, anogenital and body sniffing, and proximity ( $p < .025$ ). BAT activation/inactivation had no such effects. Nevertheless, there were a number of significant sex-specific OT x BAT interactions, as well as BAT-specific main effects on the frequency of competing non-social behaviors, such as solitary grooming ( $p < .01$ ). These results indicate a complex relationship between oxytocin, brown fat, and the expression of social behavior in mice.

## P1.5 DEVELOPMENT OF A CLINICALLY-RELEVANT ANIMAL MODEL FOR MENOPAUSAL SYMPTOMS

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The menopausal transition is characterized by a decline in steroid hormones and is associated with a suite of symptoms burdening the quality of life of aging women, such as hot flashes, cognitive impairment, sleep disruptions and emotional problems. We studied the interactions among these symptoms using the ovariectomized (OVX) female marmoset (*Callithrix jacchus*). Middle-aged females ( $n = 7$ , 5.4 years old) were tested for cognitive performance, thermoregulation, emotional reactivity and sleep during 3 experimental phases, lasting 3 weeks each: baseline, estradiol replacement (ethinyl estradiol EE2, 4  $\mu\text{g}/\text{kg}/\text{day}$  p.o) and EE2 withdrawal. During each phase, marmosets participated in (1) 15 days of cognitive testing using object discriminations and reversals on a touchscreen system; (2) a thermoregulation challenge during which a heating source was placed on the abdomen and facial temperature changes were recorded using thermal imaging and (3) a social separation task where they were temporarily separated from their partner. We also measured 48 hours of sleep weekly using implanted transmitters for EEG and EMG. General linear mixed models were used for data analysis. Preliminary results indicate that Treatment predicted cognitive performance such that object reversals were significantly more difficult than discriminations at baseline ( $t = 3.26$ ,  $p = 0.002$ ) and EE2 withdrawal ( $t = 2.86$ ,  $p = 0.0083$ ) but not during EE2 replacement ( $t = 1.34$ ,  $p = 0.19$ ). Facial temperature changes did not differ according to treatment. Analysis of sleep patterns and emotional reactivity is underway. Supported by NIH grant AG053841.

## P1.6 USE OF RNA-SEQ TO COMPARE THE BRAIN TRANSCRIPTOME OF WILD MICE WITH EXTREME SOCIAL PHENOTYPES

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Appropriate social interactions influence animal fitness by impacting several processes, such as mating, territory defense, and offspring care. Due to its intrinsic unpredictability and potential to fluctuate, the social environment is one of the more complex components of an individual's environment. By studying social behavior in the lab, we greatly reduce this complexity, but potentially lose some of the proximate signals associated with the neural control of social behavior. On the other hand, studying animals in their natural environment may entirely dilute any signal. In this study, we used a natural wild population of house mice for which social behavior is tracked continuously and remotely. We collected brain samples from individuals that consistently showed extreme social behavior phenotypes, as characterized by overnight encounters with other conspecifics. We extracted RNA from three brain regions (cortex, hypothalamus and hippocampus), as well as from the whole brain and subjected these samples to RNA sequencing (RNA-seq) in order to perform an unbiased search for differences in gene expression between the different social phenotypes. Our results indicate that the dopaminergic synthesis pathway is involved in the differentiation between the two phenotypes, but only in females. We will discuss the origin of these sex differences, as well as the relevance of dopaminergic signaling in this context.

## P1.7 CORTICAL OXYTOCIN RECEPTORS AND ALLOPARENTAL CARE IN PRAIRIE VOLES

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All mammals depend on early parental care for their future well-being, and early environment is often critical to normal neurobehavioral development. Prairie voles (*Microtus ochrogaster*) form monogamous pair bonds and provide biparental care to offspring. However, vole parents provide different amounts of care, quantified by the amount of physical contact between parents and pups. Differential amounts of parental care is associated with many differences in behavior and neuroanatomy. Oxytocin, a neuropeptide involved in social bonding, is one candidate peptide which may mediate these differences, and the role of cortical oxytocin receptors (OXTR) in social behavior is under-explored. In this experiment, pups were cross-fostered on postnatal day 0 and underwent an alloparental care test on PND23-25. Their brains were then collected and we used autoradiography to quantify and compare OXTR expression in cortical regions. Preliminary results indicate that OXTR binding in the offspring was not predicted either by the rearing parents' parental behavior or by the biological parents' rearing behavior. However, OXTR binding in the corpus callosum ( $t = -3.26$ ,  $p = 0.004$ ) significantly predicted total alloparental contact with the test pup, while S1 was marginally significant ( $t = -2.05$ ,  $p = 0.052$ ), as was the insula ( $t = -2.00$ ,  $p = 0.058$ ). Higher binding in these areas was associated with less alloparental care. These results suggest a link between cortical OXTR density and alloparental care in virgin animals.

## P1.8 CANNABINOID RECEPTOR EXPRESSION AND MANIPULATIONS REFLECT SOCIALITY IN MICROTUS

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Endocannabinoids, like anandamide, modulate certain aspects of social behavior, including play, reward, and anxiety. The regional distribution of cannabinoid receptors—particularly CB1—is highly conserved in the animal kingdom, but subtle differences in limbic densities do emerge across individuals, sexes, and species. These findings suggest that endocannabinoids may contribute to the organization of both social and mating systems. To test this theory directly, we conducted a series of experiments using a comparative approach in *Microtus*: (1) we used autoradiography to provide the first distributional map of CB1 within the brains of both monogamous prairie voles and promiscuous meadow voles, (2) we compared receptor densities across sexes and species in limbic regions, (3) and we explored the effects of systemic CB1 antagonists or anandamide facilitators on pair bonding in prairie voles. The distribution of CB1 was similar across vole species. However, we found profound differences in CB1 densities with prairie voles generally having higher CB1 binding in regions of the social behavior and socio-spatial neural networks. We found no evidence of sex differences in any measured region within either species, and systemic CB1 antagonism did not affect partner preference formation. However, disinhibition of anandamide signaling facilitated social contact with a mate in females. These findings suggest that the endocannabinoid system correlates with social organization in *Microtus* and may be involved in certain aspects of species-typical behavior.

## P1.9 CHARACTERIZATION AND NEUROENDOCRINE CORRELATES OF MATING AND PARENTAL BEHAVIOR IN THE ENDANGERED AMARGOSA VOLE (*MICROTUS CALIFORNICUS SCIRPENSIS*)

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The Amargosa vole is an arvicoline rodent native to the Amargosa River basin in the Mojave Desert. This species is critically endangered as a result of habitat loss due to climate change, human encroachment, and predation by invasive species (e.g. house cats). Amargosa vole reproductive behavior has remained uncharacterized; however, this information is invaluable for species rehabilitation. In this series of studies, we considered two aspects of Amargosa vole reproductive behavior, as well as neuroendocrine correlates. In Study 1, we characterized the Amargosa vole mating system, i.e. whether they demonstrate monogamous or promiscuous behavior. We developed a modified partner preference test and compared Amargosa voles performance to that of prairie voles after 24-hours and 1-week of cohabitation in females, and 48-hours and 1-week-1-day of cohabitation in males. In Studies 2a and 2b, we aimed to determine if Amargosa voles demonstrate bi-parental care. In Study 2a we considered the time it takes for parents to retrieve an infant in a novel environment. In Study 2b, we considered what parental care parents demonstrate toward infant stimuli. Amargosa vole mothers retrieve pups significantly faster than fathers, although four of five fathers do retrieve pups. Amargosa vole mothers generally demonstrate more care than fathers. In study 3, we examine and compare OXTR and V1aR distributions in the brains of Amargosa voles (14 female, 11 male), prairie voles (15 female, 17 male), and meadow voles (10 female, 10 male). Together, these findings improve our general understanding of Amargosa vole reproductive behavior.

#### P1.10 FATHERHOOD ALTERS GENE EXPRESSION WITHIN THE MPOA

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Female parenting is obligate in mammals, but fathering behavior among mammals is rare. Only 3–5% of mammalian species exhibit biparental care, including humans, and mechanisms of fathering behavior remain sparsely studied. However, in species where it does exist, paternal care is often crucial to the survivorship of offspring. The present study identifies new gene targets linked to the experience of fathering behavior in a biparental species using RNA sequencing. In order to determine the pattern of gene expression within the medial preoptic area that is specifically associated with fathering behavior, we identified genes in male prairie voles (*Microtus ochrogaster*) that experienced one of three social conditions: virgin males, pair bonded males, and males with fathering experience. A list of genes exhibiting different expression patterns in each comparison (i.e. Virgin vs Paired, Virgin vs Fathers, and Paired vs Fathers) was evaluated using the gene ontology enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes pathways analysis to reveal metabolic pathways associated with specific genes. Using these tools, we generated a filtered list of genes that exhibited altered patterns of expression in voles with different amounts of social experience. Finally, we used NanoString to quantify differences in the expression of these selected genes. These genes are involved in a variety of processes, with enrichment in genes associated with immune function, metabolism, synaptic plasticity, and the remodeling of dendritic spines. The identification of these genes and processes will lead to novel insights into the biological basis of fathering behavior.

#### P1.11 PROLACTIN PREVENTS CHRONIC STRESS-INDUCED ANHEDONIA IN OVARECTOMIZED FEMALE RATS

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Postpartum depression (PPD) afflicts approximately 15% of new mothers with debilitating symptoms. The lack of or early cessation of breastfeeding is a unique risk factor for PPD. Women who bottle-feed exclusively are more likely to develop PPD and prospective studies suggest cessation of breastfeeding often precedes depressive symptoms. Thus, certain aspects of lactation may buffer against the development of PPD. Breastfeeding promotes the release of the peptide hormone, prolactin (PRL). Beyond its role in supporting lactation, PRL influences multiple aspects of physiology and behavior including social behavior, neural plasticity, and stress responses in rodent models. Stress is a significant risk factor for depression and abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis have been implicated in the etiology of depression, including PPD. We sought to determine whether prolactin reduces stress-induced depression-like behavior in female rats. Ovariectomized rats were either non-stressed or received chronic variable stress (CVS) and received daily subcutaneous injections of ovine PRL (1 mg/kg) or saline vehicle. Anhedonia was assessed with the sucrose preference test (SPT) at 3 time points during the study: the first day of PRL treatment, 9 or 10 days after the initiation of CVS, and after 20 days of CVS. Chronic prolactin treatment prevented the development of stress-induced sucrose anhedonia in CVS females. In conjunction with these data, we have labelled for tyrosine hydroxylase (TH) expression in the ventral tegmental area to determine whether CVS or PRL alter dopamine-producing cells. This research has critical implications for a neuroendocrine mechanism by which lactation confers resilience against depression.

### P1.12 PERINATAL BISPHENOL A EXPOSURE ALTERS BRAIN OXYTOCIN RECEPTOR EXPRESSION IN A SEX- AND REGION-SPECIFIC MANNER IN RATS: A CLARITY-BPA CONSORTIUM FOLLOW UP STUDY

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Bisphenol A (BPA) is a well-characterized endocrine disrupting chemical commonly used in manufacturing that is detectable in the environment and humans worldwide. Rodent and human studies show that early life BPA exposure may impact the developing brain and sexually dimorphic behaviors. The CLARITY-BPA (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) program was established to assess multiple endpoints, including neural, across a wide dose range. Studies from our lab as part of (and prior to) CLARITY-BPA have shown that BPA disrupts estrogen receptor expression in the developing brain, and some evidence of oxytocin (OT) and oxytocin receptor (OTR) disruption in the hypothalamus and amygdala. Central OT is important for modulation of many behaviors in mammalian species including aspects of social recognition, anxiety, parental care and other socioemotional behaviors. In this CLARITY-BPA follow up study, we used remaining juvenile rat tissues to test the hypothesis that developmental BPA exposure affects OTR expression across the brain. Perinatal BPA exposure (2.5, 25, or 2500 µg/kg body weight (bw)/day) spanned gestation and lactation with dams gavaged from gestational day 6 until birth and then the offspring gavaged directly through weaning. Juveniles of both sexes sacrificed and OTR expression assessed by receptor binding. Our results demonstrate prenatal exposure to BPA can eliminate sex differences in OTR expression in hypothalamic regions and that male OTR expression may be more susceptible. Our data also identify a sexually dimorphic sub-region of the BNST not previously reported in juvenile rats that is also susceptible to BPA.

### P1.13 ESTROGEN EFFECTS ON NUCLEUS ACCUMBENS CORE MEDIUM SPINY NEURON ELECTROPHYSIOLOGICAL PROPERTIES AND OPEN FIELD ANXIETY-RELATED BEHAVIOR

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The brain operates under a dynamic neuroendocrine environment that differs by sex. Naturally occurring hormone cycles in adult female humans and rodents induce sex differences in neuron function and in the phenotype of many behaviors, including those related to reward and motivation, and associated disorders such as anxiety and depression. This indicates that the neural substrate instrumental for these behaviors, including the nucleus accumbens core (AcbC), is susceptible to the influence of ovarian hormones. Recent findings suggest that the electrical properties of the AcbC's major output neurons, medium spiny neurons (MSNs), robustly differ by estrous cycle phase. These changes in MSN electrical properties produce sex differences between female and male MSNs. Given these findings, it is critical to investigate how female ovarian hormones modulate MSN electrophysiological properties and their downstream effects on AcbC-mediated behaviors. Here we use a hormone replacement paradigm to investigate how ovarian hormones modulate the intrinsic electrophysiological and excitatory synaptic input properties of adult rat AcbC MSNs as well as AcbC-mediated locomotor and anxiety-related behaviors using the open field behavior assay. Estradiol injected females showed an increase in MSN intrinsic excitability and excitatory synaptic input properties in addition to an increase on anxiety-related behaviors in the open field arena. These findings indicate how ovarian hormones modulate the electrophysiological properties of AcbC MSNs and their downstream effects on AcbC-mediated behaviors thus providing a new framework for understanding the regulation of motivated behaviors and other AcbC functions and disorders by of ovarian hormones.

#### P1.14 GENETIC SEGREGATION OF, AND AROMATASE COLOCALIZATION IN, EXCITATORY VS INHIBITORY CELL TYPES IN SONGBIRD AUDITORY CORTEX

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Neuromodulation can sharpen signal-to-noise ratios in sensory circuits to aid animals in processing and responding to ethologically-relevant stimuli. In the auditory caudomedial nidopallium (NCM) in songbirds, social interactions rapidly increase estradiol (E2), and increased E2 enhances neurophysiological responses to conspecific vocalizations (i.e., song). However, the network mechanism of E2's action on auditory circuits remains unknown. The enzyme that synthesizes E2 from precursor androgens, aromatase (ARO), is widely expressed in NCM and co-localizes to some extent with parvalbumin, a protein marker of inhibitory neurons. An important next step is to map NCM circuit components anatomically and physiologically and determine distribution of ARO within these components. We employed AAV viral constructs to target calmodulin-dependent protein kinase II (CAMKII) and glutamate decarboxylase (GAD) selective promoters in NCM to express channelrhodopsin within putative excitatory and inhibitory neurons, respectively. Using a fiber optic coupled to a tungsten electrode we then photoidentified infected single units, and obtained their waveform and auditory response properties. We found a striking segregation of broad vs. narrow waveforms in CAMKII+ and GAD+ single units respectively, suggesting that, as in mammalian cortex, an important component of NCM circuit architecture may be feed-forward inhibition to rapidly quench excitation. Next, to examine the extent to which E2 is synthesized in broad and narrow-spiking cells, we infected NCM with both CAMKII and GAD viruses and co-labeled for ARO. The distribution of ARO in these physiologically distinct populations of NCM neurons and its implications for neuromodulation of NCM circuit dynamics will be discussed.

#### P1.15 SEX DIFFERENCES IN ANDROGENIC REGULATION OF MOUSE MAJOR URINARY PROTEINS

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Major urinary proteins (MUPs) are pheromones which have been implicated in regulating sexually differentiated socio-sexual behaviors such as dominance hierarchies, inter-sex aggression and opposite-sex attractivity in mice. Mouse MUP production is itself sexually differentiated, with adult males excreting 3-4 times more MUPs than

females, including a distinct MUP (Darcin) which is normally undetectable in female urine. To evaluate the androgenic contribution to sexually differentiated MUP excretion, male and female mice were gonadectomized and treated with chronic-release dihydrotestosterone Silastic implants, and excreted MUPs were measured using gel electrophoresis. The expected sex difference in MUP excretion was observed in sham-operated intact mice but not gonadectomized, vehicle-treated mice. Also as expected, dihydrotestosterone treatment maintained masculine MUP excretion in gonadectomized males. Unexpectedly, dihydrotestosterone treatment of gonadectomized females did not increase their MUP excretion significantly. These results indicate that androgens are sufficient for masculine MUP excretion in male but not female mice. This suggests that reported increases in MUP excretion following testosterone treatment of female mice may depend on estrogenic actions. Furthermore, these observations suggest an organizational component to the sexual differentiation of MUP excretion.

## P1.16 MUTATION IN THE VASOPRESSIN GENE DECREASES BEHAVIORAL AROUSAL AND ELIMINATES THE SEX DIFFERENCE IN SOCIAL REINFORCEMENT IN ADOLESCENT RATS

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Recent studies have implicated arginine vasopressin (AVP) in adolescent social development. However, it is not known how AVP influences adolescent social behavior. We have found that AVP-deficient Brattleboro rats exhibit an atypical social behavior phenotype that is associated with decreased arousal. These findings question whether AVP regulates adolescent social behavior exclusively through its regulation of general arousal or whether it also impacts social-specific systems that regulate social motivation. To test these possibilities, we compared the behavioral arousal and social motivation of male and female adolescent homozygous (Hom) Brattleboro rats to their heterozygous (Het) and wild type (WT) littermates using the open field test and an operant conditioning paradigm. Consistent our previous findings, male and female adolescent Hom rats traveled less distance, spent more time inactive, and entered the center of the arena fewer times in the open field test than their Het and WT littermates. In the operant conditioning test, WT male rats directed a greater proportion of their responding toward the social stimulus compared to WT females. This sex difference, however, was absent in Hom rats. These findings indicate that adolescent males are more sensitive to the reinforcing properties of social stimuli than females, and that this sex difference is dependent on a functional AVP system. Collectively these data suggest that AVP modulates adolescent behavior through both general arousal and social motivational mechanisms. Current studies are investigating the neural circuits through which AVP regulates social motivation and arousal.

## P1.17 RAPID MODULATION OF AROMATASE ACTIVITY IN ORGANOTYPIC CULTURES OF THE SONGBIRD BRAIN

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Neural estrogens have rapid and specific modulatory effects on perception, processing, and production of acoustic signaling. Mechanisms regulating the transient rise and fall of estrogens within discrete neural circuits is not fully understood, however, it is likely regulated by post-translational regulation of the estrogen-synthetic enzyme, aromatase. Zebra finches possess complex neural circuitry for control of song and express aromatase in many brain regions, including the caudomedial nidopallium (NCM) and hippocampus (HP), involved in auditory processing and learning and memory respectively. To examine phosphorylating conditions on aromatase activity, we measured aromatase activity in slice cultures of both the NCM and HP. Glutamate suppressed aromatase activity in slices of

the NCM (as shown previously in vivo) but was less effective in the HP. Presumably, glutamate excitation increased intraneuronal Ca<sup>2+</sup> and Ca<sup>2+</sup>-dependent kinase activity, increasing aromatase phosphorylation to inhibit activity in NCM. This conclusion was supported by studies with partially purified supernatants of NCM and HP treated with cyclosporin, an inhibitor of calcineurin, a Ca<sup>2+</sup>-dependent phosphatase. High cyclosporin concentration decreased aromatase activity consistent with the conclusion that phosphorylation decreases aromatase activity. Interestingly, cyclosporin abolished glutamatergic inhibition of aromatase in NCM slices, possibly by interfering with glutamate-induced neurotoxicity or by suppressing alternate calcineurin-dependent functions. These results are largely consistent with previous studies of brain aromatase but point to possible local mechanistic differences. Brain aromatase experiences rapid regulation via phosphorylation/ dephosphorylation events via kinases and phosphatases.

## P1.18 SEX DIFFERENCES IN THE CONFIGURATION OF MEDIAL AMYGDALA CIRCUITS FOR SOCIAL BEHAVIOR

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An important goal for neuroscience is to understand how individual and group differences in the configuration of neural circuits specialize patterns of behavior for the needs of different individuals. Aromatase, and the neurons in the brain that express the enzyme, are critical for establishing sex differences in social behavior as well as sex differences in neuroanatomy. A large population of aromatase neurons is present in the medial amygdala of mice, and the representation of social stimuli by the activity of medial amygdala neurons displays clear sex differences. Here, we identify a potential anatomical basis for those sex differences. In particular, we found that sensory input to aromatase neurons is derived near-exclusively from the anterior AOB, which selectively responds to chemosensory cues from conspecific animals. Through the coordinated use of mouse transgenics and viral-based circuit tracing strategies, we were able to identify a clear sex difference in the configuration of sensory inputs from the accessory olfactory bulb to aromatase-expressing medial amygdala neurons in male versus female mice. This difference in anatomy may mediate, at least in part, sex differences in medial amygdala mediated social behaviors.

## P1.20 DEVELOPMENTAL SEROTONIN HAS SEX-SPECIFIC EFFECTS ON NEURONAL EXCITABILITY

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Neonatal serotonin guides important developmental processes, impacting outcomes such as neuronal excitability and cell death. Sex differences have been reported during development in both serotonin levels and serotonin receptor type expression. For example, female rats have elevated expression of an inhibitory serotonin receptor compared to males, leaving male neurons possibly more susceptible to over-excitation. This sexually dimorphic serotonin data fits with the growing body of literature suggesting that the male brain in general is more 'easily excitable'. Seizures are one behavioral measure of excitation/inhibition imbalance and sex differences in seizure behaviors have been reported, with males experiencing more severe seizures and a lower seizure threshold than females. In addition, serotonin can modulate seizure activity. Therefore, we examined the potentially sex-specific effects of serotonin agonist 5-methoxytryptamine (5MT) on NMDA-induced seizure behavior and neuronal damage in the hippocampus of young rats (males, females and females given testosterone on the day of birth). On postnatal day 14, animals were given injections of 5MT or saline ip, followed by an injection of NMDA or saline ip 30 minutes later. Seizure behavior was then recorded for 30 minutes. In response to NMDA treatment, males and androgenized females displayed a more severe seizure profile compared to control females; however, 5MT pretreatment abolished these sex differences. Because serotonin is known to modulate neuronal excitability by altering glutamate

receptors, the effect of 5MT on NMDA receptor expression in the hippocampus of males, females and androgenized females was also examined.

### P1.21 RELATIONSHIP BETWEEN HIPPOCAMPAL EXTRACELLULAR AND CIRCULATING LEVELS OF ESTRADIOL IN FREELY-MOVING FEMALE RATS

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Estradiol (E2) is synthesized not only by the ovaries but also by the brain, suggesting that the steroid may modulate cognition through either or both neuromodulator and hormonal actions. However, the relationship between circulating and brain E2 levels and their relative contributions to modulation of learning and memory are unclear. To begin to identify the contributions of E2 derived from central vs. peripheral sources, we used in vivo microdialysis to measure E2 concentrations in samples (60 min each during 4-6 hrs) of hippocampal extracellular fluid in rats with different circulating E2 levels. On the day of microdialysis, rats in proestrus, i.e. the high E2 stage, had higher hippocampal levels than did rats at estrus or diestrus, mirroring expected blood levels. In other rats, serum E2 levels were depleted by ovariectomy and restored by peripheral E2 injections (s.c., 45 µg/kg) 48 and 24 hrs before microdialysis. Rats that received E2 had high hippocampal E2 levels but so did oil-treated rats with relatively low serum E2 concentrations. When E2 was injected (s.c.) during microdialysis, hippocampal E2 levels increased quickly in rats at low hormone states but not at high hormone states. Thus, the results that brain levels do not always merely passively follow circulating levels may reveal an interaction and independence of the two E2 compartments. Current work blocking central synthesis of estradiol prior to microdialysis will help clarify the contribution of brain-derived E2 to total hippocampal content.

### P1.22 SOCIAL INFLUENCE ON MALE SPATIAL DISTRIBUTIONS IN MATING AGGREGATIONS

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For frogs and toads, the relationship between male call characteristics and the spatial distribution in a chorus is crucial for determining mating success. We mapped the spatial locations and call characteristics of every male gray treefrog (*Hyla versicolor*) in a chorus for three consecutive years. There were significant correlations between the calling behaviors of a focal male and his one nearest neighbor at smaller nearest-neighbor distances, thus representing a denser local environment for focal males. Both call duration and pulses per call were significantly higher for focal males, however, call rate was significantly lower when nearest-neighbor distance was small. Point pattern analysis showed that males in these populations were not randomly distributed. Rather, when viewed on a nightly basis, males often form mini-clusters, which we suggest represent segregation based on social interactions. We created agent-based models to investigate possible decision-making rules male treefrogs may use to choose territories within a chorus. Models currently support both the importance of call amplitude and male frog energy reserves as key factors in determining the spatial structure of a chorus similar to field patterns. This suggests vocal interactions between individual male gray treefrogs and their nearest neighbors may be critical determinants of spatial distributions of territories in a chorus. Given the preference of females for males with particular call characteristics that are closest to their own location, such distributions could alter sexual selection processes. (Supported by NSF IOS #1257777, #0725187)

### P1.23 FECAL TRANSPLANTATION ALTERS CIRCULATING CORTISOL OF MALE AND FEMALE SIBERIAN HAMSTERS IN THE ABSENCE OF ANTIBIOTICS

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The gut-brain axis is a bi-directional communication network that links the gut microbiome and host behavior. Recent studies have shown that experimentally manipulating gut microbiome composition using antibiotics causes genus-specific and sex-specific changes in bacterial abundance. While antibiotic administration is frequently used to alter the gut microbiome, most previous studies have not assessed or controlled for the non-microbial effects of antibiotics. In the current study, we investigated how changes to the gut microbiome influence behavior without the presence of antibiotics and if these changes could be transferred to other individuals. We repeated a pre-existing methodology, which has shown that administering a broad-spectrum antibiotic to Siberian hamsters (*Phodopus sungorus*) correlates with sex-specific changes in the gut microbiome and aggression. Male and female donors were administered either saline (control group) or the broad-spectrum antibiotic Enrofloxacin (experimental group), and fecal boli from these individuals was orally transplanted to experimentally-naïve animals after antibiotics was no longer detected in donor animal feces. Hamsters that received a fecal transplant from experimental animals displayed no significant difference in aggressive or other social behaviors during a resident-intruder paradigm, regardless of sex. However, both males and females that received fecal transplants from antibiotic-administered individuals exhibited significantly lower cortisol levels than animals transplanted with fecal boli from the control group. These findings suggest that fecal transplantation alters the gut microbial composition and physiology of recipient animals, yet does not affect social behavior. Moreover, these data suggest that these changes persist in the absence of antibiotics.

#### P1.24 NEUROENDOCRINE BASIS OF SOCIAL COMPETENCE AND COGNITION IN DYNAMIC COMMUNITIES OF A HIGHLY SOCIAL CICHLID FISH

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Individual variation in “cognitive style” (how an individual approaches a cognitive task) can be predicted by more general consistent behaviors such as aggression, neophobia, and sociability. Social competence, the ability to make context-appropriate behavioral decisions, thus should be influenced by cognitive style and general behavioral tendencies. Yet we know very little about how the social environment influences the neuromolecular processes underlying this interconnected web of social competence, cognitive style and behavioral tendencies. We investigate these questions by manipulating naturalistic communities of the cichlid fish *Astatotilapia burtoni*, a model system in social neuroscience, to quantify the behavioral styles and space use patterns of socially dominant and subordinate individuals. We assess individuals' cognitive performance and style by testing them in a spatial maze, followed by a reversal, a novel object recognition task, and a social competence task. This test suite is repeated after an experimental perturbation that allows some subordinate males to ascend in social status. Throughout, we assay circulating glucocorticoid and androgen levels. We then use quantitative real-time PCR of the immediate-early genes *egr-1* and *c-fos* to determine to which extent the neural activity patterns in core nodes of the vertebrate social decision-making network (SDMN) correlate with behavior, cognitive style and performance, and social competence. Finally, we also measure the activity of genes associated with stress reactivity and social behavior. Taken together, this experimental design provides a uniquely comprehensive investigation of the cognitive, behavioral, and mechanistic underpinnings of decision-making in a complex and dynamic social community.

#### P1.25 INTRANASAL VASOPRESSIN CHANGES BEHAVIOR DURING COURTSHIP IN A DOSE-DEPENDENT MANNER IN CALIFORNIA MICE (*PEROMYSCUS CALIFORNICUS*)

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Vasopressin (AVP) is a neuropeptide that modulates complex social behaviors such as pair bonding, aggression, and stress. Human studies have found many prosocial effects of AVP, yet several key animal studies have shown links between AVP and aggression. The differences in effects may relate to doses used or social context of administration. In particular, there is a gap in our understanding of how AVP influences social introductions, such as courtship in monogamous species. Here we use a dose response study to examine how different doses of AVP influence social interactions between males and females. We assess AVP's effects on aggressive, affiliative, and stress-related behaviors during an encounter with a novel member of the opposite sex in the strictly monogamous and territorial California mouse. Females and males were administered one of four treatments using intranasal administrations: saline control, 0.05 IU of AVP (low), 0.5 IU of AVP (medium), or 5.0 IU of AVP (high). We found dose-response effects in aggression and stress; low and medium doses but not high doses increased aggression and, in parallel, low and medium doses but not high doses decreased stress. We also found female-only effects; all AVP doses increased female approaches toward a novel male but only the high AVP dose increased affiliation toward a novel male. Using western blots to measure protein expression, we found that pMAPK expression increased with all doses of AVP in the prelimbic area of female mice. Results from other brain areas will be reported.

## P1.26 LONG-TERM IMPACT OF EARLY LIFE STRESS ON ANXIETY-LIKE BEHAVIOR: SEX DIFFERENCES IN OLD AGE

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Prior studies from our lab and others have demonstrated that early life stress impacts males and females differently. Using a maternal separation paradigm where rats were separated from their dam for either 180 min (maternally separated, MS) or 15 min (early handling, EH) daily from 2-14 days of age, we previously reported that prior to puberty male MS rats had significantly greater anxiety-like behavior compared to EH males and both MS and EH females. Notably, prepubertal females did not demonstrate any differences in anxiety-like behavior based on separation condition. The current study extended this work by examining the impact of early life stress on aged rats. Male and female rats were maternally separated in early life and anxiety-like behavior was tested at 600-700 days of age. All females were in persistent diestrus at the time of testing. Aged males in the MS condition displayed significantly more anxiety-like behavior than aged EH males or females in either the MS or EH condition. There were no significant differences between MS and EH aged females. Hair samples were taken at the time of testing to determine the impact of early life stress on corticosterone levels as well. The current findings extend the previously reported sex difference in anxiety-like behavior in prepubertal rats to aged rats, adding to research indicating that the long-lasting effects of early life stress impact the sexes differently.

## P1.27 SOCIAL INSTABILITY STRESS ADMINISTERED EITHER IN ADOLESCENCE OR ADULTHOOD HAS A LASTING EFFECT ON PREFERENCES FOR NATURAL REWARDS IN MALE AND FEMALE RATS

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Rats that undergo social instability stress (SS; daily 1 h isolation+pairing with new cage partner for 16 days) in adolescence have a higher intake of sucrose (under conditions of competition) and show more social approach than do control (CTL) rats. Here, we investigated whether SS administered in adolescence (postnatal day [P]30-45) versus adulthood (P70-85) influenced the trade-off between social preference and sucrose preference by having rats choose to spend time with an unfamiliar peer versus access to 0, 2, 5, or 10% sucrose (each concentration

tested on a separate day,) and tested either days or weeks after the SS procedure relative to CTL rats. The factors of Sex, Age of SS, and Time since SS were not significant, nor did these factors interact with sucrose concentration. The Group (SS, CTL) by Concentration interaction was significant ( $p=0.002$ ): The preference for social was larger in SS than in CTL rats at the 0% concentration ( $p<0.001$ ) only. For SS rats, the preference for social decreased between 0 and 2% ( $p=0.028$ ) and between 2 and 5% ( $p=0.001$ ), and CTL rats only decreased between 5 and 10% ( $p=0.037$ ). In separate tests, SS and CTL rats did not differ in their preference (~56%) to spend time near an unfamiliar versus familiar peer, nor did they differ in preference (~60%) for 5% versus 0% sucrose. Thus, social instability has a lasting effect on reward systems in both sexes, and adolescents are not more susceptible than adults.

## P1.28 THE EFFECTS OF LIGHT AND ESTRADIOL ON GENE EXPRESSION IN THE SUPRACHIASMATIC NUCLEUS

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The circadian timekeeping system is governed by a master circadian oscillator located within the suprachiasmatic nucleus (SCN) of the hypothalamus. Light mediates circadian rhythm outputs and gene expression through inputs onto the SCN. Activity and transcription-associated circadian parameters within the SCN are also affected by circulating estradiol. Further, estradiol interacts with light in the early evening to modify photic responsiveness in female mice. Despite the observed functional relationship between light, estradiol, and circadian activity rhythms, the molecular mechanism(s) underlying these effects in the female central nervous system are poorly understood. Here, we tested the hypothesis that estradiol alters the expression of transcriptional networks within the SCN. Ovariectomized mice were implanted with a pellet containing either cholesterol (CTL) or estradiol (50  $\mu\text{g}$ ) and permitted access to running wheels. In the early subjective night, a time when light causes a maximal shift in the timing of rhythmicity, animals of both treatment groups were either pulsed with light (1 hr) or allowed to continue running in the dark. SCN were then collected and estradiol and light-induced changes in gene regulatory networks were quantified and analyzed using a medium throughput gene expression assay. In the early evening estradiol exerts much greater control over the SCN transcriptional milieu than light, and estradiol overwhelmingly downregulates gene expression compared to CTL animals. Further, we identified multiple overlapping gene regulatory networks enriched by estradiol and/or a pulse of light. The work presented here advances our understanding of how estradiol and light mediate transcriptional patterning within the SCN.

## P1.29 GESTATIONAL CORTICOSTERONE EXPOSURE LEADS TO ANXIETY-LIKE BEHAVIOR IN *PEROMYSCUS CALIFORNICUS*

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Stressful environments during pregnancy may cause an increased amount of corticosterone (CORT) in offspring. This increase in CORT levels may underlie differences in anxiety-like behaviors seen in offspring exposed to this period of high stress. Animal models of prenatal stress have shown a negative impact on social behavior and anxiety-like behavior and while previous studies used models of prenatal infection and maternal separation as stressors, the current study aims to assess the impact of injections of corticosterone during the gestational period on anxiety-like behaviors in a social interaction setting. Mothers were injected on gestational days 15-20 with either CORT (10mg/kg) or vehicle. On post-natal day 65, offspring underwent a social interaction test consisting of an open field phase followed by an interaction phase in which a stimulus animal was placed in a wire mesh cage on one

side of the open field. Results of the study show a main effect of treatment, such that CORT treated animals showed a decrease in rearing behavior suggesting an increase in anxiety-like behavior. A main effect of sex was found, such that males spent more time in the interaction zone and more time exploring the stimulus cage than females. Consistent with previous research, an interaction between treatment and sex was found such that CORT treated females spent more time facing toward the cage than CORT treated males suggesting that stressed females show more vigilance. These preliminary results support the use of prenatal injections of CORT as a sufficient stressor during development.

### P1.30 EVALUATION OF OVARIAN HORMONE-DEPENDENT BEHAVIOR IN A FEMALE RAT MODEL OF THE HUMAN BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) Val66Met SINGLE NUCLEOTIDE POLYMORPHISM

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Fluctuations in ovarian hormones across the rat estrous cycle and in ovariectomized and hormone-replaced rats modulate numerous behaviors including anxiety, learning, and memory. Estrogens also increase expression of BDNF in the brain. A common functional single nucleotide polymorphism occurs in the human BDNF gene (Val66Met). The Met/Met variant downregulates BDNF signaling and increases risk for certain neural disorders including Alzheimer's disease in women. Female Met/Met mice show increased anxiety and distinct cycle-dependent variations in memory and exploratory behaviors compared to Val/Val mice. Thus, Val/Met genotype likely determines behavioral sensitivity to hormones. To evaluate this possibility, Val/Val and Met/Met rats were tested on the open field task at different estrous cycle stages. A genotype by stage interaction in total distance travelled was observed: Val/Val rats exhibited decreased locomotor activity in diestrus (low hormone stage) whereas Met/Met rats did not differ in activity between stages. Compared to Val/Val rats, Met/Met rats had prolonged estrus, suggesting altered reproductive processes, which may lead to dysregulated physiological and behavioral responses to hormones. The opposing effects of estradiol on response and place learning were also assessed in ovariectomized Val/Val and Met/Met rats. Estradiol improved place and impaired response learning in Val/Val but not in Met/Met rats, further implicating BDNF signaling in estrogen-regulated cognition. Ongoing studies examine Val66Met effects on additional endocrine measures and neural signaling pathways. Understanding how this BDNF polymorphism modulates lifelong endocrine functions will guide the development of interventions to enhance the quality of life for women at risk for brain and behavioral dysfunctions.

### P1.31 TESTICULAR ANDROGENS MODULATE DIFFERENTIALLY ABSENCE SEIZURES IN ADULT MYELIN MUTANT TAIEP RATS

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Sexual differentiation of the brain is a process that change anatomically and physiological and this early modify the expression of various behavioral traits. However, less is known about the role of androgens in cerebral pathology such as epilepsy. In our laboratory, we have a myelin mutant rat named taiep, acronym of their symptoms: tremor, ataxia, immobility, epilepsy and paralysis. Subjects (Ss) had an initial hypomyelination followed a progressive demyelination in the central nervous system due to an accumulation of microtubules in the oligodendrocytes. The epilepsy is present on both sexes and in all cerebral cortex with a characteristic spike-wave discharge (SWD) similar to absence seizures. SWD is a sexually dimorphic pattern being males more affected than females. The aim of this study was to analyze the role of testicular androgens on SWD. All Ss were maintained under standard conditions and

the experimental protocol approved by IACUC. We used male taiep rats at 6 months to record SWD along 24h. Orchiectomy was performed in newborn and at 3 months old. We did sham-surgery for control Ss.

There were significant differential effects of orchietomy depending of the age of the Ss, because neonatal castration produced a significant decrease but in adult rats produce a significant increase in the frequency of SWD along the circadian cycle, but there were not changes in their duration. Our results showed that androgens had an organizational and activational effects on this type of generalized epilepsy.

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### P1.32 CENTRAL IMMUNE ALTERATIONS IN A GESTATIONAL STRESS MODEL OF POSTPARTUM DEPRESSION

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Postpartum depression (PPD) affects at least 15% of all new mothers. Although peripheral immune changes have been linked in some studies to PPD, little is known about how the brain's immune system is modified in PPD. To address this gap, we used a gestational stress rodent model of PPD that recapitulates the critical behavioral symptoms found in depressed human mothers along with neural remodeling in brain areas relevant to PPD including the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAc). Pregnant Sprague-Dawley rats were subjected to either chronic variable stress from gestational days (GD)7-20 or remained unstressed. Animals were sacrificed one day before (GD21) or one week after (postpartum day 8, PD8) parturition and brain tissue collected for qPCR to assess mRNA expression of several pro-inflammatory cytokines [interleukin (IL)-1B, IL-6, and tumor necrosis factor alpha (TNF $\alpha$ )] and markers of microglial phagocytosis [CD68, integrin alpha M (ITGAM), complement component 3 (C3), and complement component 1 (C1q)]. A separate cohort of stressed and unstressed mothers was perfused on PD8 and immunohistochemistry for Iba-1 performed to quantify microglial density and number. Our results show increases in microglial density and number in the mPFC and NAc of stressed mothers on PD8. Gestational stress also produced region- and timepoint-specific effects on the expression of pro-inflammatory cytokines and microglial phagocytic markers. Overall, our results indicate that gestational stress impacts the peripartum neuroimmune environment which could have important implications for understanding the mechanisms underlying neural and behavioral abnormalities in PPD.

### P1.33 SPEXIN/NEUROPEPTIDE Q FUNCTIONS AS AN ANXIOLYTIC IN HIGH-FAT DIET FED FEMALE MICE

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High-fat diet has been shown to trigger metabolic dysfunction and its central nervous system consequences can manifest as hypothalamic inflammation, anxiety, and depression in obese patients. Neuropeptides play a significant role in the hypothalamic regulation of energy expenditure and response to obesity. In the last decade, spexin/neuropeptide Q, was identified as the most downregulated gene expressed in visceral adipose tissue of morbidly obese patients. Recent investigation into the neuroendocrine function of SPX revealed its therapeutic potential in treatment for anxiety and depression. Intense spexin immunoreactivity was detected in pyramidal cells of the hippocampus and paraventricular nucleus of the hypothalamus. Therefore, we hypothesized that spexin treatment may regulate corticotropin-releasing hormone actions within the hippocampus and hypothalamus. To

investigate this hypothesis, we challenged female C57BL/6 mice with high-fat diet and investigated the metabolic and hormonal profile of spexin-treatment. Additionally, we performed a behavioral analysis of anxiety and hippocampal function. The metabolic and hormonal profile of spexin-treated animals reveals a novel function of spexin in hypothalamic-pituitary-adrenal axis and glucose homeostasis. Spexin-treatment disrupted cycles, increased catecholamine production within the ovaries, and lowered estradiol. Endogenous spexin levels are also regulated by circulating glucose, and increasing concentrations of glucose inhibit spexin synthesis and secretion. Within the anterior pituitary, spexin synthesis was upregulated by corticotropin releasing factor which may indicate that spexin acts on the HPA axis to regulate responses to stress and steroidogenesis. Our behavioral analysis reveals that spexin may act as an anxiolytic by increasing exploration of novel environment and improving nest building quality.

## P1.34 CHARACTERIZATION AND MANIPULATION OF THE PARENTAL BRAIN IN MALE AND FEMALE ROCK DOVES

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Parental care of offspring is essential to maximize fitness in many species throughout the animal kingdom. As a result, new parents undergo major changes in physiology and behavior to promote offspring survival in predictable and unpredictable conditions. While much is known about neuroendocrine mechanisms modulating these changes, we know less about genomic mechanisms driving these changes in male and female parents. To fill this gap, our team characterized gene expression states of the hypothalamus, pituitary, and gonads of mothers and fathers of the socially monogamous, bi-parental rock dove (*Columba livia*) at multiple stages of parenting including nest building, egg laying, egg incubation, chick hatch, and nestling stages. Next, we manipulated the timeline of the offspring development to distinguish genomic signatures that are driven by cues from the offspring from those that are driven by internal cues from within the parent. Our manipulations include a range of unpredictable changes to the parenting lifecycle including early hatching, delayed hatching, prolonged incubation, and termination of parenting (with egg or chick removal). All data are public and the statistical analyses can be reproduced in the cloud using Binder at <https://github.com/macmanes-lab/DoveParentsRNAseq>. In conclusion, by comparing the results of the characterization and manipulation study in both male and female parents, we provide a deeper understanding of the parental brain and how both sexes respond to predictable and unpredictable changes during offspring development.

## P1.35 SEX DIFFERENCES IN MICROGLIA FUNCTION, SYNAPTIC PATTERNING, DOPAMINE RECEPTORS, AND BEHAVIORAL INHIBITION FOLLOWING PRENATAL ALLERGEN EXPOSURE

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In utero exposure to maternal allergic conditions increases risk for neurodevelopmental disorders that are far more common in males (e.g., autism, ADHD), yet little is known about how prenatal inflammation alters sex-specific brain development. We previously showed that prenatal allergen exposure programs hyperactivity, a loss of attentional flexibility in male and female rats, and perturbs social behaviors in males only. Here, we tested whether early life allergic inflammation impacts brain development via altering microglia function. Adult female rats were sensitized to ovalbumin (OVA), bred and challenged on gestational day (GD) 15. Fetal or neonatal brains were assessed for microglia number and phagocytic activity or cytokine and phagocytosis gene expression in developing medial prefrontal cortex (mPFC) or dorsal striatum. Other animals were grown to adulthood and dendritic spine density and gene expression for dopamine and histamine receptors were assessed. We found increased gene expression for interleukin 6 and the phagocytic marker CD68 in both males and females acutely post-OVA. OVA increased

microglia number in the forebrain post-challenge. In the striatum, but not mPFC, on postnatal day (PD) 0, phagocytic microglia counts were increased in males, but not females. Adult striatum, but not mPFC, showed decreased dendritic spine density in both males and females after OVA exposure prenatally, but males also showed decreased striatal levels of histamine receptor 3 and dopamine receptor 2. These studies show that prenatal allergic inflammation alters microglia function and striatal development, particularly in males, and microglia may thus regulate sex-specific risk for neurodevelopmental disorders.

### P1.36 AN UPDATED META-ANALYSIS ON THE RELATIONSHIP BETWEEN TESTOSTERONE AND HUMAN AGGRESSION

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A previous meta-analysis found a relatively weak positive correlation ( $r = .08$ ) between baseline testosterone (T) and human aggressive behaviour (Archer et al., 2005). A growing body of work indicates that T levels are not static, but instead, fluctuate rapidly in the context of competitive interactions. There is some evidence in both human and non-human models that such context dependent fluctuations in T may serve to modulate ongoing and/or future aggressive behaviour. In the current meta-analysis, we investigated the extent to which baseline T and/or context-dependent fluctuations in T map onto variability in human aggressive behaviour. Our search yielded 100 studies with over 19,000 participants. Overall there was a small positive correlation between baseline T and aggression ( $r = .06$ ). This relationship was stronger in men ( $r = .08$ ) relative to women ( $r = -.006$ ) and was stronger for samples collected in the morning ( $r = .10$ ) relative to the afternoon/evening ( $r = -.003$ ). In addition, competition-induced changes in T were positively correlated with aggressive behaviour ( $r = .14$ ). This effect was stronger in men ( $r = .19$ ) relative to women ( $r = .03$ ). Examination of funnel plots did not reveal evidence of publication bias. In summary, the results of our meta-analysis indicate that baseline T is positively correlated with aggressive behaviour in men, but not women. Notably, context dependent fluctuations in T were more strongly correlated with aggressive behaviour in men compared to baseline T.

### P1.37 TESTOSTERONE MEMBRANE BINDING IN GOLDFISH BRAINS

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We have recently observed that testosterone can rapidly stimulate behavioral responses towards pheromones in male goldfish through androgen-receptor mediated mechanisms. Here, we describe our initial attempts to characterize where those effects are mediated by identifying putative testosterone (T) membrane binding in the brain. Using T conjugated to bovine serum albumin and fluorescein (T-BSA-FITC), we have identified non-nuclear binding in several forebrain areas with three different approaches. We have infused the molecule into the 3rd ventricle, in vivo, applied the molecule to thick, unfixed brain sections cut with a vibratome (100-200  $\mu\text{m}$ ), and applied the molecule to fresh frozen brain sections cut with a cryostat (60  $\mu\text{m}$ ). With all three approaches, signal appeared to surround cells and/or nuclei, with little overlap with nuclei, the extent depending on the method used and, presumably, the amount of membrane disruption prior to binding. In some areas, fibrous extensions from those cells were also observed. Non-nuclear signal was especially prominent, though not exclusively localized, in the olfactory bulbs and several nodes of the forebrain Social Behavior Network (SBN). We are currently working to verify the specificity of the signal with testosterone competition assays and by comparing binding patterns of T-BSA-FITC to that of BSA-FITC.

### P1.38 PRENATAL EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS ALTERS MATE PREFERENCE, ODOR PREFERENCE, AND OLFACTORY PROCESSING IN ADULT RATS

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Environmental endocrine-disrupting chemicals (EDCs) represent a serious concern for human and wildlife populations due to their capacity to disrupt hormone-dependent biological processes. Here, we examined how prenatal exposure to EDCs act in a sex-specific manner to disrupt social and olfactory behavior in adulthood. Pregnant dams were injected daily from embryonic day 8-18 with 1mg/kg A1221, a mixture of polychlorinated biphenyls (weakly estrogenic), 1mg/kg vinclozolin, a commercial fungicide (anti-androgenic), or the vehicle (6% DMSO in sesame oil). We found that adult offspring resulting from this exposure paradigm had impaired mate preference behavior. When allowed to freely explore two opposite-sex stimulus animals, one with circulating sex steroid hormones (gonadectomized and hormone-replaced) and one without (gonadectomized only), vehicle-treated male and female rats spent more time investigating the stimulus animal with hormone replacement. Male and female animals exposed to A1221 showed no preference. Vinclozolin treatment abolished preference in males but not females. A similar pattern of impairment was observed when animals investigated only the odor of stimulus animals: A1221 females, and A1221 and vinclozolin males, spent similar times investigating both stimulus options. A habituation/dishabituation test, conducted using filter paper soaked with urine from either of the two stimulus animal options (sexual stimulus) or non-sexual odors (acetic acid and sesame oil) revealed that all treatment groups had normal odor discrimination ability. These results suggest that impairments in mate and odor preference behavior are not due to changes in olfactory processing. Supported by NIEHS R01ES023254-01 to ACG.

### P1.39 EFFECTS OF DEVELOPMENTAL EXPOSURE TO BISPHENOL-S ON SEXUAL BEHAVIOR IN MALE RATS

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Bisphenol-S (BPS) is an endocrine disrupting chemical that has replaced BPA in many household products, but it is unclear whether it is a safe alternative. BPS exposure negatively affects gamete production and hormone secretion in male rodents. We investigated the impact of developmental BPS exposure on male sexual behavior in Long-Evans rats. Dams of experimental animals were paired with stud males on the day of estrus as determined by vaginal cytology. BPS was administered orally via pipette to each dam at a dose of 50µg of BPS in 0.3% saline vehicle /kg body weight/day beginning on the day of pairing and continuing until parturition. Control dams received saline. Pups continued treatment with BPS or saline from PND1 until PND45 to encompass puberty, a developmental time point when disruption of normal hormone function can negatively affect adult sexual behavior in rodents. At 60 days of age, 30-minute sexual behavior tests were conducted under dim red light during the dark phase of the 14:10 LD cycle. Males were paired with a sexually receptive female and behaviors video recorded. Mounts, intromissions, ejaculations and anogenital investigation frequency was recorded by observers blind to treatment. Preliminary analyses reveal that there were no effects of BPS exposure on any male sexual behaviors measured. Thus, in comparison to circuits regulating hormone release and gamete production, the brain regions controlling sexual behavior may be less sensitive to the negative effects of developmental exposure to BPS.

### P1.40 THE IMPACT OF ESTROUS CYCLE AND NOVELTY ON FEMALE RAT BEHAVIOR IN THE OPEN FIELD TEST

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Many natural factors impact animal behavior. In females, one important consideration is hormone status due to cyclic hormone changes such as in the menstrual cycle in humans and the estrous cycle in rats. These behaviors include those related to anxiety, depression, and motivation, which are often assessed in rodents using the open field test. In female rats, exploratory behaviors such as locomotion and propensity to enter areas perceived as dangerous fluctuate naturally across the estrous cycle. However, it is not well-explored as to how behavioral differences induced by hormone cycles interact with other factors such as exploration in a novel environment. Thus, hormone-induced behavioral differences may be masked by novelty-induced behavioral changes. Here, we aim to disassociate differences in exploratory behaviors in the context of the estrous cycle from differences resulting from a novelty effect. We hypothesized that behaviors in the open field such as total distance traveled and time spent in the center would be increased both during initial exposure to the open field as well as in the estrus stage compared to diestrus stage, when hormone effects are limited. We found that both the estrous cycle stage and day of exposure to the open field influenced exploratory behavior. This is important to note in the context of the open field test, as hormone-induced behavioral differences may not be detected as robustly due to the presence of the novelty effect. This approach to open field testing should be considered when exploring hormone-induced behavioral changes across the natural cycle.

#### P1.41 NEUROESTROGEN-DEPENDENT TRANSCRIPTIONAL ACTIVITY IN THE BRAINS OF ERE-LUCIFERASE REPORTER MICE FOLLOWING SHORT- AND LONG-TERM OVARECTOMY

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Previous work in our lab has demonstrated that estrogen receptors are transcriptionally active in the absence of ovarian estrogens. The current work aims to determine if brain-derived estrogens act on estrogen receptors to influence transcription after short- or long-term loss of ovarian function. Experiments were conducted using ERE-Luciferase reporter mice, which express the gene for luciferase driven by consensus ERE, allowing for quantification of ERE-dependent transcription. Brain regions examined were hippocampus, cortex, and hypothalamus. In Experiment 1, short-term (10-day) ovariectomy had no impact on ERE-dependent transcription across brain regions as compared to intact controls. In Experiment 2, chronic intracerebroventricular (icv) administration of the aromatase inhibitor letrozole significantly decreased transcriptional activity in 10-day ovariectomized mice across brain regions, indicating that the sustained transcription in short-term ovariectomized mice is mediated at least in part via actions of neuroestrogens. Additionally, icv administration of estrogen receptor antagonist ICI-182,780 blocked transcription across brain regions, providing evidence that sustained transcription in ovariectomized mice is estrogen receptor-dependent. In Experiment 3, long-term (70-day) ovariectomy significantly decreased ERE-dependent transcription across brain regions, though some residual activity remained. In Experiment 4, chronic icv letrozole administration had no impact on transcription in 70-day ovariectomized mice across brain regions, indicating that the residual ERE-dependent transcription in long-term ovariectomized mice is not mediated by neuroestrogens. Overall, results indicate that actions of neuroestrogens contribute to maintenance of ERE-dependent transcription in the brain following short-term, but not long-term loss of ovarian function.

#### P1.42 BIDIRECTIONAL RAPID AND NON-RAPID EFFECTS OF ESTRADIOL ON VOLUNTARY WHEEL RUNNING BEHAVIOR IN ADULT FEMALE AND MALE RATS

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Sex differences in motivated behaviors have been measured in several species, including humans and rats. The sex steroid hormone estradiol mediates aspects of these sex differences. A key brain region controlling these behaviors is the nucleus accumbens, which in adult rats exclusively expresses membrane estrogen receptors that enable rapid estradiol action. Thus, we tested whether estradiol can rapidly change motivated locomotion by assessing voluntary wheel running. Gonadectomized adult female and male adult rats were placed in running wheel cages and received 3 days of either estradiol benzoate (EB) or vehicle injections. This EB priming protocol mimics the repeated estradiol exposure generated by the natural adult female hormone cycle and induces comparable levels of voluntary wheel running. On the fourth day, all rats received an injection of EB to assess rapid effects of estradiol on voluntary running. EB-exposed males and females increasingly elevated running over the 4 days of EB injections, indicating non-rapid estrogen sensitivity. However, EB-exposed females significantly decreased running between 15-45 minutes after EB injection on Day 4, and this decrease in running was much larger than in EB-exposed males. In a separate study, we also found that estradiol decreased excitatory signaling onto nucleus accumbens core neurons only in females, suggesting a potential mechanism for the observed rapid effects in behavior. These findings suggest that: 1) estradiol neuromodulation of motivated locomotion is influenced by hormone state and sensitivity is sex-specific, and 2) rapid and non-rapid responses to estradiol can be bidirectional on a single behavior.

### P1.43 GENITAL STIMULATION FACILITATES A SEXUAL REWARD STATE IN MALE AND FEMALE MICE

*Thanh Phung, Firyal Ramzan, D. Ashley Monks*

Cells and Systems Biology | University of Toronto Canada

Genital tactile stimulation is seen as a precursor to sexual arousal and is recognized as an initiator of CNS arousal. Previous rodent studies have demonstrated that tactile clitoral stimulation can induce a reward state in female rats. However, it is unknown whether tactile genital stimulation could also induce a similar hedonic state in male rodents. The present study examined the ability of genital stimulation in mice of both sexes to induce a conditioned place preference (CPP). Sexually naïve and gonadally intact C57BL/6 mice were randomly assigned to receive either genital stimulation or dorsum stimulation. Stimulation was conducted at a rate of 1 stimulation per second for one minute prior to being placed in one distinctive side of a nonbiased CPP box for two minutes. A session of conditioning consisted of 5 rounds of stimulation and place exposure per day. Conditioning sessions alternated with sham sessions where mice were similarly handled but no genital stimulation occurred. Place exposure was for non-preferred side (conditioning) and preferred side (sham). CPP was assessed once all animals had completed 5 conditioning and sham sessions. It was found that all animals subjected to genital stimulation developed a significant CPP, whereas a significant CPP for dorsum stimulation was only developed in male mice. This suggests that despite morphological differences, the clitoris and the glans penis possess a similar role in generating a reward state upon stimulation. Additionally, the development of a significant CPP in male mice who received dorsum stimulation highlights a sex-difference in tactile reward.

### P1.44 OXYTOCIN NEURONS ARE SUFFICIENT FOR MC4R-MEDIATED SEXUAL FUNCTION IN MICE

*Erin Semple, Jennifer W. Hill*

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The melanocortin pathway has been implicated in both metabolism and sexual function of both males and females. When the melanocortin 4 receptor (MC4R) is knocked out globally, male mice display obesity, low sexual desire, and copulatory difficulties; however, it is unclear whether these phenotypes are interdependent. To elucidate the neuronal circuitry involved in sexual dysfunction in MC4R knockouts, we re-expressed the MC4R in these mice exclusively on Sim1 neurons (tbMC4RSim1 mice) or on a subset of Sim1 neurons, namely oxytocin neurons (tbMC4Rox mice). The groups were matched at young ages to control for the effects of obesity. Interestingly, young MC4R null mice had no deficits in sexual motivation or erectile function. However, MC4R null mice were found

to have an increased latency to reach ejaculation compared to control mice, which was restored in both tbMC4RSim1 and tbMC4Rox mice. These results indicate that melanocortin signaling via the MC4R on oxytocin neurons is important for normal ejaculation independent of the male's metabolic health. Interestingly, our recent data also show a critical role for oxytocin neurons in mediating melanocortin-driven reproductive behavior and function in female mice.

## Poster Session II

Friday, June 21, 2019, from 4:00pm to 6:00pm

### P2.1 CRISPR-CAS9 GENERATION AND BEHAVIORAL CHARACTERIZATION OF A SYRIAN HAMSTER V1aR RECEPTOR KNOCKOUT

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The advancement of CRISPR-Cas9 for genetic modification has made possible the generation of new knockout animal models. Syrian hamsters are an attractive target for CRISPR-mediated gene modification due to their widespread use in biomedical research, particularly as a model in preclinical studies of psychiatric disorders. Numerous social behaviors in hamsters and other species are controlled by the nonapeptide neurochemical signal vasopressin and one of its receptor subtypes (V1aR). Notably, selective stimulation of V1aR increases inter-specific aggression and flank marking in male and female hamsters. As such, we sought to disrupt the *AVPR1A* gene and to assess these two vasopressin-dependent behaviors. METHODS/RESULTS: Hamster embryos were injected at the single-cell stage with Cas9 and gRNA targeting *AVPR1A*, producing hamsters carrying various mutant *AVPR1A*. Of these, a mosaic female produced offspring carrying an 11bp or a 10bp deletion, both at the start codon of *AVPR1A*. Radioligand binding assays showed little to no selective V1aR binding in knockout hamsters homozygous for the 11bp deletion or heterozygous for both deletion alleles, indicating that the function of *AVPR1A* was disrupted. When compared to WT and heterozygous (-11/WT or -10/WT) littermates, however, male and female knockout hamsters were more aggressive toward a same-sex conspecific ( $p < .05$ ) and engaged in more odor-stimulated flank marking ( $p < .01$ ). This behavioral result is in direct opposition to our prediction, as pharmacological evidence indicated that activation of the V1aR facilitates these behaviors. CONCLUSIONS: These data show that V1aR activation is not required for the expression of flank marking or aggression in constitutive V1aR knockouts.

### P2.2 EFFECTS OF FEMALE REPRODUCTIVE STATUS AND PREGNANCY STRESS ON CENTRAL SEROTONIN 2A AND 2C RECEPTOR BINDING DENSITY

*Erika M. Vitale, Joseph S. Lonstein*

Psychology Department and Neuroscience Program | Michigan State University USA

Mammalian mothers show a unique suite of behavioral changes around parturition that include caregiving, maternal aggression, and low anxiety. The neurotransmitter serotonin (5-HT) regulates these and other socioemotional behaviors, and findings from our lab using laboratory rats has revealed reproductive state-dependent changes in expression of central 5-HT receptors that may be responsible for peripartum behavioral change. Specifically, we found less serotonin 2C receptor (5-HT<sub>2C</sub>) mRNA in the dorsal raphe (DR) and more serotonin 2A receptor (5-HT<sub>2A</sub>) mRNA in the medial preoptic area (mPOA) at parturition and early lactation compared to diestrus virgins. Additionally, repeated variable stress (RVS) during pregnancy disrupted caregiving and increased depressive-like behaviors, and these behaviors correlated with 5-HT receptor mRNA in the mPOA and DR. The current study aimed to determine whether 5-HT receptor binding is affected by reproductive status and RVS. Receptor autoradiography is being used to determine densities of 5-HT<sub>2A</sub> in the mPOA and 5-HT<sub>2C</sub> in the DR. In Experiment 1, three female

reproductive states will be compared – diestrus virgins, day of parturition, and postpartum day 7 (PP7). In Experiment 2, mothers exposed to RVS or not during pregnancy will be compared. We predict 5-HT<sub>2A</sub> binding will be higher in the mPOA at parturition and PP7, 5-HT<sub>2C</sub> binding will be lower in the DR at these times, and stress during pregnancy will prevent the normative postpartum expression of these receptors. This work may suggest altered 5-HT receptor expression underlying stress-induced maladaptions in maternal caregiving and affective behaviors, with implications for human postpartum depression.

## P2.3 MATERNAL EXPERIENCE-DEPENDENT CHANGES IN IMMEDIATE EARLY GENE AND PHOSPHORYLATED RIBOSOMAL PROTEIN S6 EXPRESSION IN MATERNAL NEURAL CIRCUITS

*Heather S. Mayer, Danielle S. Stolzenberg*

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Repeated experience with infants increases maternal responsiveness, however the neural mechanisms underlying this behavioral modification are largely unknown. We previously reported that pup-naïve mice care for pups in their home cage, but repeated pup experience is required for maternal care in a novel environment. Further, mice with sub-threshold experience that ignore pups have higher immediate early gene (IEG) expression in neural pathways that regulate infant aversion and lower IEG expression in regions that regulate maternal motivation. We hypothesize that experience alters the response of these pathways to pups such that regions regulating pup attraction (ventral tegmental area) become more sensitive to pup stimuli whereas regions regulating pup aversion (anterior/ventromedial nuclei) become unresponsive. Our results indicate that whereas repeated pup experience produced no differences in IEG expression in response to pups in the home cage, in a novel environment pup-induced IEG expression is significantly altered by pup experience. Further, we assessed the extent to which experience-induced changes in IEG expression overlap with phosphorylation of ribosomal protein S6 (pS6). Phosphorylation of S6 occurs in response to some of the same intracellular signaling cascades that activate IEG expression, however because this ribosomal subunit is involved in the translation of mRNA transcripts within a cell, isolation of the pS6 protein and associated mRNA transcripts can also provide a readout of transcriptional activity in activated neurons. Thus, pS6 expression can subsequently be used to identify changes in the experience-induced transcriptional response to pups throughout these regions. This work has been supported by R01 HD087709.

## P2.4 DEVELOPING TO DISPERSE: AGE-DEPENDENT MOVEMENT, RISK TAKING, AND OBJECT INVESTIGATION OF WILD MICE IN NOVEL SPACES

*George S. Prounis, Linda Wilbrecht*

Department of Psychology, and Helen Wills Neuroscience Institute | UC Berkeley USA

To achieve independence adolescent mammals must disperse from the natal site and be motivated to engage in high-risk exploration for distal resources. Changes in striatal dopamine (DA) systems are believed to play a role in regulating these motivational changes. The scope of this transition may be muted in strains of mice engineered in the lab. The steppe mouse (*Mus spicilegus*) is a wild-living congener of house mice. We posit that steppe mice exhibit phenotypes shaped by ecological selection which, proximal to adolescence, reflect changes that are critical for dispersal. These changes include increased locomotion, risk taking, and novel object investigation, and may correlate with patterns of striatal DA signaling. I examined the behavior of steppe mice at various post-weaning ages (postnatal day (P) 22-120) within an open field apparatus. This included measuring the behavior of mice towards a novel object placed within the apparatus. Between ~P60-80, male mice exhibited peaks in total distance travelled, risk taking (i.e., time spent in the center), and time spent interacting with the novel object. I then determined how striatal DA signaling changes between P30 and P60 in steppe mice. I used a synthetic nanosensor-based optical catecholamine sensor to compare evoked dopamine release across striatal subregions (i.e., dorsolateral, dorsomedial (DMS), and ventral (VS) striatum) in male mice prior to (P30), during (P60), and after (P120) the

observed peaks in behavior. My preliminary results support that evoked DA is higher at P60 than at P30, and most significantly in the DLS.

## P2.5 UNCOVERING THE CIRCUIT CONFIGURATIONS OF AVP-EXPRESSING NEURONS

*Jonathan Woodson, Cohavit Gil, Joseph Bergan*

Neuroscience and Behavior | University of Massachusetts Amherst USA

The neuropeptide Arginine Vasopressin (AVP) plays a critical role in mammalian homeostatic stress response as well as social behavior. AVP produced in the hypothalamus regulates water osmolality and vasoconstriction in the body and through connections made within the brain it is involved in social regulation, aggression, and anxiety. However, the AVP-dependent links between social behavior, homeostatic function, and disease are not well understood. AVP-expressing neurons are found in only a few areas in the brain but are thought to receive synaptic input from brain regions distributed throughout the nervous system. This study investigates the circuit configurations of AVP expressing neurons in the rodent hypothalamus. We targeted two main AVP producing populations, the paraventricular nucleus (PVN) and supraoptic nucleus (SON) using retrograde tracing techniques to identify afferent and efferent synaptic connections made by these populations of AVP-expressing neurons. AVP neurons in the SON and PVN display region-specific anatomical configurations that reflect their unique contributions to social behavior and homeostatic function. This includes differing inputs from thalamic and hypothalamic areas. Our preliminary results show demonstrate sex differences in inputs from social regions of the hypothalamus to AVP-expressing neurons in the PVN. This proposed work reveals new insights into the organization of social behavior circuits in the brain, and how neuropeptides act centrally to modulate social behaviors.

## P2.6 CHARACTERIZATION OF V1a-RELATED PROTEINS IN THE BRAINS OF COMET GOLDFISH, *CARRASSIUS AURATUS*

*Katherine R. Torrey, Leah C. Wilson, Richmond R. Thompson*

Neuroscience Program | Bowdoin College USA

We recently sequenced two V1a-related genes in goldfish: a “canonical” gene that would translate a full-length receptor protein and a 3’ truncated version. We have now generated two custom antibodies, one that should recognize both forms and one that is selective for the long, canonical form. Initial Western blot analyses suggest that both genes are translated. Immunohistochemical analyses indicate that both antibodies stain similar regions of the brain, including cells in the preoptic area that may be autoreceptors on vasotocin-producing cells, as well as cells and processes in the tectum and hindbrain that are likely targets of descending vasotocin projections. We also observe staining in small cells and processes along the midline, particularly in the forebrain, that appear to be radial glial cells, as indicated by co-localization with glial fibrillary acidic protein. While both antibodies mark similar, overlapping regions, the canonical antibody appears to recognize antigens on cells in the preoptic area and hindbrain more strongly, whereas the antibody that recognizes both forms appears to mark glia-like processes more strongly, suggesting that the truncated product may be more prevalent in those cells. We are continuing to characterize the distributions of antigens recognized by both antibodies in the goldfish brain.

## P2.7 IMPACT OF VARIATION IN NON-BREEDING PHOTOPERIOD ON HPG STIMULATION IN SPRING MIGRATORY BIRDS

*Adam M. Fudickar, Dustin E. Brewer, Dillon Gaughan*

Environmental Resilience Institute | Indiana University USA

Increasing photoperiod in winter and spring stimulates the avian hypothalamic-pituitary-gonadal axis (HPG), resulting in the seasonal transition to reproduction. Existing models of seasonal timing suggest that stimulation of the HPG occurs when a population specific photoperiodic threshold is reached. In many avian populations, autumn

migration results in individuals spending months preceding reproduction at different latitudes and therefore experiencing different photoperiods. Here we asked whether within population variation in photoperiod in winter and spring leads to intrapopulation variation in timing of the seasonal activation of the HPG. In late summer we captured male song sparrows (*Melospiza melodia*) from a breeding population in southern Indiana, USA (39.16°N,86.53°W) and randomly assigned them to one of two indoor aviaries under the natural photoperiod of the site of capture. In mid-October, when song sparrows migrate south, we shifted the photoperiod of one aviary to the natural photoperiod at the southern extent of their wintering range (27.95°N,82.46°W), simulating autumn migration. To compare the seasonal timing of HPG development, beginning in mid-February, once a week we measured baseline and maximum testosterone using a standardized gonadotropin-releasing-hormone (GnRH) challenge. If intrapopulation variation in photoperiod in winter and spring contributes to variation in readiness to breed in spring, then migratory populations that are broadly dispersed outside of breeding will exhibit greater variation in breeding dates than populations that are more concentrated geographically. Greater variation in breeding dates could give populations greater capacity to respond to environmental variability, and thus greater resilience as the environment changes.

## P2.8 DEVELOPING TECHNIQUES TO VISUALIZE AND QUANTIFY ALCOHOL-INDUCED CHANGES TO MYELINATED AXONS OF THE MEDIAL PREFRONTAL CORTEX

*Andrea Silva-Gotay, Kyle Lucier, and Heather N. Richardson*

Psychological and Brain Sciences | University of Massachusetts Amherst USA

During adolescence, neural circuits undergo maturational changes that impact neural processing and behavior. Binge drinking at an early age in humans is associated with cognitive impairments and alcohol use disorder later in adulthood. In line with these findings, we found that early adolescent drinking reduces myelin in the medial prefrontal cortex (mPFC). Identification of the specific axonal circuit affected and underlying mechanisms will give insight into the functional consequences of these axonal changes. The current project focused on optimizing techniques to distinguish between myelinated and unmyelinated axons within prefrontal pathways with the long-term goal of isolating the specific prefrontal axons impacted by alcohol. We first compared different tract tracers in male and female rats and found that intra-mPFC injection of 3,000 MW fluorescein dextran amine (FDA) resulted in superior axonal labeling compared to adeno-associated virus (AAV2/1-CAG-GFP). We next confirmed that survival timeline of FDA could be manipulated to optimize anterograde vs retrograde transport along mPFC axons. We then compared immunofluorescent labeling and confocal imaging of myelin versus label-free imaging of myelin using spectral confocal reflectance (SCoRe) microscopy and found this latter technique more optimal for visualizing myelin on traced axons. Finally, we assessed quantification approaches and established that the density of afferent and efferent myelinated axons can be quantified by integrating co-localization and threshold analyses of SCoRe using NIS Elements Advanced Research analysis software. Altogether these results support a combination of techniques that will enable us to assess alcohol-induced changes in specific myelinated fiber pathways in developing animals.

## P2.9 INFLUENCE OF SONG QUALITY AND ENVIRONMENT ON ESTRADIOL AND IMMEDIATE EARLY GENE RESPONSE TO SONG IN THE CANARY (*SERINUS CANARIA*)

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Female songbirds are thought to make mate choice decisions based on male song quality. Male canaries (*Serinus canaria*) produce songs with “special” syllables that are highly salient to females – eliciting high rates of sexual displays and enhanced immediate early gene (IEG) expression. First we verified that playback of special syllables elicited enhanced IEG expression then we tested the effect of experience with different quality male songs. Photostimulated female canaries were housed in sound attenuated chambers and played pseudosongs containing

either three special syllables or three non-special syllables, an intro, and an outro. We quantified plasma estradiol (E2) via ELISA and the IEG ZENK via immunohistochemistry in the caudal mesopallium (CMM) and nidocaudal mesopallium (NCM), two auditory areas important in processing conspecific song. Females that heard special syllable pseudosongs exhibited higher ZENK expression in CMM. To assess effects of experience, photostimulated females were exposed to playback of song with or without special syllables for 14 days. Birds were then played one of the aforementioned stimuli or silence. Females who experienced song with special syllables had lower plasma estradiol concentrations after final song playback. ZENK expression in CMM and NCM was equivalent for song with and without special syllables. This study indicates that estradiol concentrations may mediate changes in song responses, serving as a mechanism for modulating mate choice in differing song environments. In addition, CMM exhibits an IEG response bias to special syllables in limited acoustic contexts, but not in full song, which may contain additional biologically relevant information.

## P2.10 SEX AND PUBERTAL STATUS AFFECT SPINE DENSITY ON INTRATELENCEPHALIC CORTICOSTRIAL NEURONS IN THE MOUSE MEDIAL PREFRONTAL CORTEX

*Kristen Delevich, Nana J. Okada, Ameet Rahane, and Linda Wilbrecht*

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The prefrontal cortex (PFC) exhibits grey matter thinning and dendritic spine pruning that extends late into adolescence. This protracted maturation is believed to support cognition but may also confer psychiatric vulnerability during adolescence. Currently, little is known about how different cell types in the PFC mature or whether puberty plays a causal role. Pyramidal Tract (PT) and Intra-Telencephalic (IT) cells are two dominant classes of layer 5 excitatory neurons that exhibit distinct anatomical and electrophysiological properties. While PT-type neurons are labeled by Thy1-YFP reporter lines, IT-type neurons are more difficult to access and less is known about their structural maturation. Here, we leveraged retro-AAV to investigate apical dendritic spine pruning in cross-corticostriatal IT (CCstr-IT) neurons in the dorsomedial prefrontal cortex (dmPFC), comparing late juvenile (PD 29) and young adult (PD 60) mice. We found a main effect of age and sex on CCstr-IT apical dendritic spine density, but no interaction. These findings indicate that males exhibit significantly lower apical spine density on CCstr-IT neurons than females but prune to a similar extent. We next performed prepubertal gonadectomy or sham surgery at PD25 and compared CCstr-IT spine density at PD60. Males that underwent prepubertal castration had significantly higher CCstr-IT spine density compared to sham males. Ongoing work is examining the effect of prepubertal ovariectomy on pruning. Our findings suggest that IT-type neurons exhibit significant sex differences in spine density, and that spine pruning onto CCstr-IT neurons is regulated by pubertal gonadal hormones in males.

## P2.11 THE RISE OF THE SCHOLAR COMMUNICATOR: A MODEL TO SUPPORT SCIENCE COMMUNICATION AND DIVERSITY BY FACULTY

*Rebecca M. Calisi Rodríguez*

Neurobiology, Physiology, and Behavior | University of California, Davis USA

Public misunderstanding and mistrust of science and scientists have generated a voting public that is skeptical of climate change, opposed to vaccines, and scientifically illiterate. Better science communication is crucial to fixing this situation, as well as for increasing the diversity of people doing the science. However, scientists are not always the best communicators, and journalists and professional communications staff do not always fully understand or correctly interpret scientific discoveries. Here stands the fundamental and timely need for science faculty “Scholar Communicators” who can bridge this gap to enhance the way we share discoveries and broaden inclusion in our fields. I offer a model of how my college created a new position to support and reward my efforts as a Scholar Communicator, and what I have accomplished with this support thus far. I suggest challenges and opportunities in expanding this model to other schools and the potential benefits to science and society.

## P2.12 PGF<sub>2α</sub> DRIVES MALE ATTRACTION TO REPRODUCTIVE FEMALES THROUGH AN EVOLUTIONARILY DIVERGENT PATHWAY

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Pheromones play essential roles for survival and reproduction in many species. In most fishes, prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) acts as a female reproductive hormone, eliciting mating behavior. In addition, PGF<sub>2α</sub> acts in some species as a sex pheromone to induce males' courtship. Here, we aim to investigate the behavioral responses and molecular mechanisms underlying pheromonal signaling between African cichlids (*Astatotilapia burtoni*). Our results reveal that male cichlids can distinguish gravid and non-gravid female solely by olfactory cues, but they are insensitive to PGF<sub>2α</sub>. Genomic data indicate that African cichlids are insensitive to PGF<sub>2α</sub> because they lack an odorant receptor, Or114, which has been shown to detect PGF<sub>2α</sub> in other species. Surprisingly, males show strong preference to females injected with PGF<sub>2α</sub>, and this attractiveness is independent of the PGF<sub>2α</sub> receptor *Ptgfr*. These results suggest that, although PGF<sub>2α</sub> is not sufficient as a pheromone to induce male preference, it still plays a vital role in mediating females' attractiveness. One possible explanation is that, instead of sensing PGF<sub>2α</sub>, male cichlids detect PGF<sub>2α</sub> metabolites to evaluate the reproductive stage of females. We have shown that most common PGF<sub>2α</sub> metabolites, such as 15-keto PGF<sub>2α</sub>, 13,14-dihydro-15-keto PGF<sub>2α</sub> and 13,14-dihydro PGF<sub>2α</sub>, are not the key pheromones to drive male's mating preference. Further biochemistry approaches, combining column extraction and liquid chromatography, will identify the pheromone candidates that induce mating preference in cichlids. Molecular genetic techniques will be used to identify the olfactory receptor(s) responsible for detection of this chemosensory signal.

## P2.13 INTERACTIONS OF MATERNAL CARE AND PATERNAL PRESENCE IMPACT THE NONLINEAR TRAJECTORIES OF OFFSPRING SOCIAL DEVELOPMENT

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Variation across early life social experiences, such as in the quality of maternal care or the presence or absence of a father, is known to impact offspring social behavior and neurobiology. However, we know little about the potential interactions between different forms of early social experiences, nor how such interactions may shape developing phenotypes. To address this gap, we manipulated the rearing environment of prairie vole (*Microtus ochrogaster*) pups by raising them either with or without their fathers. Concurrently, we used a well-established handling manipulation to elicit group differences in parental care behaviors. We measured parental behaviors across the rearing period, then tested offspring behavior during their juvenile and adult stages to compare how the behavioral trajectory of these groups vary across development. We found that while offspring reared by single mothers received less overall care, they were generally more prosocial and less aggressive than pups reared biparentally. Mothers provided more care than fathers, and parental behaviors changed as pups aged. We found group differences in defensive and social approach behaviors during the juvenile period, but these differences were not seen when assessed in adulthood. Our findings suggest that the behavioral traits induced by variation in early experiences are constrained to particular points in development, and that the ontogeny of social traits is nonlinear in nature. Furthermore, rearing experience impacted oxytocin, but not vasopressin, cell densities in the hypothalamus, highlighting a potential mechanism by which behavioral differences may be mediated.

## P2.14 HIGH-YAWNING MALE RATS RAISED BY SPRAGUE-DAWLEY DAMES IMPROVE THEIR EJACULATORY PERFORMANCE

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High-yawning (HY) subline from Sprague-Dawley (SD) rats were obtained by a strict inbreeding process. HY male rats have higher spontaneous yawning frequencies around 20 yawns/h and Sprague-Dawley just had 2 yawns/h. HY male rats had a higher proportion of non-copulators subjects (Ss) when they allow copulate 30 min. HY dams had a different maternal display with longer intervals to retrieve the pups, built lower quality nests and higher proportion of atypical and re-retrieving. The aim of this study was to analyze the maternal display, and male sexual behaviors in pups raised by cross- and in- fostering interchanges.

All Ss were maintained under standard conditions and all the experiments approved by IACUC.

Our results showed maternal behavior was different displayed by cross- and in- fostering HY with respect to SD dams, however each component is quite stable between groups. HY raised by HY dams had a higher proportion of non-copulators (NC) and sluggish (SI). However, when HY males are raised by SD dams they increased male rats with average (Av) and precocious type of copulatory pattern. SD male rats raised by HY dams they worsened sexual performance of SD because they increased the proportion of Av and SI copulators. So, maternal care is able to modify the proportion of ejaculatory pattern and it is relevant because is an adequate model for child that are abused that could have an impact in their sexual life in adulthood.

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## P2.15 INJECTION OF A SEROTONIN PRECURSOR MODIFIES MALE RESPONSE TO FEMALE REJECTION VOCALIZATIONS IN A WEIGHT-DEPENDENT MANNER

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Neuromodulatory systems, like the serotonergic system, innervate regions involved in both sensation and social behavior, making them likely candidates for representing a social information in sensory systems. In an auditory midbrain nucleus (inferior colliculus; IC) of male house mice, levels of serotonin are sensitive to both auditory and social stimuli. Serotonin in the IC of males increases when males are with a female partner, but the increase is negatively correlated to the rejection behaviors the female exhibits, including broadband vocalizations (BBVs). Serotonin in the IC of males may therefore encode female receptivity during sexual interactions. We hypothesized that elevated serotonin reduces the sensitivity of males to female rejection. In order to investigate this hypothesis, male CBA/J mice (n=12) were each exposed to a female and a female with BBV playback while injected with saline or a serotonin precursor known to increase serotonin in the IC (5-Hydroxytryptophan; 5-HTP) in random order. Male vocal courtship behavior was measured and quantified. 5-HTP decreased vocal behavior compared to saline injection trials. The effect of 5-HTP on the responses of males to BBV playback depended on the weight ranks of males within their social groups. For males that weighed the least, 5-HTP increased vocalizations in response to playback while for males that weighed the most, 5-HTP suppressed vocalization to BBV playback. These results indicate that increasing serotonin in the auditory system can modify behavior response to a social vocalization, but the direction of that modification may depend on underlying differences in male social status.

## P2.16 ACCELERATED CLEARING AND MOLECULAR LABELING OF LARGE TISSUE SAMPLES USING MAGNETOHYDRODYNAMIC FORCES

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Studying large biological samples with fluorescence microscopy is impeded by light scattering within the tissue, which makes most biological tissues opaque. Chemical strategies to render tissues transparent have existed for over a century, but these techniques often quench fluorescence. Here we describe a novel strategy to render

opaque tissue samples transparent and rapidly label them with antibodies for large volume fluorescence microscopy, building on an exciting and growing field of techniques developed specifically to clear and fluorescently label large tissue samples. This approach utilizes a magnetohydrodynamic force to accelerate the removal of lipids from and the introduction of fluorescent antibody labels into intact tissue samples. This strategy complements a growing array of tools that enable high-resolution 3-dimensional anatomical analysis of intact tissue with fluorescence microscopy. We have effectively used the technique to clear and label multiple species and tissues, and found that it is inexpensive, straightforward, and compatible with existing strategies for fluorescence microscopy that allow high-quality imaging of intact tissues from diverse species.

## P2.17 MATE PAIR SEPARATION AND ASSOCIATED CHANGES IN HIPPOCAMPAL GLUCOCORTICOID RECEPTOR mRNA EXPRESSION INDUCE CHANGES IN THE ACOUSTIC FEATURES OF SONG IN MALE ZEBRA FINCHES

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Zebra finches, like many other birds, are monogamous, biparental, and form life-long pair bonds. In our previous study, we investigated the effects of mate pair separation on circulating corticosterone concentrations and changes in mineralocorticoid receptor (MR), glucocorticoid receptor (GR), and corticotropin releasing hormone (CRH) gene expression in the hippocampus in male and female finches. Birds were assessed in three treatments: (1) the male or female being removed from their respective mate (2) the male or female remaining with their mate, but a new stimulus female was introduced, or (3) the subjects were handled but not separated from their mate or the stimulus female. We observed significant increases in plasma corticosterone concentrations in response to both mate pair and stimulus female separation in both males and females. In the hippocampus, females exhibited a significant up regulation in MR, but not GR mRNA, whereas males exhibited a significant down regulation of both MR and GR mRNA in response to mate pair separation. In this same experiment, we recorded song behavior for 48 hours. We found that at 24 and 48 hours post removal, relative to baseline, males who had lost their mate sang syllables with lower frequency modulation (FM) variance. Likewise, pair bond removed males sang syllables with lower goodness of pitch variance. Furthermore, hippocampal GR mRNA was positively correlated with FM variance. Our findings suggest that the psychosocial stress of mate pair separation is associated with the modulation of song stereotypy perhaps via changes in glucocorticoid feedback.

## P2.18 THE INFLUENCE OF ER $\alpha$ -MEDIATED ERE-DEPENDENT AND ERE-INDEPENDENT SIGNALING ON BEHAVIORAL ASSESSMENTS OF MOOD AND COGNITION IN FEMALE MICE

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17 $\beta$ -estradiol (E2), alters a variety of components involved in mood and cognition. Previous studies demonstrate that alterations in E2 levels affect behaviors involved in anxiety, sociability, and memory. However, the underlying mechanisms to regulate mood and cognition are underexplored. Mechanisms that may modulate these behaviors are through the control of gene expression by way of estrogen response element (ERE)-dependent and ERE-independent ER $\alpha$  signaling. We assess whether behaviors involved in mood and cognition are differentially affected in three ovariectomized (OVX) female mouse models: a total ER $\alpha$  knock out (ERKO), a novel ER $\alpha$  knock in/knock out (KIKO) that lacks a functional DNA-binding domain, and wild type (WT) controls. In order to evaluate anxiety-like behavior and locomotion, we utilized the open field test, elevated plus maze, and Light/Dark box. Results demonstrate differences in anxiety-like behavior attributed to genotype; however, further analysis suggests this difference is due to locomotor activity. To assess sociability and memory, we employed the three-

chamber test. Outcomes on social preference demonstrate that estrogen-treated KIKO females have increased entries into the novel mouse chamber, suggesting a greater socialization preference. Social recognition memory results reveal that estrogen-treated KIKO females spend greater time with the familiar mouse, indicating estrogen treatment disrupts social recognition memory. ERKO estrogen-treated mice follow a similar trend on social recognition memory. This study reveals that estrogen-treated OVX WT and ER $\alpha$  transgenic mice perform differently on measures of locomotion, sociability, and social memory, highlighting an unexplored mechanism by which ERE-mediated ER $\alpha$  signaling can regulate behavior.

## P2.19 CENTRAL MANIPULATION OF ARGININE VASOTOCIN AFFECTS JUVENILE SOCIAL BEHAVIOR AND NEUROENDOCRINE GENE EXPRESSION IN A HIGHLY SOCIAL FISH

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Social behavior is fundamental to evolutionary fitness and health, yet little is known about the neuromolecular mechanisms underlying its development. We use the highly social African cichlid fish, *Astatotilapia burtoni*, to investigate juvenile behavior and its underlying neuroendocrine mechanisms. First, we demonstrate that the repertoire of juvenile social behavior is largely similar to that of adults, but key differences reveal processes of behavioral development. Most strikingly, social status formed when juveniles differ in size, but not when size-matched. Importantly, relative size not only affected the interacting pair, but also extended to other group members. Next, we tested the hypothesis that juvenile status is regulated by arginine vasotocin (AVT), a highly conserved regulator of social behavior, including in adult *A. burtoni*. We engineered juvenile groups such that status was unlikely to emerge and manipulated AVT signaling using intracerebroventricular injection of AVT, V1aR antagonist Manning Compound, or vehicle. We then observed behavior and quantified neural gene expression. Pharmacological manipulation specifically affected social status but not rates of interaction. In the presence of a Manning Compound-treated juvenile, agonistic efficiency (proportion of approaches leading to displacement) was significantly higher, indicating status establishment. This phenotype was associated with tightly correlated expression of genes encoding nonapeptides and their receptors, as well as glucocorticoid receptor 1. In contrast, nonapeptide and stress axis gene expression was not correlated in groups with an AVT-treated juvenile. Our results expand our understanding of the context-specific emergence of juvenile social status and support a similar regulatory role for AVT over development.

## P2.20 THE AFRICAN SPINY MOUSE AS A MODEL FOR SOCIALITY

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Surprisingly few studies have examined similarities and differences in the mechanisms modulating both reproductive and non-reproductive social behavior (i.e., sociality), and how those mechanisms evolved. Although work in birds, fish, and insects has begun to address those relationships, there are few mammalian organisms in which the mechanisms that support social behaviors in both reproductive and non-reproductive contexts can be examined and compared. This is because very few mammals are social outside of reproductive contexts, and thus, there are a lack of mammalian models that exhibit non-reproductive sociality and are also tractable for neuroscience studies. Here we introduce a highly social rodent, the African spiny mouse (*Acomys cahirinus*), as a model for studying sociality. We describe basic reproductive characteristics, including a cooperatively breeding mating system and precociality. In order to lay a foundation for future social neuroscience studies with spiny mice, we characterized nonapeptide (vasopressin, VP; oxytocin, OT) neuron distribution throughout the brain. Notably, analyses revealed a robust OT cell group in the anterior hypothalamus (AH). To our knowledge, OT-immunoreactive

(-ir) neurons in the AH have not been reported in rats, mice, or voles, but have been documented in Mongolian gerbils, Chinese striped hamsters, naked mole rats, and tree shrews (each with only 1-3 AH OT-ir neurons). We observed a dense cluster of, on average, 15 OT-ir neurons in the AH of the spiny mice, adjacent to the taxonomically widespread AH VP neuronal population. Future studies aim to systematically characterize the social behavior and nonapeptide functions of spiny mice.

## P2.21 TESTOSTERONE, CORTISOL, AND THE BEHAVIORAL EXPRESSION OF COMPETITIVE EFFORT

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Transient increases in testosterone are thought to promote dominance behavior aimed at enhancing social status. These behavioral efforts are also associated with cortisol responsivity as competition is a social and often physical stressor. Individuals differ in their status motivation and subsequent competitive effort displayed in contests for status. In a series of three studies involving men and women (total N = 605), testosterone and cortisol responses were tested in relation to performance in a laboratory task of competitive will, the willingness to endure discomfort in an attempt to be a winner, a behavioral expression of competitive effort. The moderating role of social context in terms of the physical presence of an opponent (Study 1), the sex of an opponent (Studies 1-3), the number of opponents (Studies 2-3), and competition outcome (Study 1: relative win/loss; Studies 2-3: rank among a group of 3-8 participants) were tested across studies. Testosterone and cortisol were assayed from saliva samples obtained before and after competition. Across all studies, testosterone and cortisol response was positively associated with competitive will performance, an effect that was stronger among male participants. Further, competitive will performance and its relationship to testosterone and cortisol response were heightened in the group context, the presence of more than two and up to seven other opponents. Specific data on the moderating factors within each study will be presented. Overall, this series of studies provides novel evidence that individual differences in competitive effort predict how levels of testosterone and cortisol change during competition.

## P2.22 GUNS, TESTOSTERONE, AND AGGRESSION: A PRE-REGISTERED REPLICATION OF KLINESMITH ET AL. (2006)

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Klinesmith and colleagues (2006) reported that interacting with a gun (versus a board game) for just 15 minutes led to a substantial rise in testosterone concentrations (Cohen's D = 1.53) and aggressive behaviour (Cohen's D = 1.52) in healthy young men. Some key limitations of this highly cited study include having a very small sample size (n = 30), an exclusive focus on men, and the use of a control condition (board game) that differed in many ways from the experimental condition. In the current pre-registered experiment, we sought to replicate this finding using a much larger sample size of both men and women (n = 240) and included of a control object that was more similar in terms of size, colour, and number of parts. Preliminary analyses (based on n = 160 participants, 50% women) indicated that men engaged in more aggressive behaviour relative to women. However, we observed no effects of experimental condition (gun vs. control object) on either testosterone concentrations or aggressive behaviour. Moreover, gender/sex did not interact with experimental condition to predict testosterone concentrations or aggressive behaviour. Thus, preliminary analyses suggest no effects of experimental exposure to a gun on testosterone concentrations and/or aggressive behaviour. These findings highlight the importance of conducting well-powered replication studies to verify the robustness of previous human social neuroendocrine research that has drawn conclusions on the basis of very small sample sizes.

## P2.23 LONG INTERSPERSING ELEMENT 1 SHOWS ALTERNATE EXPRESSION DUE TO STRESS IN A SEX-SPECIFIC PATTERN

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Line1—a retrotransposon that comprises ~17% of the human genome and ~23% of the rat genome—is aberrantly expressed in psychiatric disorders such as schizophrenia, bipolar disorder, and Rett syndrome, suggesting it may play an important role in neurodevelopment. Though Line1 expression was previously thought to be quiescent during typical developmental conditions, recent evidence suggests that Line1 expression may actually be affected by environmental experiences. Once expressed, Line1 has the ability to self-replicate via reverse transcription of an RNA intermediate and can subsequently reinsert itself throughout the genome. We sought to understand whether early life stress (ELS), a known risk factor for the development of later psychiatric disorders, would affect Line1 expression. Our study uses a neonatal predator odor exposure (POE) paradigm to model ELS in rats. We examined Line1 using RT-qPCR at two different timepoints, neonatal (P3) and juvenile (P33), to assess whether ELS would alter Line1 expression levels. We also were interested in whether biological sex mitigates the impact of ELS on Line1 expression given that we know there are sex differences within the developing brain. Our results provide evidence that Line1 expression is sensitive to ELS and that these changes are sex-specific. These data suggest the intriguing possibility that ELS may induce genetic diversity within the developing brain.

## P2.24 SEX-DEPENDENT EFFECTS OF CHRONIC VARIABLE STRESS ON DISCRETE CORTICOTROPIN-RELEASING FACTOR RECEPTOR 1 CELL POPULATIONS

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Anxiety and depression are strikingly more prevalent in women compared with men. Dysregulation of corticotropin-releasing factor (CRF) binding to its cognate receptor (CRFR1) is thought to play a critical role in the etiology of these disorders. In the present study we investigated whether there were sex differences in the effects of chronic variable stress (CVS) on CRFR1 cells using CRFR1-GFP reporter mice and a 9-day CVS paradigm. Brains were collected from CVS and stress naïve mice following exposure to the open field test. This CVS paradigm effectively increased anxiety-like behavior in female and male mice. In addition, we assessed changes in activation of CRFR1 cells (co-localization with c-Fos and phosphorylated CREB (pCREB)) in stress associated limbic structures, including two sexually dimorphic CRFR1 cell groups in the AVPV/PeN (F>M) and PVN (M>F). CVS increased CRFR1-GFP cell number as well as the number of CRFR1/pCREB co-expressing cells in the female but not male AVPV/PeN. We further used CRFR1-Cre mice and stereotaxic infusion of a Cre-specific AAV to demonstrate that AVPV/PeN CRFR1 cells innervate several stress-regulating brain regions including the PVN, lateral septum, and periaqueductal gray area. These connectivity patterns demonstrate a potential role of this nucleus for sex-specific stress regulation. In addition, CVS induced a female-specific reduction in CRFR1/c-Fos cells within the anteroventral bed nucleus of the stria terminalis and a male-specific reduction in CRFR1/c-Fos cells in the PVN. Overall, these sex-specific effects of CVS on CRFR1 populations may have implications for sex differences in stress-induction of mood disorders.

## P2.25 OXYTOCIN RECEPTOR KNOCKDOWN IN THE DORSOMEDIAL TEGMENTUM INCREASES INFANTICIDE AND DISRUPTS MATERNAL SOCIOEMOTIONAL BEHAVIORS IN POSTPARTUM RATS

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Oxytocin (OT) is well-known for positively influencing mammalian maternal caregiving. OT acts in many brain sites to affect postpartum behaviors, but midbrain sites sensitive to OT, such as the dorsal raphe and ventrolateral periaqueductal gray (together termed the dorsomedial tegmentum) are rarely studied despite being known to be involved in motherhood. We previously found a ~250% increase in oxytocin receptor (OTR) autoradiographic binding and ~60% higher OT-immunoreactive fiber density in the dorsomedial tegmentum of postpartum rats compared to diestrus virgins. Additionally, we demonstrated that ~40% of serotonergic neurons in the female rat dorsomedial tegmentum express OTR immunoreactivity. These postpartum increases in OT measures in the dorsomedial tegmentum may affect serotonergic control of postpartum behaviors. Here we hypothesized that elevated OT signaling specifically in the dorsomedial tegmentum influences the display of maternal socioemotional behaviors. To test this hypothesis, we created an adeno-associated virus expressing a short-hairpin RNA (shRNA) targeted to OTR mRNA and a scrambled control shRNA. We found that knocking down OTRs in the dorsomedial tegmentum led to higher rates of postpartum infanticide, less nursing, and more non-pup directed behaviors. OTR knockdown also increased postpartum aggression, decreased postpartum anxiety, and increased dams' depressive-like behaviors. Because OTR knockdown in the dorsomedial tegmentum also decreased serotonin-immunoreactive fiber length in the primary somatosensory cortex (S1), we believe the knockdown effects are due to disrupted S1 plasticity necessary to optimize maternal tactile sensitivity to offspring. These data indicate that the dorsomedial tegmentum is an understudied target where oxytocin acts to optimize maternal caregiving.

## P2.26 EXPRESSION OF ION CHANNEL GENES AND STEROID RELATED GENES IN A BRAIN REGION CONTROLLING SEXUALLY DIMORPHIC COMMUNICATION IN ELECTRIC FISH

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The electric organ discharges (EODs) of South American electric fish are a good model for studying mechanisms of sex differences. Closely-related species differ in the direction and magnitude of sex differences in EOD frequency (EODf), and EODf is controlled by a single brain region, the pacemaker nucleus (Pn). EODf is a communication signal that varies across species and/or sex. EODf is differentially regulated by sex-steroid hormones in two congeneric species (*Apteronotus albifrons* and *A. leptorhynchus*) that differ in the direction of EODf sexual dimorphism. Using RNAseq and qPCR, we characterized expression of genes for numerous steroid hormone receptors and steroidogenic enzymes in the Pn of both species. Ongoing experiments are examining species and sex differences in expression of these hormone-related genes. Sexually dimorphic firing rates of Pn neurons are controlled by voltage-gated ion channels, and we hypothesize that steroid hormones influence sex differences in EODf by regulating ion channel gene expression in the Pn. Preliminary RNAseq data suggested that regulation of ion channel expression (KIR 3.1, SCN1b, KVb2, etc.) may regulate sexually dimorphic EODf in *A. albifrons* and/or *A. leptorhynchus*. We used qPCR to validate this finding. SCN1b expression was greater in *A. albifrons* than in *A. leptorhynchus*, but did not differ between the sexes. Expression of KIR3.1 and Kvb2 did not differ significantly between sexes/species, which suggests that differences in expression of these genes may not underlie sexually dimorphic EODf. Ongoing experiments are examining sex differences in expression of additional ion channel genes.

## P2.27 VARIATIONS OF SOCIAL STATUS: IDENTIFYING THE NEUROENDOCRINE CHARACTERISTICS OF DOMINANCE STYLES IN A HIGHLY SOCIAL CICHLID FISH

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Across time and context, social groups and their members can vary considerably with different individuals occupying specific roles or classes. This variation arises from different social, physiological, neuromolecular, and genetic factors, and has important consequences for social interactions and group structure. Here we examine naturalistic communities of the highly social African cichlid fish, *Astatotilapia burtoni*, to uncover the neuromolecular pathways that give rise to and are affected by individual variation using measures of hormonal, neuromodulatory, and transcriptomic patterns associated with social behaviors within a dynamic social environment. While males of this species can be easily distinguished as either brightly colored, territorial, aggressive and reproductively active dominant (DOM) males and dull, non-territorial, and reproductively suppressed subordinate (SUB) males, few studies have examined the neuroendocrine and molecular basis of individual variation across DOM males. We monitored males and females from eight communities over six weeks and found remarkable and consistent variation in the behavior associated with DOMs, with corresponding changes in social interactions and group dynamics. We then linked this behavioral variation with levels of glucocorticoid and sex steroid hormones as well as the transcriptomes of several forebrain regions that are critical nodes in the Social Decision-Making Network (SDMN). Our results demonstrate how the integration of complex behavioral, physiological, and molecular co-variance structures to the regulation of social behavior allows us to understand the mechanisms that generates individual variation within highly dynamic social groups, with consequences for individual well-being and reproductive success.

## P2.28 VASOPRESSIN RECEPTOR DISTRIBUTION IN GREEN ANOLES (*ANOLIS CAROLINENSIS*)

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Vasopressin signaling in the brain is known to affect social decision-making. The production and release of vasopressin from various neuronal populations has been shown to have discrete behavioral functions across a variety of vertebrate taxa. Additionally, vasopressin receptor distribution has been linked to behavioral phenotype in mammals and birds. However, little is known about the vasopressin receptor distribution in reptiles, as well as their involvement in social behavior regulation. The current study is an initial examination of vasopressin receptor distribution in a commonly examined reptilian species, the green anole (*Anolis carolinensis*). To quantify receptor expression, we employed autoradiography using a mammalian V1a receptor-binding ligand. To determine intraspecific variability, we included male and female subjects, from both the breeding and non-breeding season. We here describe the distribution of vasopressin receptor in the forebrain, midbrain, and hindbrain of green anoles. Principal Components Analysis (PCA) was used to reduce brain-wide vasopressin receptor expression into two primary components. PCA1 was positively correlated with receptor expression throughout the brain, and did not differ between sexes or across seasons. PCA2 correlated primarily with hindbrain receptor expression and a sex difference was observed, with females possessing more receptor than did males. We also examined receptor expression in females across reproductive state (reproductive state fluctuates even within-season and is associated with hormonal changes). Gravid females were generally found to possess higher vasopressin receptor expression than vitellogenic or nonreproductive females. The possibility of using this receptor quantification approach to explain individual variability in social behavior expression is discussed.

## P2.29 APOE GENOTYPE, SEX, AND 17 $\beta$ -ESTRADIOL INFLUENCE MEMORY CONSOLIDATION AND HIPPOCAMPAL PROTEIN EXPRESSION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Loss of circulating estrogens at menopause is associated with increased risk of Alzheimer's disease (AD) relative to men. Women carriers of the APOE4 genotype are more likely than women APOE2 or APOE3 carriers and men of any APOE genotype to develop AD. However, interactions among APOE genotype, sex, and 17 $\beta$ -estradiol (E2) are not well characterized. In a mouse model of AD, we examined effects of sex and APOE on memory, and tested whether E2 mediates memory consolidation. Gonadally-intact males and females expressing 5 familial AD mutations (5xFAD-Tg) and human APOE3 (E3FAD) or APOE4 (E4FAD) were trained on object recognition (OR) and object placement (OP) tasks to test object and spatial memory formation. Two weeks later, mice were trained with novel objects. Five minutes later, the dorsal hippocampus (DH) was dissected from one hemisphere for Western blotting, and the other hemisphere collected for dendritic spine analyses. To determine whether E2 mediates memory consolidation in EFAD females, ovariectomized E3FADs and E4FADs were trained in the OR and OP tasks, received an immediate post-training infusion of E2 into the DH, and memory was tested 4 or 24 hours later. Male E3FADs exhibited intact OR and OP memory, whereas female E3FADs and E4FADs of either sex did not, suggesting preserved memory in E3FAD males relative to females, and impaired memory in E4FAD mice. E2 enhanced OR and OP memory in E3FAD, but not E4FAD, females. DH protein expression was impacted by APOE genotype and sex. Additional protein and spine density analyses are ongoing.

## P2.30 SOCIAL INSTABILITY IN ADOLESCENCE ALTERS DENDRITIC MORPHOLOGY IN MEDIAL PREFRONTAL CORTEX AND ITS RESPONSE TO STRESS IN ADULT RATS

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Women are more susceptible to many stress-linked psychological disorders, including depression and posttraumatic stress disorder. Dysfunction of prefrontal cortex is implicated in many of these disorders. Thus, understanding how stress influences prefrontal cortex could shed light on the neurobiological underpinnings of these sex-biased disorders. Chronic restraint stress (CRS) induces sex-specific changes in pyramidal neurons in adult rodent medial prefrontal cortex (mPFC). For example, apical dendrites of male rats retract after 10 days of CRS, which is followed by outgrowth after 7 days of rest. Conversely, female rats exhibit minimal changes throughout the post-stress period. Adolescence is an important period for HPA axis development and synapse maturation; thus, stress during this time could alter stress-sensitive brain regions and later stress-induced changes in the brain. However, little is known about how stress in adolescence affects these sex-dependent stress-induced changes in adulthood. We investigated the effects of adolescent social instability stress (SIS) on adult dendritic morphology in the mPFC of male and female rats. We then examined dendritic reorganization following CRS with and without a rest period in adolescently-stressed rats. Adolescent SIS profoundly reorganizes dendrites in adult males and females. In addition, CRS reduces apical dendritic length and increases thin and mushroom spine density in adolescently-stressed males given a rest period. Conversely, CRS produces outgrowth, increases thin spine density, and decreases mushroom spine density in adolescently-stressed females given a rest period. These results suggest that stress during adolescence alters development of the prefrontal cortex and may modulate stress-induced dendritic changes in adulthood.

## P2.31 INVESTIGATING THE EFFECTS OF THE NEONICOTINOID THIACLOPRID ON THE NEUROENDOCRINE DEVELOPMENT IN ZEBRAFISH AND MOUSE

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The extensive use of neonicotinoids, a class of widely used insecticides targeting the insect nicotinic receptors of the cholinergic system, raises concerns over its potential adverse effects in vertebrates. Indeed, the nicotinic receptors are widely distributed in the vertebrate peripheral and central nervous systems and play fundamental functions during development. In the current study, we investigated the effects of thiacloprid on neuroendocrine system in parallel in zebrafish and mouse models. In our first study, we exposed zebrafish larvae from 1 day post fertilization (dpf) to 6dpf to 10<sup>-6</sup> M, 10<sup>-7</sup> M or 10<sup>-8</sup> M thiacloprid. 50-60 larvae were analyzed for each treatment and the experiments were repeated 7 times. Whole heads were analyzed by qPCR for endocrine (estrogen receptor alpha, estrogen receptor beta 1 and beta 2 and aromatase), proliferative (PCNA, neurogenin) and synaptic (synaptophysin, synapsin IIa and BDNF) markers. None of these markers were affected by the treatment in our experimental conditions when compared to control samples. In a second study, we treated mice dams during gestation, from embryonic day 5.5 to 15.5 with 6mg/kg/day thiacloprid via ingestion. 35 days old male and female offspring were euthanized and prefrontal cortex, hippocampus, hypothalamus, amygdala and cerebellum are currently investigated for the expression of the same endocrine, proliferative and synaptic markers as those used in fish, as well as doublecortin. This set of experiments will allow us to better understand the potential impact of these molecules on the central nervous system during development.

## P2.32 EFFECTS OF TEMPERATURE-INDUCED SEX-REVERSAL ON ARGININE, VASOTOCIN (AVT) AND GnRH NEURONS IN THE BRAIN OF NILE TILAPIA NEOMALES (*OREOCHROMIS NILOTICUS*)

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Sex determination in Nile tilapia results from both genetics and environment. During sexual differentiation, genetically XX females (Fxx) can be masculinized by high water temperature, therefore differentiating into functional XX neomales (Mxx). Mxx have been found in the wild, but the physiological consequences of this sex-reversal are unclear. Here we address this topic by examining two neuronal populations known to vary between sexes or male morphs (AVT and GnRH neurons) as well as sex steroid concentrations.

Blood and brain of adult XY males (Mxy), Mxx and Fxx were sampled. Brains were immunostained for AVT and GnRH. Immunoreactive neurons were counted and their size measured in different subdivisions of the preoptic area (POA) (for AVT and GnRH1), in the terminal nerve ganglion and the midbrain (for GnRH3 and GnRH2 respectively). Sera were assayed for testosterone, 17 $\beta$ -estradiol and 11-ketotestosterone.

Mxx present fewer AVT-expressing neurons in the mPOA than Fxx. However, neomales possess bigger AVT neurons in the pPOA than the other groups. Circulating hormonal concentrations did not differ between males. Interestingly though, Mxx present fewer GnRH1 neurons than either Fxx or Mxy. No difference was found for either GnRH2 or GnRH3.

Together our data indicate that temperature-induced sex-reversal could affect subtle aspects of AVT and GnRH1 neuronal populations, which are linked to cortisol production and gonadal maturation respectively. Although Mxx exhibit fewer GnRH1 neurons than Mxy, the circulating sex steroid concentrations do not seem to be affected, suggesting that LH and FSH concentrations or receptors may be modified.

## P2.33 EFFECTS OF ESTETROL ON THE NEGATIVE AND POSITIVE FEEDBACK OF ESTROGENS ON LH SECRETION

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Estetrol (E<sub>4</sub>) is a natural estrogen acting as an agonist of nuclear estrogen receptor alpha (ER $\alpha$ ) and an antagonist of its membrane signaling. E<sub>4</sub> dose-dependently blocks ovulation in female rats. However, the mechanism underlying this contraceptive effect are unknown. To determine whether E<sub>4</sub> acts centrally to control ovulation, we tested its effect on the negative and positive feedback of estradiol (E<sub>2</sub>) on LH secretion. Chronic treatment with E<sub>2</sub>, E<sub>4</sub> alone (0.3-3mg/kg) or both combined reduced LH secretion compared to vehicle in ovariectomized females. E<sub>4</sub> alone also mimicked the effect of E<sub>2</sub> on the number of immunoreactive nuclei for progesterone receptor (PR) in the arcuate nucleus. As expected, in ovariectomized females chronically treated with a low dose of E<sub>2</sub>, estradiol benzoate (EB) alone or combined with progesterone (P) induced a LH surge and the associated increase in the number of activated preoptic kisspeptin (Kp) and GnRH neurons assessed by the expression of the immediate early gene cFos. However, E<sub>4</sub> blocked the effect of EB on both LH secretion and the activation of Kp and GnRH neurons when it was provided alone but not when it was combined to P. Together, these results indicate that E<sub>4</sub> mimics E<sub>2</sub> effects on the negative feedback on LH secretion and PR expression suggesting an action on nuclear ER signalling, but it blocked the induction of the positive feedback and the associated neuronal activation in the absence of P suggesting an antagonistic effect of E<sub>4</sub> on the membrane ER as previously shown in peripheral tissues.

## P2.34 ANDROGENIC REGULATION OF COURTSHIP BEHAVIOR VIA THE MUSCULAR SYSTEM

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Systemic androgens are important for the expression of appetitive mating behaviors. Androgens can influence mating displays via muscles that have evolved to produce rapidly oscillating acoustic signals used for mate attraction. For these superfast muscles to oscillate at high speeds (100-200 Hz), they forgo ability to produce substantial force or maintain those speeds for a prolonged time. This, however, is not the case for the muscle mediating the roll-snap mating display of the male golden-collared manakin (*Manacus vitellinus*). The roll-snap is produced by repeatedly striking the radii together as the wings are raised above the midline to produce a loud "snap." In each roll-snap there can be between 5-20 snaps at speeds of >55 Hz. Blocking peripheral androgens decreases the number and time between snaps, suggesting that this male-specific behavior is androgen-sensitive. The site of action for androgen control of roll-snaps is likely the scapulohumeralis caudalis (SH) – a humoral retractor muscle that assists in powering flight and has the contractile properties necessary to produce this rapid display. Here, we examined the how androgens influence the speed and endurance of the SH in response to increasing stimulation frequencies. Treatment with flutamide, an androgen receptor antagonist, significantly decreased the contractile speeds of the SH at all stimulation frequencies. However, there was no appreciable decrease in relative muscle endurance throughout the stimulation train (8 pulses). Along with previous results, these findings suggest that androgens act in the SH to support the superfast contractile kinetics without a trade-off in muscle endurance.

## P2.35 USING A PSYCHOPHARMACOGENETIC APPROACH TO IDENTIFY THE PATHWAYS THROUGH WHICH, AND THE PEOPLE FOR WHOM TESTOSTERONE PROMOTES AGGRESSION

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Little is known about the pathways through which testosterone promotes aggression or about the people in whom this effect is observed. In the current studies, we used pharmacological challenge paradigms to investigate the extent to which testosterone rapidly modulates human aggressive behaviour. Across two studies (Study 1, n = 120; Study 2, n = 308) we found that testosterone rapidly increased aggressive behaviour, but only among men with risky personality profiles consisting of dominance, impulsivity, and independent self-construal. In Study 2, we found that this drug x personality interaction was most robust among men with fewer cytosine-adenine-guanine (CAG) repeats in exon 1 of the androgen receptor (AR) gene, a polymorphism associated with increased AR efficiency. Testosterone's effects were rapid (~30 min after administration) and mediated, in part, by subjective reward associated with aggression. These findings suggest that testosterone may promote human aggression through an AR-related mechanism and to have stronger effects in men with the select personality profiles because it more strongly upregulates the subjective pleasure they derive from aggression. Given other evidence that testosterone regulates reward through dopaminergic pathways, and that the sensitivity of such pathways is enhanced among individuals with the personality profiles we identified, our findings may also implicate dopaminergic processes in testosterone's heterogeneous effects on aggression.

## P2.36 SEX DIFFERENCES IN JUVENILE SOCIAL RECOGNITION: ROLE OF OXYTOCIN IN THE BED NUCLEUS OF THE STRIA TERMINALIS

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The ability to recognize and respond to previously encountered conspecifics is crucial for normal social interaction. The neuropeptide oxytocin (OT) and its corresponding receptor (OTR) have been identified as a central neural system required for social behavior, and sex differences in the organization of the OT system have been linked to the sex-specific regulation of social recognition in adult rats. Here, we sought to determine the role of OTR within the posterior region of the bed nucleus of the stria terminalis (BNSTp) in the regulation of social recognition in juveniles. We first determined whether juveniles show similar temporal patterns of social recognition to adults, by testing whether 5-week-old male and female rats were able to recognize a same-sex conspecific 30, 60, or 120 minutes following initial investigation. Juvenile males showed social recognition 30 and 60 minutes following the initial encounter, but not after 120 minutes, similar to what has been previously seen in adults of both sexes. Juvenile females, however, did not show social recognition at any time point tested, indicating a developmental difference in social recognition ability in females but not in males. We are currently testing whether OT administered to the BNSTp is sufficient to induce social recognition in females and to prolong social recognition in males. Finally, we will determine the extent to which OTR expressing cells within the BNSTp are activated following social investigation in both sexes. Together, these results will provide insight into how the BNSTp-OT system regulates social recognition in juvenile animals.

## P2.37 INTERACTION BETWEEN IRISIN AND GnRH-CONTAINING NEURONS AS MARKER OF REPRODUCTIVE BEHAVIOR IN METABOLIC STRESS CONDITION IN ADULT MALE RHESUS MONKEY

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Irisin is a novel, exercise induced myokine, derived from the proteolytic cleavage of fibronectin type III domain containing protein (FNDC5) and secreted into general circulation. The presence of irisin immunoreactivity in central and peripheral tissues indicates that irisin may play a crucial role in metabolism and reproduction. Present study was conducted to identify the direct neuronal interaction between irisin and GnRH-containing neurons in the hypothalamus of rhesus monkeys under metabolic stress condition.

Four adult intact male rhesus monkeys were used for this study. Two monkeys were kept under normal fed condition while two were subjected to 48h fasting. Dual label immunofluorescence was performed on hypothalamic sections using specific antibodies.

Plasma testosterone ( $P < 0.01$ ) and blood glucose ( $P < 0.05$ ) levels showed significant reduction after 48h fasting. The number of irisin cell bodies in the ARC significantly ( $P < 0.05$ ) increased after fasting. Irisin neuronal fibers were identified making frequent contacts with GnRH perikarya in MBH area of monkeys under fed condition. Soma to soma contact were also identified between irisin and GnRH in fasting condition. Co-localization of irisin and GnRH were also evident in cell bodies under fasting condition.

Close neuronal contact between irisin nerve fibers and GnRH perikarya in the ARC area may act as contributing factor to down regulate the primate reproductive axis under metabolic challenge. Present findings also broaden the physiology of irisin regulation of the primate reproductive behavior. Furthermore, additional studies are warranted to ascertain the mechanisms by which irisin influences reproductive behavior under different conditions.

## P2.38 BLOCKING OXYTOCIN RECEPTORS IN THE DORSAL RAPHE FOLLOWING A HORMONE-SIMULATED PREGNANCY ALTERS POSTPARTUM ANXIETY-LIKE BEHAVIOR IN FEMALE SYRIAN HAMSTERS

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Peripartum mood disorders are the most common complication associated with childbirth. Despite this, the underlying neurobiological mechanisms remain poorly understood. Previous research suggests that the drop in estrogen at parturition may lead to changes in neurobiology and behavior. Indeed, our laboratory has demonstrated that estrogen withdrawal following a hormone-simulated pregnancy in female hamsters leads to an increase in oxytocin-immunoreactive neurons in the paraventricular nucleus of the hypothalamus (PVN), and a concurrent increase in oxytocin receptor density in the dorsal raphe nucleus (DRN). This neural plasticity is correlated with an increase in anxiety behavior in the elevated plus maze. We hypothesized that altered oxytocin signaling between the PVN and DRN during the peripartum period was responsible for increased anxiety behavior. To test this hypothesis, female hamsters were ovariectomized and implanted with an intracranial cannula targeting the DRN. Following recovery, all females underwent a hormone-simulated pregnancy, in which they were administered daily injections of estrogen and progesterone that approximate early and late pregnancy. After 17 days, one group of females was withdrawn from estrogen, simulating postpartum estrogen withdrawal, while the other group continued to receive estrogen injections. During this time, the behavior of all females was assessed in the open field and elevated plus maze. 10 minutes prior to each behavioral test, females were given an infusion of oxytocin antagonist or vehicle into the DRN. Preliminary results indicate an interaction between hormone condition and drug condition. Specifically, blocking oxytocin receptors decreases anxiety only in hormone-withdrawn females.

## P2.39 PREVENTING THE ACCUMULATION OF $\Delta$ FosB IN THE NUCLEUS ACCUMBENS OF FEMALE MICE DURING A HORMONE-SIMULATED PREGNANCY CHANGES ANXIETY-LIKE BEHAVIOR DURING THE PERIPARTUM PERIOD

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We have previously found that  $\Delta$ FosB, a transcription factor associated with long-term neural plasticity, is increased in the nucleus accumbens (NAc) of female mice following a hormone-simulated pregnancy. What's more, this neural plasticity is associated with alterations in anxiety like behavior. Here, we test the hypothesis that preventing the accumulation of  $\Delta$ FosB during a hormone-simulated pregnancy will ameliorate anxiety behavior following a hormone-simulated pregnancy. Female mice were ovariectomized and given bilateral stereotaxic injections into the NAc of an adeno-associated virus containing  $\Delta$ JunD, a dominant negative inhibitor of Delta FosB, or a control vector. Following recovery, all females underwent a hormone-simulated pregnancy, in which they were administered daily injections of estrogen and progesterone that approximate early and late pregnancy. After 21 days, one group of females was withdrawn from estrogen, simulating postpartum estrogen withdrawal, while the other group continued to receive estrogen injections. During this time, the behavior of all females was assessed in the open field and elevated plus maze. Preliminary data indicate an interaction between hormone condition (estrogen withdrawn vs. sustained) and virus injection ( $\Delta$ JunD vs. control). Specifically, preventing the accumulation of DeltaFosB during a hormone-simulated pregnancy did not change the high-anxiety phenotype following estrogen withdrawal. However, it did prevent the low anxiety phenotype during simulated pregnancy. This suggests that increased hormone levels during pregnancy may increase the accumulation of  $\Delta$ FosB in the NAc, resulting in a low anxiety behavioral phenotype. However, increased  $\Delta$ FosB may not be related to postpartum anxiety following estrogen withdrawal.

## P2.40 EFFECTS OF POSTPARTUM MATERNAL STRESS ON OFFSPRING BEHAVIOR IN THE ELEVATED ZERO-MAZE IN FEMALE AND MALE RATS

*Kayla C. De Lorme, Cassandra Pull, Kim Ngan Hoang, Laryssa McLouth, Ai Motomura, and Amanda V. Landaverde*

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Intergenerational trauma is the transmission of the effects of trauma from one generation to the next, and has been studied in humans in a variety of cultural contexts. There are two routes one may investigate intergenerational trauma: social transmission and epigenetic inheritance. Social transmission includes changes in parental behavior towards offspring because of the trauma, and thus, can be studied using an animal model. The present study examined the effects of postpartum maternal stress on offspring anxiety in rats, and explored differential effects of sex and age through the inclusion of both females and males during adolescence or adulthood. From postpartum days 8-10, mothers were taken from their home nest, brought into separate rooms, and put into an empty aquarium for a 5-minute acclimation period. They were then exposed to predator odor (Stressed) or control odor (Control) for 30-minutes. The offspring remained undisturbed in their home nests during the maternal stress paradigm. Pups were weaned at postnatal day (P)26 and tested for anxious behavior using the elevated zero-maze during adolescence (P37) or adulthood (P58). There was a significant maternal group x sex interaction on nose-pokes in which males in the control maternal group nose-poked into the open portion more often than the control females (regardless of age), whereas males and females did not differ in nose-pokes in the stressed maternal group. Thus, control males are more exploratory than control females, but this behavioral sex difference is eliminated with postpartum maternal stress.

## P2.41 SOCIAL EXPERIENCE MODULATES SEX-SPECIFIC ELECTROCOMMUNICATION BUT NOT STEROID HORMONES IN A TERRITORIAL APTERONOTID FISH

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Communication signals serve many functions across social context. Experience with familiar social partners can modulate the types of signals produced. These signaling dynamics are often regulated by steroid hormones that influence sex-specific differences in communication. Weakly electric apteronotid fishes communicate with electric organ discharges (EODs). Chirps, brief increases in EOD frequency, are produced during social encounters. Chirping is sexually dimorphic and responsive to steroid hormones. However, chirps are often studied in response to playbacks, so conclusions about their function are simplified. Here, we investigate how social experience modifies chirp use and the production of 11-KT and cortisol in a territorial apteronotid fish (*Apteronotus albifrons*). Fish were housed in opposite-sex pairs, same-sex pairs, or in isolation for six weeks and recorded overnight once a week. Blood samples were collected before and after treatment for hormone analysis. Although previous studies using playbacks showed males and females have similar chirp rates, we found that chirp rate varied across social context. There was a strong social novelty response, after which chirp rate declined. Chirp rate was greater on the first night of social pairings in male-male dyads, but decreased quickly, suggesting chirps may function in agonistic interactions in a context-dependent way. Individuals did not show any significant changes in 11-KT or cortisol in response to social experience. Like chirping, it is possible hormones responded earlier during the transition from isolated to social conditions. These results suggest that while social experience impacts chirp dynamics, it is not mediated by steroid hormones on this timescale.

## P2.42 VASOPRESSIN MODULATES GLUTAMATE SIGNALING IN THE LATERAL SEPTUM OF JUVENILE RATS IN SEX-SPECIFIC WAYS: IMPLICATIONS FOR SEX-SPECIFIC REGULATION OF SOCIAL PLAY BEHAVIOR

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Social play is a highly rewarding behavior, is essential for the development of social skills, and is impaired in children diagnosed with autism, a disorder with a strong sex bias in prevalence. We recently showed that the arginine vasopressin (AVP) system in the lateral septum (LS) regulates social play behavior in opposite directions in male and female juvenile rats. We further showed that glutamate (glu) is involved in the sex-specific regulation of social play by the LS-AVP system. Intriguingly, males show higher LS-glu release than females at baseline and during social play while pharmacological blockade of the AVP V1a receptor (V1aR) in the LS eliminates this sex difference by increasing LS-glu release in females only. Here, we aimed to determine the origin of the sex difference in glu release. Retrograde tracing (using cholera toxin subunit B, CtB) combined with c-Fos and vglut2 (marker for glu) was used to investigate potential sex differences in social play-induced activation of glu projections to the LS. We found that females have more activated glu projections from prefrontal cortex subregions to the LS compared to males. Males have more activated glu-positive CtB-positive neurons in the CA1 of the ventral hippocampus and periaqueductal gray. This research will help understanding the sex-specific regulation of social play, which could be an important step towards better understanding the neural basis of sex-biased social disorders such as autism.

## P2.43 SEX DIFFERENCES IN SOCIAL BEHAVIOR AND LEARNING IN THE GRAY-SHORT-TAILED OPOSSUM (*MONODELPHIS DOMESTICA*)

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Nearly all species engage in a variety of social interactions, however little is known about the laboratory opossum (*Monodelphis domestica*), a nontraditional animal model. Using a repeated measures design, with social experience as the within-subjects factor and sex as the between-subjects factor, we tested the hypothesis that social experience modulates social behavior in a sex-dependent manner (12 females, 12 males). We also investigated sex differences in the habituation-dishabituation (5 females, 5 males) and individual (social) recognition (3 females, 3 males) tasks. Same-sex dyads were tested over the course of three consecutive 10-minute social interactions, with a 24-hour inter-trial interval. Males displayed higher levels of aggression, open mouth posture, and flees compared to females; females expressed higher levels of nonsocial behavior. Levels of social behavior were highest during the first social interaction compared to subsequent trials. Interestingly, there was a social experience x sex interaction for duration of social behavior and latency to attack. Males displayed higher levels of social behavior during trial one compared to subsequent trials, whereas females showed consistently lower levels of social behavior across trials. Males' attack latency decreased over trials, whereas the females' latency increased. Both males and females habituated in response to non-social and social stimuli, and demonstrated dishabituation when presented with novel stimuli. Our results suggest that just as in rats, mice, and hamsters, previous social experience modulates the way the *Monodelphis* responds to social stimuli. Moreover, this species demonstrates non-associative learning abilities that are similar to other laboratory animals.

## P2.44 BEHAVIORAL AND EPIGENETIC CONSEQUENCES OF OXYTOCIN TREATMENT AT BIRTH

William M. Kenkel<sup>1\*</sup>, Allison M. Perkeybile<sup>1</sup>, Jason R. Yee<sup>1,2</sup>, Hossein Pournajafi-Nazarloo<sup>1</sup>, Travis S. Lillard<sup>3</sup>, Elizabeth F. Ferguson<sup>3</sup>, Kelly L. Wroblewski<sup>3</sup>, Craig F. Ferris<sup>2</sup>, C. Sue Carter<sup>1†</sup>, and Jessica J. Connelly<sup>3†</sup> †authors contributed equally to this work

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Oxytocin is used in a pproximately half of all births in the U.S. during labor induction and/or augmentation. However, the effects of maternal oxytocin administration on offspring development have not been fully characterized. Here, we used the socially monogamous prairie vole to examine the hypothesis that oxytocin exposure at birth can have long-term developmental consequences. Maternally administered oxytocin increased methylation of the oxytocin receptor (*Oxtr*) in the fetal brain. As adults, oxytocin-exposed voles were more gregarious, with: increased alloparental caregiving towards pups and increased close social contact with other adults. Cross-fostering indicated that these effects were the result of direct action on the offspring, rather than indirect effects via postnatal changes in maternal behavior. Male oxytocin-exposed offspring had increased oxytocin receptor density and expression in the brain as adults. These results show for the first time, long-term effects of perinatal oxytocin that may be mediated by an epigenetic mechanism.

## P2.45 TESTOSTERONE RECEPTOR, TRPM8, REGULATES SEXUAL REWARD AND SATIETY

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Testosterone regulates dimorphic sexual behaviors in all vertebrates. However, the molecular mechanism underlying these behaviors remains unclear. Here, we report that a newly identified rapid testosterone signaling receptor, TRPM8, regulates dimorphic sexual behaviors. We found that despite higher steroid milieu, TRPM8<sup>-/-</sup> male mice exhibit a delayed sexual satiety, increased mounting frequency indiscriminate of sexes, and increased aggression compared to controls, while TRPM8<sup>-/-</sup> females display increased olfaction-exploratory behaviors. Furthermore, neuronal responses to acute testosterone application on amygdala were attenuated in TRPM8<sup>-/-</sup> males but remained unchanged in females. Moreover, activation of dopaminergic neurons in the ventral tegmental area following-mating was impaired in TRPM8<sup>-/-</sup> males. Together, these results suggest that TRPM8 mediates sex-reward mechanism in males, and its depletion leads to a delayed sexual satiety phenomenon.

## Poster Session III

Saturday, June 22, 2019, from 3:30pm to 5:30pm

### P3.1 LC-MS/MS PROFILING OF SYSTEMIC AND BRAIN STEROID LEVELS IN A SONGBIRD

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In some species, territorial aggression is expressed in the non-breeding season, when the gonads are regressed and circulating levels of sex steroids are very low. In such species, brain-derived steroids ("neurosteroids") might promote non-breeding aggression. Here, in wild territorial male song sparrows, we measured steroids using liquid chromatography-tandem mass spectrometry (LC-MS/MS), a cutting-edge technique that is highly specific and sensitive and allows simultaneous measurement of multiple analytes. We examined a panel of 10 steroids: pregnenolone, progesterone, corticosterone, dehydroepiandrosterone, androstenedione, testosterone, 5 $\alpha$ -dihydrotestosterone (5 $\alpha$ -DHT), 17 $\beta$ -estradiol (E2), 17 $\alpha$ -estradiol, and estrone. We explored seasonal changes in steroids in the blood and in 10 microdissected brain regions that regulate social behavior. As expected, systemic androgen levels were higher in the breeding season. Furthermore, in the breeding season, 5 $\alpha$ -DHT levels were 20-fold higher in specific regions than in blood. In addition, E2 and estrone were detectable in the brain but not in the blood. In breeding and non-breeding seasons, progesterone varied across brain regions, despite similar levels in the circulation. Taken together, these results indicate that steroid levels are locally regulated within the brain and are not a simple reflection of levels in the circulation. For the first time in songbirds, we measured a panel of bioactive sex steroids and their precursors with great spatial resolution in the brain and obtained a clearer picture of natural neuroendocrine fluctuations in wild animals. These data suggest that steroid profiling by LC-MS/MS will be broadly useful and open the door for a new era of comparative neuroendocrinology.

### P3.2 INJECTIONS OF A V1aR ANTAGONIST INTO THE DORSAL RAPHE AND LATERAL HABENULA ALTER COMMUNICATION IN MALE MICE

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The neuropeptide arginine-vasopressin (AVP) has long been implicated in the regulation of social behavior and communication in diverse taxa, often through its actions on the V1a receptor (V1aR) and in a sex-different and steroid-dependent way. One source of sex-different brain AVP is the steroid-sensitive and sexually-dimorphic AVP neurons in the bed nucleus of the stria terminalis (BNST). Indeed, we have demonstrated that these BNST-AVP neurons regulate social behavior in a sex-dependent manner. Potential targets of these BNST-AVP cells include the

dorsal raphe (DR) and lateral habenula (LHb), areas known to be important for social behavior, yet few studies have investigated AVP action within these regions. Consequently, to test if V1aR action in the DR or LHb control social behavior in a sexually dimorphic manner, we administered a highly-specific V1aR antagonist (or saline vehicle) in the DR and LHb of C57BL/6 male mice and tested its effects on social investigation, social communication (urine marking, ultrasonic vocalizations (USV)), and territorial aggression. Preliminary results indicate that injecting the V1aR antagonist into the DR changed the repertoire of USV syllables produced toward females, whereas injecting it into the LHb reduced overall USV production. Additionally, V1aR antagonist injections into the DR increased investigation of male competitors and decreased urine marking toward males. Further work on DR/LHb in female mice will reveal if V1aR in the DR and LHb drive sex differences in social behavior and communication.

### P3.3 INDEPENDENT AND INTERACTIVE EFFECTS OF SHORT-TERM ESTROGEN REPLACEMENT AND LONG-TERM PHYSICAL ACTIVITY POST MENOPAUSE ON BRAIN AND BEHAVIOR

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We characterized the long-term, interactive effects of transient estrogen replacement (TER) and continuous physical activity (CPA) on brain and behavior in a rodent model of menopause. Middle-aged rats were ovariectomized and replaced with estradiol (E2) or vehicle (VEH) implants. Rats were placed in running wheels 2h/d for 5d/wk thereafter. However, wheels were locked for half the rats in each group. Implants were removed 6 wks after ovariectomy and 4 wks later behavior was assessed in an open field (OF), elevated plus maze (EPM), and Morris water maze (MWM). Voluntary wheel running was higher in E2 versus VEH runners and after implants were removed, although there was a significant decline in activity in E2 pre-exposed runners, they still ran twice as much as VEH pre-exposed runners, on average. All groups habituated to the OF although E2 pre-exposed rats travelled a greater distance relative to VEH pre-exposed rats. E2 pre-exposed rats spent more time in the open areas of the EPM and travelled a greater distance in the open arms than VEH pre-exposed rats. There were no differences between groups in spatial learning or memory in the MWM. However, E2 pre-exposed rats began to widen their search for the platform within the target quadrant after the first 30s of the probe trial, relative to VEH pre-exposed rats. Preliminary analyses indicate a TER x CPA effect on whole brain weight as well as hippocampal neurogenesis and neuroinflammation. Thus, postmenopausal neural and behavioral plasticity can be differentially modulated by mono- or combination-therapy approaches.

### P3.4 ROLE OF ANDROGEN RECEPTORS DURING SEXUAL DIFFERENTIATION OF THE RAT BRAIN

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The brain differentiates into a female brain unless testosterone (T) is present during a critical window of time. In rats, there is a surge of T around the time of birth (perinatal period; PP). The purpose of this study was to examine the effects of blockade of androgen receptors (AR) during the PP using flutamide (F) on adult rat behaviors such as open field (OF), spatial working memory (SWM) and sexual motivation (SM) as well as the expression of AR and estrogen receptors (ER)- $\alpha$  and ER- $\beta$  in the hippocampus, hypothalamus, and amygdala. Four timed-pregnant rats were divided into two groups: experimental group received F during PP whereas the control group received vehicle. Adult male rats underwent SM testing where they were exposed to an estrus and an ovariectomized rat. Both groups spent more time with the estrus rat suggesting that SM was not affected by AR blockade. Furthermore, male

rats receiving F exhibited anxiety-like behavior. Spatial working memory test measured the amount of time spent in the arms with or without food. There was no significant difference in the time spent with food by either of the groups suggesting a lack of effect of AR in SWM. Reverse-phase PCR was carried out to quantify the levels of AR, ER- $\alpha$ , and ER- $\beta$  in the hippocampus, hypothalamus, and amygdala using  $\beta$ -actin as an internal control. The expression of any of the receptors studied was not altered by the blockade of AR suggesting its limited role in causing anxiety-like behavior.

### P3.5 GPER-1 ACTIVATION DIFFERENTIALLY ALTERS PREFERENCE FOR COCAINE IN MALE AND FEMALE RATS

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There are sex differences in susceptibility to addiction and drug-taking behaviors. A higher percentage of female rodents prefer cocaine to natural rewards than males do and females are more motivated than males to attain drugs of abuse. Research from the Becker Laboratory has shown that these heightened addiction-like behaviors in females are modulated by estradiol, where estradiol potentiates cocaine-induced dopamine levels in the dorsal striatum (dSTR). The role of estradiol, and other gonadal hormones, on addiction-like behaviors in males, however, is not well understood. The current experiment used ICI 182,780 (ICI) and G1 to manipulate estradiol receptors (ER) (ER $\alpha$ , ER $\beta$  and GPER-1) in the dSTR. The first experiment used a conditioned place preference paradigm to determine whether ER manipulation alters preference for 10mg/kg cocaine in male or female rats. We found that treatment of ICI (ER $\alpha$ / $\beta$  antagonist and GPER-1 agonist) or G1 (GPER-1 agonist) into the dSTR of male rats blocks the preference for cocaine. Neither treatment alters female's preference. These data suggest that GPER-1 regulates preference for cocaine in males only. The second experiment utilized qPCR to investigate GPER-1 expression within the dSTR between the sexes and found no difference. Together, these data suggest that GPER-1 activation decreases the rewarding effects of cocaine in males, but not females. Furthermore, it appears that there are sex differences in the effect of estradiol receptor activation on motivation for drugs of abuse: enhancing motivation in females while attenuating motivation in males.

### P3.6 THE ROLE OF ANTIDEPRESSANTS ON ZEBRA FINCH PAIR BOND MAINTENANCE

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Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are a highly prescribed drug. Yet, the exact neurobiological mechanisms, as well as its impacts on social relationships, are not well understood. A recent study found that, in female Eurasian starlings, exposure to ecologically relevant doses of fluoxetine (Prozac) reduced the amount of courtship behaviors they received by males, indicating that these females may have been considered less attractive as mates (Whitman et al., 2018). The aim of the present study was to test the effects of physiological SSRI dose on male and female courtship and pairing behavior in zebra finches. Eurasian starlings and zebra finches are closely related songbirds in which males perform courtship behaviors to a preferred female and the female chooses a mate based on those behaviors. I hypothesized that injecting fluoxetine weakens the strength of a previously established pair bond after a 48-hour separation period. I allowed pair bonds to form in mixed sex aviaries for two weeks then injected four birds of one sex with either one of two doses of fluoxetine (5mg/kg or 10mg/kg) dissolved in 0.9% sterile saline, or 0.9% sterile saline (control) into the pectoral muscle for three consecutive days. Pairs were then separated for 48 hours and the focal subject was tested in a 2-choice preference test. Following injections, males, but not females, exhibited significant differences in pair bonding behaviors. While in the 2-choice preference tests, both sexes exhibited a significant difference in time spent near their established mate.

### P3.7 DO PRENATAL EDC EXPOSURES INCREASE VULNERABILITY OF PERIADOLESCENT FEMALE RATS TO MALE SEXUAL AGGRESSION?

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Endocrine-disrupting chemicals (EDCs) are ubiquitous in our environment. Prior work has shown that prenatal EDC exposures cause latent effects on brain development and behavior. Heightened stress reactivity during adolescence also produces lasting effects on adult phenotypes. However, the potential interaction of two such insults is unknown. Here, we tested whether prenatal EDCs altered the behaviors and stress reactivity in female rats exposed to vinclozolin (a fungicide), a PCB mixture, or vehicle (n=18) in utero from E8-18. From P35-41, females were given 30-minute sessions of either sexual conspecific aggressive response (SCAR) with a sexually-experienced adult male, or no exposure (n=9) every other day. One hour after their last SCAR, animals were euthanized (n=30). A one-way ANOVA showed marginally significant EDC treatment effects on timing of vaginal opening (VO) ( $F_{2,48} = 2.993$ ,  $p = 0.059$ ). A bootstrap analysis of these data showed that the F value of the difference in VO timing across EDC treatment groups had a probability of occurring twice every hundred times (i.e.,  $p \approx 0.0248$ ). A linear regression showed a significant relationship between VO timing and the number of mounts a female received across all SCAR sessions ( $F_{1,23} = 7.171$ ,  $p = 0.0134$ ). Thus, EDCs influence pubertal timing of female rats, which in turn influences how sexually experienced, adult male rats behave towards them during SCAR. Ongoing hormone assays and immunohistochemistry will provide additional insights into how prenatal and adolescent insults may interact in causing an adverse stress response.

### P3.8 GLUCOCORTICOID PROFILING VIA LC-MS/MS IN BLOOD AND MICRODISSECTED BRAIN REGIONS: EFFECTS OF AN EARLY-LIFE STRESSOR

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Glucocorticoids (GCs) are steroids secreted by the adrenal glands and play critical roles in stress responses, immunity, and development. From post-natal day (PND) 2 to 12, mice show greatly decreased adrenal GC secretion at baseline and in response to stressors, termed the stress hypo-responsive period (SHRP). During the SHRP, baseline GC levels are higher in the brain than in the blood, suggesting local GC production. We hypothesized that the brain rapidly increases local GC production in response to an acute stressor. Here, we administered 5% isoflurane (an anesthetic and stressor) in oxygen, oxygen (vehicle control), or neither (baseline) to PND5 and PND13 mice. Mice were exposed to either isoflurane or oxygen for 3 min and euthanized at 30 min. Baseline animals were immediately euthanized after removal from the home cage. Using liquid chromatography tandem mass spectrometry (LC-MS/MS), we measured 7 steroids in blood, hypothalamus, cerebral cortex, and hippocampus with a high degree of specificity and sensitivity. At PND5, isoflurane had little effect on corticosterone levels in the blood, but increased corticosterone levels in the brain in a region-specific manner. At PND13, isoflurane increased corticosterone levels in the blood and brain, with a greater increase in blood than in brain. Taken together, these data indicate that during the SHRP, the brain increases local GC production in response to an acute stressor. These novel data indicate that the brain actively regulates local GC levels rather than simply being a passive recipient of systemic GCs produced by the adrenal glands.

### P3.9 EXAMINING THE ROLE OF OXYTOCIN IN RESPONSE TO AVERSIVE VOCAL STIMULI FOLLOWING PAIR BOND FORMATION

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While the behavioral phenotype of an individual animal is generally considered to be fixed in social isolation, the social environment within which an animal exists can lead to alterations in behavioral responses. However, in monogamous vertebrates, little is known about how the formation of a pair bond modulates the behavioral phenotypes of the individuals within the pair bond. Recent evidence from our lab suggests that individuals of the monogamous bi-parental California mouse (*Peromyscus californicus*), displaying either proactive or reactive phenotypes, exhibit behavioral plasticity following pair bond formation; in an aversive vocal stimulus-approach task (VSAT), pair bonded individuals altered their behavior to become more similar to their mate. It is likely that social recognition and mate awareness are necessary to induce this behavioral change, however little is known about the biological mechanisms underlying behavioral plasticity following pair bonding. In the present study, we examined changes in approach behavior to an aversive conspecific vocal stimulus before and after pair bonding in conjunction with the administration of intranasal oxytocin (OT), a neuropeptide known to modulate several social behaviors, including individual discrimination and social bonding. We are also investigating the neural correlates of behavioral plasticity following the aversive VSAT and OT administration in pair bonded individuals by examining changes in immediate early gene (IEG) expression in the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAc), regions critical to social decision-making.

### P3.10 TAMOXIFEN OR ESTRADIOL LIMITED TO THE INDUCTION PHASE ENHANCE THE EXPRESSION OF LOCOMOTOR SENSITIZATION TO NICOTINE 9 DAYS LATER IN OVARECTOMIZED AND INTACT FEMALE RATS

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Estradiol (E2) enhances nicotine-induced locomotor sensitization in rodents, but whether E2 is required during the induction phase and/or the expression phase is unknown. Here, ovariectomized (OVX) female rats were injected with 5µg estradiol benzoate (EB) 30 minutes before two nicotine (0.4mg/kg) administrations (induction phase), on challenge day (9 days later), at both time points, or at neither time point (4 groups, n=12/group). On each day that rats were given nicotine, locomotor activity (distance travelled) was quantified for 1hr after injection; sensitization was defined as the increase in distance travelled from induction to expression. Rats given EB during induction traveled further on expression day than on induction (p<0.001), while OIL pre-treated rats travelled equal distances during induction and expression (p=0.23). These results were replicated in Expt 2., where we administered 10µg of E2 instead of 5µg EB. Next, gonadally intact (Expt 3) or OVX (Expt 4) rats were administered the selective estrogen receptor modulator tamoxifen (1mg/kg) during the induction phase only. Tamoxifen enhanced expression of sensitization relative to OIL vehicle in both intact (p=0.021) and OVX (p <0.001) females. Although EB, E2 and tamoxifen all enhanced sensitization, EB and E2 are agonists of all forms of estrogen receptors, whereas tamoxifen is an antagonist of intracellular estrogen receptors [ER $\alpha$ /ER $\beta$ ] and an agonist of membrane bound g-coupled protein estrogen receptor 1 [GPER1]). Thus, E2 during induction enhanced expression of sensitization, even when absent at expression, which may involve actions at GPER1 (rather than ER $\alpha$  and ER $\beta$ ).

### P3.11 MINERALOCORTICOID RECEPTORS ARE REQUIRED FOR THE DEVELOPMENT AND MAINTENANCE OF CA2'S MOLECULAR PROFILE AND FOR CA-2-DEPENDENT BEHAVIOR

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Exposure to stress is a risk factor in the development, onset, and exacerbation of several neuropsychiatric disorders, including depression, schizophrenia, and PTSD. Mineralocorticoid receptors (MRs) are critical for regulating behavioral responses to stress, and within the hippocampus, their highest expression is in area CA2. CA2 pyramidal neurons have a distinct molecular makeup resulting in a plasticity-resistant phenotype that distinguishes them from cells in CA1 and CA3. Thus, we asked whether MRs regulate CA2 neuron properties and related

behaviors. Using three conditional knockout methods at different stages of development, we found a striking decrease in all tested CA2 markers, an effect mimicked by chronic antagonism of MRs. Furthermore, embryonic deletion of MRs also disrupted input into the hippocampus from the supramammillary nucleus and enabled synaptic potentiation of the normally LTP-resistant synaptic currents in CA2. We also found that CA2-targeted MR knockout was sufficient to disrupt behaviors observed with whole brain MR deletion. MR knockout mice exhibited normal social investigation behavior; however, these mice failed to discriminate between a familiar and a novel conspecific. In addition, MR knockout mice showed hyper-reactivity in response to novel objects. Finally, we tested the mice for anxiety-like behavior in an elevated plus maze and found that mice with a CA2-targeted deletion of MRs spent more time in the open arms of the maze, suggesting an anxiolytic-like behavioral phenotype. Together, these results demonstrate a novel role for MRs in regulating CA2's molecular profile and provide insight into their role in regulating CA2-related behavior.

### P3.12 TRKB ACTIVATION IS REQUIRED FOR 17 $\beta$ -ESTRADIOL-INDUCED ENHANCEMENT OF HIPPOCAMPAL MEMORY CONSOLIDATION

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The potent estrogen 17 $\beta$ -estradiol (E2) is known to enhance memory consolidation in object placement (OP) and object recognition (OR) tasks, however the molecular mechanisms underlying these effects are not fully understood. Brain derived neurotrophic factor (BDNF) is an important regulator of hippocampal memory and is also known to interact with E2, however whether BDNF plays a mechanistic role in E2-induced enhancement of memory consolidation remains unknown. Previously, we demonstrated that infusion of E2 into the dorsal hippocampus (DH) leads to increases in BDNF and pro-BDNF proteins via epigenetic modification of *Bdnf* gene promoters. Here, we examined the role that BDNF signaling with its receptor TrkB may play in the effects of E2 on hippocampal memory consolidation. To determine whether TrkB activity is required for the memory enhancing effects of E2, female C57BL/6 mice were ovariectomized and cannulated in the DH and dorsal third ventricle. Immediately following object training, mice were infused with vehicle or a non-memory impairing dose of ANA-12, a TrkB antagonist, into the DH and vehicle or E2 into the dorsal third ventricle. Object placement or object recognition memory was then tested 24 or 48 hours later, respectively. We found that ANA-12 blocked the memory-enhancing effects of E2, suggesting that BDNF/TrkB signaling is necessary for E2-induced memory enhancement. Current work is examining the molecular mechanisms that couple E2 to TrkB activation in the DH. In sum, this work will provide new insight into how E2 exerts its effects on hippocampal memory consolidation.

### P3.13 HORMONAL RESPONSES TO BOTH REAL AND SIMULATED SOCIAL CHALLENGES IN A COMPETITIVE FEMALE BIRD

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Many male vertebrates respond to aggressive encounters by elevating circulating testosterone (T) levels. Though there is growing evidence that female aggression is adaptive and that females can make and respond to T, we still lack a full understanding of how females hormonally respond to social challenges. We addressed this question in tree swallows (*Tachycineta bicolor*), a system in which females compete for limited nesting sites and female aggression is at least partially mediated by T. Here, we induced social challenges and measured T responses in pre-laying females in two ways: (1) using decoys to simulate territorial intrusions and (2) experimentally removing nesting sites to increase competition. We found that females did not elevate circulating T levels following real or simulated social challenges, despite showing aggressive responses, which stands in sharp contrast to our previous finding that females are physiologically capable of elevating T during this same breeding stage. Future work will investigate potential alternative mechanisms for responding to social challenges, such as socially modulating local (i.e., neural) T sensitivity instead of systemic T levels.

### P3.14 GESTATIONAL EXPOSURE TO POLYCHLORINATED BIPHENYLS SHOW SEX AND BRAIN REGION SPECIFIC EFFECTS ON DOPAMINE MODULATING SYSTEMS IN ADOLESCENT RATS

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Polychlorinated biphenyls (PCBs) are environmental contaminants known to be acutely neurotoxic, immunotoxic, and endocrine-disrupting. However, little is known about how PCBs affect hormone-sensitive immune signaling in the brain. Exposure to PCBs is highest during gestation and infancy, periods crucial to neurodevelopment and sensitive to hormones and therefore perturbation. Development of dopaminergic systems linked to reproductive and behavioral maturity continue to occur through adolescence. Dopaminergic signaling is sensitive to disruption by both PCBs and neuroinflammation. Therefore, this study tests the hypothesis that perinatal PCB exposure with or without later inflammatory challenge alters expression of dopaminergic genes in hypothalamic and mesocorticolimbic systems in adolescence. To do so, Sprague-Dawley rats were exposed to an environmentally relevant mixture and dose of PCBs (or vehicle) perinatally and adolescent offspring were given lipopolysaccharide (LPS, or vehicle) 3-4 hours prior to brain tissue collection. Exposure to PCBs increased expression of both *Drd1a* and *Drd2* dopamine receptors only in males in the hypothalamus but not midbrain, prefrontal cortex, or striatum. Given the greater hormone sensitivity of the hypothalamus relative to the other brain regions studied, and the sex-specific effects, these results indicate endocrine mechanisms of PCB action. These adolescent results differ from those found in neonatal animals, where dopaminergic enzymes and transporters but not receptors were altered by PCBs. It is possible that neonatal changes in outcomes related to dopamine content later drive adolescent changes in dopamine sensitivity. This highlights the importance of studying endocrine disrupting compounds in both sexes and in developmental contexts.

### P3.15 DEVELOPMENTAL EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBS) ON ACTIVATIONAL MORPHOLOGY OF MICROGLIA IN THE ADULT BRAIN

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Polychlorinated biphenyls (PCBs) are environmental contaminants known to cause sex-specific changes in hormone signaling in the brain as well as perturbations in peripheral immune function. The possible effects on microglia, an immune cell in the brain, however, are not known. This study tests the hypothesis that developmental exposure to PCBs has sex-specific effects on microglia in the adult prefrontal cortex, either on basal number or activational status, or microglial responses to an immune challenge by lipopolysaccharide (LPS). Pregnant Sprague-Dawley rats were given an environmentally relevant mixture and dose of PCBs or oil orally during gestation. Adult offspring were given an injection of LPS or saline 24 hours prior to euthanasia. Immunohistochemistry was performed to label microglia with IBA1 and then quantify activational status. Microglia tend to exist in a ramified state under basal conditions, and become hyperramified and then reactive upon detecting inflammatory signals. Preliminary data indicate that males are more sensitive to the low doses of LPS used in this experiment, as males exposed to LPS showed more hyperramified microglia than saline exposed animals. However, effects of PCBs and interactions between PCB and LPS on the number of ramified and reactive microglia was found in females but not males. Analysis of tissue co-labeled for IBA1 and TLR4 is ongoing. These results indicate that developmental PCBs can alter microglial activity in the adult brain; this is of great interest given the role of microglia and neuroimmune functions in a host of neural disorders.

### P3.16 MELATONIN FACILITATES SEASONAL CHANGES IN STEROIDOGENESIS AND AGGRESSIVE BEHAVIOR IN MALE SIBERIAN HAMSTERS

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Numerous studies across animal taxa have demonstrated a positive correlation between gonadal steroids and aggression during the breeding season. However, it is becoming increasingly clear that alternative neuroendocrine mechanisms, which are independent of circulating gonadal steroids, are critical in modulating aggressive behavior. Such mechanisms are particularly important for seasonally-breeding animals that are more aggressive during the short-day (SD) photoperiods of the non-breeding season, despite gonadal regression and reduced circulating steroid levels. While the mechanisms underlying SD aggression are not well understood, previous work from our lab suggests that the pineal hormone melatonin and the adrenal androgen dehydroepiandrosterone (DHEA) are important in facilitating non-breeding aggression in Siberian hamsters (*Phodopus sungorus*). To investigate the role of melatonin in mediating seasonal changes in steroid synthesis and aggressive behavior, we housed male hamsters in long days (LD) or SD, treated them with either timed melatonin or saline injections, and quantified aggression after 9 weeks of photoperiodic housing. Following behavioral testing, we assessed whether melatonin mediates seasonal changes in steroidogenesis by measuring circulating hormone levels and neurosteroid levels in regions of the social behavior network that are associated with aggressive or reproductive behaviors. LD hamsters administered melatonin (LD-M) exhibited SD-like levels of aggression. Interestingly, LD-M and SD animals reduced circulating DHEA and T in response to an aggressive encounter, whereas LD animals elevated circulating androgens. Neurosteroid profiles will also be presented and compared across brain regions and seasonal phenotypes. Collectively, this study provides insight into how melatonin modulates the neuroendocrine circuits underlying seasonal aggression.

### P3.17 ROLE OF VASOPRESSIN IN THE VENTRAL PALLIDUM IN REGULATING JUVENILE SOCIAL PLAY BEHAVIOR

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Social play is predominantly displayed by juveniles of many mammalian species, including rodents and humans. Engagement in social play helps develop social competence throughout life. Children diagnosed with autism spectrum (ASD) show decrease involvement in social play. Moreover, ASD is more prevalent in males than females. Thus, there is a need to better understand the neural mechanisms underlying social play in both sexes. We recently showed that vasopressin acting in the lateral septum (LS) of juvenile rats regulates social play behavior in a sex-specific manner. Vasopressin projections to the LS originate in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA). We further showed that the ventral pallidum (VP) also receives vasopressin projections from these two regions. Here, we hypothesized that, similar to the LS, vasopressin in the VP regulates social play in a sex-specific manner. We found that the VP and LS show a similar sex difference in vasopressin fiber density, with denser vasopressin fibers in juvenile males. In contrast, VP and LS show a brain region-specific sex difference in vasopressin 1a receptor (V1aR) binding density, with denser V1aR binding in the female LS and male VP. Using a specific V1aR antagonist, we are currently determining the effects of V1aR blockade in the VP on social play behavior in juvenile males and females. This study will provide insights into the brain regions recruited by vasopressin for the regulation of social play behavior as well as the larger neural network modulated by the BNST/MeA-vasopressin system.

### P3.18 EFFECTS OF SOCIAL INSTABILITY STRESS IN ADOLESCENCE IN FEMALE RATS ON SOCIAL INTERACTION AND GENE EXPRESSION IN SOCIAL BRAIN REGIONS

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Adolescence is an important time of development of social brain regions. Social instability stress in adolescence (SS; daily 1h isolation+change of cage partner postnatal days [P] 30-45) leads to deficits in social behavior in SS rats compared with controls (CTL) in males; less is known in females. In expt1, SS and CTL male and female rats underwent a social interaction (SI) test soon (P46) or long (P70) after the SS. Irrespective of time post-stress and sex, SS rats spent less time in SI than CTL rats ( $p=0.002$ ), although females spent less time in SI than males ( $p<0.001$ ). Thus, these results replicated our previous findings of decreased SI after SS in males and extend them to females. In expt2, the effect on SI in females was not replicated (smaller sample). Nevertheless, SS females had higher corticosterone concentrations and lower Zif268 immunoreactive cell counts in the cingulate and infralimbic cortices after SI than did CTLs at P46 (all  $p<0.01$ ) and did not differ from CTLs at P70. In expt3, brains were collected at P46 and P70 for RT-qPCR. Effects of SS on expression were observed for glucocorticoid receptor, mineralocorticoid receptor, and oxytocin receptor that depended on age and brain region (prefrontal cortex, hippocampus). There was effect of SS for corticotrophin releasing hormone receptor or vasopressin receptor1 at either age. These results extend our findings of long-lasting heightened responses to psychostimulants and decreased spatial memory after SS in females to show that their social development also is altered.

### P3.19 NEUROPROTECTION OF SPHINCTER MOTONEURONS WITH GONADAL HORMONES AFTER SPINAL CORD INJURY

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Spinal cord injury (SCI) results in lesions that destroy tissue and spinal tracts, leading to deficits in locomotor function. We have shown that after SCI, surviving somatic motoneurons undergo dendritic atrophy that can be prevented by treatment with gonadal hormones. SCI also results in deficits in autonomic function, with urinary problems being the most common reported by SCI patients. Here we tested if treatment with estradiol (E) and dihydrotestosterone (DHT) has similar protective effects on sphincter motoneuron structure and function after SCI. Gonadally intact young male rats received either a sham or a T9 contusion injury. Immediately following contusion, rats were implanted with subcutaneous Silastic capsules filled with E and DHT or left blank. Urinary void frequency and volume were measured at 3 weeks after SCI. One week later, motoneurons innervating the external urethral sphincter (EUS) muscle were labeled with cholera toxin-conjugated HRP, and dendritic arbors were reconstructed in three dimensions; lesion volume, and tissue sparing were also assessed. Void frequency decreased and void volume increased after SCI; both were dramatically improved by treatment with E+DHT. Contusion injury resulted in large spinal cord lesions, and treatment with E+DHT had no effect on lesion size or spared white and gray matter. Similar to what we have previously reported for somatic motoneurons, dendritic length in EUS motoneuron was decreased by 42% after SCI, and this atrophy was prevented by treatment with E+DHT. Together, these results indicate that the use of gonadal hormones could be an effective treatment after SCI.

### P3.20 TUMOR-INDUCED COGNITIVE DYSFUNCTION: A ROLE FOR ESTROGENS?

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Breast cancer patients frequently experience cognitive dysfunction during and after treatment. Recent studies indicate the cause of cognitive impairment is likely multi-modal; chemotherapy, tumor biology, surgery, stress, and hormones are all potential contributors. The majority of breast cancer patients are post-menopausal, and therefore have low levels of circulating estrogens. Additionally, many survivors are treated with long-term (>20 years) estrogen receptor antagonists or aromatase inhibitors. Therefore estrogens, which are involved in modulation of cognition, might be involved in cancer-related cognitive impairment. We investigated the effects of a breast cancer tumor and its removal on cognitive performance and serum estradiol-17 $\beta$  (E2) in a mouse model of breast cancer. Intact and ovariectomized (OVX) mice were given tumors (or sham surgery), and half of the tumors were subsequently resected (survivors). OVX mice performed more poorly than intact mice during cognitive tasks such as the novel object recognition and fear conditioning tests, and the presence of a tumor reduced performance further. Uteri weighed less and serum E2 concentrations were reduced with ovariectomy, but E2 was modulated by tumor and tumor resection. Intact mice with tumors had disrupted estrous cycles; they spent more days in diestrus (and fewer days in metestrus), and some tumor-bearing mice discontinued cycling. Lastly, hippocampal expression of estrogen receptor  $\alpha$ , pro-inflammatory Il-1 $\beta$  and Il-6, and synaptogenesis genes Syn and Bdnf was modulated with tumors and tumor resection. Thus, neural inflammation and synaptic plasticity, both estrogen-mediated events, are potential contributors to the observed cognitive dysfunction.

### P3.21 DO CAVITY-NESTING SPECIES HAVE REDUCED SEXUAL DIMORPHISM IN GENE EXPRESSION AND HORMONAL VARIATION?

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In many animals, aggression is critical for competition over nest sites, and can determine which individuals get to reproduce. This is particularly true for cavity-nesting birds that must locate cavities to nest. In cavity-nesting species, both males and females compete to acquire and defend nesting territories in addition to males. Female aggression has only recently been recognized as an adaptive behavior and how its underlying genomic and hormonal mechanisms compare to those of males is not well understood. We compare circulating testosterone (T) along with neural gene regulation of sex steroid receptors influencing aggression between male and female cavity- and non-cavity-nesters, to understand how both gene expression, and hormonal modulation of the behaviors they regulate, might contribute to functional adaptations of the cavity-nesting phenotype. If selection acts similarly on the sexes within cavity-nesters but not their close relatives, we might expect reduced sexual dimorphism in hormonal and gene expression profiles across cavity-nesters. This hypothesis is supported in a pair of species (family Turdidae) during territorial establishment: testosterone (T) levels in cavity-nesting *Sialia sialis* females were significantly higher compared to non-cavity-nesting *Turdus migratorius* females, but males did not differ in T levels. These results are consistent with the hypothesis that convergent selection on male and female cavity-nesters to compete over territories could minimize sex differences in underlying mechanisms, via 'masculinization' of females.

### P3.22 SEASONAL SHIFTS IN NEURAL GENE EXPRESSION IN A TERRITORIAL FEMALE SONGBIRD

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Aggressive behaviors typically decline seasonally as animals transition from a period of intense social instability to parental care, and decades of research in males suggests declining testosterone (T) levels mediate this seasonal pattern. However, in females, which can face reproductive consequences of elevated T even prior to the arrival of offspring, it is still unclear how aggression is regulated. An emerging model organism for female-female competition

is the tree swallow (*Tachycineta bicolor*), the females of which fiercely compete for territories early in the breeding season. Aggression in these females is, in part, T-mediated; however, females demonstrate the ability to display aggression past the seasonal decline in T that occurs during incubation. Here, we use RNA-seq to explore seasonal patterns of gene expression across three behaviorally relevant neural tissues (hindbrain, nucleus taenia, and hypothalamus) and test the hypothesis that aggression-related genes show differential expression from territory establishment to incubation. We found hundreds of differentially expressed genes in the nucleus taenia and hypothalamus, while expression in the hindbrain remained relatively stable. Gene Ontology analyses revealed that processes related to neural plasticity changed across breeding stages, along with processes related to activity, self-maintenance, and immune function. We also found a potential shift in the neurogenomic mechanisms regulating aggression, with genes related to sex steroids being upregulated during territory establishment and non-steroidal genes (e.g., nonapeptides) being upregulated during incubation. Collectively, these data highlight important gene regulatory pathways that may underlie behavioral plasticity in females.

### P3.23 METHOD MATTERS; CONSIDERATIONS FOR REPORTING HPA NEGATIVE FEEDBACK

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Because of the importance in being able to shut down the glucocorticoid response once a stressor is over, many researchers have become increasingly interested in assessing the hypothalamic-pituitary-adrenal (HPA) negative feedback system. However, there are several defensible ways to report negative feedback efficacy, each of which incorporates various aspects of HPA physiology. Here, we review six different methods for reporting HPA negative feedback and their prevalence in the literature, and reanalyze a dataset of wild house sparrows (*Passer domesticus*; n=58) caught during different life history stages to show that even though most of the methods give values that are correlated with each other, they yield distinct statistical results. Because the method of reporting negative feedback matters so much for the end results, we encourage researchers to converge on a common method for reporting HPA negative feedback, or at the very least, make raw data available so alternative measures can be calculated. We also advise caution in comparing results among studies using different methods to assess HPA negative feedback.

### P3.24 RE-EVALUATING TESTOSTERONE AS A PHENOTYPIC INTEGRATOR

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Testosterone (T) co-regulates many different fitness-related traits, generating an integrated set of phenotypes that work well together, e.g. courtship displays, aggression, and enhanced spermatogenesis during social competition. Thus, T is thought to play a central role in behavioral evolution; however, its structure and function are highly conserved over millions of years of evolution. This apparent paradox may be resolved if the evolution of T-mediated traits is achieved via independent regulation of one or more components of endocrine systems. Here, we evaluate regulation and evolution of these integrated phenotypes, focusing on T, its cognate receptor (androgen receptor) and related endocrine components. We pose predictions about the endocrine mechanisms generating organismal phenotypic integration, and we assess these predictions using data that we have generated from wild birds over the last decade. We find limited support for integration across developmental and evolutionary time, and we close by highlighting research priorities that will enhance our understanding of behavioral evolution by continued cross-talk between behavioral ecology and endocrinology.

### P3.25 KNDy NEURONAL SENSITIVITY TO GHRELIN AND THE IMPACT OF 17 BETA-ESTRADIOL

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The gut peptide, ghrelin, potentially mediates negative energy states and the neuroendocrine control of reproduction by acting through its receptor, growth hormone secretagogue receptor (GHSR). GHSR is expressed in hypothalamic arcuate (ARC) Kisspeptin/Neurokinin B/Dynorphin (KNDy) neurons, known to regulate reproduction and energy balance. We have previously shown 17-beta-estradiol (E2) increases Ghsr expression in KNDy neurons 6-fold, increasing their sensitivity to ghrelin. We hypothesize that E2-induced GHSR expression augments KNDy sensitivity during states of elevated ghrelin (fasting) to disrupt reproduction and reduce energy expenditure in females. We developed a Kiss1-specific GHSR knockout to determine the impact of GHSR in ARC KNDy neurons. We found no differences in vaginal opening or estrous cyclicity between experimental and control females. In ovariectomized females with or without E2 replacement, metabolic rates (V.O<sub>2</sub>, V.CO<sub>2</sub>) and substrate utilization (RER) were lower in experimentals and food intake and activity were increased in E2-treated experimentals compared to controls. Fasting glucose levels were higher in experimentals than in controls, regardless of steroid. In a separate cohort of mice, Luteinizing Hormone (LH) pulsatility was measured in fasted and ghrelin injected experimentals and controls. Fasting reduced LH pulses in control females, but not experimental females and ghrelin reduced LH in OVX+E2 control females about 90 min post-injection but not in 2 of 3 OVX+E2 experimentals. Collectively, these data suggest that GHSR activation in KNDy neurons modulates metabolism, glucose homeostasis, and LH pulsatility and illustrates a novel mechanism for E2 and ghrelin to control KNDy neurons and their physiological functions.

### P3.26 THE ROLE OF SOCIAL REWARD IN RELATION TO PAIR BOND FORMATION AND MAINTENANCE IN ZEBRA FINCHES

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Socially monogamous partnerships involve many behavioral components that vary both within and across species. Zebra finches are relatively unique as a small songbird that maintains strong life-long partnerships. Here we used a conditioned place preference (CPP) paradigm to compare the reinforcing properties of a mate during courtship and pair maintenance. Briefly, our CPP paradigm had three stages. (1) Pre-Test: each partner was exposed to the full cage. (2) Reward-Conditioning: each pair was housed on half of the cage (either a yellow or blue side). (3) Post-Test: each partner again had access to the full cage. Time spent on the conditioned side was compared during the Pre-Test and Post-Test. The zebra finches only formed CPP during courtship, and this effect was much stronger in females. The strength of the CPP during courtship was not strongly related to whether or not the pair copulated during the conditioning phase. This experiment suggests that while social reward is clearly important for courtship, it is possible that it plays less of a role in pair-bond maintenance. Such an effect could be consistent with the effect of pair bonding on the dopamine system described in mammals. To further compare the role of social reward during pair bonding, we are currently conducting two follow-up experiments. Firstly, we are quantifying the effect of D1 and D2 agonists on CPP during courtship and pair maintenance, and secondly, we are describing changes in the reinforcing value of the partner during the early weeks of pair bonding.

### P3.27 EDC MIXTURE DISRUPTS MATERNAL BEHAVIOR AND THE HYPOTHALAMIC CONTROL OF PUBERTY TRANSGENERATIONALLY THROUGH EPIGENETIC MECHANISMS

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Endocrine disrupting chemicals (EDCs) are a rising concern for public health due to their ubiquity as complex mixtures. Our goal was to study the effect of an EDC mixture on female sexual development during 3 generations.

Female rats (F0 generation) were orally exposed to a mixture of 13 anti-androgenic and estrogenic EDCs or corn oil for 2 weeks before gestation until weaning. The mixture was composed of plasticizers, fungicides/pesticides, UV filters, parabens and acetaminophen at doses representing human exposure. Sexual development (vaginal opening, GnRH secretion, estrous cyclicity and folliculogenesis) and maternal behavior were studied from F0 to F3 generations. At PND21, mediobasal hypothalamus of the F1 and F3 were removed for gene expression, histone modifications and DNA methylation analysis of target genes.

F1 and F2 females showed decreased maternal licking behavior while spending more time resting alone. F2 and F3 females showed delayed vaginal opening, decreased percentage of regular estrous cycle, decreased GnRH interpulse interval and altered late stage folliculogenesis. This phenotype was associated with transcriptional and epigenetic alterations of hypothalamic genes involved in reproductive competence and behavior like kisspeptin (*Kiss1*), oxytocin (*Oxt*), estrogen (*Esr1*), glutamate (*Grin2d*), dopamine signaling (*Th*) as well as glucocorticoid activity (*Nr3c1* and *Crh*). We have found alterations in repressive (H3K27me3, H3K9me3) or active (H3K4me3, H3K9ac) histone marks concomitant with transcriptional activity.

Overall, gestational and lactational exposure to an environmentally relevant EDC mixture transgenerationally affects sexual development throughout epigenetic reprogramming of the hypothalamus. Some of the effects could be mediated by alterations of maternal behavior.

### P3.28 EFFECTS OF EARLY-LIFE EXPOSURE TO CLOMIPRAMINE ON SOCIOEMOTIONAL BEHAVIORS AND INFLAMMATION

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Dramatic hormonal fluctuations that occur during the peripartum period can lead to alterations in brain chemistry that result in postpartum mood and anxiety disorders. Recent research has highlighted the role of the immune response in the pathogenesis of these mood and anxiety disorders in non-maternal populations. In fact, in non-maternal populations, inflammation in brain regions such as the orbitofrontal cortex (OFC) is 30% higher in people with obsessive-compulsive disorder (OCD) compared to healthy controls. Less is known about inflammation in the brain of postpartum females. Using a pharmacologically-induced model of OCD in Sprague-Dawley rats, we exposed pups to the tricyclic antidepressant, clomipramine, during postnatal days 9-16 or a saline control. We observed that during the postpartum period, rat mothers previously-exposed to clomipramine during early development engaged in more passive nursing postures and more OCD-like behavior compared to control mothers. The rat mothers that experienced early exposure to clomipramine also expressed more pro-inflammatory IL-1 $\beta$  in the OFC compared to saline control mothers. We are currently analyzing additional pro- and anti-inflammatory markers in these mothers and in males. Our findings suggested that increased inflammation in the OFC may be a mechanism associated with OCD behavior in maternal and non-maternal populations.

### P3.29 AAS INCREASE SENSITIVITY TO DOPAMINE D2 RECEPTORS FOR RATS IN AN EFFORT DISCOUNTING TASK

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Anabolic androgenic steroids (AAS) are performance-enhancing drugs used by world-class and rank-and-file athletes. AAS abuse is linked with risky decision-making, ranging from drunk driving to unsafe sex. Our lab uses operant behavior in rats to test effects of AAS on decision making. In our previous study, AAS rats worked harder for a food reward. In an operant discounting task, rats chose between a small easy reward (1 lever press for 1 sugar pellet) and a large difficult reward (2, 5, 10, or 15 presses for 3 pellets). Rats treated chronically with testosterone (7.5mg/kg) previously showed a greater preference for the large reward lever vs controls. Effort discounting is sensitive to dopamine, and AAS alter dopamine receptor expression in reward circuits. We determined if AAS increase sensitivity to dopamine D1 antagonist (SCH23390) or D2 antagonist (eticlopride) during effort discounting. There was no effect of AAS on effort discounting at baseline (large reward selection at FR5: AAS-treated rats 69.0±5.0%, vehicle-treated rats 74.5±4.4%). At 0.01mg/kg, the D1 antagonist significantly reduced large reward preference across both groups (FR5: AAS: 33.3±10.1%, vehicle: 42.1±9.6%,  $F(1,16)=24.1$ ). In response to D2 antagonist eticlopride (0.06mg/kg) there was an effect of testosterone ( $F(1,16)=7.8$ ), an effect of eticlopride ( $F(1,16)=50.5$ ), and an eticlopride x testosterone interaction ( $F(1,16)=9.9$ ) with greater reduction in AAS-treated rats (FR5: AAS: 30.2±7.2%, vehicle: 48.1±9.2%). This suggests that AAS alter effort-based decision making via increased sensitivity to dopamine D2 receptors.

### P3.30 NEONATAL PROGESTERONE IMPAIRS COGNITIVE FUNCTION

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The synthetic progestin, 17 $\alpha$ -hydroxyprogesterone caproate (17-OHPC) is routinely used for the prevention of premature birth in at-risk women, despite little understanding of potential effects on developing brain. Our work in rodents suggests that the developing brain is sensitive to progestins. Previous studies have shown that 17-OHPC impairs performance in set-shifting and delay discounting tasks. In the current study, we investigated the effects of 17-OHPC (0.5mg/kg) or vehicle from postnatal days 1 through 14 on cognitive function in adulthood. Cognitive function was assessed in males and females (n=8-10/group) by operant responding for sugar pellets, measuring delayed reinforcement or reversal learning. For delayed reinforcement, the rat must wait 15 seconds for pellets after responding on a lever. Delay is signaled by a light or un signaled. For reversal learning, the rat must respond on the lever under a stimulus light, and then learn to respond on the unlit lever. For delayed reinforcement, rats earned more pellets under signaled vs un signaled conditions. Likewise, males made more responses and earned more pellets, compared with females. 17-OHPC-treated rats earned fewer pellets than controls when a light was present. For reversal learning, results were similar. With rule reversal, females required more trials than males, and 17-OHPC-treated rats required more trials than controls. This suggests that 17-OHPC during development may alter cognitive function. These developmental neurobehavioral effects of a drug in widespread clinical use during pregnancy highlight the need to re-evaluate benefits and potential outcomes of a prophylactic progestin administration for the prevention of premature delivery.

### P3.31 ACUTE SOCIAL DEFEAT STRESS DRIVES NEUROINFLAMMATION VIA MICROGLIAL PRIMING IN THE vmPFC

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With growing interest in the intersection between psychological stress and the immune system, there is little doubt that the two are heavily intertwined, especially in prolonged stress conditions. Nevertheless, we know little regarding whether acute psychological stress drives an innate immune response. The ventromedial aspect of the prefrontal

cortex (vmPFC) is critical for emotion regulation during acute stress and has been argued to mediate stress resiliency. On the other hand, this region is especially vulnerable to highly salient stress experiences, such as those occurring during acute social defeat stress. Indeed, we have shown susceptibility to such stress corresponds with increased risk for oxidative stress in the vmPFC. In this study, we demonstrate that an acute social defeat stressor drives a marginal recruitment of vmPFC microglia, the resident immune cells of the brain. Importantly, the degree of microglial activity is greatly increased if the subject is given a subsequent immune challenge via an intraperitoneal injection of the endotoxin, lipopolysaccharide (LPS). Male Syrian hamsters were acutely defeated and, 24 hours later, injected with 0, 20, 100, or 500 ug/kg LPS. All animals were then euthanized 4 hours after defeat. Immunolabeling for the proteins Iba-1 and CD68 were then performed on vmPFC tissue, to determine microglial morphology and likelihood of phagocytosis, respectively. We found a LPS dose-dependent increase in the microglial response which was exaggerated by acute social defeat stress. This indicates that even an acute social stress can drive neuroinflammatory processes which, if unchecked, could prove detrimental to vmPFC anatomical integrity.

### P3.32 PACED MATING BEHAVIOR IN SEXUALLY EXPERIENCED RATS IS INFLUENCED BY LATENCY TO RECEIPT OF EJACULATIONS AND HORMONE REGIMEN

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Paced mating behavior varies both as a function of sexual experience and the criterion used to end the test. Sexually experienced female rats spend more time with the male, return faster after intromissions, and display more proceptive behaviors near the male relative to sexually naïve rats. Additionally, experienced rats take significantly longer to return after ejaculation than naïve rats when the test end criterion is 30 minutes but not 15 intromissions. Experiment 1 explored whether the difference in contact-return to ejaculation is better explained by learning across tests or latency to receive each ejaculation when mating. Return latency to the first three ejaculations in each of four mating tests, ending at 30 minutes or 15 intromissions, was assessed. Rats receiving 30-minute tests showed significantly longer return latencies after the second and third, but not first, ejaculations than rats receiving 15 intromission tests. Experiment 2 tested whether hormone regimen affects paced mating behavior in sexually experienced rats. Sexually experienced rats were primed with 10 ug estradiol benzoate (EB) + 1 mg progesterone (P) or EB-Alone (2 ug EB for 6 days) and received a 15-intromission paced mating test. Rats primed with EB-Alone were fully receptive, but showed significantly longer latency to return after intromissions and ejaculations, significantly less time with the male, and significantly longer test durations compared to being primed with EB+P. Future experiments are needed to determine physiological processes factoring into heightened sensitivity to stimulation with longer latencies to multiple ejaculations or when tested with EB-Alone.

### P3.33 INVESTIGATING CELLULAR MECHANISMS OF COPING RESPONSES AND DOMINANCE STATUS

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There are a great deal of individual differences in how humans and other animals cope with stress. Differences in coping are linked to several environmental factors, including social dominance. This study investigated whether coping responses predict dominance status in male and female Syrian hamsters and whether the maintenance of dominance relationships alters subsequent coping responses. The study also investigated underlying cellular mechanisms by dual immunofluorescence labelling for deltafosB and dopamine type-1 receptors within the nucleus accumbens. We hypothesized that the maintenance of dominance relationships would increase active coping strategies in dominants and passive coping strategies in subordinates. Finally, we hypothesized that animals with a proactive response will express higher levels of deltafosB and dopamine type-1 receptors in the nucleus accumbens. Male and female hamsters were paired with a same-sex partner in daily aggressive encounters for two weeks. To assay coping strategies before and after the formation of dominance relationships, we tested animals in a series of

behavioral tests, including open field, novel object exploration, elevated zero maze, light/dark transition, Porsolt forced swim, and social defeat tests. We found that dominance status has a greater effect on stress-induced anxiety-like and depression-like behavior in male hamsters compared to female hamsters. Because most preclinical neuroscience research is conducted exclusively in male animals, these data will extend our understanding of sex-differences in the expression of passive and active coping strategies. In addition, these data indicate that dominance status plays a role in the development of coping strategies and stress vulnerability.

### P3.34 CASTE BUT NOT SEX DIFFERENCES IN THE EFFECTS OF SOCIAL NOVELTY ON CELL PROLIFERATION IN A EUSOCIAL MAMMAL

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Changes in the social environment can influence adult neurogenesis in a manipulation- and sex-dependent manner. For example, male hamsters exposed to novel aggressive individuals show increased olfactory bulb neurogenesis. Group-housed rats given chronic electric shocks do not have sex differences in new neuron survival. However, socially isolated males display decreased new neuron survival while females display an increase following shock. Naked mole-rats (NMR) are eusocial mammals with large colony sizes dominated by a single breeding female. Subordinate NMRs have increased doublecortin expression in the basolateral amygdala when paired with a novel female, but not a novel male, suggesting a sex-specific increase in threat assessment. Furthermore, female same-sex pairs display less huddling and more shoving than male same-sex pairs, consistent with their competitive matriarchal hierarchy. We examined the effects of exposure to a novel or familiar NMR on cell proliferation in neurogenic brain regions. We injected EdU, a marker of cell division, into sex-balanced groups of adult subordinate soldier and worker NMRs and paired them for 30 minutes with either a familiar or novel conspecific every 24 hours for 7 days. We then quantified EdU expressing cells in the dentate gyrus (DG), subventricular zone (SVZ), and olfactory bulb. We show that soldiers have higher levels of SVZ cell proliferation than workers. Exposure to novel animals decreased cell proliferation in the DG. Our findings suggest a caste differentiated response to unfamiliar individuals. Soldiers may be more primed to detect odor cues, reflected by a caste-specific difference in proliferation in the SVZ.

### P3.35 DECIPHERING EXPERIENCE-DEPENDENT PLASTICITY IN MATERNAL PUP GATHERING BEHAVIOR USING ADULT FEMALE RETT SYNDROME MICE

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Cohabitation of adult nulliparous mice with pups and mother induces maternal behavior in them in a hormone-independent manner. Such non-hormonal factors are thought to be important in mediating plasticity, likely through chromatin remodeling of specific neural circuitry (Stolzenberg and Champagne, 2016). We have previously shown that nulliparous mice deficient in Methyl CpG-binding protein 2 (MECP2) display inefficient pup gathering behavior, likely due to atypical auditory processing of ultrasonic vocalizations from pups (Krishnan, Lau et al, 2017). Furthermore, we identified a crucial mechanism involving extracellular matrix structures called perineuronal nets (PNNs) which play a major role in structural plasticity of parvalbumin+ GABAergic networks in the auditory cortex. The auditory cortex of MECP2-deficient females had increased numbers of PNNs, which when removed, improved pup gathering performance, demonstrating the crucial structural role that PNNs provide in learning and plasticity.

Many questions remain: How do the nulliparous wild types learn and perform the behavior well? What neural circuits are critical for this learning? By using whole brain immunostaining, imaging and quantification approaches, we found that regions in the primary somatosensory cortex of adult wild type female undergo dynamic changes in PNN expression after learned maternal behavior experience. Mecp2-deficient females exhibit atypical PNN expression before and after this experience, which is correlated with their inefficient pup retrieval performance. Taken together,

our data suggest that MECP2 regulates the expression of PNNs, in a region-specific, hemisphere-specific manner, thereby affecting adult plasticity essential for learning and execution of efficient pup retrieval task.

### P3.36 THE INFLUENCE OF DIETARY CHOLINE ON HIPPOCAMPAL $\alpha 7$ NICOTINIC ACETYLCHOLINE RECEPTORS

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Prenatal stress is associated with deficits in learning and memory. These changes may be due, at least in part, to alterations in  $\alpha 7$  nicotinic acetylcholine receptors (nAChRs). nAChRs are well-known mediators of learning and memory, and prenatal stress changes levels of these receptors in the hippocampus and prefrontal cortex. Our lab has found that intake of dietary choline during gestation rescues the negative effects of prenatal stress on adult spatial memory function. However, the mechanisms by which choline mitigates the negative effects of prenatal stress on memory function are unknown. Choline is a direct agonist of  $\alpha 7$  nAChRs. Therefore, we hypothesize that choline mitigates the effects of prenatal stress on memory function via changes in hippocampal  $\alpha 7$  nAChRs. Pregnant dams were stressed during their last week of gestation (days 14-21). Offspring were weaned at 21 days of age and assigned to same-sex same-diet cage-mates. In adulthood, offspring brains were collected and processed for quantitative autoradiography using 125I alpha-bungarotoxin ( $\alpha 7$  selective) ligand. Data analysis is near completion and the results will be presented at SBN. The results will have implications for mental illnesses with links to stress during the prenatal period such as schizophrenia, depressive disorders and anxiety.

### P3.37 EFFECT OF PARITY GROUP ON NEURONAL ACTIVATION IN FEMALE MICE

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Past research suggests that parity may contribute to hormonal responses in the brain. It has been hypothesized that lactating dams will experience lower neural activity when compared to virgin dams, likely as a result of sensitization to hormonal changes. These hormonal differences seen amongst the parity groups are operationalized as differences in neural activity; neural activity can be measured with cFos, an indirect marker. This study investigated the possible influences of parity group on neural activity, and its implications towards hormonal differences. Mice were divided into three groups; lactating dams (n= range of 4-10), sensitized virgins (n= range of 4-10), and naive virgins (n= range of 5-10). Mice brains were extracted and stained with cFos staining, then investigated utilizing Zeiss microscopy. Two distinct brain regions, the frontal cingulate cortex, and the anterior olfactory nucleus, were analyzed with a one-way ANOVA on IBM SPSS 22. While the differing parity groups experienced mean differences in these regions, the means were not statistically significantly different from one another. The anterior olfactory nucleus revealed no significant differences between naive virgins and sensitized virgins ( $p = .464$ ); naive virgins and lactating dams ( $p = .993$ ); and lactating dams and sensitized virgins ( $p = .559$ ). The frontal cingulate cortex revealed no significant differences between naive virgins and sensitized virgins ( $p = .632$ ); naive virgins and lactating dams ( $p = .999$ ); and lactating dams and sensitized virgins ( $p = .662$ ).

### P3.38 EFFECTS OF ADOLESCENT CHRONIC MILD STRESS ON FEMALE WISTAR AND KYOTO RATS

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Mood disorders are common and symptomatically challenging illnesses to treat. Despite years of research to understand underlying mechanisms and develop more effective treatments, numerous challenges still exist. There

are many stress models and genetic strains used to study mood disorders, however the majority have been developed with adult males. This is problematic considering that affective disorders are more common in women, and many develop during adolescence. Additionally, studies have shown that there are fundamental behavioral and physiological differences between males and females in response to stressful stimuli, furthering a need to develop sex-specific paradigms to model the etiology of mood disorders in females. In this study, we tested stress susceptibility of Wistar (Ws) and Kyoto (Ky) female rats by using a chronic mild stress (CMS) paradigm during late adolescence (days 45-66). We measured body weight, food intake, and corticosterone levels during CMS to evaluate physiological effects. Immediately following CMS, animals underwent behavioral assessments of helplessness, anxiety, and anhedonia. Ky rat demonstrated endogenous behavioral and hormonal abnormalities that many symptom-presenting patients with depression exhibit, making them an appropriate model for testing therapeutics. Ws rats demonstrated more CMS-induced changes, indicating that Ws are more ideal for understanding the causal links between stress and susceptibility to mood disorders. These tests are repeated during late adulthood (~90 days) to determine long-term effects. The validation of these sex-specific models of mood disorders allow for more studies on the underlying mechanisms driving these disorders and ultimately contribute to the development of novel therapeutic strategies.

### P3.39 OXYTOCIN ANTAGONISM INCREASES DEPRESSION-LIKE BEHAVIOR IN NULLIPAROUS BUT NOT POSTPARTUM RATS

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Oxytocin (OT) is a neuropeptide and has pleiotropic effects on maternal behavior, learning and memory, stress responses, and social behavior. During the postpartum period, oxytocin is released in a pulsatile pattern associated with suckling from offspring. Absence of nursing eliminates the intermittent peaks of oxytocin during the postpartum period. In humans, lower oxytocin release during breastfeeding postpartum was related with higher depression symptoms. Further, women who do not breastfeed are at greater risk for postpartum depression. In rodent models, OT has antidepressant like effects in the forced swim test and learned helplessness test. Thus, OT may be an important mediator of depression and depression-like behaviors in postpartum females. We sought to determine whether oxytocin receptor antagonism would alter depression-like behavior differently in reproductively naïve and early postpartum rats. We tested rats in the forced swim test (FST) on two consecutive days (FST 1: 15 min; FST 2: 5 min). Rats received oxytocin receptor antagonist (OTA; 3 mg/kg ip) or saline 30 min before testing in FST 2. OTA increased immobility in FST 2 in nulliparous rats, but not postpartum rats. Antagonism of oxytocin receptors differentially affects depression-like behavior in postpartum and nulliparous rats: OTA did not alter depressive-like behavior in the postpartum female but did increase depressive-like behavior in nulliparous rats. Using immunohistochemistry for c-Fos, we are currently identifying how OTA alters activation of brain regions involved in stress and affect in nulliparous and early postpartum rats.

### P3.40 HYPOCRETIN ANTAGONISM'S INFLUENCE ON POSTPARTUM ANXIETY AND PUP RETRIEVAL IN MICE

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Postpartum anxiety is a detrimental condition that causes disruptions in maternal care to offspring and negatively impacts the health of a mother and her offspring. However, little is known about the underlying neurobiological causes of postpartum anxiety. High levels of hypocretin (HCRT), an arousal related peptide, has been associated with increased anxiety in non-lactating animals, and we know that there is increased HCRT activity during lactation in dams. Antagonizing HCRT receptor 1 (HCRTr1) decreases anxiety in non-lactating rodents, so we wanted to explore if this was true in lactating mice. Using two doses of SB-334867 (10 mg/kg, 30 mg/kg), a HCRTr1 antagonist, and a modified light/dark box protocol to include a pup retrieval task, we saw that HCRTr1 antagonism

increased anxiety behaviors and decreased pup retrieval. Dams given a low dose spent less time in the light (M = 119.06, SEM = 25.54) compared to our vehicle group (M = 217.13, SEM = 24.70), and dams given a high dose (M = 11.53, SEM = 2.94) entered the light less often than our vehicle group (M = 21.87, SEM = 2.12). Additionally, dams given the high dose retrieved less pups (M = 0.13, SEM = 0.13) than our vehicle control group (M = 1.00, SEM = 0.26). These results indicate that HCRT's role on anxiety behaviors could differ in the postpartum period compared to non-lactating mice, and that HCRT antagonism impairs maternal behaviors like pup retrieval.

### P3.41 UNORTHODOX CIRCADIAN RHYTHMS IN MICE LACKING COMMENSAL MICROBES

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Present in all living organisms, from prokaryotes to vertebrates, circadian clocks impart daily temporal structure in behavior. Cellular circadian oscillators have periods of ~24 h and are mutually coupled to one another; a hierarchical network structure allows them to function as pacemakers, synchronizing period and phase at the organ- and organismal-level. Here we examine how the trillions of microbes that co-inhabit the body influence basic aspects of brain function and behavior. The host circadian system sustains daily rhythms in physiology (e.g., body temperature), behavior (e.g., locomotor activity, ingestive behavior) and brain function (learning, affective state), but also maintains daily rhythms in the abundance, membership, and function of symbiotic microbes in the gut ecosystem. Emerging evidence indicates that communication between the host circadian system and the gut microbiota is bidirectional, but the extent to which the trillions of gut microbes impact the generation and expression of organismal circadian rhythms has not been directly examined. To examine the impact of the gut microbiota on the host circadian network, we developed a novel, non-invasive, wireless method for continuous assessment of circadian rhythms in spontaneous home cage locomotor activity (LMA) and core body temperature (Tb) in freely-behaving germ-free (GF) mice housed in sterile flexible-film isolators as compared to specific pathogen free (SPF) mice harboring a full microbial community housed under nearly identical conditions. In the presence and absence of gut microbiota, circadian rhythms in LMA and Tb were examined.

### P3.42 MATERNAL EXPERIENCE-DEPENDENT AUDITORY CORTICAL PLASTICITY IS CIRCUIT- AND STIMULUS-SPECIFIC AND REQUIRES METHYL-CpG-BINDING PROTEIN 2 (MECP2) IN MICE

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Cohabitation of adult nulliparous mice with pups and mother induces maternal behavior in them in a hormone-independent manner. Such non-hormonal factors are thought to be important in mediating plasticity, likely through chromatin remodeling of specific neural circuitry (Stolzenberg and Champagne, 2016). We have previously shown that Methyl CpG-binding protein 2 (MECP2), a chromatin remodeling protein and gene regulator, in the auditory cortex is essential for efficient pup retrieval task in a learned maternal behavior paradigm. Furthermore, we showed atypical plasticity in parvalbumin+ (PV+) GABAergic neurons of nulliparous MECP2- heterozygous surrogate mice (*Hets*), compared to wild-type littermate controls (WT) (Krishnan, Lau et al, 2017). These results led us to speculate that *Hets* had atypical auditory processing phenotype. Here we show that maternal experience in WT triggers PV+-mediated disinhibition of auditory responses in deep-layer pyramidal neurons that is selective for behaviorally-relevant pup vocalizations, by performing extracellular recordings in awake mice. These neurons also exhibit sharpened tuning for pup vocalizations following maternal experience. All of these neuronal changes are abolished in *Hets*, suggesting that they are essential for efficient execution of pup retrieval task. Taken together, our data

suggests that MECP2 regulates the timing of plasticity through PV+ neuronal networks, which ultimately affects adult plasticity essential for learning and execution of efficient pup retrieval task.

### P3.43 RECONSTRUCTING VASOPRESSIN PATHWAYS IN THE BRATTLEBORO RAT

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The neuropeptide, arginine vasopressin (AVP), has been implicated in a number of neurodevelopmental disorders that impact social and emotional development (e.g., autism and ADHD). Nevertheless, we do not understand how AVP modulates behavioral development or how its altered function contributes to neurodevelopmental disorders. The Brattleboro rat, which lacks AVP due to a mutation in the *Avp* gene, is an ideal model to study the impact of life-long AVP disruption. Brattleboro rats suffer from diabetes insipidus – excessive drinking and urination due to the loss of AVP action on the kidney. We have found that adolescent Brattleboro rats also exhibit atypical social behavior associated with decreased arousal. To determine the pathway responsible, we developed a viral-rescue approach to restore AVP within a single pathway, beginning with the paraventricular nucleus of the hypothalamus (PVN). Infusion of a recombinant adeno-associated virus containing a functional *Avp* gene and promoter rescued AVP within magnocellular cells of the PVN and fiber projections to the posterior pituitary and limbic structures. Water intake was markedly reduced, ameliorating the symptoms of diabetes insipidus, but behavioral arousal was unaffected. These findings indicate that the hyporaoused phenotype of adolescent Brattleboro rats is not due to the loss of AVP function in PVN magnocellular cells or a side effect of diabetes insipidus. Instead, parvocellular pathways likely underlie AVP regulation of arousal during adolescence. More broadly, these experiments illustrate a novel approach that “reconstructs” individual pathways in genetic mutant models to assess their role in behavioral phenotypes.

### P3.44 RNA-SEQ REVEALS DISTINCT REGIONAL TESTOSTERONE-SENSITIVE AND INSENSITIVE PATTERNS IN SEXUALLY DIMORPHIC GENE EXPRESSION IN THE BRAIN OF JAPANESE QUAIL

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Male and female Japanese quail display distinct physiology and behavior as a result of genetic differences and differential exposure to hormones during development and adulthood. The genes underlying these differences are largely unknown, especially in birds. The present study investigated transcriptomic sex differences in three brain regions (medial preoptic nucleus [POM], ventromedial nucleus of the hypothalamus [VMN] and nucleus taeniae of the amygdala [TnA]) of adult male and female quail left gonadally intact or gonadectomized and treated with testosterone (GDX+T). Overall, POM showed the largest number of differentially expressed genes (DEG). As expected, some DEG turned out to be sensitive to testosterone treatment while others were insensitive, but GDX+T also uncovered DEG that were not different in intact subjects suggesting that T (or ovarian hormones) actively “repress” some otherwise sexually-dimorphic genes. Some DEG were identified in only one nucleus and tended to be more T-sensitive, particularly in the POM which, surprisingly, had female-bias from autosomes and male-bias from the Z chromosome. In contrast other DEG, most of them T-insensitive, were common to several nuclei. DEG common to POM and VMN were most abundant, being mostly male-biased and located on sex chromosomes. Most

DEG common to all nuclei are only expressed in females suggesting they are located on chromosome W. Three patterns of DEG thus emerge in response to testosterone: T-sensitive, T-insensitive, and DEG normally repressed by T, each depending on neuroanatomical and chromosomal location, representing sets of candidate genes that could explain fundamental behavioral sex differences in adult birds.

### P3.45 NOVEL APPROACHES FOR NEUROTOXICOLOGY: USE OF THE PRAIRIE VOLE TO ASSESS THE IMPACT OF DEVELOPMENTAL FLAME RETARDANT EXPOSURE ON SOCIAL BEHAVIORS

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The rapidly rising incidence of neurodevelopmental disorders is raising speculation that environmental contaminants may be contributory. Firemaster 550 (FM550) is one of the most prevalent flame-retardant (FR) mixtures used in foam-based furniture and baby products. We and others have published evidence of developmental neurotoxicity and sex specific effects of FM550 on anxiety-like and exploratory behaviors in rats and zebrafish. To test the hypothesis that FM550 affects social behavior, we investigated the impact of perinatal FM550 on a range of social behaviors in prairie voles. Virtually unknown to toxicologists, the prairie vole (*Microtus ochrogaster*) is a uniquely valuable model organism for examining environmental impacts on sociality because it is spontaneously prosocial and displays pair bonding behaviors. Dams were exposed to three, human relevant doses of FM500 via subcutaneous injections throughout gestation, and pups were then exposed daily until weaning. Adult offspring of both sexes were then subjected to multiple tasks including open field, novel object recognition, and partner preference. Effects were dose responsive and sex specific, with females more affected. Behavioral effects included elevated anxiety, decreased social interaction, decreased exploratory motivation, and altered social preference for novel versus familiar animals. FM550 also sex-specifically affected pair bond formation, with a loss of preference in males. Our studies demonstrate the utility of the prairie vole for investigating the impact of chemical exposures on sociality and attachment. The data support the hypothesis that developmental FR exposure impacts the social brain and future studies will probe the possible mechanisms by which these effects arise.

### P3.46 EFFECTS OF EARLY LIFE STRESS ON MCC AND DOPAMINE RECEPTOR EXPRESSION

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Zebra finches are an excellent model of learning and memory. Developmental nutritional stress (NS), a model for early life adversity, is known to cause learning deficits in male zebra finches, evidenced by reduced song complexity. Although the neural basis of the NS learning deficit is not well understood, genes likely play a role. One candidate is the gene coding for the enzyme 3-methylcrotonyl carboxylase (MCC), which is necessary for leucine catabolism. MCC deficiency is known to cause cognitive deficits and learning disabilities, positing that MCC is important for learning. Additionally, dopamine plays an important role in learning. In male zebra finches, MCC and dopamine receptors (D1a and D2) are both present in the song-learning pathway, and NS may cause learning deficits by altering expression of dopamine receptors and MCC in the song pathway. Female zebra finches exposed to NS were unable to choose males on the basis of song quality, suggesting that NS also causes learning deficits in females. However, not much is known about the presence of MCC and dopamine in the learning pathways in female zebra finches. The present study will investigate the extent to which NS reduces MCC and dopamine receptor (D1A and D2) expression in song and auditory pathways of NS zebra finches of males and females. By examining the effect of

NS on MCC and dopamine receptor expression, our results will help elucidate the role of MCC and dopamine in learning, and also elucidate the neural correlates of early life adversity.