

Japan-U.S. Brain Research Cooperation Program
Information Exchange Seminar FY2011: Report

Field: _____

1. Seminar title: Neurobehavioral Mechanisms of Affiliative Behavior and Cooperation: Prospects for Translational Advances for Psychiatric Disorders

2. Dates, from 10/23/2011 to 10/25/2011

3. Location: Conference Center, Emory University, Atlanta, GA, USA

4. Coordinators

Japanese Coordinator

Name Sonoko Ogawa, Ph.D.
Title Professor
Affiliation University of Tsukuba

U.S. Coordinator

Name Larry J. Young
Title Professor
Affiliation Emory University

5. Participants:

Japan: Invited participants 20 people

Others 2 people

(Please give names, titles and affiliations of invited participants)

<u>Name</u>	<u>Title</u>	<u>Affiliation</u>
Yasuo Sakuma	Professor	Nippon Medical School
Katsuhiko Nishimori	Professor	Tohoku University
Sonoko Ogawa (organizer)	Professor	Tsukuba University
Akemi Tomoda	Professor	Fukui University
Haruhiro Higashida	Professor	Kanazawa University
Masamichi Sakagami	Professor	Tamagawa University
Takefumi Kikusui	Professor	Azabu University
Kazuo Hiraki	Assoc. Prof.	The University of Tokyo
Haruhiko Bito	Assoc. Prof.	Tokyo University
Kazutaka Mogi	Asst. Prof.	Azabu University
Miho Nagasawa	Asst. Prof.	Azabu University
Mumeko C Tsuda	Post Doc	University of Tsukuba
Eriko Yamamoto	Res Associate	Tokyo University
Hanako Suzuki	Grad Student	Kumamoto University
Maki Sasaki	Grad Student	Tohoku University
Keisuke Sato	Grad Student	Tohoku University
Toshihiro Endo	Grad Student	Tokyo University
Shota Okabe	Grad Student	Azabu University
Mami Kawashima	Grad Student	Nippon Medical School
Teiko Kawahigashi	Grad Student	Nippon Medical School

U.S.: Invited participants 17 people Others 135 people

(Please give names, titles and affiliations of invited participants)

<u>Name</u>	<u>Title</u>	<u>Affiliation</u>
Larry Young (organizer)	Professor	Emory University, Yerkes
Frans de Waal	Professor	Emory University, Yerkes
Michael Numan	Professor	Boston College
Bill Hopkins,	Professor	Agnes Scott College, Yerkes
Zuoxin Wang	Professor	Florida State University
Jeffrey French	Professor	University of Nebraska
Ami Klin	Professor	Yale University
James Goodson	Assoc. Prof	Indiana University
James Rilling	Assoc. Prof.	Emory University
Adam Guastella	Assoc. Prof	University of Sydney
Lisa Parr	Asst. Prof.	Emory University, Yerkes
Jennifer Bartz	Asst. Prof.	Mount Sinai School of Medicine
Sarah Brosnan	Asst. Prof.	Georgia State University
Francis Champagne	Asst. Prof.	Columbia University
Todd Ahern	Post Doc	Univ. Mass. Amherst
Meera Modi	Grad. Stud.	Emory University
Victoria Wobber	Grad. Stud.	Harvard University

6. Seminar Outline and Significance:

Historically, the vast majority of neurobiological research related to social behavior focused on sexual and agonistic behavior. However, more recently there has been an explosion of research on the neurobiology and psychology of non-sexual prosocial behaviors such as affiliation, parental behavior, social bonding and cooperation. Researchers in the field use a wide range of experimental approaches, ranging from molecular and genetic, to brain imaging and purely behavioral studies. The goals of this workshop were to bring together leading scientist as well as junior investigators and trainees studying prosocial behavior and affiliation from US and Japan to discuss recent findings and to foster research collaborations. Participation in this workshop, and establishing collaborations was expected to allow the participants to transcend the boundaries of their own research field by combining the expertise and opportunities in genetics, behavior, cognition, and neuroscience to illuminate the neural basis of affiliative processes in humans and animal models. Young scientists (students and post-docs) were also invited to participate in the workshop to inspire development of the next generation of interdisciplinary social neuroscientists.

We have carefully selected participants to cover top scientists from the multiple approaches to this topic, while keeping with a unifying theme. The participants ranged from geneticist and behavioral biologist to clinicians working with psychiatric populations and all of them were leading researcher in their field.

7. Seminar Results and Future Implications:

This workshop was hosted by The Center for Translational Social Neuroscience (CTSN) and the Center for Behavioral Neuroscience and held at the Emory University. The program included presentations from leaders in the fields of social psychology and social neuroscience from the US and Japan. Topics included the biology of social bonding, affiliation, cooperation, empathy, parental care, and the potential for translating this biology into therapies for psychiatric disorders. The workshop was a great success with over 175 registrants from all over the country and the world. Participants included 12 Japanese investigators and 8 students, and one participant from Australia. The CTSN provided travel awards to 13 students and post-docs from across the US. Presentations were video recorded and will be available online.

In this workshop, we could greatly stimulate interaction between scientists from US and Japan as well as students and trainees from both sides. Particularly, by reserving one-third of each presenter's time for discussion, we could exchange a lot of ideas for future studies. Round table seating at the lunches/dinners with a mixture of US and Japanese PI's and trainees also

facilitated informal discussion. In addition, we spent ample time for poster sessions to encourage trainees to participate further studies on social and affiliative behavior. All these activities greatly helped to establish new collaborations between participants.

One of implications of this workshop is promotion of social neuroscience as a new field of study particularly in the Japanese side, in which studies of biological and neuroendocrine basis of social behavior has not gained so much attention yet. There were a number of new and exciting presentations. Those included 1) roles of oxytocin and vasopressin not only in classical animal model, ie., voles, but also in human-dog interactions, capuchins, chimpanzees, and cooperative behavior in humans, 2) modulation of social behavior by steroid receptor dependent mechanisms as well as other brain system such as the CaMK signaling, 3) importance and molecular mechanisms of epigenetic modulation of social behavior, and 4) application of findings in basic research to studies in the field of clinical psychiatry which facilitate understanding of human mental and social disorders. It is expected all presentations and discussion during the workshop will result in budding and further development of a new field of translational social neuroscience in both US and Japan sides.

Workshop on Prosocial Behavior

Neurobehavioral Mechanisms of Affiliative Behavior and Cooperation: Prospects for Translational Advances for Psychiatric Disorders

Sponsored by the CTSN and CBN

Additional support provided by the U.S. – Japan Brain Research Cooperative Program (BRCP), NIMH, Japan Society for the Promotion of Science, and CleverSys, Inc

Sunday, October 23, 2011

- 8:00- 8:55 AM** Check-In at desk in main lobby of Emory Conference Center (pick up meeting agenda and name tag), & Poster Set-Up (please get directions from desk assistants)
- 8:00 – 8:55** Continental Breakfast provided in Silverbell Pavilion
- 8:55** **Larry Young:** Welcome (Silverbell Pavilion)

Theme 1: Neural and molecular mechanisms of bonding and the social brain (Larry Young, Chair)

- 9:00** **Larry Young:** Oxytocin, vasopressin, and the evolution of monogamy
- 9:25** **James Goodson:** Nonapeptide mechanisms of gregariousness, bonding and social diversity in birds
- 9:50** **Yasuo Sakuma:** GnRH neurons in puberty: GABA, chloride transporter, neuroactive steroids
- 10:15** **Zuoxin Wang:** Vasopressin and its associated circuit for mate guarding
- 10:40** **COFFEE BREAK** (Provided)
- 10:55** **Katsuhiko Nishimori:** Oxytocin receptor-expressing neurons and social behaviors: studies with a genetically engineered animal model
- 11:20** **Jeffrey French:** Peptides, steroids, and pairbonding in primates
- 11:45** **Haruhiko Bito:** CaMK signaling and mouse social behavior
- 12:10 PM** **Lunch Break (Emory Conference Center Dining Room - Provided)**

Theme 2: Neural basis of parent-infant interaction
(Sonoko Ogawa, Chair)

- 1:10** **Michael Numan:** Neuroanatomical circuitry for mammalian maternal behavior: Parallels with pair bonding
- 1:35** **Sonoko Ogawa:** Neural mechanisms of social behavior: Role of steroid receptors
- 2:00** **Frances Champagne:** Epigenetic effects of early life social experiences in rodents: Consequences for neuroendocrine and reward pathways
- 2:25** **Takefumi Kikusui:** Mother-pup interactions and its role on infant development
- 2:50** **COFFEE BREAK** (Provided)
- 3:05** **Masaki Kakeyama:** Effects of maternal chemical exposure on social anxiety and learning NOTE: Due to family illness Toshihiro Endo will present instead.
- 3:30** **Todd Ahern:** Impact of early family dynamics on adult social behavior: Insights from prairie voles
- 3:55** **Kazutaka Mogi:** Developmental role of neonatal oxytocin in social behavior
- 4:20- 6:10** **Poster Session**
- 6:10** **End of Day 1**
- 6:30 – 8:00** **Private (Invitation only) Southern Barbeque Banquet** (Starvine Room).

Monday, October 24, 2011 (Silverbell Pavilion)

- 8:00 – 8:55** Continental Breakfast provided in Silverbell Pavilion

Theme 3: Cooperation, cooperative communication, and brain function
(Takefumi Kikusui, Chair)

- 9:00** **Frans de Waal:** Empathy and altruism in primates
- 9:25** **Miho Nagasawa:** Reciprocal communication and endocrine response in human-dog interactions
- 9:50** **Victoria Wobber:** Comparing the psychology and cognitive development of the two *Pans*: Are bonobos self-domesticated?
- 10:15** **Lisa Parr:** Exploring face space in nonhuman primates
- 10:40** **COFFEE BREAK** (Provided)
- 10:55** **Sarah Brosnan:** Hormonal and behavioral mechanisms regulating cooperative and prosocial behaviors in capuchins
- 11:20** **Masamichi Sakagami:** Multiple neural circuits in social decision-making

- 11:45** **Bill Hopkins:** Preliminary findings on the role of vasopressin receptor polymorphism on social behavior and cognition in chimpanzees
- 12:05 PM** **Kazuo Hiraki:** NIRS and EEG studies of infant-mother interactions in humans
- 12:30** **James Rilling:** Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in humans
- 12:55** **Lunch Break (Emory Conference Center Dining Room - Provided)**

Theme 4: Translational Opportunities in Social Neuroscience
(Adam Guastella, chair)

- 2:00** **Ami Klin and Warren Jones:** Landscapes of enculturation: Social entrainment and disruptions thereof in autism
- 2:25** **Akemi Tomoda:** Abnormal brain development in maltreated children
- 2:50** **COFFEE BREAK** (Provided)
- 3:05** **Meera Modi:** The prairie vole as a predictive model for prosocial therapeutics
- 3:30** **Haruhiro Higashida:** CD38 as a critical molecule for oxytocin release and social recognition and its clinical implication in autism
- 3:55** **Jennifer Bartz:** Person- and context-dependent nature of oxytocin's effects in humans and their therapeutic implications
- 4:20** **Adam Guastella:** Oxytocin and processing of social information in healthy and clinical population
- 4:45** **Larry Young:** Closing remarks
- 4:50** **End of Public Conference**
- 6:00 – ??** **Informal Networking for Speakers and Trainees** (Great Hearth in the Conference Center main building)

Tuesday, Oct 25, 2011

Yerkes National Primate Research Center: Bourne Room

10:00 AM-12:00 PM Informal Discussion & Networking: potential collaboration opportunities among (Coffee and snacks provided)

Workshop Organizing Committee

Larry Young
Sonoko Ogawa
Takefumi Kikusui
Yasuo Sakuma

Local Organizing Committee

Larry Young
Ingrid Budreckas
Becky Kinhead
Sara Freeman
James Burkett
Katie Barrett

Poster Presenters

No.	Presenters	Title	Affiliation
P-1	T.H. Ahern	Impact of Early Family Dynamics on Adult Social Behavior: Insights from Prairie Voles	Quinnipiac University
P-2	D.S. Carson	Randomized Controlled Trial of Intranasal Oxytocin for Children with Autism: Research Protocol	Stanford University
P-3	B.A. Tabak	Associations of Oxytocin Receptor Gene (OXTR) Polymorphisms with Cooperation, Perceived Partner Personality, and Emotional Reactions to Betrayal	University of California, Los Angeles
P-4	C.E. Barrett	Resilience to Early Life Stress in Prairie Voles (<i>Microtus ochrogaster</i>): Potential Moderation by Oxytocin Receptors	Emory University
P-5	A.P. Borrow	Maternal Care but not Plasma Oxytocin Affects Social Behavior across the Estrous Cycle	SUNY, Binghamton
P-6	Q. Meng	Effects of Post-weaning Adverse Peer Interactions on Emotional and Social behaviors	Boston College
P-7	J.L. Goodson	Antisense Knockdown of VIP in the Anterior Hypothalamus Reduces Aggression in a Territorial Finch	Indiana University
P-8	K.M. Dumais	From Anti-social to Pro-social: Do Sex Steroids and Oxytocin Play a Role?	Boston College
P-9	C. Lieberwirth	Social Isolation Affects Various Behaviors and Adult Neurogenesis in the Adult Female Prairie Vole (<i>Microtus ochrogaster</i>)	Florida State University
P-10	M.A. Kingsbury	VPAC Receptor Antagonism Modulates Social Responses to Novelty	Indiana University
P-11	S.W. Chang	Inhaled Oxytocin Amplifies Both Vicarious Reinforcement and Self Reinforcement in Rhesus Macaques (<i>Macaca mulatta</i>)	Duke University
P-12	S. Okabe	Sensitization to Pups Facilitates Maternal Retrieving and Neural Responses in the Medial Preoptic Area in Mice	Azabu University, Japan
P-13	E.K. Edmiston	Childhood Maltreatment Effects Face Processing	Vanderbilt University
P-14	C.J. Smith	Vasopressin Regulates Play-fighting in Sex- and Context-specific Ways	Boston College
P-15	C.L. Muller	ASD-Associated Serotonin Transporter Variant Causes Impairments in Social Communication and Interaction	Vanderbilt University Medical Center
P-16	T. Kawahigashi	Identification of Truncated Estrogen Receptor α variants in the mouse	Nippon Medical School, Japan
P-17	C.M. Hostetler	Effects of Heterosexual Social Housing on Ethanol Intake in Prairie Voles	Oregon Health and Science University
P-18	K. Sato	Analysis of OXTR on Maternal Behavior by Nuclei-Specific Gene Manipulation	Tohoku University, Japan
P-19	A.M. Kelly	Antisense knockdown of BSTm vasotocin cells produces sex-specific effects on sociality and responses to novelty	Indiana University
P-20	B.R. Howell	Developmental Effects of Adverse Early Experience on Brain White Matter and Behavior	Emory University
P-21	M.C. Tsuda	Peri-Pubertal Onset of Male Aggression Disrupted by Neonatal Maternal Separation Experience	University of Tsukuba, Japan
P-22	A.L. Smith	<i>In-vivo</i> PET Imaging of Neural Oxytocin Receptors	Emory University
P-23	I. Shalev	Vasopressin needs an audience: neuropeptide elicited stress responses are contingent upon perceived social evaluative threats	Hebrew University, Israel; Duke University
P-24	A.C. Keebaugh	Increasing Oxytocin Receptor Expression in Pre-pubertal Female Prairie Voles Enhances Alloparental Responsiveness and Partner Preference Formation in Adults.	Emory University
P-25	M. Kawashima	Actin Dynamics Involved in Sexual Dimorphism of the Preoptic Area in the Rat Brain by Estrogen	Nippon Medical School, Japan
P-26	J.S. Mascaro	Compassion Meditation Enhances Empathic Accuracy and Related Neural Activity	Emory University

No.	Presenters	Title	Affiliation
P-27	D.S. Pradhan	Context is Critical for Understanding the Relationship between Androgens and Aggressive behavior	Georgia State University
P-28	T.K. Solomon-Lane	A Fitness-based Analysis of Social Aptitude: Behavioral Responses to Reproductive Conflict	Georgia State University
P-29	L. McGraw	Uncovering the genomic architecture of male pair bonding behavior in an emerging model organism, the prairie vole (<i>Microtus ochrogaster</i>)	North Carolina State University
P-30	D.S. Stolzenberg	Epigenetic Modifications in the Regulation of Maternal Experience in Mice	University of Virginia
P-31	A.E. Parrish	Capuchin Monkeys Show Active Transfer of Tools But Not Food in a Cooperative Tool-Use Task	Georgia State University
P-32	E. Yamamoto	Recognition of Conspecific Body Movement in Pigeons (<i>Columba livia</i>)	University of Tokyo, Japan
P-33	W. Kirihata	Intralocus sexual conflict in the zebra finch (<i>Taeniopygia guttata</i>)	Cornell University
P-34	A. Saito	Fathers Have Higher Motivation for Parenting than Mothers in Common Marmoset (<i>Callithrix jacchus</i>)	University of Tokyo, Japan
P-35	M. Sasaki	Ndn Deficient Mice Cause Impaired OXTR System in Brain and Defect in Social Behaviors; an ASDs-like Animal Disease Model	Tohoku University, Japan
P-36	S.M. Freeman	Detecting and Localizing Oxytocin Receptor and Vasopressin 1a Receptor in Non-human Primate Brain Tissue	Emory University
P-37	H. Suzuki	Risk Factors Predicting Depressive Symptoms of Children in Residential Foster Care Facilities in Japan	Kumamoto University, Japan
P-38	L.B. King	A SNP in the Prairie Vole Oxytocin Receptor Gene Exhibits Allelic Imbalance and Predicts Individual Variation in Oxytocin Receptor Density in the Nucleus Accumbens	Emory University
P-39	B.L. Pearson	Social and Psycho stimulant Reward in Hypo- and Hyper-social Mice	University of Hawaii
P-40	S.J. Mooney	Oxytocin-immunoreactive neurons in the PVN of the naked mole-rat: The role of social status	University of Toronto, Canada
P-41	A.S. Smith	Stress Recovery and Oxytocin Release in the PVN are influenced by Social Interactions in Female Prairie Voles	Florida State University
P-42	J.A. Solyst	Face-Selective Neurons in the Monkey Hippocampus	Emory University
P-43	E. Hecht	“Unnatural selection” in canids: A new model for genetics, neuroanatomy, and behavior	Emory University
P-44	E. Hecht	Neural adaptations for social learning: Connectivity and responsivity of the mirror system in macaques, chimpanzees, and humans	Emory University
P-45	A. Sullivan	The Sociosexual Brain Disrupted	NC State University
P-46	M.A. Holschbach	Cell proliferation in the dorsal raphe nuclei of pregnant and lactating rats	Michigan State University

P-1: Impact of Early Family Dynamics on Adult Social Behavior: Insights from Prairie Voles

T.H. Ahern

Center for Behavioral Neuroscience, Department of Psychology, Quinnipiac University, Hamden, CT, USA

Early-life experience has the potential to exert a profound influence on adult behavior and neurophysiology. Prairie voles are highly affiliative, socially monogamous, and biparental, thus providing an ideal mammalian model for the study of early social environment on the development of sociality. In the wild, single mothers, two parents, or communal groups rear prairie vole pups. We recreated some of this variation in the laboratory and compared biparental (BP) and single-mother (SM) conditions. Our first study quantified family dynamics, including pup-care and coordination within the two conditions. Our second analysis examined how these rearing conditions influenced the pups' adult behavior, with a particular focus on sociality. Our third analysis investigated the effects of rearing on the organization of socially relevant neuropeptide systems in adulthood. The analyses revealed several striking differences. SM-reared pups were alone on the nest more ($P < 0.001$) and licked and groomed less ($P < 0.01$) than BP-reared animals, in part because BP parents coordinated parental activities. As adults, BP- and SM-reared offspring manifested significantly different rates of social behavior. Compared to BP-reared animals, SM-reared adults exhibited lower rates of allomaternal care ($P < 0.01$), a delayed onset of partner preference formation ($P < 0.01$), and decreased pup-directed licking and grooming postpartum ($P < 0.05$). Rearing condition also affected the brain in a region-specific manner. SM-reared adults had significantly lower densities of oxytocin receptor (OTR) in the bed nucleus of the stria terminalis ($P < 0.05$) and higher densities of corticotrophin-releasing factor receptor 2 (CRF-R2) in the dorsal raphe ($P < 0.05$). They also had a greater number of OT mRNA clusters in the paraventricular nucleus of the hypothalamus ($P < 0.01$). Interestingly, there were no group differences in the density of several socially relevant neuropeptide receptors (V1aR, OTR, CRF-R1, or CRF-R2) in the ventral forebrain (all $P > 0.7$). Overall, our findings reveal that early social dynamics help sculpt adult social behavior, and the further use of this rodent model may reveal to what degree various neural systems are sensitive to early experience and regulate adult social behavior.

P-2: Randomized Controlled Trial of Intranasal Oxytocin for Children with Autism: Research Protocol

D.S. Carson, A.Y. Hardan, and K.J. Parker

Department Psychiatry and Behavioral Science, Stanford University School of Medicine, Stanford, CA, USA

Oxytocin (OT) is a neuropeptide implicated in a wide range of social behaviors including attachment bonds, emotion recognition, eye gaze to social cues, and memory for socially relevant information. Social impairments are a core feature of autism, and emerging evidence suggests that OT biology is dysregulated in individuals with autism. This proposal tests the effects of intranasal OT administration on measures of social behavior and cognition in children with autism. Primary outcomes will be the impact of OT on social responsiveness as determined by a parent/teacher as well as safety measures. Secondary outcomes will be the impact of OT on 1) observed social interaction with an investigator, 2) emotion recognition, and 3) eye gaze. Additionally, this study seeks to identify factors (pre-treatment plasma OT levels and severity of pre-treatment social impairments) that contribute to treatment response efficacy. Participants will be randomized to OT (24IU BID) or placebo (BID) for 8-weeks. All participants will then be invited to participate in an 8-week open-label (24IU BID) extension study. At present, existing pharmacotherapies target only associated features of autism, with no effective drug treatments for the social impairments. This research therefore has high potential to lead to the development of more effective treatments and earlier interventions for children with autism.

P-3: Associations of Oxytocin Receptor Gene (OXTR) Polymorphisms with Cooperation, Perceived Partner Personality, and Emotional Reactions to Betrayal

B.A. Tabak¹, M.E. McCullough², C.S. Carver² and M.L. Cuccaro²

University of California, Los Angeles¹, CA, University of Miami², FL, USA

Variation in the gene that encodes the oxytocin receptor (OXTR) has predicted individual differences in social-cognitive and behavioral functioning, including some prosocial behaviors. To date, no study has investigated OXTR as a predictor of reactions to betrayals of trust while cooperating for mutual benefit. We examined how variation in 10 SNPs on OXTR related to individual differences in behavior, emotional reactions, and partner perceptions following a betrayal of trust in an iterated prisoner's dilemma game. Following correction for multiple testing, one SNP (rs237887) and two haplotypes (A-rs237887, C-rs2268490; G-rs237887, C-rs2268490) were significantly associated with post-betrayal levels of happiness. One haplotype (C-rs9840864, T-rs2268490) was significantly associated with post-betrayal levels of anger. The present findings suggest that variation on OXTR may contribute to individual differences in emotional reactions to betrayals in trust.

P-4: Resilience to Early Life Stress in Prairie Voles (*Microtus ochrogaster*): Potential Moderation by Oxytocin Receptors

C.E. Barrett^{1,2} and L.J. Young^{1,2,3}

Center for Translational Social Neuroscience, Emory University, Atlanta, GA¹; Yerkes National Primate Center, Atlanta, GA²; Department of Psychiatry and Behavioral Science, Atlanta, GA³, USA

Environmental influences during critical periods of neural development can significantly impact adult socio-emotional regulation. Early life stress, particularly resulting from a lack of maternal attention, may lead to hyperactive stress responses and abnormal social interactions in adulthood. We examined the effects of stressors during the postnatal period on adult attachment behavior in the highly social prairie vole. This socially monogamous species forms lifelong pair bonds between mates, which are assessed in the laboratory using the partner preference paradigm. Between PND1-14, entire litters underwent daily 3hr social isolations from siblings and parents. Effects of this paradigm on parental behavior was assessed during 3-1hr periods throughout the day, and anxiety-like behavior in the EPM and open field, alloparental care for novel pups, and partner preference formation were assessed in adult offspring. This separation protocol enhanced maternal licking and grooming immediately upon return of the pups ($p < 0.05$), but not 3 or 6hrs after reunion. As adults, both sexes displayed decreased willingness to explore open arms of the EPM as compared to control, unmanipulated litters ($p < 0.05$). There was no impact in either sex on alloparental behavior. Interestingly, this early isolation differentially affected male and female offspring in their readiness to form partner preferences. After 48hr of cohabitation, isolated male voles formed preferences more readily than did controls ($p < 0.05$). Conversely, isolated females did not display a partner preference after 48 hrs of cohabitation, whereas control females did. To explore the neural mechanisms underlying the disruption in partner preference formation in females, we quantified oxytocin receptor (OTR) density in the nucleus accumbens (NAcc), which is critical for partner preference formation. Early social isolation did not significantly alter NAcc OTR expression ($p > 0.05$). However, in isolated females, but not controls, there was a strong positive correlation between time spent with the male partner and oxytocin receptor binding in the nucleus accumbens ($p < 0.05$). Females with low NAcc OTR expression that experienced early life stress were unable to form social bonds, whereas high expressing females did. This suggests that females expressing low levels of OTR in the NAcc may have a heightened susceptibility to disruptions in social development. Overall, male voles displayed more resilience against early stress than females, consistent with female bias in mood and anxiety disorders.

P-5: Maternal Care but not Plasma Oxytocin Affects Social Behavior across the Estrous Cycle

A.P. Borrow¹, L.R. Moscovice², and N.M. Cameron^{1,2}

Psychology Department, SUNY Binghamton, Binghamton¹, NY; Biology Department, SUNY Binghamton, Binghamton, NY², USA

Natural variations in maternal care have been demonstrated to impact the reproductive systems of human and rodent females. In rats, receiving lower levels of licking and grooming (Low LG) during the first week of life is predictive of greater hormone increases during proestrus compared to females exposed to higher levels of licking and grooming (High LG). Phase of estrous cycle is also thought to impact social learning and social behavior in several species. This study sought to investigate potential differences in oxytocin plasma levels and in affiliative behavior across the estrous cycle as a function of maternal care exposure. High LG (n=14) and Low LG (n=12) adult females pair housed with same-sex siblings were assessed daily for estrous cycle phase via vaginal lavage. Social behaviors were recorded over three 30-minute dark-cycle observations during which the “focal” female in each pair was in proestrus, estrus, and diestrus. It was found that focal High LG offspring, but not Low LG offspring, were mounted by their cage mates significantly more often while in proestrus than in estrus ($p=.039$) or diestrus ($p=.039$). Low LG offspring displayed differences across estrous cycle in frequencies of rough and tumble play ($p=.042$) and partner grooming received ($p=.036$), with the greatest levels occurring while focals were in estrus. Plasma OT levels were also measured and showed no differences in maternal care or in phase of estrous. These findings suggest that variations in maternal care and the state of estrus, but not in OT plasma levels, affect the social behavior of female rats.

P-6: Effects of Post-weaning Adverse Peer Interactions on Emotional and Social behaviors

Q. Meng, R. Bredewold, C.J. Smith, and A.H. Veenema

Neurobiology of Social Behavior Laboratory, Department of Psychology, Boston College, Chestnut Hill, MA, USA

Exposure to peer interactions in early life is important for the development of emotional and social behaviors. However, adverse peer interactions (e.g. victimization through peer bullying) can have detrimental effects on this development. Here, we aimed to develop an animal model of adverse peer interactions in early life by mimicking victimization through peer bullying. In this model, a 3-week-old male rat (the “victim”) is housed with two older same-sex rats during the first two weeks after weaning. We hypothesized that the age, and hence body weight, difference, would induce adverse interactions between the “victim” and the two older peers, which would, in turn, lead to changes in emotional and social behaviors in the “victim”. Indeed, we found that being housed with two older peers increased anxiety-related behavior in the victims and that this was dependent on the body weight difference between victims and peers. Specifically, when the victim-peer body weight ratio was 1:1.5, there was only a trend toward an increase in victims’ anxiety-related behavior as measured on the elevated plus-maze ($p=.076$), while with a ratio larger than 1:2.5, victims showed a significant increase in anxiety-related behavior ($p < 0.05$) compared to controls. We are currently investigating the impact of adverse peer interactions on play-fighting and are comparing this with the impact of absence of peer interactions (post-weaning isolation) and standard peer interactions (post-weaning social housing). We anticipate that this new animal model will provide insights to understanding the neurobiological mechanisms underlying alterations in behavior seen in children exposed to victimization through peer bullying.

P-7: Antisense Knockdown of VIP in the Anterior Hypothalamus Reduces Aggression in a Territorial Finch

J.L. Goodson

Department of Biology, Indiana University, Bloomington, IN, USA

Vasoactive intestinal polypeptide (VIP) neurons and/or fibers are distributed in virtually all regions of the basal forebrain and midbrain that are known to influence aggression and other social behaviors, and exogenous VIP is known to promote resident-intruder aggression in the territorial violet-eared waxbill (*Uraeginthus granatina*), an estrildid finch. However, the importance of endogenous VIP for the regulation of aggression has not previously been demonstrated, and relevant cell groups have not been identified. Indeed, the behavioral functions of VIP are poorly known in general. We now show that knockdown of VIP production in the anterior hypothalamus by antisense oligonucleotides reduces territorial aggression relative to scrambled oligonucleotide controls in male and female waxbills. Antisense infusions reduce VIP-immunoreactive cell numbers in the anterior hypothalamus by approximately 55% (measured following colchicine treatment, which blocks axoplasmic transport) without reducing VIP production in other hypothalamic areas, and virtually abolish aggressive displacements. To our knowledge, these data represent the first identification of VIP neurons that contribute the regulation of social behavior

P-8: From Anti-social to Pro-social: Do Sex Steroids and Oxytocin Play a Role?

K.M. Dumais, T.E. Mayer, C.J. Smith, R. Bredewold and A.H. Veenema

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Compared to male rats, virgin female rats show enhanced social recognition, but reduced social investigation of juvenile conspecifics. Virgin female rats also show low social interest in pups, while maternally experienced females readily approach and take care of pups as a result of sex steroid-induced changes in the oxytocin system around the time of birth. We investigated to what extent maternal experience as well as estrus cycle phase affect social interest (as measured by social investigation) and social recognition. We tested the hypothesis that (i) increased social interest toward pups of maternally-experienced females will generalize to an increased interest toward 4-week old juvenile conspecifics and (ii) social interest will depend on the estrus cycle phase, with estrus females showing the highest interest in juveniles. Our results confirm that females show reduced social investigation, but enhanced social recognition, compared to males. However, maternal experience did not increase social investigation or social recognition of juveniles. We further found that estrus females show enhanced social recognition compared to diestrus, proestrus, or metestrus females, suggesting a possible role of estrogen and progesterone in female social recognition. However, estrus females did not show an increase in social investigation. To further examine the neurobiological basis of the observed, robust sex difference in social investigation, we quantified oxytocin receptor (OTR) binding in forebrain regions of male, virgin female, and maternally experienced rats to test the hypothesis that OTR binding will positively correlate with social investigation scores. Initial findings indeed show positive correlations between social investigation scores and OTR binding in the dorsal caudate putamen and intermediate lateral septum. However, when analyzing within sex, social investigation scores do not correlate with OTR. In conclusion, low social interest, or "anti-social" behavior, of virgin female rats towards juveniles is not altered by either maternal experience or estrus phase. Female rats also show lower OTR binding in specific forebrain regions compared to males, suggesting a link between social interest and OTR in the brain.

P-9: Social Isolation Affects Various Behaviors and Adult Neurogenesis in the Adult Female Prairie Vole (*Microtus ochrogaster*)

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Disruptions of the social environment, such as long-term social isolation, are distressing and can induce various changes to the normal homeostasis of the distressed animal. In the socially monogamous prairie vole (*Microtus ochrogaster*), social isolation has been shown to provoke anxiety-related behavior and to decrease the rate of cell proliferation in selective brain areas in females. In the present study, we examined the effects of long-term (6 weeks) social isolation in adulthood on various behavioral parameters in the female prairie vole. Sexually naïve adult females were either same-sex sibling-housed (Control) or socially isolated (Isolation). After 6 weeks, the animals were tested for anxiety-like behaviors (in the open field and elevated plus maze tests), depression-like behaviors (in the forced swim test), social behaviors (in the affiliation test), and social memory (in the social recognition test). Our data indicate that social isolation increased anxiety- and depression-like behaviors and altered social affiliation without disrupting social memory. Furthermore, in a second set of animals, we examined the effects of long-term social isolation on cell proliferation (assessed by an endogenous cell proliferation marker, Ki67), cell survival (assessed by an exogenous cell division marker, 5-bromo-2'-deoxyridine, BrdU, that was injected into animals prior to the social manipulation), cell differentiation (assessed by fluorescent double-labeling using BrdU and NeuN), and cell death (using TUNEL labeling). Social isolation reduced cell proliferation, survival, and neuronal differentiation and altered cell death in the dentate gyrus of the hippocampus as well as in the amygdale. Together, our data suggest that social isolation not only impairs cell proliferation and survival in selected brain areas but also alters affects anxiety-like, depression-like, and affiliative behaviors in a behavior-specific manner-- , but also impairs both cell proliferation and survival in a brain region-specific manner—promoting the need to further investigate a possible link between altered neurogenesis within the limbic system and behavioral changes in adult female prairie voles.

P-10: VPAC Receptor Antagonism Modulates Social Responses to Novelty

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In both mammals and birds, vasoactive intestinal polypeptide (VIP) neurons and fibers are present in virtually every brain area that is important for social behavior. VIP influences aggression in birds, social recognition in rodents, and modulates prolactin secretion in both taxa, but few studies have examined the social relevance of this peptide. VIP effects are mediated by VPAC receptors, which bind both VIP and pituitary adenylate cyclase activating peptide. Within the lateral septum and medial bed nucleus of the stria terminalis, VPAC receptors are found at a higher density in gregarious finch species relative to territorial species, suggesting the hypothesis that VPAC receptor activation promotes social contact and/or preference for larger groups. Here we here test this hypothesis in zebra finches (*Taeniopygia guttata*), as well as examine the relevance of VPAC receptors to anxiety-like processes. Intraventricular infusions of the VPAC receptor antagonist, neurotensin6-11–mouseVIP7-28, strongly reduce social contact when animals are tested in a novel environment, but have no effect on preferred group sizes. In preference tests for novel versus familiar individuals, the antagonist reduces the percent of time spent with novel birds, but in females only. Although preliminary, tests of novelty-suppressed feeding and exploration revealed no effect of VPAC antagonism on general anxiety-like behaviors. Overall, these results suggest that endogenous activation of VPAC receptors promotes social contact under novel conditions and with novel individuals, a function that may be accentuated in gregarious species.

P-11: Inhaled Oxytocin Amplifies Both Vicarious Reinforcement and Self Reinforcement in Rhesus Macaques (*Macaca mulatta*)

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People attend not only to their own experiences, but also to the experiences of those around them. Such social awareness profoundly influences human behavior by enabling observational learning, as well as by motivating cooperation, charity, empathy, and spite. Oxytocin (OT), a neurosecretory hormone synthesized by hypothalamic neurons in the mammalian brain, can enhance affiliation or boost exclusion in different species in distinct contexts, belying any simple mechanistic neural model. Here we show that inhaled OT penetrates the central nervous system and subsequently enhances the sensitivity of rhesus macaques to rewards occurring to others as well as themselves. Roughly, two hours after inhaling OT, monkeys increased the frequency of prosocial choices associated with reward to another monkey when the alternative was to reward no one. OT also increased attention to the recipient monkey and the time it took to render a decision. By contrast, up to about 2 hours following inhalation, OT increased selfish choices associated with delivery of reward to self over a reward to the other monkey, without affecting attention or decision latency. Despite the differences in species typical social behavior, exogenous, inhaled OT causally promotes social donation behavior in rhesus monkeys, as it does in more egalitarian and monogamous ones like prairie voles and humans, when there is no potential cost to self. These findings potentially implicate shared neural mechanisms.

P-12: Sensitization to Pups Facilitates Maternal Retrieving and Neural Responses in the Medial Preoptic Area in Mice

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We previously reported that social experiences such as mating enhance parental behavior in mice. However, there is little knowledge about the underlying neural mechanisms that enhances parental behavior by social experiences. In this study, we investigated the effects of sensitization to pups on the parental behavior in C57BL/6j (B6) mice.

Virgin female mice were individually introduced into a clean cage 2 days before sensitization to pups. On the treatment day, subjects were divided into 3 groups: the long sensitized group (LS) which received 20min-exposure to 3 pups for 6 times with 3min intervals, the short sensitized group (SS) which received 20min-exposure only once, and non-sensitized group (NS). Four days after these treatments, all subjects were exposed to the 3 pups again and the latency of retrieving each pups was measured. As a result, SS and NS groups showed a significantly longer latency to retrieve each pups than those of LS group. This suggests that longer sensitization to pups enhanced parental behavior in virgin female mice.

Secondly, to clarify the responsive nuclei for enhancement of parental behavior by sensitization to pups, we analyzed the c-fos expressions by immunohistochemistry. We focused on the medial preoptic area (mPOA) which have reported to be important in maternal behavior. When we observed the c-fos expression 1.5h after each sensitization treatments, the SS group showed more c-fos positive cells compared to the NS group. Furthermore, the LS group showed more c-fos positive cells compared to the SS and NS groups. Those indicate that the induction of c-fos expression was depended on the strength of sensitization to the pups. On the other hand, when we analyzed the c-fos induction by 5min-exposure of the 3 pups 4 days after the sensitization to pups, the manner of c-fos induction was different. The LS group showed more c-fos positive cells on the mPOA compared to the SS and NS groups. But, there was no difference of c-fos positive cells between the SS and NS groups. These results suggest that mPOA contribute to heightened parental behavior by sensitization to pups.

P-13: Childhood Maltreatment Effects Face Processing

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The ability to interpret social information is critical for successful interaction with others. While facial cues contain important information for guiding social interactions, not all humans are equally expert at face processing. This variation in face processing ability may be due to a variety of developmental, genetic, and environmental factors. For example, both inhibited adults and adults with a history of childhood maltreatment show alterations in face processing ability. The neural correlates of these face-processing deficits are not well understood. These deficits could be secondary to a heightened sensitivity to perceived threat, which includes overtly threatening people and situations, as well as novel people and situations. In this study, we chose to examine participants with inhibited temperament and varying exposure to childhood maltreatment. We hypothesized that among young adults with an inhibited temperament, severity of childhood maltreatment would correlate positively with blood-oxygenation-level-dependent (BOLD) fMRI signal change in regions subserving face processing and novelty detection during viewing of novel and familiar faces. Childhood maltreatment and temperament were assessed using standard self-report measures. Degree of childhood maltreatment was positively correlated with increased BOLD signal change in response to novel faces in two brain regions—the bilateral fusiform face area and the left hippocampus. These findings suggest that adults with both inhibited temperament and maltreatment history may be particularly vulnerable to neural alterations in regions subserving face processing and novelty detection. This may help to explain the increased risk of social dysfunction and social anxiety disorder among inhibited individuals and those with childhood maltreatment exposure.

P-14: Vasopressin Regulates Play-fighting in Sex- and Context-specific Ways

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The vasopressin system within the lateral septum modulates neural responses to a variety of social stimuli. We recently demonstrated a role for the septal vasopressin system in the regulation of play-fighting behavior in male and female juvenile rats. Play-fighting is usually tested in home-cage settings, which provide a familiar and less fearful environment. However, social behaviors like play-fighting are not limited to this particular environment. Yet, little is known about the influence of different social contexts (e.g. familiar versus unfamiliar) on vasopressin-regulated social behaviors. In the current study, we investigated the extent to which the effects of the septal vasopressin system on play-fighting are dependent upon the social context. Play-fighting was tested in 5-week-old juvenile rats by exposing each rat to a sex- and age-matched unfamiliar rat in a familiar (home-cage) and an unfamiliar (novel-cage) context using a counterbalanced order. In vehicle-treated rats, the percentage of time spent play-fighting did not differ between males and females or between home-cage and novel-cage settings. However, administration of the specific vasopressin V1a receptor antagonist $(\text{CH}_2)_5\text{Tyr(Me)AVP}$ into the lateral septum enhanced play-fighting in males and reduced play-fighting in females in the home-cage setting, confirming our previous findings. Conversely, blockade of septal V1a receptor did not alter play-fighting in either sex in the novel-cage setting. Furthermore, administration of vasopressin into the septum did not alter play-fighting in either sex in the home-cage setting, but decreased play-fighting in females in the novel-cage setting. These findings suggest that the modulation of play-fighting by the septal vasopressin system is social context-specific. While home-cage findings suggest that the septal vasopressin system inhibits play-fighting in males and stimulates play-fighting in females, the opposite is found in novel-cage settings, at least in females. Together, these data may contribute to a better understanding of the impact of different social contexts on the regulation of social behavior.

P-15: ASD-Associated Serotonin Transporter Variant Causes Impairments in Social Communication and Interaction

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Elevated whole blood serotonin (5-HT) levels are present in approximately a quarter of individuals with autism spectrum disorder (ASD). In addition, there is robust evidence of genetic linkage with ASD in the 17q11 region that contains *SLC6A4*, the gene encoding the serotonin transporter. A rare serotonin transporter (SERT) coding variant that causes elevated 5-HT transport, Gly56Ala, is over-transmitted in male ASD probands and associated with specific behavioral features and traits. We have developed mice that express the SERT Ala56 variant to characterize its effect on behavior and brain development. Ala56 mice exhibit elevated whole blood 5-HT levels, recapitulating the hyperserotonemia endophenotype observed in ASD. Using *in vivo* chronoamperometry, we have found that the Ala56 variant leads to increased clearance of 5-HT in the hippocampus. Pharmacological manipulation of the serotonergic system reveals both presynaptic and postsynaptic receptor hypersensitivity in Ala56 mice. Initial behavioral studies have indicated that Ala56 mice display altered social communication and interaction, core behavioral domains in ASD. When separated from their dams at postnatal day 7, we observed a two-fold decrease in ultrasonic vocalizations in Ala56 pups than littermate controls. In the three-chamber test of sociability, Ala56 mice failed to show a preference for another mouse versus an inanimate object. Upon encountering a wild type age- and sex-matched mouse in the tube test for social dominance, we observed that Ala56 mice withdrew from the tube significantly more than littermate controls. Interestingly, we found that chronic fluoxetine treatment partially reversed the decreased social dominance of Ala56 mice in the tube test. Our studies to date reveal multiple physiological, pharmacological, and behavioral phenotypes in the SERT Ala56 mice that provide insights into the role of the serotonergic system in ASD.

P-16: Identification of Truncated Estrogen Receptor α variants in the mouse

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The estrogen receptor α (ER α) gene has a multiple promoter system, and alternative splicing generates several ER α mRNA variants. The expression levels and patterns of ER α variants in the brain have been correlated with aging and neuronal diseases. We therefore examined mouse ER α mRNA variants using rapid amplification of cDNA ends (RACE) and RT-PCR. We cloned multiple mRNA variants encoding C-terminally- and N-terminally-truncated ER α products (CTERPs and NTERPs) from the brain, pituitary, and uterus. CTERP and NTERP mRNAs were generated by alternative splicing of novel terminal exons and alternative usage of intronic promoters, respectively. RT-PCR analysis revealed that CTERPs were widely distributed while NTERPs are preferentially expressed in the brain and pituitary. Moreover, we constructed expression vectors and analyzed the subcellular localization and the transcriptional activation abilities of the variant proteins in transfected HEK293 cells using immunocytochemistry and luciferase reporter assay. We found the nuclear localization of CTERPs and the extra-nuclear localization of NTERPs. CTERPs constitutively activated estrogen response element (ERE)-driven promoters, whereas they repressed transcriptional activation of the promoters by full-length ER α . NTERPs had no ability to activate the ERE promoters regardless of estradiol. Our results indicate that alternative splicing and alternative usage of intronic promoters of the mouse ER α gene contribute to the remarkable diversity of ER α mRNAs and proteins with distinct functions.

P-17: Effects of Heterosexual Social Housing on Ethanol Intake in Prairie Voles

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The prairie vole (*M. ochrogaster*) has recently been proposed as an animal model for understanding social influences on ethanol drinking. Same-sex social housing is associated with higher levels of alcohol preference compared to isolation, as well as robust coordination of ethanol consumption. Under certain social conditions, an animal will alter their own consumption to match the intake of another. The current study examined whether heterosexual pairs display similar patterns of socially influenced drinking. In Experiment I, adult voles were housed in male-female pairs for five days and then placed in mesh-divider cages or isolation housing. Subjects were then given a two-bottle choice test with water and ethanol in increasing concentrations (3%, 6%, and 10% for 4 days each), followed by tastants saccharin and quinine (2 days each). There was no effect of either housing or sex on ethanol preference ratio or g/kg consumed. This contrasts with findings in same-sex pairs. Consistent with same-sex pairs, socially housed subjects had significantly lower quinine preference than isolated subjects, while social housing did not affect saccharin preference. There was a positive correlation between 3% ethanol preference ($r=0.51$) between members of mesh-housed pairs. No other drinking measures were significantly correlated in either group. In Experiment II, adult voles were given a two-bottle choice test (10% ethanol) for 4 days. Subjects were categorized as either low (<5g/kg/day) or high drinking (>9g/kg/day), with remaining animals removed from the study. Subjects were then placed in mesh-divided social housing for 4 days, and then returned to isolation for a final 4 days, with continuous access to alcohol in a two-bottle choice test. During social housing, subjects were paired with an opposite-sex low or high drinking partner. From the baseline isolation period, low drinkers decreased, whereas high drinkers increased alcohol consumption during social housing. From baseline, consumption did not differ when animals were returned to isolation. There were no effects of the sex of the subject, or of social partner's drinking status. These results contrast with same sex pairs, in which high drinkers reduce alcohol consumption during and following social housing with a low drinker. Together, our research suggests that the sex of the social partner influences patterns of drinking in this species.

P-18: Analysis of OXTR on Maternal Behavior by Nuclei-Specific Gene Manipulation

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Recently, neurohypophyseal hormone oxytocin (OXT), widely demonstrated as a neuromodulator has been revalued with its functions. We generated oxytocin receptor (OXTR) knockout (*Oxtr* ^{-/-}) mice, and reported the essential roles of OXTR in regulation of maternal behavior (Takayanagi et al., 2005). Next, we generated OXTR-Venus knock in mice to study the distribution of neurons expressing OXTR in the brain and to characterize them, and we found that OXTR was expressed widely in the various nuclear regions (Yoshida et al., 2009). In this report, first we analyzed the activation of neuron with *Oxtr* ^{-/-} and *Oxtr* ^{+/+} mice, when maternal behavior was induced by adding pups to the tested mice. In the results, the number of c-Fos-positive cells, indicating the activated neurons, decreased in the lateral septal nucleus (LS) of the *Oxtr* ^{-/-} mice in comparison with *Oxtr* ^{+/+} mice. The LS was reported to be one of the centers regulating maternal behaviors (Leckman et al., 2002) and we detected high expression of OXTR in that nuclei (Yoshida et al. 2009). Next, in order to functionally rescue *Oxtr* gene at the restricted regions in the brain of *Oxtr* ^{-/-} mice, we developed AAV-*Oxtr* vector (Sato et al., 2009). The *Oxtr* ^{-/-} mice injected with AAV-*Oxtr* vector into the LS, showed rescued phenotype in the maternal behavior after parturition. These data strongly suggested the critical role of OXTR expressed in the LS for maternal behavior.

P-19: Antisense knockdown of BSTm vasotocin cells produces sex-specific effects on sociality and responses to novelty

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Arginine vasotocin (VT) cells in the medial bed nucleus of the stria terminalis (BSTm) and their projections throughout the basal forebrain are linked to species differences in gregariousness across estrildid finches that vary selectively in their modal species-typical group sizes. Homologous vasopressin (VP) circuits likely promote pair bonding in monogamous voles. These BSTm VT/VP cells and their projections are also sexually dimorphic ($m > f$) in many species. Until recently, however, only indirect evidence suggested that this system promotes gregariousness or modulates other aspects of behavior. Using VT antisense oligonucleotides to selectively knock down VT production in the BSTm of male zebra finches, we previously showed that BSTm VT neurons 1) strongly promote preferences for the larger of two groups ("gregariousness"), 2) slightly decrease social contact durations, and 3) strongly decrease anxiety-like responses to novelty, as shown using tests of exploration and novelty-suppressed feeding. In the present study we show that VT knockdown in females has no effect on social preferences and exploration, but impacts novelty-suppressed feeding in a manner that is strikingly consistent with males. These manipulations suggest that gregariousness is modulated via different mechanisms in male and female zebra finches, and that VT effects on anxiety-like behaviors are modulated both similarly and differently across sexes, depending upon the context.

P-20: Developmental Effects of Adverse Early Experience on Brain White Matter and Behavior

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Early experiences, specifically those involving primary caregivers, are important for socioemotional development in primates. Humans with histories of adverse early experiences such as abuse and neglect are at higher risk for developing psychopathologies including depression, anxiety, and behavioral disorders like conduct disorder. The alterations in the brain that underlie these alterations in social behavior are not well understood due to limitations of human research. Our group utilizes a nonhuman primate model of poor maternal care to investigate the complex relationship between the brain and alterations in emotionality and social behavior. Our model is characterized by physical abuse and intense rejections by the mother during infancy. These behaviors are often interspersed by bouts of competent maternal care much like in humans. Using this model we have investigated long-term effects on social behavior and emotional reactivity, which include increases in aggression, impulsivity and anxiety, and are currently following these alterations throughout development. Our current longitudinal developmental study also aims to determine how alterations in brain development unfold and are related to differences in social behavior using *in vivo* neuroimaging, including magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), allowing us to investigate the structural integrity of specific white matter tracts longitudinally. We are using population-based atlases and tractography to relate development of specific circuits to early experiences. Preliminary results suggest experience related alterations in prefrontal-limbic circuits, including the uncinate fasciculus, which is involved in emotional regulation and reactivity. We hope to shed light on the neurobiological mechanisms underlying behavioral alterations related to adverse early experience to design effective therapies.

P-21: Peri-Pubertal Onset of Male Aggression Disrupted by Neonatal Maternal Separation Experience

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Early adverse experiences in animals have been known to markedly affect the development of subsequent emotional and anxiety-related behaviors, but effects on social behaviors remain largely unknown. Recently, we reported that MS experience influences the development of female but not male social behaviors in adulthood (Tsuda et al, 2006 and 2010). However, whether MS affects social behavior during the adolescent period in male mice is not known. In our recent studies using estrogen receptor β knockout and wild type mice, MS was found to affect the onset and/or expression of male aggression during the pubertal period (Tsuda et al, 2007). Results suggested that MS possibly delays the pubertal onset of male aggressive behavior. In the present study, we further investigated MS effects on the development of male social behaviors by examining social behavioral responses toward same sex stimulus mice and aggressive behaviors during the peri-pubertal period using C57BL/6J male mice.

Between postnatal days 1 through 14, MS pups were separated daily (3h) from the dam. All mice were weaned on postnatal day 21 and then examined for behavioral responses toward same sex stimulus mice in the social investigation test at 5-6 weeks of age and aggressive behaviors from 5-9 weeks of age. Results showed that MS suppressed aggressive behaviors from 5-9 weeks of age compared to control males, but had no effect on social investigative behaviors. Possible neuroendocrine bases of the effects of MS in male mice were investigated by examining levels of oxytocin (OT) and vasopressin (AVP) immunopositive cells in the paraventricular nucleus (PVN) and plasma testosterone in 4 weeks (before puberty onset) to 6 weeks (after puberty onset) old male mice. Results showed that pubertal plasma testosterone levels were significantly lower in MS male mice compared to control mice. Furthermore, peri-pubertal male mice of MS group had lower numbers of AVP positive cells in the PVN, whereas they had an increased number of OT positive cells compared to control mice. These results collectively suggest that MS greatly modified the pubertal development of neuroendocrine systems associated with the regulation of male aggressive behaviors, which may have contributed to the suppression of aggression during adolescence in MS males.

P-22: *In-vivo* PET Imaging of Neural Oxytocin Receptors

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The standard procedure for obtaining diagnoses of autism spectrum disorders as well as several other behavior disorders has been limited primarily to behavior observation. To alleviate the uncertainty of these diagnoses due to the individual variation found in all species, our research efforts have been focused on the development of a tool that would enable *in vivo* quantification of brain receptors known to be related to social behavior. Our primary target has been the oxytocin receptor. Our means for achieving our research goals was to take advantage of positron emitting isotopes and the imaging technology known as PET, or positron emission tomography. We have recently discovered a small molecule ligand, which is potent and selective for the oxytocin receptor, can be labeled with the positron-emitting isotope F-18, and has the ability to penetrate into the brain. This compound, [F-18]ALS-II-69, has been investigated *in vivo* via PET using rats and a non-human primate as our animal models. Our preliminary results have provided images of what we believe to be the first *in vivo* images obtained of the oxytocin receptor density in both the rat brain and the cynomolgous monkey brain. We are currently conducting various experiments to verify this data.

P-23: Vasopressin needs an audience: neuropeptide elicited stress responses are contingent upon perceived social evaluative threats

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The nonapeptide arginine vasopressin (AVP) plays an important role in hypothalamus-pituitary-adrenal axis regulation and also functions as a social hormone in a wide variety of species, from voles to humans. In the current report we use a variety of stress inducing tasks, including the Trier Social Stress Test (TSST) and intranasal administration of AVP to show that intranasal administration of this neuropeptide leads to a significant increase in salivary cortisol and pulse rate, specifically in conditions where subjects perform tasks in the presence of a social evaluative threat (task performance could be negatively judged by others). In contrast, in conditions without a social evaluative threat (no task condition, modified TSST without audience and bike ergometry), subjects receiving AVP did not differ from subjects receiving placebo. Thus, exogenous AVP's influence is contingent upon a circumscribed set of initial conditions that constitute a direct threat to the maintenance of our social selves. Stress evoked by social threat is an integral part of social life and is related to self-esteem and in extreme forms, to poor mental health (e.g., social phobia). Our findings suggest that AVP is a key component in the circuit that interlaces stress and social threat and findings offer inroads to our understanding of individual differences in sociability and in stress response elicited in threatening social situations.

P-24: Increasing Oxytocin Receptor Expression in Pre-pubertal Female Prairie Voles Enhances Alloparental Responsiveness and Partner Preference Formation in Adults.

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Oxytocin receptors (OXTR) in the nucleus accumbens (NAcc) promote alloparental behavior and partner preference formation in female prairie voles. There is significant individual variation in OXTR binding in the NAcc and virgin juvenile and adult females with a high density of OXTR in the NAcc display an elevated propensity to display alloparental behavior toward novel pups. Over-expression of OXTR in the NAcc of adult female prairie voles using viral vector gene transfer facilitates partner preference formation, but has no effect on alloparental behavior, even though OXTR antagonists infused into the NAcc blocks both behaviors. Therefore, we hypothesized that long-termed increases OXTR signaling during development may underlie the relationship between adult OXTR density in the NAcc and alloparental behavior. To test this hypothesis, we used viral vector gene transfer to increase OXTR density in the NAcc of prepubertal, 21 day old female prairie voles and tested for both alloparental behavior and partner preference formation as adults. Consistent with a developmental impact of OXTR signaling, adults over-expressing OXTR from weaning display both increased alloparental behavior and partner preference formation. Thus, the relatively acute impact of elevated OXTR signaling in the NAcc on partner preference formation previously reported appears to be dissociable from effects of longer term, developmentally relevant OXTR signaling necessary for modulating alloparental behavior. These results are consistent with the hypothesis that oxytocin can have both long-term "organizational" effects as well as acute "activational" effects on affiliative behaviors.

P-25: Actin Dynamics Involved in Sexual Dimorphism of the Preoptic Area in the Rat Brain by Estrogen

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Estrogen is a key regulator to establish the sexually differentiated morphology in the rat brain. The volume of the sexually dimorphic nucleus (SDN) of the preoptic area (POA) is several times larger in males than in females. However, the mechanisms of estrogen action in the developing brain to induce sex-specific differences in the POA have not been elucidated yet. We identified 14 estrogen-responsive genes in POA by DNA microarray and *real-time* RT-PCR analyses using total RNA prepared from the brain slices containing SDN-POA of female rats treated with estrogen for one or four day(s) after the birth. In the present study, we examined the expression of these estrogen-responsive genes by Western-blot analysis. Among them, protein kinase C delta (PKC- δ) was significantly up regulated by estrogen in the region containing SDN-POA at postnatal day 5 (PD5). Further analyses revealed that the Rac1-PAK1-LIMK1-cofilin pathway, a downstream pathway of PKC- δ , was modulated by estrogen. We found that estrogen was involved in the signaling through the PAK1-LIMK1-cofilin pathway in the region containing SDN-POA at PD5. Surprisingly, the regulation of phosphorylation of cofilin at serine 3 was observed at SDN-POA by immunohistochemistry, suggesting that actin dynamics is a cue to create a sexual dimorphism in SDN-POA at the critical periods. Finally, we examined the Rac1-to-cofilin pathway using a primary cell culture to confirm the mechanism. This is the first study revealing a potential signaling cascade with which estrogen regulates actin dynamics for cell migration in SDN-POA to induce sex-specific differences during the critical periods.

P-26: Compassion Meditation Enhances Empathic Accuracy and Related Neural Activity

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Recent studies have investigated the neurobiology of empathic accuracy as well as pharmaceutical interventions that may enhance it. However, no studies to date have investigated the effects of behavioral interventions designed to enhance the empathic response. Given that Buddhist meditative techniques have been used for 2 ½ millennia in large part to cultivate compassion and empathy towards others, it is worth investigating whether these techniques amplify empathic accuracy in newly trained meditators. We used a randomized, controlled and longitudinal investigation of a secularized analytical compassion meditation program adapted from the 11th century Tibetan Buddhist *lojong* tradition and employed a battery of social cognitive, neurobiological, personality, and behavioral assessments in order to systematically test the ways in which the practice of compassion meditation led to changes in empathy. Of interest here, subjects completed the Reading the Mind in the Eyes task while receiving a functional MRI (fMRI) scan. Randomization to the meditation group, compared to the control group, enhanced empathic accuracy. The meditation group also had increased neural activity in the inferior frontal gyrus, and this increase in activity accounted for a significant amount of the variance in changes in accuracy. These results represent the first to indicate that a meditation technique enhances empathic accuracy. In addition, this is the first study to show an enhancement of empathy-related neural activity due to a behavioral intervention and it suggests that compassion meditation may represent a unique behavioral intervention for enhancing empathy.

P-27: Context is Critical for Understanding the Relationship between Androgens and Aggressive behavior

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Aggression, one of the most prominent displays of animal communication, is also a widely studied proximate phenomenon. Despite the diversity in natural systems and approaches used to decipher the origin and mechanisms that control agonistic behaviors, it is expressed in tightly regulated windows, dependent on several ecological and social factors. In fish, 11-Ketotestosterone (KT) is the primary potent androgen responsible for activating male breeding morphology and behavior. *Lythrypnus dalli* is a bi-directionally sex changing fish in which 1) KT induces male typical external genital papillae morphology and gonadal function in females, 2) both sexes have similar levels of systemic, brain, and gonadal KT, 3) brain KT levels are several fold higher than the gonads, and 4) both systemic and brain KT, but not gonadal KT, increase transiently during protogynous sex change. These data suggest that we have a limited understanding of how endogenous steroids affect the steroid load within specific tissues. A traditional approach to understanding steroid effects is to examine how systemic steroid manipulations modify behavior and morphology. A socially permissive environment for protogynous sex change induces rapid and transient increases in aggressive behavior and levels of brain and systemic KT. We investigated the role of exogenously elevated cholesterol (control) or KT in the dominant individual in a pair of *L. dalli* females. Within 2 h, there were rapid, subtle, and transient effects on aggressive behavior of KT implanted alphas, and reciprocal effects on betas. On d 3 and d 5, all KT treated females, but not controls, had male typical genital papillae. Despite the dramatic elevation in brain and systemic KT 5 d after implant, overall rates of aggressive behavior remained unaffected. Considering the role of context in shaping the stage for aggression is critical, especially when studying complex hormone-behavior relationships.

P-28: A Fitness-based Analysis of Social Aptitude: Behavioral Responses to Reproductive Conflict

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Although the fitness benefits of sociality are undisputed, it remains unclear how individual social behavior contributes to emergent group dynamics and subsequent individual / group fitness optimization. To test whether certain classes of social behavior and/or group dynamics maximize reproductive success, we quantified egg production and recorded agonistic, affiliative, and reproductive behavior in stable social groups of blue-banded gobies (*Lythrypnus dalli*), a highly social, marine fish that forms harems of a dominant male, and multiple subordinate females. The male fertilizes and cares for eggs contributed by each female in the group. As males increase their fitness by increasing the reproductive success of their females, two factors, in combination, determine reproductive output: 1) the number of eggs laid and 2) the percentage of those eggs that males fertilize, keep healthy, and protect from predation (e.g., females). Alpha female aggression drives down the number of eggs produced by reducing the number of total new clutches laid. Subordinate females may compensate for some of alpha's negative influence on group fitness by avoiding agonistic interactions. No single male behavior explains the variation in eggs laid. In contrast, males with high agonistic efficiency, the percent of approaches that result in displacement, have higher egg retention. Agonistic efficiency, however, is neither necessary nor sufficient for high fitness. Rather, it is an example of a broader class of socially apt behaviors that are associated with certain emergent properties of social group interactions. This work explores the fitness consequences of these behavioral phenotypes.

P-29: Uncovering the genomic architecture of male pair bonding behavior in an emerging model organism, the prairie vole (*Microtus ochrogaster*)

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Unlike most mammalian species, including commonly used animal models such as mice and rats, the prairie vole is highly affiliative, socially monogamous, and biparental. Research in prairie voles, combined with studies of closely related, but asocial vole species, has led to a partial understanding of the neurobiological basis of monogamy, social attachment, nurturing behaviors and social cognition. However, the contribution of the genome in regulating social behaviors is largely unknown. To begin to address this question, we have initiated two complementary approaches to begin to expand our understanding of the genetic architecture of male pair bonding behavior. First, using a selective breeding regime, we are generating two lines of prairie voles where males either display a high propensity to form pair bonds with their mates or do not form pair bonds at all. After five generations of experimental evolution, we have already observed significant divergence in pair bonding behavior between lines. Second, we have developed several genomic resources for the prairie vole including a 10x coverage BAC library, full-length sequences of BAC clones containing 20 behaviorally relevant genes, ~2.8 Mb of prairie vole sequence, identification of ~750 single nucleotide polymorphisms (SNPs), a vole-mouse cytogenetic map and a comprehensive gene catalog from seven vole tissues representing ~16,000 genes. We are utilizing these combined resources to generate a time-course analysis of transcriptome changes within the brain (amygdala, hypothalamus, and ventral striatum) as male prairie voles form a pair bond with their mates. In ongoing, parallel studies using an asocial vole species and the selective breeding lines described above, we will be able to further delineate the transcriptome differences in social versus asocial brains. These studies demonstrate the utility and feasibility of using non-traditional, but exemplary model species for understanding the biological basis of complex behaviors.

P-30: Epigenetic Modifications in the Regulation of Maternal Experience in Mice

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Subtle differences in the amount of time new mothers spend with infants at birth have substantial effects on the quality of their subsequent maternal care, which in turn affects infant development. Therefore, understanding how an initial mother-infant interaction produces stable changes in gene expression and sustains high levels of maternal care is essential for understanding how these mechanisms might fail in mothers that fail to bond with their infants. We have recently shown that, like humans, subtle differences in the amount of maternal experience in mice substantially affect maternal behavior. For example, whereas 2 days of pup experience (2 hours/day) promoted maternal responsiveness in the familiar home cage, at least 4 days of pup experience was necessary for females to respond to pups and retrieve them on a novel T-maze. Here we report that administration of sodium butyrate (NaB), a drug that enhances experience-induced histone acetylation, accelerated the expression of estrogen receptor beta (*Esr2*), oxytocin (*Oxt*), oxytocin receptor (*Oxtr*) and cyclic AMP response element binding protein binding protein (*Crebbp*; a histone acetyltransferase) in the medial preoptic area (MPOA), a critical neural site for maternal responsiveness. The enhancement of gene expression in MPOA by NaB was sufficient to enhance maternal responsiveness, because NaB treated females with 2 days of experience also responded to pups in the novel T-maze. Taken together, our data show that NaB enhanced the effects of maternal experience on maternal care and suggest that histone acetylation is one mechanism through which experience induces and sustains high levels of maternal care.

P-31: Capuchin Monkeys Show Active Transfer of Tools But Not Food in a Cooperative Tool-Use Task

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Early experimental studies on prosocial behavior among non-human primates have led to conflicting results, even within the same species. These contradictory findings have been argued to be due to interactions taking place in the direct context of food, a highly valued resource for all animal species. Instead of using food-sharing as the sole measure of prosocial behavior, the current study examined prosocial behavior among capuchin monkeys (*Cebus apella*) in a tool-use task that combined both food and non-food transfers, to better understand the species-typical cooperative tendencies and the potential differential treatment of foods and non-foods in a prosocial task. We investigated whether capuchin monkeys would transfer a necessary tool to a partner in conditions in which both monkeys (cooperative payoff) or only the partner (altruistic payoff) benefited. Notably, tool transfer in both payoff conditions was overwhelmingly active in nature, which is atypical in the context of food sharing outside of the callithrichids. In contrast to this, food sharing was exclusively passive. Moreover, capuchins were more attentive to the contingencies of the task in the altruistic, rather than cooperative, payoff situation, indicating that the presence of food for the subject may affect decision-making. These data indicate that capuchin monkeys treat food and non-foods differently within the same task and that even active prosocial behavior is present in certain circumstances amongst primates other than humans and other cooperatively breeding species. These results both expand our understanding of prosocial behavior in non-human primates and provide novel experimental approaches to address this unresolved issue.

P-32: Recognition of Conspecific Body Movement in Pigeons (*Columba livia*)

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We examined whether pigeons (*Columba livia*) recognize body movement patterns in conspecific stimuli. Experiment 1 examined whether they discriminate between individuals (physical characteristic cues) and behavioral states (body movement pattern cues) in conspecific stimuli. Four types of conspecific video images were used as stimuli. These were video clips of two conspecifics (individuals A and B) in two different behavioral states (excited or sedated). Half of the subjects were trained to discriminate the two different states, irrespective of the individual (behavioral state discrimination group), and the others were trained to discriminate the individuals, irrespective of the behavioral state (individual discrimination group). Both groups of the subjects successfully discriminated the conspecific video image stimuli using behavioral states or the individuals as cues. Additionally they showed successful transfer to novel stimuli, suggesting that the body movement patterns and individuals were used as a discriminative cue. Experiment 2 examined whether pigeons discriminate biological motion (BM) stimuli using body movement patterns as same as video image stimuli. BM stimulus refers to display consisted of a number of small bright dots attached to the principal joints of the pigeon's body. Two types of video image stimuli and two types of BM stimuli were used as sample and comparison stimuli. Pigeons were presented with the sample, and then were trained to respond to the correct comparison stimulus according to the body movement patterns of the stimuli (matching-to-sample and oddity-from-sample tasks). The pigeons acquired the discrimination between body movement patterns in the video image stimuli, but they did not in the BM stimuli. We will discuss about visual processes underlying body movement pattern discrimination based on the results of two experiments.

P-33: Intralocus sexual conflict in the zebra finch (*Taeniopygia guttata*)

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Intralocus sexual conflict (IASC) occurs when a shared trait is encoded by the same set of genes, and opposing sex-specific selection on this trait prevents one or both sexes from reaching their phenotypic optima. IASC may be especially prominent when a trait that promotes high fitness for males results in low fitness for females, and when this trait is highly correlated between the sexes. A common assumption of sexual selection theory is that females will choose the best quality males to produce offspring of the best quality. In contrast, IASC indicates that mating with the best male may not always be the best strategy, due to possible detrimental effects on daughters. Thus, we propose that males and females will choose to mate with partners that will help combat the effects of IASC and maximize fitness of both daughters and sons. In the zebra finch (*Taeniopygia guttata*), beak color is highly correlated between parents and offspring of the same and opposite sex. Females in this species often prefer red-beaked males, whereas males prefer orange-beaked females, resulting in opposing optimal beak colors for the sexes and potential IASC. However, there is evidence for low between-female agreement in choosing males based on beak color, making assortative mating a possibility. We are currently testing whether birds are choosing partners based on beak color compatibility using a mate choice paradigm. Beak color is correlated with testosterone level, and choosing a mate based on this trait may have important implications for reproductive success, both in terms of offspring fitness and coordination of parental behaviors. We predict that partners possessing opposite beak colors will be the most successful in coordinating parental behaviors and have offspring with the highest fitness. Therefore, males and females will choose partners most compatible with their own phenotype. Testosterone affects males and females differentially, and compatibility of this physiological trait may have significant effects on the resulting offspring. In this way, mating to reduce IASC may help in facilitating cooperation between parents and maximizing the fitness of both male and female offspring.

P-34: Fathers Have Higher Motivation for Parenting than Mothers in Common Marmoset

(*Callithrix jacchus*)

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Common marmosets are cooperative breeders and their parental or alloparental behavior has been evaluated on the basis of the frequency of carrying infants in a family group. However, under such a situation, the amount of time spent on carrying did not directly reflect the level of motivation for parental or alloparental behavior because of interference by other family members. To directly evaluate the motivation for such behavior in common marmosets, animals should be tested where each subject is separated from other family members. We adopted the infant-retrieval test to compare the motivation for parental or alloparental behavior among family members; 8 fathers, 8 mothers, 14 older brothers, and 9 older sisters. We measured the time from the infant presentation to the retrieval of the infant by each subject as the index of the motivation. We conducted the test when the infant age was 1-8 days old. All the fathers invariably retrieved their infants promptly, but some mothers did not. This variation of responsiveness of mothers was partially explained by the amount of their experience of having their own infants. There was a tendency that inexperienced mothers took a longer time to retrieve infants than experienced ones. Older siblings took a significantly longer time to retrieve infants than fathers during the first few days, but their latency became the same as that of parents in the 8-day test period. Our present findings indicate that fathers' motivation is invariably high whereas mothers' is more variable, and that parental and alloparental behavior may change depending on experience.

P-35: Ndn Deficient Mice Cause Impaired OXTR System in Brain and Defect in Social Behaviors; an ASDs-like Animal Disease Model

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Prader-Willi syndrome (PWS) is a complex genetic disorder that occurs due to the lack of expression of paternally imprinted genes on chromosomal 15q11-q13. It is characterized by hyperphagia, abnormal thermoregulation, developmental delay, and so on. *Necdin* (*Ndn*) in this locus is one of the suspected genes responsible for PWS. *Ndn*-deficient mice display phenotypes similar to PWS, such as abnormal behaviors and impairment in neuronal development. We focused to study the pathogenic mechanism in the PWS using *Ndn*-deficient mice. Reduction in the number of the OXT-producing neurons in the PVN was reported in the recent study with the PWS patients. Similar etiology was observed with the *Ndn*-deficient mice. We reproducibly confirmed it in the PVN, and further we detected the reduced density of OXT-producing neurons in the supraoptic nucleus (SON; another nucleus for central OXT) in the mutant mice. Next, to study the physiological similarity between the PWS patients and the mutant mice, we tested the thermoregulation and sociality of *Ndn*-deficient mice. They showed acute decrease in rectal temperature just after the exposure to cold. We also detected notable decrease of OXTR-expressing neurons in the Ventromedial hypothalamic area (VMH), which is one of the central thermoregulatory neurons. By the social recognition test, we detected significant difference with the mutant mice in comparison with that of the wild-type animals, in a couple with the decreased number of OXTR-expressing neurons in the LS. It might have novel implication to understand the physiological mechanism of PWS, if decreased number of the OXTR-expressing neurons in these nucleus were also observed in the PWS patients.

P-36: Detecting and Localizing Oxytocin Receptor and Vasopressin 1a Receptor in Non-human Primate Brain Tissue

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The neuropeptide oxytocin (OT) mediates many of the physiological changes associated with parturition in mammals, including uterine contractions and lactation, and plays a critical role in the brains of animals to mediate prosocial behavior and attachment, such as maternal care and pair bonding in monogamous species. Studies in humans using intranasal administration of OT have shown that OT can positively affect certain social behaviors, such as trust, empathy, face perception, and emotion recognition. I am interested in studying the potential contribution of OT to the expression of social behavior in non-human primates. In order to begin to study this system in the brains of primates, it is critical to determine in what brain areas the OT receptor (OTR) is expressed. However, the neuroanatomical distribution of OTR in primate brain has not been elucidated due to technical limitations in the pharmacological tools available for this system. These limitations in localizing OTR in primates have significantly hindered research in this field. To ameliorate this, I am working on two new visualization methods. First, I am modifying a commonly used method called receptor autoradiography for use in postmortem primate tissue in order to provide the necessary neuroanatomical foundation for future studies of OT and primate behavior. Second, I am helping to develop an OTR PET ligand for *in vivo* neuroimaging, which could be used to characterize the brain pathology for conditions characterized by deficits in social behavior, such as autism, as well as for behavioral problems such as child abuse, to determine whether the OT system is involved. This poster presents our progress to date on both of these new visualization efforts.

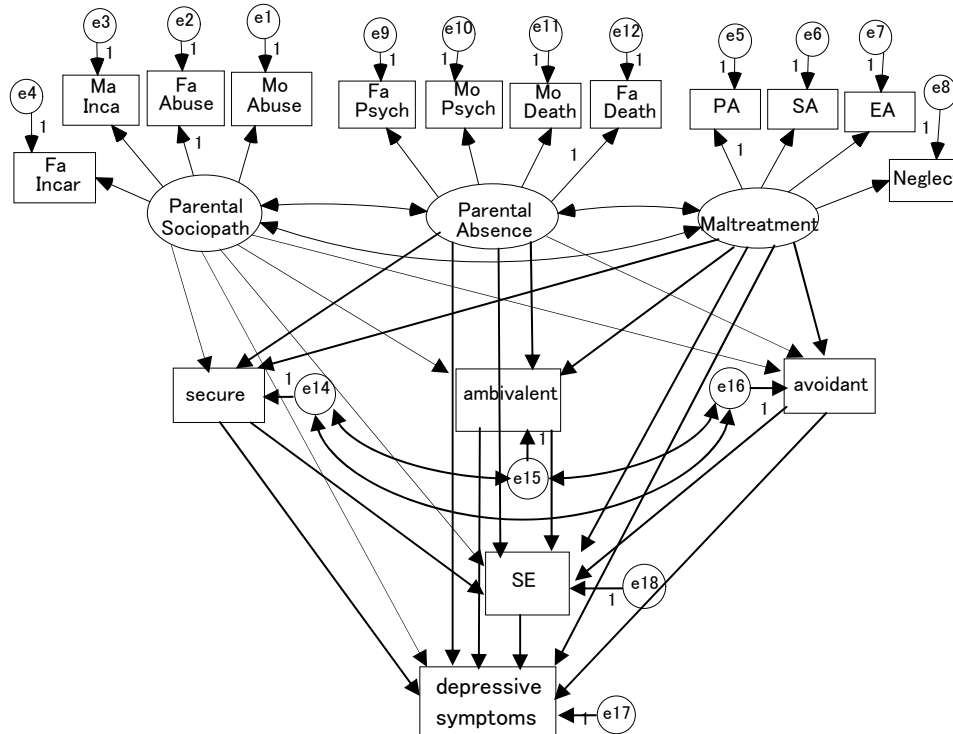
Poster 37: Risk Factors Predicting Depressive Symptoms of Children in Residential Foster Care Facilities in Japan

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This study was conducted to investigate the relationships among adverse childhood experiences (ACEs), attachment, self-esteem, and depressive symptoms among children living in residential foster care facilities in Japan. Three hundred and fifty children (female=197; male=153) aged from 9 to 18 years old (mean=13.50±2.36) and their case workers from sixteen facilities (return rate of 50%) participated in the study. Informed consent and assent were obtained before participation. Children answered questionnaires on attachment, self-esteem, and depressive symptoms, and case workers answered questionnaires on ACEs. Structural equation model using Amos was created to analyze the data (Figure 1). The proposed model had a good fit (GFI=.96, AGFI=.94, CFI=.95, RMSEA=.03, $p=.023$). It revealed that maltreatment defined with abuse and neglect was directly predictive of avoidant attachment style, which influenced depressive symptoms directly, and ambivalent attachment style, which in turn affected depressive symptoms directly and through self-esteem. Also, parental sociopath defined with parental incarceration and substance or alcohol abuse was directly predictive of depressive symptoms. It also was predictive of secure attachment style, which affected depressive symptoms directly, and through self-esteem. Parental absence defined with parental psychopathology and death did not significantly predict any of the variables tested in this model. The findings indicate the importance of providing mental health care with reconstruction of attachment and self-esteem among children who have experienced maltreatment and parental criminal activities prior to entry into care.

Figure1 SEM testing the relationships among ACEs, attachment, self-esteem and depressive symptoms



P-38: A SNP in the Prairie Vole Oxytocin Receptor Gene Exhibits Allelic Imbalance and Predicts Individual Variation in Oxytocin Receptor Density in the Nucleus Accumbens

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Diversity in brain oxytocin receptor (*Oxtr*) expression is associated with species differences and individual variation in social behavior. Monogamous prairie voles have high densities of OXTR in the nucleus accumbens (NAcc) compared to non-monogamous species, and OXTR signaling in NAcc is necessary for partner preference formation. There is remarkable individual variation in OXTR density in the NAcc that is not present in non-striatal brain regions. Females with higher OXTR density in the NAcc display higher levels of alloparental nurturing behavior, and increasing OXTR density in the NAcc using gene transfer facilitates partner preference formation. To test the hypothesis that genetic polymorphisms contribute to this variation in *Oxtr* expression, we used pyrosequencing to survey for allelic expression imbalance (AEI) of *Oxtr* mRNA in the NAcc of individual prairie voles. AEI compares mRNA levels derived from each allele, identified by a single nucleotide polymorphism (SNP) within an individual. AEI is indicative of linked regulatory elements contributing to variation in gene expression rather than epigenetic factors. We resequenced the *Oxtr* from 19 prairie voles to identify common SNPs within *Oxtr* exons. We then identified five animals heterozygous at SNP 2 (C/T), which lies within the 3' untranslated region of the *Oxtr*. Genomic DNA (gDNA) and cDNA derived from NAcc were amplified by PCR and pyrosequenced. The relative abundance for the T to C allele was calculated. The ratios for cDNA were divided by the average gDNA ratio to normalize against assay bias. The cDNA T/C ratios for SNP 2 ranged from 1.16 – 9.00, indicating consistent AEI, with T always greater than C. Log transformed T/C ratios were greater for cDNA than gDNA from the same individuals ($p < 0.05$, paired t-test), confirming that *Oxtr* exhibits AEI in prairie vole NAcc. We then genotyped 10 voles with known extremes of NAcc OXTR density: 5 High and 5 Low. Each of the 5 High OXTR voles were heterozygous C/T while all 5 Low voles were homozygous C/C at SNP 2. The C/T genotype was associated with high OXTR density ($p < 0.01$, fisher exact test). These data suggest the T allele of SNP 2 is either causative or linked to a regulatory variant that potentiates *Oxtr* expression. Thus, SNP 2 is a useful marker to predict NAcc OXTR densities at birth. As SNPs in the human OXTR have been linked to variation in social behavior, and reduced OXTR has been reported in autism, the prairie vole may be useful for modeling OXTR genetic contributions to human cognition.

P-39: Social and Psycho stimulant Reward in Hypo- and Hyper-social Mice

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A variety of inbred and mutant strains of mice exhibit impairments in social behaviors and restricted, repetitive behaviors; these constitute face validity for autism models. However, existing tests are often unable to evaluate the psychological state eliciting the impaired social interactions. A series of studies was conducted to assess social behavior and motivation in hyper-social methyl CpG binding protein 2 (*Mecp2*) and hypo-social BTBR T+tf/J (BTBR) mice. BTBR mice show a pronounced deficit in a social-conditioned place preference paradigm compared to socially normal C57Bl/6J mice. Alongside social measures, psycho stimulant responsivity was reduced in BTBR and *Mecp2* mutant mice, relative to their respective controls, suggesting potential alterations of positive-incentive evaluations in mice with disparate forms of sociability. Inflexibility in reinforced responses to socially relevant stimuli through development may underlie aberrant social behavior phenotypes. Ongoing research aimed to clarify the roles of nucleus accumbens dopamine in social motivation in these strains, as well as the potential developmental and therapeutic implications of disturbances in these systems will be discussed

P-40: Oxytocin-immunoreactive neurons in the PVN of the naked mole-rat: The role of social status

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Naked mole-rats (*Heterocephalus glaber*) are colonial rodents exhibiting the strictest reproductive dominance hierarchy among mammals. Several reproductive brain regions, including the paraventricular nucleus of the hypothalamus (PVN), are larger in breeders than subordinates. The PVN is a primary site for production of oxytocin (OXT), a peptide hormone that regulates a number of sexual and social behaviors. To determine if OXT neurons contribute to the status differences in PVN volume, we performed immunohistochemistry to visualize OXT neurons in the brains of dominant breeders and subordinate non-breeders from established colonies. Stereological analysis of OXT-immunoreactive (OXT-ir) cell number and volume revealed that subordinates had significantly more OXT-ir neurons in the PVN than breeders. No differences were found in OXT-ir cell volume. OXT production in this region is regulated by acute and chronic stress in rodents; the larger number of OXT-ir neurons in subordinates may be due to the constant antagonism from dominant breeders that is thought to maintain the social hierarchy. However, subordinates also exhibit a number of prosocial behaviors including alloparental care, food procurement, burrow maintenance, and colony defense. Many of these behaviors are mediated by OXT in other mammals. Thus, higher numbers of OXT-producing neurons may also contribute to these behaviors in naked mole-rats. Subordinates that were removed from their colonies and paired with a same- or opposite-sex subordinate conspecific for 6 months showed numbers of OXT-ir neurons approaching that of breeders, suggesting that removal from the colony and release from subordination decreases OXT-ir neuron number in the PVN.

P-41: Social Support Attenuates the Stress Response and Promotes Oxytocin Release in Female Prairie Voles

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Stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis depends on contextual factors and can have pathological consequences. Interestingly, social support may attenuate this response, yet the neuroendocrine mechanism is unknown. The prairie vole (*Microtus ochrogaster*) is a monogamous rodent that forms long-term pair bonds. In females, social interaction reduces basal HPA activity while promoting the release of hormones that may regulate this process. In a series of experiments, we stressed pair-bonded female prairie voles while varying contextual and social factors, examined their anxiety-like behaviors by an elevated plus maze test, and measured circulating corticosterone (CORT) levels by an RIA. In Experiment 1, females were exposed to environmental novelty, conspecific aggression, or immobilized restraint stress. All three stress groups showed an increase in circulating CORT compared to control females, but only immobilized females displayed more anxiety-like behaviors. In Experiment 2, females were immobilized acutely or repeatedly over 3 or 7 days. Females habituated to subchronic and chronic immobilization physiologically and behaviorally as their CORT levels and anxiety-like behaviors were lower than acutely immobilized females. In Experiment 3, immobilized females recovered alone or with their male partner for 30-min. Social support attenuated the stress response as the immobilization-induced increases in CORT and anxiety-like behaviors were eliminated when females recovered with their male partner. In Experiment 4, oxytocin, vasopressin, and corticotrophin-releasing hormones (CRH) content and receptor densities were assessed in brain tissue punches from females in Experiment 3. Oxytocin, but not vasopressin or CRH, content in the paraventricular nucleus (PVN) was significantly lower after 30-min of social support, indicating a support-induced oxytocin release. Together, our data suggest that in female prairie voles the stress response depends on stress conditions and the social environment, and social support may attenuate the stress response by promoting PVN oxytocin release. (Supported by NSF Graduate Research Fellowship and NIMHR01-058616).

P-42: Face-Selective Neurons in the Monkey Hippocampus

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The ability to recognize previously encountered individuals as familiar is a critical skill for human and non-human primates living in large, stable social groups. Autistic individuals show impairments in recognition memory for faces, but the neurophysiological mechanisms of this ability are currently poorly understood. Selective responses of single neurons to faces have been recorded from rhesus macaques in the inferior temporal cortex; amygdala, orbitofrontal cortex, and prefrontal cortex, suggesting a network of neuronal ensembles that selectively process faces. Single neurons in the human hippocampus can discriminate novel and familiar stimuli through changes in firing rate, and most are category specific, i.e., respond preferentially to faces or objects. However, face-selective neurons have previously not been described in the macaque hippocampus. We examined the activity of 126 hippocampal neurons while tracking gaze as monkeys viewed images of novel faces compared to novel non-face stimuli. During recordings, two monkeys performed the Visual Preferential Looking Task (VPLT), which assesses recognition memory by measuring the reduction in time spent looking at an image when it is repeated compared to when it is novel. Nearly 9,000 complex images were presented, with each image presented exactly twice. All images were categorized as face (containing faces of humans and animals) or non-face (a wide variety of other stimuli). Sixty-four neurons (51%) gave significant responses to faces relative to the baseline pre-stimulus period. Seventeen (27%) of these face-responsive cells were considered face-selective in that their average response to faces was significantly different than that to non-face stimuli. This difference enables these cells to accurately discriminate between faces and non-faces, according to ROC analysis. Critically, face-selective neurons exhibited modulations of firing rate selectively in response to faces, and previous studies in our lab have found that the degree of this firing rate modulation is correlated with memory strength. Future experiments will identify the effect of oxytocin on the activity of face-selective neurons in the hippocampus and amygdala and correlate this effect with recognition memory for faces.

P-43: “Unnatural selection” in canids: A new model for genetics, neuroanatomy, and behavior

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Disorders of social behavior have a substantial impact on society. Treatment development is limited by our understanding of these disorders' underlying physiology and genetics, which, in turn, is limited by the validity of animal models. We introduce a novel and uniquely powerful approach for studying the neural basis of social behavior. This is a comparison between canids that vary in affiliation/aggression behavior – specifically, domestic foxes, domestic dogs, and wild canids. Two strains of the silver fox (*Vulpes vulpes*) have been developed at the Russian Institute of Cytology and Genetics in Siberia. One strain was selectively bred for affiliative behavior towards humans (tameness). The other was selectively bred for aggression. The two strains show striking inherited differences in their social behavior; the tame individuals resemble domestic dogs and are actually sold as pets. Endocrine differences between the strains are well established, and genetic differences are just beginning to be investigated. Endocrine and genetic information is also available in various domestic dogs and wild canids. However, neural differences between these groups have never been addressed. To that end, we are comparing structural and DTI scans of tame and aggressive domesticated foxes, various breeds of domestic dogs, and wild canids. This approach presents a uniquely powerful research opportunity for several reasons. First, our datasets afford investigation at multiple levels: behavior, neuroanatomy and connectivity, neurophysiology, and genetics. Second, within-species comparisons of variation in social behavior allow for an unparalleled level of control. Finally, canids themselves are an excellent but understudied model system for human social behavior: they are among the most intelligent, most socially complex, and largest-brained mammals, and they can pass tests of social cognition that are failed even by chimpanzees, our closest living relatives. Like humans, canids acquire social skills during a developmental critical period in which specific environmental inputs have specific effects on adult behavior. This critical period has been well characterized in various domestic and wild canid species, providing particular significance for developmental disorders of social behavior like autism.

P-44: Neural adaptations for social learning: Connectivity and responsivity of the mirror system in macaques, chimpanzees, and humans

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Social learning varies across primate species. Humans have a broad and complex repertoire of socially transmitted behaviors. We can duplicate not only the result of an observed action, but also the specific kinematic method in which it is achieved. In contrast, macaques duplicate only observed actions' results. These species differences in behavior are paralleled by species differences in brain activity. Both humans and macaques have a fronto-parietal action observation/execution matching system. In macaques, this system responds only to object-directed actions – those that involve results. In humans, it also responds to purely kinematic, non-object-directed actions. The chimpanzee mirror system has never been studied, but presents an important comparison point because chimpanzees' social learning abilities are intermediate to macaques' and humans'. We hypothesized that species differences in social learning may be related to which aspects of observed actions are "mirrored" in the brain. Because each node of the mirror system performs a different type of information processing, species differences in the connectivity between these nodes could produce species differences in which aspects of observed actions can be "mirrored" and thus copied. We compared diffusion tensor imaging scans in macaques, chimpanzees, and humans. In macaques and chimpanzees, the preponderance of this circuitry consists of frontal-temporal connections via the extreme/external capsules. In contrast, humans have more substantial temporal-parietal and frontal-parietal connections via the middle/inferior longitudinal fasciculi and the third branch of the superior longitudinal fasciculus. In chimpanzees and humans but not macaques, this circuitry includes connections with inferior temporal cortex. In humans alone, connections with superior parietal cortex were also detected. We also performed FDG-PET in four chimpanzees, providing the first functional neuroimaging data on the chimpanzee mirror system. Each subject was scanned in four separate conditions: action execution, transitive action observation, intransitive action observation, and rest. In both execution and transitive observation, chimpanzees activated frontal and parietal regions homologous to macaque and human "mirror areas." In intransitive observation, these activations were weaker and more variable across subjects. Together with our DTI data, this suggests that the human mirror system is uniquely adapted for copying the kinematic details of observed actions. We present a model linking species differences in mirror system connectivity and responsivity with species differences in social learning behavior.

P-45: The Sociosexual Brain Disrupted

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It has been hypothesized that the purported increase in childhood neurobehavioral disorders may result, in part, from exposure to endocrine disrupting compounds during critical windows of development. Bisphenol A (BPA) is a xenoestrogen that leaches from polycarbonate plastics and epoxy resins. Human exposure is greater in infants and children than adults prompting concern that it may interfere with hormone-dependent development and behavior. Similarly, phytoestrogens found in soy have also become a concern due to rapidly elevating consumption levels. Here we explored the impacts of a human-relevant exposure to these two ubiquitous endocrine disruptors by 1) orally exposing rats via drinking water to BPA (1mg/L) from gestation through adolescence thereby maintaining chronic, low exposure during critical windows of development and 2) additionally testing a soy based diet versus a soy free diet in conjunction with BPA exposure. We hypothesized that low dose BPA exposure during critical periods of hypothalamic organization would result in reduced exploratory behavior and elevated anxiety in rats, and that a soy diet would compound the impacts. BPA and soy alone each significantly increased anxiety-like behavior in both sexes of juvenile rats while the combination of the two did not. Adult male BPA exposed rats displayed significant social recognition deficits. To explore the neuroendocrine mechanisms potentially underlying these behavioral changes, we quantified the expression of a group of candidate genes known to be important for sexually dimorphic sociosexual behavior, in the extended olfactory amygdala. Altered genes included ER β , Kiss1, Mc4R, AVP and OT. Some of these have been associated with neurobehavioral disorders in humans, particularly children.

P-46: Cell proliferation in the dorsal raphe nuclei of pregnant and lactating rats

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Pregnancy and the postpartum period are associated with profound neurobehavioral changes. These changes are accompanied by time- and region-specific alterations in cell proliferation and survival within the brain. Although research on this outside of the hippocampal formation and olfactory system is sparse, recent findings suggest that reproductive experience does affect cell proliferation and survival elsewhere (e.g. maternal experience increases cell survival in the nucleus accumbens and bed nucleus of the stria terminalis; Akbari et al., 2007). Here we report the recent discovery of abundant cell proliferation in the dorsal raphe of adult female rats during pregnancy and lactation, but not before mating, using immunohistochemistry against Ki-67, an endogenous protein present in dividing cells throughout mitotic stages. This increase in cell proliferation may provide enhanced regulation of the serotonergic system, a system crucial for nursing and other maternal and emotional behaviors. In addition, three other brain areas (supraoptic nucleus, the periventricular nucleus, locus coeruleus) contained many Ki-67 immunopositive cells, but this was true regardless of reproductive stage. We are currently using bromodeoxyuridine (BrdU) to determine whether dorsal raphe cell survival is also enhanced in reproductively-experienced females or if the proliferated cells die before reaching maturity. An understanding of neural plasticity within the serotonin system and elsewhere in the maternal brain is crucial to better comprehend the suite of changes associated with reproduction and parenthood.

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