This video series was made possible through a generous grant from the National Institute of General Medicines (Grant Number: 5 R25 GM133017-03), awarded to Cohen Veterans Bioscience (Principal Investigator: Chantelle Ferland-Beckham, PhD)

Module 1, Video 6: Sex differences in adult social behavior

In the past three decades, rapid advancements in molecular, cellular and genetic methodologies, as well as the implementation of cutting-edge imaging technologies, have accelerated our understanding of animal and human social behavior. While the most frequently studied aspect of adult social behavior is the regulation of sexual and reproductive behaviors, other social behaviors such as social recognition, social learning, and aggression have also been shown to have sex-specific patterns of regulation. Gonadal hormones regulate most social behaviors. Many of these sexually dimorphic differences may be linked to the higher incidence and/or severity of risk-taking disorders, impulsive behaviors, and disorders characterized by altered social behavior such as autism spectrum disorders [1], early onset schizophrenia [2], and violence and impulsive aggression [3, 4]. Differences in social behavior may also underlie sex-specific differences in the response to social stressors [5]. In this video, we will take a look at what is known about sex differences in social behaviors, focusing on social recognition, social learning and aggression.

Social recognition, or the ability to tell the difference between conspecifics, is important for social interactions. This behavior is important for the establishment and maintenance of social hierarchies, social bonds, mate choice, territoriality, and avoidance of infected or sick individuals.

Most evidence supports that estrogens enhance social recognition in adults of both sexes, with little to no effect during the sexual differentiation phase of development [6, 7] [8] [9] [10] [11]. The alpha form of the estrogen receptor appears dominant [12-14], although a role for estrogen receptor-beta and possibly androgen receptors cannot be completely ruled out [6]. The neural circuitry that controls social recognition is not fully understood but likely involves many of the brain regions known to exhibit sex differences and contribute to the expression of sex-typic behaviors. In males, the lateral septum is particularly implicated in social recognition [15, 16], whereas the medial amygdala is critical in both sexes [17].

The mechanism by which estradiol enhances social recognition is not well understood but it may diverge in the two sexes since the neuropeptide arginine vasopressin is necessary for social recognition in males but not females [18, 19]. Thus, understanding the commonalities and differences between males and females in how estrogens regulate this essential behavior is important.

This video series was made possible through a generous grant from the National Institute of General Medicines (Grant Number: 5 R25 GM133017-03), awarded to Cohen Veterans Bioscience (Principal Investigator: Chantelle Ferland-Beckham, PhD)

Estrogens also regulate another form of social behavior known as social learning. Social learning is learning that occurs by observing or interacting with another animal, typically a conspecific, or its products, like urine. Social learning is observed in both males and females but the two sexes are often not directly compared or the sex of the subjects is not reported [21]. Observed sex differences in social learning among rodents, birds, and humans have largely indicated that females outperform males, although in humans, these sex differences may be more nuanced [6]. Research on the role of sex hormones in social learning to date has been limited to the effect of estrogens in females, particularly for one type of social learning—the social transmission of food preferences [6, 22, 23]. In rodents, when an observer interacts briefly with a conspecific—or demonstrator—that has eaten a distinctively flavored food, the observer's preference for whatever food the demonstrator ate is enhanced through social learning.

This behavior is evolutionarily adaptive, is observed in mice, rats, and gerbils and fluctuates with natural hormonal changes during the estrous cycle, pregnancy, and parturition [24-27].

There is ample evidence that estradiol plays a critical role for both blocking and enhancing social learning; the outcome is mediated by which receptor is activated [20, 28, 29]. However, the brain regions underlying social learning are still unknown.

Outside of mating, the best studied type of social behavior is aggression. Aggression occurs in both males and females, but the type of aggression is different. Males exhibit the more commonly studied overt territorial aggression while females exhibit non-overt, dominance-type aggression to an unfamiliar same-sex intruder [6, 30, 31].

Aggression in a number of species is dependent on sex hormones. Gonadectomy reduces aggression in both males and females, which can be reversed in both sexes with estradiol or androgen treatment [20, 30-33]. Hormone effects on aggression are both organizational and activational [33, 34].

While hormonal regulation of aggression is similar between sexes, the mechanisms of action are different. As observed using knockdowns or knockouts, estradiol receptor alpha promotes male and inhibits female territorial aggression [35-37]. Opposite effects have been observed with estradiol receptor beta [38]. Further studies are needed to determine if estradiol receptor alpha and beta sex differences correspond to different brain regions implicated in different types of aggression.

This video series was made possible through a generous grant from the National Institute of General Medicines (Grant Number: 5 R25 GM133017-03), awarded to Cohen Veterans Bioscience (Principal Investigator: Chantelle Ferland-Beckham, PhD)

Hormones, particularly estradiol, play an important role in all types of social behavior but the role of hormones in social behavior regulation is particularly important around the time of puberty and sexual maturity. At puberty, males of most rodent species disperse and must establish their own social relationships with conspecifics of both sexes. Hormone enhancement of their social behavior is thus adaptive for survival. For females, regardless of whether they remain in their natural burrow (as is the case for rats) or disperse like mice, must also establish social hierarchies with other females after puberty. Thus, it is also adaptive for gonadal hormones to regulate social behavior in females [39, 40].

As we have demonstrated in this video, social behaviors are critical to many aspects of animal survival and many social behaviors show clear differences between males and females, which could be the result of sex hormones or sex differences in social peptides such as AVP and oxytocin. Studying the potential for sex differences in social behavior in rodents is important, particularly when it comes to modeling human conditions in which social interactions go awry, including autism, which shows a 4:1 male preponderance. But more work is needed to understand the mechanism for the divergent patterns in hormone receptor-specific regulation of social behaviors. These described differences are also important to consider when designing studies that incorporate social behaviors.

References

1. Lai, M.-C., et al., *Biological sex affects the neurobiology of autism.* Brain, 2013. **136**(9): p. 2799-2815. DOI
2. Shepherd, A.M., et al., *Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia.* Neurosci Biobehav Rev, 2012. **36**(4): p. 1342-56. DOI
3. Caspi, A., et al., *The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders?* Clinical psychological science : a journal of the Association for Psychological Science, 2014. **2**(2): p. 119-137. DOI
4. Rice, T.R., *Violence among young men: the importance of a gender-specific developmental approach to adolescent male suicide and homicide.* Int J Adolesc Med Health, 2015. **27**(2): p. 177-81. DOI
5. Beery, A.K. and D. Kaufer, *Stress, social behavior, and resilience: insights from rodents.* Neurobiol Stress, 2015. **1**: p. 116-127. DOI
6. Ervin, K.S., et al., *Estrogen involvement in social behavior in rodents: Rapid and long-term actions.* Horm Behav, 2015. **74**: p. 53-76. DOI
7. Gabor, C.S., et al., *Interplay of oxytocin, vasopressin, and sex hormones in the regulation of social recognition.* Behav Neurosci, 2012. **126**(1): p. 97-109. DOI

This video series was made possible through a generous grant from the National Institute of General Medicines (Grant Number: 5 R25 GM133017-03), awarded to Cohen Veterans Bioscience (Principal Investigator: Chantelle Ferland-Beckham, PhD)

8. Axelson, J.F., M. Smith, and M. Duarte, *Prenatal flutamide treatment eliminates the adult male rat's dependency upon vasopressin when forming social-olfactory memories.* Horm Behav, 1999. **36**(2): p. 109-18. DOI
9. Pierman, S., et al., *Activational effects of estradiol and dihydrotestosterone on social recognition and the arginine-vasopressin immunoreactive system in male mice lacking a functional aromatase gene.* Horm Behav, 2008. **54**(1): p. 98-106. DOI
10. Hlinák, Z., *Social recognition in ovariectomized and estradiol-treated female rats.* Horm Behav, 1993. **27**(2): p. 159-66. DOI
11. Spiteri, T. and A. Agmo, *Ovarian hormones modulate social recognition in female rats.* Physiol Behav, 2009. **98**(1-2): p. 247-50. DOI
12. Sánchez-Andrade, G. and K.M. Kendrick, *Roles of α- and β-estrogen receptors in mouse social recognition memory: effects of gender and the estrous cycle.* Horm Behav, 2011. **59**(1): p. 114-22. DOI
13. Imwalle, D.B., E.M. Scordalakes, and E.F. Rissman, *Estrogen receptor alpha influences socially motivated behaviors.* Horm Behav, 2002. **42**(4): p. 484-91. DOI
14. Choleris, E., et al., *Involvement of estrogen receptor alpha, beta and oxytocin in social discrimination: A detailed behavioral analysis with knockout female mice.* Genes Brain Behav, 2006. **5**(7): p. 528-39. DOI
15. Appenrodt, E., M. Juszczak, and H. Schwarzberg, *Septal vasopressin induced preservation of social recognition in rats was abolished by pinealectomy.* Behav Brain Res, 2002. **134**(1-2): p. 67-73. DOI
16. Everts, H.G. and J.M. Koolhaas, *Differential modulation of lateral septal vasopressin receptor blockade in spatial learning, social recognition, and anxiety-related behaviors in rats.* Behav Brain Res, 1999. **99**(1): p. 7-16. DOI
17. Ferguson, J.N., et al., *Oxytocin in the medial amygdala is essential for social recognition in the mouse.* J Neurosci, 2001. **21**(20): p. 8278-85. DOI
18. Bluthé, R.M. and R. Dantzer, *Social recognition does not involve vasopressinergic neurotransmission in female rats.* Brain Res, 1990. **535**(2): p. 301-4. DOI
19. Everts, H.G. and J.M. Koolhaas, *Lateral septal vasopressin in rats: role in social and object recognition?* Brain Res, 1997. **760**(1-2): p. 1-7. DOI
20. Choleris, E., et al., *Sex differences in the brain: Implications for behavioral and biomedical research.* Neurosci Biobehav Rev, 2018. **85**: p. 126-145. DOI
21. Choleris, E. and M. Kavaliers, *Social learning in animals: sex differences and neurobiological analysis.* Pharmacol Biochem Behav, 1999. **64**(4): p. 767-76. DOI
22. Galef, B.G., D.J. Kennett, and S.W. Wigmore, *Transfer of information concerning distant foods in rats: A robust phenomenon.* Animal Learning & Behavior, 1984. **12**(3): p. 292-296. DOI

This video series was made possible through a generous grant from the National Institute of General Medicines (Grant Number: 5 R25 GM133017-03), awarded to Cohen Veterans Bioscience (Principal Investigator: Chantelle Ferland-Beckham, PhD)

23. Valsecchi, P., Galef, B. G., *Social Influences on the Food Preferences of House Mice (Mus Musculus).* International Journal of Comparative Psychology, 1989. **2**(4). DOI, DOI2
24. Choleris, E., et al., *Differential effects of dopamine receptor D1-type and D2-type antagonists and phase of the estrous cycle on social learning of food preferences, feeding, and social interactions in mice.* Neuropsychopharmacology, 2011. **36**(8): p. 1689-702. DOI
25. Fleming, A.S., et al., *Olfactory-based social learning varies as a function of parity in female rats.* Psychobiology, 1994. **22**(1): p. 37-43. DOI
26. Sánchez-Andrade, G., B.M. James, and K.M. Kendrick, *Neural encoding of olfactory recognition memory.* J Reprod Dev, 2005. **51**(5): p. 547-58. DOI
27. Choleris, E., et al., *Estrogenic involvement in social learning, social recognition and pathogen avoidance.* Front Neuroendocrinol, 2012. **33**(2): p. 140-59. DOI
28. Clipperton, A.E., et al., *Differential effects of estrogen receptor alpha and beta specific agonists on social learning of food preferences in female mice.* Neuropsychopharmacology, 2008. **33**(10): p. 2362-75. DOI
29. Ervin, K.S., et al., *Activation of the G protein-coupled estrogen receptor, but not estrogen receptor α or ß, rapidly enhances social learning.* Psychoneuroendocrinology, 2015. **58**: p. 51-66. DOI
30. Clipperton Allen, A.E., et al., *Agonistic behavior in males and females: effects of an estrogen receptor beta agonist in gonadectomized and gonadally intact mice.* Psychoneuroendocrinology, 2010. **35**(7): p. 1008-22. DOI
31. Clipperton-Allen, A.E., et al., *Effects of an estrogen receptor alpha agonist on agonistic behaviour in intact and gonadectomized male and female mice.* Psychoneuroendocrinology, 2011. **36**(7): p. 981-95. DOI
32. Trainor, B.C., et al., *Photoperiod reverses the effects of estrogens on male aggression via genomic and nongenomic pathways.* Proc Natl Acad Sci U S A, 2007. **104**(23): p. 9840-5. DOI
33. Brain, P.F. and M. Haug, *Hormonal and neurochemical correlates of various forms of animal "aggression".* Psychoneuroendocrinology, 1992. **17**(6): p. 537-51. DOI
34. Berretti, R., et al., *Neonatal exposure to estradiol decreases hypothalamic allopregnanolone concentrations and alters agonistic and sexual but not affective behavior in adult female rats.* Horm Behav, 2014. **65**(2): p. 142-53. DOI
35. Yang, C.F., et al., *Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males.* Cell, 2013. **153**(4): p. 896-909. DOI
36. Sano, K., et al., *Differential effects of site-specific knockdown of estrogen receptor α in the medial amygdala, medial pre-optic area, and ventromedial nucleus of the*

hypothalamus on sexual and aggressive behavior of male mice. Eur J Neurosci, 2013. **37**(8): p. 1308-19. DOI

37. Scordalakes, E.M. and E.F. Rissman, *Aggression and arginine vasopressin immunoreactivity regulation by androgen receptor and estrogen receptor alpha.* Genes Brain Behav, 2004. **3**(1): p. 20-6. DOI
38. Ogawa, S., *Differential Roles of Two Types of Estrogen Receptors in the Regulation of Neuroendocrine Functions and Socio-Sexual Behaviors.* 動物心理学研究, 2004. **54**(1): p. 49-58. DOI
39. Schultz, L.A. and R.K. Lore, *Communal reproductive success in rats (Rattus norvegicus): effects of group composition and prior social experience.* J Comp Psychol, 1993. **107**(2): p. 216-22. DOI
40. Becker, J.B. and G.F. Koob, *Sex Differences in Animal Models: Focus on Addiction.* Pharmacological reviews, 2016. **68**(2): p. 242-263. DOI