Journal Club

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Sex-Dependent Differences in Nucleus Accumbens Regulation of Aggression and Social Investigation

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Review of Borland et al.

Throughout the animal kingdom, dominance relationships establish stable hierarchies that are important for regulating access to limited resources, such as food, territory, and mates (Yan et al., 2024). Formation of these structured relationships requires shifts in aggressive and submissive behavior among individuals and is highly adaptive because these hierarchies allow animals to avoid conflict and conserve energy. Experience-dependent changes in behavior often occur through a process of positive reinforcement, and winning aggressive encounters is known to be rewarding.

The nucleus accumbens (NAc) is a key structure in the mesolimbic dopamine system that regulates reinforcement learning, motivation, and reward processing. It contains a high density of dopamine-receptor-expressing neurons that receive input from several limbic and cortical regions, including the ventral tegmental area (VTA) and the medial prefrontal cortex (mPFC; Xu et al., 2024). The NAc plays a critical role in the rewarding aspects of aggression, as demonstrated through conditioned place preference assays in mice (Golden et al., 2016). Also, the positive reinforcing effects of aggression in hamsters are associated with phasic increases in dopamine in the NAc core (Cross et al., 2025). Nevertheless, much remains unknown about the cellular mechanisms and neural circuitry in the NAc regulating behavioral plasticity after repeated aggressive encounters.

Borland et al. (2026) investigated how NAc activity regulates experience-dependent changes in aggression and social investigation. Investigating aggression in traditional rodent models can be challenging because female mice and rats do not consistently display robust aggressive behavior under standard housing conditions. In contrast, both male and female Syrian hamsters readily exhibit territorial aggression, making them a valuable model for investigating sex differences in the neurobiological mechanisms underlying changes in aggression. Initial investigations evaluated whether repeated social interactions produce behavioral changes and alter activity of NAc neurons in male and female Syrian hamsters. Behavioral testing consisted of four social encounters lasting 5 min each, during which resident male and female hamsters remained in their home cage while a novel male intruder was placed in the subject's cage. Behavioral scoring quantified several types of social behaviors performed by the subject, including social investigation, aggression, and attacks. During each social interaction, fiber photometry was used to measure calcium signals from neurons in the NAc core.

Surprisingly, resident males did not exhibit significant changes in social investigation or NAc calcium signals following repeated social encounters. In contrast, female residents exhibited shorter attack latencies on all testing days compared to Day 1, as well as reduced durations of social investigation prior to attack. Females also exhibited increased calcium signals in the NAc on Days 2 and 3 relative to Day 1. Because greater NAc activity is associated with positive reinforcement of aggression (Xu et al., 2024; Cross et al., 2025), these findings suggest that aggression is more rewarding in female hamsters than in males. This is supported by prior research demonstrating that same-sex social interactions are more rewarding for female hamsters than for males, which may be mediated by oxytocin receptors in the VTA (Borland et al., 2019). However, it remains unclear whether these effects primarily reflect reinforcement, in which aggressive interactions become rewarding through repeated experience, or motivation, which increases the drive to initiate aggressive behavior.

Borland and colleagues next examined whether chemogenetic inhibition of NAc neurons affects aggressive behavior. To test this, they bilaterally injected an inhibitory DREADD virus to suppress neuronal activity within the NAc in a new set of animals that were exposed to repeated aggressive encounters. Inhibiting NAc neurons in female hamsters increased latency to attack but did not reduce total aggression duration, suggesting that NAc activity may contribute to the motivational drive to engage in aggression rather than the display of aggressive

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behavior. In contrast, chemogenetic inhibition of NAc neurons did not alter aggression in males, suggesting that NAc activity may not be necessary for territorial aggression in male hamsters.

To elucidate the neural circuits by which the NAc regulates social investigation and aggression, Borland and colleagues investigated the role of NAc-projecting neurons in the medial prefrontal cortex (mPFC). The mPFC provides strong excitatory input to the NAc to regulate reward-seeking and goal-directed behaviors (Xu et al., 2024). Chemogenetic activation of mPFC terminals in the NAc during each resident-intruder interaction reduced the amount of social investigation females directed toward the male intruder, but it did not affect their aggressive behavior. In contrast, stimulation of the mPFC–NAc pathway in males increased social investigation and prolonged the latency to attack. These findings demonstrate that activation of an mPFC–NAc pathway has opposite effects in males and females on social motivation in competitive situations.

Most of the previous research into the neural mechanisms regulating experience-dependent changes in aggression has focused on male subjects and has been interpreted through the lens of the winner effect (Yan et al., 2024). In males, winning an aggressive encounter increases the density of androgen receptors in the NAc and ventral tegmental area (VTA), which may prime these brain regions to enhance future aggressive behavior (Fuxjager et al., 2010). However, androgens do not appear to contribute to aggression-related behavioral plasticity in females (Rosvall, 2013), which suggests that aggression in females is regulated by different cellular mechanisms than in males. Borland et al. (2026) provide additional evidence for this by showing that while chemogenetic inhibition of NAc neurons did not affect aggression in males, it reduced the motivation for aggression in females. Furthermore, mPFC terminals in the NAc had an inhibitory effect on aggression in males, but not in females.

The lack of an inhibitory role for a mPFC–NAc pathway in females indicates that inputs from other brain regions may regulate NAc activity. The NAc also receives glutamatergic inputs from the basolateral amygdala, ventral hippocampus, and paraventricular nucleus of the thalamus, all of which influence reward and reinforcement through contextual or homeostatic cues (Xu et al., 2024). It is not yet known how this circuitry differs in males and females to uniquely regulate experience-dependent changes in aggression. Another avenue for future research is whether sex differences in NAc circuits contribute to differences between males and females in motivation to engage in other social behaviors, such as social play or sexual behavior.

Additional studies should also identify the specific neural ensembles in the NAc underlying the reinforcing effects of aggression in female hamsters. Borland and colleagues suppressed activity across the entire NAc; however, the NAc is composed mainly of two populations of inhibitory medium spiny neurons (MSNs), expressing D1 or D2 receptors and supporting different aspects of motivated learning (Xu et al., 2024). Interestingly, D1-expressing neurons in the NAc have been shown to control the reinforcing effects of aggression in male mice (Aleyasin et al., 2018). This is consistent with the traditional view that D1 MSNs promote reward-seeking behavior and D2 MSNs prevent reward seeking. However, new research shows that, rather than coding for opposite valence, D1 and D2 receptors in the NAc core work together to enhance reward learning by tracking the salience of stimuli and predictability of outcomes, respectively (Zachry et al., 2024). Additionally, cholinergic interneurons receive inputs from MSNs to locally regulate dopamine release to influence reward-seeking behavior, and GABAergic interneurons work alongside MSNs to enhance inhibitory neurotransmission (Xu et al., 2024). To fully understand the neural and behavioral sex differences reported in Borland et al. (2026), future work should investigate the recruitment of these specific MSN and interneuron populations during female aggression.

Notably, all male intruders were used for both male and female subjects to create similar testing conditions for all subjects. This approach ensured that male and female subjects were exposed to the same type of social stimulus during testing, rather being exposed to same-sex intruders that differed in sex between male and female subjects. In contrast, using same-sex intruders would have resulted in male subjects interacting with male intruders and female subjects interacting with female intruders. It is worth investigating whether the role of the mPFC–NAc pathway in social motivation and aggression depends on the sex of the intruder.

In conclusion, the study by Borland et al. (2026) deepens our understanding of the neural circuitry underlying aggression by demonstrating that NAc activity reinforces aggressive behavior in female hamsters, while mPFC–NAc activity suppresses aggression and promotes social investigation in males. These opposing behavioral responses demonstrate substantial sex differences in how the NAc regulates the reinforcing effects of aggression.

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