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Charting a Path toward Aggression

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Hypothalamic stimulation can elicit complex behaviors such as aggression, but how discrete motor components of such behaviors are organized at the circuit level remains largely unknown. In this issue of *Neuron*, Falkner et al. (2020) find that complex neural representations get transformed into a simplified action signal along a hypothalamic-midbrain pathway.

The hypothalamus was found to be critical for the expression of aggressive behavior nearly a century ago. Following the delineation, through lesions and stimulations, of a broader "hypothalamic attack area," studies in rodents identified the ventrolateral part of the ventromedial hypothalamus (VMHvl) as one key area for aggression. In mice, the VMHvl contains 4,000–5,000 almost exclusively glutamatergic neurons, about half of which co-express estrogen receptor 1 (Esr1) and progesterone receptor. Strikingly, activation of VMHvl$^{Esr1/PR}$ neurons alone elicits attacks toward intruders, whereas silencing or ablating this population inhibits aggression (Lee et al., 2014; Yang et al., 2013). While many VMHvl neurons fire in a manner time locked with attacking (Lin et al., 2011), overall VMHvl ensemble activity is heterogeneous, encoding intruder sex as well as information about past, present, and future aggression (Falkner et al., 2016; Lin et al., 2011). In addition, these representations are profoundly shaped by social experience (Remedios et al., 2017; Yang et al., 2017). Thus, rather than being a simple command node for instinctive aggression, the VMHvl contains complex and highly malleable representations more commonly associated with cortical or hippocampal circuits. How are these representations decoded by downstream areas to select appropriate motor behaviors? In this issue of *Neuron*, a new study by Falkner et al. (2020) sheds light onto how action selection is achieved along a specific hypothalamus-to-midbrain pathway.

The VMHvl is embedded into an intricate circuit, with VMHvl^{Esr1} neurons alone projecting to more than 60 target areas (Lo et al., 2019). Projections to the lateral periaqueductal gray (lPAG) are likely involved in aggression-related action selection because (1) they constitute the most prominent VMHvl output outside the hypothalamus (Lo et al., 2019), (2) the PAG is activated after attacking (Lin et al., 2011), and (3) PAG lesions impair stimulated aggression. Moreover, PAG neurons were recently shown to integrate threat information to compute escape decisions (Evans et al., 2018). Focusing on this projection, Falkner et al. (2020) first used viral tracing and optogenetic circuit mapping to identify excitatory connections between glutamatergic VMHvl (VMHvl^{vGlut2}) and glutamatergic, but not GABAergic, lPAG (lPAG^{vGlut2}) neurons. Biting attacks being a key component of intruder-directed aggression in mice, Falkner et al. (2020) hypothesized that lPAG^{vGlut2} neurons are connected to jaw muscles. Indeed, polysynaptic retrograde tracing from one of these muscles—the superficial masseter—labels a subset of lPAG^{vGlut2} neurons that predominantly receive VMHvl input. VMHvl^{vGlut2} neurons therefore form direct connections with lPAG^{vGlut2} neurons, which in turn indirectly connect to jaw musculature (Figure 1).

Next, Falkner et al. (2020) tested the behavioral function of this projection in mice confronted with male or female intruders. Artificial stimulation of the VMHvl elicits attacking (Lee et al., 2014; Lin et al., 2011), but optogenetic activation of VMHvl^{vGlut2}-lPAG projections failed to reliably induce aggression. This might be due to the requirement for other projections to be co-activated. In contrast, chemogenetic silencing of lPAG^{vGlut2} neurons selectively reduced attack duration during aggressive episodes. Importantly, and in contrast to VMHvl silencing (Lin et al., 2011), this manipulation affected neither sexual behavior nor chemoinvestigation. Additional control experiments demonstrated that silencing lPAG^{vGlut2} neurons did not generally interfere with orofacial motor actions. The specificity of these effects is intriguing, hinting at behavior-specific modules within the lPAG. Correspondingly, optogenetic activation of lPAG^{vGlut2} neurons could be expected to elicit aggressive, but not sexual, behavior.

Is this specificity reflected in lPAG activity during behavior? Electrophysiological recordings showed that firing in a subset of neurons was aligned to attack onset, with a smaller number of neurons activated during chemoinvestigation. As a population, lPAG neurons were significantly more attack than chemoinvestigation selective and did not encode intruder sex. This markedly contrasts with the VMHvl, where population activity (in sexually experienced mice) predominantly represents conspecific sex rather than behavior (Remedios et al., 2017) and where a larger proportion of neurons is male selective (Lin et al., 2011). These observations suggest that lPAG neural representations are indeed more action selective than those in the VMHvl.

Falkner et al. (2020) next addressed whether lPAG neurons have a specific role in coordinating attack-relevant jaw musculature. In an elegant experimental preparation, they simultaneously recorded lPAG neural activity and superior masseter electromyographic (EMG) signals in behaving mice. lPAG activity during male interactions was partially predicted by EMG signals and the activity of a subset of lPAG neurons during attacking was significantly correlated with EMG activity. In contrast, EMG signals during other orofacial behaviors, such as grooming or feeding, were not associated with

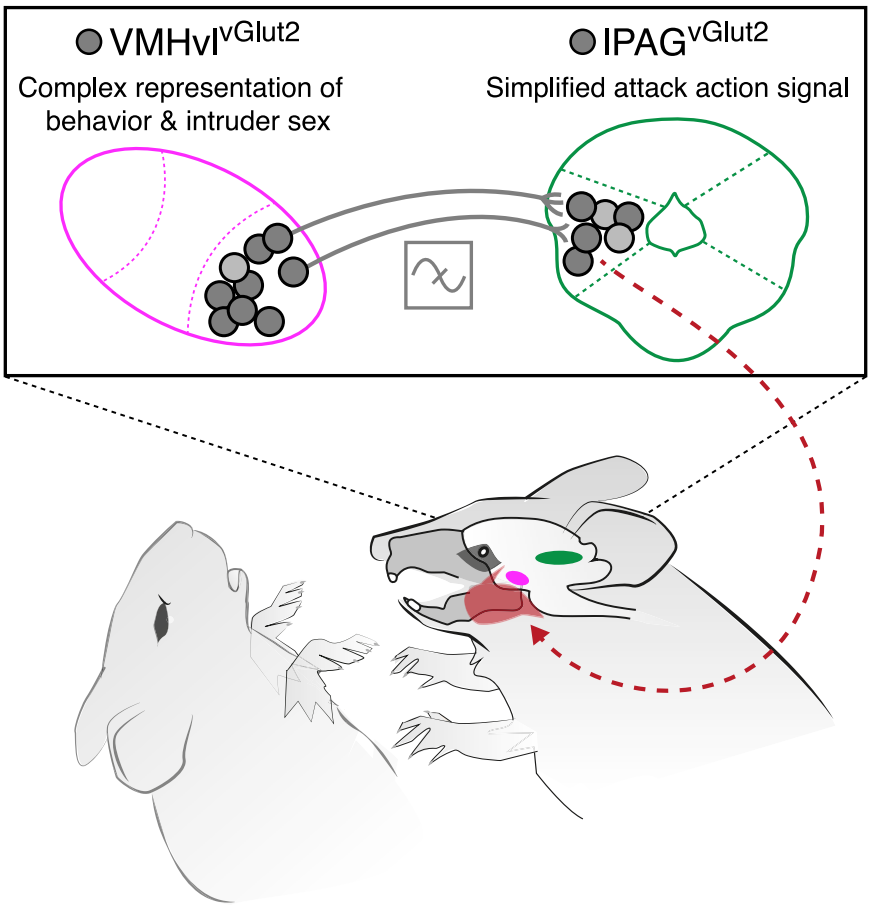

Figure 1. Action Selection along a Hypothalamus-Midbrain Circuit
Excitatory VMHvl neurons form synapses onto glutamatergic neurons in the lPAG, which indirectly connect to the superior masseter jaw muscle involved in biting attacks during mouse aggression. The VMHvl population overall encodes complex behavioral parameters, as well as intruder sex, and the activity of lPAG projections is male biased, "filtering out" female signals. Glutamatergic lPAG neurons integrate these (and likely other unknown) inputs to generate a simplified action selection signal.

increased lPAG firing. This further supports the notion of a subset of lPAG neurons driving aggression-specific motor programs.

Does this selectivity arise postsynaptically in the lPAG or do lPAG-projecting VMHvl^{vGlut2} neurons already carry action-specific information? In order to address this question, Falkner et al. (2020) simultaneously recorded population calcium activity from lPAG-projecting VMHvl^{vGlut2} neurons on one side of the brain and from all VMHvl^{vGlut2} neurons on the other. On both sides, activity increased during attacking and investigation of males, but it was decreased in lPAG-projecting VMHvl^{vGlut2} neurons (relative to the entire VMHvl^{vGlut2} population) during female interactions. Importantly, there was no evidence for attack-specific tuning of lPAG projections. It therefore appears that VMHvl-to-lPAG projections act as a "contrast filter" for sex but that action selection is computed further downstream in the lPAG (Figure 1). Finally, to characterize this transformation, Falkner et al. (2020) simultaneously recorded population activity from VMHvl^{vGlut2} and lPAG^{vGlut2} neurons. Cross-correlation analysis revealed that during male, but not female, interactions, VMHvl^{vGlut2} activity precedes lPAG^{vGlut2} activity and that both population activities are more highly correlated during attack than during chemoinvestigation. This indicates that VMHvl neurons indeed drive lPAG activity prior to attack bouts.

Altogether, the study by Falkner et al. (2020) suggests a model in which the VMHvl conveys stimulus-specific, but not action-selective, information to a subpopulation of lPAG^{vGlut2} neurons that orchestrate aggressive motor actions. The authors elegantly demonstrate that complex hypothalamic population codes can be transformed into simplified action signals in the midbrain. Naturally, this work raises several questions. First, the VMHvl is involved in several other behaviors such as mating, feeding, and defense, and artificial activation of VMHvl^{Esr1} neurons alone can evoke either mating or aggression, depending on stimulation strength (Lee et al., 2014). Projections to the PAG—and, in fact, most other projections (Kim et al., 2019)—do not seem to exhibit behavior-specific activity. How does the VMHvl thus orchestrate different behaviors? Second, which information is conveyed by the VMHvl's many other projections? Because VMHvl neurons send collateralized projections to multiple targets (Lo et al., 2019), signals to the lPAG should be widely broadcast. Third, do lPAG^{vGlut2} neurons encode a general decision to attack or rather coordinate specific aggression-related action plans? Are they involved in other behaviors associated with biting attacks, such as infanticide or predatory aggression? Artificially activating these neurons in carefully controlled behavioral contexts may answer these questions. Finally, which information do lPAG neurons use to compute action selection? Sex-biased signals from the VMHvl-lPAG pathway are presumably insufficient for this purpose. lPAG neurons might therefore integrate additional information, but it remains unclear which information and from where. Addressing these questions will be a formidable yet exciting challenge. The work by Falkner et al. (2020) provides a valuable entry point for further mechanistic studies into how action selection is computed in midbrain circuits.

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Arbitrating Computational Models of Observational Learning

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How do we learn in the absence of direct experience? In this issue of *Neuron*, Charpentier et al. (2020) proposes a new computational account of observational learning, which arbitrates between choice imitation and goal emulation.

Humans have a remarkable ability to learn how to navigate an environment in the absence of direct experience by simply observing others (Olsson et al., 2020). For example, imagine traveling to a foreign country and trying to order food without being able to understand the menu. How would you accomplish this? One strategy is to simply copy others ahead of you in line—a form of imitation learning. This will likely result in successfully getting something to eat but does not ensure that you will enjoy it. An alternative strategy is to instead infer other people's goals and emulate the one that is most consistent with your own. This requires the additional computation of inferring a model of another person's mental state (Gonzalez and Chang, 2019).

In this issue of *Neuron*, Charpentier et al. (2020) sought to explore this question to better understand how humans learn from observations. Using a novel behavioral task, participants observed another agent choose between two of three presented slot machines. Each slot machine paid out a token color (e.g., green, red, or blue), but only one color could be exchanged for money, which was unknown to the participants. Thus, participants could only learn which machine to pick by observing the other agent's choices. Participants were told that the other agent knew which color yielded money and that the winning color could change across trials. Participants had information about the token color probabilities for each slot machine and were able to see the outcome (e.g., token color) after the agent's choice. Showing participants the token color returned by the chosen slot machine and not its explicit value required participants to estimate which color was valuable based solely on the agent's actions.

Suppose the other agent selects the left slot machine (Figure 1A). From this example, it is clear that the agent is not interested in the red token but uncertain whether the other agent's goal was to maximize the probability of a blue or green token. During all trials of a given block, the position (i.e., left, middle, or right) and probability distributions of each slot machine are fixed; however, the unavailable option varies to modulate the difficulty of goal inference. For example, if the rightmost machine in Figure 1A was unavailable to the agent, a left choice would then clearly indicate a goal to obtain the rewarding blue token. In a third of the trials, participants were able to play the game themselves for the potential to earn money (Figure 1B). If the participant selected the middle slot machine after observing (Figure 1A), then they most likely believed that the other agent's goal was to maximize green rather than blue tokens. Across blocks, the authors manipulated the uncertainty of the outcome probability distributions and also switched which color is associated with a payoff, akin to a hidden reversal.

Charpentier et al. (2020) evaluated support for two different observational learning strategies. The "choice imitation" model simply learned which slot