

Internal States and Behavioral Decision-Making: Toward an Integration of Emotion and Cognition

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Social interactions, such as an aggressive encounter between two conspecific males or a mating encounter between a male and a female, typically progress from an initial appetitive or motivational phase, to a final consummatory phase. This progression involves both changes in the intensity of the animals' internal state of arousal or motivation and sequential changes in their behavior. How are these internal states, and their escalating intensity, encoded in the brain? Does this escalation drive the progression from the appetitive/motivational to the consummatory phase of a social interaction and, if so, how are appropriate behaviors chosen during this progression? Recent work on social behaviors in flies and mice suggests possible ways in which changes in internal state intensity during a social encounter may be encoded and coupled to appropriate behavioral decisions at appropriate phases of the interaction. These studies may have relevance to understanding how emotion states influence cognitive behavioral decisions at higher levels of brain function.

Survival and reproduction are mediated by innate, goal-directed activities (LeDoux 2012; Sternson 2013), such as feeding, drinking, mating, fighting, and escape from a predator. Each such activity is characterized by its own complex collection of actions,⁶ modulated by sensory information from multiple modalities. Furthermore, these actions are often organized in a characteristic sequence or progression, from an initial appetitive or motivational phase, to a more directed investigative phase, to a final consummatory phase (Fig. 1A; Berridge 2004). For example, in the case of an agonistic encounter between conspecific males, the appetitive phase includes investigation to determine the sex and assess the relative size or strength of the opponent; this is often followed by threat displays and then finally overt attack or retreat (Miczek et al. 2007). This progression is also accompanied by an increasing risk of injury, illness, or death; therefore, such behavioral transitions involve cost–benefit decisions (Gillette et al. 2000; Hirayama et al. 2012).

Progression through these different phases of an aggressive or sexual encounter is typically associated with an escalating internal state of motivation, arousal, or drive (for concepts and definitions, see Berridge 2004; LeDoux 2012). The concept of drive has proven useful to behavioral neuroscience and fits with our intuitive experience of behavior—not as a sequence of independent motor acts, but as a continuous escalation of a single state (e.g., from annoyance to anger to rage). But it is difficult

to determine through observation alone whether drives are a component of neural computation, playing a causal role in the control of behavioral decisions, or simply epiphenomena. Konrad Lorenz formulated a “hydraulic” metaphor to explain how different behavioral actions might be successively released under the control of an escalating internal drive (or motivational) state, with different drives for different behaviors (Fig. 1B; Lorenz and Leyhausen 1973; Berridge 2004). Although this model invoked a causal role for the level of drive states in controlling transitions or “decisions” between different behaviors, it made no predictions as to how such a role might be implemented in neural hardware.

In a view complementary to Lorenz's Tinbergen proposed that behavioral decisions are made in a hierarchical manner: More generic choices between competing or “opponent” activities (e.g., to engage in fighting or mating) are made before more specific selections of a particular action (e.g., between a threat display and a bite) (Fig. 1C; Tinbergen 1950). He further suggested that each decision stage could be mediated by a group of mutually inhibitory “centers” in the brain, with successive decision stages connected in a feed-forward manner to form a behavioral decision tree (Tinbergen 1950, 1951).

Although Tinbergen's model is useful as a heuristic, it leaves open a number of important theoretical issues. First, it does not explain why different actions controlled by “third-level” command centers progress through a characteristic sequence during an escalating encounter nor suggest how such progressions might be controlled. Second, it does not distinguish whether the higher-order (“second-level”) centers that control different activities (mating, fighting) exert some control over decisions be-

⁶The word “activity” is used here operationally to describe an ongoing behavior, such as “aggression”; “action” is used to describe a specific motor program executed during that activity, such as biting (Anderson and Perona 2014).

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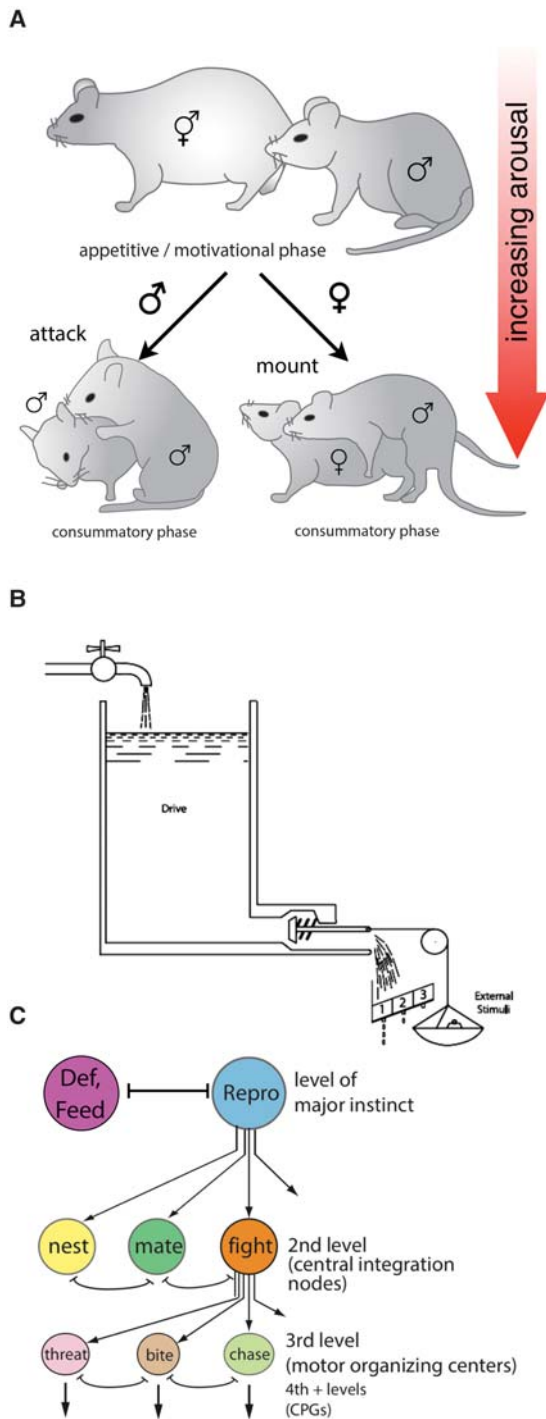


Figure 1. (A) Progression from investigative to consummatory phases of social behavior. (B) Lorenz's "hydraulic" metaphor for the control of behavior by internal drive states. (C) Tinbergen's hierarchical model for behavioral decisions (Tinbergen 1950). (B, Reprinted from Berridge 2004, with permission from Elsevier; C, modified from Anderson 2012.).

tween actions dictated by third-level command centers, or rather simply act as a switch or gate, that permits such activities to occur. Finally, it does not integrate this hierarchical view of behavioral decision-making with

any sort of internal drive or arousal states during a social interaction or consider whether and how such states might contribute to the control of such progressive decisions.

The question of how escalating internal states influence decisions between competing behaviors or actions, while fascinating, has not been widely investigated at the level of neural mechanism. To approach this subject, a number of basic questions need to be addressed. How are behavioral states, such as arousal or motivation, encoded or instantiated in the brain (Berridge 2004; Pfaff et al. 2005)? How is the escalation of these states implemented? Are these states behavior-specific, or generic (Devizze et al. 2006)? At what node(s) in a decision hierarchy or network do such states exert their influence on behavioral decisions? How are these influences exerted mechanistically? And is the level or intensity of such escalating states important in the actual control of behavioral decisions?

Here, we summarize our efforts to begin to approach these questions, in the context of innate behaviors, with a focus on aggression. We have pursued parallel studies in the mouse and in the vinegar fly *Drosophila melanogaster* in an effort to identify underlying evolutionarily conserved principles of neural circuit function across species. Our hope is that these studies may also prove relevant to understanding the link between internal states and decision-making in higher organisms, such as the integration of emotion and cognition in humans (Salzman and Fusi 2010).

STATE-DEPENDENT CONTROL OF SOCIAL BEHAVIORS IN *DROSOPHILA*

A Neuron and a Neuropeptide That Control Aggressive Arousal

Evidence from many systems suggests that neuromodulators, such as biogenic amines or neuropeptides, are important regulators of internal states and behavior (Insel and Young 2000; Nassel and Winther 2010; Bargmann 2012; Marder 2012; Taghert and Nitabach 2012). As a first step toward understanding the neural coding of a state of aggressiveness, we carried out a screen for neuropeptide-secreting neurons that control agonistic behavior in *Drosophila* (Asahina et al. 2014). This screen identified a small cluster (three to five cells) of male-specific, fruitless (*FruM*)-expressing neurons (Fig. 2A–C) that contain the neuropeptide *Drosophila* tachykinin (DTK, Fig. 2A, inset) and that profoundly influence levels of aggressiveness. Thermogenetic activation of these neurons increased aggression (Fig. 2D), whereas inhibition of these neurons strongly reduced fighting (Fig. 2E; Asahina et al. 2014). Overexpression of the *DTK* peptide in *DTK*-expressing neurons potentiated the aggression-promoting effect of activating these cells, whereas deletions in the *DTK* gene reduced it (Fig. 2F). Importantly, activation of these neurons had no effect on courtship or mating behavior. Together, these data identified a cell type and a gene that play a major role in controlling inter-male aggression in flies. Interestingly, homologs of *DTK* such as Substance P have been implicated in aggression in mammals

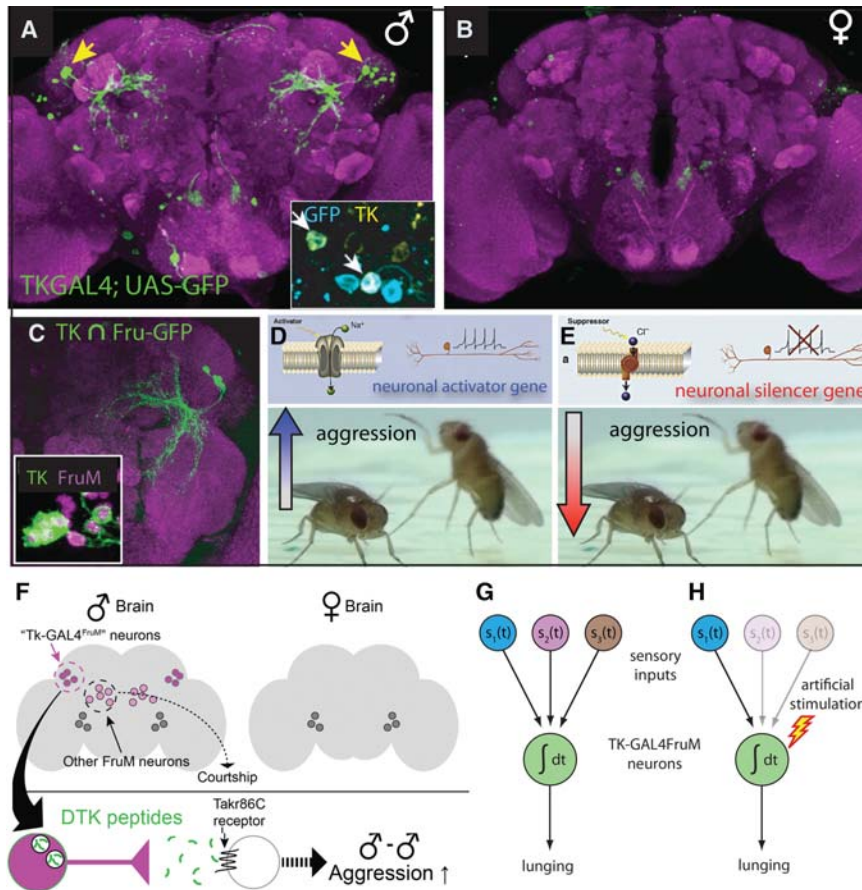


Figure 2. (A,B) Identification of a population of aggression-promoting, sexually dimorphic neurons in male flies that express the neuropeptide *Drosophila* tachykinin (DTK) (A, inset). Yellow arrowheads (A) indicate cell bodies. (C) TK-GAL4 neurons express the male-specific sex-determination factor Fru^M (inset). (D,E) Activation of TK-GAL4^{FruM} neurons increases aggression (D), whereas inhibition of these neurons decreases aggression (E). (F) The aggression-promoting function of TK-GAL4^{FruM} neurons is enhanced by release of DTK peptides. (G) TK-GAL4^{FruM} neurons are proposed to integrate the effects of multiple classes of sensory stimuli over time ($s_1(t)$, $s_2(t)$, etc.). (H) Artificial enhancement of TK-GAL4^{FruM} neuronal activity can bypass the requirement for some of these sensory stimuli. (D,E, Cartoons modified from Borst 2009, with permission from Elsevier; F, reproduced from Asahina et al. 2014.)

(including humans), by genetic and pharmacological studies (Shaikh et al. 1993; Katsouni et al. 2009; Coccaro et al. 2012).

Do DTK^{FruM} neurons simply direct a motor program of aggression or do they regulate an internal aggression-promoting state, such as motivation or arousal? Arousal often involves an increased sensitivity to sensory cues, such that the threshold for release of a stimulus-driven behavior is reduced (Van Swinderen and Andretic 2003, 2011; Davidze et al. 2006). Interestingly, artificial activation of DTK^{FruM} neurons could evoke aggression even in the absence of sensory cues that are normally required for aggression, such as male-specific pheromones (Fig. 2G,H; de la Paz Fernandez et al. 2010; Wang and Anderson 2010; Wang et al. 2011). In some cases, activation of DTK^{FruM} neurons supplemented with excess DTK peptide could even promote attack toward a moving fly-sized inanimate object (Asahina et al. 2014). These data suggest that DTK^{FruM} neurons promote a state of arousal or motivation that is apparently aggression-specific. Our previous work has provided evidence of other behavior-

specific forms of arousal in *Drosophila* (Lebestky et al. 2009).

We have recently suggested that emotions are internal states that are characterized by certain general properties, or emotion primitives, common to different emotions in a single species and that apply to emotions across species (Anderson and Adolphs 2014). These properties include persistence, scalability, valence, stimulus degeneracy, and generalization (trans-situationality). Neuropeptides have properties that could contribute to encoding some of these emotion state features (Flavell et al. 2013; for review, see Insel and Young 2000; Berridge 2004; Nassel and Winther 2010; Bargmann 2012). For example, the concentration of DTK could encode the scalability (intensity) of an aggressive state, whereas slowly decaying levels of the peptide, determined by its rate of degradation, could underlie a persistent state of aggressiveness. The relationship between DTK gene dosage and the aggression-promoting activity of TK^{FruM} neuron activation suggests that levels of DTK might control the intensity of aggression, but whether these neurons can induce a persistent state of aggress-

siveness is not yet clear. Work from Kravitz and others indicates that biogenic amines, such as octopamine, dopamine, and serotonin, also influence levels of aggressiveness in *Drosophila* (Dierick and Greenspan 2007; Zhou et al. 2008; Mundiyanapurath et al. 2009; Alekseyenko et al. 2010, 2013; Certel et al. 2010; Andrews et al. 2014), as well as in other arthropod species (Stevenson et al. 2005; for review, see Kravitz and Huber 2003), and likely contribute to aggressive state control as well.

Neurons That Control Persistent Social Behavior States in *Drosophila*

The ability to identify neurons that control persistent behavioral states requires a means of activating such neurons in freely moving animals, with millisecond time resolution. This requirement is, of course, afforded by optogenetics; however, the use of optogenetics in *Drosophila* has been limited by the inability of blue light to penetrate the flies' cuticle. Recently, this obstacle has been overcome by the development and application of red-shifted opsins such as ReaChR (Fig. 3A) and Chrimson (Lin et al. 2013; Inagaki et al. 2014; Klapoetke et al. 2014).

In a proof-of-principle application of this technology, we performed optogenetic stimulation of different populations of interneurons that control wing extension, which mediates male courtship song (Kohatsu et al. 2011; von Philipsborn et al. 2011); (Fig. 3B,C; for review, see Yamamoto et al. 2014). Strikingly, activation of P1 interneurons in single male flies evoked probabilistic and persistent wing extension that lasted for many minutes following stimulus termination (Fig. 3D; Inagaki et al. 2014). In contrast, activation of a descending interneuron, pIP10 (Fig. 3B; von Philipsborn et al. 2011), evoked wing extension in a deterministic manner time-locked to the onset and offset of photostimulation (Fig. 3E). Similar observations were made independently using IR laser-based transient thermogenetic activation of P1 and pIP10 (Bath et al. 2014). Interestingly, transient activation of P1 neurons in pairs of male flies evoked persistent aggression (Fig. 3F; E Hoopfer and DJ Anderson, unpubl.). These results indicate that P1 neurons can regulate aggression as well as courtship (Fig. 3G), although whether their influence on aggression is direct or indirect remains to be determined.

The persistent effect of P1 neuron activation on courtship raised the question of whether these neurons might be involved in internal states of arousal or motivation associated with such reproductive behaviors. Social isolation is known to increase both courtship and aggression in flies (Wang et al. 2008; Liu et al. 2011), as well as in many other animal species (Koike et al. 2009; Toth et al. 2011). Strikingly, social isolation potentiated the effect of optogenetic activation of P1, but not of pIP10 neurons, to promote wing extension (Inagaki et al. 2014). Moreover, this effect was associated with an increased excitability of P1 neurons, as determined by combined optogenetic stimulation and calcium imaging experiments. These data suggest that P1 neurons could form

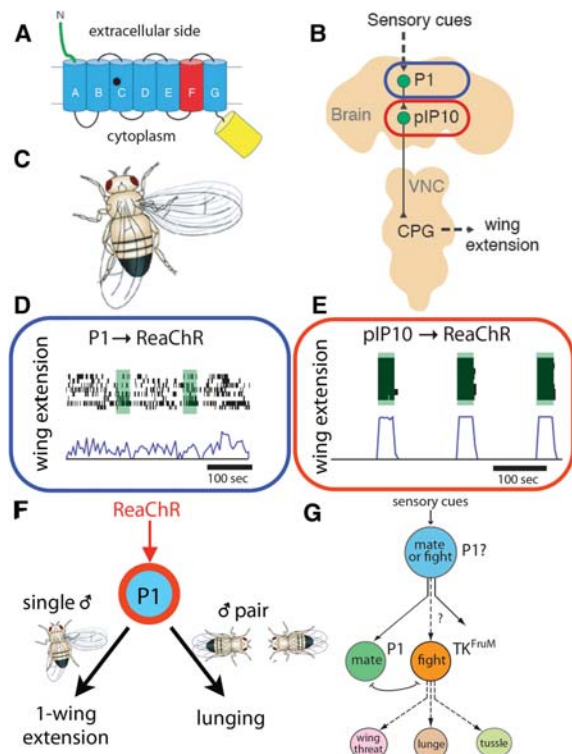


Figure 3. (A) Schematic illustrating the red-shifted opsin ReaChR (Lin et al. 2013; Inagaki et al. 2014). (B,D) Cartoon illustrating two classes of interneurons that control wing extension (C) in male *Drosophila*. (D,E) Optogenetic activation of P1 and pIP10 neurons evokes persistent and time-locked wing extension in single *Drosophila* males, respectively. (F) Schematic illustrating dual effect of P1 activation by ReaChR to evoke courtship behavior (1-wing extension) in single males (left), and aggressive behavior in pairs of males (right) (E Hoopfer et al. in prep.) (G) Schematic illustrating possible circuit relationship between P1 neurons and TK-GAL4^{FruM} neurons. (B–C, Modified from von Philipsborn et al. 2011; D,E, modified from Inagaki et al. 2014.)

part of the neural substrate for an internal state change that reflects social experience and that affects multiple social behaviors (Wang et al. 2008; Liu et al. 2011). The persistent behavioral effects of P1 activation might then serve to perpetuate the influence of past environmental conditions on behavior.

NEURAL CONTROL OF AGGRESSION IN MICE

Classic experiments by Hess in the late 1920s demonstrated that electrical stimulation of the hypothalamus could elicit aggressive displays in cats (Hess 1928), such as the “*affektiven Abwehr-reaktion*” (“*affective defensive reaction*”), in which the animal exhibited hissing, baring of teeth, and laid-back ears characteristic of a state of “*rage*” (Hess and Brügger 1943). This transformative experiment suggested that artificial stimulation of a specific brain region could evoke an emotion state and its associated behavioral expression.

Hess's findings raised three major questions: (1) What neurons are sufficient to evoke aggression when artificially stimulated? (2) Are those same neurons required for normal aggressive behavior? (3) Are those neurons normally active during aggressive behavior? (Kruk 2014). Despite almost a century of follow-up research (for review, see Kruk 1991; Siegel et al. 1999; Siegel 2004; Adams 2006; Miczek et al. 2007; Nelson and Trainor 2007; Anderson 2012; Falkner and Lin 2014; Yang and Shah 2014), until recently, these questions have remained unanswered.⁷ They could potentially be addressed by bringing to bear powerful genetic tools for neural circuit manipulations available in mice. Surprisingly, however, in the 70 yr since Hess's initial paper, there was no report of brain-stimulated aggression in mice,⁸ despite the fact that such manipulations are routine in other rodent species such as rats and hamsters (Kruk 2014).

Identification of an Aggression Locus in the Mouse Hypothalamus

To identify neurons activated during aggression, we carried out multi-electrode, single-unit recordings from the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl), in freely behaving male mice (Lin et al. 2011). We chose VMHvl because it overlaps the so-called hypothalamic attack area (HAA) identified by microstimulation experiments in rats (Kruk et al. 1988; Hrabovszky et al. 2005) and because it is labeled strongly by *c-fos* following aggression (Newman 1999; Veening et al. 2005; Lin et al. 2011). Extracellular recording in VMHvl revealed that it contains neurons with dynamic and heterogeneous responses during social encounters, with some units activated during male–male (Fig. 4A) or male–female (Fig. 4B) interactions, or both (Fig. 4C; Lin et al. 2011); a small number of units were active exclusively during attack or mounting (Fig. 4D). Thus, VMHvl contains a mixture of neurons active during different phases and different types of social encounters (Fig. 4E).

To investigate a causal role for VMHvl neurons in aggression, we optogenetically activated these cells, using channelrhodopsin-2 (ChR2), in an anatomically restricted (but not cell-type-specific) manner (Lin et al. 2011). Photostimulation elicited time-locked attack toward males, females, and inanimate objects, with a latency of a few seconds. Chemogenetic inhibition using an

⁷The main reasons for this are that (1) the electrical stimulation techniques used did not have sufficient resolution to distinguish relevant neurons from fibers-of-passage; (2) lesion experiments in relevant hypothalamic regions yielded conflicting results; and (3) methods for recording the activity of single units in freely moving animals were not available.

⁸We now know that this is because the experiment does not work. Because the mouse brain is much smaller than the rat brain, electrical current delivered to sites containing attack neurons spreads to adjacent sites that promote defensive behaviors, which are dominant to social behaviors such as fighting and mating (at least when artificially stimulated). The advantage of optogenetic activation is that it allows restriction of activation to cell bodies, by combining focal injection of viruses with localized photostimulation.

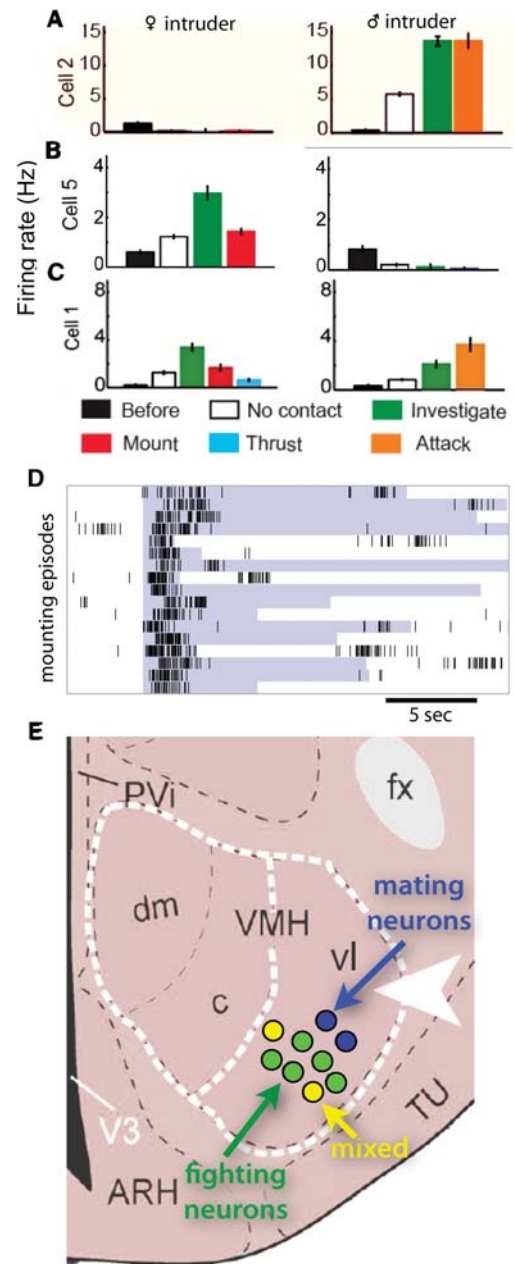


Figure 4. (A–C) Average firing rates (in 5-sec bins) for three individual units recorded in the VMHvl of a male mouse during the indicated social behavior epochs (established by manual annotation of videos at 30 Hz) (Lin et al. 2011). (D) Raster plot of an individual unit in VMHvl during mounting. Each row illustrates a separate trial. Shading indicates periods where mounting occurred. (E) Schematic illustrating mixed population of neurons in VMHvl that are responsive during male social behavior. (Modified from Anderson 2012.)

ivermectin-gated chloride channel (Slimko et al. 2002; Lerchner et al. 2007) reversibly reduced agonistic behavior (Lin et al. 2011). However, the temporal resolution of this method was insufficient to determine whether these neurons were required during attack per se. Surprisingly,

neither manipulation caused any change in male–female mating behavior, despite the presence of female-responsive units in VMHvl (Lin et al. 2011).

Genetic Identification of Hypothalamic Aggression Neurons

The foregoing experiments indicated that VMHvl contains neurons involved in attack, but they did not identify these cells. They also did not account for the function of

VMHvl neurons activated by females; in principle, such neurons could promote mating, inhibit aggression, or both (Anderson 2012). To address these issues, we sought to identify molecular markers for these neurons. We found that VMHvl contains a subset (~40%) of neurons that express the type 1 estrogen receptor (*Esr1*; Fig. 5A), ~30% of which are activated during attack as determined by double-labeling for *c-fos* (Fig. 5H; Lee et al. 2014). To manipulate the function of these neurons, we generated gene-targeted mice expressing Cre recombinase in *Esr1*⁺

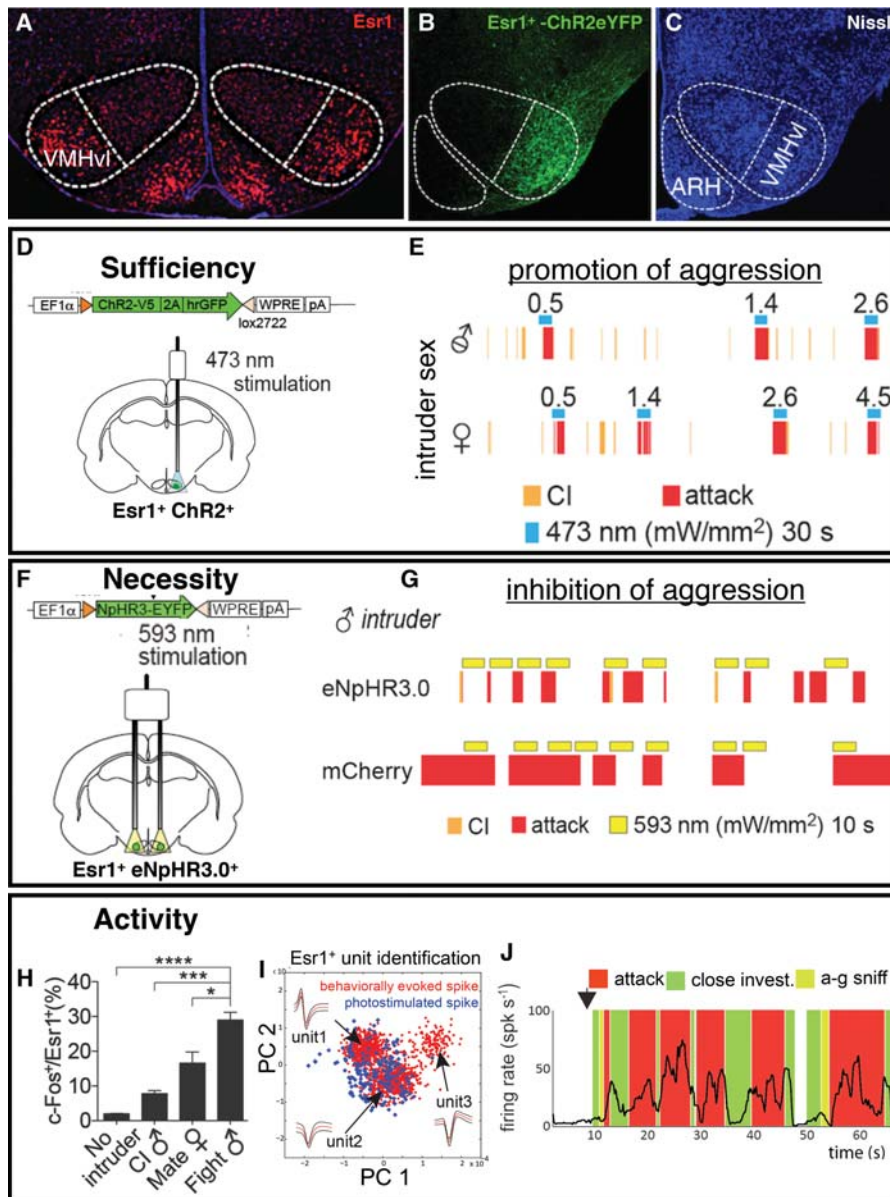


Figure 5. (A) Expression of *Esr1* in VMHvl. (B) Expression of eYFP in *Esr1*⁺ neurons in an *Esr1-Cre* mouse injected in VMHvl with a Cre-dependent AAV encoding ChR2-eYFP. (C) Nissl staining of the same section as in B. ARH, arcuate nucleus. (D,E) Optogenetic activation of VMHvl *Esr1*⁺ neurons promotes attack. (F,G) Optogenetic inhibition of VMHvl *Esr1*⁺ neurons inhibits attack compared to control (mCherry). (H) Induction of c-FOS in *Esr1*⁺ neurons following different social interactions. CI, close investigation. (From Lee et al. 2014.) (I,J) An *Esr1*⁺ neuron expressing ChR2 in VMHvl, identified by optogenetic phototagging using a chronically implanted optrode array, is active during attacks (J). (I) Plot illustrating overlap in principal component space between waveforms of optogenetically (blue) and behaviorally (red) evoked spikes from *Esr1*⁺ neurons in VMHvl. PC, principal component.

neurons, allowing cell-type-specific expression of optogenetic effectors in VMHvl (Fig. 5B,C).

Optogenetic activation of $Esr1^+$ neurons in VMHvl indicated that they were sufficient to promote attack (Fig. 5D,E), whereas activation of $Esr1^-$ neurons was not (Lee et al. 2014). Time-resolved optogenetic inhibition of $Esr1^+$ neurons interrupted ongoing attack (Fig. 5F,G), indicating that their activity is required during this consummatory phase of an aggressive encounter, confirming and extending earlier loss-of-function studies (Lin et al. 2011; Sano et al. 2013; Yang et al. 2013).⁹ Finally, preliminary experiments using optogenetic phototagging (Lima et al. 2009) to identify $Esr1^+$ neurons in multi-electrode recordings indicate that these cells exhibit increased spiking rates during attack (Fig. 5I–J; R Remedios and DJ Anderson, unpubl.). Together, these data indicate that $Esr1^+$ neurons in VMHvl fulfill the three major criteria necessary to identify them as attack neurons (Kruk 2014): they are sufficient to elicit attack when artificially stimulated; they are necessary for naturally occurring attack; and they are active during normal aggressive behavior.

Scalable Control of Social Behavior by VMHvl $Esr1^+$ Neurons

Systematic variation of optogenetic stimulation parameters revealed, unexpectedly, that although high levels of stimulation evoked attack, lower levels¹⁰ evoked nonagonistic social behaviors, including sniffing or close investigation (CI) and attempted mounting (Figs. 6A, 7A; Lee et al. 2014). Mounting was evoked toward normal and castrated males as well as females, with equal efficacy. Remarkably, in some cases, the social behaviors evoked within a single stimulation session could be shifted, simply by increasing the light intensity used for photostimulation, from mounting to attack (Fig. 6A,B). The threshold for mounting and CI was similar, and approximately six- to sevenfold lower than that required to evoke attack (Fig. 6C).

Together, these data suggest that optogenetic activation of VMHvl $Esr1^+$ neurons evokes different social behaviors in a scalable manner (Lee et al. 2014): Low-intensity stimulation evokes appetitive and sexual behavior—social investigation and mounting—whereas higher intensities evoke attack (Figs. 6B, 7A). Interestingly, we have

recently observed similar results following optogenetic stimulation of GABAergic neurons in the medial amygdala (Hong et al. 2014), a structure that projects indirectly to VMHvl (Canteras et al. 1992, 1995; Swanson 2000). We have also observed scalable control of different defensive behaviors—avoidance, freezing, and flight—following stimulation of a different subpopulation of VMH neurons located in its dorsomedial subdivision (Kunwar et al. 2015). These observations suggest that scalable control may be a general feature of hypothalamic cell populations controlling innate motivated behaviors. Although such stimulation intensity-dependent changes in evoked behavior have been previously observed using electrical methods (von Holst and von Saint Paul 1960, 1962), the use of optogenetic tools to restrict activation to genetically identified neuronal cell bodies rules out the possibility that such behavioral switches simply reflect current spread to neighboring brain regions, a possibility that could not be excluded in early studies.

Role of $Esr1^+$ Neurons in Male–Male Social Interactions

Several lines of evidence suggest that the relationship between increasing optogenetic stimulation of VMHvl $Esr1^+$ neurons, and the change in evoked behavior from investigation to attack, reflects a control mechanism that operates during naturally occurring male–male social encounters. First, the fraction of $Esr1^+$ neurons that are activated ($c-fos^+$) following attack is approximately five- to sixfold higher than after close investigation without attack (Fig. 5H; Lee et al. 2014). Second, electrophysiological recordings in VMHvl indicate that the average spiking rate ramps up quickly during the progression from CI to attack and that investigation is more likely to be followed by attack when the spiking rate is high (Fig. 6E; Lin et al. 2011; Falkner et al. 2014). Finally, and most importantly, time-resolved optogenetic inhibition delivered during the initial phase of a social encounter interrupts close investigation (Fig. 6D; Lee et al. 2014). Thus, inhibition of $Esr1^+$ neurons can interrupt either close investigation or ongoing attack (Fig. 7B), depending on when photostimulation is delivered. Together, these data are consistent with the idea that the behavioral progression during a male–male aggressive encounter is controlled in a scalable, threshold-dependent manner, according to the level of activity among VMHvl $Esr1^+$ neurons (Fig. 6B).

Role of $Esr1^+$ Neurons in Male–Female Social Interactions

A role for VMHvl in male sexual behavior is unexpected, as this function has traditionally been assigned to the MPO (Simerly 2002; Yang and Shah 2014). Optogenetic stimulation experiments should be interpreted with caution, because artificial patterns of activation could produce abnormal behaviors. Male mounting has been suggested to be a “default” social behavior (Stowers

⁹Previous studies indicated that killing progesterone receptor (PR)-expressing neurons in VMHvl (which overlap $Esr1^+$ neurons by 90%) partially reduced aggression (Yang et al. 2013), as did RNAi-mediated knockdown of $Esr1$ in VMHvl (Sano et al. 2013). However, because of the long delay between the manipulation and behavioral testing (2–3 wk), these studies could not distinguish a permissive requirement for VMHvl, e.g., in the detection of chemosensory cues essential for male–male recognition, from a requirement during attack per se.

¹⁰“Lower levels” were achieved by (1) injecting fewer ChR2-expressing viral particles; (2) incubating the animals for a shorter period of time following viral injection (which results in lower levels of ChR2 expression); (3) reducing the light intensity used in photostimulation; and (4) reducing the frequency of photostimulation (although reduced frequency was less effective than reduced light intensity). These data suggest that it is the number of activated cells, and the level of activity per cell, which is responsible for the observed behavioral differences.

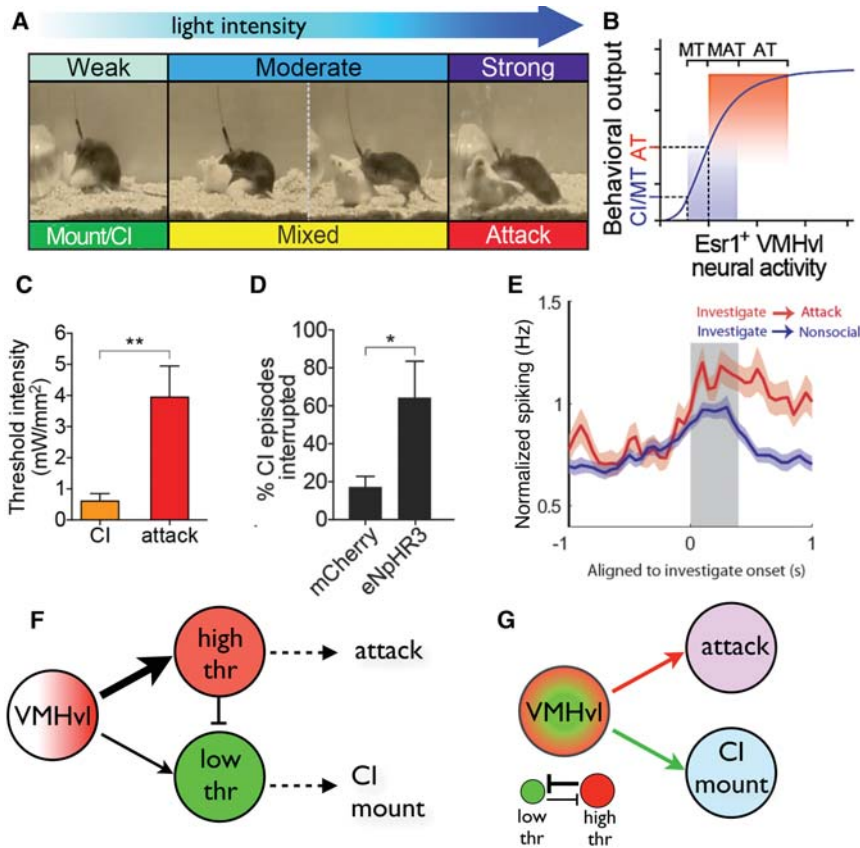


Figure 6. (*A,B*) Social behavior evoked by optogenetic stimulation of VMHvl $Esr1^+$ neurons switches from close investigation (CI) and mounting at low light intensity, to attack at high intensity. (*C*) Threshold intensities required to elicit CI versus attack. (*D*) Interruption of naturally occurring close investigative behavior (CI) by optogenetic inhibition of $Esr1^+$ neurons delivered during sniffing (vs. mCherry control). (*E*) Average spiking activity during the last 400 msec of sniffing preceding subsequent attack (red) or nonsocial behavior (blue). A higher level of spiking during the sniffing period predicts subsequent attack. (*F,G*) Alternative models to explain intensity dependence of optogenetically evoked behaviors from $Esr1^+$ neurons. (*F*) The level of activity among a common population of VMHvl $Esr1^+$ neurons activates behavior-specific downstream centers with low versus thresholds for activation. Thickness of arrows indicates relative level of activity in VMHvl output required to produce behavior. (*G*) Distinct and mutually inhibitory subsets of VMHvl $Esr1^+$ neurons controlling mounting (green) or attack (red) have low versus high thresholds for activation, respectively; output from the dominant population (red vs. green arrows) determines behavioral outcome. (*A–D*, Modified from Lee et al. 2014; *E*, modified from Falkner et al. 2014, with permission from the Society for Neuroscience.)

et al. 2002); thus, low-intensity stimulation of VMHvl $Esr1^+$ neurons could lead to mounting by default. Nevertheless, genetic ablation of progesterone receptor (PR)-expressing VMHvl neurons (Yang et al. 2013) (which highly overlap $Esr1^+$ neurons) or knockdown of $Esr1$ mRNA in VMHvl (Sano et al. 2013) both significantly reduced male mounting toward females. These data are consistent with the idea that VMHvl does play a role in normal male sexual behavior. However, acute optogenetic inactivation of $Esr1^+$ neurons did not interrupt normal male–female mounting *in media res* (Fig. 7B; Lee et al. 2014).¹¹ Interestingly, the average spiking rate in VMHvl

decreased dramatically as male–female sexual encounters progressed from investigation and mounting to intromission and ejaculation (Lin et al. 2011). It is possible, therefore, that the role of $Esr1^+$ neurons in male sexual behavior is limited to the detection of chemosensory cues required for recognition of females, rather than for male copulatory behavior per se.

Our finding that mounting was evoked by weaker optogenetic stimulation of VMHvl $Esr1^+$ neurons than was required to trigger attack was also unexpected. However, it is consistent with the observation that fewer of these neurons are c-fos⁺ following an encounter with a female, than with a male (Lin et al. 2011; Lee et al. 2014; Fig. 5H). Does this mean that the decision of whether to fight or mate is controlled simply by the level of population activity among VMHvl $Esr1^+$ neurons? It is possible that a low level of output from VMHvl activates low-threshold neurons in a downstream target structure that mediates CI or mounting, whereas a higher level of output

¹¹Negative results must also be interpreted with caution, however, especially in the case of loss-of-function manipulations. The inability to arrest mounting by optogenetic inhibition of $Esr1^+$ neurons could reflect a redundant role for other structures (e.g., MPO), or incomplete inhibition of activity. Genetic ablation (Yang et al. 2013), although it lacks temporal resolution, completely eliminates the activity of a given population of neurons.

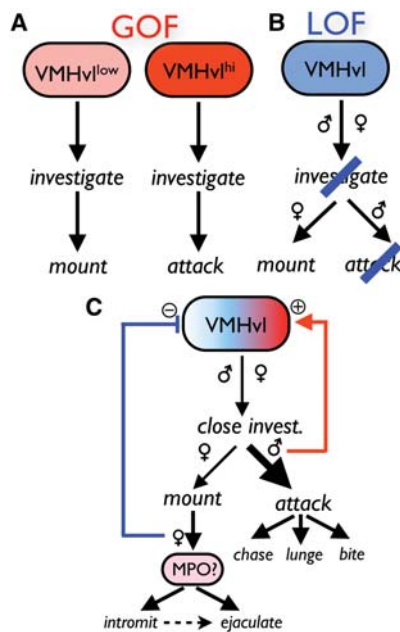


Figure 7. (A,B) Summary of gain-of-function (A, GOF) and loss-of-function (B, LOF) phenotypes obtained by optogenetic manipulation of VMHvl $Esr1^+$ neurons. Blue bars in B indicate behaviors interrupted by optogenetic inhibition. (C) Schematic illustrating a hypothetical view of the function of $Esr1^+$ neurons in VMHvl during a normal male–male or male–female social encounter. Thickness of arrows denotes relative level of output (spiking rate and/or number of active output neurons required to produce behavior). Blue versus red shading in VMHvl indicates gradual decrease (blue) or increase (red) in average spiking rate during an evolving male–female (blue) or male–male (red) social encounter. Colored arrows indicate behavioral feedback. See text for details.

activates high-threshold neurons in a different target that mediates attack; the latter could then inhibit the former (Fig. 6F). Alternatively, the intensity-dependent effects of optogenetic stimulation might reflect the existence of different, sex-specific subpopulations of $Esr1^+$ neurons, with female-specific neurons activated at a lower threshold than male-specific neurons (Lee et al. 2014).¹² If so, then asymmetric and reciprocal inhibition between these $Esr1^+$ neuronal subpopulations could determine whether output from these neurons promotes mating or fighting (Fig. 6G).

Whether the optogenetic results (Fig. 7A) reflect intensity coding or cellular heterogeneity, our electrophysiological recordings suggest a dynamic and time-evolving role for VMHvl neurons during a natural social encounter (Fig. 7C). Most of the neurons activated during both male–female and male–male encounters are most active at the initial phases of a social encounter (Lin et al. 2011). Perhaps these neurons promote approach and close (anogenital) investigation of a conspecific to identify intruder

gender, which requires detection of short-range, sex-specific pheromonal cues (Fig. 7C, “close invest”; Brennan and Zufall 2006; Dulac and Wagner 2006). The recognition of a male would promote further social investigation, ramping up the activity of VMHvl neurons in a positive-feedback manner, until the threshold for attack was reached (Fig. 7C, red arrow). The recognition of a female would promote initial attempts at mounting, with further interactions driving a reduction of activity in VMHvl and initiating the engagement of other structures, such as the MPO, that may promote the consummatory phase of a sexual encounter (Fig. 7C, blue arrow). This speculative scenario incorporates both sex-specific subpopulations and dynamic changes in population activity among VMHvl $Esr1^+$ neurons during social encounters.

SOCIAL BEHAVIOR CONTROL CENTERS: RHEOSTATS OR SWITCHES?

The foregoing data indicate that artificial activation of VMHvl (and MeApd) neurons at different intensities can evoke different types of social behavior at different thresholds (Hong et al. 2014; Lee et al. 2014) and that the average spiking rate among VMHvl neurons increases as animals progress from investigative to attack behavior (Lin et al. 2011; Falkner et al. 2014). Together, these findings raise the intriguing possibility that VMHvl encodes the intensity of an escalating state of arousal, motivation, or drive, in a graded manner according to its level of activity (Fig. 8A, “social behavior control center”). This increasing level of activity may reflect changes in sensory input as a social encounter evolves over time (e.g., via an increase in the concentration of olfactory cues during close investigation) (Fig. 8A, “sensory inputs”). Such escalation could, in turn, be used to control transitions between different behaviors by activating lower-level command centers controlling these behaviors (Fig. 8A; B₁, B₂, etc.) at different thresholds, perhaps according to the level of tonic inhibition imposed on such centers (Fig. 8A, “action selection”). Such a model is analogous to the size principle proposed by Henneman to explain the progressive recruitment of larger motor units during muscle engagement (Henneman 1985). In this way, VMHvl could both encode the intensity of an internal state and couple the intensity of that state to behavioral decisions. Such a model integrates the Lorenzian view of behavioral control by drive state intensity (Fig. 1B) with the Tinbergian view of hierarchical control of behavioral decision-making (Fig. 1C).

Alternatively, VMHvl could act simply as a permissive switch, or gate, for social behavior, whereas action selection would be controlled by sensory inputs that act directly on the lower-level command centers (Fig. 8B). In this scenario, the level of motivation or arousal would have to be encoded elsewhere in the brain and might be a consequence, rather than a cause, of escalating behavior. The essential difference between these models is that in one case, the control center simply determines whether or not aggression or mating will occur (Fig. 8B), whereas in

¹²Note, however, that optogenetic stimulation of $Esr1^+$ neurons in VMHvl slices, together with calcium imaging using GCaMP6s, did not induce a different pattern of neuronal activity at low versus high stimulation intensities, but rather simply increased the number of active neurons and the average level of activity per cell (Lee et al. 2014).

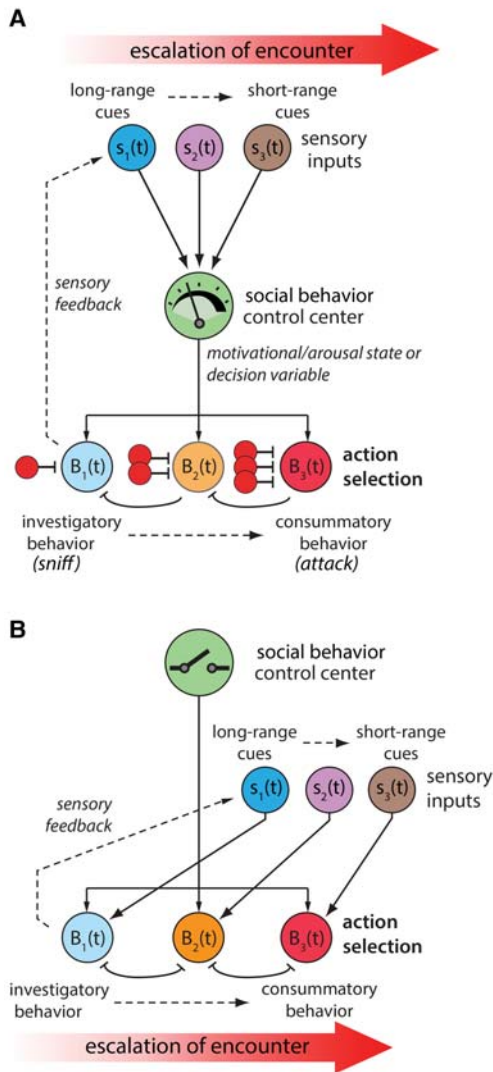


Figure 8. Alternative models for the control of action selection during an escalating social encounter. (A) Neurons in a social behavior control center (green) function like a rheostat, which encodes the intensity of an escalating internal state (arousal, motivation, or drive) according to the integrated sensory input converging on this center. Common outputs from this center project to lower-level command centers controlling distinct behavioral actions occurring at different times ($B_1(t)$, $B_2(t)$, etc.); each command center receives the same amount of input from the higher-level center. Command centers controlling investigatory (appetitive) to consummatory actions are held under progressively higher levels of tonic inhibition (red circles). Therefore, release from this inhibition occurs with progressively stronger output from the higher-level center, as the intensity of the internal state associated with the social encounter escalates. (B) Alternative model in which the social behavioral control center functions simply as a switch or gate to allow agonistic behavior to occur, and different behavioral actions are controlled by the direct influences of changing sensory cues on lower-level command centers during an evolving social encounter. Models that combine features of A, B are not illustrated but also possible.

the other case, it also controls the type of lower-level behavioral action that is selected (Fig. 8A). Distinguishing between these alternatives will require new methods

for imaging neural population activity in freely behaving animals (Ghosh et al. 2011; Ziv et al. 2013; Jennings et al. 2015), more specific tools for identifying and functionally manipulating neuronal subtypes and their connectivity (Zeng and Madisen 2012; Oh et al. 2014), as well as the application of modeling and theory. The combination of such approaches should yield new mechanistic insights into the neural control of animal behavior and may shed light on the interaction between emotion states and decision-making in humans.

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