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Neural mechanisms of persistent aggression

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Abstract

While aggression is often conceptualized as a highly stereotyped, innate behavior, individuals within a species exhibit a surprising amount of variability in the frequency, intensity, and targets of their aggression[1]. While differences in genetics are a source of some of this variation *across* individuals (estimates place the heritability of behavior at around 25–30%)[2], a critical driver of variability is previous life experience. A wide variety of social experiences, including sexual, parental, and housing experiences can facilitate "persistent" aggressive states, suggesting that these experiences engage a common set of synaptic and molecular mechanisms that act on dedicated neural circuits for aggression. It has long been known that sex steroid hormones are powerful modulators of behavior, and also, that levels of these hormones are themselves modulated by experience. Several recent studies have started to unravel how experience-dependent hormonal changes during adulthood can create a cascade of molecular, synaptic, and circuit changes that enable behavioral persistence through circuit level remodeling. Here, we propose that sex steroid hormones facilitate persistent aggressive states by changing the relationship between neural activity and an aggression "threshold".

Although aggression is a ubiquitous, highly conserved social behavior, individuals will vary substantially in their degree of aggressivity. This can be manifested as differences in the duration of individual attacks, the length of the attack bouts, and the time between bouts, in some cases leading to epochs with sustained or persistent aggression that can last many minutes (Figure 1A). In addition to these acute changes, individuals may exhibit more long-term signatures of persistence, characterized by the frequency that they enter these high aggression states. These sustained periods of aggression have had many names across decades of research, including "aggressive arousal", "attack-readiness", and "temporal persistence"[3–5]. The common phenomenon that these terms all attempt to capture is that the likelihood of attack at any given moment is highly dependent on a fluctuating internal state that represents both experiential and motivational variables, relative to a threshold for attack. Neural activity in relevant nodes for aggression may explicitly encode this fluctuating internal state and the threshold represents the "readout" mechanism of this activity, providing a lower bound for enabling attack-triggering mechanisms. Changes in an individual's aggressive internal state may bring an individual closer to this threshold, and

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make repeated attacks bouts more likely. Alternatively, decreases in motivational or internal state move an individual away from the threshold, making attack less likely. Acute increases in activity may arise from moment-to moment changes social-sensory-independent internal motivational state[6] or through access to specific sensory cues Social sensory information can be acquired without self-motion (an intruder approaches), or can be actively acquired (an intruder is approached), and during these encounters, aggression-relevant sensory information may be the "trigger" for attack by pushing an individual across the threshold. Ethologists frequently use the term "releasing stimulus" to describe sensory stimuli that overwhelmingly facilitate the initiation of a stereotyped behavior[7].

In addition to these short timescale changes in sensory and motivational state, other, more long timescale variables may also modify an individual's internal state and change the likelihood of attack. In particular, previous experience strongly affects the likelihood of aggression, decreasing the latency to first attack, as well the duration and frequency of attack. Animals may be "primed" for attack, either through previous attack[8] or merely through exposure to sensory information. For example, investigating an anesthetized conspecific decreases attack latency to the next animal encountered[9,10], demonstrating that sensory information may have long-lasting effects on the motivational state of the animal. These data suggest that prior exposure brings neural activity closer to a threshold, such that a similar level of sensory input on the second exposure is more likely to cross the threshold. This concept of an aggression threshold also has a literal analog in stimulation experiments that target aggression-promoting brain regions. When animals are behaviorally "primed" with previous access to aggression, the intensity of electrical stimulation required to evoke attack is decreased[11,12], suggesting that this priming may push activity closer to the threshold such that less sensory activation is required.

One framework for understanding how experience can lead to behavioral persistence is that experience can change the relationship between neural activity that reflects the individual's internal state and the attack threshold. We propose that this might happen in three separate, but not mutually exclusive ways (Figure 1B). First, increased aggression-relevant sensory input might generate attack by driving activity across the threshold. This might occur either from changes in the tuning or gain modulation of sensory circuits, or in changes to sensory acquisition behaviors. Second, changes in internal or motivational state might keep neural activity hovering close to the threshold, increasing the likelihood of crossing the threshold. Lastly, changes in the threshold itself might lead to persistent aggression. In this case, if the threshold itself was "lowered", less input would be required to generate an attack. Here, we will explore recent data that points to a generalizable mechanism to implement this experience-dependent change and speculate about the brain regions that might perform these computations.

Neural circuits for aggression

While the patterning of social actions is, in many cases, a brainwide phenomenon, there exist dedicated circuits within the brain that have a clear role in the generation and maintenance of an aggressive state (Figure 2A). Critical nodes in this circuit exist as part of the "social behavior network" (SBN), a highly recurrent set of subcortical regions,

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largely in the hypothalamus, amygdala, and midbrain, whose functions and connectivity are extremely conserved throughout evolution[13,14]. The known functions and connectivity of these circuits in mammals has been extensively reviewed elsewhere[15], so we will not detail the role of each node here. Briefly, key regions for aggression in both sexes include reciprocally connected regions of the hypothalamus (especially the ventromedial hypothalamus, ventrolateral area [VMHvl], ventral premammillary area, medial preoptic area [MPOA], and anterior hypothalamus), septal and amygdalar regions (including the medial and posterior amygdalae [MeA, PA], lateral septum [LS], and bed nucleus of the stria terminalis [BNST]), midbrain structures with connectivity to downstream motor pathways (most importantly, the periaqueductal gray [PAG]), and a newly implicated region in the basal forebrain, the substantia innominata[16]. Several regions within this network have been shown to be sensitive to specific social stimuli and aggression-promoting cues[17–19]. Aggressive information in this circuit may be somewhat hierarchically organized: for example, neural activity in the PAG exhibits higher selectivity to the motor aspects of attack, rather than the sensory or preparatory signals[20]. However, due to strong recurrent connectivity between network nodes, the aggression network defies simple feedforward descriptions, and instead, many regions conjunctively encode information about the sensory world, actions performed, and the individual's internal state[18,21].

Beyond being anatomically conserved, brain regions in this circuit express an evolutionarily conserved constellation of hormone receptors[13,22,23]. In particular, receptors for circulating sex hormones (including androgens, estrogens, and progesterone) are expressed at varying levels in nearly every node in this circuit[22,24,25]. This ability to be responsive to network-wide changes in circulating hormones that are broadcast after specific social events likely bestows this network with the ability to be updated with experience. While hormonal influences have long been known to have a bidirectional relationship to aggression, how hormonal activation changes the computations performed by this circuit to facilitate attack remain broadly unknown.

Gonadal hormones are required for experience-dependent change in aggression

Since their initial identification in the early 20th century[26–30], decades of classic research has demonstrated the powerful control that the sex steroid hormones estradiol (E2), testosterone (T), and progesterone (P4) exert on animal behavior[27,31–35]. Comparative work across metazoan phyla points to conserved roles for these molecules across species[27], showcasing their broad evolutionary benefits. In contrast to previous literature suggesting that sex hormones exclusively organize neural circuits during early critical periods in development[33,36], long-term changes in hormone milieu (including changes to both circulating hormone levels and receptors) during adulthood can shift neural gene expression, and consequently neural circuit connectivity, function, and ultimately behavior.

Hormones exert their primary control over neural function via intracellular hormone receptors. Additionally, steroid hormones bind to and signal via numerous membrane receptors, including the G-protein coupled estrogen receptor (GPR-30/GPER), the

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membrane associated estrogen receptor (mER), various classes of membrane associated androgen receptor (mAR), the estrogen receptor-X, and the GABAA receptor[37–41], endowing them with the capacity for both acute and long-term change. Intracellularly, E2 acts at estrogen receptor alpha (ERα) and beta (ERβ); T acts at the androgen receptor (AR); and, P4 acts at the progesterone receptor (PR). Further, T is converted to E2 in the brain by aromatase, enabling it to act both directly at ARs and indirectly at ERα and ERβ. These hormone receptors are transcription factors and following binding to their hormone ligand, promote and repress transcription of entire sets of genes[42,43]. Thus, a change in the hormonal state (here defined as the current concentrations of serum sex hormones and their relative proportion to each other), will induce transcriptional changes. In turn, these hormonally regulated transcriptome dynamics will alter the protein composition of hormone-sensitive neurons, leading to changes in their connectivity, activity, and function[42–44]. Consistent with the role of sex hormones in modulating social behavior, the corresponding nuclear hormone receptors are found throughout the SBN and associated brain circuits[25,45–47]. For example, a recent mouse *in situ hybridization* study showed that neural populations in mouse MPOA and BNST often coexpress ERs, ARs, PRs, and aromatase, but at different levels and in different combinations across cell types[22]. Similar findings have been observed in hamsters with subsets of SBN neural populations coexpressing ERs and ARs[48]. Further, recent research focused on ERα, AR, PR, and aromatase-expressing neurons throughout SBN nodes demonstrates a clear role of these hormone-sensitive neurons in controlling a variety of social behaviors across many contexts[49–54]. Collectively, these data suggest a complex and flexible interplay between hormone milieu and the function of distinct neural populations to promote social behavior expression according to the given sensory and hormonal state of the individual.

Hormones and behavior exert a bidirectional influence over each other during aggression. Numerous social experiences lead to persistent increases in aggressive behavior. These include housing and sexual experience with the opposite sex, pregnancy, parturition and lactation, pup exposure, social isolation or overcrowding, repeated aggressive experience, and competition[14,55–58]. Although gonadal hormones are required for experience-induced changes in aggressive behavior in males and females, the specific relationship between T or E2 levels and this persistent increase remain unclear. In classic experiments to determine the relationship between serum T levels and sexual experience-induced increases in aggression, orchiectomized rats were treated with a range of T doses[59]. Aggression was abolished in orchiectomized rats but present in orchiectomized rats with T treatment, increasing as a function of T concentration up to physiological T levels: rats treated with supraphysiological T showed equivalent aggression as rats with physiological T treatment. These data suggest that while basal T is required for the experience-induced increase in aggression, T spikes above the average physiological range do not further increase aggression.

In a recent update to this finding, Stagkourakis and colleagues[58] probed the role of T in the persistent aggression increases that follow repeated aggressive experience. They exposed subject mice to five consecutive days of intruders and recorded aggression towards intruder mice. Consistent with recent work demonstrating that aggression is rewarding in a subset of male mice[6], they found that only a subset of aggressor mice show increases in aggression following repeated experience. Strikingly, Stagkourakis et al. show that aggressor

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mice have higher basal T compared to non-aggressors both prior to and after training and that aggressive experience increases T levels in aggressor but not non-aggressor mice. Consistent with the notion that a hormone concentration threshold is required for aggression, Stagkourakis et al. found that one week of T treatment was sufficient to elicit aggression in non-aggresssors. It is of note that the daily fluctuations in T in male rats exceed the experience-induced increases in T that are associated with changes in social behavior[55,60]. For example, whereas sensory exposure to a rat in estrus leads to a doubling of T levels in male rats within half an hour, spontaneous daily T fluctuations reach peaks 10–20 times baseline levels within the same time period[55]. Finally, orchiectomized rats require greater hypothalamic stimulation to evoke conspecific attack compared to intact controls, or orchiectomized rats with T replacement[61]. These data demonstrate that basal T levels may reorganize SBN circuits to facilitate aggression. Further, these data show that social sensory and behavioral experience can increase T levels; however the effects of these increases remain unclear. Taken together, this suggests sex steroid hormones are capable of adjusting the relationship between input and motor output and may contribute to social experience induced circuit plasticity.

Changes in the aggression threshold may be mediated by hormone-dependent plasticity

How do changes in hormone level result in changes in the relationship between neural activity and an aggression threshold? Recent data from across a variety of social contexts provides strong evidence that activation by steroid hormones drives neural plasticity through alterations in synaptic connectivity, excitability, and neural activity itself (Figure 2B).

Hormone-mediated changes in synaptic strength may serve to amplify incoming sensory information. For example, in the VMHvl of male mice, aggression is correlated with dendritic spine density[58]. Consistent with the hypothesis that basal T levels organize SBN connectivity to enable or promote aggression, androgenic manipulations that influence adult aggressive behavior also affect VMHvl synaptic density: orchiectomized rats show a decreased number of VMHvl spine and shaft synapses compared to intact males[62,63] and perinatal T supplementation increases VMHvl synapse density in intact females[63]. T also promotes synapse formation outside the VMHvl, suggesting a potentially broad role across the social behavior network for androgens in synapse formation. For example, in the MPOA of male hamsters, T promotes local dendritic spine density: gonadally intact and orchietomized males with T replacement show greater spine density than orchietomized males without replacement[64]. In addition to T, E2 also regulates spine density and dendrite complexity in the VMHvl[65,66]. During proestrus, when ovarian E2 production peaks, VMHvl neurons from female mice show greater spine density and dendritic branching than VMHvl neurons from female mice in diestrus (when E2 levels are low), or from male mice[66]. Further, E2 treatment in Ovx mice increases spine density to levels seen in intact females. Beyond spine density increases, E2 promotes increased VMHvl neural expression of neurosteroid and neuropeptide receptors, including the progesterone receptor, mu-opioid receptor, cholecystokinin receptor A, and melanocortin-4 receptor[44]. E2 regulates spine density across the social behavior network as well with exogenous treatment leading

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to increases in LS and PAG spine density[67,68]. In addition, a recent study examining E2 binding and ERα-mediated gene expression within the BNST found that E2 stimulated ERα in BNST induces expression of genes associated with neurotransmitter receptors, synaptic organization, and synaptic plasticity[43]. Nevertheless, the relationship between E2-induced changes in SBN synaptic connectivity and the expression of specific social behaviors, including aggression, remains unexplored and fertile ground for future research.

Recent work has also demonstrated that changing basal levels of hormones can directly alter the sensory representations in the social behavior network[69]. In an elegant study that combined hormone manipulation and multiphoton cellular resolution imaging, McHenry et al showed that high levels of E2 increased the neural response in females to male related cues in the MPOA. These data suggest hormone levels control the “gain” on this sensory input. It is likely hormones may mediate similar computational changes in aggression circuits following experience-dependent hormonal change.

The most direct evidence for hormone-dependent changes to an aggression circuit comes from a recent paper, where the authors identified a glutamatergic projection from the posterior amygdala (PA) to VMHvl ERα^{+} neurons that undergoes long-term synaptic potentiation in aggressor mice following aggression experience[58]. The authors manipulated the strength of the synapse by inducing LTP and LTD *in vivo* and demonstrated that strengthening or weakening this synapse facilitates or abolishes the effects of aggression experience, indicating that amygdalo-hypothalamic synaptic strength underlies the experience-induced increase in aggression. Additionally, the authors found that whereas LTP could not be induced in control, non-aggressor mice, T treatment of non-aggressors permitted the induction of LTP at the PA→VMHvl^{ERα} synapse *ex vivo* and *in vivo* in these animals. This has the functional effect of increasing the gain of VMHvl^{ERα} neuronal responses to PA input, bringing them closer to a theoretical attack threshold. Taken together, these data suggest that T acts as a permissive gate on plasticity and may point to a potential mechanism whereby experience-dependent hormones facilitate the maintenance of a persistent state.

Beyond changes in local spine density which may serve to amplify sensory information, recent data has demonstrated that hormones have the power to remodel local and long-range circuits in the social behavior network. For example, in their study of E2 regulation of ERα mediated BNST gene expression, Gegenhuber et al. found that E2-driven ERα activation promoted the expression of a variety of neurite wiring genes in BNST neurons of adult mice across sexes, such as *Brinp2*, *Unc5b*, and *Enah*[43]. Additionally, VMHvl Progesterone Receptor expressing (PR^{+}) neurons in females increase the density of their presynaptic sites to the anteroventral periventricular hypothalamus (AVPV) during estrus, following the E2 surge during proestrus[54]. Using optogenetic-assisted circuit mapping, Inoue et al. demonstrated that this increased projection density was correlated with an increased excitatory postsynaptic current response in AVPV neurons following VMHvl^{Pr} stimulation. These data indicate that the increased density of the presynaptic site was associated with a functional strengthening of the VMHvl^{Pr}→AVPV synapse. Next, Inoue and colleagues demonstrated that this strengthened VMHvl^{Pr}→AVPV synaptic connectivity required the action of E2 at ERα in VMHvl^{Pr} neurons. Optogenetic inhibition of the VMHvl^{Pr}→AVPV

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projection in E2 and P4 treated Ovx mice abolished lordosis in response to sexually motivated male mice.[54]

These data support the idea that multi-day changes in hormonal state can lead to large-scale circuit remodeling, changing the routing of information and the computational properties of the larger circuit. Through both local and long-range circuit remodeling, neurons in the aggression network may become more tightly coupled, requiring less sensory input to drive attack.

Where does the threshold “live” in the brain?

While the precise neural implementation of the aggression threshold is not yet known, several recent studies have provided hints about brain areas that are involved in driving overall levels of aggressive arousal (Figure 2C). In particular, neural recordings from the VMHvl and the pSI have suggested that activity in these areas may approximate a unidimensional attack-likelihood signal. In both cases, neural activity during the sensory phase of aggression that does *not* lead to attack is lower than activity that does result in attack, suggesting that if activity does not cross a threshold, attack is not initiated[16,18]. The VMHvl, which is well-positioned to integrate information from many nodes in the social behavior network[70], increases activity both to aggression relevant sensory information, such as conspecific urine, but also increases during sensory-independent motivation prior to aggression[6,71]. Both regions send major projections to the PAG, in particular the lateral PAG, suggesting that the PAG may be the neural implementation of the threshold itself. Using simultaneous recordings of glutamatergic neurons in the VMHvl and the PAG, Falkner et al. showed that the VMHvl is sensitive to sensory and preparatory signals prior to attack, while the PAG has its peak response during attack itself[20]. The PAG, which appears to have a role in the gating of other innate behaviors, including vocalization and escape[72,73], lacks this graded response and instead exhibits an all-or-none response during the action, consistent with that of a threshold. The role of hormone receptors, which are also richly expressed in the lateral PAG in particular[25,46], likely have a role in determining the precise relationship between the graded inputs and the all-or-none behavioral output.

Future Directions

Overall, the effects of experience-dependent hormonal changes provide a mechanistic implementation of how experience may lead to persistent aggressive states by facilitating attack likelihood. Given the density of hormone receptor expression and interconnectivity of the social behavior network, it is likely that the effects of T and E2 extend network-wide, taking advantage of circulating hormones’ ability to act as a broadcast signal. New tool development for multisite monitoring of neural activity dynamics[74,75] and modeling of inter-nodal relationships[76,77] will be crucial for uncovering how these synaptic connectivity alterations affect the network-wide computations and functions critical for behavioral expression.

Given this framework, several critical open questions remain. First, while it is clear that hormonal modulation can remodel neural circuits on several timescales, we do not

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yet know whether these events are specific to hormone sensitive circuits. For example, do changes in synaptic connectivity modulate the strength of specific hormone-sensitive subnetworks? Beyond this, how do the actions of different hormones, broadcast in response to different behavioral events, change crosstalk in this network? In addition, our formulation of aggression arousal or attack-likelihood as a unidimensional signal here is almost certainly oversimplified, and new models[78], which explicitly quantify how internal state shapes sensory-motor transformation during behavior, will be critical to interpreting neural activity.

We hope that new models of behavior that take into account hormone-mediated synaptic change will usher in a new science of computational neuroendocrinology. While the ability of researchers to monitor blood serum hormone levels over time has been limited by the small body mass of lab rodents, the successful development of novel fluorescent indicators for neuromodulatory molecules raises the possibility of future tracking of *in vivo* sex hormone dynamics across broad timescales. Such tool development would enable the design of experiments to quantify the relationship between short-term and longitudinal sex hormone dynamics and ongoing neural activity and behavior, allowing new insight. Researchers could pair these tools with manipulations to inactivate hormone-sensitive neural populations, knock down identified gene targets in hormone-sensitive neural populations, or block sex hormone receptors in these populations. Such manipulations would allow for the testing of the hypotheses that shifting hormonal state drives gene expression changes in distinct neural populations to alter neural activity patterns. This will change the likelihood of a given sensory stimulus to “release” attack or the likelihood of experience to generate persistent changes in neural computations and, consequently, social behavior.

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Highlights

- Social experience generates persistent aggressive states.
- Changes in experience-dependent sex hormones remodel local and long-range circuits in the brain's "social behavior network".
- Circuit-level remodeling may change the relationship between neural activity and an aggression "threshold".

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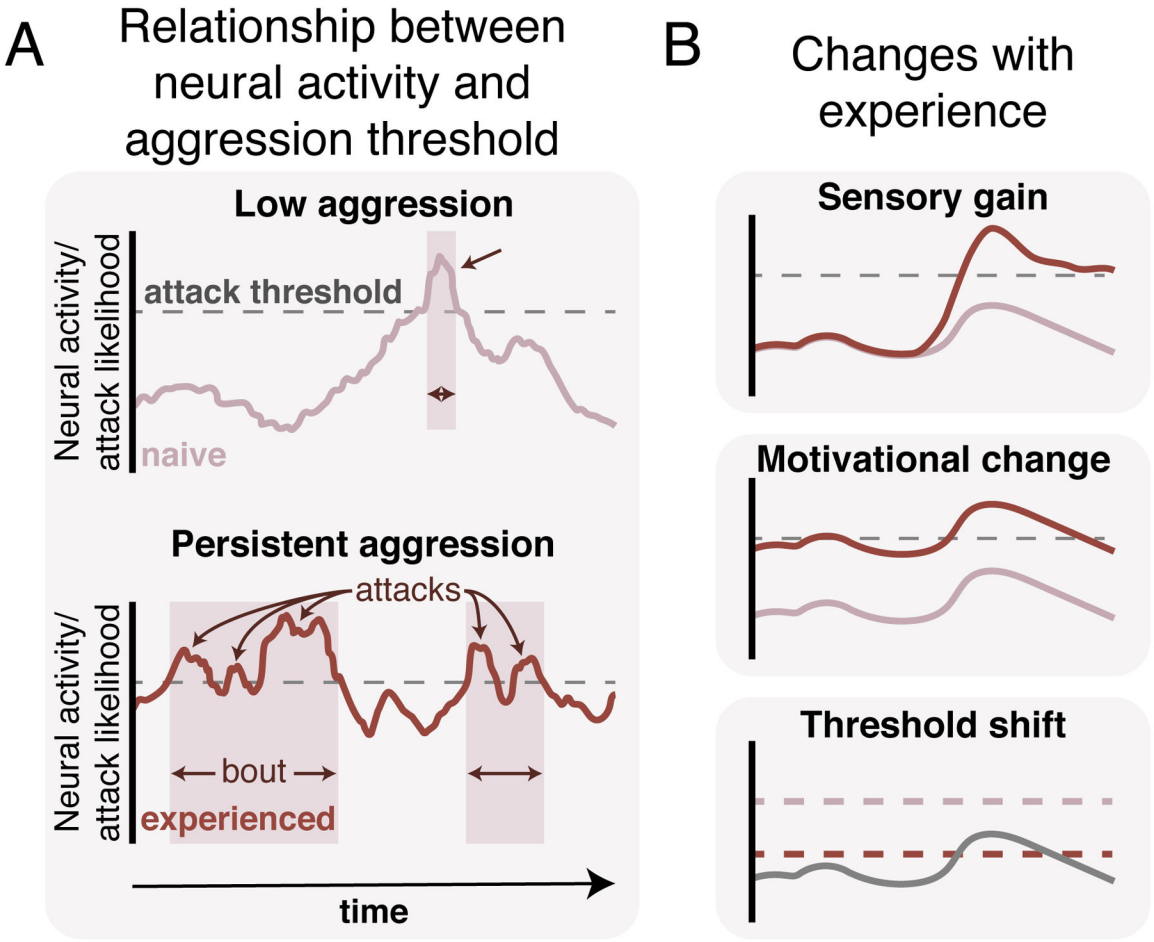

Figure 1. Experience-dependent changes in neural encoding of aggression.

(A) We propose that neural activity within individual nodes of the social behavior network may represent attack likelihood. Increases in activity bring the animal closer to a theoretical attack threshold (dotted lines): once neural activity crosses this threshold an attack is triggered in an all-or-none manner (arrows). Multiple attacks in quick succession constitute bouts (shaded background). ***(B)*** Different manners in which experience may change neural encoding of attack likelihood. Top: Changes in sensory gain where the same stimulus will drive an increased neural response following experience. Middle: Changes in a motivational internal state will drive a shift in overall activity levels, bringing an animal closer or further from the attack threshold. Bottom: Experience can lower or raise the attack threshold itself leading to a decrease or increase in the amount of input needed to “release” attack.

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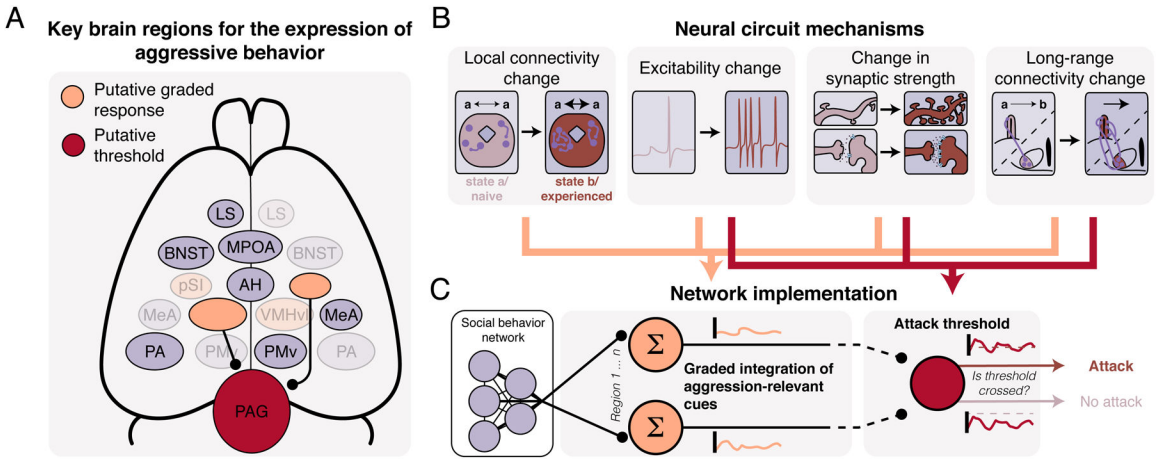

Figure 2. Circuit mechanisms underlying hormone- and experience-dependent development of persistent aggression.

(A) Brain regions with identified roles in aggressive behavior. Putative graded response and threshold regions highlighted. Shading of contralateral regions done for display purposes. ***(B)*** Hormone- and experience-driven circuit changes within the overlapping aggressive and social behavior networks. ***(C)*** Proposed relationship between circuit plasticity and neural encoding of attack likelihood. Some circuit changes are more likely to affect graded representation of attack likelihood whereas others are more likely to change the relationship between neural activity and putative attack threshold. Abbreviations: LS, lateral septum; MPOA, medial preoptic area; BNST, bed nucleus of the stria terminalis; AH, anterior hypothalamus; pSI, posterior substantia innominata; VMHvl, ventromedial hypothalamus, ventrolateral area; MeA, medial amygdala; PA, posterior amygdala; PMv, ventral premammillary area; PAG, periaqueductal gray.