Trends in Genetics

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Feature Review

The Neural Mechanisms of Sexually Dimorphic Aggressive Behaviors

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Aggression is a fundamental social behavior that is essential for competing for resources and protecting oneself and families in both males and females. As a result of natural selection, aggression is often displayed differentially between the sexes, typically at a higher level in males than females. Here, we highlight the behavioral differences between male and female aggression in rodents. We further outline the aggression circuits in males and females, and compare their differences at each circuit node. Lastly, we summarize our current understanding regarding the generation of sexually dimorphic aggression circuits during development and their maintenance during adulthood. In both cases, gonadal steroid hormones appear to play crucial roles in differentiating the circuits by impacting on the survival, morphology, and intrinsic properties of relevant cells. Many other factors, such as environment and experience, may also contribute to sex differences in aggression and remain to be investigated in future studies.

Highlights

Depending on the species, aggressive behaviors can differ both quantitatively and qualitatively between sexes.

In rodents, social experiences, including social isolation, mating, winning, and losing, impact differentially on aggressive behaviors between sexes.

Similar brain regions mediate male and female aggression in mice, although the number and response intensity of relevant cells may differ.

Sex hormones, such as estrogen and androgen, play important roles during development to differentiate male and female aggression circuits.

Sex hormones are necessary to maintain a high level of aggression in adult male mice but not in female mice.

Overview of Aggression Studies in Males and Females

For over a century, aggression has been a topic of investigation by ethologists, psychologists, biologists, and more recently neuroscientists. Niko Tinbergen, an influential ethologist, conducted decades of field studies and concluded that instinctive behaviors including aggression, mating, parental behaviors, and building have characteristic species-specific stereotypical motor patterns [1]. He proposed that these stereotypical behaviors are genetically preprogrammed and are triggered by specific sensory inputs. He further argued that behavioral decision is not solely determined by extrinsic stimuli but is also influenced by internal states defined by the prior experiences and circulating hormonal status of an animal. He envisaged that both extrinsic and intrinsic signals are integrated at each circuit node to enable animals to take the most relevant behavioral actions on a moment-to-moment basis. His hypothesis, as well as others ([2], p. 273), influenced researchers in the following decades, leading to recent discoveries of circuit nodes of instinctive behaviors that are genetically defined and hard-wired [3–14], but at the same time are highly flexible [15,16]. One of the themes in the current review is to highlight the recent array of work carried out using novel genetic approaches that have brought back to light the study of aggression circuitry in rodents.

Despite the requirement for aggression in the survival of both sexes, aggression is sexually dimorphic. It is more prevalent in males owing to selective pressures associated with limited mating opportunities [17–19]. In many species, males have evolved bigger body sizes and sometimes specialized body parts for fighting [20]. While females are typically not as aggressive as males, the level of aggression in females increases dramatically during lactation in mammals for the purpose of protecting their young, although females in non-mammalian species often also aggressively protect their young [21,22]. Thus, aggressive behaviors differ between sexes in both expression and modulation to fit the needs of each sex. The second theme of this review

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will be to discuss sex differences in aggressive behaviors and the potential underlying neural and hormonal mechanisms, focusing on rodents as the primary animal model.

Sexually Dimorphic Aggressive Behaviors

Patterns of Aggressive Behaviors in Males and Females

The degree to which aggression differs between sexes varies from species to species. For example, in some species, only one sex is equipped with weaponry body parts, and thus aggression expression using those weaponry parts is inevitably sex-specific. In rodents, while males and females differ in body size, no sex-specific body part has evolved for the purpose of aggression. Thus, females and males of various rodent species, such as mice, rats, and hamsters, express aggression in qualitatively similar ways using biting as their main strategy to harm an opponent, although the level of aggression, as measured by attack frequency and duration, is typically higher in males than in females, with the exception of hamsters [23]. While both males and females bite the opponent, fine differences in biting patterns have been reported. In mice and rats, females usually attack female intruders on their back and male intruders on their vulnerable body parts, such as head and ventral surface [10,24–26]. By contrast, resident male mice bite male intruders on both their back and head [10,27] (Figure 1). Importantly, the biting patterns in males and females are not fixed but are influenced by many factors, such as the defense strategy of the opponent and the relative size of the animals [28–30]. While resident male rats deliver most bites to the back of male intruders under normal conditions, male rats mostly bite the head and snout of anaesthetized male intruders [30,31]. When large Swiss Webster lactating females (~35 g) encounter smaller C57 young adult males (~20 g) or juvenile intruders, the bites are mostly directed to the back of the intruder [7]. Thus, both males and females can employ back- or head-attack strategies depending on who they are fighting against.

The Influence of Social Experience on Aggression in Males and Females

Although aggression is considered to be a hard-wired behavior, its level is not stationary. Age, housing condition, sexual experience, and winning or losing experiences are some of the known factors that can influence aggression level, often differentially in males and females (Table 1) [32]. First, male and female mice differ in their developmental course of aggression.

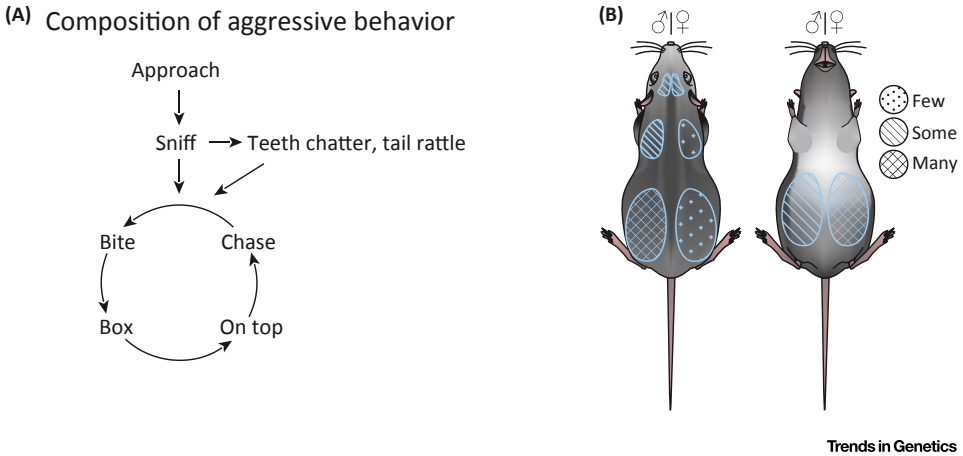

Figure 1. Sexually Dimorphic Aggression Behaviors. (A) Aggression can be divided into appetitive phase (approach and sniffing) and a variety of consummatory actions (chase, bite, and box). (B) The body parts that male and female rodents target during attacks differ.

Glossary

Aggression circuit: the cells in the brain and their connectivity that generate and modulate aggressive behaviors.

Androgen receptor (AR): a nuclear receptor that is activated upon binding of ligands such as testosterone and dihydrotestosterone to regulate transcription.

Anteroventral periventricular nucleus (AVPV): a small nucleus in the preoptic area of hypothalamus. It contains abundant kisspeptin-expressing neurons and regulates the activity of gonadotropin-releasing hormone (GnRH) neurons which constitute of the initial step in the hypothalamic–pituitary–gonadal axis.

Bed nucleus of the stria terminalis (BNST): a cluster of nuclei adjacent to the stria terminalis, which is a fiber bundle carrying signals from the amygdala to the hypothalamus, septum, and other brain regions. The BNST has been proposed as extended amygdala and is involved in anxiety, aversion, and various social behaviors.

Corticotropin-releasing hormone (CRH): a peptide hormone that is generated and secreted by neurons in the periventricular nucleus of the hypothalamus. It is generally released during stressful conditions to activate the HPA axis.

Conspecific: a member of the same species (noun) or animals that belong to the same species (adjective).

Estrogen receptor (ER): there are two classes of estrogen receptors, ERα and ERβ, that are encoded by *Esr1* and *Esr2*, respectively. They are nuclear receptors that are activated upon binding of estrogen (estradiol).

Immediate-early gene mapping: immediate-early genes are a set of genes that are rapidly upregulated by cell firing or other intracellular events (e.g., increase in cAMP concentration). Immediate early gene mapping is to examine the expression pattern(s) of immediate early gene(s) in the brain after the behaviors of interest.

Kisspeptin: a peptide, encoded by the *Kiss1* gene, that is a ligand for GPR54.

Lateral septum (LS): the septal nuclei are situated below the rostrum of the corpus callosum and consist of medial, lateral, and posterior parts.

Table 1. Influence of Various Social Experiences on Aggressive Behaviors in Males and Females

Type of experience	Change in aggressive behavior[a]	
	Males	Females
Social isolation	Increased	Decreased
	Brain [38][b]	Hood [34][b]
	O'Donnell *et al.* [37][b]	Increased
	Matsumoto *et al.* [36][b]	Kuchiiwa and Kuchiiwa [39][b]
Sexual experience	Increased	Increased
	Insel *et al.* [40][c]	Albert *et al.* [44][d]
	Getz *et al.* [41][c]	
	Flannelly *et al.* [42][d]	
	Goyens and Noirot [43][b]	
Winning experience	Increased	Decreased
	Dugatkin [45][e]	Silva *et al.* [52][b]
	Hoefler [46][f]	Unchanged
	Whitehouse [47][f]	Hood and Cairns [34][b]
	Beaugrand *et al.* [48][g]	
	Forster *et al.* [49][h]	
	Oyegbile and Marler [50][b]	
	Drummond and Canales [51][i]	
Defeat experience	Decreased	Unchanged
	Hsu *et al.* [53]	Taravosh-Lahn and Delville [60][m]
	Penn *et al.* [15][j]	Van de Poll *et al.* [57][d]
	Hofmann and Stevenson [54][k]	
	Rutishauser *et al.* [55][l]	
	Potegal *et al.* [56][m]	
	Van de Poll *et al.* [58][d]	
	Kudryavtseva *et al.* [59][b]	
	Jeffress and Huhman [57][m]	

[a]Aggression in males and females is differentially influenced by various social experiences including social isolation, sexual experience, winning experience, and defeat experience. Species are indicated as follows: [b]mouse; [c]prairie vole; [d]rat; [e]model; [f]spider; [g]fish; [h]lizard; [i]bird; [j]fly; [k]cricket; [l]lobster; [m]hamster.

While male mice have a sharp rise in aggression around the end of puberty (45 days), the emergence of aggression in female mice occurs during adulthood (90 days) and the level of aggression further increases at midlife (270 days) [33–35].

Furthermore, social isolation has been consistently shown to increase the frequency of attacks and shorten attack latency in male mice [36–38], whereas its effect on female mouse aggression remains controversial. One study showed that isolation housing abolished aggression in female mice of a low-aggression strain, but did not change aggression in females of a high-aggression strain [35]. However, in a more recent study it was found that the strength of aggressive bites towards an inanimate object increases with weeks of social isolation in female mice [39].

The LS receives massive inputs from hippocampus and projects mainly to the hypothalamus. It has been implicated in regulating anxiety and social behaviors, especially aggression.

Main olfactory epithelium (MOE): an epithelium in the nasal cavity where olfactory sensory neurons reside for detecting volatile odors. This is the first stage of the main olfactory system.

Medial amygdala (MEA): a nucleus in the amygdala that relays olfactory information to the hypothalamus.

Medial dorsal thalamus (MD): part of thalamus that is strongly reciprocally connected with the prefrontal cortex. It also receives information from amygdala, basal forebrain, and other subcortical regions.

Medial prefrontal cortex (mPFC): the frontal cortex is the frontal part of the cerebral cortex. It has been indicated in numerous cognitive functions including attention, inhibitory control, habit formation, working memory, and long-term memory. The medial part of the frontal cortex is suggested to be more relevant for social behaviors.

Non-volatile: refers to non-vaporized molecules that are predominantly detected by the vomeronasal organ.

Nucleus accumbens (NAc): a region in the basal forebrain that has been implicated in motivation, reward, and reinforcement.

Optogenetic: a technique that manipulates or controls the activity or molecules within the targeted cells by introducing genetically modified light-sensitive molecules (e.g., channelrhodopsin) and delivering light to the cells.

Paraventricular nucleus of the hypothalamus (PVN): a nucleus in the periventricular zone of hypothalamus that is situated adjacent to the third ventricle. It consists of many neurons synthesizing a variety of neuropeptides, such as CRH, oxytocin, and vasopressin. Many neurons project to the posterior pituitary.

Periaqueductal grey (PAG): a midbrain structure that surrounds the aqueduct. It receives extensive inputs from hypothalamus, prefrontal cortex,

Sexual experience appears to consistently increase aggression in males, but its effect on females varies with species. In monogamous prairie voles, after 24 h of cohabitation with repeated mating experience, both males and females increased aggression towards strangers [40,41]. In mice and rats, the experience of mating also enhances aggression in males [42,43], while its effect on females remains unclear. In one study [44], aggression was elevated in female rats that were cohabitated with castrated males with testosterone implants. However, such increases may not be due to the mating experience *per se*, but instead to pseudopregnancy after repeated mating.

Males with winning experience are more willing to escalate a fight and have a higher probability of winning in future agonistic encounters. This phenomenon, referred to as the winner effect [45], is evident across a variety of invertebrate and vertebrate species [46–51]. Studies on winner effect in females are few and results vary among species. It was reported that, in female California mice, attack latency significantly decreased with repeated resident–intruder tests [52]. However, no change in attack latency or frequency was found during repeated testing in ICR mice, an aggressive laboratory mouse strain (*Mus musculus*) [34].

In contrast to the winner effect is the loser effect. Defeat experience reduces the willingness of an animal to engage in a fight and decreases the likelihood of winning in future agonistic encounters [53]. Studies in *Drosophila* [15], crickets [54], lobsters [55], hamsters [56,57], rats [58], and mice [59] consistently demonstrated that losing in fights significantly reduces male aggression, either transiently or permanently [57]. Studies on the loser effect in females are less common. The limited studies performed support a lack of loser effect in female rodents. For example, it was found that juvenile female hamsters subjected to daily attack by adult females and males developed similar agonistic behaviors as unattacked controls [60]. Defeated female rats show similar levels of aggression in future agonistic encounters as winners [61]. Recently, a female social defeat paradigm was established in mice by using males with artificially activated **ventromedial hypothalalmus, ventrolateral part** (VMHvl; see Glossary) [62]. This paradigm will be useful in future studies to understand the behavioral consequences of social defeat in female mice.

The Rewarding Value of Aggression

In species ranging from fish to primates, some individuals make extensive efforts to display aggressive actions [63–72]. Recently, using a **self-initiated aggression-seeking task**, it was shown that >50% of aggressive male mice learned to voluntarily poke a nose port repeatedly to gain access to a weak intruder and attack it immediately [16]. The aggression-seeking behaviors extinguished rapidly when the subordinate intruders were replaced with non-subordinate intruders, suggesting that winning experiences, but not social interaction alone, drive aggression-seeking behaviors [16]. Consistent with this idea, it was found that aggressive male mice strongly prefer the test chamber in which the male mice experienced winning over a chamber that was not associated with winning [73,74]. In addition, microdialysis studies further revealed that dopamine levels are elevated in the **nucleus accumbens** (NAc) in anticipation of a fight and after fighting [75]. Thus, aggressive experience towards subordinates can be rewarding, at least for some individuals. Given the generally higher level of aggression in males, it is not surprising that all aggression-seeking studies have thus far used male subjects. We speculate that the lack of winning effect in female mice and rats may suggest that the attacking experience is not rewarding in females. Future studies using the aggression-seeking task or aggression-mediated conditional place preference test in female animals will test this hypothesis directly.

and other brain regions, and the PAG projects to brainstem areas relevant for motor and autonomic control. It has been implicated in defense, motor control of social behaviors, and pain regulation.

Pharmacogenetic: a technique that manipulates or controls the activity of molecules within targeted cells by introducing genetically modified receptors that can be activated upon ligand binding (e.g., a modified form of human M3 muscarinic receptor).

Self-initiated aggression-seeking task: a behavioral task to assess the aggressive motivation of a test animal. Subjects learn to initiate a trial by performing a specific action such as nose poke for a subsequent opportunity to attack a weaker intruder.

Vasopressin (AVP): a nine amino acid peptide hormone that is synthesized in the hypothalamus. It has been implicated in regulating water balance and social behaviors.

Ventral premammillary nucleus (PMv): a nucleus in the medial hypothalamus that is posterior to the VMHvl. It receives strong inputs from medial amygdala and projects mainly to other parts of medial hypothalamus.

Ventromedial hypothalamus, ventrolateral part (VMHvl): a subnucleus in the medial hypothalamus that is essential for male and female aggression. It is also crucial for female sexual receptivity.

Volatile: refers to vaporized molecules that are predominantly detected by the main olfactory epithelium.

Vomeronasal organ (VNO): a second olfactory organ in the nasal cavity where vomeronasal neurons reside for the detection of pheromones. This is the first stage of the accessory olfactory system.

Essential Brain Regions for Male and Female Aggression

Sexually dimorphic aggressive behaviors are presumably caused by sex differences within the **aggression circuits**. Chemosensory cues from **conspecifics** are first detected by vomeronasal receptors in the nose, and are then relayed to the hypothalamus through the olfactory bulb and amygdala. Signals are further relayed to the midbrain for subsequent motor actions [76]. In Figure 2 and Table 2 we summarize our current knowledge regarding the brain regions that influence male and female aggression. In short, nearly all regions that have been shown to be associated with male aggression are also found to influence female aggression, pointing to a shared aggression circuitry between sexes. In the next section we describe the aggression circuit in males and females from the sensory end to the motor end, with a special focus on the hypothalamus, whose function in aggression has been studied most extensively.

Main and Accessory Olfactory Bulbs

Rodents rely on olfactory cues for triggering aggression. **Volatile** cues of conspecifics and **non-volatile** cues (pheromones) are detected by specific receptors expressed in olfactory sensory neurons in the **main olfactory epithelium** (MOE) and **vomeronasal organs** (VNO), respectively, and are further relayed to the main olfactory bulb (MOB) or accessory olfactory

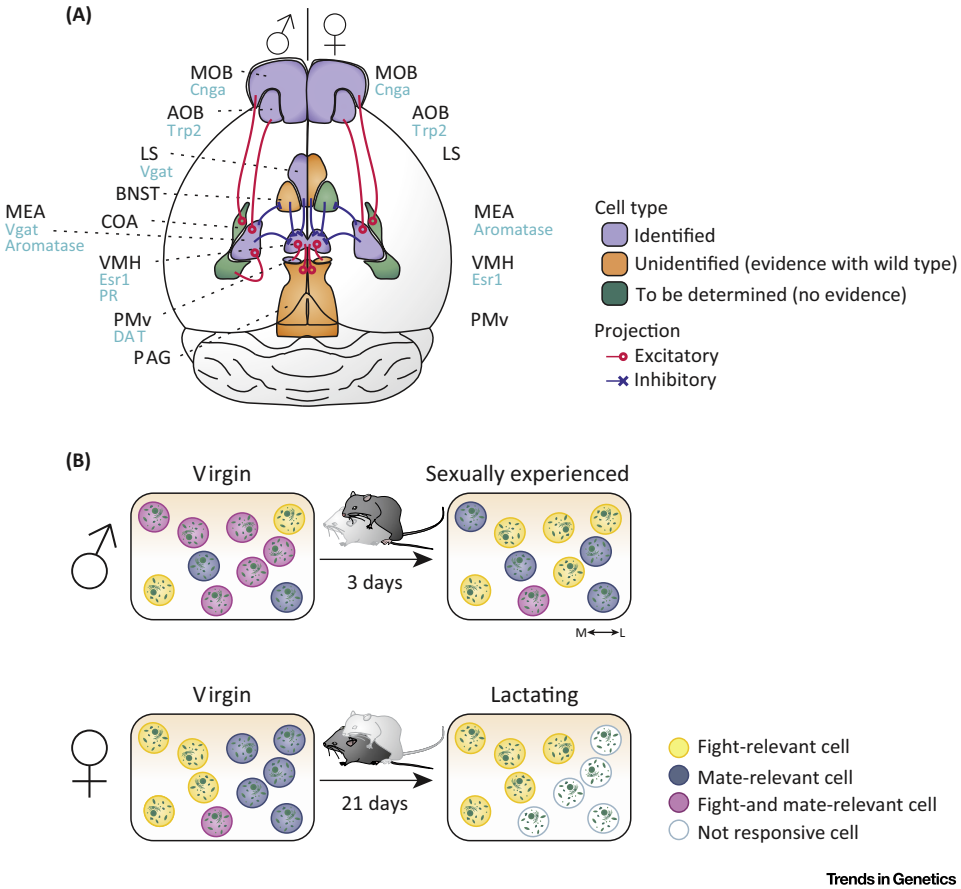

Figure 2. Aggression Circuitry in Male and Female Rodents. (A) Aggression circuit nodes and cell types in male and female mice. (B) Sexually dimorphic and experience-dependent organization of aggression- and mating-related cells in the ventrolateral part of the ventromedial hypothalamus (VMHvl). For abbreviations of brain regions please refer to the main text and the Glossary.

Table 2. Brain Regions and Genes Relevant for Aggression in Male and Female Rodents[a]

Region	Gene	Males	Females
MOE	*Cnga*	Mandiyan *et al*. [80][b]	Fraser *et al*. [81][b]
		Fraser *et al*. [81][b]	
VNO	*Trp2*	Stowers *et al*. [82][b]	Kimchi *et al*. [83][b]
MEA	*Vgat*, aromatase (*Cyp19A1*), *Npy*	Hong *et al*. [11][b]	Unger *et al*. [10][b]
		Unger *et al*. [10][b]	
		Padilla *et al*. [90][b]	
LS	*Vgat*	Wong *et al*. [131][b]	Not available
BNST	Not available	Padilla *et al*. [90][b]	Not available
VMH	*Esr1*/PR (*Pgr*)	Lin *et al*. [119][b]	Hashikawa *et al*. [121][b]
		Yang *et al*. [9][b]	
		Lee *et al*. [6][b]	
PMv	DAT	Not available, but see Stagkourakis *et al*. [136][b] and Soden *et al*. [135][b] for DAT	Motta *et al*. [134][c]
PAG	Not available	Mos *et al*. [139][c]	Lonstein *et al*. [142][c]

[a]Brain regions and molecularly identified neurons (if available) within those structures that are crucial for male and female aggression (see also Figure 2); [b]mouse studies; [c]rat studies.

bulb (AOB) in parallel [76–79]. Impairment of MOE or VNO, either by lesioning or gene deletion (*Cnga*, cyclic nucleotide-gated channel [80,81]; or *Trpc2*, transient receptor potential cation channel, subfamily C, member 2 [82,83]), attenuates aggression in both males and females. Information in the MOB is further relayed to five major regions including piriform cortex, cortical amygdala, olfactory tubercle, anterior olfactory nucleus, and lateral entorhinal cortex [84]. However, the function of these regions in aggression remains to be studied.

Medial Amygdala and Bed Nucleus of the Stria Terminalis

Information in the AOB is relayed to the **medial amygdala** (MEA) and the **bed nucleus of the stria terminalis** (BNST), which in turn project to the hypothalamus. MEA also receives MOB information indirectly through the posterolateral part of the cortical amygdala (plCOA). It was recently found that GABAergic neurons, but not glutamatergic neurons, in the MEA are sufficient and necessary for driving male aggression [11]. It was further demonstrated that a subpopulation of GABAergic cells expressing aromatase are necessary for aggression in both sexes [10]. From MEA, it remains unclear how the information is relayed to the hypothalamus for generating aggression. Although posterodorsal MEA (MEApd) projects directly to the VMHvl, its strongest recipient is BNST [85,86]. BNST has negative effects on aggression in both sexes. Electrical stimulation of the BNST suppressed aggression in cats of both sexes [87]. Microinjection of oxytocin into the BNST reduced female aggression [88]. Given that MEA cells that are relevant for aggression are GABAergic [11], it is possible that MEA activates aggression-related cells in the VMHvl by inhibiting the GABAergic cells in the BNST which project intensively to the VMHvl [89]. Consistent with this hypothesis, terminal **optogenetic** stimulation of MEA NPY-expressing neurons at the BNST, but not at the VMHvl, evokes aggression in male mice [90].

Despite a common role of MEA aromatase neurons [10] and BNST [87] in male and female aggression, both regions are sexually dimorphic. The MEA, especially the posterodorsal part, differs between sexes in its rostral–caudal extent, volume, number of cells, neuronal soma size [91,92], number of excitatory synapses [93], and gene expression pattern [94]. Several recent

studies also suggest that MEA cell responses during social behaviors are sexually dimorphic. **Immediate-early gene mapping** studies have identified two distinct MEA subpopulations defined by embryonic transcription factors that are activated differentially after mating in males and females [95]. Electrophysiological recording of MEA cells in anesthetized male and female mice showed that, in males, the female responsive cells are more abundant than male responsive cells, whereas the opposite response pattern is observed in females [96]. Recently, *in vivo* microendoscopic imaging of the MEA in freely moving mice revealed that the neural representations of various social cues, including adult males, females, and pups, change with sexual experiences differentially in males and females [97]. Lastly, blocking oxytocin signaling in the MEA impaired social discrimination in males but not in females [97,98]. Although the MEA appears to play an important role in both male and female aggression [10,11], the exact function of the MEA cells in aggression, its modulation, and circuit wiring are likely different between sexes.

Similarly to the MEA, the BNST in males and females also differs in gene expression pattern [99–102], cell number [103], and volume [102,104]. The *in vivo* responses of BNST cells during aggressive behaviors in males and females have not been reported, and should be investigated in future studies.

The Ventrolateral Part of the Ventromedial Hypothalamus

The main target of the MEA and BNST is the hypothalamus. Since the initial works demonstrating that aggression could be elicited by electrical stimulation in the cat hypothalamus [105–108], hypothalamic stimulation-elicited attack has been observed in chicken [109], herring gull [110], opossum [111], guinea pig [112], marmoset [113], macaque [114], squirrel monkey [115], and rat [116]. Microstimulation in rats mapped out a large hypothalamic attack area (HAA), from which an attack could be artificially elicited [116,117]. These detailed studies in rats compared the HAA distribution in male and female rats using hundreds of stimulation electrodes [118], and no clear sex difference was found. More recently, a series of studies identified a small region within the HAA, namely VMHvl, as an essential locus for aggression in male mice [6,9,119]. Optogenetic activation of the VMHvl cells, especially those expressing **estrogen receptor** α/progesterone receptor (ERα/PR; overlap nearly 100%), induced immediate attack, whereas **pharmacogenetic** or optogenetic inactivation of the VMHvl suppressed aggression. *In vivo* electrophysiological recording revealed an acute increase in VMHvl cell activity during natural inter-male aggression [16,76,119–122]. The essential role of the VMHvl in male aggression was further highlighted by a recent study showing that pharmacogenetic activation of the VMHvl can induce aggression in naturally non-aggressive male mice, including those that were group-housed, gonadectomized, or had compromised olfactory inputs [123].

Initial studies that manipulated the VMHvl Esr1$^+$ cell activity failed to significantly change female aggression [6,9,123]. However, a series of our experiments demonstrated that VMHvl Esr1$^+$ cells in females are essential for aggression. Immediate-early gene mapping and *in vivo* population recordings revealed high activity of VMHvl Esr1$^+$ cells during aggressive behaviors in female mice regardless of the reproductive status of the animal (lactating vs virgin), genetic background (Swiss Webster or C57BL/6), or intruder type (juveniles or adult male intruder) [7]. Consistent with the natural response patterns, it was found that pharmacogenetic silencing of VMHvl Esr1$^+$ cells reduced female aggression, whereas optogenetic activation of the cells in virgin females elicited attack towards both natural and non-natural targets (e.g., females attacked males despite the fact that, in laboratory conditions, virgin females rarely attack male conspecifics). Interestingly, VMHvl Esr1$^+$ cells also increase activity during female–female mounting. Activating the VMHvl Esr1$^+$ cells in spontaneously mounting C57BL/6 virgin females

evoked stimulation-locked mounting, whereas activating the cells in spontaneously attacking C57BL/6 lactating females or SW virgin females evoked stimulation-locked attack. Thus, VMHvl Esr1$^+$ cells can drive both mounting and attack in females, exactly as in males [6,7]. In males, the form of the behavioral output depends on the activation level of the VMHvl Esr1$^+$ cells, whereas the induced behavior in females is determined by the natural behavioral pattern of the animals at the moment of stimulation.

In females, the VMHvl, especially cells expressing both Esr1 and PR, have also been well established as an essential population for sexual receptivity [124–130]. It has been shown that electrical stimulation of the VMHvl can extend the duration of lordosis in female rats [125]. Knocking down Esr1 expression in the VMHvl reduced the sexual receptivity of female mice [126]. Because both Esr1$^+$/PR$^+$ cells are implicated in female aggression and mating, it was essential to further understand the organization of aggression- and mating-related cells within the female VMHvl. *In vivo* electrophysiological recording revealed that mating- and aggression-related VMHvl cells are distinct. In addition, using Fos Catfish mapping, a method that allows examination of *Fos* mRNA expression induced by two different behaviors, it was found that aggression- and mating-related cells reside in distinct compartments of the VMHvl: the mating-responsive cells are concentrated in the VMHvll (lateral part of VMHvl), while the aggression-related cells are concentrated in the VMHvlm (medial part of VMHvl) [7]. Laser capture microdissection and RNA-seq further revealed distinct transcriptional profiles of the VMHvlm and VMHvll cells, while tracing studies demonstrated that VMHvll (but not VMHvlm) projects to the **anteroventral periventricular nucleus** (AVPV), a sexually dimorphic region that is enriched for **kisspeptin**, a polypeptide which is essential for regulating GnRH neurons [7].

It is not yet clear whether the VMHvll and VMHvlm cellular compartments also exist in males because the fight-related and mate-related cells are spatially mixed [7] and they partially overlap at the single-cell level in the VMHvl [119,120]. Electrophysiological recording revealed that as many as 50% of the VMHvl cells that are excited by males are also excited by females, although the magnitude of cell responses between male and female stimuli often differ [119,131]. Interestingly, the extent of overlap between the male- and female-responsive cells varies with social experience [132]. It has been shown that highly overlapping Esr1$^+$ cells respond to male and female stimulus mice in sexually naïve male mice. After sexual experience, the male- and female-responsive cells start diverging within 3 days (Figure 2). Of note, most male-responsive VMHvl cells respond during both male investigation and attack [119,120], whereas the majority of female-responsive cells are activated during investigation but are suppressed during intromission and ejaculation [119]. Consistent with the lack of excitatory responses of the VMHvl cells during advanced stages of male sexual behaviors, silencing the VMHvl cells, either pharmacogenetically or optogenetically, did not change ongoing mating [6,119], although ablation of VMHvl PR$^+$ cells impaired intromission [9]. Overall, the role of VMHvl Esr1$^+$ cells in male sexual behavior is likely to be relatively minor in comparison to that in females.

Ventral Premammillary Nucleus

Another hypothalamic region that has been indicated in aggression is the **ventral premammillary nucleus** (PMv). The PMv receives inputs from the MEA [86] and projects to several hypothalamic nuclei including the VMHvl [133]. Ablation of the PMv attenuated aggression in lactating rats and reduced fighting-induced c-Fos expression in the VMHvl [134]. Although the role of the PMv in male aggression has not yet been thoroughly studied, it was found that cells in the PMv that express dopamine transporter (DAT) drive inter-male social investigation via excitatory neural transmission [135]. c-Fos mapping showed that the PMv is predominantly activated by the presence of a male intruder in both sexes [134,135], and is only minimally

activated by a female intruder in male subjects [135]. Optogenetic and pharmacogenetic experiments showed that moderate activation of the DAT(+) population induced social investigation to intruders [135,136] while strong optogenetic activation (>3 mW, 20 Hz) elicited aggression reliably in male mice. Interestingly, prolonged aggression was observed even after the termination of PMv stimulation. Slice physiological experiments demonstrated that PMv has intrinsic, and network level features that maintain its excitation once it is activated [136]. PMv neurons exhibited prolonged excitation to both excitatory and inhibitory inputs [136]. PMv DAT (+) cells create recurrent network by connecting each other with excitatory neurotransmission [136]. PMv DAT(+) cells send excitatory projection to VMHvl cells that send excitatory project back to PMv DAT cells [136]. Importantly, fast-scan cyclic voltammetry did not detect dopamine release in the VMHvl [135]. PMv DAT (+) cells control rewarding aspect of aggression and its execution by distinct projections [136]. Whereas the projection from PMv DAT (+) cells to VMHvl is sufficient for aggressive behaviors, the projection to the supramammillary nucleus (SuM) is involved in aggression reward [136]. The detailed roles of PMv in female aggression and in other social behaviors remain to be determined. Additional studies should be performed to determine whether PMv neurons encode the sensory information of conspecifics or the relevant actions during social behaviors (e.g., aggression, mating).

Periaqueductal Grey

Among the hypothalamic projection sites in the midbrain, several lines of research suggest that the **periaqueductal grey** (PAG) plays a role in aggression. c-Fos was elevated in the PAG after fighting in both males and females [7,137,138], while electric stimulation of the PAG induced aggression in male rats [116,139]. Furthermore, the VMHvl, including the subpopulation expressing Esr1/PR, projects heavily to the dorsal and lateral parts of the PAG [7,9,140]. *In vivo* recording in cats showed that cells in the dorsal and lateral parts of PAG responded during agonistic encounters [141]. However, the effect of PAG lesions on aggression has been inconsistent in both sexes, possibly because of heterogeneity of the lesion sites in the PAG and the existence of redundancy in the circuit [142–144]. How the hypothalamic information is relayed to the PAG, what cell types in the PAG are relevant for aggression, and how they differ between sexes remains unknown.

Lateral Septum

The aforementioned regions, including olfactory bulbs, MEA and BNST, VMHvl and PMv, and PAG, constitute the main circuit for controlling the sensorimotor transformation to express aggressive behaviors. Several other regions that are outside this direct 'expression' pathway have also been implicated in playing essential roles in modulating aggression. Past studies in humans and animals have consistently shown that the **lateral septum** (LS) negatively regulates aggression. Patients with tumors centered around the septum show increased irritability and aggressiveness [145]. Neural activation of LS (as measured by Fos) negatively correlated with aggression in male song sparrows [146]. Lesioning or silencing the septum area increased aggression in rats [147,148], male hamsters [149], and mice [131]. Conversely, the activation of the septum decreased aggression in male and female mice [131,150]. The LS might regulate aggression by suppressing the activity of aggression-related neurons in the hypothalamus. VMHvl neurons receive direct GABAergic inputs from the LS, and optogenetic activation of these GABAergic projections suppressed aggression in male mice [131]. Moreover, optrode recording (combined optogenetics and neural recording) showed that aggression-excited cells in the VMHvl are preferentially suppressed by optogenetic activation of projection from the LS in comparison to aggression-inhibited or non-responsive cells [131]. Given that LS receives dense inputs from the hippocampus, and that some cells show place fields [151], this pathway might modulate aggression through evaluating territoriality associated with the location of the

subject. Future studies could test this hypothesis directly by investigating the activity of LS neurons during agonistic encounters under different territorial contexts.

Medial Prefrontal Cortex and Medial Dorsal Thalamus (MD)

The prefrontal cortex, especially the dorsal medial part, is involved in the determination of social dominance [152]. It has been previously observed that male mice higher in dominance rankings possessed enhanced synaptic strengthening in **medial prefrontal cortex** (mPFC) pyramidal neurons [153]. Increasing the synaptic efficacy from the **medial dorsal thalamus** (MD) to mPFC cells increased social rank, while weakening the synapses had the opposite effect [153]. In addition, *in vivo* single-unit recordings showed that mPFC neurons display effort-related neuronal activity during competition for social dominance [154]. Future studies could potentially elucidate how hierarchical information encoded in mPFC may influence the aggression circuitry in a sex-specific manner.

Overall Differences in the Male and Female Aggression Circuits

Thus far, all the brain regions relevant for male aggression appear to also play a role in female aggression [6,7,10,32,80–83], suggesting that the aggression circuitry in rodents is likely to be qualitatively similar between sexes. This is perhaps not surprising given that aggressive behaviors involve similar motor patterns in male and female rodents. Nevertheless, quantitative differences of the aggression circuit do exist between sexes. First, the number of the aggression-related cells within each aggression relay likely differs between sexes. In males, the aggression-responsive cells are found throughout the VMHvl, whereas in females these cells are restricted to the medial half of the VMHvl [7] (Figure 2). Given that the VMHvl is larger in males than in females [155], the total number of aggression-responsive cells is likely to be higher in males than in females. Consistent with this possibility, single-unit recording from male VMHvl showed that ~40% of recorded cells increased activity during aggression, whereas only ~20% of recorded units in female mice did [7,119]. In addition, the male and female aggression-responsive cells could differ in their response magnitude. Single-unit recording revealed that the mean firing-rate increase of aggression-related cells in the VMHvl is higher in males than in virgin females [7,119,120]. The higher responses of male VMHvl neurons appear to correlate with the longer primary and secondary dendrites and the larger number of synapses in the male VMHvl than in the female VMHvl [155,156].

Aggression Circuits between Different Strains of Rodents

Aggressive behaviors not only differ between sexes but also vary widely with genetic background. In rats, an inbred male CPB-WEzob strain, which shows higher anxiety levels, upon hypothalamic stimulation predominantly attacks the head and abdominal areas of the opponent, whereas a more standardized CPB-WI Wistar strain mainly attacks the back of its opponent [157,158]. Despite differences in attack patterns between strains, the distribution of hypothalamic attack areas identified by stimulation electrodes seemed to be identical [157]. In mice, direct comparison of aggression intensity between wild mice and various inbred and outbred strains of mice showed that the aggression level of Swiss-CD1 outbred mice is comparable to that of wild mice in both sexes, while the outbred strain DBA/2 and a widely used inbred strain, C57BL/6, are much less aggressive than wild mice [159]. Despite these differences in murine strains, the hypothalamic neural substrates for aggression appear to be the same between different strains of female mice [7]. $Esr1^+$ cells in the VMHvl are necessary and sufficient for aggression in both inbred C57BL/6 mice and outbred Swiss Webster mice, and the topographic organization of aggression-related and mating related-cells within the VMHvl is also the same. It will be crucial to identify additional microscopic differences in the

aggression circuitry of male and female mice that could account for the behavioral differences observed between strains.

Developmental Mechanisms Underlying the Sex Differences in Aggression

While early studies suggested that some genes on the Y chromosome might be relevant for aggressive traits in males, solid evidence supporting unique genes for male aggression in mammals remains lacking [19,160,161]. Instead, as discussed below, current evidence supports a role for sex hormones (estrogen and testosterone) in modulating the expression of many sexually dimorphic genes during both development and adulthood for the differentiation of aggression circuits in both sexes (Figures 3 and 4) [162].

Perinatal Testicular Androgen Surge and Aggressive Behaviors

The Y chromosome gene, sex-determining region Y (*sry*) [163–165], determines the development of testes [166], which are responsible for the release of testosterone during the early postnatal period. The released testosterone is then converted to estrogen by aromatase, which then binds to ERα expressed in the amygdala, hypothalamic, and hippocampal regions to induce permanent masculinization of the male brain [167,168] (Figure 3A–C). Postnatal injection of estradiol into female pups causes the females to show a variety of male-like behaviors, including heightened aggression as well as male-style mounting and urine marking [103,167,169]. Conversely, neonatal castration of male pups dramatically reduced aggression levels in adults [170].

In addition to the action of testosterone via conversion to estrogen, testosterone also directly masculinizes the brain through its action on the **androgen receptor** (AR), which, similar to the estrogen receptors, is expressed throughout the limbic system [171–174] (Figure 3A–C). A series of studies using rats with a testicular feminization mutation (*tfm*, a null mutation of AR), as well as AR knockout mice, demonstrated that ARs are normally involved in the masculinization of many sexually dimorphic brain regions and in a variety of behaviors including aggressive and sexual behaviors, stress responses, and cognitive processing [173,175]. Most convincingly, attack duration and frequency decreased when AR was specifically knocked out in the central nervous system, supporting a role of AR in masculinizing aggressive behaviors through its action on the brain [176,177].

Circuit Masculinization during Development

How could elevated perinatal estrogen/testosterone masculinize the aggression circuitry? In a study focusing on the medial preoptic nucleus (MPOA, a region essential for sexual behaviors), it was found that the primary effect of neonatally elevated testosterone in males may be to reduce DNA methylation, thereby releasing masculinizing genes from epigenetic repression [178]. It was found that genes essential for dendritic spine structures, such as *Dbn1* (encoding drebrin 1 [179]) and *Ppp1r9b* (encoding neurabin α [180]), are particularly elevated in neonatal male mice in comparison to females [178]. Blocking DNA methylation either pharmacologically or genetically resulted in expression of these masculinizing genes and the development of male-like sexual behaviors in female mice [178]. The activated masculinizing genes may promote sexually dimorphic neural circuits in two ways (Figure 3D). First, they may increase cell survival by reducing apoptosis [103,181–183]. Early postnatal cell death is pronounced in female BNSTp and MeA, but not in VMH [103,181–184], and postnatal estrogen or testosterone injection reduced cell death and increased the survival of these cells in adult female mice [103]. Second, a perinatal surge of testosterone promotes synaptogenesis as well as axonal and dendritic growth [156,185,186] (Figure 3D). Estrogen markedly increased axodendritic synapse formation in the arcuate nucleus and MEA during the neonatal period [187,188]. In the VMHvl,

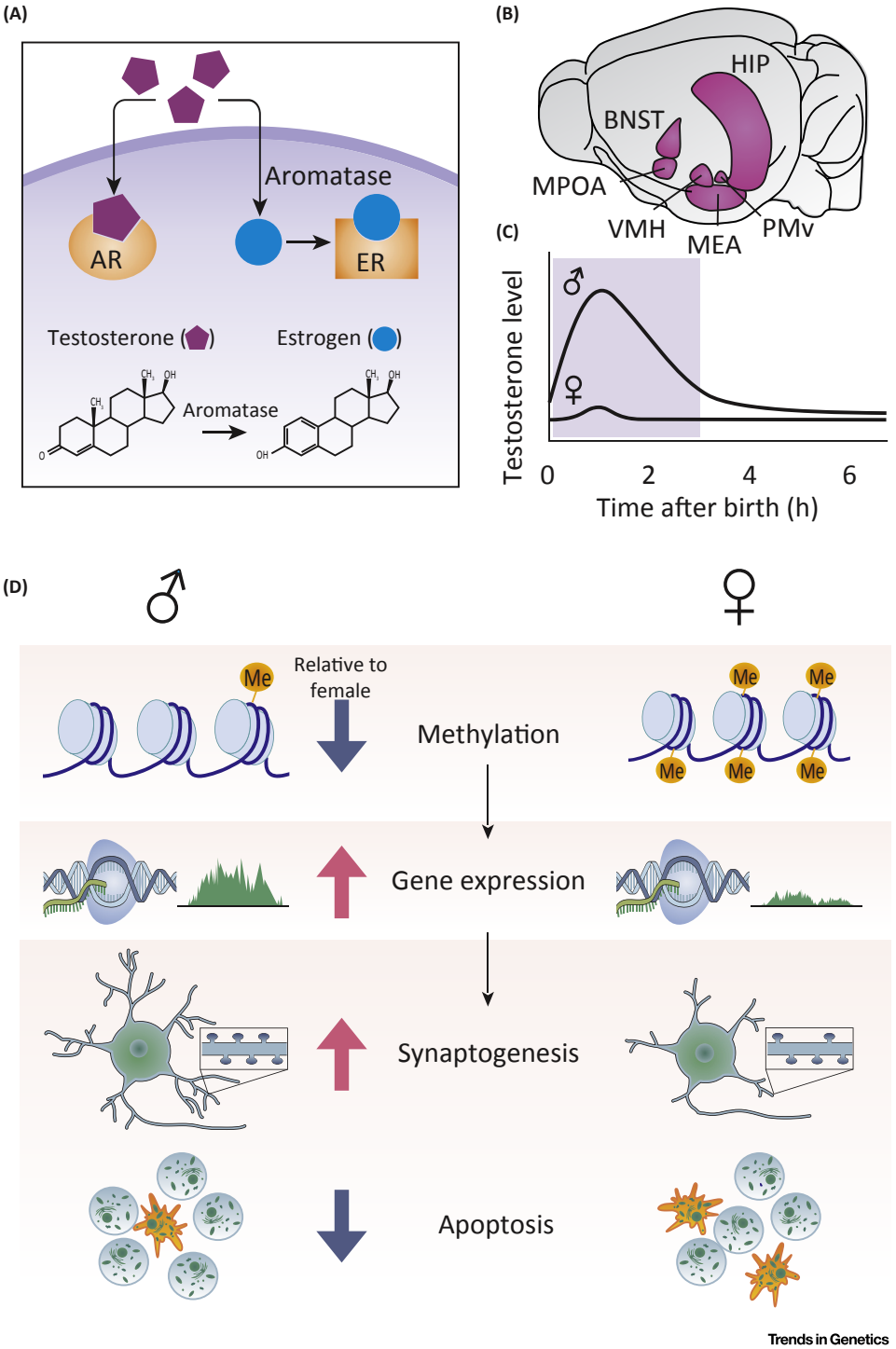

Figure 3. Neonatal Sex Hormones Masculinize the Aggression Circuit. (A) The neonatal surge of testosterone in males masculinizes the male brain via its direct action on androgen receptors and indirect action on estrogen receptors after conversion to estrogen by aromatase. (B) Brain regions enriched in androgen and estrogen receptors: both AR and ER are expressed in all the highlighted regions. Abbreviations: BNST, bed nucleus of the stria terminalis; HIP, hippocampus; MEA, medial amygdala; MPOA, medial preoptic area; PMv, ventral premammillary nucleus; VMH, ventromedial

(Figure legend continued on the bottom of the next page.)

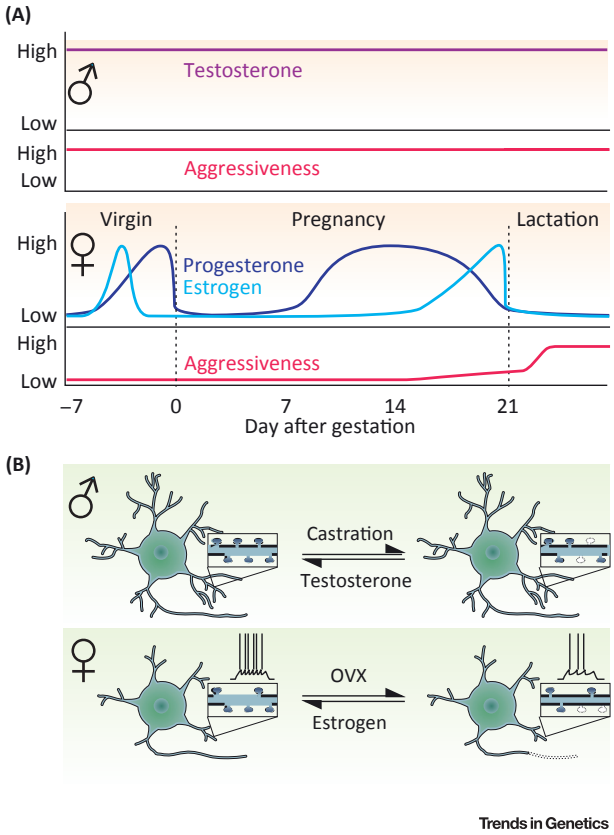

Figure 4. Circulating Gonadal Steroids during Adulthood Maintain Sex Differences in Aggression. (A) Circulating testosterone in adult males is crucial for their high levels of aggression. While circulating gonadal steroids in nonpregnant females have minimal effects on aggression, orchestrated changes in sex hormone levels during pregnancy are likely essential for elevating aggression during lactation. (B) Gonadal steroids can alter cellular morphological complexity and/or intrinsic properties in both sexes during adulthood. Testosterone maintains the high density of dendritic spines in males whereas estrogen induces synaptogenesis, dendrite elongation, and higher cellular excitability in females. Abbreviation: OVX, overiectomy.

the synaptic number is higher in males than in females [189]. When females are exposed to androgen neonatally, the number of shafts and synapses in the female VMHvl is increased to a level comparable to that of males [156]. Future studies will address whether DNA methylation suppression represents a common mechanism to differentiate sexually dimorphic behavioral circuits, and cast light on the genes that undergo demethylation in the VMHvl and other aggression-relevant brain regions.

Sexually Dimorphic Hormonal Control of Aggression during Adulthood

Control of Adult Male Aggression by Sex Hormones

Testosterone, and its aromatized product estrogen, not only masculinize the aggression circuitry during development but also have crucial roles in maintaining a high level of aggression in adult males (Figure 4A). The level of plasma testosterone positively correlates with aggression level [190–192]. In mice, castration during adulthood dramatically reduced aggression [123,193,194], whereas exogenous injection of testosterone or estrogen enhanced aggression [193–195]. Similar effects of castration and testosterone replacement are reported during hypothalamic aggression in male rats [196] (but also see [197]). Site-specific manipulations suggest that the medial hypothalamus is likely a key site through which sex hormones exert their effect in maintaining male aggression. Implantation of pellets of testosterone propionate

hypothalamus. (C) Neonatal testosterone peaks within 1–2 h after birth and only lasts for a few hours. (D) The neonatal surge of testosterone in males exerts its action by reducing DNA methylation (Me) to release a series of masculinization-related genes from repression. Disinhibited genes may have effects on cell survival and morphology.

into the medial hypothalamus, but not into its dorsal and anterior region, is sufficient to reverse castration-induced decreases in male aggression [198]. Conversely, knocking down ERα in the VMHvl using RNAi significantly reduced inter-male aggression [199]. Beyond the VMHvl, AR and ERs are expressed in nearly all other known nodes relevant for aggression, including BNST, MEA, MPOA, PMv, and PAG. Future studies using systematic site-specific gene knockdown will elucidate the importance of hormone regulation at those sites for male aggression.

How does circulating testosterone maintain male aggression? As mentioned earlier, the male VMHvl contains more synapses than the female VMHvl [156]. Adult castration reduced the number of VMHvl synapses in males, whereas testosterone application to females increased the number of synapses to a level comparable to that in males [156]. Thus, the synapses in the aggression circuitry, in other words the communication between the circuit nodes, are dynamically regulated by this sex hormone even after its initial establishment. Indeed, *in vitro* imaging studies demonstrated that estrogen, testosterone, and dihydrotestosterone, a form of non-aromatizable testosterone, could all rapidly induce spine formation in hippocampal neurons [200,201], whereas blocking estrogen synthesis in hippocampal slice cultures resulted in a significant decrease in the density of spine synapses and presynaptic boutons [202] (Figure 4B). Thus, the ability of sex hormones to modulate the aggression circuitry in adults could be essential for either increasing or decreasing aggression after particular social experiences (e.g., winning increases both testosterone levels and aggression [50]).

In addition to promoting the expression of genes relevant for synaptogenesis, sex hormones also govern many other genes with diverse functions in brain regions essential for aggression. A systematic analysis of sexually dimorphic genes expressed in BNST, POA, MEApd, VMHvl, and PMv was conducted using microarray and *in situ* hybridization. It was found that the expression of male-enriched genes requires testicular hormones, whereas the expression of female-enriched genes requires ovarian hormones [100]. For example, synaptotagmin-like protein 4 (*Sytl4*) is a male-enriched gene and its global knockout results in the reduction of male sexual behaviors, while loss of a female-enriched gene, cholecystokinin A receptor (*Cckar*), attenuates female sexual behaviors [100]. Although aggression-related genes were not identified in that study, sex hormone-controlled genes enriched in the aggression circuit are potential candidates for future studies.

Sex Hormone Control of Adult Female Aggression

In contrast to the strong influence of sex hormone on male aggression, sex hormones, specifically estrogen, do not appear to be necessary for maintaining aggressive behaviors in virgin females. Ovariectomy did not reduce natural aggression in female mice [203], nor was aggression elicited by hypothalamic stimulation in female rats [118]. Both *Esr1* knockout female mice [204] and female mice with VMHvl-specific *Esr1* knockdown show slightly increased aggression, instead of decreased aggression as in males [199,205]. In addition, most studies found that the level of female aggression is independent of the estrous cycle [206–208] (Figure 4A).

Although estrogen appears not to be required to maintain female aggression in virgin females, surges of sex hormones and other neuropeptides during pregnancy and lactation may be essential for enhancing aggression in lactating females [21]. During pregnancy in rodents, progesterone levels elevate from early pregnancy until a few days before parturition, while estrogen levels remain low during the first two thirds of pregnancy and then rise rapidly several days before parturition [209,210]. After parturition, the estrogen level plummets while several

peptide hormones, such as prolactin and oxytocin, are abundantly secreted during nursing [211,212] (Figure 4A). Remarkably, a hormonal regimen resembling the hormonal changes taking place during pregnancy followed by pup suckling could significantly increase female aggression in mice [213,214]. Surprisingly, however, neither pregnancy nor lactation affected hypothalamic stimulation-induced attack in female rats [215].

How could hormonal changes during pregnancy induce changes in the aggression circuit, while those during estrous cycle do not? One possibility is that the response of some cells to gonadal steroid hormones is duration-dependent. Although the peak plasma concentrations of estradiol and progesterone during the estrous cycle and pregnancy are in the ranges of ~100 pg/ml and ~50 ng/ml, respectively [209,216,217], the hormone elevation period is much longer during pregnancy (~1–2 weeks) than during proestrus (12 h) (Figure 4A). Thus, it is possible that aggression-related neuronal populations are relatively insensitive to sex hormones in females, and extensive exposure to the hormones is necessary to change the properties of those cells. Consistent with this idea, Esr1 is expressed at a low level in the aggression-related cellular population in the VMHvl relative to the mating-related population [7]. Another possibility is that the order of the elevation of estrogen and progesterone has a distinct impact on gene expression patterns and thus on cell properties. In the estrous cycle, estrogen precedes progesterone, while in pregnancy progesterone elevates first. Bulk RNA sequencing showed that VNO (one of the circuit nodes for aggression) transcriptional profiles during pregnancy are distinct from those in naïve females [218]. Future studies could potentially reveal changes in transcriptional profiles at each node of the aggression circuit during pregnancy and the estrus cycle, and cast light on how sex steroids may contribute to such changes.

How could the surges of sex hormones during pregnancy alter the aggression circuit? It has been shown that estradiol increases dendrite length of female VMHvl cells [219], increases spine density [220], enhances cell excitability [221,222], and promotes synaptic transmission [223] (Figure 4B). Thus, estrogen and progesterone can fine-tune the aggression circuit in many ways. However, it remains unclear whether these sex hormones act on VMHvl mating-related, aggression-related, and/or both cells during pregnancy. As the molecular identity of aggression-related VMHvl subpopulation starts to emerge [7], future studies that focus on molecularly identified aggression- or mating-related VMHvl cells will help to elucidate the hormonal modulation of social behavior circuits in females.

Regulation of Aggression by Non-Steroid Hormones

Corticotropin-Releasing Hormone

As we have seen earlier, aggression is modulated by various stressors including social defeat and isolation. The hypothalamic–pituitary–adrenal (HPA) axis is commonly activated by stressors [224]. During stress, cells in the **paraventricular nucleus of hypothalamus** (PVN) release **corticotropin-releasing hormone** (CRH), that then triggers the secretion of adrenocorticotropic hormone (ACTH), which in turn acts on the adrenal cortex to produce glucocorticoid hormones (e.g., cortisol). Significant correlations between glucocorticoid levels and aggressive behaviors have been found in a variety of species, although the correlation could be either negative or positive [225–233]. Functional studies showed that stress hormones can either decrease or increase aggression. Central infusion of CRH decreased inter-male aggression [234] and maternal aggression [235]. Stimulation of the aggression-inducible hypothalamic areas in rats rapidly activated the adrenocortical response, which in turn facilitated stimulation-induced attack [236]. When the natural adrenocortical stress response was blocked by adrenalectomy, hypothalamic stimulation-induced attack was blocked [236]. Thus, the effect

of stress hormones on aggression is likely to be complex, varying with hormone duration, concentration, and brain region, and is an interesting topic for future investigation [237].

Vasopressin

Vasopressin (AVP) is also implicated in a wide range of social behaviors including aggression [238–241]. Global knockout of one of the vasopressin receptors, V1b, reduced male aggression without affecting sexual behaviors [242]. Local application of AVP in the anterior hypothalamus enhanced aggression in male hamsters [240]. In contrast to the case in male aggression, there are conflicting results for the role of AVP in female aggression. One study showed that a centrally administered V1a antagonist increased aggression in lactating rats [243], while a different study found that local injection of a V1a antagonist in the BNST increased aggression in lactating rats [244]. The inconsistency in the experimental results in females possibly reflects complex and even opposing effects of AVP in different brain regions. Future studies using more precise approaches to manipulate AVP signaling in specific neuronal subpopulations will help to reconcile the published results and elucidate the precise function of AVP in male and female aggression.

Concluding Remarks

In rodents, aggression differs between sexes in many ways, including behavior intensity, developmental course, rewarding value, and experience-induced changes. Despite the fact that the neural mechanisms resulting in sex-specific differences in aggression remain largely unknown, current work suggests that such differences are unlikely to be due to broad structural differences in the aggression circuitry between sexes. Brain regions relevant for male aggression, from early olfactory relays to the hypothalamus, all appear to play important roles during female aggression [6,7,10,11,80–83,122]. However, at the cellular level in each circuit node, there appear to be differences in both the number and spatial distribution pattern of aggression-related cells between male and female mice. Additional properties of aggression-related cells such as intrinsic electrophysiological properties, morphology, transcriptome profile, and synaptic inputs are also likely to differ between sexes and remain to be further investigated (see Outstanding Questions). An important goal for future studies is to link the sexual dimorphism present in the aggression circuit to the differences in behavioral outputs. A potential approach for achieving this goal is to masculinize or feminize a specific node or population of cells in the aggression circuit, and then examine any possible changes in aggressive behaviors.

Sex hormones have been suggested as central players in establishing and maintaining sexually dimorphic aggressive circuits and behaviors. How different sex hormones and their receptors coordinate the control of aggressive behaviors remains poorly understood and requires further investigation [245]. Other future directions include identifying additional genetic, environmental, and experiential factors that may contribute to the sexual dimorphism observed in the aggression circuitry. In light of recent technological advances that enable precise molecular editing, single-cell RNA profiling, cell activity control, *in vivo* recording, tracing, and automated behavioral analysis, our understanding of the aggression circuit is rapidly advancing, and we are now well equipped to explore the interplay between genetics, hormones, and neural circuits that results in sexually dimorphic behaviors.

Outstanding Questions

What neural mechanisms are responsible for winner and loser effects in males, and for the potential lack of these effects in females?

What neural mechanisms are responsible for the isolation-induced increases in male aggression but not female aggression?

Is aggression, especially winning a fight, rewarding to females?

What brain regions are relevant for the expression and modulation of aggression in males and females?

What are the molecular identities of the aggression-related cells in each brain region in males and females?

How do the aggression-related cells differ in their number, response magnitude, electrophysiological properties, morphology, and synaptic inputs between sexes at each circuit node?

How do different sex hormones and their receptors coordinate the modulation of aggressive behaviors both during development and adulthood in males and females?

Are changes in sex hormones fully responsible for the increase of aggression during pregnancy and lactation in females? If so, how?

How do the specific cell types in the aggression circuitry emerge during development?

What are the molecular events (e.g., demethylation) initiated by sex hormones that lead to the differentiation of aggression circuits during the development in both sexes?

How do early life experiences contribute to the sexually dimorphic aggression circuit?

Are there other genetic factors independent of sex hormones that contribute to sex differences in aggressive behaviors?

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