



Organization of neural circuits underlying social behavior: A consideration of the medial amygdala

Tara Raam and Weizhe Hong

Abstract

The medial amygdala (MeA) is critical for the expression of a broad range of social behaviors, and is also connected to many other brain regions that mediate those same behaviors. Here, we summarize recent advances toward elucidating mechanisms that enable the MeA to regulate a diversity of social behaviors, and also consider what role the MeA plays within the broader network of regions that orchestrate social sensorimotor transformations. We outline the molecular, anatomical, and electrophysiological features of the MeA that segregate distinct social behaviors, propose experimental strategies to disambiguate sensory representations from behavioral function in the context of a social interaction, and consider to what extent MeA function may overlap with other regions mediating similar behaviors.

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Department of Biological Chemistry and Department of Neurobiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, 90095, USA

Corresponding author: Hong, Weizhe (whong@ucla.edu)

Current Opinion in Neurobiology 2021, 68:124–136

This review comes from a themed issue on **The Social Brain**

Edited by **Hailan Hu** and **Michael Brecht**

For a complete overview see the [Issue](#) and the [Editorial](#)

<https://doi.org/10.1016/j.conb.2021.02.008>

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Keywords

Neural circuits, Circuit mechanisms, Social behaviors, Medial amygdala, Aggression, Parenting, Mating.

The neural circuits that regulate social behaviors are assembled according to at least two organizational principles ([Figure 1](#)): single brain regions can coordinate several different social behaviors such as aggression, reproduction, parenting, and sociability, as well as nonsocial behavior such as feeding and self-grooming [1,2]. At the same time, behaviors as complex as social interactions are orchestrated by a broad network of regions throughout the brain. How single brain regions regulate several different social behaviors, and how single social behaviors are coordinated by broad networks throughout the brain remain significant

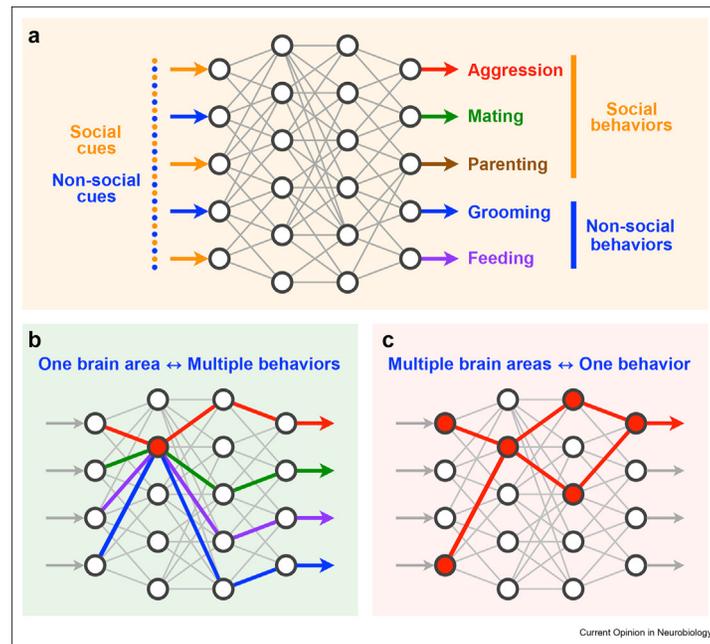
conceptual questions within social neuroscience. One unique node within the social behavior network is the medial amygdala (MeA). The MeA is critical for a wide range of social behaviors, contains both sensory and behavioral properties, and is functionally connected to a broad network of limbic regions throughout the brain. Here, we consider the organization and function of the MeA as an avenue towards addressing conceptual questions that arise in mapping the social behavior network, and propose experimental approaches towards furthering this line of understanding.

The MeA

The MeA is a division of the amygdalar complex, which plays a critical role in social behaviors ([Figure 2](#)) [3,4]. It is distinct from the more commonly studied amygdalar divisions such as the basolateral amygdala and the central amygdala, which are primarily involved in regulating positive and negative valence, and responses to fear and stress [5–8]. Compared with other amygdalar divisions, the MeA has unique anatomical, cytoarchitectural, and functional properties [3,9]. It receives strong afferent vomeronasal input from the accessory olfactory system, which carries essential social cues, and is the primary brain region that relays pheromonal signals to the rest of the brain [10–13]. The MeA also receives indirect inputs from the main olfactory system through the cortical amygdala [10].

The MeA consists of four anatomical subdivisions—anterodorsal (MeAad), anteroventral (MeAav), posterodorsal (MeApd), and posteroventral (MeApv). These subregions have markedly different anatomical features from one another, such as circuit connectivity and cytoarchitecture. While MeAad and MeApd contain a larger fraction of inhibitory neurons, MeAav and MeApv contain more excitatory neurons [14]. MeA subregions also project to a diverse set of brain areas mostly distributed in the amygdala and hypothalamus ([Figure 3](#)) [9,15]. While these subregions project densely to areas such as the bed nucleus of the stria terminalis (BNST) and the medial preoptic area (MPOA), different MeA subregions project to different subregions of the BNST and ventromedial hypothalamus (VMH). The MeAad also projects back to the accessory olfactory bulb (AOB) ([Figure 3](#)) [9]. Interestingly, many of the regions that are targets of MeA

Figure 1



Organizational principles of neural circuits regulating social behavior (a) Schematic showing broad networks of interacting brain regions coordinate transformation of sensory inputs into social and nonsocial behavioral outputs (b) A single brain region can regulate multiple different behaviors (c) Multiple brain regions can interact to coordinate a single behavior.

outputs also send reciprocal projections back to the same MeA subregions from which they received input. For example, the BNST, MPOA, VMH, posterior amygdala (PA), and ventral premammillary nucleus send reciprocal projections back to the MeA [4,9,16–21]. In addition to these reciprocal projections, the MeA also receives unidirectional input from thalamic nuclei and entorhinal and perirhinal cortices [20,22]. Although anatomical mapping of inputs and outputs of human MeA has not been well established, many of these projections observed rodents are conserved in nonhuman primates. For example, inputs from olfactory bulbs, hypothalamic nuclei, amygdalar nuclei, BNST, and entorhinal cortex have been observed in primate MeA [23–26].

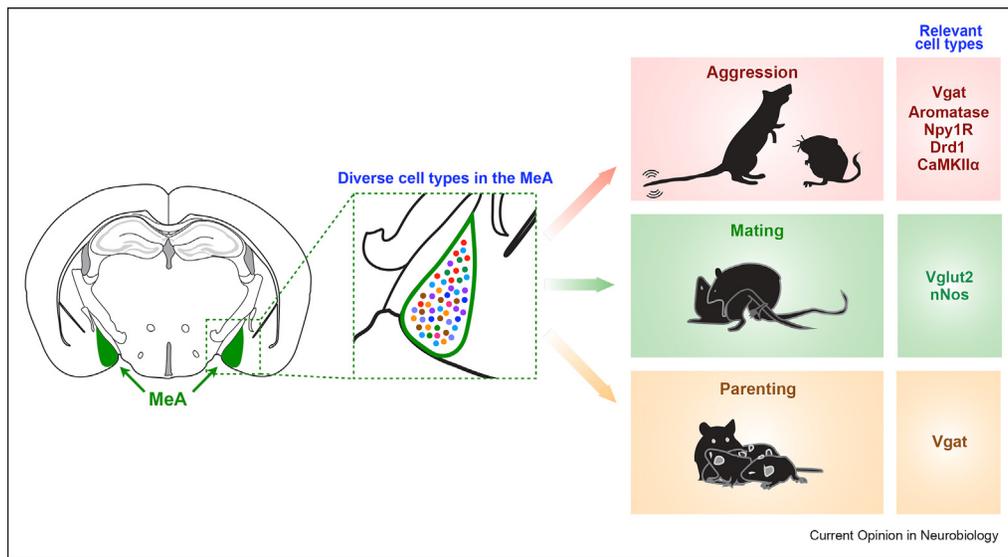
Distinct subclasses of inhibitory output neurons in the MeA arise from separate embryonic lineages (*Dbx1* and *Foxp2*) that originate from a unique migratory stream in the preoptic area of the telencephalon [27]. These two lineages display unique anatomical, electrophysiological, and behavioral properties in a sexually dimorphic manner [28,29]. In addition to the telencephalon, the diencephalon also appears to be a major source of GABAergic and glutamatergic output neurons in the MeA [30–33]. Furthermore, recent single-cell RNA sequencing studies have provided a high-resolution picture of the molecular architecture of MeA neuronal subpopulations in mice (Figure 4) [34,35]. These

studies have identified several transcriptionally distinguishable subgroups within both the GABAergic and glutamatergic neurons. These subpopulations are demarcated by the expression of a combination of different genes, notably neuropeptide genes. Moreover, a comparison between male and female MeA identified several sexually differentially expressed genes in both GABAergic and glutamatergic subpopulations [35], some of which (e.g. *Grebl1* and *Brs3*) were also identified in previous microarray studies using bulk MeA tissues [36]. Interestingly, GABAergic neurons appear to display greater sexually dimorphic gene expression than glutamatergic neurons, consistent with the sexually dimorphic behavioral functions of GABAergic neurons (discussed below) [35]. One open question is how these molecularly distinct subpopulations within the MeA relate to varying input–output circuitry and behavioral function.

Functions of the MeA in various social behaviors

An important question is what specific role the MeA plays in social sensorimotor transformation. As the MeA receives strong afferents from the AOB and is only two synapses away from the vomeronasal organ (VNO), it plays an important role in processing pheromonal signals and differentiating social sensory cues [12,13]. *In vivo* electrophysiological and optical imaging studies have

Figure 2



The MeA controls multiple types of social behaviors. The MeA, which consists of diverse cell types, plays a critical role in a broad range of social behaviors including aggression, mating, and parenting. Each behavioral function is regulated by specific cell types in the MeA, summarized in [Table 1](#).

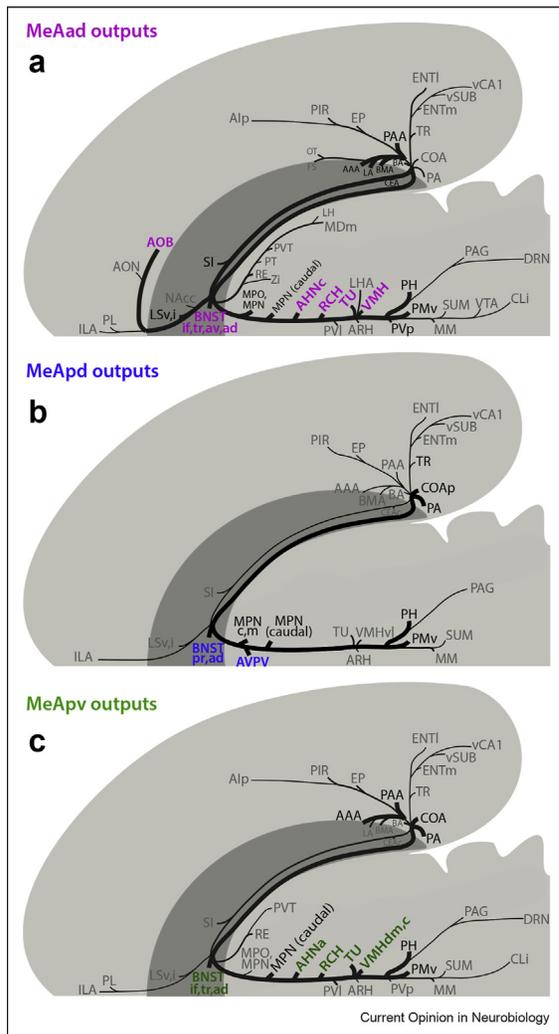
found that the MeA is critical for differentiating between various social cues, including males, females, pups, and predator cues [37,38], and its responses to male and female conspecific odors are more specific than are AOB responses [38]. Population-based coding of social cues in the MeA is dependent on prior sexual experience, and relies on the action of oxytocin [37]. Importantly, disruptions in these coding schemes impair the animal's ability to differentiate between different social targets and select the appropriate behavioral output [39]. In addition, cFos immunoreactivity studies have found that MeApv activity is modulated by the social rank of social stimuli [40].

Beyond the representation of social sensory cues, the MeA also regulates the generation of social behavioral outputs (Figure 2 and Table 1). In particular, the MeApd subregion is important for the expression of aggression. *c-Fos* labeling studies have found elevated activity in MeA during male aggressive behaviors such as attack and mounting [4,41,42], and lesion studies implicated the MeA in aggressive behavior [43,44]. Recent studies using cell-type-specific manipulations have shown that optogenetic stimulation of GABAergic, but not glutamatergic, neurons of the MeApd in males promotes aggression in a time-locked manner [45]. Conversely, optogenetic silencing of MeApd GABAergic neurons acutely suppresses ongoing aggression [45]. These findings support the notion that the MeA contains GABAergic neurons that positively promote aggression (however, it does not imply that all MeA GABAergic neurons play a unitary role in promoting aggression). Similarly, ablating or chemogenetic silencing aromatase⁺

GABAergic neurons in the MeApd decreases intermale aggression in males as well as maternal aggression against intruder males in females [46], and chemogenetic activation of Npy1R⁺ neurons in the MeA promotes aggression [47], suggesting that aggression can be controlled by specific neuronal subtypes within GABAergic population. Given that the MeA consists of heterogeneous subtypes of GABAergic neurons [34,35], it remains an open possibility that a subset of GABAergic neurons (such as certain local interneurons) may play a distinct (or even opposite) role in aggression. Interestingly, optogenetic stimulation of CaMKII α ⁺ neurons in the MeApv promotes aggression priming, the tendency to more readily express aggression after a recent aggressive encounter in males [48]. Although CaMKII α is more specifically expressed in excitatory neurons in cortical regions as well as glutamatergic neurons within the MeApv, it labels both GABAergic and glutamatergic neurons throughout the MeA [35].

Male aggression is historically thought to be related to reproductive drive, as males often compete for mating opportunities [49]. Indeed, *Fos* activity shows intermingled cells activated during fighting and mating in the MeApd [42], suggesting that the mechanism of reproductive behaviors may be partially linked to that of aggressive behavior. While lesion studies in males have implicated the MeA in mating behavior [50], its precise role remains to be further investigated. In contrast to males, female sexual behavior involves a different set of behavioral repertoires such as lordosis and seems to rely more heavily on the MeApv [51–53]. Although the MeApv is thought to be mainly involved in predator

Figure 3



Projection patterns of different MeA subregions. Schematics showing axonal projections from the MeAad (a), MeApd (b), and MeAfv (c) in rats. Major brain targets that are unique to a particular MeA subregion are highlighted in color. Figures adapted with permission from Canteras et al. [9].

defensive behavior, *Fos* labeling shows that the male lacrimal pheromone ESP1 selectively activates neurons in the MeAfv [53]. Moreover, the neurons that respond to sex pheromones in females are largely different from those responding to predator odors. In addition, exposure to the male urinary protein Darcin induces vocalization and scent marking in females, and stimulation of Darcin-responsive neurons in the MeAfv are sufficient to recapitulate these behaviors [54].

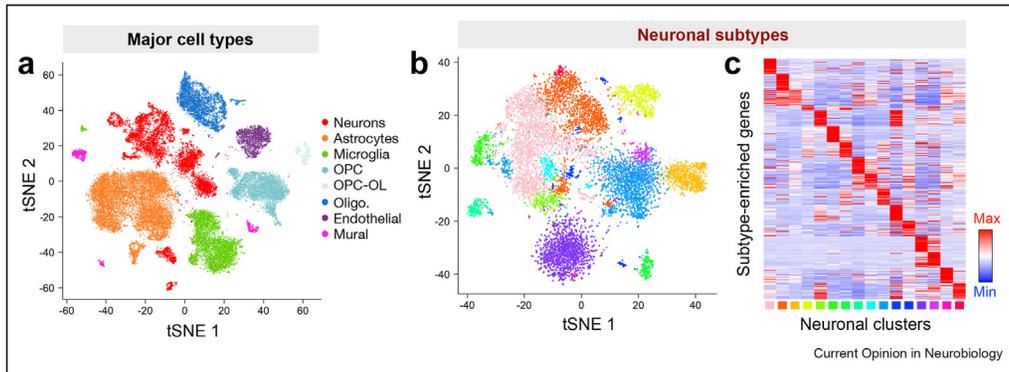
In addition to regulating interactions with adult conspecifics, the MeA also controls parenting behaviors. Early studies found that lesioning the MeA promotes parenting behavior such as pup retrieval, which seems to suggest that the MeA suppresses parenting behavior

[55–57]. However, recent studies with greater cell-type and temporal specificity identify a more nuanced role for the MeA in parenting. Optogenetic stimulation of GABAergic neurons in the MeA promotes pup-directed parenting behaviors in both male and female mice, whereas high-intensity stimulation in males induces infanticidal behavior [35]. Infanticidal behavior may depend on pheromonal input from the VNO-AOB system [58,59]. In virgin male mice (which more readily demonstrate infanticidal behaviors), the AOB and MeA both display high levels of *Fos* activity in response to pups [60], and impairments of VNO signaling induce pup retrieval in virgin males [61]. Thus, elevated VNO activity in response to pup pheromones in naïve males may hyperactivate the MeA to promote pup-directed aggression.

Finally, the MeA is also important for social recognition memory, which gives temporal permanence to an individual’s social interactions. Local infusion of oxytocin receptor antagonist into the MeA impairs social memory [62], and social memory requires oxytocin-dependent long-term depression at incoming synapses from the AOB to the MeA [63]. In addition, manipulations of the CRFR2 receptor and its associated ligand (*Ucn3*) in the MeA disrupt social novelty seeking [64]. In addition to the well-defined social functions of the MeA described above, MeA is also engaged in other behavioral contexts, such as social learning [65], group social dynamics [64], self-grooming behaviors [45], and interspecies interaction such as defensive behavior toward and avoidance of predators [37,53,66,67].

Importantly, although the function of the MeA has been difficult to elucidate in human and nonhuman primates, its involvement in social processes appears to be conserved. Recording and imaging studies in primates have found that MeA neurons respond to complex features of the social environment, such as facial expression, facial identity, pair bonding, and jealousy [68–71]. In addition, lesion studies in primates suggest a role for the MeA in social functioning. Although no studies have systematically lesioned only the MeA, large lesions that include the MeA along with other amygdalar nuclei result in decreased fear and aggression [72,73]. These studies in primates are complemented by studies in humans as well. Human MeA is thought to be important in social affiliation and maternal bonding [74,75]. Moreover, the MeA is often grouped as part of the CMA (centromedial amygdala, which includes the central nucleus of the amygdala), and the CMA is active during empathy and social reward [76,77]. Although no human lesion studies have specifically affected the MeA, large lesions of the amygdala that include MeA result in deficits in emotion recognition, while lesions that spare MeA do not affect social recognition [78,79].

Figure 4



Major cell types and neuronal subtypes of the MeA defined by single-cell RNA-seq. The MeA consists of diverse cell types (a) as well as transcriptionally distinguishable neuronal subtypes (b, c) (A) and (B), tSNE visualization of MeA major cell types and neuronal subtypes (C) Heatmap showing the expression pattern of MeA neuronal subtype markers across different neuronal subtypes. Figures adapted with permission from Ref. [35].

Disambiguating social sensory processing versus behavioral control

Given that the MeA sits at the crossroads of both sensory representations and behavioral outputs, an important question is whether the MeA is primarily involved in processing sensory stimuli, orchestrating behavioral outputs, or both. The question of disentangling sensory versus behavioral function can be difficult to address in any brain region, as behavioral outputs are strongly dependent on and linked to sensory states. Mimicking a pattern of activity that precisely recapitulates a sensory representation could theoretically produce the appropriate behavioral response to that stimulus. Similarly, silencing or impairing sensory regions can prevent the expression of a behavior (as is the case in the VNO) [80,81], not necessarily because sensory regions are the main locus where social behavior outputs are determined, but because the requisite sensory representation is not relayed to downstream nuclei, which control the appropriate social behavioral response. However, this seems unlikely to be the case in the MeA—while the MeA is only two synapses away from the vomeronasal sensory neurons, synchronous stimulation of broad classes of MeA populations induces robust behavioral repertoires in a time-locked manner across a variety of social contexts, described in Table 1. These stimulations are unlikely to precisely mimic endogenous sensory representations; if anything, they might disrupt them. That these manipulations produce specific social behavioral actions such as aggression, parenting, and sociosexual approach suggests that the MeA not only plays a role in relaying sensory cues to downstream targets, but itself controls behavioral outputs. Therefore, the MeA sits at the nexus of sensorimotor transformations and maybe the earliest stage in the vomeronasal pathway in which specific social behavioral outputs are determined.

To determine how the MeA contributes to sensorimotor transformations, one important question is whether individual neurons in the MeA are selectively tuned to sensory cues versus behavioral outputs. If individual MeA neurons represent both sensory cues and behavioral outputs, what activity patterns in these cells may differentiate the representations of each? If, however, sensory versus behavioral information is represented in different subsets of cells, what molecular, anatomical, or electrophysiological properties may differentiate these populations? Future studies that use *in vivo* electrophysiology or calcium imaging in specific cell-types or projection-specific populations may elucidate these mechanisms.

The question of whether sensory stimuli or behavioral decisions are represented in a population of neurons is an ongoing question in many areas of neuroscience, yet particularly challenging to tackle in the field of social neuroscience. Dissociating the neural correlates of sensory signals from behavioral output requires task parameters with enough temporal resolution to separate sensory cues from behavior. Although this resolution is frequently achieved in fields of neuroscience that study decision-making using tasks that have precise trial structures, often with a delay imposed [82–84], such resolution is very difficult to achieve in naturalistic settings such as social interactions, as any given social behavior may have tremendous variability from one event to another, even in the same animal. Different bouts of aggression, for example, maybe associated with different contexts and internal states and can have varying latencies, durations, and combinations of behavioral syllables (chasing, mounting, biting). Moreover, the rapid timescale in which sensory cues are transformed to social behavioral decisions makes it difficult to dissociate the two, compounded by the fact

that social cues (odor, tactile, auditory) are usually experienced in close physical proximity to the other social agent, rendering it difficult to disentangle sensory experience from behavior actions, such as approach, sniffing, and mounting. This is further complicated by the continually evolving nature of the stimulus itself—rather than responding to a single tone or odor, the animal is responding to another animal, which itself has dynamic behaviors and internal states that form a feedback loop between the two animals [1,85,86], so the sensory space and corresponding internal state of each animal is continually evolving during the course of an interaction. Despite these hurdles, social neuroscientists are already finding creative ways to circumvent these challenges by developing tasks with clear trial structures where social sensory cues and behavior decisions can be more easily isolated [87–91]. We anticipate that the development of more such tasks will lead to a clearer understanding of sensorimotor transformation in the context of social behaviors.

How does one brain area mediate several different social behaviors?

An important question that is relevant across brain regions which mediate diverse, sometimes conflicting, functions is what mechanisms might be engaged to segregate different behavioral states from each other (Figure 1). The MeA serves as a useful example to consider how molecular, anatomical, and activity-dependent features are engaged to promote distinct behaviors (Figure 2 and Table 1).

The MeA is a cytoarchitecturally diverse nucleus containing many different subtypes of neurons [34,35]. Mounting evidence suggests that different subpopulations may play different roles in behavior (Table 1). For example, optogenetic manipulation of GABAergic and glutamatergic neurons in the MeA has revealed that GABAergic neurons promote aggression and pup-directed parenting, whereas glutamatergic neurons promote self-grooming, respectively [35,45]. Ablating or silencing aromatase⁺ GABAergic neurons in MeApd decreases aggression in both male and female mice [46]. Activation of Npy1R-expressing neurons in the MeA promotes aggression [47]. Silencing of Nos1⁺ neurons in MeA in females interrupts the expression of behavioral repertoires induced by the male urinary protein Darcin—ultrasonic vocalization and urinary scent marking [54]. In addition, Vglut2⁺ cells in MeApv are important for the expression of sexually receptive lordosis behavior in females [53], and deletion of Oxt in aromatase-expressing neurons impairs male preference for female interactions [39]. It is important to note that when manipulation of a molecularly defined cell type can modulate a behavior, it does not mean that all neurons within that cell type play a unitary role in that behavior. Given the heterogeneity of neuronal subtypes, it is always a possibility that a behavior is controlled by a subset of

neurons within that cell type and/or that different subsets of that cell type may exert distinct or even opposite roles. Finer dissection of the aforementioned MeA cell types will provide new insights into the functional organization of heterogeneous MeA neurons in diverse social behaviors. Moreover, although many studies use neuromodulators or their receptors as genetic markers to manipulate molecularly defined cell types in the MeA, the functional roles of these genes have been much less understood. The remarkably diverse convergence of neuromodulator systems in the MeA suggests that neuromodulation may play a key role in shaping behaviors depending on the motivational state of the animal.

In addition to molecular features such as cell types, the MeA also uses unique connectivity patterns to compartmentalize different social behaviors. Each MeA subregion sends projections to many downstream targets (Figure 2), which may each serve unique functions. Activation of projection of MeA Npy1R⁺ neurons to BNST but not VMHvl promotes territorial aggression [47]. In addition, MeApv Drd1⁺ neurons project to both BNST and VMHdm, yet stimulation of the BNST projection induces approach of threatening stimuli, whereas stimulation of the VMHdm pathway induces avoidance of the same stimuli [67]. Moreover, activation of MeApv projections to VMHvl and BNST, but not MPOA or LS, promotes aggression in males [48]. Synaptic inputs from MeApv to VMHvl and BNST are potentiated after foot shock exposure, and depotentiating them with low-frequency stimulation prevents stress-induced aggression after foot shock [92]. Additional studies elucidating the role of specific MeA projections in different behavioral contexts will yield further insight into anatomical features used to dissociate different behaviors. Finally, some studies have also examined the functional role of inputs onto MeA. Activating inhibitory inputs from AgRP neurons that suppress MeA GABAergic neurons inhibits aggression [47]. Stimulating inputs from dorsal raphe nucleus onto MeA is also shown to suppress an attack, but it is unclear which MeA subdivision or neuronal type that mediates this effect [93]. It also remains to be determined whether individual MeA neurons that project to different downstream areas receive the same or distinct neuronal inputs. Future studies that combine projection-specific input mapping such as TRIO with circuit manipulations may identify similar mechanisms in the MeA [94].

A third mechanism by which the MeA dissociates distinct social behaviors is through coding strategies at the population level. For example, *in vivo* microendoscopic calcium imaging identifies distinct populations of neurons that encode social cues such as male, female, pup, and predator odors [11,37]. In male mice, more MeA neurons are tuned to female cues, and in female mice, more MeA neurons are tuned to male cues, which may aid in mediating reproductive behaviors in both sexes [38,39]. These

Table 1

Behavioral functions of cell-type-specific MeA neurons.

MeA subregion	Cell type	Type of Manipulation	Construct	Change in Behavior	References
MeApd	Vgat	Optogenetic	ChR2	↑ aggression in males	Hong et al. 2014 [45]
			eNpHR3	↓ aggression in males	
MeApd	Aromatase	Genetic ablation	Casp3	↓ intermale aggression in males	Unger et al. 2014 [46]
		Chemogenetic	hM4Di	↓ maternal aggression in females ↓ intermale aggression in males	
MeA	Npy1R	Chemogenetic	hM3Dq	↑ aggression in males	Padilla et al. 2016 [47]
	Npy1R (BNST projection)	Optogenetic	ChR2	↑ aggression in males	
MeApv	CaMKII α	Optogenetic	ChR2 (low freq)	↓ aggression priming in males	Nordman et al. 2020 [48]
			ChR2 (high freq)	↑ aggression priming in males	
	CaMKII α (VMH and BNST projection)	Optogenetic	ChR2 (high freq)	↑ aggression priming in males	
			ArchT	↓ aggression priming in males	
MeApd/pv	nNOS	Optogenetic	eNpHR3	↓ female attractive response to male pheromone Darcin	Demir et al. 2020 [54]
MeApv	Vglut2	Chemogenetic	hM4Di	↓ sexual receptivity (lordosis) in females	Ishii et al. 2017 [53]
MeApd	Vgat	Optogenetic	ChR2 (low int)	↑ pup grooming in females and males	Chen et al. 2019 [35]
			ChR2 (high int)	↑ pup attack in males	
			eNpHR3	↓ pup grooming in females	
MeA	Ucn3	Optogenetic	ChR2	↑ social novelty preference in males	Shemesh et al. 2016 [64]
		Chemogenetic	hM4Di	↓ social novelty preference in males	
MeApv	Drd1 (VMH projection)	Optogenetic	ChR2	↑ avoidance of threat in males	Miller et al. 2019 [67]
			Jaws	↓ avoidance of threat in males	
	Drd1 (BNST projection)	Optogenetic	ChR2	↑ approach to threat in males (including conspecific aggression)	
			Jaws	↓ approach to threat in males	

population-based coding schemes are highly dependent on prior sexual history in males, as well as the actions of the neuropeptide oxytocin [37,39]. In males that lack Oxt expression in MeA aromatase neurons, strong population responses to female cues become less tuned and more broadly responsive to predator and male cues [39]. These tuning properties to distinct social cues may overlap with molecular and anatomical features defined above. For example, cells that preferentially respond to a particular social stimulus may belong to a molecularly defined or projection-specific subpopulation of neurons. Further studies recording from specific populations of neurons will clarify these possibilities.

In addition to the representation of social sensory cues, different activity patterns are associated with distinct behavioral outputs. For example, fiber photometry recordings of GCaMP6 activity show moderate activity during pup grooming and high activity during pup attack [35]. This is consistent with scalable optogenetic activation experiments that promote distinct behaviors at different levels of intensity—low-level stimulation promotes pup grooming, whereas high-level stimulation

promotes infanticidal attack behavior [35]. Moreover, scalable optogenetic activation of MeApd GABAergic neurons can lead to mounting (low-intensity stimulation) versus attack (high-intensity stimulation) in intermale interactions [45,48]. Similarly, low-frequency optogenetic stimulation of MeApv CamKII α ⁺ neurons suppresses aggression, whereas high-frequency stimulation increases aggression [48]. These studies provide intriguing insights into how different levels of neural activity in MeA may promote different behaviors. Multiple possibilities may explain these observations. Different levels of activity may potentially recruit different subpopulations of neurons that play distinct roles in a particular behavior—for instance, pup retrieval and infanticidal behaviors may be modulated by two distinct ensembles of neurons that are preferentially activated by low- or high-intensity stimulations. Alternatively, different levels of activity may recruit different sizes of a common population such that the size of the recruited population modulates different behavioral outputs. Finally, higher levels of activity may reflect the same ensemble of neurons firing at a higher frequency. Distinguishing between these various possibilities will

require future studies using *in vivo* electrophysiology or calcium imaging that confer cellular identity resolution.

How is one brain region integrated into the broader circuitry for social behavior?

Although the MeA plays a critical role in a diverse set of social behaviors, there are also several other brain regions and circuits that contribute to the same social processes. For example, the neural representation of distinct social cues such as conspecific sex, social identity, dominance status, and offspring has been observed in other brain regions such as the VMHvl [42,95,96], as well as the prefrontal cortex [97–101] and hippocampus [102,103]. Aggressive behaviors are also modulated by a broad network of regions, including most notably VMHvl [42,87,95], as well as the lateral septum [104], nucleus accumbens [91], PA [105–107], BNST [108], dorsomedial hypothalamus [109], and periaqueductal gray (PAG) [110]. Parenting and infanticidal functions of the MeA overlap with other regions including MPOA [111–116], and sensory regions such as VNO [58–61] and auditory cortex [117–119]. Finally, social recognition memory is also mediated by a broad network of areas including hippocampal areas CA2 [120,121] and vCA1 [102,122–124], prefrontal cortex [125], and olfactory circuits [126]. Although this is not an exhaustive description of all circuits and regions that share overlapping functions with the MeA, it serves to illustrate heterogenous brain regions that form a larger network for complex social behaviors.

Given that a multitude of regions beyond the MeA is implicated in any given social behavior, we can ask whether these brain regions play similar or different roles and how they contribute to making specific social decisions. One conceptual question is where a particular social decision is made. Are social decisions made in a single locus, or shaped and modulated by multiple brain areas? Manipulations of neural components using optogenetics and chemogenetics suggest that different brain areas may serve overlapping functions in a behavior—for example, manipulations of MeA, VMHvl, and PAG all lead to increases or deficits in aggressive behavior. However, another possibility is that while manipulations of several regions may all lead to an apparently common behavioral output, each may play unique roles in modulating that behavior that are hidden when using binary manipulations to activate or silence a circuit. For example, a recent study used multi-site recording strategies to identify that elements of an aggressive encounter are hierarchically represented in a step-wise, linear fashion along the VMHvl-IPAG-jaw circuit [110]. Within this circuit, male social sensory cues represented in the VMHvl are relayed through a monosynaptic circuit to the IPAG and jaw, which represent finer aspects of the aggressive bout—IPAG

neurons are selective for the attack, while the jaw muscle is selective for the bite specifically [110]. The use of a similar experimental framework may prove informative in understanding the coding properties of the MeA in relation to its inputs and outputs as well. Although it is currently unclear how MeA signals compare with signals in downstream regions such as VMHvl, the MeA may function as an intermediate layer of processing by integrating chemosensory input from the vomeronasal network with behavior outputs and routing these signals to appropriate downstream regions mediating specific social behaviors, such as aggression and parenting. Alternatively, some overlap in function may indeed exist between some nuclei, and this may serve as a redundant or compensatory mechanism to ensure that critical functions are maintained even when circuit dysregulation occurs in a brain region.

Parsing out these possible models may be best achieved using multi-site or brain-wide recording strategies that enable direct comparison of coding strategies across nuclei [127–132]. For example, simultaneous paired recordings from the MeA and VMHvl during bouts of aggression, or MeA and MPOA during parenting, would enable time-locked comparison of neural dynamics in both regions, potentially revealing distinct coding properties during the sensory cues, onset, and completion of behavior bouts. The resolution required for such analysis may not be attainable when comparing coding properties across studies that have performed recordings from single brain regions. It may also provide an additional layer of experimental rigor in social behaviors where the imposition of a trial structure is not feasible. In these cases, although behavioral variability across events may confound a comparison of cross-trial neural dynamics, simultaneous recordings of two brain regions would still enable time-locked comparison during a single behavior event. Additionally, as the distinct roles of MeA subregions and cell-types in various behaviors were mostly studied in different research groups using different technologies and behavioral paradigms, it would be important to directly compare these cell-types using identical experimental conditions. New developments in machine learning-based animal tracking and behavior analysis also show promise to streamline behavior analysis across laboratories and paradigms [127,133–136].

Concluding remarks

Although this review has focused on the organization and functions of the MeA, many of the conceptual considerations and challenges can be extended and applied to other brain regions, which also mediate a variety of social behaviors. The basic principles by which single brain regions coordinate multiple social behaviors, and multiple brain regions interact to

orchestrate a single social behavior stand out as critical knowledge gaps facing the field of social neuroscience as we continue to articulate a social behavior network in the brain. Increasingly precise tools for tracing, recording, and manipulating specific circuit components will enable the dissection of molecular, anatomical, and electrophysiological mechanisms that segregate behavioral functions within a single brain region. Employing multi-site recording strategies of multiple regions simultaneously will enable comparison of regional heterogeneity of function on a fine scale during social encounters. Furthermore, the development of social behavior assays that take advantage of a trial structure will enable us to more readily disambiguate the neural representations of sensory and motor components of a social interaction. The expansion of experimental tools and novel behavioral assays will prove useful in addressing the range of conceptual issues under consideration and contribute to a clearer understanding of how social behaviors are coordinated by neural circuits.

Conflict of interest statement

Nothing declared.

Acknowledgements

The authors would like to thank Dayu Lin, Joshua Corbin, Samara Miller, Emily Wu, Lyle Kingsbury, James Dang, and an anonymous reviewer for thoughtful comments on this manuscript. They also thank Samara Miller for providing part of the illustration in Figure 2. This work was supported in part by NIH grants T32-NS048004, F32-MH123049, R01-NS113124, and RF1-DA048811, a Searle Scholar Award, a Klingenstein-Simons Fellowship, a Packard Foundation Fellowship, a McKnight Scholar Award, a Vallee Scholar Award, a Mallinckrodt Scholar Award, and a Keck Foundation Junior Faculty Award.

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