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Neural control of parental behaviors

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Parenting is a multicomponent social behavior that is essential for the survival of offspring in many species. Despite extensive characterization of individual brain areas involved in parental care, we do not fully understand how discrete aspects of this behavior are orchestrated at the neural circuit level. Recent progress in identifying genetically specified neuronal populations critical for parenting, and the use of genetic and viral tools for circuit-cracking now allow us to deconstruct the underlying circuitry and, thus, to elucidate how different aspects of parental care are controlled. Here we review the latest advances, outline possible organizational principles of parental circuits and discuss future challenges.

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Introduction

Parenting comprises multiple species-specific behavioral responses to infants, with the ultimate goal of ensuring offspring survival. Over the course of the last few decades, considerable progress has been made in identifying brain areas contributing to parental behavior, mainly in female rodents (rats, voles, hamsters, gerbils) as well as in rabbits, sheep and birds. In recent years, the laboratory mouse (*Mus musculus*) has emerged as an attractive model system, due to its robust parental care, genetic tractability as well as the availability of powerful tools for circuit mapping and interrogation in this species. Here we will first focus on the behavioral components of parenting in male and female mice before discussing advances in identifying the underlying circuitry. Finally, we will review different parenting systems and report recent progress in understanding the genetic landscape of parenting.

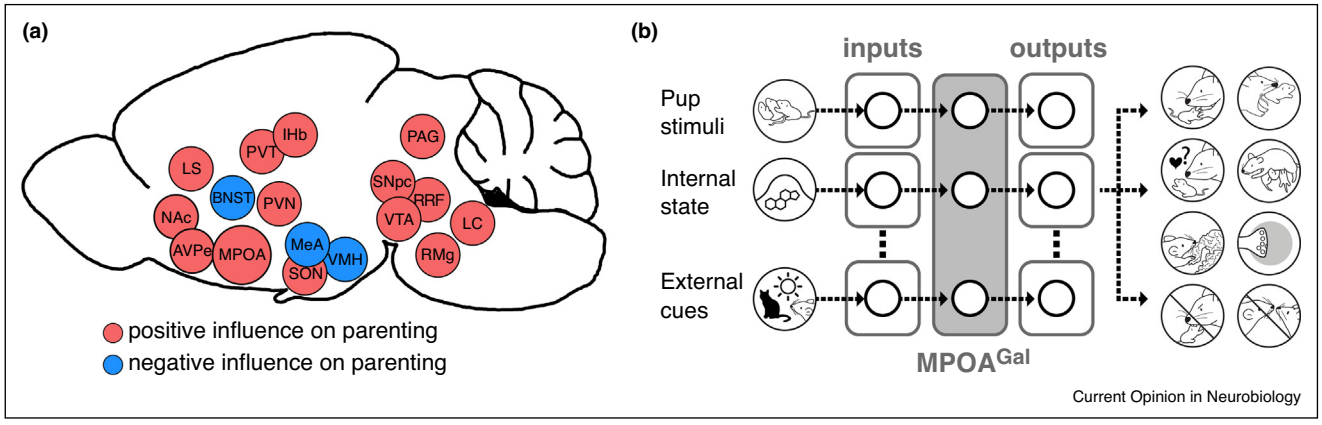
Parenting — a model of naturalistic social behavior

Parenting consists of multiple, stereotypic, species-specific behavioral components that, together, increase the likelihood of offspring survival and its optimal development [1]. In mice, parental animals display nest building, increased chemoinvestigation of pups, retrieval to the nest, grooming, licking, crouching, and, in females, nursing. These behaviors are associated with a heightened motivation to interact with young [2], a hallmark of the postpartum period. In addition, parenting is often associated with the temporary suppression of other, potentially competing social activities such as mating or male–male aggression. Importantly, while both virgin and sexually experienced females display parental care in laboratory mouse strains, parenting is typically more robust in mothers [3,4]. In male mice, the difference in parenting behavior between virgin and sexually experienced animals is even more pronounced: virgin males robustly attack and kill pups, becoming parental only in the weeks following mating [5,6••,7•]. Such increases in pup-directed attention and care indicate that parenting is associated with distinct hormonal states that are tightly linked with reproduction (see below). There is now good evidence for the existence of shared neural circuits between males and females, modulation of which can nevertheless result in the expression of sexually dimorphic behaviors: for instance, parenting (typically displayed by females) or mounting (typically displayed by males) can be elicited in both sexes in animals deficient in vomeronasal sensing [8,9]. In wild type animals, the vomeronasal system provides sex-specificity of these behaviors by repressing parenting in males [6••] and male-like mounting in females [8]. Investigating the mechanisms underlying these phenomena has the exciting potential for uncovering general principles of neural circuit modulation.

Towards a circuit-level analysis of parental behavior

Based on observable components of parenting, what can be hypothesized about the underlying circuitry? A large body of lesion studies and classical pharmacological manipulations, primarily in female rats, has identified many brain areas involved in the control of parenting [1,10–12], some of which proposed to represent the core of a social behavior network [13] (Figure 1a). In particular, hypothalamic regions, and primarily the medial preoptic area (MPOA), have been shown to function as critical control nodes for the expression of parental behavior: (1) MPOA lesions disrupt parental behavior [14], (2) receptors for known modulators of parenting (estrogen,

Figure 1



Anatomy and circuit logic of the neural control of parenting. **(a)** Key rodent brain areas involved in the positive and negative regulation of parenting based on lesions or pharmacological manipulations. **(b)** Working model of neural circuits underlying behavioral components of parenting in rodents. Inputs carrying chemosensory, visual, auditory and tactile pup stimuli as well as internal signals and other contextual environmental cues (predators, conspecifics, and so on) are likely to be integrated by MPAO^{Gal} neurons, a control hub for parental behavior in both sexes. MPOA^{Gal} neurons can then orchestrate the discrete motor (grooming, licking, retrieval, crouching) and motivational aspects of parental behavior. In addition, parental circuits are likely to negatively regulate pup-directed aggression as well as conflicting conspecific interactions, such as mating or male-male aggression. *Abbreviations*: AVPe, anteroventral periventricular nucleus; BNST, bed nucleus of the stria terminalis; LC, locus coeruleus; LS, lateral septum; MeA, medial amygdala; NAc, nucleus accumbens; PAG, periaqueductal grey; PVN, periventricular hypothalamic nucleus; PVT, periventricular thalamic nucleus; RRF, retrorubral field; RMg, raphe magnus nucleus; SNpc, substantia nigra pars compacta; SON, supraoptic nucleus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

progesterone, prolactin, oxytocin) are highly expressed in this area [1] and (3) direct stimulation of the MPOA with estrogen facilitates parental behavior [15,16]. However, since individual hypothalamic nuclei and other brain areas participate in many behaviors and physiological states (and conversely, individual behaviors and states are encoded by distributed networks [13,17]), a key question has been whether molecularly defined neuronal populations can be identified that are both necessary and sufficient for the neural control of parenting.

Wu *et al.* recently used induction of the immediate early gene *c-fos* as a molecular readout of neural activity in the hypothalamus of male and female mice and found that MPOA neurons expressing the neuropeptide Galanin (MPOA^{Gal}) are activated by parenting in both sexes [6••]. This molecular identification represented a crucial advance, since the MPOA is involved in a variety of other behaviors and physiological functions [11]. Using conditional neuronal ablation and optogenetic stimulation, Wu *et al.* subsequently demonstrated that MPOA^{Gal} neurons are necessary and sufficient for the expression of parental behavior in both males and females [6••]. This population therefore constitutes a critical node (or 'hub') in a distributed parenting circuit, manipulation of which suffices to elicit specific behavioral effects. Although the synaptic inputs and downstream projections of MPOA^{Gal} neurons remain to be described, several hypotheses about such a parenting control hub can be proposed (Figure 1b): (1) it should receive multimodal sensory inputs, representing olfactory, auditory and/or tactile pup cues, (2) these inputs should be extensively integrated by MPOA^{Gal} neurons, which (3) should control discrete aspects of parental behavior, such as pup grooming, nest building or the motivation to interact with pups, potentially via different downstream projections. In addition, (4) competing behaviors, such as mating, aggression or eating might be acutely suppressed during parenting, either via lateral interactions between hypothalamic nodes controlling either behaviors or via dedicated downstream projections. Finally, (5) the activity of this circuit is expected to be strongly modulated by the animal's reproductive state. Classical dye tracing in rats has linked the MPOA to many of the brain areas involved in parenting (Figure 1a) [18–20]. Since some of these areas have well-established general roles, this has resulted in a working model in which projections to the mesolimbic reward system (VTA, NAc, see Figure 1a) may mediate parental motivation, whereas projections to the midbrain (PAG, RRF) may control motor aspects of parenting [1,11]. These circuit elements might be modulated by projections from the paraventricular hypothalamic nucleus (PVN), the lateral habenula (lHb), and by serotonergic inputs from the dorsal raphe nucleus [1]. Despite these anatomical and conceptual advances, the functional organization of the circuits within which parenting-relevant MPOA neurons are embedded remains largely hypothetical.

Recent findings from partially mapped circuits controlling feeding [21–26], sleep [27,28] and defensive behaviors [29,30] have illustrated possible organizational principles of circuit nodes controlling instinctive

behaviors. Agouti-related peptide — expressing neurons in the arcuate nucleus (ARC^{AgRP}) send out non-branching projections, several of which are sufficient to independently evoke feeding [21]. By contrast to this segregated architecture, projections from steroidogenic factor-1 (SF1) — expressing neurons in the ventromedial hypothalamus (VMH^{SF1}) are collateralized, targeting both the periaqueductal grey and the anterior hypothalamic nucleus, which mediate immobility and avoidance behaviors, respectively [29]. It remains to be determined which of these circuit motifs, one-to-one or one-to-many, is used by $MPOA^{Gal}$ neurons controlling parenting (Figure 1b).

Finally, careful monitoring of $MPOA^{Gal}$ neuronal activity during parental behavior will be required to determine the exact role of this population. Several recent studies have cast doubt onto a simplistic 'command neuron' concept in which activation of genetically identified hypothalamic neurons invariably triggers specific behaviors. For example, rather than directly driving feeding behavior, ARC^{AgRP} neurons might encode a negative-valence teaching signal that the animal aims to overcome by eating [31] and which is modulated by experience [32]. Likewise, the role of VMH neurons in aggression is unexpectedly complex: optogenetic stimulation of estrogen receptor — expressing neurons in the ventrolateral VMH ($VMHvl^{Esr1}$) elicits either aggression or mating depending on laser intensity [33], and whether or not progesterone receptor — positive VMH neurons (VMH^{PR}) elicit aggression depends on social context and chemosensory inputs [34,35]. Similarly, the use of more naturalistic and/or challenging behavioral assays might uncover more complex roles for $MPOA^{Gal}$ neurons in parental behavior.

Parenting depends on reproductive state

The above observations indicate that rather than being fixed, the expression of parental behavior is highly flexible, and strongly depends on the animal's reproductive state. The peripartum period is characterized by profound fluctuations in levels of several hormones, including estrogen (E), progesterone (PR), prolactin (PRL), and oxytocin (OXT) (reviewed elsewhere [11,12]). These hormonal changes (Figure 2a) are thought to coordinate parturition with the onset of parenting. Indeed, mothers are significantly more parental than virgin females [3,4] and steroid hormone treatment protocols mimicking pregnancy can induce maternal behavior in virgin or ovariectomized rats which normally avoid pups [36,37].

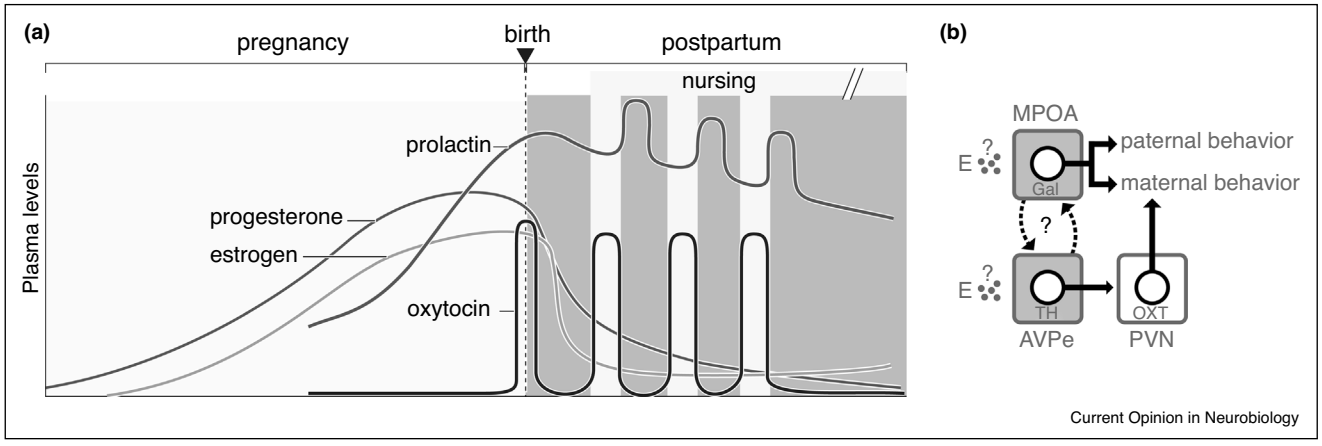
An increase in parental care during the peripartum period is also observed in males in species with paternal behavior [1], even though the contribution of hormonal factors to paternal behavior remains unclear. Importantly, $MPOA^{Gal}$ neurons are necessary for parenting in both fathers and mothers, and elicit parental behavior irrespective of reproductive state when optogenetically activated [6]. The question therefore is whether $MPOA^{Gal}$ neurons are themselves particularly sensitive to the hormonal factors associated with parental state (Figure 2b) or whether most (or all) circuit elements are hormone-responsive. As mentioned above, hormone receptors are densely expressed in the MPOA and direct hormonal stimulation of the MPOA facilitates parenting. Intriguingly also, expression levels of E-receptor and OXT receptors in the MPOA are positively correlated with natural variations in maternal care [38,39]. Despite recent progress, hormone receptor expression in specific MPOA cell types and other brain areas involved in parenting remains incompletely described [40,41]. A particularly remarkable effect of hormonal modulation on parenting was reported by Marlin *et al.* who found that OXT activity on OXT receptor expressing neurons in the auditory cortex (A1) of mouse dams increases the salience of pup calls, facilitating retrieval [42••]. In this case, OXT was shown to act by reducing cortical inhibition within seconds, and by increasing the temporal correlation of inhibition and excitation over minutes to hours, thereby enhancing pup call representation and perceptual salience [42••]. Another recent study found that OXT directly inhibits dopaminergic (DA) neurons in the VTA and indirectly inhibits DA neurons in the substantia nigra (SN) via local recruitment of GABAergic interneurons [43•]. Since both regions have previously been implicated in maternal behavior in female rats (Figure 1a) [44–47], OXT might modulate several circuit elements involved in parental behavior in a cell-type specific manner. Importantly, however, the specific mode of action of OXT is still not fully understood due to its considerable cross-reactivity with vasopressin receptors [48].

Do parental circuits in turn control hormonal state? Non-conditional tracing studies have described projections from the MPOA to the PVN [19] — a key area for homeostatic and neuroendocrine control — but it remains unknown which PVN populations are targeted. Scott *et al.* recently found that tyrosine-hydroxylase (TH)-expressing neurons in the anterior periventricular nucleus (AVPe) influence parenting in females (the equivalent neurons are involved in aggression in males) [49]. Intriguingly, the authors identified monosynaptic $AVPe^{TH} \rightarrow PVN^{OXT}$ connections, thereby linking $AVPe^{TH}$ activity to OXT release (Figure 2b) [49]. This indicates, that parental circuits are not only regulated by, but are also capable of directly influencing, hormonal states.

The diversity and genetics of parental behavior

Such flexibility and state-dependency in the expression of parental behavior might be highly adaptive in changing environments and/or social structures. In mammals, parental care is especially elaborate, requiring considerable investment, sometimes over the course of many

Figure 2



Peripartum hormone levels and hormonal regulation of parental circuits. **(a)** Plasma hormone levels during and after pregnancy. Estrogen, progesterone and prolactin increase throughout pregnancy while estrogen and progesterone drop rapidly around birth. Right before birth, oxytocin levels surge, initiating uterine contractions. In the postpartum period, prolactin pulses promote milk production, alternating with oxytocin pulses which stimulate milk ejection in response to suckling. **(b)** Genetically identified components of parenting circuits. $MPOA^{Gal}$ neurons promote parenting in both sexes and estrogen stimulation of the MPOA promotes parental behavior in females [6••]. $AVPe^{TH}$ neurons promote parental behavior exclusively in females and form monosynaptic connections with oxytocin-expressing neurons in the PVN [49••].

years (an estimated 13 million calories are required to raise a human child to independence [50]). This monumental task is performed by a single parent (uniparental care), by both parents (biparental care) and by related as well as unrelated group members (alloparental care) in different species. Overwhelmingly, this burden is shouldered exclusively by females, with biparental care only occurring in 5–10% of mammalian species, for example, in laboratory mice, prairie voles (*Microtus ochrogaster*) or old-field mice (*Peromyscus polionotus*), as a consequence of social monogamy [51]. Male uniparental care is even more exceptional and has not been observed in mammals, although male-biased care systems exist in some primates, for instance in titi monkeys (*Callicebus oenanthe*), where the father almost exclusively carries the infant [52]. In recent years, it has become increasingly recognized that alloparenting may have been a critical factor in the evolution of large-brained, slow maturing apes and humans [50]. This has been attributed to the insurance that alloparenting (and cooperation in general) provides against caloric shortages during child development [50,53]. Interestingly, alloparenting is much more common in humans than in apes, in which females are reflexively possessive of their newborns [50].

This form of cooperative care is also common in mice [54] and is associated with increased lifetime reproductive success and increased pup survival [55]. Even laboratory mice engage in communal parenting, although this is often obscured by single-pair breeding conditions [54]. Alloparenting seems to have evolved as an adaptation to ecological constraints, such as high population density [56] and arid or scarce environments [57]. Together, these examples illustrate that parenting styles can be much more diverse than often appreciated.

What are the genetic and neural bases underlying such differences in parenting modes, and the expression of parental behavior in general? Cross-fostering experiments between non-paternal meadow voles and highly paternal prairie voles [58], as well as between rat mothers displaying different levels of maternal care [59] have shown that early childhood experience can shape later parental behavior. However, the fact that parenting does not have proximate benefits for the caregiver and entails considerable sacrifices suggests that this behavior is largely driven by evolutionarily shaped, hard-wired neural circuits (Figure 1b). Selective breeding studies indicate that nest building is under genetic control [60] but until recently, very little was known about the genetic basis underlying variations in parental behavior. Bendesky *et al.* addressed this question using quantitative genetics in offspring obtained from crossing deer mice (in which males are promiscuous and non-parental), to old-field mice (in which males are monogamous and highly parental). This study found that parental care overall is affected by many regions spread across the genome, pinpointing 12 genetic loci, 8 of which had sex-specific effects [61]. Furthermore, these data suggest that while some loci affect multiple pup-directed behaviors (e.g. crouching, licking, retrieval), nest building is more genetically independent. This genetic modularity might be reflected in the existence of discrete neuronal modules for the control of different aspects of parenting (Figure 1, 'Towards a circuit-level analysis of parental behavior'). Since each of the loci identified by Bendesky *et al.* comprises hundreds of

genes, a crucial next step will be to zoom in on transcripts with functions directly associated with, or more indirectly modulating, pup-directed behaviors.

Conclusions and future directions

Considerable progress has been made in identifying molecularly defined neuronal populations and circuit elements involved in the control of parenting and other instinctive behaviors and physiological states such as aggression [33,34,62,63], mating [33,62], sleep [28,64], feeding [21,65] and thermoregulation [66,67]. However, several challenges lie ahead.

First, neurons controlling a specific behavior or state have mostly been defined by a single molecular marker that identifies many, but not all, of the neurons, and overlaps with other, functionally distinct neuronal subsets — for example, $MPOA^{Gal}$ in parenting [6••], ARC^{AgRP} in feeding [68,69] or $VMHvl^{Esr1}$ in aggression [33]. Combinatorial expression of several 'signature genes' might therefore represent functionally relevant neuronal ensembles more completely. Recently for instance, three peptide markers (CCK, CRH, TAC1) were found to be necessary to specify, and functionally address, sleep-promoting neurons in the preoptic area [64]. Intersectional use of multiple, orthogonal transgenes will thus be necessary to subdivide existing expression patterns.

Second, using these and other approaches in the ever-expanding toolbox available for circuit-cracking in the mouse brain [70], the next step will be to define the circuits into which identified 'hub neurons' are embedded, followed by a detailed functional characterization of these circuits to reveal the logic underlying parental behavior. It will be particularly interesting to address whether discrete aspects of multicomponent behaviors are controlled by specific circuit elements. Scott *et al*. recently mapped projections from $AVPe^{TH}$ neurons, revealing extensive intra-hypothalamic connectivity. However, since these neurons affect parenting only in females [49••], a canonical circuit for parental care in both sexes still awaits characterization. Due to their above-mentioned characteristics, $MPOA^{Gal}$ neurons are ideal candidates to constitute a control hub in such a circuit.

Another formidable, but essential task will be to link this circuit architecture with the genetic landscape uncovered by Bendesky *et al*. [61••]. It will be particularly interesting to identify genes in loci affecting specific aspects of pup-directed behaviors (e.g. retrieval, licking, among others) and to investigate the molecular and neural mechanisms by which they exert their effects.

By connecting these behavioral, circuit-level and genetic domains, insights obtained from studying parenting have the exciting potential to inform how other types of (social) behaviors are controlled and to further our general understanding of the neural basis of behavior.

Conflict of interest statement

Nothing declared.

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