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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.

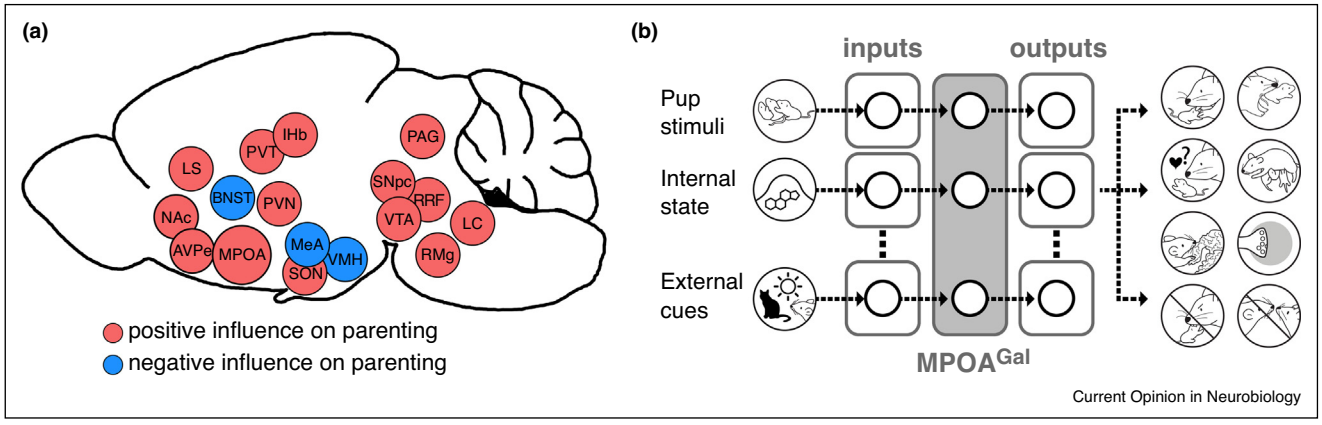
Parenting — a model of naturalistic social behavior

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