REVIEW ARTICLE

Integration of olfactory and auditory cues eliciting parental behavior

Briana R. McRae[1,2] | Valentine Andreu[1,2] | Bianca Jones Marlin[1,2,3]

[1]Department of Neuroscience, Columbia University, New York, New York, USA

[2]Mortimer B. Zuckerman Mind Brain and Behavior Institute, New York, New York, USA

[3]Department of Psychology, Columbia University, New York, New York, USA

Correspondence
Bianca Jones Marlin, Department of Psychology, Department of Neuroscience, Mortimer B. Zuckerman Mind Brain and Behavior Institute, Columbia University, 3227 Broadway, New York, NY 10027, USA.
Email: bjm2174@columbia.edu

Abstract

Parental care is crucial for the survival of all mammalian species. Given the evolutionary importance of parenting, this behavioral repertoire must be supported by circuitry that is innate but also capable of learning and flexibility – adjusting to changing environmental demands. In rodents, parental care is triggered by the perception of cues emitted by a pup. Caregiver-pup interactions are often composed of multimodal sensory stimuli that require caregivers to integrate across sensory modalities. In this review, we focus on two sensory modalities essential for the parental experience: smell and hearing. We examine how smell and hearing are combined with other senses to identify offspring in need of care. Understanding how multimodal stimuli are integrated in the caregiver brain to inform parental behavior is an important step in understanding the circuitry that underlies this complex and crucial behavioral repertoire. In this review, we will discuss recent advances in the field of rodent parental behavior, highlighting studies that have begun to disentangle the neural circuitry that processes the multisensory cues that are involved in caregiver-offspring interactions.

KEYWORDS
auditory, maternal behavior, multisensory, olfaction, parental behavior

1 | INTRODUCTION

The ability of a caregiver to provide appropriate parental care is crucial for the success of a species. This requires the caregiver to perceive relevant cues from their environment and respond accordingly to optimize offspring well-being. The cues that engage parental behavior circuits are composed of multimodal sensory stimuli, spanning olfactory, auditory, visual, somatosensory, and gustatory modalities (Figure 1). In this review we ask: how do different sensory systems work together to facilitate successful caregiving? If different sensory systems work conjunctively, how and where does this multisensory processing occur in the parental brain? While theories of multisensory integration in parenthood have been discussed for decades, it remains difficult in practice to identify how distinct sensory modalities uniquely and concurrently contribute to such complex behavior.

In this review, we aim to highlight recent advances in the field of rodent parental behavior, specifically focusing on studies that have begun to disentangle the neural circuitry that processes the multisensory cues that are involved in caregiver-offspring interactions. Understanding how multimodal stimuli are integrated in the caregiver brain to inform parental behavior is an important step in understanding the circuitry that underlies this complex and crucial behavioral repertoire.

Early studies set a precedent for isolating the different sensory modalities of pup cues involved in a specific parental behavior. Some of the earliest work done in rats used selective impairment of lactating mothers' senses to demonstrate that unisensory deprivation is insufficient to completely abolish maternal behavior.[1] This study suggested that multisensory pup cues are, at least in part, redundant signals that are evolutionarily advantageous if a sensory system is damaged. Later studies provided nuance in mice by noting that a given parental behavior is a process that can be broken down into phases.[2–4] Each phase may rely on a different sense or subset of senses. For example,
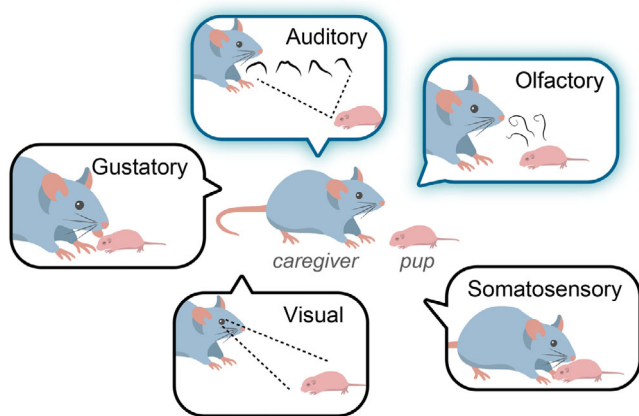
wileyonlinelibrary.com/journal/jne

FIGURE 1 Multisensory cues involved in parental behavior. Parent-offspring interactions in rodents involve a combination of olfactory, auditory, gustatory, visual, and somatosensory cues. Auditory and olfactory cues (blue) are the focus of this review.

the act of pup retrieval was described as a parental behavior in which a caregiver undergoes four stages of action: (1) elicitation, in which the caregiver is made aware of a pup isolated outside the nest, (2) location, identifying where the pup is, (3) recognition, in which the caregiver recognizes the pup and may identify it as its own offspring or an alien, and (4) action, in which the caregiver brings the pup back to the nest.[2,3] These observations argue that distal cues (such as audition) mediate the elicitation phase, a mix of distal and proximal cues (such as audition and olfaction) mediate location, and proximal cues (such as olfaction, gustation, and somatosensation) mediate recognition. Recent advances in the tracking, segmentation, and analysis of poses and movement sequences continue to refine the study of parental behaviors, such as pup retrieval, in response to complex offspring stimuli.[5–8] Altogether, this study highlights the complexity of parental behavior and calls for rigorous investigation of the multisensory cues that are involved in each component of its performance.

For this review, we chose to focus mainly on two sensory modalities: olfaction and audition. Olfaction and audition are two of the primary senses through which rodents participate in social interactions, and they span relatively more proximal (olfaction) and distal (audition) ranges of perception.[3,9] Additionally, olfactory and auditory sensory systems in particular have been shown to exhibit plasticity in the context of parenthood, suggesting that they play key roles in learned aspects of parental behavior.[10,11]

There is a growing body of literature surrounding the interaction of olfactory and auditory cues with other types of sensory cues during parental behavior in rodents. Here, we highlight several exciting studies of multisensory parental behavior in mice and rats, which have well-characterized sensory systems and parental behaviors. It is essential that we acknowledge some of the limitations of laboratory models with low genetic diversity and limited phenotypic variability due to decades of artificial selection, inbreeding, and adaptation to captivity. Clear differences in phenotypes of maternal behavior have been reported between strains of inbred mouse lines, as well as

between inbred versus outbred animal strains.[12–18] Furthermore, research involving other animal models like titi monkeys (*Callicebus cupreus*), subsocial bees (*Ceratina calcarata*), mandarin voles (*Microtus mandarinus*), and California mice (*Peromyscus californicus*) presents unique opportunities to study parenting, but are outside the scope of this review.[19–21]

2 | CUES ELICITING PARENTAL BEHAVIOR: OLFACTION

Olfaction is one of the key senses by which rodents explore their environment to process social stimuli. Conspecific information in rodents can come from olfactory cues in urine, skin, or specialized glands.[22–24] The olfactory system encompasses two pathways: (1) the main olfactory pathway, which includes the main olfactory epithelium (MOE) and the main olfactory bulb; and (2) the vomeronasal pathway, which includes the vomeronasal organ (VNO) and the accessory olfactory bulb.[25] Olfactory cues from the pup have an essential role in the initiation and coordination of maternal behavior in mammals.[26,27] In rats it has been reported that, while mothers are attracted or neutral to pup odor, pup-naïve virgin females show an aversion to pup odors. Moreover, a bulbectomy in virgin rats facilitates the emergence of parental behavior.[26] Most mouse mothers who are unable to smell following the surgical removal of their olfactory bulbs cannibalized their pups, indicating that the ability to smell offspring is essential for adaptive maternal behavior.[28,29] Interestingly, further research showed that experienced mouse mothers did not cannibalize their pups when anosmic, which suggests that experience can override the importance of smell for maternal behaviors.[30] Other methods of disrupting the olfactory system in mice have also led to impairments in pup retrieval, nest building, and other maternal behaviors. These methods include the deletion of adenylyl cyclase-3 (AC3), an essential part of the olfactory signal transduction cascade, and the mutation of voltage-gated sodium channels Na(v)1.7 to prevent the firing of olfactory sensory neurons.[31,32]

There is some evidence of plasticity in the mammalian olfactory system during motherhood.[27,33–35] To assess changes in sensory processing of pup-derived chemosignals linked to pregnancy, Navarro-Moreno et al.[36] analyzed changes in the expression of immediate early genes in the main olfactory bulb, VNO, and accessory olfactory bulb of virgin and late pregnant female mice. They reported changes in the processing of pup-derived chemosignals by the end of pregnancy in both olfactory pathways. In humans, mothers reported having a heightened sense of smell during pregnancy, but there is limited explanation for the cause of this effect.[37] In sheep, mitral cells, which are the main olfactory bulb output neurons, were shown to undergo changes following parturition, specifically in their responsiveness to the scent of their offspring.[38] Vinograd et al.[11] recorded mitral cell activity before and after pregnancy in mice. They examined how the processing of pure odors and behaviorally relevant odors (i.e., male mouse urine, female mouse urine, peanut butter, trimethylthiazoline, nest odor) changes with motherhood. Using in vivo two-photon

calcium imaging, they compared the odor responses of mitral cells in primiparous lactating mothers (3–5 days after parturition) to that of age-matched naïve females. Mitral cell responses to pure odors became sparser following the transition to motherhood. This sparsening was not observed in response to behaviorally relevant odors. Enhanced inhibition was also observed in the main olfactory bulb of mothers, which could be a potential explanation for the sparser representation of behaviorally irrelevant odors. This study highlights the olfactory system as a potential locus of change in the maternal brain.

The vomeronasal pathway is critical for identifying sex- and species-specific chemical cues in rodents, which play a central role in mating, territorial aggression, and defensive responses to predators.[39–41] However, its role in mouse parental behavior has been contested, with existing literature suggesting that the VNO is not necessary for parental behavior in mice.[42–44] A recent study suggested that the main olfactory and vomeronasal systems are coactivated during interaction with pups in late pregnant female mice.[36] However, odor-evoked activity in the MOE was shown to be required for maternal pup retrieval, while the VNO was not necessary and deemed redundant to the MOE.[45] This literature suggests that the MOE plays a role in adaptive parental behaviors; on the other hand, the VNO has been deemed necessary for aggressive behaviors. The act of maternal aggression, for example, required functional MOE and VNO.[42,45–47] Similarly, in virgin males, the VNO is essential for the stereotypical infanticidal behavior observed in virgin male mice.[43,48] Surprisingly, VNO ablation also led to an uncharacteristic display of parental care from virgin male mice and rats, suggesting that the VNO typically plays a role in regulating infanticidal behavior and suppressing paternal behavior in virgin males.[43,44,49] Overall, the main and vomeronasal olfactory systems both play a role in parental behavior, though in different capacities.

3 | CUES ELICITING PARENTAL BEHAVIOR: AUDITION

In the context of rodent parental behavior, auditory cues play a significant role in the communication between offspring and caregiver. One well-studied example of parent-offspring communication occurs when pups are separated from the nest. Pups have a limited ability to thermoregulate, so when they are separated from the nest and begin to cool, they emit ultrasonic vocalizations (USVs), which have stereotyped spectral and temporal characteristics.[50–52] The USVs of a pup isolated from the nest, termed pup isolation calls, occupy a frequency range between 40 and 100 kHz, with syllables grouped into bouts occurring at 3 to 8 Hz.[50,51,53–55] In mice, the timing between call syllables has been shown to affect neural responses to pup calls and pup retrieval probability in caregivers of varying pup care experience.[55,56] Once perceived by an experienced caregiver, these isolation calls elicit phonotaxis (movement towards the source of sound) and the act of pup retrieval, in which the caregiver picks up the pup and returns it back to the safety of the nest.[51] While auditory stimuli are certainly not the only relevant pup cues for mice caregivers, one can imagine

how auditory stimuli are particularly beneficial for detecting and locating a lost pup from a relatively large distance.[57] Prior work in mice has suggested that the presentation of pup isolation calls alone, without pairing other pup-emitted stimuli, is sufficient in eliciting the phonotaxis behavior typical of pup retrieval.[58,59] Additionally, mouse pups that are unable to produce vocalizations due to genetic mutation receive less maternal care.[60] However, whether deaf adult mice demonstrate deficits in their capacity to provide maternal care is still contested. Existing literature suggests that impaired hearing leads to impoverished maternal care in virgin female mice, but not in experienced mothers, implying that experienced mothers may develop compensatory methods to support offspring well-being or that pup vocalizations are only crucial during the learning of maternal care.[61,62] Despite disagreements in the field, auditory cues appear to be important for parental behavior, particularly in eliciting the initiation of pup retrieval.

Aside from the caregiver-offspring communication that occurs via auditory signals in rodents, the auditory system is dynamic in the context of parental behavior due to its demonstrated experience-dependent neural plasticity. A growing body of work continues to elucidate how neural plasticity, particularly that which shifts the excitatory/inhibitory (E/I) balance in primary auditory cortex (A1), accompanies an animal's transition from virgin to maternal brain.[10,55,56,63–69] This shift appears to favor pup calls such that they become more salient stimuli that evoke reliable A1 firing. Changes in E/I balance are driven not only by the experience of natural childbirth and pup rearing, but also by the social transmission of alloparenting, observation of pup care, and neuromodulatory pairing in virgin female mice.[10,55,56,63–69] Research in mice has begun to identify neuromodulators and genes that facilitate this experience-dependent plasticity that accompanies the learning of maternal behavior, including the hormones oxytocin and estradiol, as well as the gene MECP2.[10,70–72] Furthermore, a subset of this study has demonstrated that left A1 in particular shows lateralization of pup vocalization perception in experienced mothers, which suggests a possible parallel to the left lateralization of human vocal perception and social communication.[10,58,66,73,74] This lateralization may be due, in part, to the observed distribution of oxytocin receptors favoring left A1.[10,75] Altogether, the auditory system presents itself as an attractive entry point into the adaptive parental brain.

4 | INTEGRATION OF OLFACTORY AND AUDITORY CUES

Olfactory and auditory processing have already been shown to interact in the context of parental behavior. A study by Cohen et al.[64] focused on the representation of both olfactory and auditory stimuli in A1 of mice. The authors exposed female mice to pup calls, pup odor, and a combination of both stimuli while simultaneously recording from A1. In the absence of auditory cues, the authors found that the presentation of pup odor led to a decrease in spontaneous A1 firing in lactating mothers. Furthermore, A1 responses to pure tones and

pup calls were altered when the mothers were exposed to pup odors, as compared to air alone. These data suggest that olfactory and auditory cues work in concert to amplify responses in maternal A1, a locus for parental care. Recordings from primary somatosensory cortex (S1) and monitoring of heart and breathing rates during odor presentation ruled out the possibility that this effect was caused by a global increase in maternal arousal. Interestingly, virgin female mice with prior alloparenting experience also showed similar multisensory integration in the auditory cortex, but pup-naïve virgins did not, suggesting that this multisensory integration is experience-dependent. The authors reasoned that since this odor-specific change in A1 activity was temporally delayed and long-lasting after odor presentation, it must not rely on direct olfactory-auditory projections. This study implies that pup odors facilitate the detection and recognition of pup isolation calls, linking these senses which are uniquely positioned to detect pups in need of care. A previous study in mice has shown that auditory and olfactory cues are together involved in other behaviors, such as predator avoidance.[76] Further research in humans and mice has shown that auditory cues could affect olfactory processing, implying that this relationship is bidirectional.[77,78]

Following up on their study, Cohen et al.[65] next looked at the role of specific cell types in mice in the transition from virgin to maternal state that results in experience-dependent pup call and odor responses in A1. The authors focused on layer 2/3 of A1, specifically looking at populations of excitatory pyramidal neurons and inhibitory parvalbumin-expressing neurons. The authors compared response properties such as the "best frequency," or the frequency that elicited the strongest response, in A1 of naïve virgins and lactating mothers. While there was no group difference in the best frequency reported for pyramidal neurons, lactating mothers showed an increased average best frequency of parvalbumin-expressing neurons. This suggests that the transition from virgin to maternal state involves the retuning of these inhibitory cells. The authors returned to the investigation of contingency between pup calls and odors in maternal A1 and showed that pup odor exposure led to decreased spontaneous and sound-evoked responses in parvalbumin-expressing neurons. Through what is likely feedforward inhibition, this led to the disinhibition of pyramidal neurons, allowing mother mice to exhibit the expected heightened responsiveness to pup calls.[56] Pup odors had no effect on tuning properties in naïve virgins.

Altogether, these studies position A1 as a region in which olfactory and auditory pup cues interact. This study supports the idea that a shift in E/I balance facilitates the enhanced tuning to pup cues observed during an animal's transition into motherhood, as previous mouse studies have also found.[10,55] Marlin et al.[10] demonstrated that maternal experience causes a shift in A1 E/I balance that is facilitated by the neuropeptide oxytocin, which is synthesized in the paraventricular nucleus of the hypothalamus (PVN) and supraoptic nucleus. Pairing oxytocin with pup calls in pup-naïve virgin females led to a decrease in inhibitory input to pup call-responsive A1 neurons, leading to an initial disinhibition of A1. Inhibitory inputs were eventually retuned to match excitatory inputs, allowing for more robust and time-locked pup call-evoked neural responses, mirroring those observed in female mice with maternal experience. Notably, the authors found that oxytocin receptors are expressed in inhibitory neurons in A1, including parvalbumin-expressing neurons. These findings, combined with the recordings from parvalbumin-expressing neurons described by Cohen et al. suggest that changes in inhibitory signals in A1 affect E/I balance in a way that favors more robust responses to pup calls. Furthermore, the findings reported by Cohen et al. demonstrate that this shift in E/I balance not only affects the auditory system, but also indirectly affects how olfactory pup cues are perceived.

5 | INTEGRATION OF AUDITORY AND VISUAL CUES

One context in which researchers have highlighted the importance of cooperative auditory and visual cues is in the social transmission of parental behavior. Specifically, this area of work has focused on how pup-naïve virgin female mice quickly learn to express alloparenting behaviors, or to provide parental care for non-biological pups that are not biologically their own. While pup-naïve virgin female mice do not reliably retrieve isolated pups, cohousing a naïve virgin with a mother and litter leads to the expression of retrieval behavior.[79-81] The process of virgin female mice learning maternal behavior via social transmission has been shown to be facilitated by oxytocin.[10] Marlin et al. demonstrated that cohoused virgins receiving systemic oxytocin injection or optogenetic stimulation of oxytocinergic neurons in the PVN increase their rate of successful retrieval behavior. Schiavo et al.[55] recently elaborated on this finding to reveal that naïve virgin females start with innate A1 tuning to stereotypical pup calls. As virgins gained pup experience, A1 tuning broadened, predicting more reliable pup retrieval. Altogether, this study detailed how neuromodulation leads to a retuning of the virgin A1 to increase the salience of pup calls as they become behaviorally relevant via cohousing with a mother and pups. These studies focused on the perception of pup auditory cues, which leaves unanswered: what other sensory cues contribute to the learning process of a virgin cohoused with a mother and pups?

Following up on this study, Carcea et al. studied natural multisensory learning in an innovative way. In a documentary-style study, the authors tracked the behavior and neural activity of pup-naïve virgin female mice as they were cohoused with either a mother and pups, or pups without their mother, for multiple days.[63] This data-rich approach demonstrated that virgin females who were cohoused with a mother and pups reliably performed pup retrieval earlier than virgin females who were cohoused with pups alone. When the authors characterized multiple days of recorded behavior, they showed that mothers seemingly encouraged pup interaction with virgin females by "shepherding" stray virgins back into the nest. Moreover, Carcea et al. observed mothers placing pups in the vicinity of virgins before retrieving them, potentially demonstrating successful pup retrieval for the benefit of the naïve virgin.

While constantly monitoring behavior, the authors recorded neural activity in the PVN of the cohoused virgin females. They found that retrieval observation evoked responses in the virgin PVN. To test

the importance of visual observation, the authors had virgin females observe maternal pup retrieval in one of three conditions: a transparent barrier, an opaque barrier, or no barrier separating the virgin from the mother and pups. Virgins who observed maternal pup retrieval through the transparent barrier performed at similar rates to virgins who had no barrier. Virgins separated by an opaque barrier did not learn retrieval behavior. Importantly, stimulating axonal projections from visual areas terminating onto oxytocinergic neurons in the PVN was sufficient to facilitate learning in virgins behind the opaque barrier. This suggests that visual cues are key for the social learning of maternal behavior. Additionally, the authors found that PVN projections to left A1 were activated in virgins as they observed pup retrieval, indicating the involvement of the auditory system. Notably, the authors did not demonstrate whether olfactory cues were able to permeate the barriers used, leaving the role of the olfactory system in this process unclear. This study suggests that virgin females can acquire maternal behavior via auditory cues and oxytocin signaling, but the visual information that accompanies cohousing accelerates this learning process.

6 | INTEGRATION OF AUDITORY AND SOMATOSENSORY CUES

While a large body of research has revolved around pup USVs, mouse pups also emit vocalizations in a lower frequency range, termed wriggling calls. Wriggling calls were initially regarded as non-communicative, but research continues to uncover the relevance of wriggling calls to parental behavior in mice.[57] These calls fall in a frequency range below 20 kHz, with most power occurring below 10 kHz. They are most often emitted from pups who are reaching towards the mother's teats for milk or are crawling in the nest.[53] Therefore, wriggling calls are usually accompanied by somatosensory cues, including the sensations of pushing towards the mother's ventral trunk and suckling. Ehret et al. played wriggling calls through a speaker while mothers crouched in a suckling position overactive versus paralyzed pups. The authors found that wriggling calls paired with active pups elicited significantly more maternal licking than wriggling calls paired with paralyzed pups, who did not stimulate the mother's ventral trunk.[53] This early study started to uncover how the auditory cue of wriggling calls might interact with active pup somatosensory cues to elicit maternal behavior. Further research in rats showed that the cortical representation of the ventral trunk increases in lactating mothers, as compared to postpartum non-lactating mothers or virgin controls.[82] Additional work in mice identified that perineuronal nets, extracellular matrix structures that restrict synaptic plasticity, might play a role in regulating plasticity in maternal primary somatosensory cortex.[83] This suggests that cortical plasticity is needed for the representation of pup somatosensory cues, further emphasizing their importance.

More recent studies have investigated pup suckling using functional magnetic resonance imaging (fMRI) in rats, a non-invasive technique that measures the blood oxygenation-level-dependent (BOLD)

response as a proxy for neural activity.[84–86] This neuroimaging method is of particular interest in the context of multisensory integration because it allows researchers to measure whole-brain activity, spanning the multimodal primary sensory areas and subcortical nuclei. Febo et al. used fMRI in rats to investigate the multisensory experience of nursing. The authors measured the evoked BOLD response to four conditions: (1) lactating mothers exposed to their pups for 5 minutes of suckling, (2) lactating mothers exposed to artificial suckling via a manual pump, (3) lactating mothers exposed to gentle rubbing of the nipple area with a flat wooden ruler, and (4) virgin females exposed to the same gentle rubbing stimulus.[85] As expected, the authors observed robust activation in the somatosensory cortex across all conditions. Interestingly, lactating mothers receiving live pup or artificial suckling showed an increased BOLD response in other sensory cortices, as well, including the auditory cortex. It is unclear why areas such as the auditory cortex showed an increased BOLD response evoked by a purely tactile stimulus. One might note the possibility that the nursing pups were also producing wriggling calls. A limitation of this study is that the authors did not control for any potential pup vocalizations during the mother-pup scan. However, the mechanical sounds produced during an fMRI scan likely drowned out the sound of pups beneath the mother's abdomen.[87] Furthermore, the occurrence of pup vocalizations still would not explain the auditory cortex activation observed in the artificial suckling condition.

Here, Febo et al. observed activity in multiple cortical areas during suckling in lactating mothers, suggesting that repeated nursing experiences lead to the association of different sensory cortical sites. This integration may serve to heighten the mother's sensitivity to pups that are in need of feeding, similar to how pup odors heighten a mother's sensitivity to pup calls when the pups are in need of retrieval.[64,65]

7 | INTEGRATION OF OLFACTORY AND SOMATOSENSORY CUES

A previous study has demonstrated that virgin male mice display infanticidal behavior toward pups.[88] Isogai et al. sought to identify which sensory cues trigger infanticidal behavior. Specific sensory features of the pups were added and subtracted to examine necessary components for the infanticidal behavior.[89] The authors first observed that virgin males attack live pups in the dark, as well as dead pups, suggesting that pup visual features, vocalizations, body temperature, and movement were not necessary for the behavior. This narrowed down their search to chemosensory and tactile cues.

Pup-directed aggression was tested in virgin males using different versions of dummy pups covered in pup-derived odors. Using selective deletion of morphological features, the authors identified discrete pup features essential to pup-targeted aggression. A block shape with hind legs, front legs, and a tail induced aggressive behavior in virgin males, although not as dramatic as a real pup or a more realistic dummy pup shape. This confirms the importance of shape recognition through somatosensory cues, combined with chemosensory cues, in triggering pup-directed aggression in mice.

The authors next narrowed down which chemosensory cues within pup-derived odors were key to eliciting pup-directed aggression. As previously mentioned, the VNO is essential for the infanticidal behavior typically observed in virgin male mice.[44] Using the immediate early gene *Egr1* to measure vomeronasal activity, the authors identified seven vomeronasal receptors activated by pup exposure. Using biochemical purification, they found two pheromonal compounds that were essential for infanticidal behavior: the submandibular gland protein C and hemoglobin beta. Surprisingly, those compounds were not specific to pups, but rather are compounds resulting from mother-pup cohabitation.

Altogether, the authors showed that pup-mediated somatosensory inputs and pheromonal cues were coincidently prompting pup-directed aggression from virgin male mice. This study illustrates how future work can apply a similar feature reduction paradigm to elucidate the underpinnings of other inherently multisensory experiences. In the context of pup-directed aggression, this study also opens new avenues to dissect the circuits underlying the combination of these sensory modalities.

8 | HORMONES, MATING, AND MULTISENSORY EXPERIENCE

Beyond the multimodal external stimuli that we discussed in this review, we would be remiss to not acknowledge the internal cues that also factor into parental behavior. Hormonal changes are arguably some of the most influential internal factors involved in the development of parental behavior. In mammals, these hormonal changes include fluctuations in estrogen, progesterone, oxytocin, vasopressin, serotonin, and prolactin that begin during pregnancy and sometimes continue to oscillate postpartum.[90–92] Due to the fact that parental behavior involves not only learned experiences but also innate physiological changes, there is a large body of research dedicated to disentangling how pup cues recruit neuromodulatory responses, which then affect the performance of parental behavior in rodents. As previously mentioned, oxytocin has been shown to play an important role in facilitating the emergence of pup retrieval in female mice, as well as the initiation of caregiving behaviors in virgin male mice.[10,63,93,94] Moreover, oxytocin has been identified as a potential modulator of protective behaviors in maternal rats, such as conditioned threat response.[95] Beyond oxytocin, numerous neuromodulators have been shown to affect neural responses to stimuli, suggesting that they likely also play a role in multisensory processing.

Influenced at least in part by hormonal fluctuations, internal clocks appear to play a role in the emergence of parental behavior. While virgin male mice are typically infanticidal, their behavior appears to become more paternal a few days after mating. However, their infanticidal tendencies reemerge around 60 days after mating – just long enough for any offspring of their own to be carried to term by the mother and weaned at the appropriate age.[43,88,96–98] A study by Wu et al.[44] discovered that a subset of neurons in the medial preoptic area (MPOA), specifically a population that expresses the

neuropeptide galanin, was crucial in inhibiting infanticidal behavior in virgin males. Stimulating this neuronal population not only abolished pup-directed aggression, but also induced paternal behavior in virgin males. Similarly, in female mice, there appears to be an internal clock that governs preparatory nesting, a phenomenon that consists of pregnant mothers building tall brooding nests weeks before giving birth.[99] In a recent study by Topilko et al.,[99] the authors used whole-brain immediate early gene immunolabeling via the iDISCO+ clearing and staining method to identify neuropeptidergic neurons in the Edinger-Westphal nucleus that were crucial for preparatory nesting. Similar to the timeline of virgin male mice's switch from infanticidal to paternal behavior, the authors concluded that preparatory nesting is triggered by mating but requires a successful impregnation to be maintained over time until birth. Altogether, these studies highlight how neuropeptides play an important role in governing the timing of parental behavior in both sexes.

9 | THE FRONTIERS OF MULTISENSORY INTEGRATION IN PARENTAL BEHAVIOR

This review covers numerous exciting studies of the multisensory processing of infant cues. However, there is still much to be discovered about how multimodal stimuli are integrated in the rodent parental brain. Two unresolved questions are: (1) where do multimodal stimuli first converge in the rodent brain? and (2) how do multimodal stimuli interact in the rodent brain to inform parental behavior?

On the topic of where multimodal information first meets in the rodent brain, we consider two hypotheses. One hypothesis is that multimodal stimuli are integrated early in ascending sensory pathways, such as primary sensory cortices – an idea supported by existing work in mice, extensively detailed in this review.[64,65] This body of work demonstrated that the presentation of pup odor led to a decrease in spontaneous firing and an enhancement of the detection of pup calls in A1 of lactating mothers.[64] This is in agreement with other studies, beyond the study of parental behavior, that has detailed crossmodal responses in the midbrain, thalamus, and sensory cortices, which are all in the early ascending sensory pathways.[100–104] However, Cohen et al. describe a key nuance that sets their findings apart from previous auditory-olfactory integration work, namely that the multisensory integration they observed in A1 was slow to develop and was modulated by the continuous presence of the odor. The authors argued that the gradual onset and offset of this interaction implied that this multisensory phenomenon is not mediated through direct projections from olfactory regions to A1, which challenges the first hypothesis.[64] However, perhaps the elongated effect of odor on A1 firing can be explained by differences in how olfactory and auditory stimuli travel through space and reach the cortex.

This brings us to a second hypothesis, which is that multimodal stimuli are integrated later, in brain regions downstream of primary sensory cortices, such as neuromodulatory, motivation-related, or associative areas, some of which have already been described in our review.[10,55,63] Existing literature has pointed to several areas of

interest, some of which are highlighted in Figure 2. For example, Okabe et al.[105] demonstrated that various non-sensory brain regions showed increased activity, as measured by c-Fos expression in mice, in response to combined auditory and olfactory pup cues compared to when only one cue was presented. These regions of interest include the medial preoptic area (MPOA), the bed nucleus of the stria terminalis (BNST), and the amygdala (AMY). A large body of research surrounding the MPOA, BNST, and AMY has shown that these areas are important for the control and onset of parental behavior in male and female mice and rats.[44,95,106–114] These findings suggest that these brain areas could be integrating both auditory and olfactory cues. Other regions may also respond to multimodal infant cues. For example, the ventral tegmental area (VTA) receives projections from the MPOA and has been presented as a key node between the motivation and motor systems, and recent studies have found reward prediction signals in VTA during pup retrieval.[111,115] As described in this review, the PVN has also been demonstrated to respond to stimuli relevant to parental care.[63] Additionally, the prefrontal cortex (PFC) has been shown to be associated with the onset of maternal behavior and the processing of other multisensory behaviors.[116,117]

Further research is required to elucidate which, if any, of these regions play a crucial role in integrating across multimodal pup stimuli. Then, a subsequent question would be where this information travels after it converges in the brain. It is possible that multisensory information converges, then exerts top-down effects on primary sensory cortex (such as via projections from PVN to A1).[63] Alternatively, multisensory information could converge and then be passed on to areas higher in the processing hierarchy (such as via projections from PVN to PFC).[118] Alternatively, the sensory processing underlying complex parental behaviors may be best described as a network rather than a collection of hierarchical pathways, as suggested by Navarro-Moreno et al.[119] Evidently, there is still much to be determined about where multisensory infant stimuli are represented in the parental rodent brain and how we should conceptualize this complex perceptual process.

On the topic of how multimodal stimuli interact in the rodent brain to inform parental behavior, one can imagine numerous hypotheses, as represented in Figure 3. Here, we conceptualize how multimodal pup cues, such as odor and sound, may interact to inform parental drive, which could represent evoked neural activity, hormone levels, or behavioral output (such as the likelihood of a rodent to retrieve an isolated pup back to the nest). The first hypothesis states that pup multimodal stimuli are redundant, such that removing one unimodal stimulus has no effect on parental behavior, as long as another stimulus is available (Figure 3A).[1] One can imagine how this is evolutionarily advantageous, such that damage to one sensory system would not disrupt parental behavior altogether. As previously described, Isogai et al.[89] suggest that visual stimuli are redundant cues, as they reported that virgin male mice will attack pups in full darkness, which motivated their investigation of other sensory modalities. The second hypothesis implies that multimodal stimuli combine linearly, in an additive fashion (Figure 3B). This is supported by a study showing that mice prefer multimodal social stimuli compared to isolated sensory cues when engaged in a social recognition task.[120] One study argued that auditory, olfactory, and somatosensory cues are all necessary for successful social recognition in mice.[121] Multimodal stimuli may also combine in a superadditive fashion, where the overall effect of the combined stimuli is greater than the linear addition of the stimuli, as previously described by Okabe et al.[105] (Figure 3C). It is
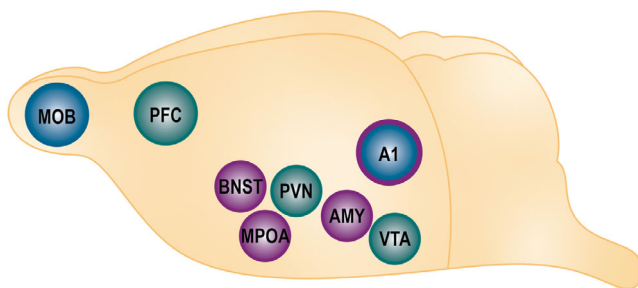

FIGURE 2 Brain regions relevant for parental care. Main loci for unisensory processing of olfactory and auditory offspring cues include the main olfactory bulb (MOB) and primary auditory cortex (A1) (blue). Demonstrated sites of multisensory integration include A1, bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), and amygdala (AMY) (purple). Putative non-sensory sites for multisensory integration include the prefrontal cortex (PFC), paraventricular nucleus of the hypothalamus (PVN), and ventral tegmental area (VTA) (green).
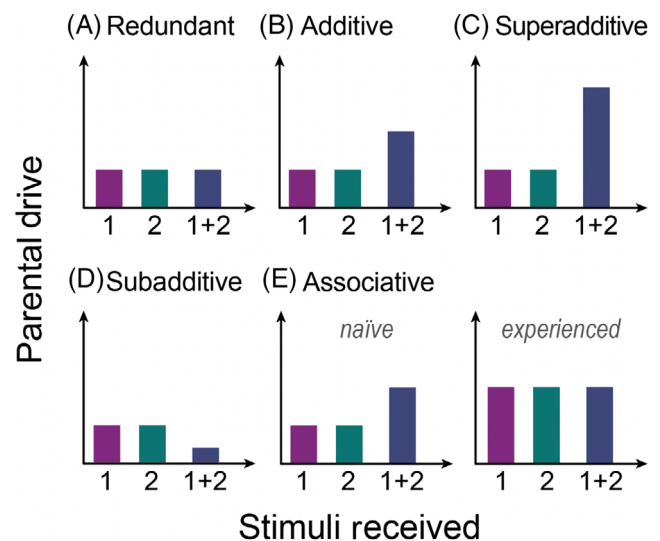

FIGURE 3 Hypotheses on how multisensory information is integrated in the parental brain. Multisensory information could be considered Redundant (A), Additive (B), Superadditive (C), Subadditive (D), or Associative (E). Parental drive represents evoked neural activity, hormone levels, or behavioral output (such as the likelihood of a rodent to retrieve an isolated pup back to the nest). Stimuli received include exposure to olfactory cues (1), auditory cues (2), or the combination of both (1 + 2). Notably, stimuli 1 and 2 are not restricted to olfactory and auditory cues but could represent other pairs of stimuli.

also possible that the combination of two distinct cues might reduce the effect that each cue contributes alone, in a subadditive fashion (Figure 3D). For example, Komura et al. reported that when rats were performing an auditory and visual decision-making task, cue-evoked auditory responses were suppressed when the visual cue presented conflicting information.[100,122] Finally, another alternative hypothesis is that multisensory cues become associative with experience (Figure 3E). As an animal gains parental experience and exposure to the rich extent of pup stimuli, different unimodal stimuli might become associated with one another, such that the presentation of one stimulus might eventually lead to the activation of multiple sensory areas, even when not all the stimuli are present. This idea is discussed by Febo et al.,[85] in light of their finding that pup suckling causes activation in sensory cortices beyond the somatosensory system.

10 | CONCLUSION

When a mammal becomes a parent, infant-derived cues take on new meaning. As covered in this review, research in rodents has demonstrated that experience-dependent changes in parental behavior are driven by neural plasticity – the basis of how the brain adapts to the environment. Understanding how pup cues are contextualized through innate and learned neural mechanisms will reveal how the adult brain remains flexible in the face of changing environmental demands and how it adapts to best respond to and care for offspring.

As we have detailed here, the multisensory nature of parental behavior is a basis for investigating how multisensory cues inform other goal-directed behaviors, such as foraging and mating. Systematic investigations of the individual and combined contributions of each sensory modality will require the use of state-of-the-art techniques, which the field is primed to take advantage of. Going forward, methods such as optogenetics and chemogenetics will be key to mimicking sensory experiences in a highly controlled manner.[123] Whole-cell electrophysiology and calcium imaging will facilitate the measurement of neural activity at the single-cell level, allowing for the precise tracking of encoded sensory information, which can then be modeled using computational techniques, such as complex neural networks. By using advanced molecular biology and genetic tools, we will be able to assess multiomic changes in sensory neurons in their evolution across parenthood. Expanding our perspective to incorporate the integration of multiple sensory systems, whole-brain imaging techniques such as immediate early gene mapping and neuroimaging will provide access to anatomical connections and real-time responses, respectively, across sensory systems as they work together to process complex stimuli. Because behavior is the ultimate output of these computations, continuous behavioral tracking will be key in uncovering the nuances of how parental behavior is expressed.

The neural circuitry and mechanisms that support parent-offspring bonds are thought to provide the initial neural template for other types of social relationships in mammals.[124,125] Therefore, uncovering the complex circuitry underlying parental behavior will be valuable for investigating other behaviors relying on similar architectures, such as pair-bonding, mate choice, and social recognition. Overall, the field of multisensory integration in parenthood will advance our understanding of how animals navigate their social world.

AUTHOR CONTRIBUTIONS

Briana Rose McRae: Conceptualization; writing – original draft; writing – review and editing. **Valentine Andreu:** Conceptualization; writing – original draft; writing – review and editing. **Bianca Jones Marlin:** Writing – review and editing.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

ORCID

Briana R. McRae https://orcid.org/0000-0003-0696-0566
Valentine Andreu https://orcid.org/0009-0009-8483-8188
Bianca Jones Marlin https://orcid.org/0000-0002-4275-7891

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jne.13307.

DATA AVAILABILITY STATEMENT

Not available.

REFERENCES

1. Beach FA, Jaynes J. Studies of maternal retrieving in rats. III. Sensory cues involved in the lactating female's response to her young 1. *Behaviour*. 1956;10(1):104-124. doi:10.1163/156853956X00129
2. Chantrey DF, Jenkins BAB. Sensory processes in the discrimination of pups by female mice (*Mus musculus*). *Anim Behav*. 1982;30(3):881-885. doi:10.1016/S0003-3472(82)80162-0
3. Wei D, Talwar V, Lin D. Neural circuits of social behaviors: innate yet flexible. *Neuron*. 2021;109(10):1600-1620. doi:10.1016/j.neuron.2021.02.012
4. Alsina-Llanes M, De Brun V, Olazábal DE. Development and expression of maternal behavior in naïve female C57BL/6 mice. *Dev Psychobiol*. 2015;57(2):189-200. doi:10.1002/dev.21276
5. Mathis A, Mamidanna P, Cury KM, et al. DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. *Nat Neurosci*. 2018;21(9):1281-1289. doi:10.1038/s41593-018-0209-y
6. Winters C, Gorssen W, Ossorio-Salazar VA, Nilsson S, Golden S, D'Hooge R. Automated procedure to assess pup retrieval in laboratory mice. *Sci Rep*. 2022;12(1):1663. doi:10.1038/s41598-022-05641-w
7. Wiltschko AB, Tsukahara T, Zeine A, et al. Revealing the structure of pharmacobehavioral space through motion sequencing. *Nat Neurosci*. 2020;23(11):1433-1443. doi:10.1038/s41593-020-00706-3

8. Stevenson PK, Casenhiser DM, Lau BYB, Krishnan K. Systematic analysis of goal-related movement sequences during maternal behaviour in a female mouse model for Rett syndrome. *Eur J Neurosci*. 2021;54(2):4528-4549. doi:10.1111/ejn.15327

9. Carandini M, Churchland AK. Probing perceptual decisions in rodents. *Nat Neurosci*. 2013;16(7):824-831. doi:10.1038/nn.3410

10. Marlin BJ, Mitre M, D'amour JA, Chao MV, Froemke RC. Oxytocin enables maternal behaviour by balancing cortical inhibition. *Nature*. 2015;520(7548):499-504. doi:10.1038/nature14402

11. Vinograd A, Fuchs-Shlomai Y, Stern M, et al. Functional plasticity of odor representations during motherhood. *Cell Rep*. 2017;21(2):351-365. doi:10.1016/j.celrep.2017.09.038

12. Champagne FA, Curley JP, Keverne EB, Bateson PPG. Natural variations in postpartum maternal care in inbred and outbred mice. *Physiol Behav*. 2007;91(2):325-334. doi:10.1016/j.physbeh.2007.03.014

13. Weaver ICG, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004;7(8):847-854. doi:10.1038/nn1276

14. Murgatroyd CA, Peña CJ, Podda G, Nestler EJ, Nephew BC. Early life social stress induced changes in depression and anxiety associated neural pathways which are correlated with impaired maternal care. *Neuropeptides*. 2015;52:103-111. doi:10.1016/j.npep.2015.05.002

15. Chalfin L, Dayan M, Levy DR, et al. Mapping ecologically relevant social behaviours by gene knockout in wild mice. *Nat Commun*. 2014;5(1):4569. doi:10.1038/ncomms5569

16. Berendzen KM, Sharma R, Mandujano MA, et al. Oxytocin receptor is not required for social attachment in prairie voles. *Neuron*. 2022; 111:787-796. doi:10.1016/j.neuron.2022.12.011

17. Olazábal DE, Young LJ. Oxytocin receptors in the nucleus accumbens facilitate "spontaneous" maternal behavior in adult female prairie voles. *Neuroscience*. 2006;141(2):559-568. doi:10.1016/j.neuroscience.2006.04.017

18. Olazábal DE, Young LJ. Species and individual differences in juvenile female alloparental care are associated with oxytocin receptor density in the striatum and the lateral septum. *Horm Behav*. 2006;49(5):681-687. doi:10.1016/j.yhbeh.2005.12.010

19. Bales KL. Parenting in animals. *Curr Opin Psychol*. 2017;15:93-98. doi:10.1016/j.copsyc.2017.02.026

20. Robinson KJ, Bosch OJ, Levkowitz G, Busch KE, Jarman AP, Ludwig M. Social creatures: model animal systems for studying the neuroendocrine mechanisms of social behaviour. *J Neuroendocrinol*. 2019;31(12):e12807. doi:10.1111/jne.12807

21. Bendesky A, Kwon YM, Lassance JM, et al. The genetic basis of parental care evolution in monogamous mice. *Nature*. 2017; 544(7651):434-439. doi:10.1038/nature22074

22. Mykytowycz R, Goodrich BS. Skin glands as organs of communication in mammals. *J Invest Dermatol*. 1974;62(3):124-131. doi:10.1111/1523-1747.ep12676776

23. Natynczuk SE, Macdonald DW. Scent, sex, and the self-calibrating rat. *J Chem Ecol*. 1994;20(8):1843-1857. doi:10.1007/BF02066226

24. Stopka P, Janotova K, Heyrovsky D. The advertisement role of major urinary proteins in mice. *Physiol Behav*. 2007;91(5):667-670. doi:10.1016/j.physbeh.2007.03.030

25. Dulac C, Wagner S. Genetic analysis of brain circuits underlying pheromone signaling. *Annu Rev Genet*. 2006;40(1):449-467. doi:10.1146/annurev.genet.39.073003.093937

26. Lévy F, Keller M, Poindron P. Olfactory regulation of maternal behavior in mammals. *Horm Behav*. 2004;46(3):284-302. doi:10.1016/j.yhbeh.2004.02.005

27. Lévy F, Keller M. Olfactory mediation of maternal behavior in selected mammalian species. *Behav Brain Res*. 2009;200(2):336-345. doi:10.1016/j.bbr.2008.12.017

28. Gandelman R, Zarrow MX, Denenberg VH, Myers M. Olfactory bulb removal eliminates maternal behavior in the mouse. *Science*. 1971; 171(3967):210-211. doi:10.1126/science.171.3967.210

29. Vandenbergh JG. Effects of central and peripheral anosmia on reproduction of female mice. *Physiol Behav*. 1973;10(2):257-261. doi:10.1016/0031-9384(73)90307-7

30. Seegal RF, Denenberg VH. Maternal experience prevents pup-killing in mice induced by peripheral anosmia. *Physiol Behav*. 1974;13(2):339-341. doi:10.1016/0031-9384(74)90056-0

31. Wang Z, Storm DR. Maternal behavior is impaired in female mice lacking type 3 adenylyl cyclase. *Neuropsychopharmacology*. 2011; 36(4):772-781. doi:10.1038/npp.2010.211

32. Weiss J, Pyrski M, Jacobi E, et al. Loss-of-function mutations in sodium channel Nav1.7 cause anosmia. *Nature*. 2011;472(7342):186-190. doi:10.1038/nature09975

33. Dulac C, O'Connell LA, Wu Z. Neural control of maternal and paternal behaviors. *Science*. 2014;345(6198):765-770. doi:10.1126/science.1253291

34. Gschwend O, Abraham NM, Lagier S, Begnaud F, Rodriguez I, Carleton A. Neuronal pattern separation in the olfactory bulb improves odor discrimination learning. *Nat Neurosci*. 2015;18(10):1474-1482. doi:10.1038/nn.4089

35. Poindron P. Mechanisms of activation of maternal behaviour in mammals. *Reprod Nutr Dev*. 2005;45(3):341-351. doi:10.1051/rnd:2005025

36. Navarro-Moreno C, Sanchez-Catalan MJ, Barneo-Muñoz M, et al. Pregnancy changes the response of the Vomeronasal and olfactory systems to pups in mice. *Front Cell Neurosci*. 2020;14:593309. doi:10.3389/fncel.2020.593309

37. Cameron EL. Pregnancy and olfaction: a review. *Front Psychol*. 2014; 5:67.

38. Kendrick KM, Lévy F, Keverne EB. Changes in the sensory processing of olfactory signals induced by birth in sheep. *Science*. 1992; 256(5058):833-836. doi:10.1126/science.1589766

39. Dulac C, Torello AT. Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nat Rev Neurosci*. 2003;4(7):551-562. doi:10.1038/nrn1140

40. Haga S, Hattori T, Sato T, et al. The male mouse pheromone ESP1 enhances female sexual receptive behaviour through a specific vomeronasal receptor. *Nature*. 2010;466(7302):118-122. doi:10.1038/nature09142

41. Papes F, Logan DW, Stowers L. The Vomeronasal organ mediates interspecies defensive behaviors through detection of protein pheromone homologs. *Cell*. 2010;141(4):692-703. doi:10.1016/j.cell.2010.03.037

42. Kimchi T, Xu J, Dulac C. A functional circuit underlying male sexual behaviour in the female mouse brain. *Nature*. 2007;448(7157):1009-1014. doi:10.1038/nature06089

43. Tachikawa KS, Yoshihara Y, Kuroda KO. Behavioral transition from attack to parenting in male mice: a crucial role of the Vomeronasal system. *J Neurosci*. 2013;33(12):5120-5126. doi:10.1523/JNEUROSCI.2364-12.2013

44. Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, Dulac CG. Galanin neurons in the medial preoptic area govern parental behavior. *Nature*. 2014;509(7500):325-330. doi:10.1038/nature13307

45. Fraser EJ, Shah NM. Complex chemosensory control of female reproductive behaviors. *PLOS One*. 2014;9(2):e90368. doi:10.1371/journal.pone.0090368

46. Leypold BG, Yu CR, Leinders-Zufall T, Kim MM, Zufall F, Axel R. Altered sexual and social behaviors in trp2 mutant mice. *Proc Natl Acad Sci*. 2002;99(9):6376-6381. doi:10.1073/pnas.082127599

47. Stowers L, Holy TE, Meister M, Dulac C, Koentges G. Loss of sex discrimination and male-male aggression in mice deficient for TRP2. *Science*. 2002;295(5559):1493-1500. doi:10.1126/science.1069259

48. Nakahara TS, Camargo AP, Magalhães PHM, et al. Peripheral oxytocin injection modulates vomeronasal sensory activity and reduces pup-directed aggression in male mice. *Sci Rep*. 2020;10(1):19943. doi:10.1038/s41598-020-77061-7

49. Mennella JA, Moltz H. Infanticide in the male rat: the role of the vomeronasal organ. *Physiol Behav*. 1988;42(3):303-306. doi:10.1016/0031-9384(88)90087-X

50. Castellucci GA, Calbick D, McCormick D. The temporal organization of mouse ultrasonic vocalizations. *PLOS One*. 2018;13(10): e0199929. doi:10.1371/journal.pone.0199929

51. Ehret G. Infant rodent ultrasounds – a gate to the understanding of sound communication. *Behav Genet*. 2005;35(1):19-29. doi:10.1007/s10519-004-0853-8

52. Zippelius HM, Schleidt WM. Ultraschall-Laute bei jungen Mausen. *Naturwissenschaften*. 1956;43(21):502. doi:10.1007/BF00632534

53. Ehret G, Bernecker C. Low-frequency sound communication by mouse pups (*Mus musculus*): wriggling calls release maternal behaviour. *Anim Behav*. 1986;34(3):821-830. doi:10.1016/S0003-3472(86)80067-7

54. Liu RC, Miller KD, Merzenich MM, Schreiner CE. Acoustic variability and distinguishability among mouse ultrasound vocalizations. *J Acoust Soc Am*. 2003;114(6):3412-3422. doi:10.1121/1.1623787

55. Schiavo JK, Valtcheva S, Bair-Marshall CJ, Song SC, Martin KA, Froemke RC. Innate and plastic mechanisms for maternal behaviour in auditory cortex. *Nature*. 2020;587(7834):426-431. doi:10.1038/s41586-020-2807-6

56. Liu RC, Linden JF, Schreiner CE. Improved cortical entrainment to infant communication calls in mothers compared with virgin mice. *Eur J Neurosci*. 2006;23(11):3087-3097. doi:10.1111/j.1460-9568.2006.04840.x

57. Haack B, Markl H, Ehret G. Sound Communication between Parents and Offspring. *The auditory psychobiology of the mouse*. Charles C Thomas Publisher, Ltd; 1983.

58. Ehret G. Left hemisphere advantage in the mouse brain for recognizing ultrasonic communication calls. *Nature*. 1987;325(6101):249-251. doi:10.1038/325249a0

59. Sewell GD. Ultrasonic communication in rodents. *Nature*. 1970; 227(5256):410. doi:10.1038/227410a0

60. Hernandez-Miranda LR, Ruffault PL, Bouvier JC, et al. Genetic identification of a hindbrain nucleus essential for innate vocalization. *Proc Natl Acad Sci*. 2017;114(30):8095-8100. doi:10.1073/pnas.1702893114

61. Wu WL, Wang CH, Huang EYK, Chen CC. Asic3−/− female mice with hearing deficit affects social development of pups. *PLOS One*. 2009;4(8):e6508. doi:10.1371/journal.pone.0006508

62. D'Amato FR, Populin R. Mother-offspring interaction and pup development in genetically deaf mice. *Behav Genet*. 1987;17(5):465-475. doi:10.1007/BF01073113

63. Carcea I, Caraballo NL, Marlin BJ, et al. Oxytocin neurons enable social transmission of maternal behaviour. *Nature*. 2021;596(7873): 553-557. doi:10.1038/s41586-021-03814-7

64. Cohen L, Rothschild G, Mizrahi A. Multisensory integration of natural odors and sounds in the auditory cortex. *Neuron*. 2011;72(2): 357-369. doi:10.1016/j.neuron.2011.08.019

65. Cohen L, Mizrahi A. Plasticity during motherhood: changes in excitatory and inhibitory layer 2/3 neurons in auditory cortex. *J Neurosci*. 2015;35(4):1806-1815. doi:10.1523/JNEUROSCI.1786-14.2015

66. Elyada YM, Mizrahi A. Becoming a mother—circuit plasticity underlying maternal behavior. *Curr Opin Neurobiol*. 2015;35:49-56. doi:10.1016/j.conb.2015.06.007

67. Galindo-Leon EE, Lin FG, Liu RC. Inhibitory plasticity in a lateral band improves cortical detection of natural vocalizations. *Neuron*. 2009;62(5):705-716. doi:10.1016/j.neuron.2009.05.001

68. Shepard KN, Lin FG, Zhao CL, Chong KK, Liu RC. Behavioral relevance helps untangle natural vocal categories in a specific subset of core auditory cortical pyramidal neurons. *J Neurosci*. 2015;35(6): 2636-2645. doi:10.1523/JNEUROSCI.3803-14.2015

69. Tasaka G, Feigin L, Maor I, et al. The temporal association cortex plays a key role in auditory-driven maternal plasticity. *Neuron*. 2020; 107(3):566-579.e7. doi:10.1016/j.neuron.2020.05.004

70. Krishnan K, Lau BYB, Ewall G, Huang ZJ, Shea SD. MECP2 regulates cortical plasticity underlying a learned behaviour in adult female mice. *Nat Commun*. 2017;8(1):14077. doi:10.1038/ncomms14077

71. Lau BYB, Krishnan K, Huang ZJ, Shea SD. Maternal experience-dependent cortical plasticity in mice is circuit- and stimulus-specific and requires MECP2. *J Neurosci*. 2020;40(7):1514-1526. doi:10.1523/JNEUROSCI.1964-19.2019

72. Moreno A, Gumaste A, Adams GK, et al. Familiarity with social sounds alters c-Fos expression in auditory cortex and interacts with estradiol in locus coeruleus. *Hear Res*. 2018;366:38-49. doi:10.1016/j.heares.2018.06.020

73. Ruthig P, Schönwiesner M. Common principles in the lateralization of auditory cortex structure and function for vocal communication in primates and rodents. *Eur J Neurosci*. 2022;55(3):827-845. doi:10.1111/ejn.15590

74. Levy RB, Marquarding T, Reid AP, Pun CM, Renier N, Oviedo HV. Circuit asymmetries underlie functional lateralization in the mouse auditory cortex. *Nat Commun*. 2019;10(1):2783. doi:10.1038/s41467-019-10690-3

75. Mitre M, Marlin BJ, Schiavo JK, et al. A distributed network for social cognition enriched for oxytocin receptors. *J Neurosci*. 2016; 36(8):2517-2535. doi:10.1523/JNEUROSCI.2409-15.2016

76. Halene TB, Talmud J, Jonak GJ, Schneider F, Siegel SJ. Predator odor modulates auditory event-related potentials in mice. *Neuroreport*. 2009;20(14):1260-1264. doi:10.1097/WNR.0b013e3283300cde

77. Seo H-S, Hummel T. Auditory–olfactory integration: congruent or pleasant sounds amplify odor pleasantness. *Chem Senses*. 2011;16: 301-309.

78. Wesson DW, Wilson DA. Smelling sounds: olfactory-auditory sensory convergence in the olfactory tubercle. *J Neurosci*. 2010;30(8): 3013-3021. doi:10.1523/JNEUROSCI.6003-09.2010

79. Koch M, Ehret G. Estradiol and parental experience, but not prolactin are necessary for ultrasound recognition and pup-retrieving in the mouse. *Physiol Behav*. 1989;45(4):771-776. doi:10.1016/0031-9384(89)90293-X

80. Stolzenberg DS, Champagne FA. Hormonal and non-hormonal bases of maternal behavior: the role of experience and epigenetic mechanisms. *Horm Behav*. 2016;77:204-210. doi:10.1016/j.yhbeh.2015.07.005

81. Rosenblatt JS. Nonhormonal basis of maternal behavior in the rat. *Science*. 1967;156(3781):1512-1514. doi:10.1126/science.156.3781.1512

82. Xerri C, Stern J, Merzenich M. Alterations of the cortical representation of the rat ventrum induced by nursing behavior. *J Neurosci*. 1994; 14(3):1710-1721. doi:10.1523/JNEUROSCI.14-03-01710.1994

83. Lau BYB, Layo DE, Emery B, et al. Lateralized expression of cortical Perineuronal nets during maternal experience is dependent on MECP2. *eNeuro*. 2020;7(3). doi:10.1523/ENEURO.0500-19.2020

84. Febo M, Numan M, Ferris CF. Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. *J Neurosci*. 2005;25(50):11637-11644. doi:10.1523/JNEUROSCI.3604-05.2005

85. Febo M, Stolberg TL, Numan M, Bridges RS, Kulkarni P, Ferris CF. Nursing stimulation is more than tactile sensation: it is a multisensory experience. *Horm Behav*. 2008;54(2):330-339. doi:10.1016/j.yhbeh.2008.02.024

86. Ferris CF, Kulkarni P, Sullivan JM, Harder JA, Messenger TL, Febo M. Pup suckling is more rewarding than cocaine: evidence from functional magnetic resonance imaging and three-dimensional computational analysis. *J Neurosci*. 2005;25(1):149-156. doi:10.1523/JNEUROSCI.3156-04.2005

87. Blazquez Freches G, Chavarrias C, Shemesh N. BOLD-fMRI in the mouse auditory pathway. *Neuroimage*. 2018;165:265-277. doi:10.1016/j.neuroimage.2017.10.027

88. McCarthy MM, vom Saal FS. The influence of reproductive state on infanticide by wild female house mice (*Mus musculus*). *Physiol Behav*. 1985;35(6):843-849. doi:10.1016/0031-9384(85)90248-3

89. Isogai Y, Wu Z, Love MI, et al. Multisensory logic of infant-directed aggression by males. *Cell.* 2018;175(7):1827-1841. doi:10.1016/j.cell.2018.11.032

90. Kohl J, Autry AE, Dulac C. The neurobiology of parenting: a neural circuit perspective. *Bioessays.* 2017;39(1):e201600159. doi:10.1002/bies.201600159

91. Pawluski JL, Li M, Lonstein JS. Serotonin and motherhood: from molecules to mood. *Front Neuroendocrinol.* 2019;53:100742. doi:10.1016/j.yfrne.2019.03.001

92. Yukinaga H, Hagihara M, Tsujimoto K, et al. Recording and manipulation of the maternal oxytocin neural activities in mice. *Curr Biol.* 2022;32(17):3821-3829.e6. doi:10.1016/j.cub.2022.06.083

93. Inada K, Hagihara M, Tsujimoto K, et al. Plasticity of neural connections underlying oxytocin-mediated parental behaviors of male mice. *Neuron.* 2022;110(12):2009-2023. doi:10.1016/j.neuron.2022.03.033

94. Olazábal DE. Role of oxytocin in parental behaviour. *J Neuroendocrinol.* 2018;30(7):e12594. doi:10.1111/jne.12594

95. Rickenbacher E, Perry RE, Sullivan RM, Moita MA. Freezing suppression by oxytocin in central amygdala allows alternate defensive behaviours and mother-pup interactions. *eLife.* 2017;6:e24080. doi:10.7554/eLife.24080

96. Elwood RW. Inhibition of infanticide and onset of paternal care in male mice (*Mus musculus*). *J Compar Psychol.* 1985;99(4):457-467. doi:10.1037/0735-7036.99.4.457

97. McCarthy MM, Vom Saal FS. Inhibition of infanticide after mating by wild male house mice. *Physiol Behav.* 1986;36(2):203-209. doi:10.1016/0031-9384(86)90004-1

98. Perrigo G, Belvin L, Vom Saal FS. Time and sex in the male mouse: temporal regulation of infanticide and parental behavior. *Chronobiol Int.* 1992;9(6):421-433. doi:10.3109/07420529209064554

99. Topilko T, Diaz SL, Pacheco CM, et al. Edinger-Westphal peptidergic neurons enable maternal preparatory nesting. *Neuron.* 2022;110(8):1385-1399.e8. doi:10.1016/j.neuron.2022.01.012

100. Ghazanfar AA, Schroeder CE. Is neocortex essentially multisensory? *Trends Cogn Sci.* 2006;10(6):278-285. doi:10.1016/j.tics.2006.04.008

101. Wallace MT, Ramachandran R, Stein BE. A revised view of sensory cortical parcellation. *Proc Natl Acad Sci.* 2004;101(7):2167-2172. doi:10.1073/pnas.0305697101

102. Stein BE, Stanford TR. Multisensory integration: current issues from the perspective of the single neuron. *Nat Rev Neurosci.* 2008;9(4):255-266. doi:10.1038/nrn2331

103. Garner AR, Keller GB. A cortical circuit for audio-visual predictions. *Nat Neurosci.* 2022;25(1):98-105. doi:10.1038/s41593-021-00974-7

104. Gilday OD, Mizrahi A. Learning-induced odor modulation of neuronal activity in auditory cortex. *J Neurosci.* 2023;43(8):1375-1386. doi:10.1523/JNEUROSCI.1398-22.2022

105. Okabe S, Nagasawa M, Kihara T, et al. Pup odor and ultrasonic vocalizations synergistically stimulate maternal attention in mice. *Behav Neurosci.* 2013;127(3):432-438. doi:10.1037/a0032395

106. Numan M, Stolzenberg DS. Medial preoptic area interactions with dopamine neural systems in the control of the onset and maintenance of maternal behavior in rats. *Front Neuroendocrinol.* 2009;30(1):46-64. doi:10.1016/j.yfrne.2008.10.002

107. Numan M. Medial preoptic area and maternal behavior in the female rat. *J Comp Physiol Psychol.* 1974;87(4):746-759. doi:10.1037/h0036974

108. Olazábal DE, Pereira M, Agrati D, et al. Flexibility and adaptation of the neural substrate that supports maternal behavior in mammals. *Neurosci Biobehav Rev.* 2013;37(8):1875-1892. doi:10.1016/j.neubiorev.2013.04.004

109. Kohl J, Babayan BM, Rubinstein ND, et al. Functional circuit architecture underlying parental behaviour. *Nature.* 2018;556(7701):326-331. doi:10.1038/s41586-018-0027-0

110. Smith CD, Holschbach MA, Olsewicz J, Lonstein JS. Effects of noradrenergic alpha-2 receptor antagonism or noradrenergic lesions in the ventral bed nucleus of the stria terminalis and medial preoptic area on maternal care in female rats. *Psychopharmacology.* 2012;224(2):263-276. doi:10.1007/s00213-012-2749-2

111. Fang YY, Yamaguchi T, Song SC, Tritsch NX, Lin D. A hypothalamic midbrain pathway essential for driving maternal behaviors. *Neuron.* 2018;98(1):192-207.e10. doi:10.1016/j.neuron.2018.02.019

112. Lecca S, Congiu M, Royon L, et al. A neural substrate for negative affect dictates female parental behavior. *Neuron.* 2023;111:1094-1103. doi:10.1016/j.neuron.2023.01.003

113. Bosch OJ, Neumann ID. Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. *Horm Behav.* 2012;61(3):293-303. doi:10.1016/j.yhbeh.2011.11.002

114. Numan M, Bress JA, Ranker LR, et al. The importance of the basolateral/basomedial amygdala for goal-directed maternal responses in postpartum rats. *Behav Brain Res.* 2010;214(2):368-376. doi:10.1016/j.bbr.2010.06.006

115. Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol.* 1980;14(2–3):69-97. doi:10.1016/0301-0082(80)90018-0

116. Alsina-Llanes M, Olazábal DE. Prefrontal cortex is associated with the rapid onset of parental behavior in inexperienced adult mice (C57BL/6). *Behav Brain Res.* 2020;385:112556. doi:10.1016/j.bbr.2020.112556

117. Bizley JK, Jones GP, Town SM. Where are multisensory signals combined for perceptual decision-making? *Curr Opin Neurobiol.* 2016;40:31-37. doi:10.1016/j.conb.2016.06.003

118. Otero-García M, Agustín-Pavón C, Lanuza E, Martínez-García F. Distribution of oxytocin and co-localization with arginine vasopressin in the brain of mice. *Brain Struct Funct.* 2016;221(7):3445-3473. doi:10.1007/s00429-015-1111-y

119. Navarro-Moreno C, Barneo-Muñoz M, Ibáñez-Gual MV, et al. Becoming a mother shifts the activity of the social and motivation brain networks in mice. *iScience.* 2022;25(7):104525. doi:10.1016/j.isci.2022.104525

120. Contestabile A, Casarotto G, Girard B, Tzanoulinou S, Bellone C. Deconstructing the contribution of sensory cues in social approach. *Eur J Neurosci.* 2021;53(9):3199-3211. doi:10.1111/ejn.15179

121. de la Zerda SH, Netser S, Magalnik H, et al. Social recognition in laboratory mice requires integration of behaviorally-induced somatosensory, auditory and olfactory cues. *Psychoneuroendocrinology.* 2022;143:105859. doi:10.1016/j.psyneuen.2022.105859

122. Komura Y, Tamura R, Uwano T, Nishijo H, Ono T. Auditory thalamus integrates visual inputs into behavioral gains. *Nat Neurosci.* 2005;8(9):1203-1209. doi:10.1038/nn1528

123. Vetere G, Tran LM, Moberg S, et al. Memory formation in the absence of experience. *Nat Neurosci.* 2019;22(6):933-940. doi:10.1038/s41593-019-0389-0

124. Numan M, Young LJ. Neural mechanisms of mother-infant bonding and pair bonding: similarities, differences, and broader implications. *Horm Behav.* 2016;77:98-112. doi:10.1016/j.yhbeh.2015.05.015

125. Franks B, Champagne FA, Curley JP. Postnatal maternal care predicts divergent weaning strategies and the development of social behavior. *Dev Psychobiol.* 2015;57(7):809-817. doi:10.1002/dev.21326