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# Dynamic developmental changes in neurotransmitters supporting infant attachment learning

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## ABSTRACT

Infant survival relies on rapid identification, remembering and behavioral responsiveness to caregivers' sensory cues. While neural circuits supporting infant attachment learning have largely remained elusive in children, use of invasive techniques has uncovered some of its features in rodents. During a 10-day sensitive period from birth, newborn rodents associate maternal odors with maternal pleasant or noxious thermo-tactile stimulation, which gives rise to a preference and approach behavior towards these odors, and blockade of avoidance learning. Here we review the neural circuitry supporting this neonatal odor learning, unique compared to adults, focusing specifically on the early roles of neurotransmitters such as glutamate, GABA (Gamma-AminoButyric Acid), serotonin, dopamine and norepinephrine, in the olfactory bulb, the anterior piriform cortex and amygdala. The review highlights the importance of deepening our knowledge of age-specific infant brain neurotransmitters and behavioral functioning that can be translated to improve the well-being of children during typical development and aid in treatment during atypical development in childhood clinical practice, and the care during rearing of domestic animals.

## 1. Introduction

It has long been known that there is something unique about learning and remembering during infancy (i.e., first 3–4 weeks postpartum in rodents and lagomorphs, and first 11 months postpartum in humans) as evidenced by the extremes in learning and memory, including infantile amnesia and profound enduring memories throughout life in humans (Capinha et al., 2021; Chua and Downes, 2000; Cunha et al., 2014; Marta-Simões et al., 2022; Meltzoff A.N., 1995; Spahn et al., 2019; West and Bauer, 1999) and other mammals (Alberini and Travaglia, 2017; Josselyn and Frankland, 2012; Madsen and Kim, 2016; Rincón-Cortés et al., 2015). Learning early in life plays a major role in the adaptation of young to the changing environment, including adjustment of key behaviors involved in mother-young attachment, social behavior and feeding (locating nipples and milk intake). However, data concerning the neurobiological bases of early learning remain today limited in animals as well as in humans, and more importantly there is insufficient

integration and summary of this data into a framework of age-specific neurobiology of learning.

Historically, infant learning differences have been attributed to an immature brain: many brain structures and neurotransmitter systems used in adult learning are not integrated into learning until later life (Carver et al., 2000; Hayne, 2004; Káldy and Sigala, 2004; Rovee-Collier and Cuevas, 2009; Josselyn and Frankland, 2012; Travaglia et al., 2018). Equally important is the consideration that learning in early life requires some unique skills and neural features to support infant-specific behaviors (Abrous et al., 2022; Callaghan et al., 2019; Debiec and Sullivan, 2017; Lin and Wilbrecht, 2022; Svalina et al., 2022). This is a critical point that warrants more attention because understanding the infant-specific neurobiology and cognition can make it possible to develop applications that optimize for instance the attachment of infants to their mothers, and the health and well-being of human infants born at term or prematurely, and other animals domesticated or living in captivity.

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In terms of age-specific sensory learning, odor learning is particularly relevant because many mammalian infants use odor cues to locate and interact with the mother, including humans, lagomorphs, felids and rodents, i.e., altricial species with limited sensory and motor abilities at birth with dependence on parents for survival (Faust et al., 2020)), and ungulates, i.e., precocial species more developed at birth (Levy and Nowak, 2017). If in certain species newborns can respond to particular odor signals in a predisposed (i.e., not learned) way, as it has been demonstrated for the mammary pheromone in the rabbit (Coureaud et al., 2010; Schaal et al., 2003), all mammalian neonates (i.e. from altricial and precocial species) can learn novel odors before and/or after birth (Logan et al., 2012; Schaal and Orgeur, 1992). The cross-species analysis of the biological bases of early odor learning therefore takes on its full meaning, and can help to overcome remaining shortcomings with regard to early learning in general and its consequences for infants.

Here, to complement the existing reviews on network level changes in the development of odor learning (Boulanger Bertolus et al., 2016; Raine et al., 2010; Ross and Fletcher, 2019; Sullivan and Opendak, 2020; Mota-Rojas et al., 2022), we focus our review on the dynamic neurotransmitter changes that occur as the infant learning gradually transitions to adult learning. To that goal, our strategy is to mainly focus on rodents but regularly translate to humans when possible, and at the end to present another animal species, the rabbit, which is not entirely dependent upon learning for survival but can be used as a model due to its remarkable abilities to learn.

In terms of organization of the review, we begin by describing the changing ecological demands on newborn learning as they morph from dependency upon the parent for survival to complete independence. Then, we focus on the neurobiology of odor learning on core brain areas highlighted in the literature as important for infant learning and how this connects with infant ecological niche and survival. We progress through the odor pathway (olfactory bulb, piriform “olfactory” cortex, amygdala), while focusing on norepinephrine (NE) and its source the locus coeruleus (LC), dopamine (DA), glutamate and GABA. Then, we review how this system changes as pups transition to independence and adult learning. Finally, we propose future directions in the field, including possible applications and translations, and defend the interest of carrying out additional work in species to date less studied than rodents and humans, such as rabbits.

## 2. Changing ecological niche of the infant as they become less dependent on the parent requires an equally dynamic corresponding learning system

### 2.1. Attachment to the caregiver in human and nonhuman newborns

Infancy is a transitional developmental period for mammals, as the dependent newborn abruptly transitions from intrauterine dependence

on the mother to the outside world, and then slowly transitions into an independent organism capable of survival, including self-feeding and rudimentary skills at self-protection, which continues past weaning through adolescence. To support our cross-species approach, as illustrated in Fig. 1, we align maturational milestones between children and infant rodents, such as the emergence of crawling, self-distancing from the caregiver, and known major transitions in learning (Callaghan et al., 2019).

At birth, human neonates learn using a system biologically tuned to sensory stimuli associated with people, such as the sound of voices, touch, odors and the parent’s face (Anunziata et al., 2020; Delaunay-El Allam et al., 2006; Fifer, 1981; Porter and Winberg, 1999; Schaal et al., 2000; Sullivan et al., 2011). The system is also primed by experience as *in utero*, the unborn infant hears the parent’s voices and smells the mother’s odor signature defined by her major histocompatibility complex and diet (Logan et al., 2012; Pedersen et al., 1986; Pedersen and Blass, 1982; Sullivan et al., 1990). At birth, this learning expands to all sensory systems and a greater specificity quickly emerges as the infant learns to specifically orient to people doing the caregiving. Within days of birth, the infant shows a preference for the caregiver’s sensory cues and is more easily soothed by this person (including an adoptive parent), or just one sensory quality of the caregiver, such as their odor (DeCasper and Fifer, 1980; Sullivan and Toubas, 1998). From an evolutionary perspective, it seems that the infant begins to express specific prosocial behaviors towards the caregiver, which engages the caregiver to nurture and protect. Finally, cultural diversity in parenting is seen across the globe in rituals and procedures to interact with young babies, which range from minimal touching to highly interactive nurturing parents, all of which supporting attachment learning (Hrdy, 1999). In other words, the quality or specific type of care does not appear to determine attachment learning, although variations in caregiving alters the quality of the prosocial behaviors towards the attachment figure, most notably under acute stress (Ainsworth and Bell, 1970). For children, there is very limited understanding of the neural basis of attachment learning, nor for the neuroscience of expression of prosocial behaviors to the attachment figure. Furthermore, while there are reviews on human attachment expression (e.g., Hofer, 2003; Strathearn, 2007; Gee, 2022; Tabachnick et al., 2022), the potential neural mechanisms supporting attachment learning in children has received little attention. One goal of this review is to better understand the phylogenetically preserved attachment system in rodents and use this information for clues to the neurobiology of early life infant learning.

On a behavioral level, nonhuman animal research has defined a similar dependence on learning to attach to the caregiver. Probably the most well-known example of rapid attachment learning is imprinting in young birds, which also illustrates the unique features of reward during early life (Bateson, 1966; Gottlieb, 1965; Hess, 1959; Hinde, 1962; Lorenz, 1935). Indeed, the reward supporting this post-hatching avian

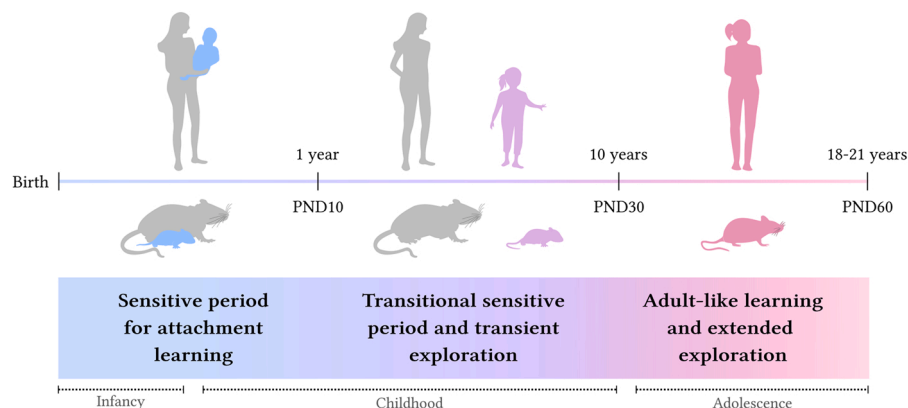


Fig. 1. Cross-species alignment of attachment learning throughout developmental periods.

learning is movement by the parent (or inanimate object) and the learned attachment behavior consists of following the moving object, suggesting this learning does not evoke preparatory responses to the reward, but rather unleashes biological prosocial attachment behaviors that greatly enhance the receiving of protection and nurturing. Research about this avian imprinting phenomenon, along with nonhuman primate research from the Harlow lab on infant-mother interactions (van der Horst et al., 2008), was important in formulating human Attachment Theory - a theoretical approach that has had a major impact on human developmental research and child rearing (Bowlby, 1969, 1991). Specifically, rapid attachment learning shown in nonhuman primates (Harlow and Harlow, 1966; Mason and Mendoza, 1998; Salzen, 1967) highlighted unique features of reward: it was not the milk but the caregiver's behavior that was the major reward supporting attachment learning (similarly to movement and not food in avian imprinting) (Harlow and Harlow, 1966). While early nonhuman primates research suggested infants needed nurturing care for attachment learning and maintenance, this paradigm shifting research went on to show that both nurturing and abusive caregiving supported attachment learning and maintained the learned prosocial behaviors towards the caregiver, although aberrant behaviors emerged (Kaffman et al., 2021; Suomi, 1995).

## 2.2. Rodent pup attachment learning behavior

This attachment learning also occurs in infant rodents, which has been useful in defining cross-species behavioral similarity and the supporting neural mechanisms. In infant rodents, attachment learning depends on olfaction, with vision and audition maturation functionally delayed for the first couple of postnatal weeks. During birth, the odor of amniotic fluid and the maternal odor fill the nest, and the birth of each pup is associated with somatosensory stimulation from maternal warmth, handling and grooming. This individual sensory stimulation by the mother critically supports pups' learning of the maternal odor (see below). Once all the pups are born, the mother retrieves and nudges pups into the nest, which is facilitated by pups orienting to the newly learned maternal odor. The mother grooms and adjusts pups and the nest, but soon lays down and pups independently engage in nipple searching and latch onto the nipple for mostly non-nutritive nursing with periodic brief milk ejections. The mother spends most of her time in the nest, but terminates a nursing bout to leave the nest and take care of her needs.

This infant odor learning is critical for pups' immediate survival: without the learned maternal odor, pups will not approach the mother and will have difficulty latching onto the nipple even when placed in direct contact. In rodents, the maternal odor is not a pheromone but an odor dependent upon the maternal diet, which means that eating new foods alters some chemical components of the mother's odor and require that pups again engage in learning the modified maternal odor (Leon, 1992). Thus, pups' learning system must enable them to learn (maternal) odors in a rapid and robust way, ensuring attachment prosocial behaviors towards the attachment figure that provides access to care and food.

Due to phylogenetically preserved attachment systems across mammalian species, investigating the neural basis of rodent neonatal learning can potentially provide a better understanding of general features of attachment neurobiology. As research explores the circuit, the olfactory based rodent attachment learning to the caregiver provides a relatively more simple experimental framework to define causal mechanisms. Indeed, extensive progress has been made primarily due to techniques that measure and manipulate acute neural processes to define causal mechanisms that go beyond the correlations established in human children research.

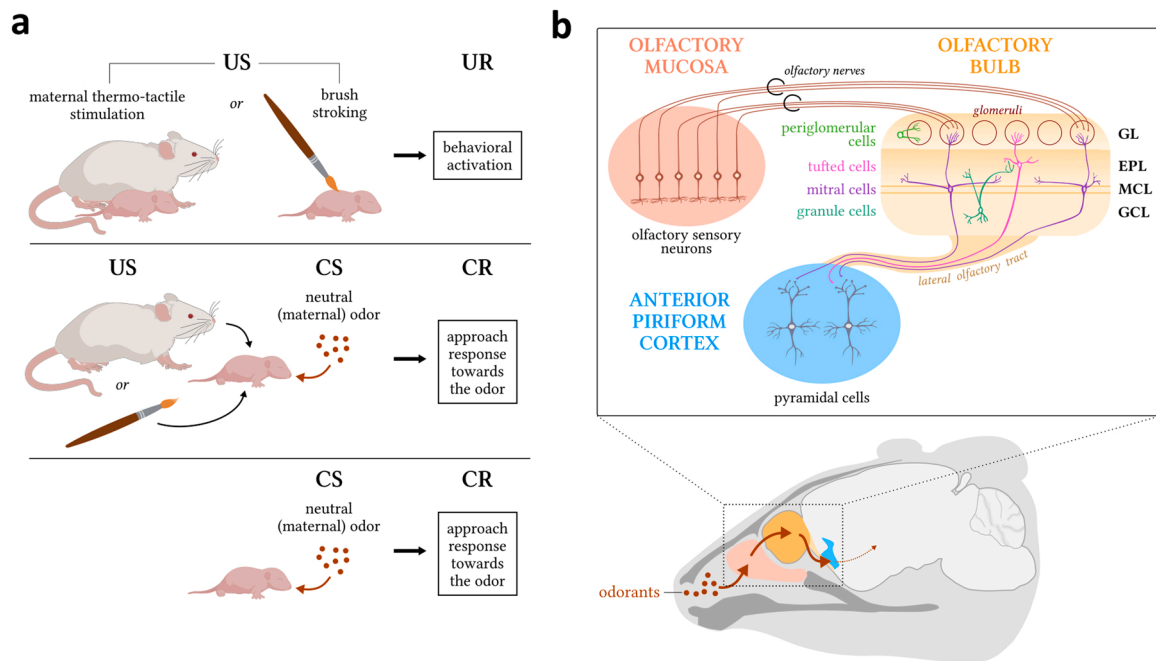
## 3. Infancy and unique features of olfactory classical conditioning

Early infant learning relies on a memory process called first-order associative learning or Pavlovian classical conditioning. In this process, an initially neutral stimulus (conditioned stimulus, CS) is associated with a reward (unconditioned stimulus, US) that elicits an unconditioned response (UR). After repeated exposures to CS+US, the CS elicits a conditioned response (CR), which is generally similar to the UR or prepares for the arrival of the reward (Dickinson and Mackintosh, 1978). This process in the infant rodent, while adhering to the basic rules of classical conditioning, does not exactly fit this framework. Yes, the conditioned association between an initially neutral odor, such as a novel odor or a maternal odor (CS) and reward, such as maternal thermo-tactile stimulation or milk (US), triggers a preference for this odor, as evidenced by approach behavior (Fig. 2a) (while comparatively, unpaired CS-US presentations do not support learning). However, CS-US pairings support attachment learning, not preparatory responses to the US. As noted earlier, avian imprinting and mammalian attachment learning do not prepare the infant for the reward or evoke CR similar to the reward; rather, it evokes the expression of prosocial attachment behaviors and nipple grasping required for suckling. This ecological phenomenon has been artificially reproduced across labs. For instance, by exposing newborn rats to a neutral odor and pairing it with a reward, such as stroking with a brush to mimic maternal grooming, is sufficient to produce the complex response to the learned odor that permits pups to express prosocial behavior towards the mother and nipple attachment (Pedersen et al., 1982; Sullivan and Hall, 1988). The ability to replicate attachment learning outside the nest has provided a framework to define the neurobiology of infant learning and its importance in supporting pups' role in procuring nurturing and protection.

A wide variety of stimuli function as an appetitive learning, including aversive stimuli. Until postnatal day 10 (PND 10), a wide variety of US's, including painful or aversive stimuli, support pup odor preference/attachment learning (Camp and Rudy, 1988). Specifically, with respect to classical conditioning, pups do not appear to differentially categorize aversive and appetitive events: stimuli traditionally categorized as appetitive, such as milk, support learning but so do painful stimuli (Camp and Rudy, 1988; Haroutunian and Campbell, 1979; Pedersen and Blass, 1982; Sullivan and Hall, 1988). For example, in adults and older pups (>PND10) odor-0.5 mA shock (or tail pinch) pairing (fear/threat conditioning) supports odor aversion learning, yet, in younger pups (<PND10), this same conditioning paradigm supports infant odor preference learning and produces a new maternal odor that serves to support prosocial behaviors and nipple latching (Sullivan et al., 2000a). Finally, stimuli with no rewarding value in older pups, such as tactile stimulation termed "stroking", which mimics maternal grooming, robustly supports attachment learning until pups are around PND10.<sup>1</sup>

Together this research suggests that newborns have an increased ability to learn approach response but a decreased probability of learning aversion response to odor stimuli during this developmental period until PND 10, called the sensitive period for attachment. Importantly, even during normal interactions, the rodent mother can step unintentionally on her pups when entering and leaving the nest, but despite this the pups must learn to approach her for their survival. This paradoxical behavior of neonates may therefore have a crucial adaptive role for them by preventing to avoid maternal odors and would thus

<sup>1</sup> A caveat to this fear learning failure is that young pups can learn to avoid odors as early as the fetal period, provided malaise induction by high shock (above 1 mA) or lithium chloride injection (inducing a gastric malaise) is used as the reward. While this learning engages the amygdala in adolescent and adult rats, rat pups younger than 21-day-old do not use the amygdala, and this learning relies on plasticity within the olfactory bulb and piriform cortex; Raineke et al. (2009).



**Fig. 2.** First-order associative olfactory learning in newborn rodents. (a) During first-order olfactory conditioning, newborn rodents are exposed to an initially neutral (maternal) odor (conditioned stimuli, CS) associated with maternal thermo-tactile stimulation or brush stroking (unconditioned stimulus, US) that elicit behavioral activation (unconditioned response, UR). This association produces a preference for this odor and an approach response towards it (conditioned response, CR). (b) Neural olfactory circuit supporting associative olfactory learning. Odor information is transmitted from the olfactory sensory neurons of the nose's olfactory mucosa towards specific glomeruli of the olfactory bulb's glomerular layer (GL). In this layer, the sensory neurons interact with the axons of the bulb's primary output neurons, mitral and tufted cells. Their interaction is modulated by inhibitory cells, including periglomerular cells. Major odor processing continues within the bulb's mitral cell layer (ML), in which GABAergic inhibition occurs again. At both of these bulb layers, extensive extrinsic modulation by neurotransmitters and hormones from the rest of the brain and body modulate the bulb's output signal to upper regions of the brain, such as the anterior piriform cortex.

ensure attachment to their caregiver regardless of the quality of interactions between the partners.

*Some effect of CS-US pairings differ between infants and adults.* Variation in the timing of CS-US pairings known to affect learning in adult rodents, in general, appear to differentially influence learning in infant pups. For example, pre-exposure to the odor CS before classical conditioning (latent inhibition), as well as uncorrelated CS and reward presentations (learned irrelevance), both of which retard/inhibit learning in adults, either enhance or have no effect on the young infant rat's learning (Rescorla, 1967; Siegel and Domjan, 1971; Campbell and Spear, 1972; Hoffmann and Spear, 1988; Rescorla, 1988; Spear and Rudy, 1991; Stanton et al., 1998; Stanton, 2000; Rush et al., 2001). Also, trace or sequential conditioning, involving a trace interval between the CS and the reward, is difficult for very young individuals and becomes more efficient with age in human infants (Cuevas and Giles, 2016) and young animals (Barr et al., 2003; Chen et al., 1991; Cheslock et al., 2003).

#### 4. Neurobiology of infant attachment learning: the role of neurotransmitters

Infants learn on the first days of life and, as reviewed above, this age-specific infant learning is maintained for the first 9 days of life in rat pups. Yet, brain areas well-known to support learning and memory in older pups and adults do not participate in young pups. For example, the amygdala supports fear/threat learning at PND10 (Sullivan et al., 2000), the hippocampus supports passive avoidance at PND17 (Alberini and Travaglia, 2017; Travaglia et al., 2018) and short- and long-term contextual fear memory at PND18 (Stanton, 2000; Stanton et al., 2021) and PND23 (Raineke et al., 2010a), while the prefrontal cortex is involved in extinction learning around PND18 (Callaghan and Richardson, 2011; Kim et al., 2009; Li et al., 2012). Unique functioning of infant circuits mediates this learning, with the locus coeruleus (LC) signaling reward equally for shock and stroking as part of the

attachment learning circuit, while the inability of threat/fear learning to engage the amygdala supporting infant lack of fear conditioning (Raineke et al., 2010b). There are myriad existing reviews for learning in infant at the system level and this will therefore not be reviewed here (Callaghan et al., 2019; Lee et al., 2020). We will instead focus on the unique role of neurotransmitters in discrete brain structures crucial for infant odor learning.

##### 4.1. Infant odor processing in the olfactory bulb

###### 4.1.1. The key role of glutamate and dopamine within the olfactory bulb

One of the major actors in the circuit for infant rat learning is the main olfactory bulb (OB), where the association between the CS odor and the US occurs. For odors to reach the main OB, odorant molecules must enter the nasal cavity and bind on odorant receptors located on olfactory sensory neurons, which are part of the olfactory mucosa. As illustrated in Fig. 2b, these sensory neurons gather to form the olfactory nerves, and the ones that express the same receptors converge onto a specific glomerulus in the main OB. The OB is a laminar structure in which mitral and tufted cells, the main outputs of the OB, process the incoming odorant information and relay that information to upper regions of the brain such as the anterior piriform cortex. Mitral/tufted cells activity is modulated by two types of inhibitory interneurons: granule cells through GABA<sub>A</sub> receptors in the external plexiform layer of the OB, and periglomerular cells through GABA<sub>B</sub> receptors in the glomerular layer of the OB (Okutani et al., 2003). Most of the odorant processing occurs in two layers of the OB, the glomerular and the mitral cell layers, with both intrinsic and extrinsic neurotransmitters being important in this processing.

Within the glomeruli, the olfactory nerves carrying odor information activate mitral/tufted cells through excitatory glutamatergic synapses (Chen and Shepherd, 1997; Ennis et al., 1996; Murphy et al., 2004; Vaaga and Westbrook, 2016). Activation of glutamate receptors on these



cells play a critical role in odor input processing and subsequent olfactory learning in adults (Moran et al., 2021), but also in newborns. Systemic and intrabulbar injection of an antagonist of the glutamate N-Methyl-D-Aspartate receptor (NMDAR) disrupt infant odor preference learning (Lethbridge et al., 2012; Weldon et al., 1997), and NMDAR are activated in odor-specific glomeruli during odor learning, but down-regulated after training. 24 h after odor conditioning, NMDAR composition is significantly modified and associated with lesser synaptic plasticity. Plasticity seems thus to be reduced following neonatal olfactory learning, which may help memory consolidation and stability by preventing further synaptic change (Lethbridge et al., 2012).

In contrast, short-term (3 h) and long-term (24 h) neonatal odor preference memory is supported by an increase of another glutamate receptor, the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), evidenced by phosphorylation of GluA1 subunit of AMPAR after conditioning and GluA1 insertion in synapses of the OB glomeruli (Cui et al., 2011; Lethbridge et al., 2012). AMPAR membrane insertion in the glomerular layer of the OB has also been recently shown to mediate the odor specificity of olfactory appetitive memory (Modarresi et al., 2016). The causal relationship between neonatal olfactory memory and GluA1 distribution in the OB has been further supported by a study that examined the impact of epigenetics on olfactory appetitive learning (Bhattacharya et al., 2017). Histone deacetylase inhibition in OB of newborn rats increased GluA1 expression 48 h and 5 days after odor conditioning, and extended odor preference memory from 24 h to 9 days. The authors hypothesized that extended odor memory was supported by a protracted expression of the AMPAR (Bhattacharya et al., 2017). Plasticity of glutamate NMDA and AMPA receptors in the OB are thus essential for specific neonatal olfactory learning and memory by contributing to the excitation of mitral/tufted cells (Fig. 3), which seems to be also a main feature of olfactory learning in adult mammals (see for instance Sánchez-Andrade et al., 2005).

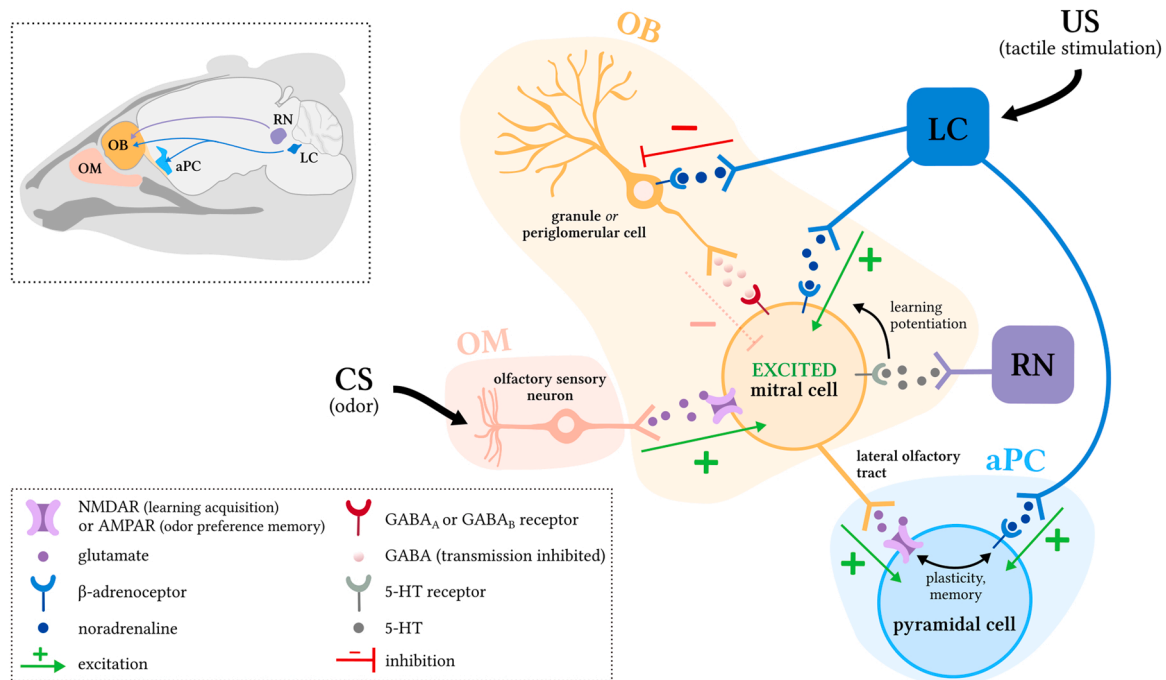
Interestingly, the mammalian OB also contains a vast population of

interneurons producing dopamine (DA) known to modulate GABAergic inhibition, thus increasing odor discrimination (Brüning et al., 1999). Previous studies have suggested that DA could also participate in newborn odor learning. Indeed, DA release increases in the OB of newborn rats during olfactory appetitive conditioning (Coopersmith et al., 1991), and activation of DA receptor D1 is necessary for odor appetitive learning (Weldon et al., 1991). It has long been suggested that there are no centrifugal DA projections into the OB (Shipley and Ennis, 1996) but recent evidence challenge this assumption and suggest that, at adulthood, DA input from midbrain to the OB are present and ablation of this DA pathway modified OB activity and impaired olfactory-driven behaviors (Höglinger et al., 2015; Zhang et al., 2019). According to the late functional maturation of the projections from midbrain DA system (Voorn et al., 1988; Naneix et al., 2012), it seems unlikely that these DA input to the OB would be functional at birth and could play a role in early olfactory learning. Therefore, the role of DA in newborn odor learning deserves to be further explored.

#### 4.1.2. Norepinephrine inputs to the olfactory bulb mediate reward processing

The neural support for young pups' reward signal is via a singular noradrenergic input coming from the locus coeruleus (LC) to the OB's mitral cells at the mitral cell layer (ML), which are primary output neurons leaving the bulb (Fig. 3). Norepinephrine (NE) appears to be a key neurotransmitter in this learning circuit.

The first months of life are characterized by exceedingly high NE levels (Candito et al., 1993; Lagercrantz, 1996), low stress hormone levels, and an amygdala absent from the trauma response, which are the conditions that support cross-species behavioral attachment learning, such as learned proximity to the caregiver regardless of the quality of care (Goksan et al., 2015; Sullivan and Lasley, 2010). For example, learning the maternal odor can be mimicked in young human infants by pairing a novel odor with stimuli engaged in parental care (i.e. touch),



**Fig. 3.** Neurotransmitters involved in associative odor learning. The upper insert shows the extrinsic inputs from the raphe nuclei (RN) and locus coeruleus (LC) to the olfactory circuit. Odor information (conditioned stimulus, CS) is transmitted from olfactory sensory neurons of the olfactory mucosa (OM) to mitral cells of the olfactory bulb (OB) through excitatory glutamate synapses. Tactile information (unconditioned stimulus, US) is transmitted from the LC to mitral cells through excitatory noradrenergic synapses. The LC also indirectly activates mitral cells by inhibiting GABAergic granule or periglomerular cells of the OB. Serotonergic inputs from the RN facilitate noradrenergic action and thus potentiate associative odor learning. Mitral cells send glutamatergic projections to pyramidal cells of the anterior piriform cortex (aPC) through the lateral olfactory tract. US processing is also mediated by LC noradrenergic inputs to pyramidal cells. Pyramidal cells are thought to associate norepinephrine activation with glutamate input to support aPC plasticity and odor memory.

inducing a preference for this odor (Sullivan et al., 1991b). NE levels is correlated with olfactory learning performance in human infants: plasma levels of NE at birth were shown to be higher in babies who showed a preference for a familiar odor than for babies who did not display any preference (Varendi et al., 2002).

In rodents, systemic and intra-OB manipulation of NE using receptor agonists and antagonists, as well as direct manipulation of the LC, have shown that noradrenergic system activation is both necessary and sufficient for olfactory conditioning in newborns (Langdon et al., 1997; McLean and Shipley, 1991; Sullivan et al., 1989, 1991a, 1992, 1994, 2000b; Shakhawat et al., 2012; Yuan, 2009). The LC presents unique hyperfunctioning and responsivity during the sensitive period: direct electrophysiological recording of the fetal and newborn LC have shown robust and prolonged (20–30 s) LC responses to noxious and pleasant tactile stimuli leading to large NE release; and the infant LC fails to habituate to repeated presentations of sensory stimuli (Kimura and Nakamura, 1985; Nakamura et al., 1987; Nakamura and Sakaguchi, 1990).

The LC is the sole source of NE for the OB with approximately 40% of LC neurons projecting to the OB (Shipley et al., 1985). At the mitral cell layer, NE directly activates mitral cells by binding to  $\beta$ -adrenoceptors (Yuan et al., 2003) (Fig. 3), and the prolonged excitatory activity of mitral cells induces olfactory learning. NE also indirectly enhances the excitation of mitral cells by modulating the dendro-dendritic synapses between mitral cells and local inhibitory GABAergic cells (granule or periglomerular cells) (Lethbridge et al., 2012): NE inhibits GABAergic cells through  $\beta$ -adrenoreceptors and the decrease of GABA release onto mitral cells leads to a disinhibition of mitral cells (Fig. 3).

Regarding GABA and bulb disinhibition, this disinhibition is a crucial process for olfactory learning. Indeed, infusion of an agonist of GABA<sub>A</sub> or GABA<sub>B</sub> receptor (two types of GABA receptor expressed by mitral cells; Okutani et al., 2003) into the OB (mimicking enhanced inhibition) blocks olfactory learning (Okutani et al., 2003, 1999). Moreover, odor preference learning is associated with a decrease in Fos protein expression in granule GABAergic cells, indicating a decrease in their activity (Roth and Sullivan, 2005). Furthermore, the degree of mitral cells disinhibition determines the type of learning that occurs. Indeed, a moderate disinhibition of mitral cells induced by a low dose of intrabulbar GABA<sub>A</sub> antagonist infusion (concomitant odor presentation) produces a preference for the odor in pups older than 10 days (Okutani et al., 1999). However, a stronger disinhibition provoked by a high dose of GABA<sub>A</sub> or GABA<sub>B</sub> antagonist infusion induces an odor aversion (Okutani et al., 1999, 2003). Such high-dose of antagonist causes non-specific odor aversion, probably, in part, because it provokes non-physiological activation of mitral cells disrupting odor-specific patterns of activity (Okutani et al., 2002, 2003). Thus, olfactory learning in rat pups is modulated through GABAergic neurotransmission. Injection of NE or GABA<sub>A</sub> and GABA<sub>B</sub> receptor antagonists can act as US to support appetitive or aversive olfactory learning (Okutani et al., 1999, 2003; Sullivan et al., 2000b).

Neonatal associative odor learning is thus mediated by the pairing between olfactory nerve stimulation and intrabulbar  $\beta$ -adrenoceptor activation generated by the processing of olfactory input (CS) and unconditioned stimulus (US), respectively. This pairing potentiates mitral cell firing through direct glutamate and NE activation, but also indirectly through the decrease of GABAergic inhibitory cells activity onto mitral cells (Lethbridge et al., 2012) (Fig. 3).

#### 4.1.3. Serotonin inputs into the olfactory bulb potentiate the NE-dependent odor learning

Besides NE, the OB receives additional extrinsic inputs that alter the excitation/inhibition balance and impact olfactory learning. Dense serotonin (5-HT) inputs from the raphe nuclei are detected in all layers of the rat OB during the first postnatal week (McLean and Shipley, 1987). Intrabulbar 5-HT depletion impairs appetitive olfactory learning in newborn rats, indicating that 5-HT is required in the OB for normal

olfactory learning (McLean et al., 1993). Intrabulbar 5-HT<sub>2</sub> receptor (a type of 5-HT receptor) is also necessary for the acquisition of appetitive olfactory learning, but not for the consolidation or retrieval of learning (McLean et al., 1996).

However, a stronger than normal NE input can induce odor learning in intrabulbar 5-HT-depleted newborns, indicating that NE can bypass 5-HT action (Langdon et al., 1997). Conversely, injection of 5-HT<sub>2</sub> receptor agonist does not induce odor learning, evidencing that 5-HT<sub>2</sub> receptor activation alone does not act as a US (Price et al., 1998). Thus, 5-HT seems to play a modulatory role in newborn olfactory learning whereas NE is sufficient and necessary for that learning. Furthermore, NE  $\beta$ -adrenoceptors and 5-HT<sub>2A</sub> colocalize and interact mainly in OB mitral cells. 5-HT has thus been suggested to facilitate the direct NE action on mitral cells during the processing of US information (Yuan et al., 2003). Therefore, odor learning is promoted by the interaction between NE, 5-HT and olfactory information inputs in mitral cells (Fig. 3). Thus infant learning is dependent upon NE but can be modulated by 5-HT.

#### 4.2. Newborn olfactory learning also relies on the anterior piriform cortex

The OB is not the only brain structure activated during neonatal odor learning. Indeed, this is also the case of the anterior piriform cortex (aPC). The aPC receives odor information from the primary OB output neurons (mitral cells) through the lateral olfactory tract, and sends feedback inputs from its pyramidal cells back to OB granule cells (Boyd et al., 2012). The aPC is altered in young pups learning as indicated by increased of neuronal activity markers, such as Fos protein expression and 2-deoxyglucose uptake, during odor preference learning in newborn rat (Raineke et al., 2009; Roth and Sullivan, 2005) potentially specific to the aPC pyramidal cells (Shakhawat et al., 2014). The aPC is also known to have extensive noradrenergic innervations (Fallon and Moore, 1978) that appear important in neonatal odor learning. The association between odor and  $\beta$ -adrenergic excitation directly in the aPC induces odor preference in newborns, whereas aPC silencing or  $\beta$ -adrenoceptors blockage during conditioning impairs this learning even with a functional OB (Morrison et al., 2013). The aPC is thus both necessary and sufficient for newborn olfactory appetitive learning, and US processing seems to require NE release from the LC to both the OB and the aPC.

Glutamate also seems to play a crucial role in the aPC. On the one hand, blocking NMDAR in the aPC during conditioning prevents odor appetitive learning (Morrison et al., 2013). Furthermore,  $\beta$ -adrenoceptor activation enhances glutamate release from the lateral olfactory tract to the aPC and enhances NMDAR-dependent long-term potentiation (LTP, a form a synaptic plasticity enhancing communication between neurons) (Morrison et al., 2013). Thus, NMDAR are thought to mediate the aPC plasticity promoted by  $\beta$ -adrenoceptor. Moreover, NMDAR activation in aPC has recently been shown to allow stimulus-specific encoding of short- and long-term odor memory. The authors have suggested that pyramidal cells NMDAR associate odor-induced glutamate input with NE activation to support odor-specific memory encoding (Mukherjee and Yuan, 2016). On the other hand, glutamate AMPAR seem to mediate the persistence of neonatal olfactory memory, similarly to what have been described in the OB. Responsiveness of aPC cells to OB inputs is prolonged from 24 h to 48 h after a multiple training odor conditioning, which extends the duration of odor memory. This aPC responsiveness is mediated by AMPAR, and enhanced AMPAR responses to odor input in the aPC correlates with the duration of neonatal olfactory memory (Fontaine et al., 2013).

In summary, olfactory appetitive learning in newborns is mediated by neural changes and plasticity in the first two brain structures of the olfactory circuit: the OB and the aPC. Norepinephrine and glutamate are crucial in both structures (Fig. 3).

## 5. Transitional sensitive period: neurobiological changes as the infant matures

Around postnatal day 10, classic features of sensitive period have terminated in rodents. For example, after PND 10, tactile stimulation loses its reinforcing value and fails to provoke odor learning as a US (Woo and Leon, 1987). Moreover, if pups are alone, odors associated with moderately painful stimuli (i.e., foot shock or tail pinch) now produce an amygdala-dependent aversion (Moriceau and Sullivan, 2006; Roth and Sullivan, 2005; Sullivan et al., 2000a). From an ecological perspective, pups begin to crawl outside the nest (Bolles and Woods, 1964), and thus the younger nest-bound learning system with a bias towards preference learning might no longer be adaptive. Indeed, without the protection of the mother and nest, pups venturing outside the nest potentially require a consequence-bound learning system that supports a more robust avoidance system.

### 5.1. Norepinephrine-dependent learning transitions due to maturation of the LC and learning

At postnatal day 10, the LC become more adult-like, including a robust reduction in NE release upon sensory stimuli, as well as the emergence of habituation to repetition of sensory stimuli (Kimura and Nakamura, 1985; Nakamura et al., 1987; Nakamura and Sakaguchi, 1990). Specifically, the LC becomes less sensitive to tactile stimuli due to an increase in auto-inhibitory  $\alpha 2$ -adrenoceptors and a decrease in auto-excitatory  $\alpha 1$ -adrenoceptors, which alters LC firing patterns and reduces NE release (Nakamura et al., 1987). Thus, the age-dependent decrease in effectiveness of tactile stimuli to be used as a US might be due, at least partially, to a decrease in their ability to activate the LC. Importantly, if NE is artificially increased in PND10 and older pups, either through systemic, intra-OB or LC stimulation, NE's ability to support pups' approach and attachment learning is reinstated (Moriceau and Sullivan, 2004a). This confirms that the termination of the sensitive period is not due to a lack of sensitivity to NE but to LC's maturation leading to a reduction in NE release.

However, NE action in the aPC seems to evolve during the transitional sensitive period. Indeed, age-dependent modulations of aPC pyramidal cells by NE have been recently demonstrated in newborn mice (Ghosh et al., 2015). As expected, odor-stroke pairing induces olfactory preference learning in PND8 but not in PND14 pups, and this learning is mediated by  $\beta$ -adrenoceptors. Interestingly, NE modulates aPC pyramidal cells in an age-dependent and dose-dependent manner. At a low dose, NE induces pyramidal cells excitation in PND8–11 pups through  $\beta$ -adrenoceptors but not after PND14. At a higher dose, NE promotes pyramidal cells inhibition for all pups, and this effect is not impaired by  $\beta$ -adrenoceptor blockade (at least in PND8–11 mice). Because noradrenergic  $\alpha 1$ -adrenoceptor can mediate the excitation of GABAergic neurons in aPC and OB, the authors have proposed that these receptors also mediate the inhibitory effects of NE in the aPC (Ghosh et al., 2015). Thus, the transitional sensitive period is characterized by developmental changes in NE action in the aPC. During the sensitive period, pyramidal cells are suggested to undergo an increased NE excitation and a reduced NE inhibition. At the end of this period, changes in NE action could be mediated by an increase in  $\alpha 1$ -adrenoceptor and/or a decrease in  $\beta$ -adrenoceptor expression or function.

### 5.2. Pyramidal cells maturation and GABAergic transmission in the anterior piriform cortex

Combinations of electrophysiological measurements and computational simulations of newborn olfactory learning have shown recently that more pyramidal cells from the aPC are responding to the maternal odor and they present a higher responsiveness to this odor before PND10 than after (Oruro et al., 2020a). This could contribute to the robust learning of the maternal odor during the sensitive period. The authors

have proposed two main reasons explaining this higher activation of pyramidal cells. First, pyramidal cells undergo maturational changes during the first postnatal weeks that modify their intrinsic electric properties. For instance, pyramidal cells have a lower threshold for inputs from the OB during the sensitive period, meaning that weaker depolarizing currents can generate action potentials (Oruro et al., 2020a). Second, in vitro electrophysiology experiments in newborns have proven that GABAergic inputs to aPC pyramidal cells are stronger after PND10 than before PND10, suggesting that the aPC of older neonates would present an enhanced inhibitory function (Pardo et al., 2018). Moreover, the effect of GABAergic transmission in the aPC changes with age. During the sensitive period, GABA input depolarizes aPC pyramidal cells instead of hyperpolarizing them, which amplifies their response to the maternal odor (Oruro et al., 2020b). Thus, GABAergic synapses would actually be excitatory during the sensitive period and potentiate maternal odor learning. However, activation of aPC GABA<sub>A</sub> receptors through the use of agonist infusion impairs the acquisition and expression of odor preference learning before PND10 (Morrison et al., 2013). This paradoxical result could be explained by the fact that an agonist infusion is equivalent to a global simultaneous activation of all GABAergic synapses, which is not a physiological situation. This massive increase in GABAergic depolarizing inputs could then have an inhibitory effect instead of an excitatory effect on pyramidal cells, through an adaptation of their firing properties.

Therefore, maturational characteristics of the GABA synapses combined to pyramidal cells maturation in the aPC could promote a transient high responsiveness of the OB-aPC circuit to the maternal odor, and thus contribute to the boundary of the sensitive period in newborns.

### 5.3. Functional emergence of the amygdala into pup fear learning and the role of corticosterone

At PND 10, pairing of an odorant CS and a shock (0.5 mA) now produces avoidance of the odor and freezing (immobility) during its presentation. This fear learning is dependent on the functional emergence of the amygdala into the learning circuit, as indicated by increased activity of the basolateral complex of the amygdala, measured by Fos and 2-deoxyglucose, and impairment of this fear learning by amygdala suppression (Sullivan et al., 2000a; Roth and Sullivan, 2005; Raineke et al., 2009; Moriceau and Sullivan, 2006). The termination of the sensitive period and pain-induced preference at PND10 is further supported by the stress neurohormone corticosterone (CORT), which plays a critical role in the amygdala-dependent fear learning. Indeed, this learning is blocked when PND10–14 pups' CORT level is pharmacologically lowered (Sullivan and Opendak, 2021), and can be induced in pups as young as PND6 (naturally low CORT levels) if CORT levels are pharmacologically increased or naturally increased by a fearful mother (Moriceau et al., 2006; Debiec and Sullivan, 2014).

A brief summary of pups' developing CORT stress system places these results into ecological relevance. In pups, trauma-induced CORT level slowly increases from PND1 to reach adult level by weaning around PND21. This slowing maturing stress system has been referred to the stress hyporesponsive period, a developmental period when trauma does not mount a stress response, which ends at PND 10 when stress hormones reach a level to alter brain and behavior (Dallman et al., 1987; Levine, 2001; Rosenfeld et al., 1992; Walker et al., 1991). As the stress hyporesponsive period ends, and trauma (i.e. shock) elevates stress hormones sufficiently to support amygdala-dependent fear conditioning, maternal presence can completely block pups' stress hormone release until PND16, thus extending the period of preventing amygdala-dependent aversion learning (Barr et al., 2009; Levine, 2001; Moriceau and Sullivan, 2006; Shionoya et al., 2007). The maternal signal appears to prevent the hypothalamic-pituitary-adrenal axis from being engaged by attenuating the NE release from the brain stem A2 onto the hypothalamic paraventricular nucleus (Shionoya et al., 2007).

CORT, which is released peripherally and has wide brain effects, is



functioning as a neurotransmitter engaging plasticity mechanisms within the amygdala to support fear learning, but producing altered neural responses throughout the brain. At a more local circuit level, pup DA is known to be altered by the mother and maternal presence blocks shock-induced DA release into the amygdala (Andersen et al., 1992; Barr et al., 2009; Opendak et al., 2021; Tamborski et al., 1990). DA appears to work in concert with CORT within the amygdala, where maternal presence blocks the DA and CORT response to shock during conditioning and the changes of AMPA receptor subunit expression critical for learning (Opendak et al., 2019).

This “social blockade” of fear is in contrast to “social buffering” in adults and older pups (beginning at PND16): social buffering does not impede fear learning but attenuates the level of fear. Furthermore, there are two exceptions when the mother does not block pup fear: 1) a fearful mother releasing the fear pheromone increases pups stress hormones and pups learn fear (Debiec and Sullivan, 2014) and 2) early life adversity prematurely increases pups’ CORT levels, enables the emergence of amygdala-dependent fear learning (Moriceau and Sullivan, 2004b) and prevents maternal presence from disengaging learning-induced changes in AMPA receptor subunit expression, because DA and CORT responses were not blocked by maternal presence (Opendak et al., 2019).

This coexistence of newborn and adult-like learning systems with the control switch regulated by maternal presence presumably provides an adapted learning system for dependence of the mother as a protector vs. a system of emerging self-protection by engaging amygdala-dependent fear.

Importantly, this age-specific maternally controlled switch of infant learning (aversion vs. preference) has recently been replicated in young children, indicating that animal research had identified an important cross-species feature of attachment (Tottenham et al., 2019). Maternal presence has also been shown to block amygdala activation as measured by fMRI in young children (Gee et al., 2014; Jessen, 2020), and replicates have been obtained in nonhuman animal research, including the guinea pig, rodents and nonhuman primates (Hennessy et al., 2009; Sullivan and Perry, 2015). This strongly suggests a homologous system across species at both the behavioral and amygdala level and suggests a cross-species bridge for translation of basic research to a better understanding of unique age-specific developmental processes in children.

## 6. Future directions

Understanding the neurobiological pathways functional early in life can help developing applied strategies to improve health and well-being in humans and domesticated animals. Development can be characterized by transitions in behavioral systems as the ecological niche changes from dependence on the parent to independence and we highlight transitions in learning across early development in underlying neurotransmitters as scaffolding these behavioral transitions. Considering behavioral transitions have been highlighted as period of vulnerability and emergence of dysfunction, understanding these transitions can be important for optimizing typical development and intervening to repair atypical development. This is particularly important in childhood clinical intervention during insecure or disorganized attachment, where compromised learning about the caregiver could be partially responsible for prosocial behavioral deficits. Furthermore, although less often highlighted in the literature, farm animal species can face significant neonatal mortality, suggesting a better understanding of the biological supports of attachment learning could allow proposing novel or adapted procedures to promote better survival and growth. This may include improvement of attachment to the mother, adoption by an unfamiliar lactating female (teats odorized with the conditioned odor stimuli), or familiarization to an object delivering food (feeder odorized with the conditioned odor stimuli).

Importantly, the generalization of model species allowing further and complementary investigations of these issues should be increased.

For instance, the rabbit may offer relevant opportunities to compare biological basis of attachment learning in a species in which some physiological/behavioral needs are *similar* to other altricial species - e. g., interaction with the mother, success in gaining milk, improved adaptation through learning - but also *different*. Indeed, rabbit pups are exposed only once and briefly per day (< 5 min) to their mother visiting the nest (Coureaud et al., 2010) and find the nipples and suck by displaying a typical orocephalic behavior in response to the mammary pheromone (MP; 2-methylbut-2-enal) emitted by rabbit mothers (Coureaud, 2001; Schaal et al., 2003; Coureaud et al., 2010). Responsiveness to the MP appears hard-wired, i.e., it is not learned before or after birth (Schaal et al., 2003; Schneider et al., 2016). Strikingly, the MP functions also as a reinforcer: rabbit pups exposed in a single and brief trial (5 min) to a new odor paired with the MP learn that odor and respond 24 h later to it by displaying the orocephalic behavior (Coureaud et al., 2006, 2014; Duchamp-Viret et al., 2021). Such MP-induced odor learning influences milk intake and social preferences (Patris et al., 2008; Jouhannau et al., 2016). Compared to rodent and human neonates, one may wonder whether rabbit pups present similar or different neurobiological mechanisms favoring fast odor learning. Preliminary results indicate that the noradrenergic system regulates odor learning through modulation of OB and aPC activation in rabbit pups as previously reported in rodent pups (Morrison et al., 2013; Shakhawat et al., 2012; Sullivan et al., 1989, 1991a, 1992, 2000b; Yuan, 2009). Indeed, systemic injection of  $\beta$ -adrenoceptors antagonist blocked both MP-induced odor memory formation as well as odor learning-induced OB and aPC activation (Ducourneau et al., in prep.) suggesting that the noradrenergic system could be a conserved neural system in neonatal odor learning in all mammals. Moreover, taking advantage of the recent demonstration of effective sensory preconditioning (based on incidental associations between neutral odors) in this neonatal model (Coureaud et al., 2013, 2022), future experiments will allow to compare the role of different neuromodulatory systems in neonatal reinforced versus non-reinforced (incidental) odor learning.

## 7. Conclusion

The child is not an immature version of the adult. Instead, the neurobehavioral learning system is specifically adapted to the age-specific behavioral expression and age-specific environment. How the neurobiology of learning changes to adapt to environment fluctuations induced by maturation is an important topic that has implications for education and child rearing. Here we have reviewed age-specific features of early life learning and its support by age-specific changes in mechanisms associated with neurotransmitters to illustrate age-specific transitions in learning. An essential message to highlight is that there is both consistency and inconsistency in learning across the life span: basic classical conditioning remains intact across the life span, but there are also age-specific differences in conditioning that are critical for age-specific adaptive interactions with the mother-infant environment (e.g. reward). These learning changes are supported by a dynamic, changing neurotransmitter system that permits adjustment of the organism to internal and external variations.

We suggest that our understanding of the neurobiology of infant learning in nonhuman animals is useful to understanding development in children. Indeed, the leading theoretical framework of infant attachment, Bowlby’s Attachment Theory, is heavily influenced by nonhuman animal research across species, including infant rodents, birds, nonhuman primates and we argue for further species diversity in translation, including lagomorphs such as the rabbit to provide greater model diversity. In addition, a better knowledge of the neurobiology of learning and underlying neurotransmission system also has possible applications in nonhuman animals in terms of breeding and welfare. The topic thus forms a cross-species unifying theme for attachment learning in early life, with consequent biological, economic and societal issues.

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