Title: Enhanced maternal behaviors in a mouse model of congenital blindness

Short running title: Maternal behaviors in blind mice

Nouhaila Bouguiyoud[1,2], Wen Bin Xie[1], Gilles Bronchti[1], Johannes Frasnelli[1,2], &
Syrina Al Aïn[1,2]

[1] Department of Anatomy, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada
[2] CogNAC Research Group, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada

*Corresponding author: Syrina Al Aïn, Université du Québec à Trois-Rivières, 3351, boul. des Forges, C.P. 500, Trois-Rivières, QC G9A 5H7, Canada. E-mail: Syrina.Alain@uqtr.ca

Acknowledgments: This work was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) (2017-06942).

Abstract

In mammals, mothering is one of the most important pro-social female behavior to promote survival, proper sensorimotor and emotional development of the offspring. Different intrinsic and extrinsic factors can initiate and maintain these behaviors, such as hormonal, cerebral, and sensory changes. Infant cues also stimulate multisensory systems and orchestrate complex maternal responsiveness. To understand the maternal behavior driven by complex sensory interactions, it is necessary to comprehend the individual sensory systems by taking out other senses. An excellent model for investigating sensory regulation of maternal behavior is a murine model of congenital blindness, the ZRDBA mice, where both anophthalmic and sighted mice are generated from the same litter. Therefore, this study aims to assess whether visual inputs are essential to driving maternal behaviors in mice. Maternal behaviors were assessed using three behavioral tests, including the pup retrieval test, the home cage maternal behavior test, and the maternal aggression test. Our results show that blind mothers: 1) took less time to retrieve their offspring inside the nest, 2) spent more time nursing and licking their offspring in the second-and third-week post-partum, and 3) exhibited faster aggressive behaviors when exposed to an intruder male, compared to the sighted counterparts. This study provides evidence that congenitally blind mothers show more motivation to retrieve the pups, care, and protection towards their pups than sighted ones, likely due to a phenomenon of sensory compensation.

Key words: Congenital blindness, maternal aggression, maternal behaviors, maternal motivation, mice.

1. Introduction

Extensive work over the past 50 years has explored mechanisms mediating caregiving/mothering behavior in a wide variety of model organisms spanning from fishes, reptiles, birds, to mammals (Bosh, 2013; Dulac et al., 2014; Kristal, 2009; Stolzenberg & Mayer, 2019). In most mammals, mothering is crucial for the survival, the optimal sensorimotor and emotional development of the offspring, as the mother is the primary contributor to ensuring care and protection (Bayerl & Bosch, 2019; Francis & Meaney, 1999; González-Mariscal & Poindron, 2002; Klampfl & Bosch, 2019; Meaney, 2001; Schaal et al., 2009). It appears that a core maternal circuit is widely conserved across several species (Numan & Insel, 2003). In rodents, the mother displays a constellation of maternal behaviors, defined by three major components: (1) maternal motivation to retrieve pups into the nest, (2) maternal care, and (3) maternal aggression (Bayerl & Bosch, 2019; Klampfl & Bosch, 2019; Numan & Woodside, 2010). More precisely, (1) maternal motivation, referring to an internal process that changes the way an individual responds to specific external stimuli (Pfaff, 1982), was classically assessed by using the pup retrieval test, (2) maternal care consists of nest building, arching/crouching over pups for facilitating access to their nipples/milk, licking/grooming to help them to urinate/defecate, and (3) maternal aggression is defined as protecting pups against predators or threatening intruders (Bayerl & Bosch, 2019; Klampfl & Bosch, 2019). All these maternal behaviors ensure the dietary, energy, thermal, and safety needs of the newly born (Bosh, 2011; Caughey et al., 2011; González-Mariscal & Poindron, 2002). These coordinated maternal behaviors are regulated by intrinsic factors, such as a variety of sensory and neuroendocrine changes during the gestation and postnatal period (Lonstein et al., 2015; Rosenblatt et al., 1979; Stern, 1989), and extrinsic factors, including pup exposure, female's reproductive life history, and the degree of sensorimotor maturity of the newly born (Poindron, 2005; Keller et al., 2019; Lévy & Keller, 2009). From the late gestation until the weaning period, all these changes operate in concert to rewire the brain and remodel the behavior of the female expressing a high level of maternal responsiveness towards sensory cues emanating from the offspring (Barrière et al., 2021; Numan & Insel, 2003; Rosenblatt & Lehrman, 1963; Stern & Lonstein, 2001; Stolzenberg & Champagne, 2016).

Accordingly, the integrity of the sensory channels of the mothers is required to detect their pups, easily localize them, nurse them, and protect them from predators and intruders (Gandelman et al., 1970; Noirot, 1969; Rosenblatt, 1967). Since rodents are macrosmatic animals, olfaction is the main sensory sense driving social behaviors (Brennan & Keverne, 2004; Swaney et al., 2008). The importance of individual sensory systems on maternal behavior regulation has been investigated by means of experimental alterations (deprivation of sensory inputs or lesion of sensory organs) or absence of the sensory systems. In rodents, *firstly*, (1: maternal motivation to retrieve pups into the nest) the ability to retrieve the pups is mainly driven by olfactory cues emitted by offspring, as anosmia, congenitally or induced by olfactory bulb cauterization or by gene mutation, results in impaired pup retrieval in female mice (Fraser & Shah, 2014; Weiss et al., 2011) and rats (Beach & Jaynes, 1956). Ultrasonic vocalizations emitted when pups are displaced from the nest are also shown to facilitate pup localization and pup retrieval in mice (Noirot, 1965; Smotherman et al. 1974) and rats (Beach & Jaynes, 1956; Kenyon et al., 1983). However, one study demonstrated that female mice have identical retrieving behavior when put in the presence of live, dead or anesthetized pups (i.e. not emitting vocalizations) (Gandelman et al., 1970), suggesting that body movements and vocalizations of the pups are not necessary to elicit retrieving behavior. Visual inputs are also important since both peripherally and centrally blinded female rats retrieved their scattered young but did so more slowly compared to sighted ones (Beach, 1937; Beach & Jaynes, 1956). *Secondly*, (2: maternal care) it has been widely established in rodents that the onset and maintenance of maternal behaviors throughout the lactational period, including nest building, nursing or licking pups, are mainly regulated by olfactory cues (Gandelman et al., 1971$_{a;b}$; 1972; Fraser & Shah, 2014; Sato et al., 2010; Vandenbergh, 1973; Weiss et al., 2011) and tactile cues (Morgan et al., 1992; Stern, 1996; Stern & Johnson, 1990). Ultrasonic vocalizations may also help the mother to avoid accidentally stepping on the pups (Stern, 1997) and to adjust her nursing position or licking (Gaub & Ehret, 2005). Interestingly, making dams blind - by enucleating or suturing the rat mother's eyes after parturition - leads to increased maternal care: mothers spent twice as much time licking (Kolunie et al., 1994) and crouching over their pups compared to sighted ones (Herrenkohl & Rosenberg, 1972). *Thirdly*, (3: maternal aggression) research in rats showed that olfactory cues from the male intruder are crucial for eliciting maternal aggression (Ferreira et al., 1987; Kolunie & Stern, 1995; Mayer & Rosenblatt, 1993), conversely to visual or auditory inputs (Kolunie et al., 1994). Taken together, these findings highlight that the sensory regulation of maternal behavior can vary depending on the specific components of maternal behavior, the experimental procedure, and the tested sensory systems (Herrenkohl & Rosenberg, 1972; Lonstein et al. 2015; Stolzenberg & Mayer, 2019).

Whilst the sensory mechanisms underlying maternal behaviors have been investigated mostly through sudden and late-deterioration sensory systems in rodents, little work to date has explored the impact of early sensory deprivation on the expression of maternal responsiveness.

To our knowledge, no study has investigated the effect of early blindness on maternal behaviors in non-human animals despite the existence of various rodent models of early visual deprivation. Therefore, the aim of the current study is to examine the impact of early blindness on maternal responsiveness using a mouse model of congenital blindness (ZRDBA strain). We performed three different tests to study the three components of maternal behavior in congenitally blind and sighted mothers: (1; maternal motivation to retrieve pups into the nest) the pup retrieval test consisted in assessing the latency to localize pups and bring them back to the nest, (2; maternal care) the home cage maternal behaviors test during which the time spent nursing, interacting, or not interacting with pups was evaluated throughout the lactational period, and (3; maternal aggression) the maternal aggression test, consisting in quantifying the latency before the first attack and the frequency and time spent attacking a male intruder.

2. Materials and Methods

2.1. Animals

A total of 88 female mice of the ZRDBA strain, bred and housed in the animal facility of the University of Québec in Trois-Rivières, were used for this study. Among them, 20 congenitally blind and 20 sighted dams were assessed for the pup retrieval test, 12 blind and 12 sighted dams were used for the home cage maternal behaviors test, and 12 blind and 12 sighted dams were assayed for the maternal aggression test. These female mice (aged of 3,5 to 4,5 months) were initially paired with 12 males (2 females and 1 male/cage), and then housed individually after impregnation in polypropylene cages with wood shavings as bedding material for nest building. Daily weight gain measurements were performed to determine the pregnancy. The day of birth was considered postnatal day 0. All mice were housed under standard environmental conditions of 12h/12h light/dark cycle (light phase: 7:00-19:00 h) at a controlled room temperature (20-22°C and 40-60% humidity). Food and water were provided *ad libitum*. Experimental procedures and animal use were permitted by the animal care committee of the Université du Québec à Trois-Rivières (2017-S.A.1), in accordance with the guidelines of the Canadian Council on Animal Care.

The ZRDBA strain has been generated by crossbreeding two strains: the sighted DBA-6 and the anophthalmic ZRDCT strains (Touj et al., 2019; 2021$_{a;b}$). The anophthalmic ZRDCT strain is characterized by an absence of the eyes, the optic tracts and the afferents retina-hypothalamus, induced by a mutation on chromosome 18 on the Rx/Rax gene (Chase & Chase, 1941; Tucker et al., 2001). Importantly, anophthalmic (Rx/Rax homozygous) ZRDBA mice are mated with sighted ZRDBA mice (Rx/Rax heterozygous) to produce half of the pups born with eyes and half of them born anophthalmic within the same litter.

2.2. Behavioral procedures

We tested three major components of maternal behaviors: maternal motivation to retrieve the pups, maternal care, and maternal aggression (Bayerl & Bosch, 2019; Klampfl & Bosch, 2019; Numan & Woodside, 2010). Each dam and her litter were tested in only one experimental test to avoid potential effects of maternal and/or pups' stress. All the recordings and coding were done using Ethovision XT software (Noldus, Virgina, USA).

2.2.1. Pup retrieval test

Behavioral experiments were carried out under dark conditions (i.e., red light) between 1 pm and 5 pm. The protocol for the pup retrieval test, adapted from Abel (1972) and Aguggia (2013), consists in assessing, in anophthlamic and sighted dams, the latency before retrieving their scattered pups into the nest on day 1, day 2 and day 3 postpartum. First, the mother was left in its own breeding cage 30 minutes prior to the test to allow it to habituate to the experimental room. Before the test, the mother was placed in an individual cage and four pups were lined up on the opposite side of the nest in the breeding cage. The recording was started once the female was put back in its empty nest and the time spent to retrieve the first pup and all the 4 pups into the nest was measured. The test lasted 15 minutes maximum. If females were unable to retrieve the pups, a score of 15 minutes was assigned.

2.2.2. Home cage maternal behavior test

The protocol, adapted from Skripuletz et al. (2010), consisted of video-recording maternal behaviors for 2 hours over 5 days. Given that mice are crepuscular creatures and are more active during dawn and dusk (Bains et al., 2018; Peirson & Foster, 2011; Peirson et al., 2018), the recordings were performed between 5-6 am and 9-10 pm. Maternal behaviors from anophthlamic and sighted females were analyzed on days 5, 10, 13, 16 and 19 postpartum (PD). A total of 6 behaviors were coded as follows: maternal behaviors design a) nursing behavior and b) mother-pup interactions in the nest (grooming and licking), while non-maternal behaviors refer to c) maternal presence in the nest with no social interaction, d) mother resting outside of the nest (resting or self-grooming), e) mother walking, and f) mother drinking/eating. The duration of maternal and non-maternal behaviors was compared between blind and sighted dams. No maternal-pup separation was performed before the test.

2.2.3. Maternal aggression test

The maternal aggression test took place on day 10 post-partum between 1 pm and 4 pm under dark conditions (i.e., red light). The highest levels of maternal aggression display were observed between 0 and 13^{th} post-partum days, after which it vanishes (Gandelman, 1972; Lonstein & Gammie, 2002). To avoid any potential infanticide by the male intruder (Vom Saal & Howard, 1982), all pups were removed from the nest prior to the tests (Lonstein & Gammie, 2002). After a 30 min habituation period, an unrelated adult male intruder (aged 2 months) was introduced into the female's home cage for a 3-min test. Intruder males were never used more than once, so any effect of previous aggression on the intruder mice was considered. Maternal attacks, referring to a female spontaneously biting or kicking the intruder (Martín-Sánchez et al., 2015), were quantified as follows: latency to the first attack, number of attacks, and total duration of attacks (Gammie & Nelson, 2001; Gammie et al., 2004).

2.3. Data analyses

Statistical analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY, USA). We verified the normal distribution of our data using the Shapiro-Wilk test. Regarding the pup retrieval test, we performed log-rank (Kaplan-Meier) tests to compare the distribution of the latencies to retrieve the first and the fourth pups of each of the 3 consecutive days (Postpartum Day (PD) 1, 2, 3) in both blind and sighted mothers. Then, we used mixed ANOVAs with *visual status* (2 levels: blind, sighted), as the between-subjects factor, and *day of testing* (3 levels: PD 1, 2, 3), as the within-subjects factor, to examine the improvement across time in both groups. Here, we compared the latency to retrieve the four pups between blind and sighted mothers.

Regarding the home cage maternal behavior test, we performed a mixed ANOVA with *visual status* (2 levels: blind, sighted), as the between-subjects factor, and *day of the testing* (3 levels: PD 1, 2, 3), as the within-subjects factor, to compare the durations of each behavioral parameter in both blind and sighted groups. When the interaction between factors was significant, Student's *t*-tests with appropriate control (Bonferroni post hoc) for multiple comparisons were applied to compare both groups on each day of the testing.

Regarding the maternal aggression test, we used Student's *t*-tests with appropriate control for multiple comparisons (Bonferroni) to compare the latency to the first attack, the number of attacks and total duration of attacks in blind and sighted mothers. For all statistical analyses, the significance level was set at $p < 0.05$.

3. Results

3.1. Pup retrieval test

As illustrated in Figure 1, Kaplan-Meier tests examined differences in the distribution of the retrieval latencies for the first and the fourth pups on 3 consecutive days postpartum (PD 1, 2 and 3) between blind and sighted mothers. On PD 1, the survival distributions of the latency to retrieve the first pup were significantly different between blind and sighted mothers ($\chi2[1] = 17.508$, $p < 0.001$), whereas the distribution to retrieve the fourth pup were similar in both groups ($\chi2[1] = 3.622$, $p = 0{,}057$). On PD 2, survival distributions of the latencies to retrieve the first and fourth pup (Fig. 4d) were significantly different between blind and sighted mothers ($\chi2[1] = 11.934$, $p < 0.001$ for pup 1 and $\chi2[1] = 5.345$, $p = 0.021$ for pup 4). On PD 3, blind and sighted dams differed significantly in the latencies to retrieve the first and fourth pups ($\chi2[1] = 17.462$; $p < 0.001$; $\chi2[1] = 11.431$, $p < 0.001$, respectively). Thus, blind dams showed shorter retrieval latencies than sighted dams for pup 1 at PD 1, 2 and 3 and for pup 4 at PD 2 and 3.

With regards to fourth-pup retrieval latencies (Figure 2), the ANOVA revealed a significant effect of *visual status* ($F(1, 38) = 10.962$; $p = 0.002$), and *day of testing* ($F(2, 76) = 28.494$; $p < 0.001$), but no interaction *visual status* * *day of testing* ($F(2, 76) = 0.445$; $p > 0.05$). Fourth pup retrieval efficiency improved from PD 1 to PD 2 ($p < 0.001$), PD 1 to PD 3 ($p < 0.001$), and PD 2 to PD 3 ($p = 0.043$).

3.2. Home cage maternal behaviors test

A) Mother nursing pups (Figure 3a): The ANOVA revealed significant effects of *visual status* ($F(1, 22) = 41.029$; $p<0.001$), *day of testing* ($F(4, 88) = 39.285$; $p<0.001$), and the interaction *visual status* * *day of testing* ($F(4, 88) = 5.117$; $p<0.001$). Blind dams spent more time nursing pups compared to sighted dams on PD 13 ($t = 3.929$, $p < 0.001$), 16 ($t = 6.570$, $p < 0.001$) and 19 ($t = 4.025$, $p < 0.001$) but not on the PD 5 ($t = 0.639$, $p > 0.05$) and PD 10 ($t = -0.171$, $p > 0.05$).

B) Mother-pup interactions in the nest (Figure 3b): There were significant effects of *visual status* ($F(1, 22) = 11.481$; $p = 0.003$), *day of testing* ($F(4, 88) = 2.798$; $p = 0.031$), and the interaction *visual status* * *day of testing* ($F(4, 88) = 4.648$; $p = 0.002$). Blind dams spent more time interacting with their pups in the nest compared to sighted dams on PD 13 ($t=5.138$, $p <0.001$) and 16 ($t = 3.933$, $p <0.001$) but not on PD 5 ($t = 0.251$, $p > 0.05$), 10 ($t= -0.502$, $p > 0.05$) and 19 ($t = 1.66$, $p > 0.05$).

C) Mother in the nest with no pups' interaction (Figure 3c): We found a significant effect of *day of testing* (F(4, 88) = 26.597 ; p<0.001), but not of *visual status* (F(1, 22) = 1.267; p = 0.272) nor the interaction *visual status * day of testing* (F(4, 88) = 1,391; p = 0.258). Bonferroni's post-hoc tests revealed significant differences between: 1) PD 5 and PD 13 / PD 16 / PD 19 (all p < 0.01), 2) PD 10 and PD 16 / PD 19 (p = 0.003 and p < 0.001, respectively), 3) PD 13 and PD 5/ PD 16 / PD 19 (p = 0.01; p = 0.031, p < 0 .001, respectively). This indicates that blind and sighted dams spent progressively more time in the nest with no pups interaction between PD 5 and PD 19.

D) Mother resting outside the nest (Figure 3d): the ANOVA yielded significant effects of *visual status* (F(1, 22) = 11.706 ; p = 0.002), *day of testing* (F(4, 88) = 18.764 ; p<0.001), and the interaction *visual status * day of testing* (F(4, 88) = 5.626 ; p<0.001). Sighted dams spent more time than blind ones resting outside the nest on PD 10 (t = -3.847, p<0.001), 13 (t = -3.043, p = 0.03) and 16 (t = -3628, p = 0.005), but no difference was observed on PD 5 (t = 0.238, p > 0.05) and 19 (t = 0.193, p > 0.05).

E) Mother walking (Figure 3e): There was no significant effect of *visual status* (F(1, 22) = 0.563; p = 0.461), *day of testing* (F(4, 88) = 1.408 ; p = 0.238), nor the interaction *visual status * day of testing* (F(4, 88) = 0.139 ; p = 0.967).

F) Mother drinking/eating outside the nest (Figure 3f)*:* There was a significant effect of *day of testing* (F(1, 88) = 6.046 ; p< 0.001), but not of *visual status* (F(1, 22) = 0.142 ; p = 0.710), nor the interaction *visual status * day of testing* (F(1, 88) = 2.283 ; p = 0.067). Bonferroni's post-hoc tests revealed significant differences between PD 10 and: 1) PD 16 (p = 0.042), and 2) PD 19 (p = 0.013). Bonferroni's post-hoc tests revealed significant differences between PD 13 and: 1) PD 16 (p = 0.005), and 2) PD 19 (p = 0.014). This indicates that blind and sighted dams spent progressively less time drinking/eating outside the nest between the second and the third week postpartum.

3.3. Maternal aggression test

Results are illustrated in Figure 4. Blind mothers exhibited the first attack faster when exposed to a male intruder (t(1, 22) = 3.664; p = 0.003). In contrast, the total duration (t(1, 22) = -1.274; p > 0.05) and frequency of attacks (t(1, 22) = -0.905; p > 0.05) towards a male intruder were similar between blind and sighted dams.

4. Discussion

The findings suggest that congenital visual deprivation results in heightened maternal behaviors on each of the three major components: (1) maternal motivation to retrieve pups into the nest, (2) care, and (3) aggression. *Regarding maternal motivation to retrieve pups,* we pointed out that blind mothers retrieved their pups to the nest faster than sighted ones. In addition, both blind and sighted dams retrieved faster their pups through the second and third trials, underlying similar learning abilities in this task. Our result is contrary to previous studies which have suggested that both peripherally or centrally blinded rat dams retrieved their pups more slowly than did sighted mothers (Beach, 1937; Beach & Jaynes, 1956). *Regarding maternal care,* we found that both blind and sighted females display high levels of maternal behaviors during the early post-partum period (PD 5), with 70% of the time nursing and liking the pups, which is consistent with previous research conducted on wild-type mice (Grota & Ader, 1974). On day 5 post-partum, when blind and sighted dams were not interacting with their pups in the nest, they spent the same time resting, walking, and eating/drinking outside the nest (6%-13%, respectively). On day 10 post-partum, both sighted and blind dams displayed similar nursing time reduction (with 50% of the time nursing the pups), associated with similar time spent resting in the nest and walking outside the nest. Additionally, sighted mothers exhibited higher time resting outside the nest than blind ones, while blind mothers tended to spend longer time eating/drinking outside the nest than their sighted counterparts. Whereas the time spent nursing the pups decreases gradually to 25% at the end of the third week postpartum in sighted ZRDBA dams, just like in wild-type dams (Grota & Ader, 1974), blind ZRDBA dams kept displaying a stable and high level of maternal behaviors until PD 19 (more than 60% of the time nursing and licking/grooming pups into the nest), and consequently, less time resting outside the nest during the second and third week postpartum (Day 13-19 postpartum). These results are in good agreement with previous findings obtained in enucleated and eyes-sutured female rats (Herrenkohl & Rosenberg, 1972; Kolunie et al., 1994). We, however, did not find any effect of the visual status on time spent resting in the nest with no mother-pup interaction, or eating/drinking and walking, ruling these mechanisms out as potential variables. *Regarding maternal aggression*, while duration and frequency of attacks toward a male intruder were similar between both groups, blind mothers initiated the first attack faster than their sighted counterparts. A previous study suggested that visual inputs from the pups or intruder are not essential to the expression of maternal aggression in rats, since blinded rat dams (by eyelid suturing on day 2 postpartum) displayed similar levels of maternal aggression one day after the procedure (Kolunie et al., 1994). Nevertheless, although the bite latency data were not statistically significant between dams temporarily deprived of visual or auditory input and controls, it is noteworthy to note that blind dams initiated the first bite of the intruder 2,5 times faster than controls and deaf dams.

The inconsistencies between our results and certain studies are likely due to differences in etiologies, onset, and duration of visual deprivation, resulting in different mechanisms of brain plasticity and subsequent behavioral adaptations. For most sensory systems, congenital and early sensory deprivation lead to much sensory compensation and higher brain reorganization than late and short visual deprivation (Chabot et al, 2007; Kujala et al., 1997; Piché et al., 2004; Qin et al., 2015; Slimani et al., 2014; Touj et al., 2021b).

Studies conducted on different murine models of early blindness (congenital, dark-reared housed, early enucleation) have established that early visual deprivation results in enhanced nonvisual sensory perception such as olfactory performance and pain sensitivity (Touj et al., 2019; 2020; 2021$_{a;b}$; Zhou et al., 2017) accompanied by enlargement of the olfactory areas (bulb and piriform cortex), auditory areas and amygdaloid complex volume (Massé et al., 2014; Touj et al., 2019; 2021a). Given that multisensory cues emitted by offspring are commonly used to trigger maternal responsiveness (retrieval, nursing) towards the pups (reviewed in Numan & Young, 2016; Numan & Isle, 2003; Dulac et al., 2014) and maternal aggression toward a threatening individual (Kolunie & Stern, 1995; Mayer & Rosenblatt, 1993), such sensory compensation may help congenitally blind dams to cope with the absence of visual inputs and to evolve behavioral adjustments toward the offspring. In other words, enhanced intact remaining modalities due to early visual deprivation, may explain the heightened maternal responsiveness seen in blind dams.

Additionally, as the pup retrieval and the maternal aggression tests were conducted under dark conditions, the faster responses displayed by blind dams toward the pups/intruder may be explained by their enhanced ability to navigate driven by non-visual sensory cues. In rodents, it has been shown that better odor perception and localization (in mice: Weiss et al., 2011; Fraser & Shah, 2014, in rats: Beach & Jaynes, 1956) and better sound acuity and spatial hearing (in mice: Noirot, 1965; Smotherman et al., 1974; in rats: Beach & Jaynes, 1956; Kenyon et al., 1983; Stern, 1990) may help mothers to efficiently retrieve their pups. In line with our results, several studies using the buried food test showed that blind rodents localized more quickly an appetent olfactory source than sighted congeners in our blinded ZRDBA mice (Touj et al., 2020), in dark-reared mice (C57BL6 strain) and in rats (Zhou et al., 2017). Accordingly, structural MRI and histological analyses conducted on the ZRDBA blind mice suggest that these behavioral/sensory adaptations may be supported by extended neuroplasticity, including enlargements of olfactory, auditory, orbital regions, amygdaloid complex and some cerebral regions mediated in navigation and spatial memory, such as fimbria-fornix and nuclei in mammillary bodies (Touj et al., 2020).

Moreover, enhanced attentional processes to respond to auditory and haptic stimuli have been evidenced in blind rodents. For example, while both blind and sighted rodents preferred exploring an attractive stimulus (ex: cage with pup, peanut butter, vanilla odor) against a neutral one (empty cage, water), blind animals spent more time exploring the attractive stimulus than sighted ones (congenitally blind mice: Touj et al., 2020; enucleated postpartumly rat: Beach & Jaynes, 1956) and less time smelling the negative odor (2MB odor) compared with sighted mice. These results indicate that early visual deprivation results in hypervigilance toward meaningful olfactory cues (appetent/rewarding or aversive/fearful).

Taken together, these findings suggest that enhanced non-visual sensory processing and/or attentional processing/awareness in congenitally blind mothers may promote enhanced maternal behaviors, leading to faster pup retrieval (motivation), higher caregiving in late lactation -2nd and 3rd week post-partum- (care), and faster aggressive responses toward an intruder (aggression). Another explanation can be proposed: increased activity and maternal-motivated behaviors in our test conditions may be explained by the endogenous circadian rhythm alteration induced by congenital blindness (Ramamurthy & Krubitzer, 2018; Iura & Udo, 2014). Although we assumed that blind mice may have synchronized their circadian rhythm with that of sighted mice as they are housed in the same breeding room under similar environmental conditions of 12h/12h light/dark cycle, future studies should investigate this question.

Interestingly, same results and mechanisms were found in humans. In the same vein, a large body of evidence showed that early blindness leads to superior perceptual processing in the remaining sensory modalities in humans, especially in audition, somesthesis and nociception (Slimani et al., 2013; 2014; 2015; Kupers & Ptito, 2011, 2014). Such enhanced performance on nonvisual tasks in blind humans is supported by intra-modal and cross-modal brain plasticity related to dramatical anatomical and functional changes (Voss & Zatorre, 2012; Kupers & Ptito, 2011, 2014; Zhang et al., 2019). With regards to olfaction, a meta-analysis showed no superiority of blind compared to sighted in humans, for olfactory identification, discrimination and threshold (Sorokowska et al., 2019), which are tasks that are typically used in clinical tests. While this seems to argue against the hypothesis of the present article, a recent study shows, inversely, a superiority of congenitally blind in the ecologically relevant olfactory tasks of odorant localization (Manescu et al., 2021). This is in line with earlier reports on audition in blind that suggest that ecological relevance is the key factor for crossmodal plasticity (Gougoux et al., 2004). As rodents' literature, behavioral adaptations were also reported in early blind women who displayed prolonged duration of breastfeeding beyond the first year postpartum, accompanied by increased physical contact/proximity and more frequent vocalizations toward their newborn (Chiesa et al., 2015; Ganea et al., 2018; Santos & Ribeiro, 2020; Thoueille et al., 2006). In addition, enhanced attentional processes to respond to auditory and haptic stimuli have been evidenced in blind humans, which may contribute to heightening non-visual sensory skills (Collignon & De Volder, 2009; Collignon et al., 2006; Hugdahl et al., 2004; Liotti et al., 1998; Pigeon et al., 2015; Topalidis et al., 2020). Visually impaired adults and children showed increased odor awareness and reactivity to smells, especially toward social and food odors (Beaulieu-Lefbvre et al., 2011; Ferdenzi et al., 2010). Overall, non-visual channels, such as olfactory, auditory, and somatosensory systems, are likely used more frequently to guarantee harmonic interaction despite the mother's impairment.

Multiple neural networks in brain areas, activated by both hormonal and environmental inputs, mediate maternal care/motivation and affective processing (Kim & Strathearn, 2016; Keyser-Marcus et al., 2001; Lee & Brown, 2002; Lonstein et al., 2015; Numan & Stolzenberg, 2009; Sato et al., 2010; Terkel et al., 1979; Uriarte et al., 2020), as well as maternal aggression (Bosch & Neumann et al., 2010; Gammie, 2005; Gammie & Nelson, 2001; Haller, 2018; Hasen & Gammie, 2005; 2006; Kohl et al., 2017). In rodents, the mPOA/BNST circuits are known to be involved in the onset and expression of maternal behavior and pup-associated motivation during the early period of lactation (Lee et al., 1999; 2022; Numan, 2007; Numan & Stolzenberg, 2009; Miceli et al., 1983; Oxley & Fleming, 2000; Petrulis, 2013; Semaan and Kauffman, 2010; Terkel et al., 1979; Tobiansky et al., 2013; McHenry et al., 2015 for review). Importantly, this core circuit has strong connections with the mesolimbic dopamine system, ventral tegmental area (VTA), nucleus accumbens (NA) and caudate putamen, involved in infant-related reward processing and in motivation (Barrière et al., 2021; Dong & Swanson, 2004; Dumont & Williams, 2004; Jalabert et al., 2009; Kudo et al., 2012; Numan, 2007; Numan & Numan, 1997; Numan & Stolzenberg, 2009; Tobiansky et al., 2013). Additionally, studies have reported that lactating female rodents expressing higher levels of maternal care and motivation had specific hypertrophies in regions involved in olfactory (MOB and AOB) and somatosensory (somatosensory cortex) information processing, in memory (hippocampus, entorhinal cortex, retrosplenial cortex) and in reward and reinforcement (striatum) processing (Barrière et al., 2021), and possess greater dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NA) (Shahrokh et al., 2010). It is worthy to note that the maternal behavior of female rodents is plastic and declines gradually until weaning, supported (in part) by a progressive mPOA and the mesolimbic dopamine system deactivation toward pup-related stimuli (Grieb et al., 2020; Pereira et al., 2009). Interestingly, high-resolution MRI and histological studies highlighted large-scale anatomical brain plasticity in the ZRDBA mice (Touj et al., 2020), in various sensory, limbic and cortical systems that regulate the expression of maternal behavior. Grey matter volume alterations induced by visual deprivation at birth were not only observed in the remaining sensory systems (olfactory, auditory, visual areas), but also in subcortical and cortical structures, such as in BNST and mPOA, anterior hypothalamic area, insular area, the central nucleus of the amygdala, overall amygdala volume, and nucleus accumbens. These volumetric differences within specific hormone-sensitive brain regions which regulate both maternal behaviors and affective processing may reflect the adaptation to the visual deprivation and the enhanced maternal motivation to retrieve the pups, care, and protection seen in anophthalmic dams. This neuroanatomical explanation should, however, be taken with caution as this research has been conducted on both males and non-lactating, anophthalmic and sighted mice.

Future studies should examine whether early visual deprivation may alter structural and functional plasticity, as well as specific maternal behaviors responsiveness, in late gestating and lactating females throughout the whole pre- and post-natal period. It is of particular interest to disentangle cellular and molecular mechanisms underlying anatomical/functional plasticity in anophthalmic mice, in terms of neural/glial cell number, neural/glial cell size, axon number, axonal arborization, synaptic density, myelination, blood flow modifications, hormonal/neurotransmitters levels and receptors' sensitivity/density (Barrière et al., 2019; Kelly et al., 2015; Zatorre et al., 2012). Furthermore, future immunoassay and neuroimaging/immunohistochemical investigations should investigate physiological (e.g., hormones/neurotransmitters) and neural circuits which support the enhanced maternal responsiveness in congenitally blind dams.

5. Conclusion

In the current study, a mouse model of congenital blindness, the ZRDBA strain, was used to assess potential behavioral adaptations induced by blindness in lactating females. The findings provide evidence that maternal performance is enhanced in congenitally blind dams, in terms of maternal motivation to retrieve the pups, care, and protection, underlined by: 1) a shorter latency to retrieve pups, 2) increased nursing/licking durations during the 2nd and 3rd week postpartum, and 3) a faster aggressive behavior toward a male intruder, compared to sighted mothers. These behavioral adaptations may be driven by sensory and attentional compensations, supported by dramatical cerebral plasticity induced by early visual deprivation. The present study reveals a profound impact of early visual deprivation on motherhood, paving the way for further physiological, anatomical and behavioral investigations to gain insight into the hormonal and neural circuits that regulate maternal responsiveness levels across the postpartum period.

REFERENCES

Abel, E. L. (1972). Suppression of pup retrieving behavior in rats following administration of L- 9-tetrahydrocannabinol. *Experientia*, *28*(10), 1187-1188. doi: 10.1007/bf01946160

Aguggia, J. P., Suárez, M. M., & Rivarola, M. A. (2013). Early maternal separation: neurobehavioral consequences in mother rats. Behavioural brain research, 248, 25–31. https://doi.org/10.1016/j.bbr.2013.03.040

Bains, R. S., Wells, S., Sillito, R. R., Armstrong, J. D., Cater, H. L., Banks, G., & Nolan, P. M. (2018). Assessing mouse behaviour throughout the light/dark cycle using automated in-cage analysis tools. Journal of neuroscience methods, 300, 37–47. https://doi.org/10.1016/j.jneumeth.2017.04.014

Barrière, D. A., Hamieh, A. M., Magalhães, R., Traoré, A., Barbier, J., Bonny, J. M., Ardid, D., Busserolles, J., Mériaux, S., & Marchand, F. (2019). Structural and functional alterations in the retrosplenial cortex following neuropathic pain. Pain, 160(10), 2241–2254. https://doi.org/10.1097/j.pain.0000000000001610

Barrière, D. A., Ella, A., Szeremeta, F., Adriaensen, H., Même, W., Chaillou, E., Migaud, M., Même, S., Lévy, F., & Keller, M. (2021). Brain orchestration of pregnancy and maternal behavior in mice: A longitudinal morphometric study. NeuroImage, 230, 117776. https://doi.org/10.1016/j.neuroimage.2021.117776

Bayerl, D. S., & Bosch, O. J. (2019). Brain vasopressin signaling modulates aspects of maternal behavior in lactating rats. Genes, brain, and behavior, 18(1), e12517. https://doi.org/10.1111/gbb.12517

Beach Jr, F. A. (1937). The neural basis of innate behavior. I. Effects of cortical lesions upon the maternal behavior pattern in the rat. *Journal of Comparative Psychology*, *24*(3), 393-440. doi: 10.1037/h0059606

Beach, F. A., & Jaynes, J. (1956). Studies of Maternal Retrieving in Rats. III. Sensory Cues Involved in the Lactating Female's Response to Her Young. *Behaviour*, *10*(1/2), 104-125.

Beaulieu-Lefebvre, M., Schneider, F. C., Kupers, R., & Ptito, M. (2011). Odor perception and odor awareness in congenital blindness. Brain research bulletin, 84(3), 206–209. https://doi.org/10.1016/j.brainresbull.2010.12.014

Bosch O. J. (2013). Maternal aggression in rodents: brain oxytocin and vasopressin mediate pup defence. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 368(1631), 20130085. https://doi.org/10.1098/rstb.2013.0085.

Bosch O. J. (2011). Maternal nurturing is dependent on her innate anxiety: the behavioral roles of brain oxytocin and vasopressin. Hormones and behavior, 59(2), 202–212. https://doi.org/10.1016/j.yhbeh.2010.11.012

Bosch, O. J., & Neumann, I. D. (2010). Vasopressin released within the central amygdala promotes maternal aggression. *The European journal of neuroscience*, 31(5), 883–891. doi: 10.1111/j.1460-9568.2010.07115.x

Brennan P.A., & Keverne E. B. (2004). Something in the air? New insights into mammalian pheromones. *Current Biology*;14:R81–R89. doi: 10.1016/j.cub.2003.12.052.

Caughey, S. D., Klampfl, S. M., Bishop, V. R., Pfoertsch, J., Neumann, I. D., Bosch, O. J., & Meddle, S. L. (2011). Changes in the intensity of maternal aggression and central oxytocin and vasopressin V1a receptors across the peripartum period in the rat. Journal of neuroendocrinology, 23(11), 1113–1124. https://doi.org/10.1111/j.1365-2826.2011.02224.x

Chabot, N., Robert, S., Tremblay, R., Miceli, D., Boire, D., & Bronchti, G. (2007). Audition differently activates the visual system in neonatally enucleated mice compared with anophthalmic mutants. The European journal of neuroscience, 26(8), 2334–2348. https://doi.org/10.1111/j.1460-9568.2007.05854.x

Chase, H. B., & Chase, E. B. (1941). Studies on an anophthalmic strain of mice I. Embryology of the eye region. *Journal of Morphology*, *68*(2), 279-301. doi: https://doi.org/10.1002/jmor.1050680205

Chiesa, S., Galati, D., & Schmidt, S. (2015). Communicative interactions between visually impaired mothers and their sighted children: analysis of gaze, facial expressions, voice and physical contacts. *Child care, health and development*, 41(6), 1040–1046. doi: 10.1111/cch.12274

Collignon, O., & De Volder, A. G. (2009). Further evidence that congenitally blind participants react faster to auditory and tactile spatial targets. Canadian journal of experimental psychology = Revue canadienne de psychologie experimentale, 63(4), 287–293. https://doi.org/10.1037/a0015415

Collignon, O., Renier, L., Bruyer, R., Tranduy, D., & Veraart, C. (2006). Improved selective and divided spatial attention in early blind subjects. Brain research, 1075(1), 175–182. https://doi.org/10.1016/j.brainres.2005.12.079

Dong, H. W., & Swanson, L. W. (2004). Projections from bed nuclei of the stria terminalis, posterior division: implications for cerebral hemisphere regulation of defensive and reproductive behaviors. The Journal of comparative neurology, 471(4), 396–433. https://doi.org/10.1002/cne.20002

Dulac, C., O'Connell, L. A., & Wu, Z. (2014). Neural control of maternal and paternal behaviors. Science (New York, N.Y.), 345(6198), 765–770. https://doi.org/10.1126/science.1253291

Dumont, E. C., & Williams, J. T. (2004). Noradrenaline triggers GABAA inhibition of bed nucleus of the stria terminalis neurons projecting to the ventral tegmental area. The Journal of neuroscience : the official journal of the Society for Neuroscience, 24(38), 8198–8204. https://doi.org/10.1523/JNEUROSCI.0425-04.2004

Ferdenzi, C., Coureaud, G., Camos, V., & Schaal, B. (2010). Attitudes toward Everyday Odors for Children with Visual Impairments: A Pilot Study. Journal of Visual Impairment & Blindness, 104(1), 55–59. https://doi.org/10.1177/0145482X1010400109

Fraser, E. J., & Shah, N. M. (2014). Complex chemosensory control of female reproductive behaviors. *PLoS One*, *9*(2), e90368. doi: 10.1371/journal.pone.0090368

Gammie S. C. (2005). Current models and future directions for understanding the neural circuitries of maternal behaviors in rodents. *Behavioral and cognitive neuroscience reviews*, 4(2), 119–135. doi: 10.1177/1534582305281086

Gammie, S. C., & Nelson, R. J. (2001). cFOS and pCREB activation and maternal aggression in mice. *Brain research*, 898(2), 232–241. doi: 10.1016/s0006-8993(01)02189-8

Gammie, S. C., Negron, A., Newman, S. M., & Rhodes, J. S. (2004). Corticotropin-releasing factor inhibits maternal aggression in mice. Behavioral neuroscience, 118(4), 805–814. https://doi.org/10.1037/0735-7044.118.4.805

Ganea, N., Hudry, K., Vernetti, A., Tucker, L., Charman, T., Johnson, M. H., & Senju, A. (2018). Development of adaptive communication skills in infants of blind parents. *Developmental psychology*, 54(12), 2265–2273. doi: 10.1037/dev0000564

Gandelman R. (1972). Mice: postpartum aggression elicited by the presence of an intruder. Hormones and behavior, 3(1), 23–28. https://doi.org/10.1016/0018-506x(72)90003-7

Gandelman, R., Zarrow, M. X., & Denenberg, V. H. (1970). Maternal behavior: differences between mother and virgin mice as a function of the testing procedure. Developmental psychobiology, 3(3), 207–214. https://doi.org/10.1002/dev.420030308

Gandelman, R., Zarrow, M. X., & Denenberg, V. H. (1971a). Stimulus control of cannibalism and maternal behavior in anosmic mice. Physiology & behavior, 7(4), 583–586. https://doi.org/10.1016/0031-9384(71)90112-0

Gandelman, R., Zarrow, M. X., Denenberg, V. H., & Myers, M. (1971b). Olfactory bulb removal eliminates maternal behavior in the mouse. *Science*, *171*(3967), 210-211. doi: 10.1126/science.171.3967.210

Gandelman, R., Zarrow, M. X., & Denenberg, V. H. (1972). Reproductive and maternal performance in the mouse following removal of the olfactory bulbs. Journal of reproduction and fertility, 28(3), 453–456. https://doi.org/10.1530/jrf.0.0280453

Gaub, S., & Ehret, G. (2005). Grouping in auditory temporal perception and vocal production is mutually adapted: the case of wriggling calls of mice. Journal of comparative physiology. A, Neuroethology, sensory, neural, and behavioral physiology, 191(12), 1131–1135. https://doi.org/10.1007/s00359-005-0036-y

González-Mariscal G., Caba, M., Hoffman K. L., Melo A. I. (2017). “Parental Behavior”. In: DW Pfaff, M Joël, editors. Hormones, Brain, and Behavior, 3rd edition, vol. 1. Oxford: Academic Press. p. 83–116. doi: 10.1016/B978-0-12-803592-4.00003-1

Gougoux, F., Lepore, F., Lassonde, M., Voss, P., Zatorre, R. J., & Belin, P. (2004). Neuropsychology: pitch discrimination in the early blind. Nature, 430(6997), 309. https://doi.org/10.1038/430309a

Grieb, Z. A., Vitale, E. M., Morrell, J. I., Lonstein, J. S., & Pereira, M. (2020). Decreased mesolimbic dopaminergic signaling underlies the waning of maternal caregiving across the postpartum period in rats. Psychopharmacology, 237(4), 1107–1119. https://doi.org/10.1007/s00213-019-05441-7

Grota, L. J., & Ader, R. (1974). Behavior of lactating rats in a dual-chambered maternity cage. *Hormones and behavior*, 5(4), 275–282. doi: 10.1016/0018-506x(74)90014-2

Haller J. (2018). The role of central and medial amygdala in normal and abnormal aggression: A review of classical approaches. *Neuroscience and biobehavioral reviews*, 85, 34–43. doi: 10.1016/j.neubiorev.2017.09.017

Hasen, N. S., & Gammie, S. C. (2005). Differential fos activation in virgin and lactating mice in response to an intruder. *Physiology & behavior*, 84(5), 681–695. doi: 10.1016/j.physbeh.2005.02.010

Hasen, N. S., & Gammie, S. C. (2006). Maternal aggression: new insights from Egr-1. *Brain research*, 1108(1), 147–156. doi: 10.1016/j.brainres.2006.06.007

Herrenkohl, L. R. & Rosenberg, P. A., (1972) Exteroceptive stimulation of maternal behavior in the naïve rat. Physiology & behavior, 8(4), 595-598. doi: 10.1016/0031-9384(72)90080-7

Hugdahl, K., Ek, M., Takio, F., Rintee, T., Tuomainen, J., Haarala, C., & Hämäläinen, H. (2004). Blind individuals show enhanced perceptual and attentional sensitivity for identification of speech sounds. Brain research. Cognitive brain research, 19(1), 28–32. https://doi.org/10.1016/j.cogbrainres.2003.10.015

Iura, Y., & Udo, H. (2014). Behavioral analyses of visually impaired Crx knockout mice revealed sensory compensation in exploratory activities on elevated platforms. *Behavioural brain research*, 258, 1–7.

Jalabert, M., Aston-Jones, G., Herzog, E., Manzoni, O., & Georges, F. (2009). Role of the bed nucleus of the stria terminalis in the control of ventral tegmental area dopamine neurons. Progress in neuro-psychopharmacology & biological psychiatry, 33(8), 1336–1346.

Kelly, E. A., Russo, A. S., Jackson, C. D., Lamantia, C. E., & Majewska, A. K. (2015). Proteolytic regulation of synaptic plasticity in the mouse primary visual cortex: analysis of matrix metalloproteinase 9 deficient mice. Frontiers in cellular neuroscience, 9, 369. https://doi.org/10.3389/fncel.2015.00369

Kenyon, P., Cronin, P., & Keeble, S. (1983). Role of the infraorbital nerve in retrieving behavior in lactating rats. Behavioral neuroscience, 97(2), 255–269. https://doi.org/10.1037//0735-7044.97.2.255

Keyser-Marcus, L., Stafisso-Sandoz, G., Gerecke, K., Jasnow, A., Nightingale, L., Lambert, K. G., Gatewood, J., & Kinsley, C. H. (2001). Alterations of medial preoptic area neurons following pregnancy and pregnancy-like steroidal treatment in the rat. *Brain research bulletin*, 55(6), 737–745. doi: 10.1016/s0361-9230(01)00554-8

Kim, S., & Strathearn, L. (2016). Oxytocin and Maternal Brain Plasticity. New directions for child and adolescent development, 2016(153), 59–72. https://doi.org/10.1002/cad.20170

Klampfl, S. M., & Bosch, O. J. (2019). Mom doesn't care: When increased brain CRF system activity leads to maternal neglect in rodents. Frontiers in neuroendocrinology, 53, 100735. https://doi.org/10.1016/j.yfrne.2019.01.001

Kohl, J., Autry, A. E., & Dulac, C. (2017). The neurobiology of parenting: A neural circuit perspective. BioEssays : news and reviews in molecular, cellular and developmental biology, 39(1), 1–11. https://doi.org/10.1002/bies.201600159

Kolunie, J. M., Stern, J. M., & Barfield, R. J. (1994). Maternal aggression in rats: Effects of visual or auditory deprivation of the mother and dyadic pattern of ultrasonic vocalizations. *Behavioral and Neural Biology*, *62*(1), 41-49. doi: https://doi.org/10.1016/S0163-1047(05)80057-3

Kolunie, J. M., & Stern, J. M. (1995). Maternal aggression in rats: effects of olfactory bulbectomy, ZnSO4-induced anosmia, and vomeronasal organ removal. *Hormones and behavior*, 29(4), 492–518. doi: 10.1006/hbeh.1995.1285

Kristal M. B. (2009). The biopsychology of maternal behavior in nonhuman mammals. ILAR journal, 50(1), 51–63. https://doi.org/10.1093/ilar.50.1.51

Kudo, T., Konno, K., Uchigashima, M., Yanagawa, Y., Sora, I., Minami, M., & Watanabe, M. (2014). GABAergic neurons in the ventral tegmental area receive dual GABA/enkephalin-mediated inhibitory inputs from the bed nucleus of the stria terminalis. The European journal of neuroscience, 39(11), 1796–1809. https://doi.org/10.1111/ejn.12503

Kujala, T., Alho, K., Huotilainen, M., Ilmoniemi, R. J., Lehtokoski, A., Leinonen, A., Rinne, T., Salonen, O., Sinkkonen, J., Standertskjöld-Nordenstam, C. G., & Näätänen, R. (1997). Electrophysiological evidence for cross-modal plasticity in humans with early- and late-onset blindness. Psychophysiology, 34(2), 213–216. https://doi.org/10.1111/j.1469-8986.1997.tb02134.x

Kupers, R., & Ptito, M. (2011). Insights from darkness: what the study of blindness has taught us about brain structure and function. *Progress in brain researc*h, 192, 17–31. doi: 10.1016/B978-0-444-53355-5.00002-6

Kupers, R., & Ptito, M. (2014). Compensatory plasticity and cross-modal reorganization following early visual deprivation. *Neuroscience & Biobehavioral Reviews*, *41*, 36-52. doi: https://doi.org/10.1016/j.neubiorev.2013.08.001

Lee, A., Clancy, S., & Fleming, A. S. (1999). Mother rats bar-press for pups: effects of lesions of the mpoa and limbic sites on maternal behavior and operant responding for pup-reinforcement. Behavioural brain research, 100(1-2), 15–31. https://doi.org/10.1016/s0166-4328(98)00109-0

Lee, A. W., & Brown, R. E. (2002). Medial preoptic lesions disrupt parental behavior in both male and female California mice (Peromyscus californicus). Behavioral neuroscience, 116(6), 968–975. https://doi.org/10.1037//0735-7044.116.6.968

Lévy, F., & Keller, M. (2009). Olfactory mediation of maternal behavior in selected mammalian species. Behavioural brain research, 200(2), 336–345. https://doi.org/10.1016/j.bbr.2008.12.017

Liotti, M., Ryder, K., & Woldorff, M. G. (1998). Auditory attention in the congenitally blind: where, when and what gets reorganized?. Neuroreport, 9(6), 1007–1012. https://doi.org/10.1097/00001756-199804200-00010

Lonstein, J. S., & Gammie, S. C. (2002). Sensory, hormonal, and neural control of maternal aggression in laboratory rodents. Neuroscience and biobehavioral reviews, 26(8), 869–888. https://doi.org/10.1016/s0149-7634(02)00087-8

Lonstein, J. S., Lévy, F., & Fleming, A. S. (2015). Common and divergent psychobiological mechanisms underlying maternal behaviors in non-human and human mammals. Hormones and behavior, 73, 156–185. https://doi.org/10.1016/j.yhbeh.2015.06.011

Manescu, S., Chouinard-Leclaire, C., Collignon, O., Lepore, F., & Frasnelli, J. (2021). Enhanced Odorant Localization Abilities in Congenitally Blind but not in Late-Blind Individuals. Chemical senses, 46, bjaa073. https://doi.org/10.1093/chemse/bjaa073

Martín-Sánchez, A., McLean, L., Beynon, R. J., Hurst, J. L., Ayala, G., Lanuza, E., & Martínez-Garcia, F. (2015). From sexual attraction to maternal aggression: when pheromones change their behavioural significance. Hormones and behavior, 68, 65–76. https://doi.org/10.1016/j.yhbeh.2014.08.007

Massé, I. O., Guillemette, S., Laramée, M. E., Bronchti, G., & Boire, D. (2014). Strain differences of the effect of enucleation and anophthalmia on the size and growth of sensory cortices in mice. *Brain Research*, *1588*, 113-126. doi: 10.1016/j.brainres.2014.09.025

Mayer, A. D., & Rosenblatt, J. S. (1993). Peripheral olfactory deafferentation of the primary olfactory system in rats using ZnSO4 nasal spray with special reference to maternal behavior. *Physiology & behavior*, 53(3), 587–592. doi: 10.1016/0031-9384(93)90157-b

McHenry, J. A., Rubinow, D. R., & Stuber, G. D. (2015). Maternally responsive neurons in the bed nucleus of the stria terminalis and medial preoptic area: Putative circuits for regulating anxiety and reward. Frontiers in neuroendocrinology, 38, 65–72. https://doi.org/10.1016/j.yfrne.2015.04.001

Meaney M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual review of neuroscience*, *24*, 1161–1192. https://doi.org/10.1146/annurev.neuro.24.1.1161

Miceli, M. O., Fleming, A. S., & Malsbury, C. W. (1983). Disruption of maternal behaviour in virgin and postparturient rats following sagittal plane knife cuts in the preoptic area-hypothalamus. Behavioural brain research, 9(3), 337–360. https://doi.org/10.1016/0166-4328(83)90137-7

Morgan, H. D., Fleming, A. S., & Stern, J. M. (1992). Somatosensory control of the onset and retention of maternal responsiveness in primiparous Sprague-Dawley rats. Physiology & behavior, 51(3), 549–555. https://doi.org/10.1016/0031-9384(92)90178-5

Noirot, E, E. (1965). Changes in responsiveness to young in the adult mouse. 3. The effect of immediately preceding performances. *Behaviour*, *24*(3), 318-325. doi: 10.1163/156853965x00084

Noirot, E, E. (1969). Serial order of maternal responses in mice. *Animal behaviour*, Volume:17, Numéro:3

Numan, M. (2007). Motivational systems and the neural circuitry of maternal behavior in the rat. *Developemntal Psychobiology*, *49*(1), 12-21. doi: 10.1002/dev.20198

Numan, M. & Insel, T.R. (2003) Hormonal and Nonhormonal Basis of Maternal Behavior. In: The Neurobiology of Parental Behavior, Springer, New York, 8-41.

Numan, M., & Numan, M. J. (1997). Projection sites of medial preoptic area and ventral bed nucleus of the stria terminalis neurons that express Fos during maternal behavior in female rats. Journal of neuroendocrinology, 9(5), 369–384. https://doi.org/10.1046/j.1365-2826.1997.t01-1-00597.

Numan, M., & Stolzenberg, D. S. (2009). Medial preoptic area interactions with dopamine neural systems in the control of the onset and maintenance of maternal behavior in rats. Frontiers in neuroendocrinology, 30(1), 46–64. https://doi.org/10.1016/j.yfrne.2008.10.002

Numan, M., & Young, L. J. (2016). Neural mechanisms of mother-infant bonding and pair bonding: Similarities, differences, and broader implications. Hormones and behavior, 77, 98–112. https://doi.org/10.1016/j.yhbeh.2015.05.015

Oxley, G., & Fleming, A. S. (2000). The effects of medial preoptic area and amygdala lesions on maternal behavior in the juvenile rat. Developmental psychobiology, 37(4), 253–265.

Peirson, S. N., & Foster, R. G. (2011). Bad light stops play. EMBO reports, 12(5), 380. https://doi.org/10.1038/embor.2011.70

Peirson, S. N., Brown, L. A., Pothecary, C. A., Benson, L. A., & Fisk, A. S. (2018). Light and the laboratory mouse. Journal of neuroscience methods, 300, 26–36. https://doi.org/10.1016/j.jneumeth.2017.04.007

Pereira, M., & Morrell, J. I. (2009). The changing role of the medial preoptic area in the regulation of maternal behavior across the postpartum period: facilitation followed by inhibition. Behavioural brain research, 205(1), 238–248. https://doi.org/10.1016/j.bbr.2009.06.026

Petrulis, A. (2013). Chemosignals and hormones in the neural control of mammalian sexual behavior. Frontiers in neuroendocrinology, 34(4), 255–267. https://doi.org/10.1016/j.yfrne.2013.07.007

Pfaff, D. W. (1982). The Physiological Mechanisms of Motivation. The Physiological Mechanisms of Motivation. Pfaff, Donald W. (Editor). Published by Springer-Verlag, New York, NY, U.S.A. ISBN 10: 0387906509

Piché, M., Robert, S., Miceli, D., & Bronchti, G. (2004). Environmental enrichment enhances auditory takeover of the occipital cortex in anophthalmic mice. The European journal of neuroscience, 20(12), 3463–3472. https://doi.org/10.1111/j.1460-9568.2004.03823.x

Pigeon, C., & Marin-Lamellet, C. (2015). Evaluation of the attentional capacities and working memory of early and late blind persons. *Acta psychologica*, 155, 1–7. doi: 10.1016/j.actpsy.2014.11.010

Poindron P. (2005). Mechanisms of activation of maternal behaviour in mammals. Reproduction, nutrition, development, 45(3), 341–351. https://doi.org/10.1051/rnd:2005025

Qin, W., Xuan, Y., Liu, Y., Jiang, T., & Yu, C. (2015). Functional Connectivity Density in Congenitally and Late Blind Subjects. Cerebral cortex (New York, N.Y. : 1991), 25(9), 2507–2516. https://doi.org/10.1093/cercor/bhu051

Ramamurthy, D. L., & Krubitzer, L. A. (2018). Neural Coding of Whisker-Mediated Touch in Primary Somatosensory Cortex Is Altered Following Early Blindness. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 38(27), 6172–6189.

Rosenblatt J. S. (1967). Nonhormonal basis of maternal behavior in the rat. Science (New York, N.Y.), 156(3781), 1512–1514. https://doi.org/10.1126/science.156.3781.1512

Rosenblatt, J. S., & Lehrman, D. S. (1963). *Maternal behavior in the laboratory rat.* In: Reingold HL, ed. Maternal Behavior in Mammals. New York: Wiley. p 8-57.

Rosenblatt, J. S., Siegel, H. I., & Mayer, A. D. (1979). Progress in the Study of Maternal Behavior in the Rat: Hormonal, Nonhormonal, Sensory, and Developmental Aspects. J. S. Rosenblatt, R. A. Hinde, C. Beer, & M.-C. Busnel (Éds.), *Advances in the Study of Behavior* (Vol. 10, pp. 225-311): Academic Press. doi: 10.1016/S0065-3454(08)60096-0.

Santos, R., & Ribeiro, V. M. (2020). Transition of blind women to motherhood from the perspective of Transitions Theory. Revista brasileira de enfermagem, 73(suppl 4), e20190234. https://doi.org/10.1590/0034-7167-2019-0234

Sato, A., Nakagawasai, O., Tan-No, K., Onogi, H., Niijima, F., & Tadano, T. (2010). Influence of olfactory bulbectomy on maternal behavior and dopaminergic function in nucleus accumbens in mice. *Behavioural brain research*, 215(1), 141–145. doi: 10.1016/j.bbr.2010.07.012

Schaal, B., Coureaud, G., Doucet, S., Delaunay-El Allam, M., Moncomble, A. S., Montigny, D., Patris, B., & Holley, A. (2009). Mammary olfactory signalisation in females and odor processing in neonates: ways evolved by rabbits and humans. Behavioural brain research, 200(2), 346–358. https://doi.org/10.1016/j.bbr.2009.02.008

Semaan, S. J., & Kauffman, A. S. (2010). Sexual differentiation and development of forebrain reproductive circuits. Current opinion in neurobiology, 20(4), 424–431. https://doi.org/10.1016/j.conb.2010.04.004

Shahrokh, D. K., Zhang, T. Y., Diorio, J., Gratton, A., & Meaney, M. J. (2010). Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology, 151(5), 2276–2286. https://doi.org/10.1210/en.2009-1271

Skripuletz, T., Kruschinski, C., Pabst, R., von Hörsten, S., & Stephan, M. (2010). Postnatal experiences influence the behavior in adult male and female Fischer and Lewis rats. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience, 28(7), 561–571. https://doi.org/10.1016/j.ijdevneu.2010.07.235

Slimani, H., Danti, S., Ricciardi, E., Pietrini, P., Ptito, M., & Kupers, R. (2013). Hypersensitivity to pain in congenital blindness. *Pain*, *154*(10), 1973-1978. doi: 10.1016/j.pain.2013.05.036

Slimani, H., Danti, S., Ptito, M., & Kupers, R. (2014). Pain perception is increased in congenital but not late onset blindness. PloS one, 9(9), e107281. https://doi.org/10.1371/journal.pone.0107281

Slimani, H., Ptito, M., & Kupers, R. (2015). Enhanced heat discrimination in congenital blindness. Behavioural brain research, 283, 233–237. https://doi.org/10.1016/j.bbr.2015.01.037

Smotherman, W. P., Bell, R. W., Starzec, J., Elias, J., & Zachman, T. A. (1974). Maternal responses to infant vocalizations and olfactory cues in rats and mice. *Behavioral Biology*, *12*(1), 55-66. doi: https://doi.org/10.1016/S0091-6773(74)91026-8

Sorokowska, A., Sorokowski, P., Karwowski, M., Larsson, M., & Hummel, T. (2019). Olfactory perception and blindness: a systematic review and meta-analysis. Psychological research, 83(8), 1595–1611. https://doi.org/10.1007/s00426-018-1035-2

Stern, J. M. (1989). CHAPTER THREE - Maternal Behavior: Sensory, Hormonal, and Neural Determinants. F. R. Brush, & S. Levine (Éds.), *Psychoendocrinology* (pp. 105-226). Amsterdam: Academic Press. doi: https://doi.org/10.1016/B978-0-12-137952-0.50008-2. Repéré à https://www.sciencedirect.com/science/article/pii/B9780121379520500082

Stern J. M. (1990). Multisensory regulation of maternal behavior and masculine sexual behavior: a revised view. Neuroscience and biobehavioral reviews, 14(2), 183–200. https://doi.org/10.1016/s0149-7634(05)80219-2

Stern J. M. (1996). Trigeminal lesions and maternal behavior in Norway rats: II. Disruption of parturition. Physiology & behavior, 60(1), 187–190. https://doi.org/10.1016/0031-9384(96)00016-9

Stern J. M. (1997). Offspring-induced nurturance: animal-human parallels. *Developmental psychobiology*, 31(1), 19–37. doi: 10.1002/(sici)1098-2302(199707)31:1<19::aid-dev3>3.0.co;2-x

Stern, J. M., & Lonstein, J. S. (2001). Neural mediation of nursing and related maternal behaviors. Progress in brain research, 133, 263–278. https://doi.org/10.1016/s0079-6123(01)33020-0

Stern, J. M., & Johnson, S. K. (1990). Ventral somatosensory determinants of nursing behavior in Norway rats. I. Effects of variations in the quality and quantity of pup stimuli. Physiology & behavior, 47(5), 993–1011. https://doi.org/10.1016/0031-9384(90)90026-z

Stolzenberg, D. S., & Champagne, F. A. (2016). Hormonal and non-hormonal bases of maternal behavior: The role of experience and epigenetic mechanisms. Hormones and behavior, 77, 204–210. https://doi.org/10.1016/j.yhbeh.2015.07.005

Stolzenberg, D. S., & Mayer, H. S. (2019). Experience-dependent mechanisms in the regulation of parental care. Frontiers in neuroendocrinology, 54, 100745. https://doi.org/10.1016/j.yfrne.2019.04.002

Swaney W. T., Curley J. P., Champagne F. A., & Keverne E. B. (2008). The paternally expressed Gene Peg3 regulates sexual experience-dependent preferences for estrous odors. *Behavioral Neuroscience*;122: 963–973. doi: 10.1037/a0012706.

Terkel, J., Bridges, R. S., & Sawyer, C. H. (1979). Effects of transecting lateral neural connections of the medial preoptic area on maternal behavior in the rat: nest building, pup retrieval and prolactin secretion. Brain research, 169(2), 369–380. https://doi.org/10.1016/0006-8993(79)91037-0

Topalidis, P., Zinchenko, A., Gädeke, J. C., & Föcker, J. (2020). The role of spatial selective attention in the processing of affective prosodies in congenitally blind adults: An ERP study. Brain research, 1739, 146819. https://doi.org/10.1016/j.brainres.2020.146819

Thoueille, É., Candilis-Huisman, D., Soulé, M. & Vermillard, M. (2006). La maternité des femmes aveugles: Du désir d'enfant au bébé réel. La psychiatrie de l'enfant, 49, 285-348. https://doi.org/10.3917/psye.492.0285

Tobiansky, D. J., Roma, P. G., Hattori, T., Will, R. G., Nutsch, V. L., & Dominguez, J. M. (2013). The medial preoptic area modulates cocaine-induced activity in female rats. Behavioral neuroscience, 127(2), 293–302. https://doi.org/10.1037/a0031949

Touj, S., Tokunaga, R., Al Aïn, S., Bronchti, G., & Piché, M. (2019). Pain Hypersensitivity is Associated with Increased Amygdala Volume and c-Fos Immunoreactivity in Anophthalmic Mice. *Neuroscience*, *418*, 37-49. doi: 10.1016/j.neuroscience.2019.08.035

Touj, S., Cloutier, S., Jemâa, A., Piché, M., Bronchti, G., & Al Aïn, S. (2020). Better Olfactory Performance and Larger Olfactory Bulbs in a Mouse Model of Congenital Blindness. *Chemical Senses*, *45*(7), 523-531. doi: 10.1093/chemse/bjaa052

Touj, S., Gallino, D., Chakravarty, M. M., Bronchti, G., & Piché, M. (2021a). Structural brain plasticity induced by early blindness. The European journal of neuroscience, 53(3), 778–795. https://doi.org/10.1111/ejn.15028

Touj, S., Paquette, T., Bronchti, G., & Piché, M. (2021b). Early and late visual deprivation induce hypersensitivity to mechanical and thermal noxious stimuli in the ZRDBA mouse. European journal of pain (London, England), 25(10), 2257–2265. https://doi.org/10.1002/ejp.1839

Tucker, P., Laemle, L., Munson, A., Kanekar, S., Oliver, E. R., Brown, N., Schlecht, H., Vetter, M., & Glaser, T. (2001). The eyeless mouse mutation (ey1) removes an alternative start codon from the Rx/rax homeobox gene. Genesis (New York, N.Y. : 2000), 31(1), 43–53. https://doi.org/10.1002/gene.10003

Uriarte, N., Ferreño, M., Méndez, D., & Nogueira, J. (2020). Reorganization of perineuronal nets in the medial Preoptic Area during the reproductive cycle in female rats. *Scientific reports*, 10(1), 5479. doi: 10.1038/s41598-020-62163-z

vom Saal, F. S., & Howard, L. S. (1982). The regulation of infanticide and parental behavior: implications for reproductive success in male mice. Science (New York, N.Y.), 215(4537), 1270–1272. https://doi.org/10.1126/science.7058349

Voss, P., & Zatorre, R. J. (2012). Occipital cortical thickness predicts performance on pitch and musical tasks in blind individuals. Cerebral cortex (New York, N.Y. : 1991), 22(11), 2455–2465. https://doi.org/10.1093/cercor/bhr311

Weiss, J., Pyrski, M., Jacobi, E., Bufe, B., Willnecker, V., Schick, B., Zizzari, P., Gossage, S. J., Greer, C. A., Leinders-Zufall, T., Woods, C. G., Wood, J. N., & Zufall, F. (2011). Loss-of-function mutations in sodium channel Nav1.7 cause anosmia. *Nature*, 472(7342), 186–190. doi: 10.1038/nature09975

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nature neuroscience, 15(4), 528–536. https://doi.org/10.1038/nn.3045

Zhang, C., Lee, T., Fu, Y., Ren, C., Chan, C., & Tao, Q. (2019). Properties of cross-modal occipital responses in early blindness: An ALE meta-analysis. NeuroImage. Clinical, 24, 102041. https://doi.org/10.1016/j.nicl.2019.102041

Zhou, Y., Fang, F. H., Pan, P., Liu, Z. R., & Ji, Y. H. (2017). Visual deprivation induce cross-modal enhancement of olfactory perception. Biochemical and biophysical research communications, 486(3), 833–838. https://doi.org/10.1016/j.bbrc.2017.03.140

CAPTIONS

FIGURE 1. Pup retrieval test on PD 1, 2, 3. Log-rank (Kaplan-Meier) statistics revealed that blind and sighted dams performed differently in most of conditions. Survival plots indicate the cumulative proportion of blind dams (black line) and sighted dams (grey line) retrieving the first and fourth pup on days 1, 2 and 3 postpartum (*p < 0.05; ***p < 0.001).

FIGURE 2. **Pup retrieval test on PD 1, 2, 3. The mixed ANOVA revealed that blind mothers displayed a shorter latency to retrieve the 4 pups compared with sighted mothers and pup retrieval efficiency improved similarly over time in both groups** (Data are shown as mean ± SEM; *p < 0.05; **p < 0.01; ***p < 0.001).

FIGURE 3. The total duration of maternal and non-maternal behaviors displayed by blind and sighted mothers throughout the lactational period on days 5, 10, 13, 16 and 19 postpartum. a) Nursing behavior: blind mothers nursed their pups longer than sighted mothers on PD 13, 16 and 19. b) Mother-pup interactions in the nest: blind mothers spent more time interacting with pups compared to sighted mothers on PD 13 and 16. c) Mother in the nest with no pup's interaction: Blind and sighted mothers spent the same time in the nest with no interaction with their pups throughout the lactational period. d) Mother resting outside the nest: sighted mothers spent more time resting outside the nest than blind mothers on PD 10, 13, and 16. e) Mother walking: Blind and sighted mothers spent the same time exploring the cage throughout the lactational period. f) Mother eating/drinking outside the nest: Blind and sighted mothers spent the same time eating/drinking throughout the lactational period (**p* <0.05, ***p* <0.01, ****p* <0.001).

FIGURE 4. Aggressive-related behaviors exhibited by blind and sighted mothers toward a male intruder. Blind mothers were faster to initiate the first attack toward a male intruder than their sighted counterparts (a), but both groups exhibited a similar total duration of attacks (b) and a similar number of attacks toward a male intruder (c). Data are shown as mean ± SEM. ***p* < 0.01.