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Motherless Rats Show Deficits in Maternal Behavior Towards Fostered Pups

ABSTRACT: *Complete maternal deprivation in rats, through artificial rearing (AR), produces deficits in subsequent maternal behavior of the offspring. These deficits are partially reversed when isolated pups are provided with additional tactile stimulation designed to simulate maternal licking (e.g., Gonzalez et al. [2001] Developmental Psychobiology, 38, 11–32). These findings highlight the importance of the early maternal environment in subsequent development. However, given the possibility that prenatal environments may differ between AR and maternally reared (MR) offspring, the deficits in the behavior of AR mothers may be driven by the characteristics of their pups derived from the effects of an altered prenatal environment. Hence differences in the neonatal pups of AR mothers may produce the alterations in the AR maternal behavior. To rule out this possibility, we employed a fostering paradigm where AR and MR mothers received cross-fostered mother-reared pups. AR mothers showed the same level of deficits in maternal behavior towards MR foster pups as they do with their own pups and these deficits were partially reversed with additional tactile stimulation. Hence, maternal behavior deficits reported in mothers who had been reared in isolation are due primarily to the direct effects of the earlier experience on mechanisms regulating their maternal behavior and not to the effects on their offspring. © 2010 Wiley Periodicals, Inc.* Dev Psychobiol 52: 142–148, 2010.

Keywords: *rat; artificial rearing; early experience; development; maternal behavior; fostering; pup-licking*

INTRODUCTION

In many mammalian species, the quality of early maternal care influences subsequent psychobiological development. In rats, a typical maternal bout involves a series of behaviors where the mother approaches her litter, gathers the pups beneath her, nurses them, and intermittently licks them (Rosenblatt & Lehrman, 1963; Wiesner & Sheard, 1933). These maternal behaviors are crucial to offspring survival, providing warmth, shelter, and nutrition. Beyond survival, maternal care modulates neurobiological systems that impact long-term cognitive,

social, and emotional development of the offspring (e.g., Fleming, O'Day, & Kraemer, 1999; Francis & Meaney, 1999; Liu, Diorio, Day, Francis, & Meaney, 2000). In particular, early experience within the maternal nest influences how the young eventually come to respond to their own offspring.

Several paradigms have been used to investigate the matrilineal transmission of mothering behavior in rats. The least intrusive method is to study the transmission of individual differences in maternal care. In rats there is a great deal of naturally occurring variation in maternal behavior that propagates across generations. In comparison to pups that receive less licking, pups that receive more licking from their mother demonstrate subsequent increased licking of their own pups (Champagne, Francis, Mar, & Meaney, 2003; Francis Diorio, Liu, & Meaney, 1999). This effect is also evident in reciprocally cross-fostered pups from high and low licking mothers, indicating that variations in maternal behavior are not

inherited but, instead, mediated by early experience (Francis et al., 1999).

The effects of early experience on subsequent maternal behavior can also be studied by experimentally manipulating the duration of mother–pup contact. For instance, neonates that are separated from the maternal nest for 3 or 5 h daily show reduced maternal behaviors towards their own pups in adulthood (Lovic, Gonzalez, & Fleming, 2001; Rees & Fleming, 2001). In our lab we have also employed a complete maternal deprivation paradigm (24 h daily). This paradigm involves artificial rearing (AR) of pups isolated in individual cups, void of any contact with their mother or littermates, (Hall, 1998) and comparing them to their maternally reared (MR) siblings. This form of rearing produces even greater deficits in maternal behavior than intermittent maternal separation (e.g., Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001). AR mothers spend less time over their pups and less time licking them (Gonzalez et al., 2001; Lovic & Fleming, 2004; Melo et al., 2006). These deficits in maternal behavior are partially reversed when isolated pups are provided with additional tactile stimulation (i.e., using a paintbrush) designed to simulate the mother's licking (Gonzalez et al., 2001; Lovic & Fleming, 2004). The effects of AR are also transferred across generations. Daughters of AR mothers show patterns of maternal behavior that are similar to their own mothers (Gonzalez et al., 2001). Taken together, these studies demonstrate that early experiences of being mothered (or not being mothered sufficiently) affect the quality of maternal care that females subsequently provide to their own offspring.

One limitation to the aforementioned studies is that AR mothers are tested with their own progeny. Consequently, it is possible that offspring of AR mothers have undergone a different *prenatal* environment in comparison to MR offspring. There is a substantial body of literature that demonstrates that the maternal environment alters neuroendocrine functioning and physiology, including regulation of the hypothalamic–pituitary–adrenal (HPA) axis (e.g., Burton et al., 2007; Francis, Diorio, Plotsky, & Meaney, 2002; Plotsky & Meaney, 1993). Fetal development is greatly influenced by the neuroendocrine state of the mother. Hence, it is conceivable that the offspring of AR mothers are physiologically different during gestation and at birth, which may affect the development of their postnatal sensorial and behavioral systems. These differences in pup characteristics could, in turn, affect how their mothers respond to them.

The above consideration is clearly important as regulation of maternal behavior in rats is modulated by various stimuli produced by the litter. For example, pups emit ultrasonic vocalizations, and olfactory cues (e.g., amniotic fluid, urination, body odor) that elicit retrieval and licking from their mothers (e.g., Allin & Banks, 1972; Brouette-Lahlou, Vernet-Maury, & Vigouroux, 1992; Noirot, 1972). Pups also engage in a number of behaviors specifically directed towards the mother. For instance, using olfactory cues elicited by the dam, pups orient themselves towards her. Once they are in close proximity to her, pups will rotate into a ventrum-to-ventrum position with the mother and subsequently seek and grasp her nipple. Maternal responsiveness is highly contingent on these pup cues (e.g., Polan & Hofer, 1999). Hence, if the physiology of offspring of AR mothers was altered prenatally, it is conceivable that they may provide different sensory or behavioral cues, thereby affecting maternal responsiveness.

In the present study, we were interested in determining whether AR mothers given MR "test" pups would continue to show deficiencies in maternal behavior. To this end, we adopted a fostering paradigm where both AR and MR mothers received mother-reared donor pups. If differences in maternal behavior between AR and MR mothers are still observed using this experimental approach, these changes can be attributed to characteristics of the mother. Given the demonstrated effects of cross-fostering in previous studies, where offspring display patterns of maternal behaviors similar to their foster mothers, we favor the possibility that isolation-induced deficits in maternal behavior are chiefly propagated to offspring postnatally. Hence, we expect that AR mothers will show deficits in maternal behavior and that these deficits will be partially or fully reversed by providing additional tactile stimulation during rearing that is designed to simulate the mother's licking. For the purposes of "comparison," we also included data from a previous study, where AR and MR mothers reared their own pups and maternal behavior was assessed, akin to previous studies (Gonzalez et al., 2001; Lovic & Fleming, 2004; Melo et al., 2006).

METHODS

Animals and Housing

The subjects in Study 1 (i.e., nonfostering) were 12 Sprague–Dawley female rats [AR-Min ($n = 5$) and MR ($n = 7$)]. In Study 2 (i.e., cross-fostering), 32 Sprague–Dawley female rats [MR-Min ($n = 7$), MR-Max ($n = 8$) and MR ($n = 17$)] were used. Methods for the two studies were almost identical, with differences in procedure highlighted here. All animals were originally obtained from Charles Rivers Farms in St. Constant, Quebec and bred at the University of Toronto at Mississauga. The animals were housed in medium size Plexiglas cages (26 cm × 38 cm × 21 cm) with woodchip shavings as bedding and ad libitum access to Purina Rat chow and water. The room temperature and humidity were maintained at 22°C and

40–50%, respectively. The animals were maintained on a 12:12 light/dark schedule, with lights off at 20:00 h. All procedures in this study conformed to the guidelines set by the Canadian Council on Animal Care and were approved by the Local Animal Care Committee.

General Procedure

For Study 1, on the day of parturition (PND 0), female dam's litters were culled to 11 pups, 5 males, and 6 females. On PND 3, two females were removed from the nest while the remaining pups were left with the dam. One of the removed pups was implanted with a cheek cannula whereas one was marked with coloring and returned to the nest (mother-reared, control; MR-CON). The female that underwent surgery was artificially reared (artificially reared, minimal stimulation; AR-MIN, see below). Given that this study was a replication of previously observed AR deficits, we were only interested in using the demonstrated extremes (AR-MIN and MR-CON) included in our previous studies. However, since cross-fostering has not yet been investigated in AR animals, all four experimental groups used in previous studies were included for Study 2. On PND 0, dam's litters were culled to 12 pups; 5 males and 7 females. On PND 3, four females were removed from the nest while the remaining pups were left with the dam. Three of the removed pups were implanted with a cheek cannula whereas one was marked with coloring and returned to the nest (MR-CON). Two of the three females that underwent surgery were artificially reared (AR-MIN and artificially reared, maximal stimulation; AR-MAX; see below). The third female that underwent surgery had the implanted cannula immediately removed after surgery, was marked with coloring and returned to the nest (mother-reared, sham operated; MR-SHAM).

Cheek Cannula Surgery

Pups were given a small amount of topical anesthetic, (lidocaine, EMLA) on the outside portion of their cheek. A leader wire (stainless steel, .25 mm in diameter) was sheathed in tubing that was flared at one end to hold the tubing in place (polyethylene tubing, PE 10 tubing) and lubricated with reagent grade mineral oil (Sigma, St. Louis, MO). Once the cheek was anesthetized, the leader wire was inserted into the pup's mouth, led over the tongue, and penetrated through the cheek. The wire was gently pulled until the flared end of the PE 10 tubing contacted with the inside wall of the cheek, at which time the leader wire was removed from the PE 10 tubing. A flat washer, followed by a T-washer (flared PE 50 tubing) was placed over the PE 10 tubing, against the outer wall of the pup's cheek. Polysporin anti-bacterial cream was applied topically to the site of penetration. The washers were secured in place with methyl methacrylate adhesive (Super Glue). The PE tubing was flushed with double distilled water to prevent blockage of the tubing. MR-SHAM also received the cheek cannula surgery; however, the PE 10 tubing used for this surgery was not flared and the wire was removed immediately following penetration of the cheek. All pups were monitored for 30 min postsurgery.

Artificial Rearing

After the surgical implantation of the cheek cannula, the pups were housed individually in plastic cups (11 cm diameter × 15 cm deep) with corn-cob bedding (Bed O' Cobbs). The plastic cups were placed into a second weighted cup, which both floated in a temperature-controlled water aquarium (water maintained at 36–40°C). The room temperature was maintained at 25°C, with a humidity level of 48%. The tops of the cups remained open to allow each pup's cheek cannula tubing to emerge and connect to nearby syringes. Each syringe was filled with milk formula diet (Messer diet; Hall, 1998) which was infused through a timer-controlled infusion pump (Harvard Apparatus Syringe, PHD 2000). The pumps were programmed to infuse milk for 10 min every hour, 24 h daily. The infusion rate of the milk was based on a fraction of the mean pup body weight, beginning at 33% of their body weight and increasing by 1% each day. Every 24 h, the pups were removed from the pumps, weighed and had their tubing flushed with distilled water. New syringes containing fresh formula were set up and the milk infusion rate was reprogrammed according to the daily mean pup body weight. AR-MIN animals were stimulated on their anogenital region (AGS), once in the morning and once at night, with a warm, wet, camel hair paintbrush, for a total of 30 s per stimulation. The purpose of these stimulations was to simulate the mother's licking of the AGS, which stimulates urination and defecation. AR-MAX animals received the same AGS as well as five general body stimulations (BS) with a dry camel hair paintbrush, for a total of 2 min per stimulation (applicable to Study 2 only). Each BS did not occur within 1 h of another BS. These stimulations were to mimic the mother rat's licking, which provides tactile stimulation. All stimulations occurred during the light phase of the L–D cycle from PND 4–16. On PND 17–18, pups were removed from the pumps, placed in small cages (15 cm × 22 cm × 10 cm) and provided with milk formula, regular rat chow as well as a mixture of the two. All stimulations ceased at this time. The cages were placed on heating pads, set on low.

Weaning

On PND 21, AR animals were paired with nonexperimental MR social partners and MR animals were weaned from their mothers and were also paired with nonexperimental MR social partners. All animals were placed in medium sized cages (26 cm × 38 cm × 21 cm) with woodchip bedding. Food and water were available ad libitum. The room temperature and humidity were maintained at 22°C and 40–50%, respectively. The animals were maintained on a 12:12 light/dark schedule, with lights off at 20:00 h.

Mating and Cross-Fostering

On PND 70–100, all animals were mated with a sexually experienced male for a period of 7 days, after which the male was removed. Females that were not impregnated were re-mated for another 7-day period. After parturition (PND 0), full litters were removed and culled to three males and three females. For Study 1, mothers received their own pups back; hence not cross-fostered. For Study 2, pups were randomly assigned from an MR mother (PND 0) to both MR and AR mother groups.

Mothers were placed into a large transparent maternal observation cage (51 × 40.5 × 21) with their biological (Study 1) or foster pups (Study 2). Shredded paper towels were placed in the center of the cage to provide the mother with material to build a nest. On PND 11, pups were removed from the litter. Each pup was weighed individually and their body lengths were measured. The gender of each pup was noted to investigate whether there were any gender differences in morphology (Study 2 only).

Maternal Observations

In both studies, maternal behavior was assessed for 5 days (PND 1, 3, 5, 7, and 9) between 1,000 and 1,500 h. The experimenter was blind to the rearing group of the subjects. During maternal observation testing, pups were removed for 2 min and nesting material was distributed evenly throughout the cage. Pups were returned to the corner opposite to the formerly constructed nest or opposite to the mother if there was no apparent nest site. Maternal observations were recorded for 10 min. Observations consisted of continuous recording of the frequency and duration of each behavior using a computer-based event recorder (BEST Software, Educational Software, Inc.; Las Vegas, NV). Maternal behaviors that were recorded included: (1) pup retrieval (dam picks up a pup in her mouth and carries it to another quadrant of the cage), (2) general pup licking (dam licks the pup on its body or flips pup onto its back and licks the AGS), (3) over pups (dam is on top of the pups either actively engaging in other maternal behaviors or nursing the pups), (4) nest building (dam builds a nest using the shredded paper towels), (5) pup sniffing (dam is sniffing the pups), (6) frequency to approach the nest site (dam approaches the litter). Nonmaternal behaviors were also recorded (i.e., self-grooming, air-sniff, eating/drinking, tail chasing, grill biting, digging, and climbing) but were combined into one measure.

Statistical Analysis

For Study 1, there were two animals that did not mate or give birth (two AR) and for Study 2, there were a total of six animals (three MR and three AR) that did not mate or give birth. These animals were therefore excluded from this study. All remaining rats (Study 1: $N = 12$; Study 2: $N = 32$) were included for all behavioral analyses. For the purpose of statistical analyses, data for the 5 days of maternal observations were averaged. In Study 1, for simplicity and comparison purposes, we only report duration of licking and time spent over pups. In Study 2, the MR-SHAM and MR-CON groups did not differ for all behaviors and were therefore combined (MR). The frequency and duration of behaviors were analyzed using one-way analysis of variance (ANOVA) followed by Tukey post hoc test, when necessary. For Study 2, pup morphology was analyzed using repeated measures ANOVA, followed by Tukey post hoc. The level of statistical significance was $p < .05$.

RESULTS

Study 1

Duration. Figure 1 shows that there was a significant group difference for the duration of pup licking (F (1,
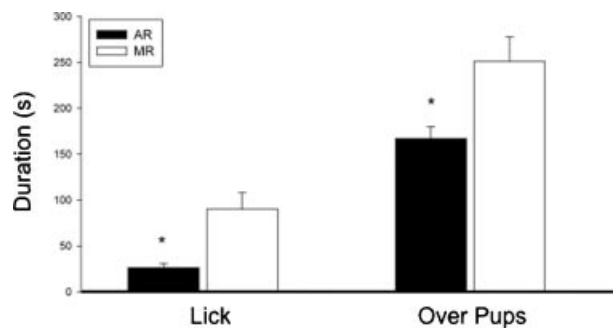

FIGURE 1 Mean durations (+SEM) of (A) licking, (B) over pups for AR ($n = 5$) and MR ($n = 7$) mothers for Study 1 (* represents group differences, $p < .05$).

10) = 8.43, $p < .05$) and time spent over pups (F (1, 10) = 6.25, $p < .05$), with AR mothers engaging in these behaviors for less time than MR mothers.

Study 2

Frequency. There was a significant group difference for frequency of pup licking (F (2, 29) = 5.41, $p < .05$). Post hoc tests revealed that the AR-MIN group licked their pups less than the MR group, while the AR-MAX group did not differ from either group. There were no group differences in the frequency of over pups, nest building, entering the nest site, pup-sniffing, and retrieval. There was a trend towards AR-MIN mothers engaging in nonmaternal behaviors more often than the MR group, but this difference was not statistically reliable.

Duration. Figure 2 shows that there was a significant group difference for the duration of pup licking (F (2, 29) = 6.75, $p < .05$) and time spent over pups (F (2, 29) = 9.44, $p < .05$). AR-MIN mothers spent significantly
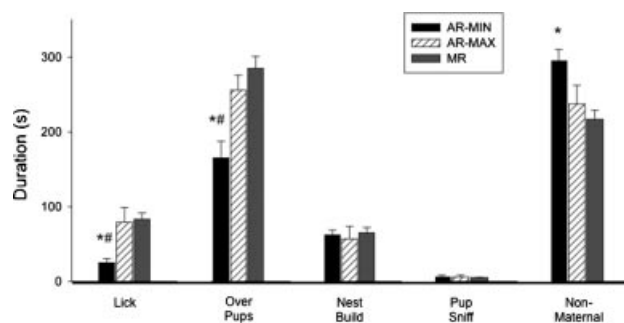

FIGURE 2 Mean durations (+SEM) of (A) licking, (B) over pups, (C) nest build, (D) pup sniff, and (E) nonmaternal behaviors for AR-MIN ($n = 7$), AR-MAX ($n = 8$), and MR ($n = 17$) mothers in Study 2 (* represents differences between AR-MIN and MR, # represents differences between AR-MIN and AR-MAX, $p < .05$).

less time licking their pups and less time over their pups than AR-MAX ($p < .05$), and MR mothers ($p < .05$). The AR-MAX group did not differ significantly from the MR group on both of these behaviors. Groups did not differ on the duration of pup-sniffing and nest building. There was a significant group difference for the duration of non-maternal behaviors ($F (2, 29) = 5.39$, $p < .05$). Post hoc tests revealed that the AR-MIN group spent significantly more time engaging in nonmaternal behaviors than the MR group, while the AR-MAX group fell between these two and did not differ significantly from either group.

Pup Morphology. As shown in Table 1, there was a significant group difference for pup length ($F (2, 28) = 4.86$, $p < .05$). Post hoc comparisons showed that pups reared by the AR-MIN group were significantly shorter in length than pups reared by the MR group ($p < .05$). The AR-MAX group fell between these groups and did not differ significantly from either. There was also a group difference in pup weight ($F (2, 28) = 3.56$, $p < .05$), such that AR-MIN pups weighed significantly less than MR pups ($p < .05$), while the AR-MAX group did not differ significantly from either group. There were no significant gender differences for pup length or weight.

DISCUSSION

The purpose of the present study was to investigate whether deficits in maternal behavior in females reared without their mothers (AR) are a consequence of altered development or due to the fact that AR mothers were tested with their own progeny, who may or may not have undergone aberrant intrauterine development. We found that AR mothers still display deficient maternal behavior when provided with MR foster pups. These deficits were partially reversed by providing additional licking-like tactile stimulation during early rearing (AR-MAX).

Table 1.   Artificial Rearing Disrupts Maternal Behavior

	Female	Male
Pup length (cm)		
AR-MIN[*]	11.2 (.3)	11.2 (.3)
AR-MAX	11.6 (.3)	11.7 (.3)
MR	12.3 (.2)	12.4 (.2)
Pup weight (g)		
AR-MIN[*]	21.4 (1.4)	21.8 (1.3)
AR-MAX	24.2 (1.4)	24.1 (1.4)
MR	25.7 (.9)	26.1 (1.0)

Note. Mean (+SEM) of pup (A) lengths (cm) and (B) weights (g) by gender on PND 11 in Study 2 for AR-MIN ($n = 7$), AR-MAX ($n = 8$) and MR ($n = 17$) mothers in Study 2 (* represents differences between AR-MIN and MR, $p < .05$).

The present study replicates and extends previous findings of maternal behavior deficits in AR-mothers tested with their own pups (Gonzalez et al., 2001; Melo et al., 2006). Here we show that AR produces postnatal maternal effects.

We also measured morphological qualities of AR and MR offspring on PND 11 in fostered pups. We found that foster pups reared by AR-MIN mothers were shorter in length, and lighter in weight than their MR counterparts. The foster pups reared by mothers that received extra tactile stimulation (AR-MAX) fell between the AR-MIN and MR groups. Since all pups used in Study 2 were fostered and randomly assigned to groups, these pups did not differ physically at birth. Hence, this difference can be attributed to differences in their postnatal environment.

It is not clear what controls the stature and weight differences in foster pups reared by AR and MR mothers. One possibility is that the variations are due to differences in the amount of maternal behavior that these pups received. Previous studies have shown that maternally deprived pups show decreased levels of growth hormones, and that these effects can be reversed if the pups are provided with maternal-like stroking stimulation (Levine, 1994; Shanberg, Evoniuk, & Kuhn, 1984). Hence, there is evidence to suggest that maternal licking fosters the physical development of the offspring. A second possibility is that the nutritional content of the milk of AR mothers differs from the milk of the MR mothers (due to long-term effects of their own early experiences, including their diets), and that these differences in maternal milk are producing these variations in the pups. This is an important consideration because differences in nutrition can affect the growth and long-term development of the offspring, independent of maternal care. It is also possible that the observed differences represent a combination of both proposed factors. Unfortunately, we only took measurements on PND 11. Given the possibility that morphological differences may change as a function of lactational day, possible differences may have been missed by this limited sampling.

A question currently being addressed examines whether AR disrupts maternal responsiveness directly or disrupts processes that mediate it. We have found that the effects of AR are widespread. For example, adult AR rats are hyperactive (e.g., Burton, Lovic, & Fleming, 2006), show attentional difficulties (Lovic & Fleming, 2004), and are more impulsive (Lovic, Fletcher, & Fleming, in preparation) in comparison to their MR counterparts. Some of these behavioral alterations have been informally observed while AR mothers interact with their pups. In comparison to MR mothers, AR mothers are less attentive towards their litters and show greater levels of activity. Maternal interactions of AR rats are also more frequently disrupted by nonmaternal behaviors (e.g., tail

chasing, grill biting, digging, etc.; see Gonzalez et al., 2001; Lovic & Fleming, 2004) and AR rats are more "distracted" by novel stimuli placed in their cage, as they spend more time exploring (Lovic & Fleming, 2004). Together, these findings raise the possibility that other behavioral deficits impair the ability of AR mothers to attend to their pups. In support of this, Lovic and Fleming have found that the levels of maternal behavior observed are correlated with performance on tasks of attention and impulsivity. Mothers that are less attentive (Lovic & Fleming, 2004) and more impulsive (Lovic, Palombo, & Fleming, in preparation) lick their pups less and spend less time over them in the nest. Whether one of these behaviors in particular plays a more prominent role in the observed maternal behavior disruptions is currently being investigated.

One limitation of the present study is that noncross-fostered comparison groups were not utilized in Study 2. Instead we used, as a noncross-fostered "comparison," Study 1, where AR and MR animals remained with their own pups. However, inclusion of this comparison within the same study would have allowed us to compare whether cross-fostering *diffentially* affects AR and MR mothers. Previous studies show fostering produces changes in mother–pup interactions, for example, mothers that are given foster pups show increased licking towards them (e.g., Maccari et al., 1995). Given the behavioral deficits exhibited by AR rats, it is conceivable that contact with novel pups may be a stressor for AR mothers or may have novelty-induced effects that influence maternal behavior. In the present study, we did not find differences between AR and MR mothers' pup-sniffing or retrieval of pups to the nest site. We also did not find that AR mothers differed in their frequency to approach the nest site. Hence AR mothers are equally "motivated" to approach the nest area. Nonetheless, it is possible that AR mothers are differentially reactive towards the foster pups upon initial introduction, but we do not have behavioral measurements of this. However, as shown in Figure 1, the duration of licking and the time spent over pups is comparable between Study 1 and 2, therefore, we favor the possibility that fostering itself did not produce a postnatal effect.

In the present study, we were specifically interested in determining whether deficits in maternal behavior in AR were due to their aversive postnatal development. Our study did not investigate the issue of whether AR pups do indeed have developmental deficits as a consequence of their prenatal environment. In order to address this issue, an additional study would be needed, where AR and MR mothers are provided with offspring from AR mothers. This would allow us to determine whether MR mothers respond differently to AR pups and whether these adopted AR offspring would show comparable morphology to MR offspring reared by MR mothers. Although this was

beyond the scope of this article, determining whether AR progeny experience an aberrant prenatal environment and subsequent behavioral consequences in an important issue worth addressing.

Social isolation paradigms in rats (i.e., maternal separation or deprivation) are useful in helping to elucidate the long-term effects of disruptions in maternal care and attachment behavior in humans with a history of inadequate care (e.g., abuse, neglect, institutionalization, etc.). A further understanding of the general behavioral alterations produced by AR may help clarify the mechanisms by which maternal care (or lack thereof) propagates across generations.

NOTES

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