Behavioural Brain Research 224 (2011) 318–325

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Dissociation between neonatal novelty-induced preferential maternal care and enhancement in cognitive, social, and emotional functions

Bethany C. Reeb-Sutherland[a,1], Akaysha C. Tang[a,b,*]

[a] Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States
[b] Department of Neurosciences, University of New Mexico, Albuquerque, NM 87131, United States

ARTICLE INFO

Article history:
Received 2 March 2011
Received in revised form 6 June 2011
Accepted 9 June 2011
Available online 17 June 2011

Keywords:
Maternal care
Maternal mediation
Maternal modulation
Post-natal handling
Neonatal handling
Neonatal novelty exposure
Spatial memory
Social memory
Aggression
Behavioral inhibition

ABSTRACT

Early life stimulation is known to produce long-lasting changes in the brain and behavior. One such early stimulation method is the neonatal novelty exposure procedure which allows the isolation of the novelty effect from several prominent confounding factors inherent to the neonatal handling procedure. In two previous studies, we found long-lasting novelty effects on different sets of functional measures without accompanying preferential maternal care, even when the observation was made immediately after the novelty manipulation, a time when such preferential care is most likely to be expressed. Here, within a single cohort of Long-Evans male rats, we demonstrate that novelty exposure leads to enhancements across several functional domains, including increased disinhibition to novelty, enhanced spatial and social memory, and reduced aggression, again without the accompaniment of preferential maternal care. These findings extend novelty exposure effects to aggression and replicate previously known novelty exposure effects on spatial and social memory with extension to new developmental stages. Most importantly, these findings do not support the hypothesis that preferential maternal care towards novelty-exposed pups mediates the observed novelty effects. We discuss the possibility that the effects of neonatal novelty exposure are *mediated* via repeated activation of the hypothalamic–pituitary–adrenal (HPA) axis that serves to inoculate pups for future exposures to novelty and novelty-induced HPA activation and that maternal influence is likely to be expressed via its *modulatory* role—the mother sets the individual-family specific behavioral and hormonal context to allow the same early life experience to have a family-specific effect.

1. Introduction

In rodent studies of early experience on development, the neonatal handling procedure has been one of the most frequently utilized manipulations. Over half a century ago, when Levine and colleagues [1] first set out to investigate the effects of neonatal stress induced by repeated electric shocks delivered to rat pups, they made an unexpected discovery – both the repeated-shock (Shock) and control (referred to as Handling) groups produced similar effects on the offspring's stress response, a faster initiation and recovery of the corticosterone stress response, in comparison to a third group that received only the standard laboratory rearing treatment (referred to as Non-Handling) [1]. Since this paradoxical finding, neonatal handling has become a frequently used paradigm for studying early experience effects on adult function [2,3]. In comparison to the Non-Handling treatment, Handling treatment involves at least the following additional factors: pup stress due to novelty exposure, separation from the dams, and handling by the experimenter and maternal stress due to her separation from the pups [4,5]. Therefore, handling as a name for the Handling treatment is more of a misnomer that can easily lead to casual unsupported conclusions, when, in reality, the actual observations only support the conclusion that it is at least some combination of the above that led to these changes in offspring physiology.

To address these well-known methodological problems and consequently improve interpretability of findings, the neonatal novelty exposure procedure was introduced to isolate the novelty component from the other confounding factors that are inherent to the neonatal handling procedure. Other laboratories have since replicated the effectiveness of this procedure in creating novelty-induced changes in the brain and behavior [6,7]. By utilizing a within-litter design, this procedure entails exposing half of a litter to a relatively novel non-home environment (Novel) while keeping the other half within the familiar home cage (Home). Therefore,

* Corresponding author at: University of New Mexico Albuquerque, NM 87131, United States. Tel.: +1 505 277 4025; fax: +1 505 277 1394.
E-mail address: akaysha@unm.edu (A.C. Tang).
URL: http://atlab.unm.edu (A.C. Tang).
[1] Present address: Department of Human Development, University of Maryland, College Park, MD 20742, United States.

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doi:10.1016/j.bbr.2011.06.010

the novelty effect is determined by comparing two groups of sibling pups that share the same mother. By further matching the experimenter handling and maternal separation between the Novel and Home siblings within the same litter, this procedure allows one to draw conclusions regarding the novelty exposure effect without differences in experimenter handling, pup separation stress, and maternal separation stress between Novel and Home pups that confound the effects of novelty. At the level of behavior, this neonatal novelty exposure procedure has previously been shown to lead to enhanced spatial memory [7–9], improved social recognition memory [10], increased recovery from novelty-induced behavioral inhibition [6,11], and increased competitive success in winning limited resources [12].

For several decades, it has been suggested that maternal care mediates the effects of early stimulation [13–18, but see also 19,20,21] based on findings of correlated handling-induced changes in the offspring and handling-induced changes in maternal care. In the case of novelty exposure-induced changes, although the novelty-exposed and home-staying siblings share the same mother, it cannot be presumed that the mother treated them similarly upon their reunion, particularly given that dams are known to discriminate between her disturbed pups, that were taken away from the nest to experience a low-temperature environment, and undisturbed pups, who stayed in the nest [22]. Therefore, some may suggest that the various effects of neonatal novelty exposure may be similarly correlated with preferential maternal care directed towards novelty-exposed rats, analogous to the greater amount of maternal care displayed by dams of the pups that experienced the handling treatment. However, it has been shown that despite a lack of retrieval-based preferential maternal care, a measure observed immediately after the novelty exposure treatment and shown to be positively associated with subsequent active nursing of the pups, novelty-induced enhancement in adult offspring's spatial memory was nevertheless observed [23]. Furthermore, in a separate study, novelty-induced enhancement in social competitiveness and the plasticity of the hypothalamic–pituitary–adrenal (HPA) axis was accompanied by a lack of retrieval-based preferential maternal care [12,23]. Together, these findings do not appear to support the hypothesis that preferential maternal care mediates novelty-induced enhancements in spatial memory, social competitiveness, and plasticity of the HPA axis.

Here, we aim to investigate, in a single cohort of rats, whether effects of neonatal novelty exposure across multiple behavioral endpoints—previously examined either separately or without a simultaneous examination of possible preferential maternal care—can be demonstrated with or without preferential maternal care. Secondly, we sought to investigate whether this dissociation can be consistently observed, because in two previous studies, one found preferential care towards the home-staying instead of the novelty-exposed pups [23] and the other found a lack of such preference [12]. A final goal of the current study was to extend the set of novelty exposure effects to include previously unexplored functions, specifically social aggression, and to extend known novelty effects to ages previously not examined.

2. Materials and methods

2.1. Experimental animals

All experimental procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and with approval by the Institutional Animal Care and Use Committee at the University of New Mexico. Twenty-two pregnant Long-Evans hooded dams (Harlan, Indianapolis, IN) arrived at the Psychology Department vivarium 10–12 days prior to giving birth. Upon arrival, each dam was individually housed in a translucent plastic cage (51 cm × 25 cm × 22 cm) and maintained on a 12-h light/dark cycle (lights on at 8:00 a.m.) with food and water *ad libitum*. Temperature and humidity were 21 °C and 25% respectively. The litter size ranged between 6 and 14 pups at the time of birth and was culled within 8 h of birth to 8 pups per litter to maintain similar litter size across dams. During culling, if the number of male pups were fewer than 8, female pups were kept to maintain the 8-pup litter size. Pups were housed with the dams until weaning on postnatal day (PND) 21 from which time on the pups were housed separately in translucent plastic cages (51 cm × 25 cm × 22 cm) without further environmental enrichment. Of the pups born, only the male offspring (N = 106) were used in this study.

2.2. Neonatal novelty exposure

On PND21, approximately one-half of each litter was pseudo-randomly assigned to the Novel and the other half to the Home conditions (split-litter design), with body size counter-balanced between the two groups by visual inspection. Apparent body size rather than precisely measured body weight was used to minimize experimenter manipulation that was not pertinent to key experimental manipulations. In comparison to the default random assignment procedure, by taking apparent body size into consideration, additional information was used to counter-balance the distribution of body size across the Novel and Home groups, thus contributing to an improved experimental design. Group membership was marked by tattooing the left and right hind paws of the Novel and Home pups using two different digit combinations: (1) left first and right fifth, and (2) right first and left fifth. The precise patterns of marking were counterbalanced between the Novel and Home groups across litters.

During PND1–21 between 10:00 and 15:00 h, the neonatal novelty exposure procedure (Fig. 1A and B) was carried out in the animal housing room and involved half of each litter spending 3 min away from the familiarity of their home cage (Novel group) and their matched control siblings remaining in the home cage (Home group). Specifically, the dam was first removed from the home cage. The Novel and Home pups were then identified by examining toe markings. Once identified, Novel rats were placed in a new cage (30 cm × 19 cm × 13 cm) lined with fresh bedding for their 3-min exposure and subsequently returned to their home cage in which the Home rats remained. During this transfer, each Novel pup was yoked to a Home pup that received a matching amount of experimenter contact at approximately the same time as the yoked Novel pup. The dam was returned to the litter after both the Novel and Home pups were reunited in the home cage. The amount of touching by the experimenter and the duration of maternal separation during this novelty exposure procedure was matched between the Novel and Home rats, thus ensuring that any difference in outcome measures between the two groups was attributable to neither dam separation nor experimenter touch. It should be noted that the total duration of separation between dams and all of her pups was less than 15 min, which does not constitute the kind of prolonged maternal separation (>3 h) known to result in deficits in offspring emotional, cognitive, and neuroendocrine function [for review, see 24].

This procedure is in contrast to the commonly used neonatal handling procedure [1–3] that utilizes a between-litter design in which the Non-Handled litters remained entirely undisturbed and the Handled litters experienced a combination of at least four manipulations: (1) "handling" of experimental animals by the experimenter; (2) separating the neonates from their mother; (3) increasing the mother's stress by separating her from her pups; and (4) exposing the neonates to an unfamiliar environment, i.e. novelty. Therefore, by using a split-litter or within-litter design, the novelty exposure component is isolated from the other three confounding factors, including maternal stress and associated maternal behavioral differences, inherent to the neonatal handling procedure [8].

2.3. Offspring behavioral measures

Offspring reactivity to a novel environment, spatial working memory, social recognition memory, and aggression were investigated longitudinally in the same cohort of rats (Fig. 1a). These functions have been previously examined at ages different from those in the present study or within the context of other experimental manipulations.

2.3.1. Disinhibition to novelty (open field test)

When exposed to a novel environment, animals typically show at least a brief period of behavioral inhibition, expressed as freezing or displaying little movement, followed by a period of increased exploration, which we refer to here as disinhibition. This rapid change in the initial behavioral response to novelty was examined using a unique open field procedure consisting of multiple shortly spaced 20-s long exposures [11,25]. In contrast to the typically used open field testing parameters which include several minutes (up to 30 min) of continuous exposure, this procedure allows efficient assessment of the rat's initial response to a novel environment.

Specifically, on PND24, animals were exposed to a novel open field (60 cm × 60 cm × 20 cm) during eight 20-s trials. An experimenter who was blind to the treatment condition tested animals in groups of eight. To maximize the initial fear of novelty, individual pups were placed in the center of the open field. At the beginning of each trial, rats were briefly covered by a cardboard box similar to the size of their body. The trial began immediately after the box was lifted and the rat was allowed to ambulate freely. To minimize interference with the rat's ongoing behavior, the experimenter remained still and in the same location during all trials. All trials were videotaped by a camera mounted directly above the open field. Activity level was defined as the number of 12 cm × 12 cm squares traversed. To quantify

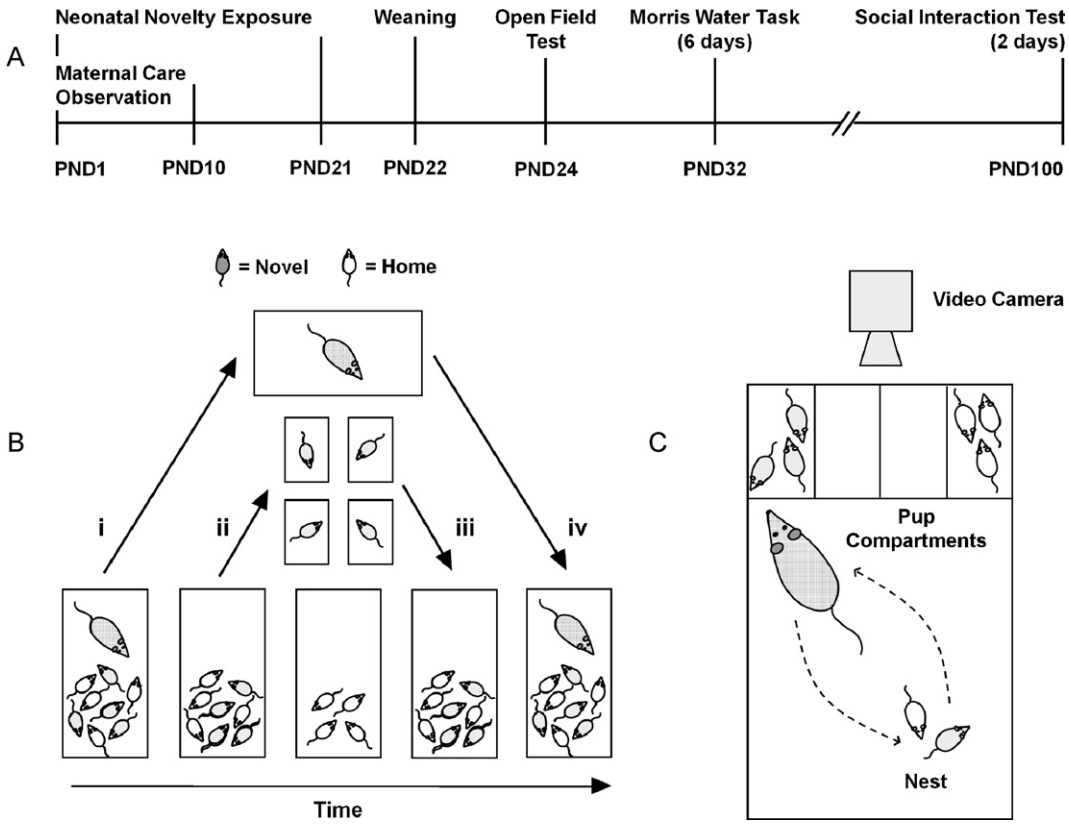

Fig. 1. Experimental methods. (A) Timeline of neonatal novelty exposure, post-exposure maternal care observation, and assessment of offspring emotional reactivity to novelty, spatial working memory, social recognition memory, and social aggression. (B) Sequential steps in neonatal novelty exposure using a split-litter design. For each litter: (i) Removal of dam from home cage. (ii) Transfer of Novel pups (solid color) to individual non-home cages (small rectangles). (iii) Return of Novel pups to home cage after a 3-min exposure to non-home cages. (iv) Return of the dam to the entire litter in the home cage. (C) Setup for observation of post-novelty-exposure pup retrieval.

the rapid initial change in behavioral inhibition upon entering the open field, we used a disinhibition score, defined as the difference in open field activity between Trial 2 and Trial 1 [T2 – T1; 11].

2.3.2. Offspring spatial working memory (Morris water task)

Spatial working memory refers to memory for spatial locations that are not permanent but frequently updated. This type of memory can be evaluated using a moving platform version of the Morris water task in which the rats must learn a new location on each day of testing instead of a fixed location across all days of testing [26–29]. At the onset of juvenility (PND32–38), we tested novelty exposure effects on such spatial working memory using our own previously tested adaption of this moving platform task (for details see Tang et al. [9] and Yang and Tang [30]).

Briefly, the rats were trained to escape the cold water (21 °C) by finding a square platform (15 cm × 15 cm) that was hidden underneath the surface of the water in a circular tank (170 cm diameter) using distal cues in the testing room. They were tested in batches of 8, which created inter-trial intervals of 5–12 min across training days. The order of the testing was counter-balanced between the Novel and Home rats and the experimenter was blind to the rats' group identity. Working memory was indexed by a normalized one-trial learning score [Norm_OTL; 30] defined as the latency difference between Trial 1 and Trial 2 normalized by Trial 1 latency (Norm_OTL = (T1 – T2)/ T1 × 100). This normalization allows for better isolation of learning taking place between the two trials by controlling for any potential differences in Trial 1 latency, which may be influenced by the rat's memory for the platform location from training on the previous day. Based on previous findings, such a one-trial learning measure is particularly sensitive to the neonatal novelty manipulation on the first of testing day that require working memory, i.e. testing Day 2 [30]. The additional days of testing beyond the initial days allowed both the Novel and Home rats to reach asymptotic performance and a lack of difference at the asymptotic performance served to confirm that the two groups did not differ in their motor, sensory, and motivational functions.

2.3.3. Social recognition memory and aggression (social interaction test)

Social recognition memory refers to the memory for a conspecific and this memory has been typically indexed by habituation in the frequency of social investigation of one rat directed towards another rat over repeated social interaction sessions [31]. On PND100, shortly after the rats entered adulthood, we tested social recognition memory between non-sibling age- and weight-matched Novel–Home pairs in a neutral testing cage following a procedure simplified from that used in our previous study [10].

Briefly, pairs of rats were observed on two consecutive days during four 5-min sessions, three sessions on day 1 and one session on day 2. Social investigation was defined as being proximally oriented to a conspecific with the tip of the nose within 1 cm of the conspecific's body while sniffing, following, nosing, or grooming. For each session, social investigation was measured from sixty 5-s video segments. An occurrence of one was counted if the presence of the behavior occurred any time during the 5-s duration.

Based on our previous findings in 7-month-old rats demonstrating novelty exposure-induced enhancement in 24-h social recognition memory, indexed by the long-term habituation (LTH) score and defined as (Day 1 S1 – Day 2 S1)/ Day 1 S1 × 100, we focused our analysis exclusively on this LTH score. It should be mentioned that this reduction in social investigation across a 24-h delay is not due to an inability of the rats to detect social stimuli [10].

The sessions of social interaction also allowed us the opportunity to observe any occurrence of biting behavior. Using the same procedure for measuring the frequency of social investigation, we similarly recorded the frequency of biting. This operational definition contains more information than that used in our previous study where only the number of rats displaying biting was reported [32]. In that earlier study, no differences in the number of rats displaying biting was found between the Novel and Home groups, perhaps due to a lack of sensitivity in the measure.

2.4. Post-novelty exposure maternal care measures

To address the question of whether Novel and Home pups were treated differentially by the dams after the novelty exposure, we used a retrieval-based procedure [23] to capture discriminative maternal care at a time when maternal discrimination was most likely to occur. This post-novelty exposure retrieval-based measure can be considered a reasonable indicator for licking-nursing-based maternal care because measures of retrieval latency after litter disturbance was found to be positively associated with licking-nursing-based measures of maternal care [23]. Following novelty exposure, Novel and Home pups were returned either on the left or the right front corner inside a plastic open-top compartment with positions counterbalanced between Novel and Home pups as well as across days (Fig. 1c). From PND1–10, maternal retrieval behaviors were videotaped for 10 min and scored

Table 1
Descriptive statistics for offspring behavioral measures (mean ± sem).

	Open field test Activity (# of squares traversed)		Morris water task Swim latency (s)		Social interaction test Investigation frequency (counts)	
	T1	T2	T1	T2	Day 1	Day 2
Novel	11.2 (.6)	13.8 (.7)	51.3 (1.9)	24.9 (3.3)	23.2 (1.0)	18.7 (1.2)
Home	10.8 (.8)	10.7 (1.0)	43.4 (2.4)	29.6 (3.3)	23.2 (1.0)	22.5 (1.0)

offline for maternal retrieval order and latency from the moment of whole litter reunion. For more details on measuring retrieval order and latency, see Tang et al. [23].

2.5. Statistical analysis

As the novelty exposure is a within-litter factor, litter was used as the unit of analysis. Paired samples *t*-tests were conducted on each dependent measure to determine whether novelty exposure had a significant effect. Wilcoxon signed rank test was also used in the case of the aggression data due to the presence of many zero values causing a non-normal distribution.

3. Results

3.1. Novelty exposure effect on open field disinhibition

At PND24, we measured the number of squares traversed during eight 20-s trials in an open field test to specifically examine disinhibition defined as an initial increase in open field activity from the first to second trial of exposure. Repeated measures ANOVA with Trial and Group as within-subjects measures revealed a significant Trial × Group interaction ($F(7,126) = 2.506$, $p = .02$), indicating that the trends in activity level across multiple trials of testing differed between the Novel and Home rats. While follow-up analyses revealed no statistically significant differences on the initial trial of exposure to the open field ($p > .20$, Table 1), Novel rats showed a greater average activity level across the first 4 trials than the Home rats ($t(21) = 2.524$, $p = .032$, data not shown) whereas no difference between Novel and Home average activity during the last 4 trials was found ($p > .2$). Most importantly, consistent with previous findings [11], we found that open field disinhibition was significantly greater in Novel compared to Home animals (Fig. 2A, $t(20) = 2.517$, $p = .02$). Table 1 displays the average open field activity for Novel and Home rats for T1 and T2.

3.2. Novelty exposure effect on learning in a Morris water task

On PND33, we measured rats' swim latency across eight trials on testing Day 2 to determine whether Novel and Home rats differ in their one-trial learning (OTL), which measures how much the rats can learn after only a single swim trial of exposure to the newly experienced platform position on that day. Because Novel animals displayed a significantly longer swim latency during T1 than Home rats ($t(20) = 2.505$, $p = .021$, Table 1), which may be interpreted as an indicator for memory of the platform location experienced on Day 1 [30], we normalized the OTL score by dividing each animal's score by their T1 latency (Norm_OTL) for the purpose of having a measure that specifically indexed working memory for recently updated information. We found that Novel rats displayed greater Norm_OTL compared to the Home rats (Fig. 2B, $t(20) = 2.450$, $p = .024$). This difference in Norm_OTL is unlikely due to differences in motor and perceptual functions because it was only present when the testing situation was novel and disappeared as the rats became familiarized with this testing situation over the subsequent trials and days of training (data not shown).

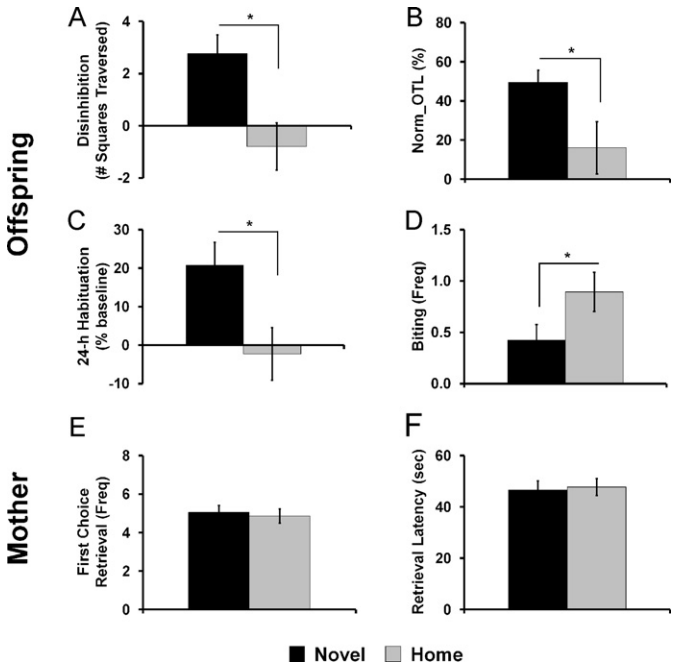

Fig. 2. Effects of neonatal novelty exposure on emotional, cognitive, and social functions and maternal care. In comparison to their home-staying siblings (Home, gray bars), novelty-exposed siblings (Novel, black bars) displayed: (A) greater disinhibition in the novel environment of an open field (PND24); (B) greater one-trial learning (Norm_OTL) in the working memory version of the Morris water task (PND33); (C) greater 24-h habituation in a social recognition test (PND100); and (D) reduced frequency of biting towards a novel conspecific (PND100). These effects were observed in the *absence* of higher maternal retrieval priority (E) and shorter maternal retrieval latency (F).

3.3. Novelty exposure effect on 24-h social recognition memory and aggression

On PND100, we measured the amount of social investigation exhibited by age- and weight-matched non-sibling Novel–Home pairs during four 5-min sessions across two consecutive days to examine 24-h social recognition memory, indexed as 24-h habituation, and defined as the decrease in social investigation from the first session on Day 1 to the first session on Day 2 [10]. Novel and Home rats did not differ in their initial levels of social interest in the new conspecific as there was no statistically significant difference in the frequency of social contact during the first session of social interaction ($p > .20$; Table 1). Consistent with our previous findings made at 7 months of age, Novel rats showed greater 24-h recognition memory when compared to Home rats (Fig. 2C, $t(21) = 2.521$, $p = .02$).

To index aggression, we measured the frequency of biting exhibited during the same four 5-min sessions of dyadic free interactions. In comparison to the high frequency of aggression observed in the intruder paradigm in which an intruder rat is placed into the home cage of a resident rat [33], the frequency of aggressive biting during the present dyadic interactions in a neutral cage was low, occurring

among only 25% of rats. Novel rats displayed *reduced* frequency of aggression compared to Home rats (Fig. 2D, $t(20) = -2.239$, $p = .037$; Wilcoxon signed rank test, $z = -1.907$, $p = .028$, one-tailed).

3.4. Novelty exposure effect on preferential maternal care

As mothers of Handled rats display greater quantity of maternal care towards their offspring and that greater maternal care is thought to act as a mediator of handling-induced changes in offspring stress regulation [17,18], it is conceivable that the above observed differences between the Novel and Home rats are mediated by preferential maternal care towards the Novel pups. From PND1–10, we observed maternal retrieval of pups to the nest immediately after novelty exposures, a measure found to be correlated with quantity of active maternal care [23]. We found that in contrast to one of our earlier studies [23] but similar to another such study [12], dams were just as likely to retrieve the Novel rats as her first choice as she would retrieve the Home rats ($p > .20$; Fig. 2E) and took a similar amount of time in retrieving her Novel and Home pups ($p > .20$; Fig. 2F).

4. Discussion

In a longitudinal study of 106 male offspring from 22 dams, we found that repeated brief neonatal exposures to novelty led to the following observations from the same cohort: greater disinhibition during the initial exposure to a novel open-field; better performance in spatial working memory; better performance in social recognition memory; and decrease in aggressive behavior during interaction with a novel conspecific. These results (1) extended the range of novelty-exposure effects to include a reduction in aggressive behaviors towards a novel conspecific and extended the previously known novelty effects on disinhibition and spatial and social memory to rats of different ages; and (2) replicated the juxtaposition of novelty effects on multiple offspring behavioral endpoints and lack of accompanying novelty-induced preferential maternal care towards the novelty-exposed pups.

4.1. Novelty effect on open field disinhibition

Behavioral inhibition, defined as a heightened tendency to withdraw from novelty in a physical or social environment, is one of the best characterized and most extensively documented temperamental characteristics in child development literature [for review see 34,35]. In rats, individual differences in behavioral inhibition towards novelty have been measured by activity level in an open field test [36]. In the current study, we examined differences between Novel and Home rats on measures of behavioral inhibition using a novel open field. We found that although both the Novel and Home rats did not show differences in their initial activity during the first 20-s exposure to the novel open field, the Novel rats increased their exploration of the new environment more rapidly than the Home rats upon second exposure. We interpret this relative increase in activity in the open field as an indicator of animal's ability to habituate to novelty. This novelty-induced enhancement in the plasticity of behavioral response to novelty suggests that behavioral inhibition in the face of novelty, a temperamental characteristic thought to be highly stable in humans [35], appears to be modifiable and highly sensitive to even very brief but systematic exposures to novelty during infancy.

It should be noted that this measure of disinhibition differs from the measure of *disinhibited attachment* which has been characterized by the inappropriate, uninhibited approach towards an adult stranger typically exhibited by young children who experienced early deprivation while living in an institution [37]. Although our construct of disinhibition and disinhibited attachment both refer to behaviors observed in the context of novelty, disinhibition here refers to how quickly an animal habituates to a new environment after having previous exposure to that environment whereas *disinhibited attachment* refers to socially inappropriate behavior upon the initial encounter with an adult stranger.

4.2. Novelty effect on spatial working memory

Neonatal novelty exposure has been previously shown to enhance spatial working memory in infant or fully grown adult rats [8,9,23]. The present results show that neonatal novelty exposure also enhanced spatial working memory in juvenile rats (PND33), thus extending the time window in which novelty-induced working memory enhancement could be demonstrated. More importantly, two aspects of this present novelty-induced working memory enhancement are to be emphasized to highlight the differences between findings of handling effects and findings of novelty exposure effects on spatial memory and their possible implications.

First, the effects of neonatal handling on spatial memory in the water task may be more precisely referred to as an effect on spatial *reference* memory because spatial memory in these studies was operationally defined by a daily average performance across many trials after the rats were tested repeatedly with a stable fixed platform location from day-to-day [38–42]. In contrast, the effects of neonatal novelty exposure on spatial memory [8,9,23], should be referred to as an effect on spatial *working* memory because spatial *working* memory is operationally defined by a reduction in swim latency between two single swim trials on a single day when the rats were given a new platform location on each day [26–29].

Second, while population level or group differences in spatial memory between the treatment and control rats can be attributed to the handling treatment or the novelty exposure procedure, offspring family-to-family differences in early experience-induced enhancement in spatial memory can only be investigated and has only been accounted for in neonatal novelty exposure studies that exposed siblings of the same rat family to the experimental and control conditions. Specifically, variations in the magnitude and direction of the novelty effect in spatial working memory across different rat families can be explained, in part, by individual differences in the mother's regulation of her own stress response, as measured by maternal basal corticosterone (CORT) concentration, an end product of the HPA axis [9]. Specifically, larger within-litter novelty-induced enhancements in spatial working memory could be found when mothers had good self-stress regulation while a smaller within-litter novelty-induced memory enhancement, and in some cases impairment, could be found when mothers had poor self-stress regulation.

4.3. Novelty effects on social recognition memory and aggression

Neonatal novelty exposure has been previously shown to enhance long-term social recognition memory measured with a 24-h delay among rats at 7 months [10] but not at 7 weeks of age [43]. The present results extended this novelty-induced enhancement effect to include rats as young as 3 months of age (PND100). More importantly, novelty exposure also reduced biting extending the behavioral endpoint to include not only recognition memory but also aggression. Two aspects of the novelty effect on aggression are emphasized to highlight differences between the ways in which aggression is studied in the literature as well as the consequences of aggression.

Studies of early experience effect on aggression [44–47] typically utilize the resident–intruder paradigm [33] which is designed to increase displays of territorial aggressive behavior by introducing the intruder rat into the home cage of a resident target rat. In

contrast, the current study was carried out in a neutral cage with two stranger rats meeting for the first time. This procedure was originally designed to minimize aggression for the sake of studying social interaction and social memory. However, even with a low occurrence of aggressive behaviors, biting was nevertheless observed (25% of total epochs) and to our surprise, this biting measure was sensitive to the novelty exposure treatment. The lower frequency of biting among the Novel rats in comparison to the Home rats indicate that brief early exposures to novelty can lead to reduction in aggressive behavior during neutral social encounters in early adulthood.

Secondly, two types of aggression that have been documented in the rodent literature include offensive aggression which is motivated by access to food or a sexual partner and defensive aggression which is motivated by fear or perceived threat [48,49]. Using measures of offensive aggression, such as winning when competing for a reward, neonatal handling [50–52] and neonatal novelty exposure [12,23] both enhanced the ability to obtain access to the reward, therefore an *increase in offensive aggression*. In contrast, due to the absence of food and sexual reward, the present study demonstrated a novelty exposure-induced *reduction in defensive aggression*. These opposite effects of neonatal novelty exposure on aggression demonstrate that the consequences of early experience of novelty is context-dependent—appearing to be adaptive because being able to compete for limited resources and at the same time minimizing potential fights by reducing physically aggressive acts towards a conspecific is more likely to improve the chances of survival.

4.4. Multiple novelty exposure effects without preferential maternal care

In contrast to the correlations found between the handling treatment and licking-grooming/arched-back nursing-based maternal care [LG-ABN; 17,18], we once again observed, this time, across multiple behavioral endpoints, a dissociation between neonatal novelty exposure effects on disinhibition to a novel environment, spatial working memory, social recognition memory, and aggression and preferential maternal care towards the novelty-exposed pups. If preferential maternal care is indeed the mediator of novelty exposure effects, then novelty effects must be correlated with preferential maternal care. Neonatal novelty exposure studies conducted by two separate laboratories [6,12,23] have found no such correlations and these repeatedly reported negative findings, at least, lower the likelihood of maternal care quantity-based mediation and question any exclusive focus on the LG-ABN-indexed maternal care. Most importantly, this lack of association between novelty exposure effects and LG-ABN-indexed maternal care suggests that the role played by the mother in novelty exposure effects may be found among maternal variables other than the mere quantity of maternal LG-ABN.

The current operational definition for preferential maternal care is based on post-novelty exposure maternal pup retrieval, induced by the disturbance of the nest as a consequence of novelty exposure. One may argue that the dams might show preferential care towards the novelty-exposed pups long after, instead of immediately after, the novelty exposure manipulation. However, we argue that the overt behavioral differences between the novelty-exposed and home-staying pups are more likely to be most discernable immediately after the novelty exposure for the dams to use as a basis for maternal discriminatory care than long after the exposure. Therefore, it is less likely or unlikely that preferential care would be triggered long after the novelty exposure. One may further argue that novelty exposure may produce latent changes beyond the acute effects and these latent changes may continue to trigger preferential maternal care. This is less likely or unlikely as well because the behavioral differences between the Novel and Home rats were expressed in the context of environmental novelty and were absent when the situation became familiar [23], which is the case when the pups are with their mother in the home environment. Thus, it is unlikely that in the familiarity of the home environment, any latent novelty effects would be expressed in the first place, subsequently triggering preferential maternal care.

One may further argue that retrieval behaviors are distinctively different from maternal licking and nursing behaviors, thus may not be a good proxy for the latter. In a separate group of rats, we have previously confirmed that faster retrieval is associated with greater maternal licking and arched-back nursing (also referred to as active nursing) during the larger time window long after the early stimulation manipulation ($r = 0.725$) [23]. Others have shown that retrieval is also positively associated with the quantity of milk in the pups' stomach [53]. All of these considerations are consistent with the claim that retrieval-based maternal care measure obtained immediately after the novelty exposure manipulation is thus far the best way to capture any possible novelty-exposure-induced preferential maternal care. These considerations should not be interpreted as exclusive because other aspects of maternal behavior for example, abusive maternal behaviors towards the pups [54] may play a role which remains to be investigated.

Finally, the mother can also play a modulatory, instead of a mediatory role, that sets distinct behavioral and hormonal contexts under which the same early life experience, such as neonatal novelty exposure or neonatal handling treatment, can produce different effects on the offspring [23]. This hypothesis of maternal *modulation* of novelty exposure effects is consistent with several lines of evidence: (1) maternal presence and contact affects pups HPA response [55–57]; (2) maternal presence can provide the critical context to determine whether approach or avoidance is learned [58,59]; and (3) maternal measures of self-stress regulation [9,60] and maternal care reliability [12] can in part account for litter-to-litter variations in the direction and magnitude of novelty exposure effects on behavioral and neuroendocrine plasticity.

4.5. Neonatal novelty exposure effects: mediation and modulation

The search for a causal link, or mediating mechanisms, between early life stimulation and its well-known effects on behavior, has produced a literature that is heavily focused on the changes related to HPA function. At the level of receptors, neonatal stimulation has been known for some time to lead to an increase in glucocorticoid receptors (GRs) in the hippocampus which can subsequently lead to enhanced regulation of the HPA axis [for review see 61]. Although it is not yet directly known whether novelty exposure increases the number of hippocampal GRs, indirect evidence from several studies conducted in our laboratory are consistent with increased GRs as a result of neonatal novelty exposure. Specifically, neonatal novelty exposure leads to enhancement of the modulation of the hippocampal neuronal excitability and synaptic plasticity by CORT at stress level concentrations [62].

At the level of physiology, early stimulation has been shown to lead to a change in the CORT stress response via handling [1,38] and a neonatal novelty-induced reduction in basal CORT concentration [10] as well as such a novelty-induced increase in the initial CORT response to environmental novelty [12]. Therefore, Novel and Home rats are most likely to have differences in both basal and evoked circulating CORT concentrations before, during, and after each of the four behavioral tests. Given the important role of GRs in hippocampal neuronal excitability [63] and synaptic plasticity [64,65] and the well-established relationship between circulating CORT and aggression [66], the observed novelty effects on hippocampal-dependent spatial memory [8,23 and present findings], social recognition memory [10 and present

findings], aggression (present findings), and disinhibition to a novel environment [11 and present findings] most likely involve differences in both GR function and circulating CORT concentration.

If modification of the HPA function is an important part of neural mechanisms underlying the functional changes in the offspring, then in completing the causal chain, one must also address the presently unanswered question of how repeated brief neonatal novelty exposures can lead to particular patterns of changes in the parameters of HPA regulation, such as basal circulating CORT levels and rates of initial rise and subsequent recovery of the HPA response. Given that exposing the newborn pups to environmental novelty increases blood CORT concentration during infancy [67,68] and affects other aspects of the developing HPA axis [69,70], we speculate that daily brief exposures to novelty may serve to inoculate the novelty-exposed pups to develop a more resistant stress response system [71] for dealing with future encounters with social and non-social environmental novelty. This inoculation may occur at the psychological level, with repeated experience of novelty resulting in the offspring becoming immune to future exposures to novelty, i.e., not responding to novelty with excessive fear and/or anxiety, and at the physiological level, with repeated exposures to elevation of circulating CORT resulting in the offspring becoming immune to future novelty-induced surges in circulating CORT, i.e., being able to regulate the circulating CORT concentration in the face of novelty to set an optimal context for neural plasticity and learning.

We further hypothesize that this novelty exposure-induced inoculation takes place in a maternal modulatory context, i.e., the post-novelty exposure context that the mother provides. The mother may facilitate the recovery of her pups' novelty-induced CORT increase via consistent or reliable post-novelty exposure care [12] and via a low basal circulating CORT level of her own [9,60] that is accessible to the nursing pups via her milk [72–74]. Conversely, if the mother is unable to provide reliable post-novelty exposure care or unable to maintain a low basal circulating CORT level, the pups would have a delayed recovery of the novelty exposure-induced CORT increase and in these instances, brief novelty exposure can end up producing a relatively prolonged elevation of circulating CORT, an effect likely to be induced by prolonged stress exposure. Therefore, individual differences in the mother's ability to regulate her own circulating CORT and in the mother's consistency of post-stress maternal care can both set distinct contexts that enable the same early experience to produce a wide range, or even opposite effects on the offspring.

5. Conclusions

The present study was motivated by recent rodent studies that claim that a greater quantity of maternal licking and arched-back nursing is the mediator for handling treatment-induced offspring differences [17,18] and aimed specifically to critically examine to what extent preferential maternal care, induced by briefly exposing a subset of siblings from a given rat family to the novelty of a non-home environment, can account for a diverse range of long-lasting effects on the offspring as assessed across multiple behavioral endpoints. We confirmed for the third time that while neonatal novelty exposure treatment can consistently induce long-lasting behavioral changes in the offspring, the same treatment does not produce detectable preferential maternal care towards the novelty-exposed pups even at a time when such preferential care is most likely to be observed, thus contradicting what would be predicted if the maternal care mediation hypothesis holds true for the novelty exposure effects.

Therefore, the single most important conclusion reached through the present and previous two studies is that preferential maternal care as a result of neonatal novelty exposure treatment is highly unlikely the mediator of the diverse range of novelty effects on offspring cognitive, social, and emotional functions. Secondly, we provided the much needed distinction and contrast between the functions we attempt to characterize and the operational definitions used in measuring these functions and the much needed replication and extension to establish consistent and reliable neonatal novelty exposure effects on the offspring at different developmental stages and on behavioral endpoints previously unexplored. In summary, regarding the role played by the mother in early experience effects on adult function, the recent studies discussed above favor the maternal modulation hypothesis [23,55–57] over the maternal mediation hypothesis [13–18]. Regarding the causal links from early stimulation to enhancement in cognitive, social, and emotional functions, the literature favors the stress inoculation hypothesis [71] over the LG-ABN-based maternal care mediation hypothesis [17,18].

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