

Research report

Developmentally stable sex-dependent modulation of turning asymmetry by neonatal novelty exposure

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Abstract

In rats, early life stimulation can enhance learning and memory and induce parallel changes in brain asymmetry. Despite persistent interest in human brain asymmetry, relatively little is known in animal models about developmental stability of early-experience effects on asymmetry and how early-experience may affect males and females differently in asymmetry measures across developmental stages. We exposed male and female neonatal rats to a novel cage for 3 min per day during the first 3 weeks of life and measured spontaneous turning behavior at juvenility (7 weeks of age) and adulthood (7 months of age). We found that (1) the effects of such neonatal novelty exposure on turning bias are developmentally stable, and (2) neonatal novelty exposure differentially modulates turning bias in males and females. We briefly discuss implications of these findings in terms of the role of brain asymmetry in modulating cognitive and emotional development. © 2004 Elsevier B.V. All rights reserved.

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1. Introduction

Neonatal novelty exposure, an early life stimulation procedure involving daily 3-min exposures to a novel environment for the first 3 weeks of life [31], has been shown to result in long-lasting changes in learning and memory, synaptic plasticity, and brain asymmetry. For example, neonatal novelty exposure improved learning in the Morris water maze task and improved retention of an odor-reward association [31]. Parallel to these learning and memory related changes, the same manipulation also induced a selective enhancement in right hippocampal synaptic plasticity [32,47], a right-shift in hippocampal volumetric asymmetry [42], and a complementary left-shift in paw preference [36]. Recently, we found that neonatal novelty exposure resulted in both enhanced social recognition and a right-shift in spontaneous turning bias in adult rats, and that individual differences in social recognition can be predicted by the right-turn bias [35]. Along with computational theories [15,25], these findings suggest that development of brain

asymmetry may be closely tied to early life stimulation effects on learning and memory, and that understanding such development may shed light on the mechanisms mediating learning and memory enhancement.

Development of brain asymmetry is clearly modulated by early stimulation [3,4,7,8,14,28,29,32,34–36,42,47]. Typically, these early life stimulation studies have not addressed the issue of long-term stability of asymmetry across development. Although changes in structural and functional brain asymmetry measures were observed at different developmental stages, they were discovered in separate groups of animals [32,34,35,42,47]. So far, little is known about the developmental stability of these effects due to a lack of longitudinal studies. The only exception was a paw preference study, in which neonatal novelty exposure induced a left-shift in paw preference that persisted from juvenility to adulthood [36], indicating that the effect of early life stimulation on brain asymmetry was stable across these two ages.

Another important aspect of brain asymmetry development concerns interactions between early life stimulation and sex differences. Our earlier studies of neonatal novelty exposure effects have primarily focused on males [32,34–36,42,47]. In two recent studies, we found that the effects of neonatal novelty exposure differed between males

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and females. Specifically, in males, neonatal novelty exposure did not affect initial disinhibition in a novel open field, whereas in females, open field disinhibition was reduced by early life stimulation [33]. Neonatal novelty exposure also affected experience-dependent modification of social investigatory behavior in a sex-dependent manner, with males showing greater habituation to a familiar conspecific over time than females [24]. Given these sex-dependent effects of neonatal novelty exposure on social memory and emotional reactivity, as well as other known sex by early life stimulation interaction effects on brain asymmetry [3,4,28,29], we speculated that the effect of neonatal novelty exposure on brain asymmetry might also be sex-dependent.

In the present study, we aimed to investigate early environmental influence on the development of brain asymmetry in both males and females. Using a longitudinal design, we measured brain asymmetry at both juvenility and adulthood using spontaneous turning bias as an index. The primary goals of this study were (1) to determine whether effects of neonatal novelty exposure on turning bias were developmentally stable, and (2) to determine whether neonatal novelty exposure differentially modulated turning bias in males and females.

2. Methods

2.1. Animals

Ten pregnant Long–Evans hooded rats arrived at our laboratory 16–17 days prior to giving birth (Charles River, Raleigh, NC). Litters were culled to eight pups with approximately four males (from 3 to 7 per litter) and four females (from 1 to 5 per litter) kept in each litter. From the pups born of these dams, 36 males and 42 females were used in this study. Pups were housed with the dam until weaning at postnatal day 21. After weaning, animals were housed individually in translucent plastic cages (51 cm × 25 cm × 22 cm) with a 12 h/12 h light/dark cycle (lights on at 7:00 a.m.) and food and water *ad libitum*. Males and females were housed within the same rooms. All experimental procedures were in accordance with the Institutional Animal Care and Use Committee at the University of New Mexico.

2.2. Neonatal novelty exposure

This procedure was derived but differs from the well-known neonatal handling method [6,16]. On postnatal day 1, approximately half of each litter was pseudorandomly assigned to the Novel group and the other half to the Home group (split-litter design) so that approximately equal numbers of males and females were in each group. Group identity was distinguished by a toe-clipping procedure on both hind paws. Two patterns of toe clipping (left first/right fifth digit or right first/left fifth digit) were counterbalanced between Home and Novel pups to avoid any lateralization

effect between groups. This procedure, performed without anesthesia, lasted less than one second per side, and was no more traumatic than other methods of group identification such as ear punching. Toe clipping did not appear to produce any prolonged stress or behavioral deficits.

The neonatal novelty exposure procedure occurred in the housing room once a day from postnatal days 1 to 21, beginning around 1:00 p.m. each day. The duration of this procedure ranged from 2 to 5 h each day. First, the dam was removed from the home cage and transferred to a separate cage. The Novel pups were then identified and individually transferred to clean, small non-home cages lined with fresh sawdust of the same type as that used in the home cage. After 3 min, the Novel pups were removed from the non-home cage and returned to the home cage in which the Home pups remained. Finally, the dam was returned to the home cage. During the transfer, each time a Home pup Novel pup was touched, a Home pup was touched in a similar manner so that the amount of experimenter contact was matched between the two groups. In this manner, both experimenter contact and maternal separation were matched between Novel and Home pups, so the only differing factor between groups was the brief daily exposure to a novel environment.

2.3. Turning behavior

Behavioral data was collected during the cage habituation sessions of a social recognition experiment, of which the results will be discussed in a separate paper [23]. To evaluate the developmental stability of turning bias, animals were observed at both 7 weeks of age (juvenility) and 7 months of age (adulthood) during two 5-min exposures to novel cages over 2 consecutive days. Thus, the turning behavior of each animal was observed over a total of four 5-min sessions: two at juvenility and two at adulthood. A total of 78 animals were observed at juvenility (Novel males: 18, Novel females: 21, Home males: 18, Home females: 21). Due to mortality, only 69 of these original animals were observed at adulthood (Novel males: 16, Novel females: 19, Home males: 14, Home females: 20).

Pairs of Novel and Home rats were observed simultaneously. Prior to the observation session, red and green food colors were applied to the Novel and Home rat, with a Q-tip, to their dorsal and lateral surfaces. The color coding was counter-balanced between the Novel and Home rats with one half of each group labeled red and the other half green. The color assignment was pre-determined by a separate person who was neither the experimenter nor the coder. This color coding allowed both the experimenter and the coder of the turning behavior to be blind to the animals' experimental conditions. During the observation sessions, pairs of animals were placed in clean translucent cages lined with fresh bedding. Both the types of cage and bedding were identical to that used for housing. A cardboard partition securely placed in the middle of the cage separated the animals and prohibited them from seeing each other. This limited the

amount of space available for forward motion, thereby increasing the rates of discrete left and right turns. Throughout the entire testing period, the relative positions of Home and Novel animals within the observation room were counterbalanced to avoid possible asymmetrical environmental influences. When the experimenter transferred animals from their housing cages to the testing cage, one pair of Novel and Home animals was moved together using both hands. To avoid any lateralization effect that may be caused by the experimenter's handedness, if the Novel rat in the first pair was handled by the right hand, then the Novel rat in the second pair was handled by the contralateral hand. Sessions were videotaped for offline analysis.

The frequencies of three separate types of movement were counted during each 5-min observation session: right turns, left turns, and rearing. A right or left turn was defined as one 90° rotation in a clockwise or counterclockwise direction, respectively. Rearing was defined as one complete up-down movement involving the animal rising up on its hind limbs. For every day of observation, the frequencies of right (R) and left (L) turns for each animal were combined into a lateralization score (L-score) to measure turning bias. This L-score (%) was defined as $(R - L)/(R + L) \times 100$. Positive L-scores indicate a rightward turning bias, whereas negative L-scores indicate a leftward turning bias. An L-score equal to 0 indicates a lack of directional turning bias.

2.4. Statistical analysis

Because more than one animal from each litter was used, we tested for litter effects using multivariate ANOVA. As there were no significant litter effects on any of the measures, including general activity levels or daily L-scores, individual animals were used as units for the remainder of the analysis. Repeated measures ANOVA with sex and group as between-subject factors were used to examine day and age effects. Since no significant day or age effects on L-score were found, we pooled data from multiple days to create average L-scores for both juvenility and adulthood, and an overall L-score averaged over both ages of observation. Univariate ANOVA was then applied to the dependent measures

of L-score, rearing, and total activity. In cases of missing data due to technical difficulties ($n = 5$), a single day of L-score at one age was used in place of the 2-day average L-score. Following significant interactions, we examined group differences using nondirectional pairwise comparisons [27]. Pearson r was used to determine the stability of turning bias between days and ages of observation.

3. Results

3.1. Neonatal novelty exposure differentially modulated turning bias in males and females

From right and left turn frequencies, an L-score was derived to evaluate the direction of asymmetric brain function underlying turning bias. Repeated measures ANOVA revealed no significant day or age effects on L-score. A two-way ANOVA revealed a significant sex by group interaction effect on the 4-day average L-score ($F = 9.148$, $P < 0.01$, d.f. = 74; Fig. 1). For males, Home and Novel animals differed in L-score ($t = -2.836$, $P < 0.01$, d.f. = 34), with Home rats displaying a left-turn bias and Novel rats displaying no directional turning bias (Fig. 1a, left). This is similar to our previous reports on the effect of neonatal novelty exposure on turning bias in that Novel males displayed a right-shift in turning bias relative to Home males [34,35]. In females, however, no difference in turning bias was found between Home and Novel animals (Fig. 1a, right). When the patterns of sex differences were examined, the direction of sex differences was opposite between Home and Novel animals (Fig. 1b). In Novel animals, females displayed more of a left-turn bias than males ($t = -2.298$, $P < 0.05$, d.f. = 37), while in Home animals, males displayed more of a left-turn bias than females with marginal significance ($t = 1.996$, $P = 0.053$, d.f. = 37).

3.2. Sex-dependent effects of neonatal novelty exposure on turning bias were developmentally stable

To examine the developmental stability of the effects of neonatal novelty exposure on turning bias, we separately ex-

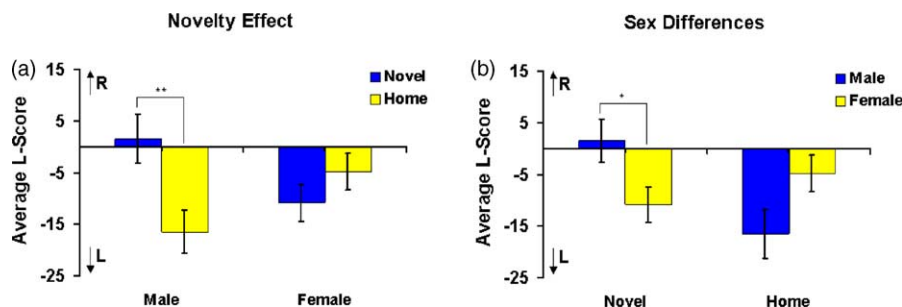


Fig. 1. Sex by neonatal novelty exposure interaction effect on average turning bias over all days of observation ($F = 9.148$, $P < 0.01$, d.f. = 74). (a) Effect of neonatal novelty exposure on turning bias is seen only in males. (b) The pattern of sex differences in turning bias is opposite between Novel and Home animals. (Note: same data displayed in panels a and b, but arranged differently). In all panels, data shown represent mean \pm S.E.M.; * $P < 0.05$, ** $P < 0.01$.

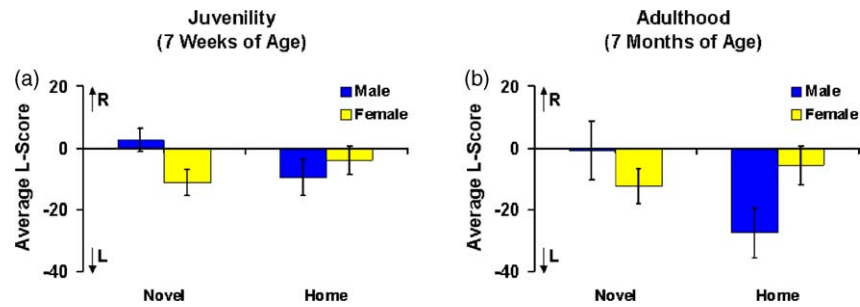


Fig. 2. Developmental stability of sex by neonatal novelty exposure interaction on turning bias. (a) At juvenility ($F = 4.424$, $P < 0.05$, d.f. = 74). (b) At adulthood ($F = 5.074$, $P < 0.05$, d.f. = 65).

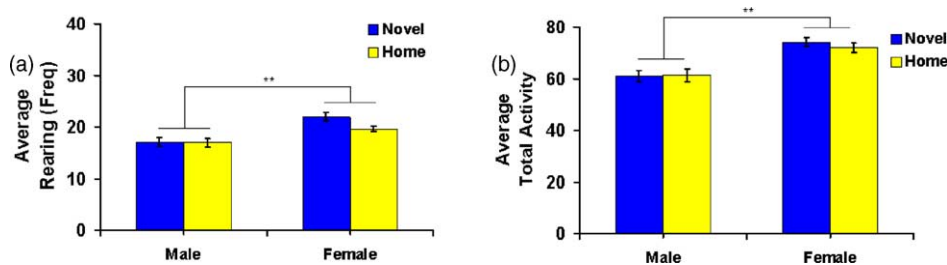


Fig. 3. General activity averaged over all days of observation. (a) Sex effect on rearing frequencies ($F = 24.119$, $P < 0.0001$, d.f. = 74). (b) Sex effect on total activity ($F = 32.242$, $P < 0.0001$, d.f. = 74).

amined the pattern of sex by group interactions at each age of observation. A two-way ANOVA revealed a significant sex by group interaction effect on the 2-day average L-score at both juvenility ($F = 4.424$, $P < 0.05$, d.f. = 74; Fig. 2a) and adulthood ($F = 5.074$, $P < 0.05$, d.f. = 65; Fig. 2b). Notice that the pattern of interaction at juvenility is similar to that at adulthood. Furthermore, the patterns of interactions at both juvenility and adulthood are similar to the pattern of interaction based on both ages combined (compare Fig. 2a and b with Fig. 1b). This stable interaction effect between sex and neonatal novelty exposure was not accompanied by stable individual L-scores. The correlation between the 2 consecutive days of testing was small but significant at juvenility ($r = 0.270$, $P < 0.025$, $n = 78$) and nearly significant at adulthood ($r = 0.245$, $P = 0.051$, $n = 64$). Over a longer interval, the correlation between juvenility and adulthood L-scores was not significant ($r = -0.037$, $P > 0.20$, $n = 69$).

3.3. Neonatal novelty exposure did not affect general activity levels

In contrast to the effects of neonatal novelty exposure on turning bias, rearing frequency and total activity (sum of rearing, right turns, and left turns) were not modulated by early life stimulation (Fig. 3a and b). Instead, there was a significant effect of sex on these general activity measures, with females showing higher rates of rearing and higher levels of total activity than males (rearing: $F = 24.119$, $P < 0.0001$, d.f. = 74; total activity: $F = 34.242$, $P < 0.0001$, d.f. = 74), which agrees with other reports of sex differences

in activity levels [18]. This contrasting pattern of effects between turning behaviors and non-turning related behaviors suggests that turning bias is independent of general activity levels and specifically reflects differences in directional preferences during spontaneous turning behavior.

4. Discussion

We examined how development of brain asymmetry in male and female rats is affected by neonatal novelty exposure. Development of brain asymmetry was assessed by a lateralization score based on spontaneous turning behavior observed on 2 consecutive days at both juvenility (7 weeks of age) and adulthood (7 months of age). We found similar patterns of sex by neonatal novelty exposure interactions at both juvenility and adulthood, suggesting that the sex-dependent effect of early life stimulation on brain asymmetry is stable across these two ages. Neonatal novelty exposure selectively affected the turning bias of males, and the pattern of sex differences in turning bias was opposite between novelty exposed and matched control animals.

4.1. Effect of neonatal novelty on sex differences in turning bias is stable across development

The first goal of the present study was to determine the stability of the effects of early life stimulation on brain asymmetry across development. We found similar patterns of sex by neonatal novelty exposure interactions on spontaneous

turning bias at both juvenility and adulthood (Fig. 2a and b), indicating that the sex-dependent effects of neonatal novelty exposure on brain asymmetry are stable at the group level. As it is possible for this stable group effect to be accompanied by a stable pattern of individual asymmetry, we examined the individual-level correlations between turning bias measured 2 days and 6 months apart across developmental stages. There was no correlation between juvenility and adulthood ($r = -0.037$), and only small correlations were found between 2 consecutive days of testing at juvenility and adulthood (r not exceeding 0.270). This lack of long-term individual stability in spontaneous turning bias is similar to that previously found in hamsters [39]. In that study, when turning bias was observed daily from postnatal days 2 to 60, the average individual correlation between any 2 consecutive days was 0.22 (close to our r of 0.245 and 0.270). Furthermore, the correlation over intervals of 5 days was nearly zero ($r = 0.02$), similar to our observed correlation over a six-month interval ($r = -0.037$). Studies of developmental stability in chick lateralization revealed similar day-to-day changes. Specifically, rapid switches between left and right hemispheric control occurred within 24 h during postnatal days 3–5 and those shifts coincided with major transitions in behavior and experience of the chicks [41].

In contrast to turning bias, the effect of neonatal novelty exposure on paw preference was highly stable and was accompanied by stable individual asymmetry over a delay of 6 months, with a correlation (r_s) of 0.927 [36]. The difference in individual-level stability between paw preference and spontaneous turning bias may reflect two different brain mechanisms underlying each form of asymmetry, the action and activation-based systems that differ in the neuromodulatory systems involved [22,38]. Regardless of the individual level stability, the current study and our previous paw preference study provide converging evidence that supports a developmental stability of early life stimulation effects on brain asymmetry.

4.2. Neonatal novelty exposure differentially affects turning bias in males

The second goal of this study was to examine whether early life stimulation affected the two sexes differently in a measure of brain asymmetry. Since the early days of neonatal handling research, the effect of early life stimulation on brain asymmetry has been predominantly studied in male animals [7,8,14,29,32,34–36,42,47]. Our finding that neonatal novelty exposure affected turning bias in males but not in females (Fig. 1a) suggests that males and females respond differently to this early life stimulation procedure. Similar sex-dependent effects have previously been reported in neonatal handling studies using a variety of asymmetry measures. In open field side preference, handled males showed an *increase* in initial left-wall preference, whereas handled females showed a *decrease* in left-wall preference [4,28,29]. In amphetamine-induced rotation, handling *decreased* left-

ward bias in males, while no change was found in females [4]. In tail pinch-induced asymmetry, handled males displayed no change, while handled females displayed a *decrease* in rightward bias [4]. In paw preference, handling *decreased* lateralization strength in male mice and *increased* the strength of lateralization in female mice, although this interaction was not significant [3]. Beyond measures of asymmetry, neonatal novelty exposure and neonatal handling have been shown to affect male and female animals differently in other areas, including social recognition memory and reactivity to stressful situations [9,20,21,24,33,43,44]. Given these previous findings and our present results, it is clear that one should not assume a priori that females will respond the same way as males to early life stimulation.

4.3. Neonatal novelty exposure reverses pattern of sex differences in turning bias

From the sex by neonatal novelty exposure interaction found in the present study, one can also examine how pre-existing sex differences might be modified by neonatal novelty exposure (Fig. 1b). This data showed that the pattern of sex differences in turning bias is reversed by neonatal novelty exposure. Specifically, among Novel animals, *females* showed more of a left-turn bias than males, while in Home animals, *males* showed more of a left-turn bias than females. Neonatal handling studies have also shown that early life stimulation can create opposite patterns of sex differences in lateralization. In handled animals, males displayed an initial left-wall preference in the open field while females did not display a directional preference, whereas the opposite was true among nonhandled animals [4,28,29]. In handled mice, females displayed stronger lateralization of paw preference than males, while the opposite pattern was found in nonhandled animals, although this interaction was not statistically significant [3]. In amphetamine-induced rotation and tail pinch-induced asymmetry, handling has been shown to result in amplification, rather than a reversal, of sex differences [4]. Thus, our present finding is consistent with the literature in that it provides further evidence that early life stimulation modifies patterns of sex differences in asymmetry.

4.4. Behavioral origin of neonatal novelty exposure effects on turning bias

The neonatal novelty exposure procedure differs from the neonatal handling method [6,16] in that it isolates the exposure to a novel environment from maternal separation and experimenter contact. Matching the amount of maternal separation and experimenter contact between the Novel and Home pups by using a split-litter design reveals that novelty exposure is sufficient to induce long-lasting changes in brain asymmetry. The sex-dependent effects of neonatal novelty exposure on brain asymmetry found in the present study may be due to differential maternal care toward novelty-exposed male and female animals. Dams have been

found to discriminate between male and female pups and to provide different maternal care depending on the sex of the offspring [19]. Stimulation of neonates has been found to lead to increased duration of maternal care and amount of maternal licking and grooming [1,17]. Thus, neonatal stimulation-induced changes in maternal care could interact with preexisting differences in treatment of male and female pups, resulting in a different pattern of sex differences between Novel and Home animals.

4.5. Asymmetric encoding of early life experience

The selective effect of neonatal novelty exposure on spontaneous turning bias in males is not an isolated finding. Rather, this change in turning bias adds to a set of neonatal novelty exposure-induced changes in structural and functional asymmetry. In a neuroanatomical study, neonatal novelty exposure produced a right-shift in hippocampal volumetric asymmetry [42]. In electrophysiological studies, long-term potentiation (LTP) and long-term depression (LTD) in the CA1 region of the hippocampus were enhanced among neonatal novelty exposed rats [37], but only in right hippocampal slices [32,47]. Consistent with this central right-shift, neonatal novelty exposure created a complementary peripheral left-shift in paw preference [36] and right-shift in spontaneous turning bias¹ [34,35]. Together, these findings provide converging evidence at neuroanatomical, neurophysiological, and behavioral levels that early life stimulation induces changes in brain asymmetry, and that the direction of these changes appears to reflect a rightward shift in brain asymmetry [7].

4.6. Functional significance of asymmetry

Since functional brain asymmetry was first reported in 1865, it has been speculated that patterns of brain asymmetry may somehow correlate with cognitive ability [13]. Early studies on amphetamine-induced rotation showed that degree of asymmetry (regardless of direction) could predict acquisition of operant behaviors and spatial discrimination [10,11,45,46]. Modern computational studies have suggested that functional lateralization may provide a computational advantage for learning [15,25]. In a social recognition task, neonatal novelty exposure extended the duration of recognition memory from less than 2 to at least 24 h [35]. Most interestingly, this enhanced social recognition memory was related to a greater spontaneous right-turn preference. This finding is analogous to the report that, in chicks, a right-hemisphere bias was associated with better social recognition [40]. Although the precise mechanisms that may mediate this asymmetry-learning connection are not yet understood, these findings nevertheless suggest the

interesting possibility that very brief and transient early life stimulation may serve to modify brain asymmetry, which may in turn modulate cognitive development. Beyond learning and memory, modulation of brain asymmetry by early experience may have further developmental implications, as brain asymmetry has been associated with emotion [5], the stress response [30], psychopathology [2,12], and the overall adaptive advantage of an organism [26].

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¹ Both a left-paw preference and a right-turn bias correspond to preferential right brain activation (see [34]).

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