



Research report

Functional brain asymmetry in adult novelty response: On fluidity of neonatal novelty exposure effects

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ABSTRACT

Novelty and surprises differentially modify the left and right sides of the brain. Here we show that repeated brief exposures to the novelty of a non-home environment during infancy and early adulthood lead to long-lasting changes in adulthood in the global bi-lateralization organization of the brain as indexed by a transiently detectable right-sided orientating bias upon the initial encounter with the novel environment. Most surprisingly, we show that in the same individuals, the short-term effect of the combined neonatal and adulthood novelty exposures on functional brain asymmetry measured at young adulthood (5 months of age) is distinctively different from the long-term effect measured at late adulthood (15 months of age). These results suggest that long-lasting, cumulative effects of early life experience on brain and behavior organization are not necessarily permanent, but continue to unfold, presumably via interactions with a multitude of unmonitored intervening life events.

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1. Introduction

Response to novelty or unfamiliarity is a fundamental capacity for all animals for it sets the stage for subsequent behavioral changes in response to varying environments. In humans, individual differences in this capacity during infancy [1] can predict individual differences in adult neural response to novelty [2]. In rats, experience of novelty during infancy leads to long-lasting changes in cognitive, social, and emotional functions as well as underlying changes in synaptic and neuroendocrine functions [3–6]. One of the most intriguing features of the novelty response is its asymmetric involvement of the two halves of the brain. In humans, novelty detection preferentially activates the right limbic circuitry [7]. In rats, behavioral reactivity to the novelty of an open field showed differential sensitivity to lesions of the left and right hemispheres [8], left and right frontal lesions and dopamine receptor blockade differentially affect neuroendocrine and autonomic stress responses [9,10]. Conversely, the initial onset of an unexpected restraint leads to an asymmetric dopamine response

in the prefrontal cortex [11]. Furthermore, repeated exposures to novelty during infancy lead to changes in paw preference [12], orienting bias in a novel environment [5,6], changes in hippocampal volumetric asymmetry [13], and an asymmetric enhancement in hippocampal synaptic plasticity [4]. Asymmetric responses to novelty have also been observed in other species [14–16].

We have identified, as a repeatable and non-invasive global index for functional brain asymmetry, a transiently expressed rightwards orienting bias, observable upon the initial encounter with a relatively novel situation [5,6]. We observed that this novelty-induced transient orienting bias can predict better social [5] and spatial [17] memory and is preferentially expressed among rats that had neonatal novelty exposure. Here, using this orienting asymmetry as a global index for bi-lateral brain organization, we examined the stability or permanency of early life novelty experience effects on functional brain asymmetry associated with novelty processing in a longitudinal study consisting of two early life manipulations and two adulthood observations. With two controlled manipulations of early experience of environmental novelty, one during infancy and one during the onset of adulthood, we aim to capture the interactive nature of cumulative experiences in development. With two repeated observations of the orienting asymmetry, one at an early stage and the other at a later stage of adulthood, we allowed ourselves the opportunity to discover whether any interaction effects of cumulative early life experience

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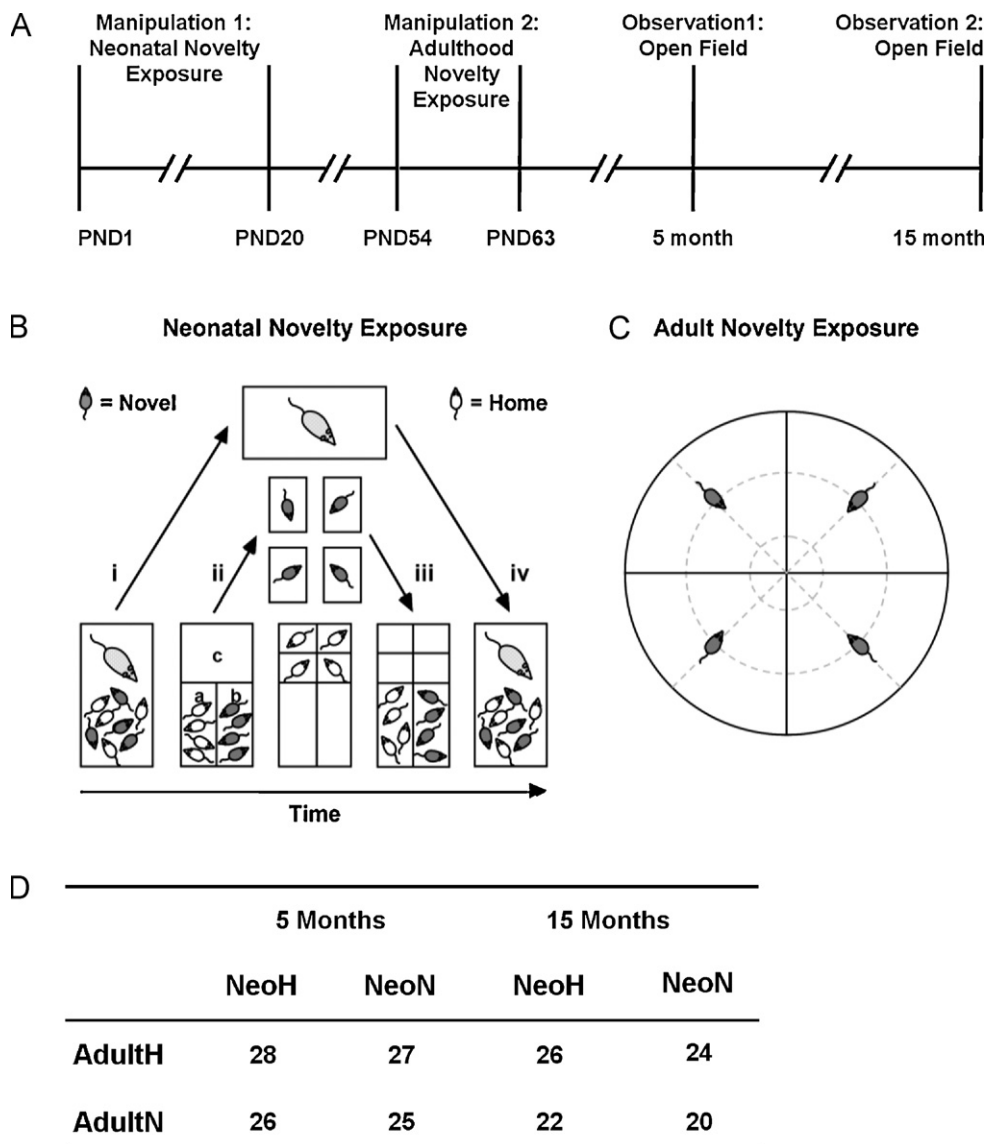


Fig. 1. Experimental methods: (A) timeline; PND: postnatal day. (B) Sequential steps in the neonatal novelty exposure procedure (split-litter design, PND 1–20): after the assignment of pups to neonatal novelty exposure conditions (NeoN, NeoH), the following is performed daily (i) Dam is removed from the home cage; (ii) After Novel and Home pups (NeoN, NeoH) are sorted into two compartments (areas a and b), Novel pups are transferred to individual non-home cages and Home pups are transferred to individual compartment in home cage (area c), both receiving a matching amount of experimenter contact; (iii) After 3 min, Novel pups are returned from non-home cages to area b in the home cage and Home pups are returned to area a in the home cage; (iv) After all dividers are removed, dam is returned to the home cage. (C) Adulthood novelty exposure (PND 54–63): after the assignment of young adult rats to adult novelty exposure conditions (HH: NeoH-AdultH; HN: NeoH-AdultN; NH: NeoN-AdultH; NN: NeoN-AdultN), the following is performed daily: the AdultN rats were removed from their home cage and placed in one of the four subsections of the Adulthood Novelty Exposure chamber for 3 min in a separate novelty exposure room and AdultH rats were handled in their home cage in the housing room. (D) Number of rats in each of the four treatment conditions at 5 and 15 months of age.

are permanent or modifiable throughout adulthood. The uniqueness of the current study lies in the repeated observations of the same cohort of individuals made both at early and late adulthood (5 and 15 months of age) and its combination with two early life environmental manipulations.

2. Methods

2.1. Participants

Nineteen pregnant Long-Evans hooded dams (Charles River, Portage, MI) arrived at the vivarium 12 days before giving birth. Litter size at birth ranged from 9 to 16 pups. Within 8 h after birth, litters were culled to eight pups maximizing the number of males. Pups were weaned on postnatal day (PND) 21 and were housed individually in transparent plastic cages (51 cm × 25 cm × 22 cm) with a 12 h light/dark cycle (lights on at 7:00 a.m.) and food and water *ad libitum*. One-hundred-

six males participated in the present study. All experimental procedures were in accordance with the Institutional Animal Care and Use Committee at the University of New Mexico.

2.2. Experimental design and procedures

During the first 3 weeks of life (infancy), pups within each litter were split into two groups: Neonatal Novel group (NeoN) being exposed to a novel environment for 3 min daily, while the Neonatal Home group (NeoH) remained in the home cage [for details see 5, 6, 18]. The assignment to the NeoN and NeoH groups was pseudo-random with the following constraints: (1) approximately one half of each litter was assigned to each group; (2) the size of the pups between the two groups was balanced by alternating the assignment of the next largest pup between the NeoN and NeoH groups. During PND 54–63 (early adulthood), each group was further divided into two groups, one exposed to additional novel experience in a sector open field for 3 min daily (Adulthood Novel, AdultN) and the other remained in the home cage (Adulthood Home, AdultH) [for details see 17]. At 5 and 15 months of

age, the rats' orienting bias was measured during exposure to a square open field (for experimental timeline, see Fig. 1A).

2.2.1. Refined neonatal novelty exposure

The neonatal novelty exposure procedure is a result of further improvement from that used in previous studies with an added control of littermate separation [5,6,18]. On PND 0, group membership was indicated by tattooing the hind paws. Both hind paws were marked to avoid a differential stimulation effect on the left and right brain given the various known effects of early stimulation on functional brain asymmetry [19]. Two patterns were used: with markings on the 1st digit of the left paw and 5th digit of the right paw (L1R5) or vice versa (L5R1). To avoid the novelty exposure treatment from being confounded by the patterns of marking, we counterbalanced the markings between Novel and Home rats across the litters.

Neonatal novelty exposure was conducted on PND 1–20 in the housing room (Fig. 1B). Between 0900 and 1500 h, the dam was first removed from the home cage and placed in a separate holding cage in the same room. The pups were identified by the experimenter as either NeoN or NeoH rats and sorted into compartments *a* and *b* within the home cage. Next, the NeoN pups were individually transferred into separate small non-home cages (30 cm × 19 cm × 13 cm) lined with fresh bedding similar to the bedding used in the home cage. The NeoH pups were also individually transferred into separate small compartments within area *c* of the home cage. The timing of transfer and experimenter handling for each NeoN pup was matched to that of the NeoH pup to maximize the similarity in experience. Both NeoH and NeoN remained isolated from their littermates for 3 min. To ensure that the duration of pup–dam separation is the same for the NeoH and NeoN rats, the dams were only returned to the home cage after all of her pups were returned to the home cage. These steps ensured that experimenter–pup, pup–pup, and dam–pup interactions were matched between NeoN and NeoH pups. Note that the total duration of separation between dams and all of her pups was no more than 15 min, which does not constitute the kind of maternal separation known to result in detrimental effects [20].

We refer to this procedure as neonatal novelty exposure because the treatments of the two groups of siblings differ only in that one group was removed from the familiarity of the home cage and the other was not. What constitutes novelty may include all changes associated with being away from the home cage, such as changes in acoustics, temperature, and olfactory environment. Therefore, these differences that constitute novelty exposure are not confounding factors. What occurs after novelty exposure and before the adulthood assessment that contributes to performance differences is a long chain of events triggered by the novelty exposure.

2.2.2. Early adulthood novelty exposure

During PND 54–63 (early adulthood) between 1200 and 1700 h, half of the neonatal novelty-exposed and half of the home-staying rats from each litter were exposed with additional novel experience (AdultN) in a sectored adulthood novelty exposure chamber (Fig. 1C, radius: 75 cm) for 3 min daily while the other half remained at home (AdultH). This resulted in a total of four treatment groups: NeoH-AdultN (5 months: *N* = 26, 15 months: *N* = 22), NeoH-AdultH (5 months: *N* = 28, 15 months: *N* = 26), NeoN-AdultN (5 months: *N* = 25, 15 months: *N* = 20), and NeoN-AdultH (5 months: *N* = 27, 15 months: *N* = 24). If a rat was assigned to the AdultN condition (NeoH-AdultN, NeoN-AdultN), it was first removed from the housing shelf to the transporting cart to be subsequently transported to a separate room for novelty exposure. Up to four rats were transported together and individually placed and remained in one of the four separate sectors of a circular open field for 3 min before being returned to the housing room (Fig. 1C). If a rat was assigned to the AdultH condition (NeoH-AdultH, NeoN-AdultH), it was also removed from the housing shelf to the transporting cart where it was picked up twice by the experimenter and placed in the opposite end of his own home cage in order to match the amount of handling that was experienced by the AdultN rats. The AdultH rats were directly returned to the housing shelf after this handling. This procedure was performed litter-by-litter to reduce within-litter variations. Within each litter, AdultH rats were handled within the housing room first, followed by exposing the AdultN rats to the sector open field. The order of NeoN and NeoH rats were counter-balanced within AdultH and AdultN conditions.

2.2.3. Assessing functional brain asymmetry in novelty response using orientation bias

At 5 and 15 months of age, functional brain asymmetry associated with novelty response was assessed in the same open field and in the same testing room. Functional asymmetry was measured by observing the direction of the initial orienting response made by each rat upon being placed in the center of a square open field (97 cm × 97 cm × 43 cm). We used an initial turn-based orientating asymmetry measure which in turn is based on a robust finding from our previous studies showing that upon entering a novel environment, rats display a novelty exposure-induced rightward shift in their turning preference [5,6,21]. This initial orienting bias differs from the robust turning or rotational asymmetry based on prolonged observations [22,23] in that the orienting bias used here is dynamic and changes as a function of environmental or situational novelty while the latter are stereotyped behaviors measured over an extended period of time.

All rats were placed into the center of a square open field facing away from the experimenter (apparatus not shown). Rats were tested in batches of 6–8 for a total

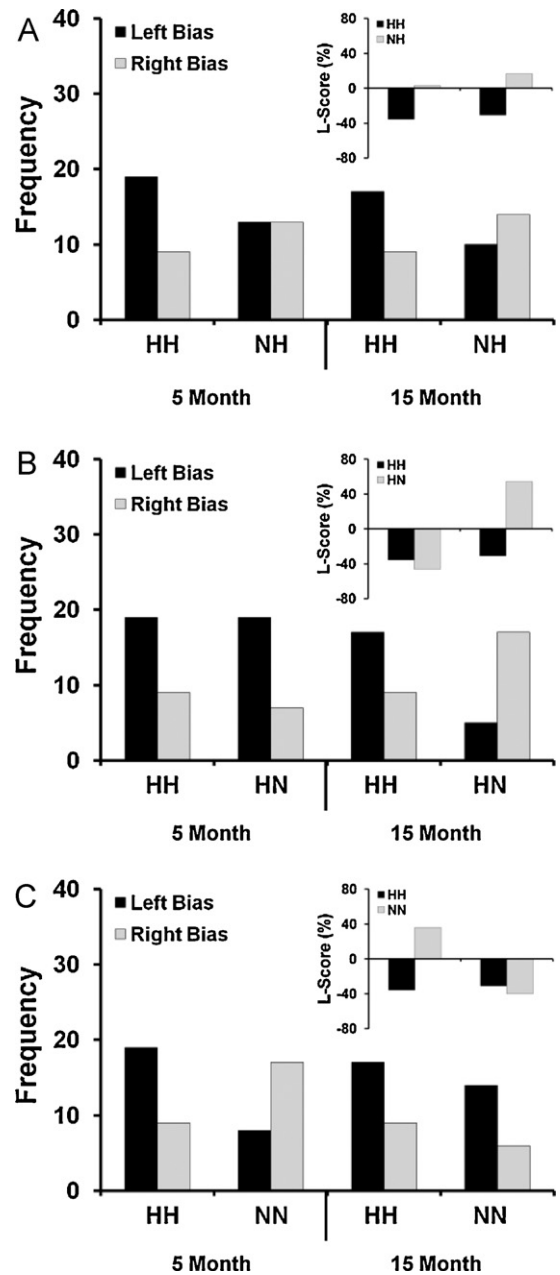


Fig. 2. Isolated and cumulative neonatal and adult novelty exposure effects on the initial orienting bias in response to exposure to a relatively novel open field. HH: NeoH-AdultH (no novelty exposure); HN: NeoH-AdultN (adulthood novelty exposure alone); NH: NeoN-AdultH (neonatal novelty exposure alone); NN: NeoN-AdultN (cumulative neonatal and adulthood novelty exposure). (A) Neonatal novelty exposure alone produces a developmentally stable rightwards shift from leftward orienting bias; (B) adult novelty exposure alone produces a delayed rightward shift from leftwards orienting bias; (C) combined neonatal and adult novelty exposure produced a shorter-term rightward shift but a longer-term return to leftward orienting bias. Chi-square tests were performed on frequency data and L score are computed for display purpose shown in insets. Figs. 2 and 3 are based on the same data but plotted in different combinations to address different questions.

of three repeated exposures (20-s duration, ~8-min inter-trial interval). The testing order was counterbalanced among all four treatment groups and rats from the same litters were tested together to minimize within-litter non-treatment-related variations. Both the experimenter and coder were blind to the group identity of the rats. Orienting response was recorded for offline coding and analysis. For each trial, a right or left orientation bias was defined as the midline of the rat's head turned 90° rightward or leftward, whichever happened first, relative to the original midline direction.

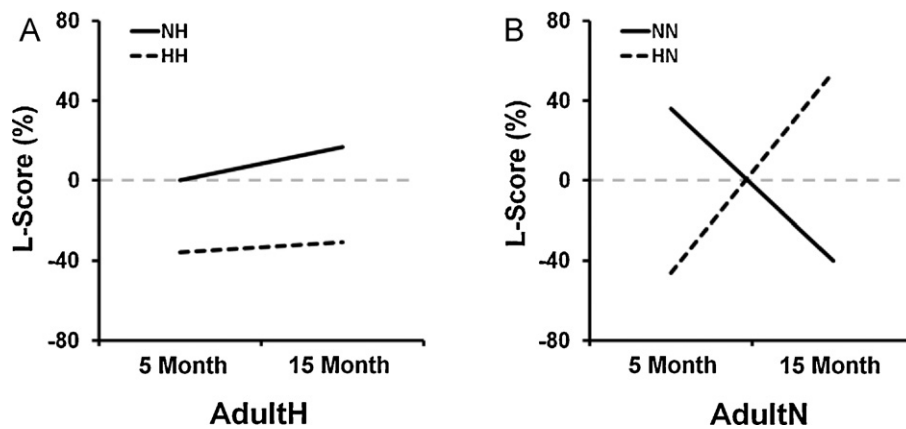


Fig. 3. Effects of neonatal novelty exposure with and without an adulthood novelty exposure. **AdultN**: rats with adulthood novelty exposure, including **HN** and **NN** rats; **AdultH**: rats without adulthood novelty exposure, including **HH** and **NH** rats. (A) For AdultH rats, the rightward shifting effect of neonatal novelty exposure is stable from 5 to 15 months of age; (B) for AdultN rats, the rightward shifting effect of neonatal novelty exposure undergoes a reversal to leftward shifting.

2.3. Statistical analysis

As there is no significant litter effect on the frequency of left and right orienting bias, individual rats were used as the unit of analysis. Chi-square tests were conducted for one- and two-way tests. Log-linear models (SPSS 17.0) were used to examine more complex interactions between neonatal novelty, adult novelty, age, and orienting bias and Z statistics were reported. For display purposes only, a lateralization score is defined for each of the four treatment groups, L-scores (%) = $(R - L) / (R + L) \times 100$; L, R: no. of left, right turners. As no significant effects were found for the 2nd and 3rd trials, only results on the 1st open field trial are reported.

3. Results

3.1. Functional brain asymmetry is jointly determined by novelty experience and age of observations

Based on the initial direction of orientation that the rat made upon entry into the open field, each individual rat was classified as having either a left or right orientation bias. The frequency data, i.e., the number of rats who have a left or right bias are shown in Fig. 2. For the rats who experienced neither the neonatal nor the adulthood novelty exposure (NeoH-AdultH rats), there is a leftward orienting bias indicated by a greater number of rats displayed a leftward orientation (5 and 15 month combined: $\chi^2(1, N=54)=6.00, p=.014$; 5-month only: $\chi^2(1, N=28)=3.58, p=.059$; 15-month only: $\chi^2(1, N=26)=2.46, p=.12$).

We found a significant 4-way interaction effect [neonatal novelty \times adult novelty \times age \times orienting bias: $Z=-3.20, p=.001$] indicating that orientation bias differed depending on whether the rats received the neonatal or adulthood novelty exposure and at what age the observations on orientation bias were made. To further address specific questions concerning separate neonatal and adulthood novelty exposure effects and their interaction effects, concerning the modifiability of neonatal novelty effects by subsequent adulthood novelty exposure, and concerning the permanency or modifiability of these early experience effects over repeated observations across adulthood, we further probed this 4-way interaction by performing subsequent focused analyses as described below.

3.2. Distinct neonatal, adulthood, and combined neonatal and adulthood novelty exposure effects

With the protection of the 4-way interaction effect, we made three separate 3-way analyses to test for separate effects of neonatal, adulthood, and combined neonatal and adulthood novelty exposure. For rats with neonatal novelty exposure alone (Fig. 2A),

in comparison to the NeoH-AdultH rats, we found *temporally stable* neonatal novelty-induced rightward shift in orienting bias shown as an increase in the number of right-turning rats among the NeoN-AdultH rats at both 5 and 15 months of age (NeoN \times orienting bias: $Z=2.080, p=.038$).

For the rats with adulthood novelty exposure alone (NeoH-AdultN; Fig. 2B), in comparison to the NeoH-AdultH rats, we found a significant interaction effect (AdultN \times age \times orienting bias: $Z=2.58, p=.01$) indicating a *temporally delayed* adult novelty-induced rightward shift among the NeoH-AdultN rats. While there was no apparent change in orienting bias at 5 months of age [$\chi^2(1, N=54)=.18, p=.68$, Fig. 2B left], there was a statistically significant latent rightwards shift at 15 months of age [$\chi^2(1, N=48)=8.73, p=.003$, Fig. 2B right].

For the rats with combined neonatal and adulthood novelty exposure (NeoN-AdultN) (Fig. 2C), in comparison with the NeoH-AdultH rats, we found a marginally significant interaction effect (NeoN-AdultH \times age \times orienting bias: $Z=1.93, p=.054$) indicating a *temporally transient* cumulative novelty-induced rightward shift on orienting bias. While there was a statistically significant rightward shift present at 5 months of age [$\chi^2(1, N=53)=6.80, p=.013$, Fig. 2C left], such a rightward bias disappeared at 15 months of age [$\chi^2(1, N=46)=.11, p=.74$, Fig. 2C right].

3.3. Distinct effects of neonatal novelty exposure with and without adulthood novelty exposure

With the protection of the significant 4-way interaction effect, we are able to further test whether the effect of neonatal novelty exposure is permanently fixed or subject to further modification by events occurring after the neonatal novelty exposure by performing two follow-up 3-way analyses for the rats with and without adulthood novelty exposure respectively (Fig. 3A and B). Without adulthood novelty exposure (Fig. 3A), we found a temporally stable neonatal novelty-induced rightwards shift in orienting bias from 5 to 15 months of age (NeoN \times orienting bias: $Z=2.080, p=.038$, also shown in Fig. 2A). In contrast, when the same neonatal novelty exposure was followed by adulthood novelty exposure (Fig. 3B), we found a significant 3-way interaction effect showing a reversal between 5 and 15 months of age, from a rightward shift at 5 months of age to a leftward shift at 15 months of age [NeoN \times age \times orienting bias: $Z=4.01, p<.001$]. These contrasting patterns of findings indicate that the effect of neonatal novelty exposure on orienting bias is not permanent but modifiable by subsequent brief exposures to yet another relatively novel environment during early adulthood.

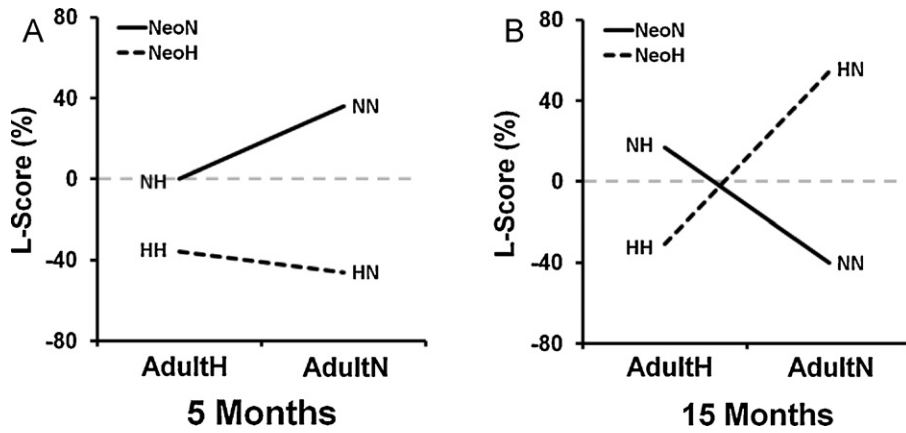


Fig. 4. Short- and long-term effects: opposite influences of adult novelty exposure on the effect of neonatal novelty exposure on orientation bias at 5 and 15 months of age. **NeoN**: rats with neonatal novelty exposure, including **NH** and **NN** rats; **NeoH**: rats without neonatal novelty exposure, including **HH** and **HN** rats. **AdultN**: rats with adulthood novelty exposure, including **HN** and **NN** rats; **AdultH**: rats without adulthood novelty exposure, including **HH** and **NH** rats. (A) At 5 months of age, adult novelty exposure potentiates the effect of neonatal novelty exposure; (B) at 15 months of age, adult novelty exposure leads to reversal of neonatal novelty exposure effect.

3.4. Distinct effects of novelty exposure at young and late adulthood

We further tested whether the interaction effect of neonatal and adulthood novelty exposure is permanent or subject to further modification by unmonitored intervening events occurring after both the neonatal and adulthood novelty exposure and between the two observations at 5 and 15 months of age. We performed two 3-way analyses on the patterns of neonatal by adulthood novelty interaction effect for the 5- and 15-month assessment respectively (Fig. 4A and B). For the 5 month assessment (Fig. 4A), we found a *temporally stable* neonatal novelty-induced rightwards shift in orienting bias at (neonatal novelty × orienting bias: $Z = 2.94, p = .003$). In contrast, for the 15 month assessment (Fig. 4B), we found a significant 3-way interaction effect at (NeoN × AdultN × orienting bias: $Z = 3.26, p = .001$) showing a reversal from a neonatal novelty-induced rightward to leftward shift. These contrasting patterns of findings at the two observations indicate that the effect of cumulative novelty exposure effects on orienting bias is not permanent but modifiable by subsequent unmonitored intervening events.

3.5. Non-additive effects of neonatal and adulthood novelty exposure

If the effect of an early event can be modified by a later event, then one may ask how the cumulative effect differs from the effects of each single event alone. Fig. 5 shows the same data in Fig. 2 but organized to facilitate the comparison between the effects of two single events alone and the effect of two events combined. From the observations made at 5 months of age (Fig. 5A), the asymmetry score for the neonatal and adulthood novelty exposure alone groups are approximately 0% and -46% and an additive model would predict a cumulative effect of -46%, a leftward bias. However, the actual observation shows that the combined neonatal and adulthood novelty exposure resulted in an asymmetry score of approximately 36%, a rightward bias. From the observations made at 15 months of age (Fig. 5A), the asymmetry score for the neonatal and adulthood novelty exposure alone groups are approximately 17% and 54% and an additive model would predict a cumulative effect of 71%, indicating a strong rightward bias. The observation shows that the combined neonatal and adulthood novelty exposure resulted in an asymmetry score of approximately -40%, indicating

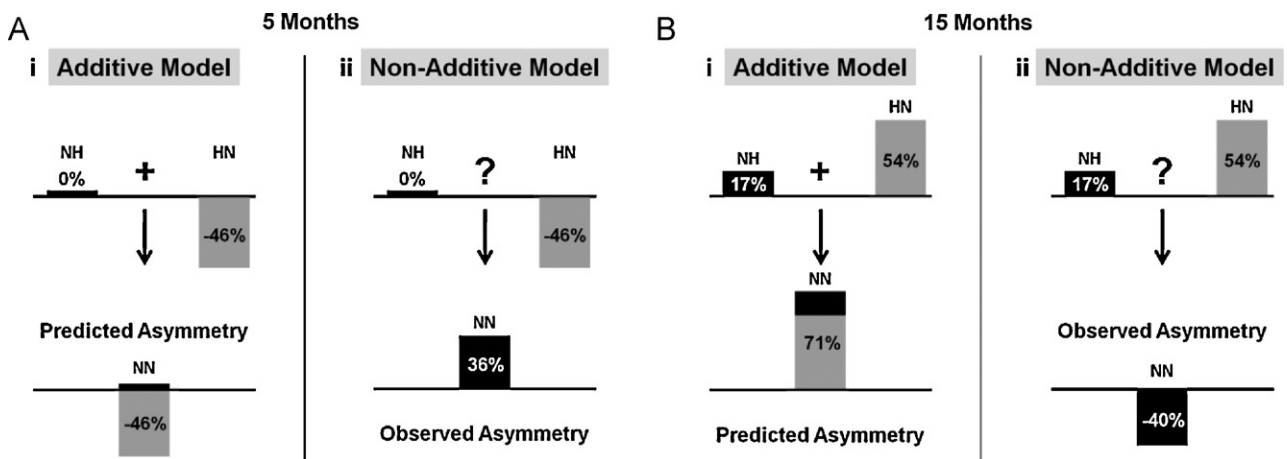


Fig. 5. Non-additive effect of neonatal and adulthood novelty exposure. (A) 5 months of age: an additive model (i) predicts a leftward bias (negative L score) in orienting response of the NN rats but the observed bias (ii) is rightwards (positive L score). (B) 15 months of age: an additive model (i) predicts a rightwards bias (positive L score) in orienting response of the NN rats but the observed bias (ii) is leftward (negative L score).

a return to a leftward bias. These observations made both at young and late adulthood provide a consistent picture that the impact of neonatal and adulthood events may not be additive and to predict cumulative effects of multiple experiences through development, it is necessary to identify the currently unknown (indicated by the question mark) non-linear function.

4. Discussion

4.1. Distinct patterns of neonatal and adulthood experience effects on functional brain asymmetry

In a longitudinal study of 106 male rats from 19 dams, we examined potential asymmetric brain activation during the initial encounter with a novel environment using a single trial-based orientation bias measure. We made two experimental manipulations of novelty experience by a brief removal from the familiarity of the home, one at infancy and one at early adulthood, and two assessments of global brain organization indexed by an orienting bias in a novel environment, one at early and another at late adulthood. We found that functional brain asymmetry as indexed by orientation bias displayed during the initial exposure to a relatively novel situation can be influenced by neonatal experience of novelty, adulthood experience of novelty, and the age of assessment during early to late adulthood.

Furthermore, we found distinct patterns of early experience effects on novelty-induced asymmetric brain activation with neonatal novelty exposure alone showing a *temporally stable* rightward shift in the orienting response, adulthood novelty exposure alone showing a *latent* expression of rightward shift, and the combined neonatal and adulthood novelty exposure showing a *transient* expression of rightward shift. These early novelty induced functional asymmetries in orienting response to novelty is in line with findings from other neonatal stimulation studies showing early experience effects on cortical asymmetry [8,10,11,21] and are internally consistent with our previously reported neonatal novelty exposure-induced functional asymmetry in handedness, orienting bias to novelty, hippocampal volume, and hippocampal synaptic plasticity [4,12,13,21]. Functionally, the right-biased rats assessed 1 day before a spatial memory test performed better in the spatial memory test on the following day, suggesting an associated functional significance of this rightwards orienting bias in response to novelty and in learning that takes place in the context of relative novelty [17].

4.2. Effects of early life experience on functional asymmetry: long-lasting but not permanent

By using a two-stage experimental manipulation at both infancy and onset of adulthood, we observed that the effect of brief neonatal experience of novelty on functional brain asymmetry during a novelty response is not permanent but modifiable by further brief experience of novelty at the onset of adulthood. By further utilizing a two-stage observation approach at both early and late adulthood, we showed that the cumulative effects of past novelty experiences are subject to further modification by unmonitored events taking place throughout adulthood. These findings suggest that, if one is not careful, a one-shot manipulation and one-shot observation approach used in development studies may lead to an unsound conclusion that neonatal or adulthood experience of novelty exposure has a “permanent” effect on brain and behavioral development when in fact, the effect of novelty exposures can be long-lasting but without being permanent, subject to continuing modification by further events via interactions among a multitude of events that make up the full context of life. If such fluidity in

early stimulation effects can be further verified using other functional measures, then it may become a norm instead of an exception that conclusions drawn from observations made at one point during development may be different from conclusions drawn from observations made at another point during development. This potential fluidity of early environmental influences suggests caution in making a general statement regarding the effects of early life experience.

4.3. Effects of early life experience on functional brain asymmetry: a lack of additivity

Previous findings on the joint neonatal and adulthood novelty exposure effects on spatial memory [17] showed that while neonatal novelty exposure and adulthood novelty exposure alone can both lead to enhanced spatial memory performance, rats that experienced both novelty exposures did not show a statistically significant improvement in spatial memory performance over the controls. The present findings offer converging evidence in support of a non-additive interaction effect between neonatal and adulthood novelty manipulation. Here the effects of neonatal and adulthood novelty exposure on brain organization are not additive as the cumulative effects of combined neonatal and adulthood novelty exposures cannot be inferred from knowing and adding the effect of neonatal novelty exposure and the effect of adulthood exposure alone. Therefore, to understand how multiple sequential events in life interact to determine a behavioral or neural outcome, one must not assume that having known the effect of each individual event in a one-shot manipulation study is sufficient to infer the joint effect without further experimentation. Given that life consists of a long-sequence of events, hence interaction among multitude of salient events is more of a norm than an exception, a multi-shot manipulation and multi-shot observation approach may facilitate the understanding of the complex interaction effect, which affords the opportunity for plasticity and modifiability for the developing organism.

4.4. Conclusions

In summary, using functional brain asymmetry measure as an index, we showed that brief exposures to environmental novelty can have long-lasting impact on global brain organization, particularly on the right-brain dominance in novelty response and that the long-lasting influence is not permanent but modifiable throughout infancy and adulthood. This persistent modifiability is at variance with the view that early life experience creates permanent effects among the offspring but consistent with the view based on human studies that early experience effects are modifiable [24]. Given this persistent modifiability by the rich subsequent context of intervening events throughout development, any effects of neonatal experience on adult function observed in a one-shot manipulation and one-shot observation study may have limited generality. To ascertain long-lasting and possibly permanent effects of early life experience, multi-shot manipulation and multi-shot observation research designs may be needed. Finally, the current findings regarding the dynamic changes in a transiently observable functional brain asymmetry measure that is sensitive to situational novelty may enrich the large body of existing literature on various relatively stable forms of functional asymmetry [25,26], such as language and handedness.

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