

Adult aggression during an initial social encounter: effects of neonatal anoxia and relation to juvenile open-field activity

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Abstract

In male Long-Evans hooded rats, we examined: (1) combined effects of neonatal anoxia and novelty exposure on aggression during adulthood; (2) open-field activity before juvenility as a predictor for adult aggression. Litters of neonates were exposed to either 100% N₂ gas (Anoxia) or room air (Control) for 25 min on postnatal Day 1 (P1). Within each of the Anoxia and Control conditions, one half of the neonates were individually exposed to a non-home cage for 3 min daily during P2–21 (Novel: $N_{\text{Anoxia}} = 15$; $N_{\text{Control}} = 13$) while the other half remained in the home cage (Home: $N_{\text{Anoxia}} = 15$; $N_{\text{Control}} = 13$). Prior to the onset of juvenility (P25), open-field activity was measured during four 20-s trials. At the onset of adulthood (P100–101), we measured the occurrence of biting during four 5-min sessions of social interaction between pairs of rats. Neonatal anoxia and novelty exposure had contrasting effects on adult aggression with the former increasing aggression and the latter having no statistically significant effect. The open-field measures before the onset of juvenility were significantly correlated with the occurrence of biting behavior during adulthood, suggesting that activity in a novel environment observed very briefly in early life may serve as a predictor for adult aggression.

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Development of aggression has been extensively studied in humans [9,23,24] and neural mechanisms underlying such development have been investigated in primate and rodents (for review, see [10,34]). One area of this research concerns identifying early-life predictors for adult aggression. Trauma studies revealed that adult aggression may be predisposed by early insults. In humans, low birth weight, early brain injury, prenatal cocaine, substance exposure, obstetrical complications, and perinatal malnutrition are associated with increased occurrence of violent delinquencies or crimes later in life (for review, see [32]). In animal models, aggressive behavior is also increased by neonatal brain lesions [3], prenatal malnutrition [16], and exposure to prenatal ethanol [21], metal (e.g., [7]), and cocaine (e.g., [15]). Furthermore, a propensity for aggression can be explained in part by individual differences in emotion-related processes (for review, see [2,11]). At the behavioral level,

activity levels of mice in an unfamiliar open field (often taken as a measure of emotional response [12]) were positively correlated with aggression toward a strange conspecific [6]; patients with impulsive aggressive disorders were more likely than control subjects to interpret neutral facial stimuli as fearful [4]. At the physiological level, measures of circulating glucocorticoids, hormonal indices of emotional responses [14], were also correlated with aggression (e.g., [25,43]). These findings highlight early aversive events and individual differences in emotional regulation as two major predictors of adult aggression.

We have previously reported that, although an anoxia-induced increase in open-field activity can be ameliorated by neonatal novelty exposure [36], the effects of neonatal anoxia on specific measures of synaptic plasticity [1] and open-field activity [36] were not similarly counteracted. Instead, neonatal novelty exposure has separate effects on a longer-lasting form of synaptic plasticity and social memory [1], and temporal patterns of open-field activity [36]. In this paper, we describe results from two post-hoc analyses on aggressive behavior during social interaction. The first deals with the effects of neonatal anoxia and neonatal novelty exposure on aggressive behavior among adult

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rats (P100–101) and the second with early life open-field activity (P25) as a predictor for adult aggression.

Eleven pregnant Long-Evans hooded rats arrived at the Psychology-Department *vivarium* at the University of New Mexico 16–17 days before giving birth (Charles River, Raleigh, NC). They gave birth to 132 pups within a time window of 24 h. Birth litter size ranged from 8 to 18 pups. Fifty-six male pups born of these dams were included in the present study. Pups were housed with the dam during the first 3 weeks of life. After weaning on P22, rats were housed individually in translucent plastic cages (51 cm × 25 cm × 22 cm) with a 12-h light/dark cycle (lights on at 7:00 a.m.) with food and water *ad libitum*. All experimental procedures were in accordance with the Institutional Animal Care and Use Committee at the University of New Mexico.

This study has a 2 × 2 factorial design in which the anoxic treatment and neonatal novelty exposure were the two fixed factors (Novel: $N_{\text{Anoxia}} = 15$; $N_{\text{Control}} = 13$; Home: $N_{\text{Anoxia}} = 15$; $N_{\text{Control}} = 13$). The anoxia treatment was a between-litter factor; the 11 litters were pseudo-randomly assigned to Anoxia ($n = 6$ litters) and Control ($n = 5$ litters) conditions. Because the primary goal of the original study was to examine whether novelty exposure could interact with anoxia, the experimental design was thus optimized for detecting the Novelty effect, by making the novelty exposure treatment a within-litter factor with each litter split into two halves pseudo-randomly: one half assigned to the Novel and the other to the Home group [35]. We did not try to optimize the anoxia effect by making it a within factor because a rather large anoxic effect was expected [36].

On postnatal Day 1 (P1), anoxia induction, culling of the litter, assignment to Novel and Home groups, and marking of group identity were carried out one litter at a time in a counter-balanced order between the Anoxia and Control litters. Neonatal novelty exposure was performed from P2–21. The open-field test was performed shortly after weaning on P25. Dyadic social interaction was observed at the onset of adulthood on P100–101. All testing was performed by experimenters blind to the animals' group identity. The order in which rats were tested was counter-balanced among experimental conditions.

On postnatal Day 1 (P1), after the dam was placed in a holding cage, pups were transferred to a plastic airtight chamber (25 cm × 20 cm × 13 cm) equipped with an air inlet at one end and an air outlet at the other. Pups were exposed for 25 min to continuous flow of either nitrogen gas (100% N₂) or room air (21% O₂/79% N₂) at a flow rate of 3 l/min. The temperature inside of the chamber was kept constant at 31 °C by partially immersing the chamber in water warmed by a submersible heater (Whisper, Tetra, VA). Immediately after the anoxia induction, each litter was culled to 8–10 pups, with females included only to maintain comparable litter sizes across litters. After culling, pups within each litter were pseudo-randomly assigned to Novel and Home groups, and the group membership was marked by tattooing the ventral surface of digits on both hind paws without anesthesia. Two different digit combinations: (a) left-first and right-fifth, and (b) right-first and left-fifth were used for Novel and Home identity and the patterns of marking were counter-balanced between the Novel and Home groups.

Neonatal novelty exposure [35] was performed daily in the housing room between 11 a.m. and 4 p.m., on P2–21 by an experimenter blind to the Anoxia versus Control conditions of the litters. After the dam was transferred to a separate holding cage in the same room, the Novel pups were identified via their toe tattooing and were individually transferred to their own clean non-home cage (28 cm × 16 cm × 13 cm) lined with fresh bedding. After spending 3 min in the new cage, the Novel pups were returned to the home cage in which the Home pups remained. During this transfer, each Novel pup was yoked to a Home pup in the following sense: when a Novel pup was picked up during the transfer, a yoked Home pup was similarly picked up but placed back into the home cage. This yoking insures that Novel and Home pups within a litter received a matching amount of experimenter contact at approximately the same time. The dam was returned to the litter after the Novel pups reunited with the Home pups. Because both experimenter contact and maternal separation were matched between Novel and Home pups, the only treatment difference experienced between the two groups was the brief exposure to a novel environment.

Latency to leave the center of the open field (60 cm × 60 cm × 20 cm) and distance traversed (number of squares) was measured across four 20-s trials before juvenility (P25). Instead of typical longer trial durations (3–5 min), this short trial duration was used to capture individual differences in the initial emotional response to an unfamiliar environment [36,37]. The juvenile period was chosen because around this time rats that experienced neonatal anoxia/hypoxia consistently displayed hyperactivity in the open-field test (e.g., [30]). The results from this open-field test have been separately published elsewhere [36].

Adult aggressive behaviors were observed between a pair of rats on P100–101 in a neutral non-home testing cage during four 5-min social-exposure sessions (Day 1: S1–S3; Day 2: S1) with inter-session intervals (ISIs) of 10 and 2 min between S1 and S2 and between S2 and S3, respectively¹ [39]. On each day, rats were first exposed to a 5-min cage habituation session (Hab). Following cage habituation, each rat was exposed to the same conspecific during all sessions except Day 1 S3 during which subsets of rats were exposed to either the familiar or a novel rat (Familiarity effect).² During ISIs, rats were kept in their home cages.

Pairs were formed between non-sibling Home and Novel rats. Within a pair, the Home and Novel rats were both from either Anoxia or Control conditions, resulting in 15 Anoxia-to-Anoxia pairs (A–A) and 13 Control-to-Control pairs (C–C). The choice of not using separate rats as stimulus animals is a key departure from convention [38]. The original motivation behind using a separate stimulus rat was to provide “stimulus equivalency” for both the experimental and control groups. Unfortunately, unlike other physical stimuli that tend to maintain constancy of their physical properties, social stimuli inevitably change according

¹ The long and short ISIs were originally selected to produce different rates of habituation between sessions.

² This manipulation during S3 was originally designed to test an interference effect on social-recognition memory.

to the individual's relationship with another conspecific. The same individual will behave differently if interacting with two individuals who lie on the opposite ends of the aggressiveness spectrum. In other words, even if an "identical stimulus animal" is paired with the experimental and control groups, the stimulus animal would not behave in the same way towards the two groups that differ. Given this inevitability and a large number of possible pairings (eight) in this experimental design, we simply studied pairs formed between Novel and Home rats within the Anoxia and Control conditions. Further studies should be conducted for other pairing conditions.

Ongoing behaviors were videotaped and coded offline. Frequencies of aggressive behaviors were measured from sixty 5-sec video segments. To allow the identification of Novel and Home rats within a pair, rats were marked on both sides of their body with either red or green food coloring prior to the testing session. If a behavior was present any time during the 5-sec duration, an occurrence of one was counted for that behavior. Aggressive behaviors initially included biting and boxing. Since boxing occurred among only 17% of the rats, only biting received further analysis.

Because the biting frequencies were severely skewed towards zero, this variable was transformed into a dichotomous variable, representing whether biting occurred at all in an individual during a given session. As no significant litter effect was found for the biting measure (p 's > 0.2) and no significant correlation in biting was found between the Novel and Home rats within pairs (p 's > 0.2), individual animal was used as the unit of analysis. Log-linear multi-way χ^2 -tests [33] were used and Z scores were given as test statistics for testing treatment effects. Logistic regressions were performed to examine the relationship between open-field activity and aggression. Occurrence of biting during S1 was used as a dependent variable because the greatest occurrence of biting was observed during this session. The strength of the relationship between the dependent and predictor variables was expressed as an odds ratio (OR), with OR > 1 indicating a positive correlation and OR < 1 a negative correlation. Effect sizes of logistic regressions were indexed as the 95% confidence interval of the ORs [31]. Correlation in biting between the Novel and Home rats within pairs was computed with the type of pairing as a dummy variable (A–A and C–C pairs) to determine whether the within-pair Novel–Home relation differed between the A–A and C–C pairs. We found no significant effect of pairing types (p > 0.2).

The number of times that a rat bit within one session ranged between 0 and 8, with a majority showing no biting at all and group averages ranged between 0.25 and 1.10, which are comparable to those reported by others [18]. In contrast to an increasing trend across repeated social exposures reported in this previous study, a decreasing trend was observed across the three consecutive sessions (21, 13, 4 rats bit during S1–S3, respectively). This trend difference most likely reflects differences in specific temporal parameters used, with the present study using very short ISIs (<10 min) and the previous study using very long ISI (2 days). During S3, biting occurred in only 1 out of 32 rats that were exposed to new partners and in only 3 out of 24 rats that were exposed to the previously seen partners. The observation

Table 1

Effects of neonatal anoxia on biting across multiple sessions (shown as NB/B)

Anoxia condition	Novelty condition		Sum
	Home	Novel	
(a) Day 1 Session 1 (S1)			
Control	11/2	10/3	21/5
Anoxia	8/7	6/9	14/16*
Sum	19/9	16/12	35/21
(b) Day 1 Session 2 (S2)			
Control	12/1	11/2	23/3
Anoxia	9/6	11/4	20/10
Sum	21/7	22/6	43/13
(c) Day 1 Session 3 (S3)			
Control	11/2	12/1	23/3
Anoxia	15/0	14/1	29/1
Sum	26/2	26/2	52/4
(d) Day 2 Session 1 (Day 2 S1)			
Control	12/1	8/5	20/6
Anoxia	13/2	13/2	26/4
Sum	25/3	21/7	46/10

NB: number of rats that did not bite; B: number of rats that did bite.

* p < 0.05.

that exposure to a new partner did not seem to increase biting may be a result of several factors, such as the very short ISI and the use of a non-home testing cage.³

We tested the combined effect of neonatal anoxia and neonatal novelty exposure on the occurrence of biting. The numbers of rats in each of the four experimental conditions displaying biting behavior are shown across all four sessions in Table 1. A log-linear χ^2 -test was applied to each of the four sessions. We found a significant main effect of Anoxia during S1 with a greater proportion of Anoxia rats biting than Control rats (Z = 2.45, p = 0.014, Table 1a). This pattern of Anoxia effect remained for S2 but with only marginal statistical significance (Z = 1.73, p = 0.084, Table 1b). During S3 and Day 2 S1, this Anoxia effect was no longer significant (p 's > 0.2, Table 1c and d). Neither the Novelty effect nor the Novelty by Anoxia interaction was significant in any of the sessions (p 's > 0.2).

We further examined whether individual differences in adult aggression could be explained by individual differences in open-field activity during juvenility. Odds ratio for the latency measure was 0.85 (p = 0.016) indicating a *negative* correlation. That is, the shorter the latency to leave the center of the open field, the more likely the rat was to bite an unfamiliar conspecific during the initial social encounter. The OR for the distance measure was 1.16 (p = 0.032) indicating a *positive* correlation. In this case, the greater the distance the rat traversed, the more likely the rat was to bite. Although significance level was reduced after partialling out the Anoxia effect, the direction and strength of

³ Due to the small number of rats exhibiting biting during S3, the Familiarity effect was not analyzed.

Table 2
Summary of logistic regressions

	Regression coefficient	Standard error	Odds ratio	95% confidence interval	<i>p</i>
(a) Before controlling for the Anoxia effect					
Latency	−0.16	0.07	0.85	(0.75, 0.97)	0.02
Squares	0.15	0.07	1.16	(1.01, 1.33)	0.03
(b) After controlling for the Anoxia effect					
Latency	−0.13	0.07	0.88	(0.77, 1.01)	0.06
Squares	0.11	0.07	1.11	(0.97, 1.29)	0.12

the relationships were essentially unchanged (compare *p*-values and 95% confidence interval of OR in Table 2).

Neonatal anoxia is one experimental treatment that captures certain aspects of birth asphyxia in humans and has been used as an animal model for investigating the impact of birth asphyxia on brain development [28,42]. As reviewed by Dilenge et al. [13], birth asphyxia occurs in 0.2–3% of live-term births, with severe symptoms including coma, seizures, autonomic and brain stem dysfunction, and mild symptoms including increased irritability, hyper-excitability, and sympathetic over-reactivity. Unfortunately, the majority of the clinical research deals with severe cases and the outcome of asphyxiated infants in functional terms, such as socialization and daily living skills, have been insufficiently investigated. Here we report that rats receiving neonatal anoxia treatment are more likely to display aggression towards conspecifics during adult social interactions. Specifically, during initial exposures to a strange conspecific, more Anoxia rats bit the conspecific than did Control rats (Table 1a). This finding suggests that early insult due to brief oxygen deprivation shortly after birth can have long lasting consequence for adult social function.

Surprisingly, we found only two studies that reported effects of anoxic/hypoxic insults on later aggression. One found that aggression toward human experimenters during a handling test was increased among rats that experienced neonatal hypoxia although a precise description of the specific aggressive behavior was not provided [26]. The other study reported an anoxia-induced decrease in fighting among aged females [41]. Our results agree with these earlier studies in that it demonstrated a clear relationship between neonatal anoxia and adult aggression. However, the direction of anoxia effect on our young adult male rats is an increase in aggression, opposite to the decrease in aggression found in aged female rats. It is not clear whether this difference is sex or age related. In several other studies of anoxia/hypoxia effects on social function, no aggressive behaviors were described [22,29,40]. It should also be pointed out that our current finding may be limited by the specific A–A and C–C pairings used. Therefore, there is clearly a need for further studies concerning the long-term impact of neonatal trauma on social interactions and its possible dependency on gender and age.

Effects of neonatal anoxia/ischemia on aspects of open-field behavior and performance in Morris water task can be reversed by subsequent mild stimulations through neonatal handling and enriched environment [8,20]. In the present study, mild neonatal stimulation via neonatal novelty exposure had no direct effect or interaction effect with anoxia on aggression. This lack of effect

parallels the lack of novelty effect on a short-lasting form of synaptic plasticity measured *in vitro* in the CA1 of the hippocampus [1] and parallels the lack of novelty effect on the average of open-field activity measured across several very brief exposures (20-sec duration) separated by very short time intervals (a few minutes) [36]. However, this lack of novelty effect on aggression is not due to an overall ineffectiveness of the novelty exposure treatment because neonatal novelty exposure did increase longer-lasting forms of hippocampal synaptic plasticity and ameliorate the anoxia effect on the open-field activity during the very first brief exposure and on the temporal changes in open-field activity across repeated sessions in the same study [1,36]. Although these findings do not allow one to pinpoint the precise differences in neural substrate mediating the anoxia and novelty exposure effects, the patterns of effects across multiple measures do suggest that neonatal trauma and subsequent mild early-life stimulation modify both shared and distinct neural mechanisms. Further isolation of the shared neural mechanisms may lead to discovery of behavioral treatment that ameliorates or reverses effects of neonatal trauma.

Identification of early-life predictors of adult aggression has been an important topic in development research [17,27]. In humans, behavioral inhibition early in life, often measured by responses to the unfamiliar, was used as a predictor for adult aggression [19], and measures of negative emotionality (e.g., frequency of irritable behavior) obtained at 1 year of age appeared to affect how intervention programs impacted later aggressive behavior at 3 years of age [5]. Our finding that the activity in an unfamiliar open field measured before juvenility was correlated with aggressive behavior during adulthood suggests that an animal model might be possible for investigating the relationship between childhood behavioral inhibition in a novel environment and adult aggression.

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