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Research report

Sex difference in temporal patterns of social interaction and its dependence upon neonatal novelty exposure

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Abstract

Rodents have been an indispensable tool for the study of the neural mechanisms underlying a variety of emotional, social, and cognitive functions and dysfunctions. Surprisingly, little is known concerning sex difference in rodent social recognition memory and its sensitivity to neonatal stimulation. During the first 3 weeks of life, we exposed male and female neonates to a novel cage for 3-min per day while the matched littermate controls remained in the home cage. At 7 weeks and 7 months of age, we measured frequencies of social investigation over repeated social exposures and found that males showed greater habituation in social investigation than females during both juvenility and adulthood and that neonatal novelty exposure affected changes in the frequency of social investigation across multiple exposures in a sex-dependent manner. We speculate that these observed sex differences may reflect a sex difference in affinity for conspecific novelty rather than memory capability.

Keywords: Sex difference; Social recognition memory; Neonatal handling; Early life experience; Social behavior; Development; Ontogeny

1. Introduction

In social animals, the ability to recognize previously encountered conspecifics is crucial for normal social function. In rodents, social recognition memory can be inferred from a decrease in the frequency or duration of social investigation after repeated exposures to conspecifics [35]. This habituation of social investigatory behaviors towards one animal can be blocked by exposure to a new conspecific—a phenomena referred to as retroactive interference [35]. The ability of the new conspecific to interfere with subsequent habituation to a previously encountered conspecific serves to cross-validate the existence of a memory trace for the previously encountered individual [29].

While there has been a recent increase in social memory research in rodents (e.g. [8,11,12,15,23,29]), very little is known concerning the ontogeny and sex difference in patterns of social interaction after repeated exposures. The majority of rodent social memory studies were conducted in either males or females and at a single point during development. The limited number of studies examining both sexes yielded conflicting results [3,35]. It remains to be determined whether social recognition differs between males and females, how early the onset of this sex difference may be observed, and how this sex difference might change from juvenility to adulthood.

For non-social functions, it is known that early life stimulation represents a major source of variance in sex differences. Neonatal stimulation, with the handling method [9,16], affected the behavior of males and females differently in exploration [41], aggression [34], emotional reactivity [4], and learned helplessness [21]. Parallel to these behavioral differences, neonatal handling also produced sex-dependent

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effects on corticosterone response [22,42], immune response [40], dopamine turnover rate [20], and callosal connections between the two cerebral hemispheres [2]. Neonatal novelty exposure [25] differentially affected male and female rats in open field emotional reactivity [27] and functional brain asymmetry [1].

These early stimulation-induced sex-dependent effects raise the possibility that patterns of temporal changes in the frequency of social interactions induced by repeated social exposures may also be sex-dependent and that sex difference in social interaction may be further modulated by neonatal stimulation. In adult male rats, both short- and long-term habituation to a previously encountered conspecific can be modulated by neonatal novelty exposure [29], a procedure shown to affect a range of functions at multiple levels of analysis [6,7,26,28,30,31,39,45,46]. Here, using a longitudinal design incorporating both male and female rats, we investigated sex-dependent effects of neonatal novelty exposure on changes in the frequency of social investigation across multiple social exposures at juvenility and adulthood.

2. Methods

2.1. Animals

Eight pregnant Long-Evans hooded dams (Charles River, Wilmington, MA) were housed in the Psychology Department vivarium for 16–17 days prior to giving birth. Within 8 h after birth, litters were culled to eight pups with as close to 50% males and females as possible. The number of males ranged from three to seven per litter and the number of females ranged from one to five per litter. A total of 27 male and 29 female rat pups were used for this study. All pups were housed with the dams until weaning at postnatal day 21. After weaning, all animals were housed individually in translucent plastic cages (51 cm × 25 cm × 22 cm) within the same housing rooms and maintained on a 12-h light/dark cycle (lights on at 0700 h) with food and water ad lib. The environment was kept at ambient temperature (21 °C) with humidity at 25%. All procedures were carried out in accordance with the guidelines established by the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Neonatal novelty exposure

Neonatal novelty exposure [25] was derived, but differs, from the well-known neonatal handling method [9,16]. On postnatal day 1, approximately one-half of the animals from each litter were pseudo-randomly assigned to the Novel group and the other half to the Home group (split-litter design) with approximately equal numbers of males and females in each group. Group membership was marked via a toe-clipping procedure. On postnatal days 1–21, the dam was first removed from the home cage and placed in a separate cage within the same room (Fig. 1a(i)). The pups were then picked up and identified by the experimenter. Novel rats were placed into separate cages lined with fresh sawdust (ii). After 3 min, Novel pups were returned to the home cage in which Home pups remained (iii). Once all pups were returned, the dam was transferred back into the home cage (iv). During transfer to and from the novel cage, each Novel pup was yoked to a Home pup such that they received a matching amount of experimenter contact at approximately the same time. By using this procedure, any difference in dependent measures between Novel and Home groups cannot be attributed to maternal separation or experimenter contact [25].

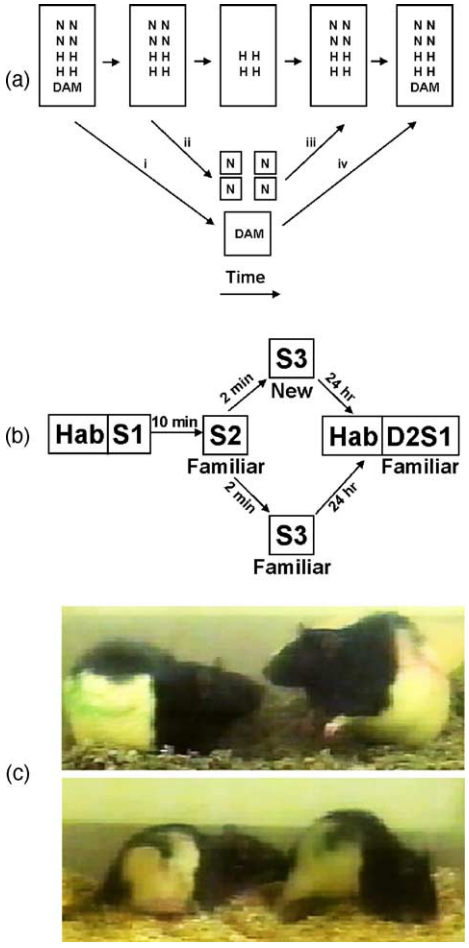

Fig. 1. Methods—(a) the neonatal novelty exposure procedure utilizes a within-litter design and consists of the following: (i) transfer of the Dam to a separate cage, (ii) transfer of the Novel (N) rats to their separate new cages, (iii) return of the Novel rats to the home cage, (iv) return of the Dam to the home cage; (b) the habituation paradigm for social recognition memory; (c) examples of social investigatory behaviors.

2.3. Social recognition memory test

To evaluate the developmental stability of social recognition memory, animals were observed at both 7 weeks and 7 months of age.[1] At each age, the test consisted of two 5-min cage habituation sessions (Hab) and four 5-min social interaction sessions over two consecutive days (Day 1: Hab, S1–S3; Day 2: Hab, D2S1) (Fig. 1b) [for details, see [29]]. During Hab, animals were allowed to habituate to the testing environment. During all other sessions, the pair of rats was allowed to interact with one another. Two pairs of animals were tested simultaneously in cages of the same size and lined with the same bedding as the home cages. Except for S1, which

[1] In this experiment, different stages of the estrus cycle were not controlled for. However, variances in female behavior did not differ from that in males.