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Peri-adolescence isolation rearing alters social behavior and nociception in rats

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ABSTRACT

Social isolation results in fundamental behavioral abnormalities in rodents which models certain neuropsychiatric disorders such as schizophrenia. However, the developmental stage that is most vulnerable to social isolation is largely unknown. In the present study, we subjected weaning rats to a four-week peri-adolescence isolation rearing (PAIR) and then returned them to social rearing for an additional four weeks until adulthood. Open field locomotion, social interaction behavior, and acute pain sensitivity were examined at different time points. PAIR rats showed moderate hyperactivity towards a novel environment, an anxiogenic-like behavioral profile, and increased aggression and social interaction behavior, the last three of which could be restored by re-socialization procedure. In addition, PAIR animals showed significantly reduced pain sensitivity even after the re-socialization period. In summary, this study advances the use of peri-adolescent isolation rearing as an animal model to study neurodevelopmental manipulation induced behavioral abnormalities.

Since Hatch and colleagues first reported behavioral abnormalities in socially isolated rats [7], a large body of evidence has suggested that post-weaning social isolation has profound, long-term effects on rodent brain and behavior. These studies have translational relevance to developmental neuropsychological disorders, in particular to several core symptoms of schizophrenia, but also to changes seen in depression [5]. The behavioral abnormalities induced by social isolation include hyperactivity in a novel environment [6], impaired prepulse inhibition (PPI) of acoustic startle [13], and deficiencies in reversal learning [14]. Social isolation also results in fundamental changes to brain neurochemistry [5]. Aberrant mesolimbic and mesocortical dopamine, glutamate, and serotonin neurotransmission have been widely reported in parallel to behavioral changes [5]. Several studies suggest that social isolation might also alter synaptic function and neuronal plasticity; for example, in isolation reared rats, synaptophysin expression was markedly reduced in the molecular layer of the dentate gyrus [26].

In previous studies, social isolation was usually conducted from weaning to adulthood. However, the specific developmental period which is most vulnerable to social isolation remains largely unknown. Adolescence is a critical period for neuronal plasticity [19], and most neurotransmitter systems including dopaminergic and glutamatergic systems mature during this stage [21]. Our recent studies suggest that peri-pubertal social isolation (from PND38-51) alters latent inhibition and dopamine expression in the nucleus accumbens of adult rats [18]. Compared with cognitive-based tests, there are very few studies on the effects of isolation rearing on social and emotional functions. Social withdraw is a prominent negative symptom in schizophrenia patients [5]. In rodent studies, while it is well established that social isolation increases aggression, the effects of social isolation on non-aggressive social interactions remains controversial [2,24]. In addition, few studies have explored the effects of social isolation on nociception and with highly contrasting results [23]. Isolation rearing did not affect nociception in the tail flick of heat sensitivity [8], but resulted in hyperalgesia in the hot-plate test and foot shock sensitivity [3,11].

In the present study, we examined the effects of social isolation during adolescence on behavior in adolescent rats, and determined whether subsequent re-socialization could restore behavioral changes. Weaning animals (PND 21) underwent four-week peri-adolescent isolation rearing (PAIR) and were returned to standard social rearing for additional four weeks until adulthood. The effects of PAIR on social interaction and acute pain sensitivity tests were determined, and open field locomotion was performed to provide an assessment of general locomotor activities and anxiety levels.

Consistent with previous PAIR studies [15,16], male Sprague–Dawley rats ($n = 32$) were obtained from the Academy of Chinese Military Medical Science (Beijing, China) on PND21. Rats were kept under controlled environmental conditions (ambient temperature 22 °C, 12 h light/dark cycle, light on at 7:00 a.m.)

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with *ad libitum* access to food and water. The experiments were performed in accordance with the guidelines of Beijing Laboratory Animal Center and National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23).

On PND21, rats were randomly assigned to either socially rearing ($n = 4$ per cage) or isolation rearing conditions ($n = 16$ per condition) and were kept for four weeks from pre-adolescent to mid-adolescent stages (PND 21–48). The animals were tested in open field and social interactions on PND48 and PND49. The isolation reared rats were then returned to group-rearing in random assignments for a four-week re-socialization period (PND49–76). During this time, socially reared rats were also randomly reassigned to a new group to ensure that any observed difference between isolation- and socially reared controls were not due to re-socialization procedures [16]. The animals reached adulthood by the end of the procedure and were tested in the following behavioral experiments: open field test (PND77), social interaction test (PND78), and acute pain sensitivity (PND 79). The acute pain sensitivity test was conducted after re-socialization to avoid any stress-induced confounding effects. All behavioral tests were conducted during the light cycle.

The open field testing apparatus was a circular arena of 180 cm in diameter with a 50 cm high wall. The test room was dimly illuminated by a 40 W bulb. The animal was placed in the corner of the field, and locomotion (distance traveled) and time spent in the central zone (defined as a circle in the center with 30 cm in diameter) were recorded for 10 min. Data were analyzed offline by EthoVision (Noldus Information Technology, Wageningen, Netherlands). The apparatus was cleaned with 10% ethanol after each testing.

The social interaction test was conducted 24 h after open field. The procedures were adapted from previous studies [20,22]. Testing took place in a dimlylit room in a black plastic box (54 cm × 54 cm × 40 cm). Habituation to the test box was conducted 4 h after open field, when each rat was placed into the box alone for 15 min under the same luminosity. The field was cleaned with 10% ethanol after each habituation trial and testing trial.

Each subject was paired with a weight-matched target animal for 10 min. All target rats were marked with a black infrared-sensitive marker (Zebra YYR1-BK120) to distinguish them from their experimental pairs. All sessions were videotaped by an infrared-sensitive video camera (Sony DCR-SR45) mounted above the box. In each social interaction pairing (a) the subject was paired with a target rat from a different home-cage of socially reared animals and (b) no rat was ever paired with the same rat twice. Videos were scored offline by a skilled rater blind to the experimental designs for rat's aggression (attacking/biting, wrestling) and social interaction behavior (approaching, sniffing, genital investigation, climbing over or under). Total duration and total number of contacts of social behaviors were both scored.

Acute thermal pain sensitivity was measured 1 day after the social interaction test. A radiant heat apparatus (100 W laser projector) was employed to induce acute pain. Thermal thresholds of rat hindpaws were measured. Each rat was placed in a plastic chamber with a glass floor under which the radiant heat apparatus was located. The beam of light was focused on the plantar surface of the left hindpaw. Paw withdrawal latency (PWL) was defined as the time between light onset and paw lift. The intensity of light was adjusted to result in the PWL value of 10 s as the baseline level. A cut-off time of 22 s was applied to avoid tissue damage [27]. Three trials of 10 min apart were conducted with each hindpaw of the animal. The first trial was used to measure the baseline level, and pain sensitivity index was measured by the difference of latency between 10 and 20 min and baselines.

Data were presented as mean ± standard error of the mean (SEM) for all measures. Statistical analyses were performed using SPSS 13 (SPSS Inc., Chicago, IL, USA). Open field performance, social interaction tests, and acute pain sensitivity were analyzed by repeated-measure analysis of variance (ANOVA) with rearing condition as between-subject factor and testing time as within-subject factor, followed by planned *t*-tests to further examine group differences. A probability level of $P < 0.05$ was considered statistically significant.

Open field activities are summarized in Fig. 1. For distance traveled (Fig. 1A), there was a significant main effect of testing time [$F(1, 30) = 41.55$, $P < 0.001$], but not of rearing [$F(1, 30) = 0.38$, $P = 0.55$]. There was a significant interaction between rearing condition and testing time [$F(1, 30) = 14.19$, $P < 0.001$]. Further analysis showed that before re-socialization, PAIR rats traveled marginally significant greater distances than socially reared controls [$t(30) = 2.03$, $P = 0.055$], whereas after re-socialization there was no difference between the two groups [$t(30) = 1.64$, $P = 0.16$]. Socially reared rats exhibited increased locomotion after re-socialization [$t(30) = 25.28$, $P < 0.001$], whereas PAIR rats showed no difference in distances traveled before and after re-socialization [$t(30) = 1.41$, $P = 0.25$]. These data suggest that PAIR rats exhibited moderate hyperactivity towards a novel environment.

For the time spent in the central zone (Fig. 1B), there was a significant main effect of testing time [$F(1, 30) = 5.62$, $P < 0.05$], but not of rearing [$F(1, 30) = 0.79$, $P = 0.38$]. The interaction between rearing condition and testing time was not significant [$F(1, 30) = 2.79$, $P = 0.11$]. Further analysis showed that before re-socialization, PAIR rats spent significantly less time in the central zone than socially reared controls [$t(30) = 2.49$, $P < 0.05$], whereas after re-socialization there was no difference between the two groups [$t(30) = 0.02$, $P = 0.98$]. PAIR rats spent longer time in the central zone after re-socialization [$t(30) = 2.43$, $P < 0.05$], whereas socially reared rats showed no difference of time spent in the central zone before and after re-socialization [$t(30) = 0.27$, $P = 0.75$]. These data suggest that PAIR rats exhibited moder-

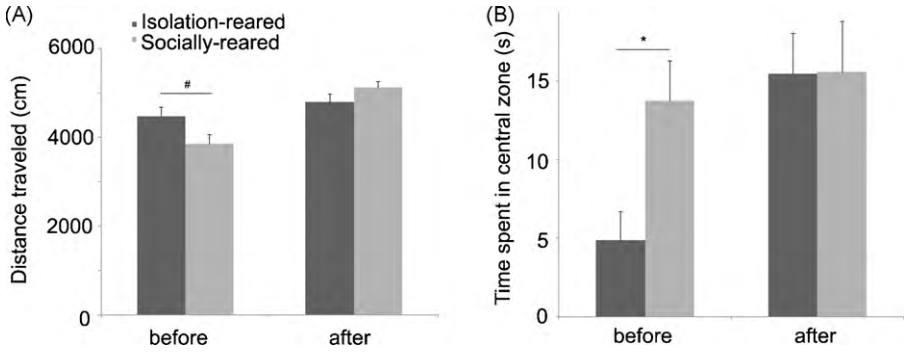

Fig. 1. The effects of peri-adolescent isolation rearing on open field locomotion before and after re-socialization, including (A) distances traveled and (B) time spent in the central zone. Results are expressed as mean ± SEM. $n = 16$ per group. #, $P = 0.055$. *, $P < 0.05$.

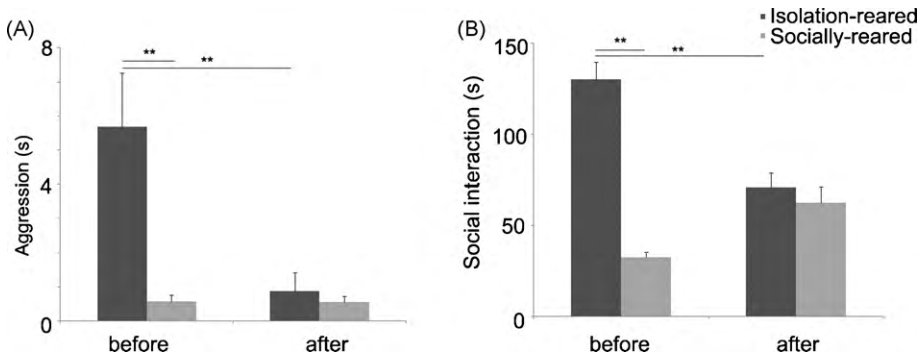

Fig. 2. Effects of peri-adolescent isolation rearing on social interaction test before and after re-socialization, including (A) aggression and (B) social interaction behavior. Results are expressed as mean ± SEM. $n = 16$ per group. **, $P < 0.001$.

ate anxiogenic-like behavior which could also be restored by re-socialization.

Total duration of social interaction behavior is summarized in Fig. 2. Total number of social contacts showed a highly similar response pattern to total duration (Supplemental Fig. 1). For aggression (Fig. 2A), there was a significant main effect of both testing time [$F(1, 30) = 12.42$, $P < 0.001$] and rearing condition [$F(1, 30) = 32.85$, $P < 0.001$]. There was also a significant interaction between rearing condition and testing time [$F(1, 30) = 14.81$, $P < 0.001$]. Further analysis indicated that before re-socialization, PAIR rats showed markedly more aggression behavior than socially reared controls [$t(30) = 5.37$, $P < 0.001$], while after re-socialization there was no difference between PAIR rats and controls [$t(30) = 1.85$, $P = 0.08$]. In addition, there was no difference of aggressive behavior in socially reared animals before and after re-socialization [$t(30) = 0.67$, $P = 0.48$]. By contrast, after re-socialization PAIR rats showed markedly reduced aggressive behavior [$t(30) = 3.22$, $P < 0.01$]. These data suggest that PAIR resulted in increased aggression, which could be restored by re-socialization procedures.

For social interaction behavior (Fig. 2B), there was a significant main effect of rearing condition [$F(1, 30) = 34.16$, $P < 0.001$], but not of testing time [$F(1, 30) = 2.64$, $P = 0.11$]. There was also a significant interaction between rearing condition and testing time [$F(1, 30) = 24.27$, $P < 0.001$]. Further analysis indicated that before re-socialization, PAIR rats showed markedly more social interaction behavior than socially reared rats [$t(30) = 13.55$, $P < 0.001$], while after re-socialization there was no significant difference between the two groups [$t(30) = 1.07$, $P = 0.49$]. In addition, after re-socialization socially reared rats showed significantly more social interaction behavior [$t(30) = 3.01$, $P < 0.01$]. Interestingly, after re-socialization PAIR rats showed markedly reduced social interaction behavior [$t(30) = 3.73$, $P < 0.001$]. Thus, as for aggression, these data suggest that PAIR resulted in increased social interaction behaviors, which could be restored by re-socialization procedures.

The effects of PAIR on acute pain sensitivity are summarized in Fig. 3. There was a significant main effect of rearing [$F(1, 30) = 6.57$, $P < 0.05$], but not of time point [$F(1, 30) = 1.03$, $P = 0.88$]. PAIR rats showed longer paw withdrawal latencies when compared with socially reared rats at 10 and 20 min time points [$t(30) = 2.19$, $P < 0.05$; $t(30) = 2.09$, $P < 0.05$]. The interaction between rearing condition and time point was not significant [$F(1, 30) = 1.07$, $P = 0.85$].

In the present study, we demonstrated that four-week peri-adolescent isolation rearing produced profound behavioral abnormalities in rats. Specifically, PAIR rats showed moderate hyperactivity towards a novel environment and a moderate anxiogenic-like behavioral profile. In addition, PAIR rats showed increased aggression and social interaction behaviors. The anxiogenic-like and increased social behaviors were able to be restored by a four-week re-socialization procedure. By contrast, PAIR animals showed reduced pain sensitivity even after the re-socialization period.

Hyperactivity towards a novel environment has been commonly observed following isolation rearing in rodents [12]. Consistent with previous findings, in the present study PAIR rats showed a moderate hyperactivity towards the open field. Previous studies suggest that Sprague–Dawley rats demonstrate much weaker hyperactivity in a novel field when compared with Lister rats [17]. In addition, we demonstrated that PAIR rats showed anxiogenic-like behavior in the open field, which was also restored by re-socialization. These data contrast with a previous study showing that re-socialization did not reverse the anxiogenic effect of isolation rearing on an elevated X-maze in rats [28]. Methodological differences including the length and the timing of isolation period, as well as testing methods may account for these differences. The effect of isolation rearing on anxiogenic-like behavior measured by elevated-plus maze tests is also controversial [5]. We previously reported that more ethological measures such as head dips can provide more sensitive measures of anxiogenic-like behavior in the elevated-plus maze test [29].

Adolescent rats participate in a much higher level of social behavior than adult animals. For instance, playing behavior in the rat peaks during early adolescence and declines rapidly afterwards. This form of social interaction is extremely sensitive to social deprivation in young animals [25]. In the present study, PAIR rats exhibited much more severe aggression and social interaction behavior than socially reared controls, both of which declined to the normal level after re-socialization procedures. Increased aggression has been widely reported after different social isola-

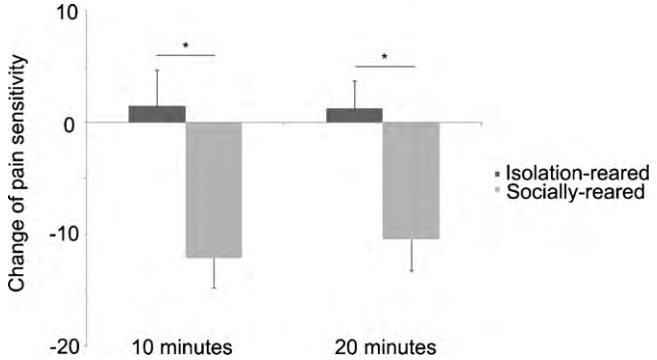

Fig. 3. Effects of peri-adolescent isolation rearing on acute pain sensitivity before and after re-socialization. Results are expressed as mean ± SEM. $n = 16$ per group. *, $P < 0.05$.

tion procedures in both rats and mice [1]. Consistent with clinical studies, a 2–10-fold increased incidence of aggressive behaviors was observed in schizophrenia patients, which is potentially mediated by a low activity allele of the catechol-O-methyl-transferase (COMT) gene [10]. Future studies are required to elucidate role of COMT in regulating isolation rearing induced increase of aggression. By contrast, Lukkes and colleagues recently reported that after three weeks adolescent isolated-rearing (PND21-42) and two weeks re-socialization (PND 43-56), PAIR rats still exhibited increased latencies for social approach and a decreased number and duration of social contacts when compared with control animals [16]. We suggest that proper time windows (for example, late adolescence) are critical for both social isolation and subsequent re-socialization procedures to affect social behavior. Ongoing studies will fully elucidate the developmental stage that is most sensitive to such environmental manipulations.

The effects of social isolation on pain perception remain controversial [23]. In our study, peri-adolescence social isolation significantly decreased acute pain sensitivity in adult rats. These data are supported by previous reports showing that juvenile isolation rearing significantly decreased pain sensitivity (hypoalgesia) [23,24], as well as clinical studies of schizophrenia patients showing reduced sensitivity to warmth perception and higher onset of thermal pain sensation [9]. However, there are contrasting reports indicating that isolation rearing had no effect in the tail flick of heat sensitivity [8], and even resulted in hyperalgesia in the hot-plate test and footshock sensitivity [3,11]. Methodological differences such as isolation duration may explain these discrepancies. For instance, Becker et al. used a much shorter social isolation procedure [3]; the duration of isolation procedure plays a critical role in determining pain sensitivity changes. Coudereau et al. also reported that the pain threshold of mice was unchanged after 8 and 15 days of social isolation, but increased after 30 days of isolation [4].

In the current study, both anxiogenic-like and social behavioral changes followed by PAIR were reversed by re-socialization procedure, whereas the reduced pain sensitivity remained unaffected. Another study with the same PAIR treatment (PND 21–48) showed that the impaired spatial learning, hippocampus neurogenesis, and long-term potentiation could be reversed by a similar four-week re-socialization procedure [15]. Taken together, we postulate that when compared with cognitive-based (such as spatial learning) or emotional-based (such as social interaction) brain functions, nociception may be more conserved and resilient to behavioral changes. The sustained hypoalgesia following PAIR could serve as a good translational model for similar symptoms observed in schizophrenia patients [9].

As PAIR-induced anxiogenic-like and social behavioral changes could be normalized by re-socialization procedures, it would be interesting to investigate whether other preclinical behavioral models of schizophrenia such as prepulse inhibition or latent inhibition show a similar response to PAIR as well as subsequent group-rearing. The PAIR model could be useful for identifying which kinds of behavior tests are more susceptive to early environmental manipulations, and advance the exploration of their underlying neural mechanisms.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2010.05.067.

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