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Pubertal isolation alters latent inhibition and DA in nucleus accumbens of adult rats

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ABSTRACT

Puberty is a critical period for neurodevelopment of schizophrenia. In the present study, we investigated the effects of peri-pubertal social isolation on psychotic behaviors in rats and its relationship to dopamine expression. Wistar male rats were randomly divided into pubertal isolation (ISO; isolate housing, 38–51 days of age) and social (SOC) groups. Latent inhibition (LI) and behavior in open field were tested during adolescence and adulthood. After the behavioral test, dopamine (DA) levels were measured in the medial prefrontal cortex (mPFC), nucleus accumbens (NAC), caudate-putamen (CPU), and the hippocampus (HIP). Pubertal social isolation impaired LI and increased the DA level in the NAC of young adult rats, but not adolescent rats, and enhanced open field locomotor activity in both adolescent and young adult rats. These data suggest that development of an LI deficit can be induced by social isolation during puberty after a developmental delay, and that NAC DA maybe involved in this process, which may mirror some aspects of the ontogency of schizophrenic symptoms.

1. Introduction

Abnormal brain development is believed to increase the risk of developing a psychosis in adulthood. Since Hatch et al. first reported the abnormal behavioral reactivity of isolated rats [1], a large body of evidence has suggested that rats reared individually post-weaning (isolation) exhibit profound behavioral, neurobiological, and neuroanatomical differences in adulthood when compared to their socially reared litter mates (socials) [2–6]. For example, isolated rearing induces sensorimotor gating deficits in rats similar to the information processing deficit observed in schizophrenia patients. Human selective attentional impairments can be modeled in the rat using the prepulse inhibition (PPI) or the latent inhibition (LI) paradigms. It has been demonstrated that rats reared in isolation from weaning display deficits in PPI compared to socially reared rats when tested in adulthood, while the disruptive effect induced by isolation can be reversed by a range of antipsychotic drugs including haloperidol and clozapine [7–10].

LI is a process by which pre-exposure to a to-be-conditioned stimulus retards the subsequent learning of a conditioned association to that stimulus [11]. LI can reflect the organisms' ability to ignore irrelevant stimuli, and occurs in a variety of classical and instrumental conditioning procedures including passive and active avoidance, and in conditioned emotional responses in many mammalian species [12]. Substantial evidence has demonstrated that the disrupted LI may provide an animal model of the widely described failure of schizophrenic patients to ignore irrelevant stimuli [13–15]. In such studies, LI deficits are chemically induced by drugs such as dopamine (DA) agonists or NMDA antagonists [16,17]; however, the effects of social isolation on LI are poorly understood.

Social isolation causes a variety of changes to brain neurochemistry. For instance, increased basal DA turnover in the nucleus accumbens (NAC) and decreased DA turnover in the medial prefrontal cortex (mPFC) following isolation rearing were shown in rats [18]. Immunoreactivity of the presynaptic protein CDCre1-1, which is normally modulated by DA neurotransmission, was also reduced in the striatum and increased in the hippocampus of isolated rats [19]. Thus, overall these studies suggest an enhanced dopaminergic activity in the NAC and ventral striatum, and reduced DA function in the PFC, of isolation-reared rats.

A large number of studies have demonstrated that the NAC is a key region involved in regulation of LI [11,20,21], and that NAC DA is involved in normal LI, as well as in LI disruption and potentiation [22–25]. For instance, measurement of extracellular DA in the NAC using microdialysis showed changes in DA release that mirrored LI [15], while a single intra-NAC injection of amphetamine prior to conditioning disrupted LI if preceded by a single systemic injection of amphetamine prior to pre-exposure [26]. Further, intra-NAC injection of haloperidol [27] or destruction of dopaminergic terminals within the NAC [28] led to LI potentiation.

In previous studies, social isolation was usually conducted during the developmental period from weaning to adulthood, where the

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animals were deprived of social contact during the juvenile, pubertal, and adult developmental stages. However, the specific period of isolation important for inducing behavioral changes is largely unknown. Puberty is a critical period of neurodevelopment, accompanied by maturational processes in the mPFC and limbic regions characterized by both progressive and regressive changes including myelination and synaptic pruning [29,30]. Furthermore, maturation of neurotransmitter systems such as the dopaminergic and glutamatergic systems occur during this period [30]. For example, the mesolimbic dopaminergic system, such as in the hippocampus, is not fully developed until as late as postnatal day (PND) 35–40 [30], while in male rats, dopaminergic D1/D2 receptors increase in density in the first weeks of life, peak at approximately PND 40, then decrease by 58–75% from puberty to adulthood [31]. As in the PFC, glutamate receptors in the hippocampus undergo substantial pruning during adolescence, with a loss of about 1/4 of NMDA receptors in hippocampal pyramidal regions between PND 28 and 60 in rats [30].

Recently, two studies have suggested that the behavior of rats is sensitive to pubertal treatment. Subchronic pubertal treatment with the NMDA receptor antagonist phencyclidine (PCP, 5 mg/kg) from PND42 to 48 resulted in social behavior deficits, a reduction in locomotion, and a modest disturbance of spatial learning in adult rats [32], while an i.p. injection of dizocilpine (0.3 mg/kg) induced higher locomotor and stereotypic activities in pubertal rats (PND 48–50 old) than in adult rats (3-month-old) [33], suggesting that puberty is a vulnerable period during development. Moreover, a recent study by Rasmussen et al. indicated that a single dose of PCP (10 mg/kg) on PND 45 produced differential effects on PPI in adolescent and adult rats, suggesting that PPI deficit induced by pubertal treatment is age-dependent [34]. Whether pubertal isolation would have differential effects on LI in adolescence and young adulthood is still unclear.

Based on the above data suggesting that puberty is a critical period for maturation of the dopaminergic limbic system, including the neural circuitry of LI, we hypothesized that social isolation during puberty would result in an LI deficit and increased DA levels in the NAC, and the effects induced by pubertal social isolation maybe differential in adolescence and young adulthood. We examined the effect of two weeks' social isolation during puberty on the LI of rats using a behavioral test, and explored its dopaminergic neural substrate by measuring DA levels in the mPFC, NAC, caudate-putamen (CPU), and hippocampus at PND 52 for adolescent rats and at PND 66 for young adult rats.

2. Materials and methods

2.1. Animals

A total of 78 male Wistar rats were obtained from the Academy of Chinese Military Medical Science on PND 21, and were housed in groups of four in one cage. Rats were kept under controlled environmental conditions (ambient temperature 22 °C, 12 h light/12 h dark cycle, light on at 7:00 a.m.) with free access to food and water. The use of animals was in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals Research, Peking University.

2.2. Experimental procedure

Rats were randomly divided into two groups at PND 38; the pubertal isolation group (ISO) in which rats were housed singly for two weeks during puberty (from PND 38–51), and the social group (SOC) in which rats were housed under normal grouped housing condition. Behaviors in open field and LI were examined immediately in adolescent rats at PND 52 (ISO, $n=20$; SOC, $n=20$), or after two weeks rehoused rearing in young adult rats at PND 66 (ISO, $n=16$; SOC, $n=22$). All rats were housed simultaneously in the same room, and could hear and smell the other rats. All behavioral testings were performed during light cycle between 7 a.m. and 7 p.m. The body weights of all rats in the ISO and SOC groups were measured at adolescence (PND 52) and in young adulthood (PND 66).

2.3. Open field

The testing apparatus was a circular arena of 180 cm in diameter, with a 50 cm high wall. The test room had a dim illumination (40 W) in order to decrease the averseness of the test. An animal was placed in the center of the field, and horizontal activity (distance traveled) was recorded for 5 min and analyzed by a computer-based system (EthoVison; Noldus Information Technology, Wageningen, Netherlands). The open field was cleaned each time after each testing [35].

2.4. Latent inhibition

1 h after open field test, LI was evaluated by conditioned avoidance. The acquisition of a conditioned reaction in a two-way shuttle box was tested with or without pre-exposure to the stimulus to be conditioned [36,37]. The computer-controlled automatic shuttle box was $64\times34\times24$ cm. The conditioned stimulus was a sound produced by a buzzer (75 dB) located on the central ceiling of the box. The unconditioned stimulus was an electric foot shock of 0.4–1.0 mA, depending on the individual sensitivity of the animals, and was delivered through stainless steel rods forming the floor. The jump threshold was defined as the foot shock sensitivity that elicited simultaneous removal of at least three paws (both hind paws) from the grid. In this way, foot shock sensitivity was defined for each rat. There was no group difference for foot shock sensitivity.

Rats in each group were randomly divided into non-preexposure (NPE) and preexposure (PE) groups. During the pre-exposure period the PE group animals were placed in the apparatus and the sound was delivered 90 times for 6 s (14 s interval) over 30 min. NPE group animals were placed in the same apparatus for 30 min without sound. The training session consisting of 50 trials was started immediately after pre-exposure. The rats were trained to move to the other side of the shuttle box after presentation of the conditioned stimulus in order to escape the unconditioned stimulus and to avoid the conditioned stimulus. The conditioned stimulus lasted for 3 s. If the rat moved to the other side of the box within this time then the noise was turned off and there was no foot shock. Otherwise a foot shock was administered. One trial was limited to 15 s if the animal failed to react within this period. The inter-trial intervals lasted for 10 s. The number of avoidance responses (response latency <3 s) were recorded for evaluation.

2.5. Measurement of dopamine levels

24 h after LI test, 10 rats from each group were randomly chosen for decapitation. Brains were removed rapidly and frozen in liquid nitrogen within 10 s. The brains were cut at −20 °C in a cryostat microtome at 50 μm thickness. The coronal sections were approximately 3.20–2.20 mm from bregma for mPFC, 2.70–0.70 mm from bregma for NAC, 1.70 to −0.40 mm from bregma for CPU (striatum), and −2.80 to −4.16 mm from bregma for hippocampus (HIP) (Paxinos and Watson, 1998). Bilateral tissue punches of the target regions were taken rapidly using a stainless steel cannula (Jiangxi Glance Medical Equipment Co., Ltd, China) with an inner diameter of 0.6 mm [38–41]. The relative size of the tissue samples can be seen in Fig. 1. The tissue samples were frozen immediately at −80 °C and stored until extraction. On the day of the assay, tissues were weighed and homogenized in 800 μl of 0.1 M $HClO_4$ containing 5 mM $Na_2S_2O_5$, 0.04 mM Na_2EDTA, and 1 ng/10 μl 3,4-dihydroxybenzylamine (as an internal standard) with an ultrasonic homogenizer (Sonic Co., Stratford, CT, USA) in ice-cold solution for 10 s. Next, the homogenate

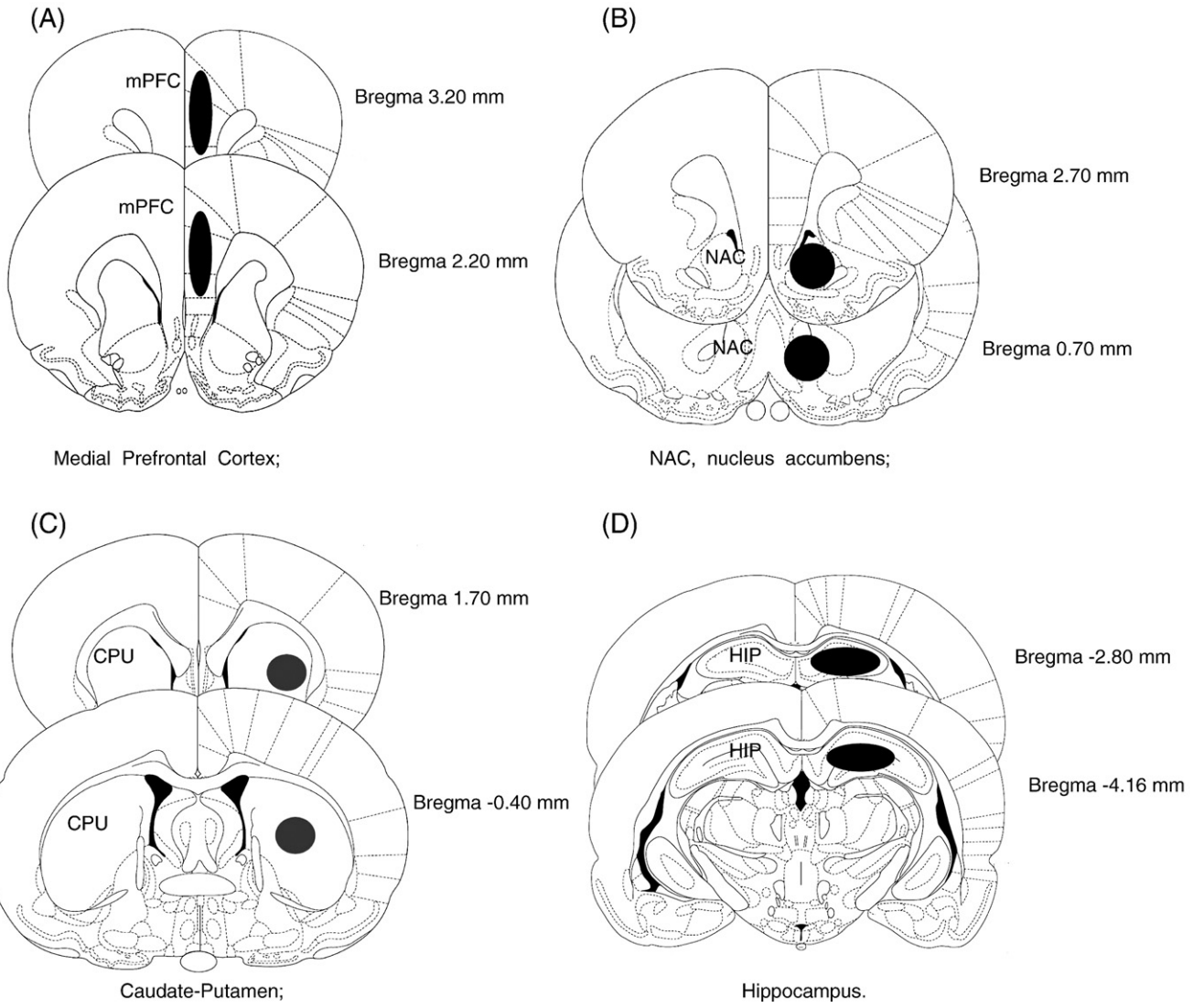

Fig. 1. Diagrams showing the rostral–caudal extent, location, and relative size of the tissue samples taken from the mPFC (A), NAC (B), CPU (C), and HIP (D). The black circle and oblong show the rostral and caudal extension, respectively, of the dissected brain area. mPFC, medial prefrontal cortex; NAC, nucleus accumbens; CPU, caudate-putamen; HIP, hippocampus.

was centrifuged at 4 °C for 30 min at 18,000 ×*g*. The DA concentrations in the supernatants were determined according to a modification of our previously described procedure [42]. Briefly, DA was detected using an LC-10A HPLC system, with LC-ECD-6A electrochemical detection (Shimadzu Co., Kyoto, Japan) using a glassy carbon electrode set at +0.7 V vs. an Ag/AgCl reference electrode. Separations were performed with a Shim-pack VP-ODS RP-C18 column (250×4.6 mm internal diameter, 4.6 μm particle diameter; Shimadzu Co.) protected with a Shim-pack GVP-ODS RP18 guard column (10×4.6 mm internal diameter; Shimadzu Co.). The column and detector were placed in the compartment of a Shimadzu CTO-10A column oven at 40 °C. The mobile phase (pH 4.0) consisted of 0.07 M NaH_2PO_4, 11% methanol, 0.06% sodium alkylsulfonate (SAS), 1% acetic acid, and 0.006% EDTA-Na_2, and was delivered at flow rate of 1.0 ml/min. The injected sample volume was 10 μl. The levels of DA were determined by an internal standard method.

2.6. Statistical analyses

Data are presented as mean ± standard error of the mean (SEM) for all measures. The analyses were performed using SPSS 13 software (SPSS Inc., China) running on Windows XP. Active avoidance responses were analyzed using a 2×2×5 ANOVA consisting of two between-subjects main factors of housing condition and pre-exposure (NPE vs. PE), and a repeated-measurement factor of blocks (5 blocks of 10 trials). Body weight, distance in open field, and DA levels from different brain regions were analyzed by two-way ANOVA using housing condition and age as between-subject factors. Following significant analyses of variance, we used the independent *t*-test as the post hoc test. A probability level of $P<0.05$ was considered statistically significant.

3. Results

3.1. Effects of pubertal social isolation on body weight

The body weights of the rats can be seen in Fig. 2. Two-way ANOVA revealed significant main effects of housing condition [$F(1, 74) = 18.16$, $P<0.001$] and age [$F(1, 74) = 74.17$, $P<0.001$], and a significant interaction between housing condition and age [$F(2, 74) = 6.32$, $P<0.05$]. Following pubertal isolation, adolescent rats exhibited a significantly lower body weight compared to pubertal grouped rats [$t(38) = 2.54$, $P<0.01$)], while

there was no difference for young adult rats in both the SOC and ISO groups. The body weights of young adult rats were increased compared to adolescent rats in both the SOC and ISO groups [$t(40) = 11.99$, $P<0.01$; $t(34) = 17.86$, $P<0.01$].

3.2. Effects of pubertal social isolation on locomotor activity in open field

The distance in open field for each group can be seen in Fig. 3. Two-way ANOVA revealed a significant effect of housing [$F(1, 36) = 8.08$, $P<0.01$], but not of age. There was no significant interaction between housing condition and age. The rats in the ISO group showed an increased distance traveled compared to rats in the SOC group during both adolescence [$t(18) = 2.35$, $P<0.05$] and adulthood [$t(18) = 2.27$, $P<0.05$).

3.3. Effects of pubertal social isolation on latent inhibition

The LI for each group can be seen in Fig. 4. For LI of pubertal rats in the SOC and ISO groups, an analysis on the number of avoidance responses revealed a main effect of blocks [$F(4, 144) = 43.29$, $P<0.01$), reflecting an overall increase of avoidance responses as a function of progressive learning. In addition, there was a significant effect of pre-exposure [($F(1, 34) = 10.16$, $P<0.01$), as well as a pre-exposure × blocks interaction [$F(4, 144) = 43.29$, $P<0.05$), reflecting the existence of LI (i.e., a significant reduction of avoidance responses in PE group animals compared with NPE group animals). Social isolation did not significantly modify the LI phenomenon (i.e., no housing condition × pre-exposure × blocks interaction) (Fig. 4A and B).

For the LI of young adult rats in the SOC and ISO groups, there was a significant effect of blocks, reflecting an overall increase of avoidance responses [$F(4, 136) = 70.53$, $P<0.01$). Nevertheless, there was no significant effect of pre-exposure and pre-exposure × blocks interaction, reflecting an LI deficit. There was a significant effect of housing condition × pre-exposure × blocks interaction [$F(4, 136) = 4.14$, $P<0.05$], reflecting an LI deficit in young adult isolates (Fig. 4C–D).

3.4. Effects of pubertal social isolation on DA level

DA levels in the NAC, mPFC, CPU, and HIP for each group can be seen in Fig. 5 and Table 1. For DA level in the NAC, two-way ANOVA revealed a significant main effect of housing condition [$F(1, 36) = 4.76$, $P<0.05$] and age [$F(1, 36) = 16.94$, $P<0.01$], and a significant interaction between housing condition and age [$F(2, 36) = 6.57$, $P<0.05$]. Pubertal isolated rats showed an increased DA level in the NAC compared to controls during adulthood [$t(18) = 2.58$, $P<0.05$), but there was no difference between the groups during adolescence (Fig. 5). DA levels in the NAC of young adult rats were significantly higher than in adolescent rats in both the SOC [$t(18) = 2.117$, $P<0.05$] and ISO [$t(18) = 4.010$, $P<0.01$) groups. There were no significant main effects of housing condition and age (two-way ANOVA) on DA levels in the mPFC, CPU, or HIP (Table 1).

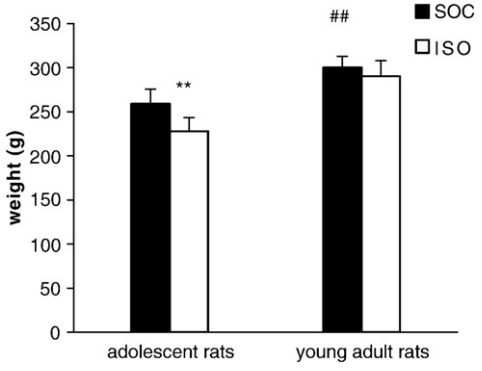

Fig. 2. Body weights of adolescent and young adult rats in the SOC and ISO groups. Pubertal isolation decreased the body weight gain of adolescent rats compared to pubertal grouped rats (two-way ANOVA, post-hoc independent t-test, $^{**}P<0.01$). $^{\#\#}$ Significant difference between different age groups (two-way ANOVA, $P<0.01$). All data are presented as mean ± SEM.

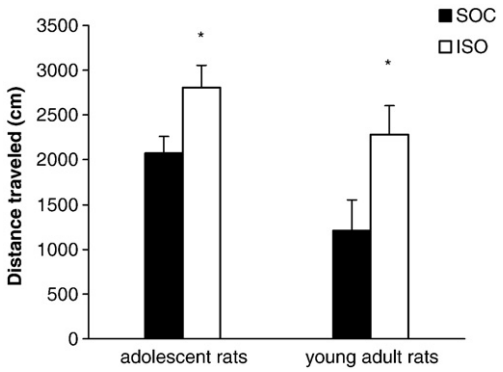

Fig. 3. Distance traveled in open field of adolescent and young adult rats in the SOC and ISO groups. Pubertal isolation increased the distance traveled of adolescent and young adult rats compared to pubertal grouped rats (two-way ANOVA, post-hoc independent t-test, $^{*}P<0.05$). All data are presented as mean ± SEM, $n = 10$ per group.

4. Discussion

Our data showed that social isolation during puberty impaired LI of young adult rats, but had no effect on LI in adolescent rats; enhanced open field locomotor activity in both adolescent and young adult rats. In line with the behavioral result of LI, 2 weeks social isolation during puberty increased the DA level of NAC in young adult rats, but not in adolescent rats.

4.1. Latent inhibition

The results from the present study demonstrated that social isolation during puberty impaired LI of young adult rats. This is in contrast to two studies showing intact LI following 12 weeks and 8 weeks social isolation after weaning using either two-way active avoidance paradigm in Sprague–Dawley (SD) rats [43] or bar-pressing for sucrose solution in Lister hooded rats [44], respectively. The LI effect is related to a number of experimental parameters, including the different unconditioned and conditioned stimulus, the interval between the pre-exposure and test phase, strain, gender, and age difference of animals [21]. Thus, the contrasting results in the previous studies may relate to the different LI model, strain, age of rats, and duration of social isolation used when compared to the present study.

More importantly, in the present study we found that the LI impairment induced by isolate housing during puberty did not appear until adult age. The post-pubertal expression of LI deficiency has been also reported in other neurodevelopmental animal models of schizophrenia, including polyriboinosinic–polyribocytidylic acid (poly I:C) injection on PND 9 [45], maternal deprivation [46], and neonatal ventral hippocampal lesion [37]. Together, these data extend the neurodevelopmental hypothesis of schizophrenia, suggesting that schizophrenic cognitive symptoms, such as LI deficient induced by manipulation during puberty or pre-existent developmental anomalies, can be expressed after developmental maturation in puberty.

4.2. NAC DA

The results from the present study demonstrated that pubertal grouped young adult rats have higher DA levels in the NAC than

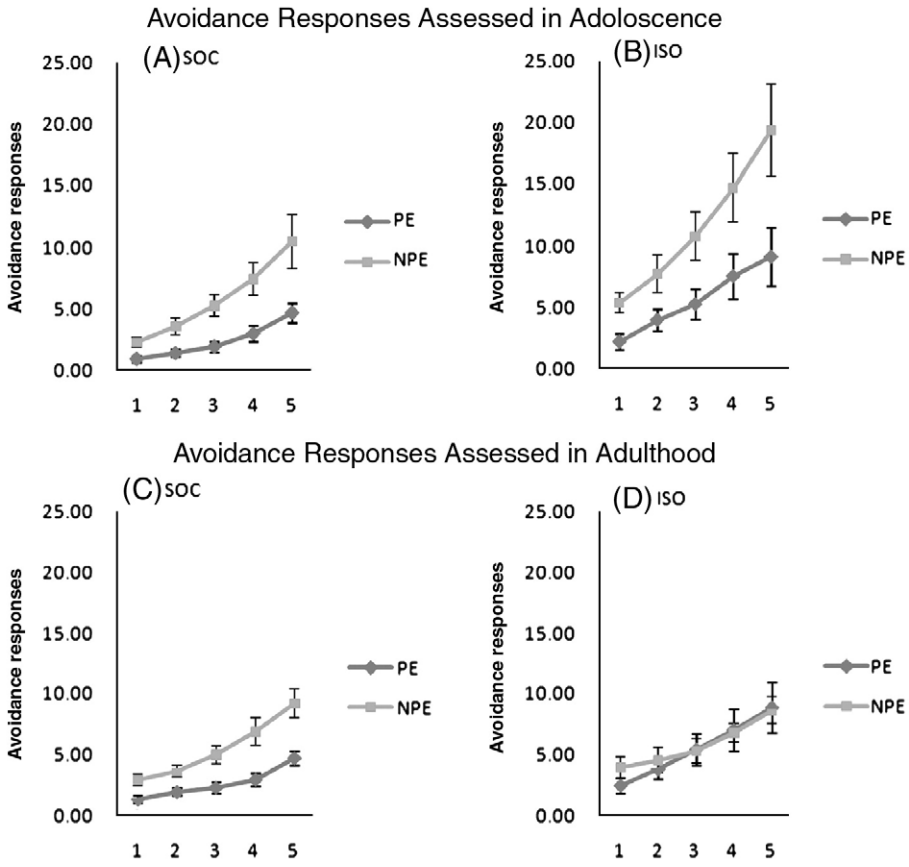

Fig. 4. Avoidance responses of PE and NPE groups in the SOC and ISO rats during adolescence and adulthood. Latent inhibition assessed using tone-CS pre-exposure in the two way AA test. Five blocks of 10 trials were used. Avoidance responses (mean ± SEM) tested in adolescence [(A) SOC, $n = 20$; (B) ISO, $n = 20$], or at two weeks after pubertal social isolation as young adults [(C) SOC, $n = 22$; (D) ISO, $n = 16$].

adolescent rats. These data are similar to a previous study showing reduced DA concentration and turnover rates in the NAC of juvenile compared to adult rats [47]. In addition to changes in DA concentration, adults may also have a lower density of D2 autoreceptors in the NAC [48,49]. Since stimulation of autoreceptors in the dopaminergic system nerve terminals inhibits DA synthesis and release, a lower density of D2 autoreceptors in the NAC may disinhibit DA synthesis and result in higher DA levels in adults [47].

We also demonstrated that pubertal social isolation increased DA levels in the NAC, but not in the mPFC, hippocampus, or striatum.

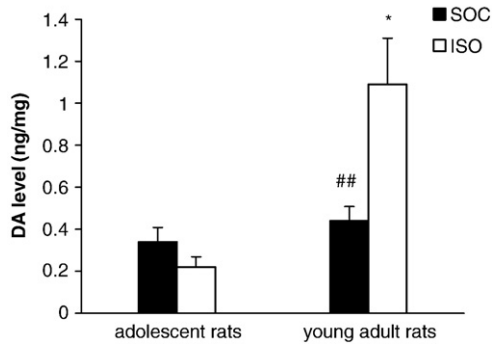

Fig. 5. DA levels in the NAC of adolescent and young adult rats in the SOC and ISO groups. Pubertal isolation increased DA content in the NAC of young adult rats compared to pubertal grouped rats (two-way ANOVA, post-hoc independent *t*-test, $^{*}P<0.05$). $^{\#\#}$Significant difference between different age groups (two-way ANOVA, $P<0.01$). Data expressed as ng/mg tissue (mean ± SEM, $n = 10$ per group).

Further, consistent with the behavioral result of LI, NAC DA level was not significantly elevated until young adulthood. Post-weaning isolated rearing has been previously shown to enhance dopaminergic activity in the NAC, suggesting a possible sensitization of the mesoaccumbens DA projection [50,51]. The major midbrain dopaminergic systems can be divided into three major categories linking the ventral tegmental area and substantia nigra neurons with the NAC, PFC, and striatum, termed the mesolimbic, mesocortical, and nigrostriatal dopaminergic systems, respectively. Studies investigating the neural substrates of LI have suggested that the mesolimbic dopamine system in particular, provides critical control in the development and expression of LI. Thus, our results suggest that puberty is a critical period for maturation of the dopaminergic limbic system, and show that pubertal sensory deprivation induced by isolation may result in abnormal development of mesolimbic dopamine circuit, which does not emerge until post-puberty, causing cognitive abnormalities such as schizophrenic symptoms.

Table 1
DA levels in mPFC , CPU and HIP of adolescent and young adult rats in SOC and ISO groups.

	Adolescence		*P*	Adulthood		*P*
	ISO	SOC		ISO	SOC	
mPFC	.070 ± .020	.038 ± .025	.458	.129 ± .043	.427 ± .154	.055
CPU	4.177 ± .958	3.255 ± .580	.403	5.176 ± .796	5.727 ± .742	.627
HIP	.115 ± .051	.048 ± .012	.388	.069 ± .016	.072 ± .029	.926

All data are expressed as ng mg^{-1}, mPFC: medial prefrontal cortex; CPU: caudate-putamen; HIP: hippocampus.

4.3. Open field

Our data demonstrated that pubertal social isolation enhanced open field locomotor activity in both adolescent and young adult rats, suggesting that only two weeks social isolation during puberty was enough to induce long-lasting enhancement of open-field activity. These data are partly consistent with previous studies demonstrating that isolation-reared rats have an altered behavioral profile when exposed to a novel environment, and especially show spontaneous locomotor hyperactivity in an open field [2,50,52–56]. Several studies have also reported that the age of the subjects during isolation is a particularly important factor for development of behavioral deficits [57].

In the present study, pubertal social adolescent rats showed relatively greater locomotor activity in open field compared to young adult rats, although the difference was not significant. Similarly, normal and greater open field locomotion in adolescent rats compared to adults has been previously described [58–60], although in contrast, less activity in open field was reported in five-week-old CD-1 mice [61] and six-week-old C57BL/6 J mice [62] when compared to adults.

4.4. Body weight

Our data demonstrated that the body weight of pubertal rats decreased after two weeks' social isolation during puberty. However, following a further two weeks rehoused in social group rearing, there was no difference between isolated-rehoused early adult rats and controls, suggesting that the influence of isolated rearing during puberty on the body weight gain could be reversed by the social group rearing. Body weight gain occurs more rapidly during development [30], supporting the greater body weight gain of pubertal grouped young adults compared to adolescent rats.

4.5. General conclusion

In summary, the results from the present study demonstrated that social isolation during puberty can have delayed developmental effects on LI in young adult rats, lasting effects on open field activity in adolescent and young adult rats, and temporary effects on body weight gain in adolescent rats. Consistent with the effect of LI deficit, pubertal social isolation induced a delayed increase in DA levels in the NAC of young adult rats. These data suggest that the expression of LI deficit induced by isolate housing during puberty occurs after a developmental delay, which is similar to the presence of pathological processes suggested to account for the cognitive deficit in schizophrenia. However, the finding of altered LI only with social isolation during the peripubertal period requires further investigation.

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