Prenatal ethanol exposure impairs spatial cognition and synaptic plasticity in female rats

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\textbf{A B S T R A C T}

Chronic prenatal ethanol exposure (CPEE) can impair long-term potentiation (LTP) in the male hippocampus. Sexually specific alterations were frequently reported in female animals that had been prenatally exposed to ethanol. This study aimed to examine the effects of CPEE on spatial learning and memory, as well as on hippocampal synaptic plasticity in female adolescent rats. Female offspring were selected from dams that had been exposed to 4 g/kg/day of ethanol throughout the gestational period. Subsequently, performance in the Morris water maze (MWM) was determined, while LTP and depotentiation were measured in the hippocampal CA3-CA1 pathway. In the behavioral test, the escape latencies in both initial and reversal training stages were significantly prolonged. Interestingly, LTP was considerably enhanced while depotentiation was significantly depressed. Our results suggest a critical role of synaptic plasticity balance, which may prominently contribute to the cognitive deficits present in CPEE offspring.

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Introduction

Fetal alcohol spectrum disorders (FASDs), caused by maternal alcohol consumption during pregnancy, were first described as fetal alcohol syndrome (FAS) (Jones & Smith, 1973). Since then, it has been reported that these devastating disorders are associated with central nervous system (CNS) malformations, mental retardation (Abel, 1984; Danis, Newton, & Keith, 1981), cognitive impairments, and behavioral dysfunctions that can vary in severity, depending on amount of alcohol consumption, duration, and timing of prenatal alcohol exposure (Aronson, Hagberg, & Gillberg, 1997; Goodlett & Eilers, 1997; Goodlett & Lundahl, 1996; Hausknecht et al., 2005).

Recent studies have shown that the brain is the most vulnerable organ to ethanol exposure; therefore, further investigation should be made to discover the mechanism and severity of ethanol-mediated impairment (Momino, Sanseverino, & Schüler-Faccini, 2008; Mooney & Miller, 2007).

CPEE-induced brain injury in offspring can manifest as life-long learning and memory deficits (Choi, Allan, & Cunningham, 2005; Gonzalez-Burgos et al., 2006). Among the deficiencies in a variety of behavioral and cognitive domains of the brain caused by prenatal exposure to ethanol, impairments in rodent spatial learning and memory abilities could be directly related to physiological and biochemical alterations in hippocampal circuitry. Spatial learning and memory deficit induced by ethanol exposure can be directly related to physiological and biochemical changes in hippocampal circuitry (Samudio-Ruiz, Allan, Valenzuela, Perrone-Bizzozero, & Caldwell, 2009; Zink et al., 2011). Studies have shown that the LTP of female offspring is significantly enhanced by CPEE; the potential mechanism of this specific effect might be involved in expression of gonadal hormones (Titterness & Christie, 2012). Although LTP in the hippocampus is well known to underlie learning and memory (Collingridge, Peineau, Howland, & Wang, 2010; Malenka & Nicoll, 1999), the function of long-term depression (LTD) on weakening synaptic strength and maintaining synaptic plasticity balance during the tasks cannot be neglected (Collingridge et al., 2010; Kemp & Manahan-Vaughan, 2007; Nicholls et al., 2008). Although previous studies mainly focused on the effect of potentiation on the neural network under the CPEE condition (Christie et al., 2005; Richardson, Byrnes, Brien, Reynolds, & Dringenberg, 2002; Titterness & Christie, 2012), only a few of those studies reported the behavior changes due to the balance of potentiation and depression.

Recently, several investigations revealed that the brains of both female humans and female rodents are more vulnerable than the brains of males to neurotoxic insult during chronic ethanol exposure.
exposure (Butler, Smith, Self, Braden, & Prendergast, 2008). It has been suggested that there are some female-specific alterations in ethanol-treated female animals. Another study reported that dimorphic properties probably reflected the diverse effects of ethanol exposure on N-methyl-D-aspartate (NMDA) receptor-mediated signaling downstream (Butler et al., 2008). Although the effects of ethanol on interactions between pregnant females and fetuses are complex, ethanol readily crosses the placenta and directly affects developing fetal cells and tissues, including those related to development of the CNS (Weinberg, Sliwowska, Lan, & Hellemans, 2008). Logically, there could be specific alterations in both CNS development and CNS function after long-term prenatal ethanol exposure to females. Moreover, in one of our previous studies, it was found that the LTP of CPEE-male adolescent rats was significantly inhibited, while depotentiation was distinctly enhanced compared to that of control male rats (An, Yang, & Zhang, 2013a). A hypothesis was therefore raised that there was a significantly enhanced compared to that of control male rats (An, Yang, & Zhang, 2013a). A hypothesis was therefore raised that there was a significantly enhanced compared to that of control male rats (An, Yang, & Zhang, 2013a). A hypothesis was therefore raised that there was a significantly enhanced compared to that of control male rats (An, Yang, & Zhang, 2013a).

Experimental procedures

Animal preparation

Adult virgin female (200–250 g) Wistar rats were obtained from the Laboratory Animal Center, Academy of Military Medical Science of People’s Liberation Army, P.R. China. All animals were group-housed with free access to water and food in an established animal house having a 12-h light/12-h dark cycle and a thermoregulated environment. Two females were paired with two males for 4–5 days until mating was confirmed by observation of a copulatory plug or the presence of sperm in a vaginal rinse under a microscope. The day that mating was confirmed was recorded as embryonic day 0 (E 0). All experiments were performed according to the protocols approved by the Committee for Animal Care at Nankai University and in accordance with the practices outlined in the NIH Guide for the Care and Use of Laboratory Animals.

Prenatal treatment

The ethanol-exposure model was established in reference to that used in previous studies (Carneiro et al., 2005; Ramachandran et al., 2001). Three groups of pregnant rats were investigated:

1) Ethanol group (n = 7), in which female rats were administered ethanol by gavage 7 days before being paired with male rats and throughout the gestational period. Four g/kg body weight ethanol was administered from 20% v/v ethanol solutions in distilled water. Rats had full access to chow and water.

2) Pair-fed group (n = 7), in which animals were administered, by gavage, a glucose solution isocalorically equivalent to ethanol-derived calories received by the ethanol group, for the same period of time. The rats had full access to water but received the weight of chow consumed by the corresponding CPEE dam during the previous 24-h period.

3) Control group (n = 5), in which female animals had ad libitum access to standard rat chow and were administered saline via gavage for the same period of time. The day of birth was identified as postnatal day 0 (PD 0). The entire litter and mother were placed in a large plastic bin with shaved wood chips as bedding.

Five litters of control groups and seven litters of other groups were used in the present study. The female offspring of each litter were randomly culled to 2 or 3 pups on PD 1 and weaned on PD 22. 35-day-old Wistar rats were selected for the present experiment. CPEE offspring rats (EF) were randomly divided into two groups: (1) CPEE female offspring group for the MWM test (n = 7), and (2) female offspring group for an electrophysiological experiment (n = 7). Pair-fed offspring rats (PF) were also randomly divided into two groups: (1) pair-fed female offspring group for the MWM test (n = 7), and (2) pair-fed female offspring for an electrophysiological experiment (n = 7). Control offspring rats (CF) were randomly divided into two groups as well: (1) control female offspring group for the MWM test (n = 7), and (2) control female offspring for an electrophysiological experiment (n = 7). The female offspring used in the present study were selected at all stages of the estrous cycle.

Morris water maze experiment

As previously described with modifications (An, Fu, & Zhang, 2015; An, Li, Yang, & Zhang, 2011, 2012; An & Zhang, 2014a; Han, An, Yang, Si, & Zhang, 2014), the MWM consisted of a 1.5-m diameter circular tank filled with water, which was maintained at 25 ± 1 °C. The tank was divided into four quadrants (I, II, III, and IV), and a 10-cm diameter platform was placed in the center of quadrant III. The rats’ movements were monitored by a CCD camera connected to a computer, through which data were collected (SLY-WMS 2.1, Sunny Instruments Co. Ltd., China). The task consisted of three stages: initial training (IT), space-exploring test (SET), and reversal training (RT). In the IT stage, there were two sessions (four trials per session) per day from PD 36 to PD 40. In each trial, the animal was released into the water until it reached and stayed on a platform. If it failed to find the platform within 60 s, the animal was placed on it for 10 s. Escape latency and swimming speed were recorded. On PD 41, one trial test was performed in the SET stage. After removing the platform from the tank, the rat was released from quadrant I and swam freely for 60 s. Quadrant dwell time and platform crossings were measured. On PD 42 and 43, the platform was placed in quadrant I. In the RT stage, the rats’ reversal-learning ability was examined. The method used and parameters recorded were the same as those in the IT stage.

In vivo LTP and depotentiation recording

On PD 36, the animals were anesthetized with 30% urethane (1.5 g/kg body weight) by intraperitoneal injection. They were then placed in a stereotaxic frame (SN-3, Narishige, Japan) for surgery and recording as described previously (An, Liu, Yang, & Zhang, 2012; An, Yang, & Zhang, 2013b; An & Zhang, 2014b). A bipolar stimulating electrode was placed in the Schaffer collateral/commisural pathway (AP = −4.0 mm, ML = 2.8 mm), and an ipsilateral recording electrode was positioned in the stratum radiatum area of CA1 (AP = −3.2 mm, ML = 2.0 mm). The optimal depth of the electrode was determined by electrophysiological criteria (Leung, 1980). Test stimuli were delivered every 30 s at an intensity that evoked a response of 50% of its maximum (range 0.3–0.8 mA). After the response stabilized, sampling was made under low-frequency stimulations (0.05 Hz) for 20 min as a baseline. After that, HFS (10 trains of 10 stimuli at 100 Hz with 2-s intertrain interval) was delivered to induce LTP. Field excitatory postsynaptic potentials (fEPSPs) were amplified (×100), filtered at 5–50 kHz, digitized, and collected at 20-kHz sample frequency (Scope Software, PowerLab; AD Instruments, Australia) every 60 s for 60 min. After LTP was recorded, LFS (900 pulses of 1 Hz for 15 min) was delivered, and single-pulse recording resumed every.
All data were presented as mean ± S.E.M. A two-way repeated-measures ANOVA was used with group and session as the factors to measure the performance of rats during the IT and RT stages. A two-way ANOVA was employed with treatment and time as two factors to measure the alterations of time coursing in fEPSPs slope. A one-way ANOVA was employed to measure the data, which were obtained from the SET stage. Data included average changes of fEPSPs slope, body weight, litter sizes, pup sex ratio, and weights of brains and hippocampi. To detect significant differences between groups, ANOVAs were supported by the Bonferroni post hoc tests. All analyses were performed using SPSS 16.0 software. A p value of less than 0.05 was considered significant.

Results

Characterization of the model of prenatal ethanol exposure

One-way ANOVA test showed a significant difference of maternal weight gain among the three groups (Table 1, F [2,20] = 11.122, p < 0.01). Bonferroni post hoc test demonstrated that the maternal body weight gains of both the EF (p < 0.05) and the PF groups (p < 0.05) were significantly decreased compared to the CF group, with no difference between the PF group and the EF group (p > 0.05). One-way ANOVA test exhibited detrimental intrauterine effects of CPEE on litter size (Fig. 1A, F[1,20] = 5.037, p < 0.01), sex ratio (Fig. 1B, F[2,20] = 5.658, p < 0.01) and birth weight (Fig. 1C, F[2,20] = 14.178, p < 0.01) among these groups. The litter size from CPEE-treated dams was smaller than that from the PF and CF dams (Fig. 1A, F[1,20] = 3.878 and 4.237, both p < 0.05), with no difference between the PF and CF groups (F[1,20] = 0.958, p > 0.05). Bonferroni post hoc test showed that the ratio of male/female pups was significantly enhanced when comparing the EF group to the PF and CF groups (Fig. 1B, F[1,20] = 3.226 and 3.693, both p < 0.05). However, no difference of sex ratio was found between the PF and CF groups (F[1,20] = 1.159, p > 0.05). The birth weight of CPEE pups was markedly reduced compared to the CF group (Fig. 1C, F[1,20] = 0.046, p < 0.05) or the PF group (p < 0.01). One-way ANOVA test showed the significant difference in body weight among groups (Fig. 1D, F[2,18] = 3.828, p < 0.05). One-way ANOVA test showed detrimental effects of CPEE on brain weight (Fig. 1E, F[2,20] = 5.891, p < 0.01) and hippocampus weight (Fig. 1F, F[2,20] = 5.345, p < 0.01) among groups. Post hoc test demonstrated that the brain weights of the EF group were significantly lower than the PF group (p < 0.05) or the CF group (p < 0.05), as were hippocampus weights (both p < 0.05). However, no statistical differences were found in birth weight, body weight change, brain weight, or hippocampus weight between the PF group and the CF group.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Weight (g)</th>
<th>ΔW (%)</th>
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<tbody>
<tr>
<td></td>
<td>W(E1)</td>
<td>W(E21)</td>
</tr>
<tr>
<td>Control</td>
<td>220 ± 7</td>
<td>305 ± 11</td>
</tr>
<tr>
<td>Pair-fed</td>
<td>224 ± 5</td>
<td>289 ± 7</td>
</tr>
<tr>
<td>Ethanol</td>
<td>231 ± 6</td>
<td>296 ± 9</td>
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</tbody>
</table>

W(E1) and W(E21) separately represent the mean body weight on day E1 and day E21. ΔW (%) represents the normalized body weight gain of rats from day E1 to day E21. Data are presented as mean ± S.E.M.

n = 7 for ethanol and pair-fed group, n = 5 for control group.

<sup>a</sup> p < 0.05, comparison between control group and pair-fed group.

<sup>b</sup> p < 0.05, comparison between control group and ethanol group.

Effects of CPEE on adolescent rats' performance in MWM

During the IT stage, the average escape latencies on successive sessions were decreased remarkably from session 1 to session 4 (Fig. 2A). The results, obtained from two-way repeated ANOVA, showed statistical differences of sessions [F(5.779,104.015] = 458.746, p < 0.001), session × group interactions (F[11.557,104.015] = 6.379, p < 0.001), and groups (F[2,18] = 92.141, p < 0.001). Post hoc test exhibited that the escape latency was significantly increased in the EF group compared to the PF group (session 2, 9, and 10, p < 0.05; session 3, 4, 5, 6, 7, and 8, p < 0.01) or the CF group (session 2, p < 0.05; session 3, 6, 7, 8, 9, and 10, p < 0.01; session 4 and 5, p < 0.001). There were no differences in swimming speed among all groups throughout testing (Fig. 2B, p > 0.05). In the SET stage, a one-way ANOVA showed the statistical differences of platform crossings (Fig. 2C, F[2,18] = 4.036, p < 0.05) and quadrant dwell time (Fig. 2D, F[2,18] = 4.480, p < 0.05) among these groups. Post hoc test showed that platform crossings were significantly reduced in the EF group compared to the PF group (F[2,20] = 0.05) or the CF group (p < 0.05), as well as quadrant dwell time (both p < 0.05). Contrarily, no difference in all the above indexes was found between the PF group and the CF group throughout the IT and SET stages.

During the RT stage, escape latencies were considerably shortened in the CF group compared to those in the EF group, indicating a significant effect of CPEE treatment. A two-way repeated-measures ANOVA confirmed statistical differences of session [F(2,572.46299] = 211.679, p < 0.001), session × group interaction [F(5.144,46.299] = 6.262, p < 0.001), and group (F [2,18] = 25.316, p < 0.001). As shown in Fig. 2A, post hoc test showed that the escape latency was distinctly prolonged in the EF group compared to the PF group (session 13, p < 0.05; session 14, p < 0.01) or the CF group (session 13, p < 0.05; session 14, p < 0.01). No differences of swimming speed were observed among all those groups throughout testing (Fig. 2B, p > 0.05). Interestingly, post hoc test showed that rats in the EF group spent a dramatically shorter time in quadrant I compared to the PF group (Fig. 2E, p < 0.05; session 13, 14, p < 0.01) or the CF group (session 13, 14, p < 0.01), and did a longer time in quadrant III in the PF group (Fig. 2F, session 13, 14, p < 0.05; session 14, p < 0.01; session 14, p < 0.01; Fig. 2F, session 13, p < 0.05; session 14, p < 0.01). There was no significant difference between the EF and PF groups in time spent in either quadrant II or IV (data not shown). Additionally, there was no difference in these measures between the PF and CF groups throughout the RT stage.

LTP and depotentiation from Schaffer collaterals to CA1

In the LTP test, Fig. 3A represents the time course of fEPSPs slopes normalized to the 20-min baseline period. The fEPSPs slopes increased immediately after HFS and stabilized to a level above the baseline period. A two-way ANOVA test showed a significant difference of groups [F(2,18] = 40.231, p < 0.001), with no time and group interaction interaction. Moreover, post hoc test showed that fEPSPs slopes were significantly higher in the EF group than the PF group (Fig. 3B, p < 0.01) or the CF group (p < 0.01). There was no difference between the PF and CF groups.

To examine whether CPEE was involved in depotentiation in female offspring, an LFS induction protocol was employed. A two-way ANOVA showed a significant difference of groups (F [2,18] = 37.692, p < 0.001), with no time and group interaction. Because there were statistical differences of potentiation among those groups before the LFS, the last 20-min LTP recording
was used as the baseline to quantify the magnitude of the depotentiation (Fig. 3A). Post hoc test showed that the depotentiation was significantly inhibited in the EF group compared to the PF group (Fig. 3C, \(p < 0.01\)) or the CF group (\(p < 0.01\)), with no difference between the PF and CF groups.

**Discussion**

The consumption of ethanol during pregnancy impairs the development of the unborn offspring and can lead to physical changes, CNS damage, and cognitive and behavioral abnormalities (Nuñez, Alt, & McCarthy, 2003; Sokol, Delaney-Black, & Nordstrom, 2003). In the present study, the hippocampal development of female offspring was particularly sensitive to the effects of prenatal exposure to ethanol, and a variety of changes in physical characteristics, brain structure, and hippocampus were observed. In the behavioral test, the results showed that the deficits of spatial cognition were associated with CPEE treatment, which was in agreement with previous studies (Iqbal, Dringenberg, Brien, & Reynolds, 2004; Riley & McGee, 2005). Interestingly, the study revealed that CPEE modulates hippocampal plasticity with obviously enhanced LTP, but hardly affected depotentiation in female offspring rats. Bidirectional effects of CPEE on synaptic plasticity could contribute to cognitive deficits.
In the current study, there were no significant differences of dams’ weight gain between pair-fed and ethanol-exposed groups. A previous study showed that the pair-fed group addressed dietary confounds associated with ethanol intake (Gil-Mohapel et al., 2011). Furthermore, others indicated that ethanol could play an important role in the prenatal period (Augustyniak, Michalak, & Skrzydlewska, 2005). The smaller litter size in the CPEE offspring group suggested that ethanol adversely affects the embryos in utero. Chronic ethanol intake at the time of conception and during pregnancy in humans is associated with increased risk of spontaneous abortion (Henriksen et al., 2004). Although the exact causes are still unclear, it is well known that alcohol interferes with the normal function of the reproductive system. For instance, alcohol alters the estrous cyclicity and levels of prolactin and luteinizing hormone, thus preventing conception and implantation (Ghimire et al., 2008). There was a significant decrease in overall body weight of female pups, which persisted into their adolescence. It has been shown that children born to alcoholic mothers were small for gestational age (Ghimire et al., 2008). Low brain and hippocampus weights were in agreement with findings that ethanol exposure causes microcephaly (Evrard et al., 2006; Shirpoor, Salami, Khadem-Ansari, Minassian, & Yegiazarian, 2009), leading to hippocampal neuronal apoptosis (Shirpoor et al., 2009), learning and memory deficits, as well as neurobehavioral dysfunctions (Wozniak et al., 2006).

Our behavioral test provided clear evidence that rats’ learning ability is disrupted under CPEE-treatment conditions. The constant swimming speed throughout the tests implied that motor function was not involved in the prolonged latencies. Due to the poor reference-learning ability, CPEE-treated rats spent more time searching for the submerged platform in disrupted quadrants (I, II, and IV). Furthermore, the learning and memory impairment

![Fig. 2. Rats’ performance in MWM tests. (A) Comparison of mean escape latency calculated for each session between three groups. (B) Comparison of mean swimming speed. During the entire MWM test, there were no significant differences in swimming speed between these three groups. (C) Comparison of mean number of platform area crossings. (D) Comparison of mean percentage of time in target quadrant. (E) Comparison of mean percentage of time in quadrant I. (F) Comparison of mean percentage of time in quadrant III. Data are expressed as mean ± S.E.M. *p < 0.05, **p < 0.01, significant difference in the EF group compared to the PF or CF group. ###p < 0.001, significant difference between the PF group and the CF group. %p < 0.05, %p < 0.01, significant difference between the EF group and the PF group. n = 7 for each group.](image-url)
contributed to prolonged escape latencies, resulting in a poorer performance in the number of crossings of the hidden platform and in the temporal distribution of the target quadrant (III) in the SET stage. CPEE-treated female offspring failed to adapt their behavior following the position change, indicating lack of cognitive flexibility. It is noteworthy that CPEE rats visited the original quadrant more often than the new target quadrant during the entire reversal-learning period. Instead, when they did not find the platform during the RT stage, their behaviors became chaotic and remained focusing on searching in the original quadrant. These findings were supported by comparing the results of previous studies. For example, during place trials in the MWM, CPEE-treated adult females showed impaired behavioral performance (Kelly, Goodlett, Hulsether, & West, 1988), which was attributed to the reduction in proportion of newly produced neurons and glia in the hippocampus (Uban et al., 2010). It has been reported that alcohol insult from E3 throughout pregnancy causes significant deficits in novelty-seeking behavior in adult females (Vaglenova et al., 2008). In addition, cognitive and behavioral defects such as high anxiety, fear (Vaglenova et al., 2008), and deficits in contextual learning (Murawski & Stanton, 2011) have also been reported.

Consistent with our previous findings (An et al., 2013a), we observed a similar spatial memory impairment between males and female on PD 35. Although many rodents were thought to exhibit gender differences in spatial cognition, the measurement of spatial abilities is subject to variability, making comparisons difficult. For example, at 80–90 days of age, Sprague–Dawley rats did not show sex differences in an MWM training task of 6 days’ duration (Wilcoxon, Kuo, Disterhoft, & Redei, 2005). One study reported that sex differences in spatial performance do not persist with age (Méndez-López, Méndez, López, & Arias, 2009). However, heavy alcohol exposure during the neonatal brain growth spurt in Long-Evans rats caused lasting spatial learning deficits only in males on PD 70 (Johnson & Goodlett, 2002). More importantly, it seems that in the water maze, younger males may have an advantage over females (Roof, 1993). Thus, at assessment (Chin, Van Skike, & Matthews, 2010; Roof, 1993), the period of ethanol exposure (Popović, Caballero-Bleda, & Guerri, 2006), and rat strain may be important, possibly reflecting a gender difference in hippocampal maturation.

Neuronal network models propose that bidirectional modifications of synaptic efficiency, such as LTP and LTD, are used for memory encoding (Bliss & Collingridge, 1993; Collingridge et al., 2010). Most studies emphasized a correlation between deficits in spatial learning and LTP. LTD is regarded as a crucial mechanism related to cognitive flexibility (Kemp & Manahan-Vaughan, 2004) which weakens memory traces during encoding of new information (Nicholls et al., 2008). These forms of synaptic plasticity, which involve information storage during hippocampus-dependent procedural learning, could coexist at a single synapse. Therefore, it could not fully explain animals’ performance based on LTP or LTD alone, since both synaptic strengthening and weakening are necessary for optimal memory storage (Neves, Cooke, & Bliss, 2008; Nicholls et al., 2008). Previously, it was reported that PSD-95–/– mice exhibited a severe impaired hippocampal LTD and an enhanced LTP, along with a profound impairment in the MWM task (Migaud et al., 1998). Upward shift of LTD/LTP modification threshold was also found in forebrain-specific calcineurin knockout mice (Zeng et al., 2001), which were impaired in the hippocampus-dependent working and episodic-like memory tasks. In a separate study, we recently reported a depressed LTP and enhanced depotentiation at the hippocampal Schaffer collateral-CA1 synapses in...
levels were not determined. Essential limitation of our study, which is that the serum ethanol hippocampi of offspring. However, it is necessary to indicate an administration of ethanol could increase the BECs and in approximately 281 mg/dL on E57 in Long-Evans rats (Dobson et al., and E15 in a mouse model (Cui et al., 2010; Jiang et al. 2007), and

In summary, our results showed that the LTP was significant enhanced while the depotentiation was excessively inhibited. This study suggests that the hippocampal function of female offspring was considerably affected by ethanol administered by gavage during the gestational period. This bidirectional effect on long-term synaptic plasticity disrupts the balance in cognitive flexibility, which could explain the crude performance in MWM tests. These results are consistent with the hypothesis that LTP and LTD are not independent, but rather are entirely in regulating cognitive events.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (31170153, 11232005) and 111 Project (B080011).

Conflict of interest: The authors declare no conflicts of interest.

Author contributions: TZ and LA conceived and designed the experiments. LA performed the experiments and analyzed the data. LA and TZ wrote the manuscript.

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