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Environmental enrichment reverses noise induced impairments in learning and memory associated with the hippocampus in female rats

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Environmental enrichment (EE) has positive effects on brain function and behavior in both healthy and behaviorally impaired animals. In earlier studies, we showed that rats exposed to noise during early development exhibited deficits in learning and memory associated with the hippocampus. In this study, we investigated whether EE provided during adulthood can reverse such noise-induced impairments. We found that four weeks of EE substantially improved learning and memory in adult female rats exposed to noise during early development. The behavioral changes observed after EE were accompanied by the restoration of parvalbumin-positive (PV+) inhibitory interneurons in the hippocampal subregions. EE also reversed noise-induced reductions in hippocampal long-term potentiation (LTP) of synaptic connections, a mechanism essential for learning and memory processing. However, an enriched environment that lacked social interaction had little effect on restoring LTP in noise-exposed rats. These findings suggest that EE effectively mitigates hippocampal impairments that stem from early noise exposure, with social interaction playing a crucial role in this recovery process.

Keywords Noise exposure, Environmental enrichment, Hippocampus-related behavior, Inhibitory interneuron, Rat

Environmental enrichment (EE) has been shown to exert a positive impact on sensory and cognitive functions by fostering brain plasticity[1–3]. For example, EE can significantly improve hippocampus-related learning and memory in healthy animals[4,5]. The behavioral improvements induced by EE are typically accompanied by increased long-term potentiation (LTP) in the hippocampus, a key mechanism crucial for learning and memory processing[6–10]. Furthermore, EE has been shown to substantially reverse various structural and functional deficits in the hippocampus in animals with modeled neurological disorders and injuries[8,11–13]. We previously reported that exposing rats to noise during early development disrupts hippocampal LTP, resulting in long-lasting impairments in hippocampus-associated cognitive functions, including spatial learning, recognition memory, and working memory[14]. While a recent study found that enriching the environment can prevent some noise-induced behavioral alterations[15], the cellular and synaptic mechanisms underlying these post-EE effects have not yet been elucidated.

Increased social interaction, sensory stimulation, and physical activity are key factors that distinguish enriched environments from standard housing conditions[1,2,16–18]. However, determining the specific effect that each of these individual factors has on post-EE behaviors is complicated by the inherent complexity of commonly employed EE protocols. Previous studies have indicated that the impact that these factors have on both brain function and behavior can vary[16–19]. In addition, while we recently delineated the influence that

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sensory stimulation has on modifications in sensory domain processing following EE rearing[16], there is a notable gap in the literature in terms of the specific contribution of social interaction to EE effects. This is surprising because altered social interaction has consistently been linked to changes in cognitive function and particularly to the learning and memory that are frequently reported as outcomes of EE exposure[5,20].

In the present study, female rats were exposed to structured noise during development (i.e., NE rats) and later housed in EE for four weeks. We evaluated the hippocampal-related learning and memory of these NE-then-EE-reared (NE-EE) rats and compared their behaviors with age-matched NE rats and naïve controls, aiming to determine whether EE could restore noise-induced behavioral impairments. Additionally, we examined changes in the hippocampal parvalbumin-positive (PV+) interneurons and the induction of LTP to explore the cellular and synaptic basis of the observed post-EE effects. Lastly, we investigated the influence of social interaction during EE by comparing the effects of enriched housing with and without social isolation.

Results

Hippocampus-related learning and memory

We began by evaluating hippocampus-related learning and memory using the Morris water maze, novel object recognition, and Y maze tests in the NE and NE-EE rats. These tests were carried out during the light phase, between 9 AM and 4 PM, starting on postnatal day (PND) 85 (i.e., one day after the NE-EE group completed EE rearing). The recorded data were compared with data obtained from the age-matched naïve rats (Fig. 1a and b). To prevent potential interference among the behavioral tasks, different groups of rats were used for each test, which led to variations in the sample size across the tests.

The Morris water maze test is widely used to assess the spatial localization and reference memory of animals, both of which are associated with hippocampal function[21–23]. As shown in Fig. 2a, the results of a two-way ANOVA (effect of training day, $F(2,144) = 142.81$, $p < 0.001$; effect of group, $F(2,144) = 20.22$, $p < 0.001$; interaction, $F(4,144) = 4.81$, $p = 0.001$) revealed that the escape latency for all three groups of rats decreased rapidly during the training phase. The NE group, however, took substantially longer time to locate the platform than the naïve group during the first two training days (both post hoc test $p < 0.01$). In contrast, EE significantly reduced time for the NE-EE group to locate the platform compared to the NE group (both post hoc test $p < 0.01$) such that the NE-EE group performed similarly to the naïve group (both post hoc test $p > 0.34$). In the test phase, the NE group spent less time in the target quadrant compared to the naïve group (Fig. 2b and c, left; one-way ANOVA, $F(2,48) = 4.63$, $p = 0.014$; post hoc test $p = 0.019$), and their latency to the former platform position was longer (Fig. 2c, right; one-way ANOVA, $F(2,48) = 7.97$, $p < 0.001$; post hoc test $p = 0.002$). In contrast, the NE-EE group exhibited behavior similar to that of the naïve group (both post hoc test $p > 0.79$).

In the novel object recognition test, which utilizes the natural tendency of rats to explore novel stimuli[24], no significant differences in the preference indices were observed among the three groups during the training phase (Fig. 2d; two-way ANOVA, effect of object, $F(1,70) = 0.24$, $p = 0.63$), with similar exploration times recorded for the identical objects. During the test phase, both the naïve and NE-EE groups displayed a strong preference for the novel object (two-way ANOVA, effect of object, $F(1,70) = 70.47$, $p < 0.001$; both post hoc test $p < 0.001$), while the NE group displayed no significant preference (post hoc test $p = 0.064$).

In the Y maze test, which is used to evaluate the hippocampus-related spatial memory and exploratory activity of rats in a novel environment[25], the NE group spent significantly less time in the novel arm compared to the naïve group (Fig. 2e and f; one-way ANOVA, $F(2,28) = 5.59$, $p = 0.009$; post hoc test $p = 0.016$). However, the NE-EE group spent significantly more time in the novel arm than the NE group (post hoc test $p = 0.01$) and exhibited exploration patterns similar to the naïve group (post hoc test $p = 0.84$). These data were further reflected in the preference index for the novel arm, with the NE group showing lower values compared to the naïve group (Fig. 2g; one-way ANOVA, $F(2,28) = 5.45$, $p = 0.01$; post hoc test $p = 0.022$), while the NE-EE group had indices that were higher than the NE group (post hoc test $p = 0.009$) and comparable to the naïve group (post hoc test $p = 0.99$).

Collectively, these results suggest that EE substantially reversed the noise-impaired learning and memory associated with the hippocampus seen in the NE rats.

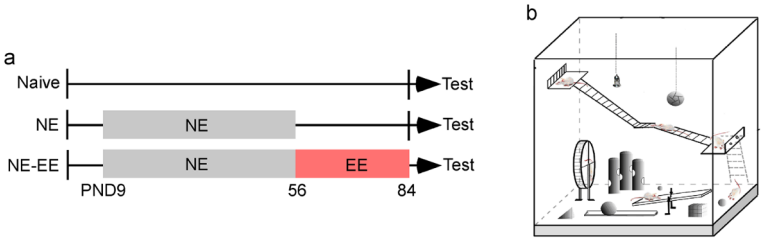

Fig. 1. Experimental timelines and schematic of the enriched housing conditions. (a) Timelines illustrating the experimental procedure for the naive, noise-exposed (NE), and NE-then-environmental enrichment (EE)-reared (NE-EE) rats. The NE and NE-EE rats were exposed to noise from postnatal day 9 (PND9) to PND56. After noise exposure, the NE-EE rats were placed in EE cages for four weeks (PND57- PND84). Rats from each group were then subjected to behavior tests, immunostaining, and long-term potentiation (LTP) induction. Separate sets of rats were used for each experiment to prevent potential cross-effects. (b) Schematic representation of the enriched environment (see also Methods).

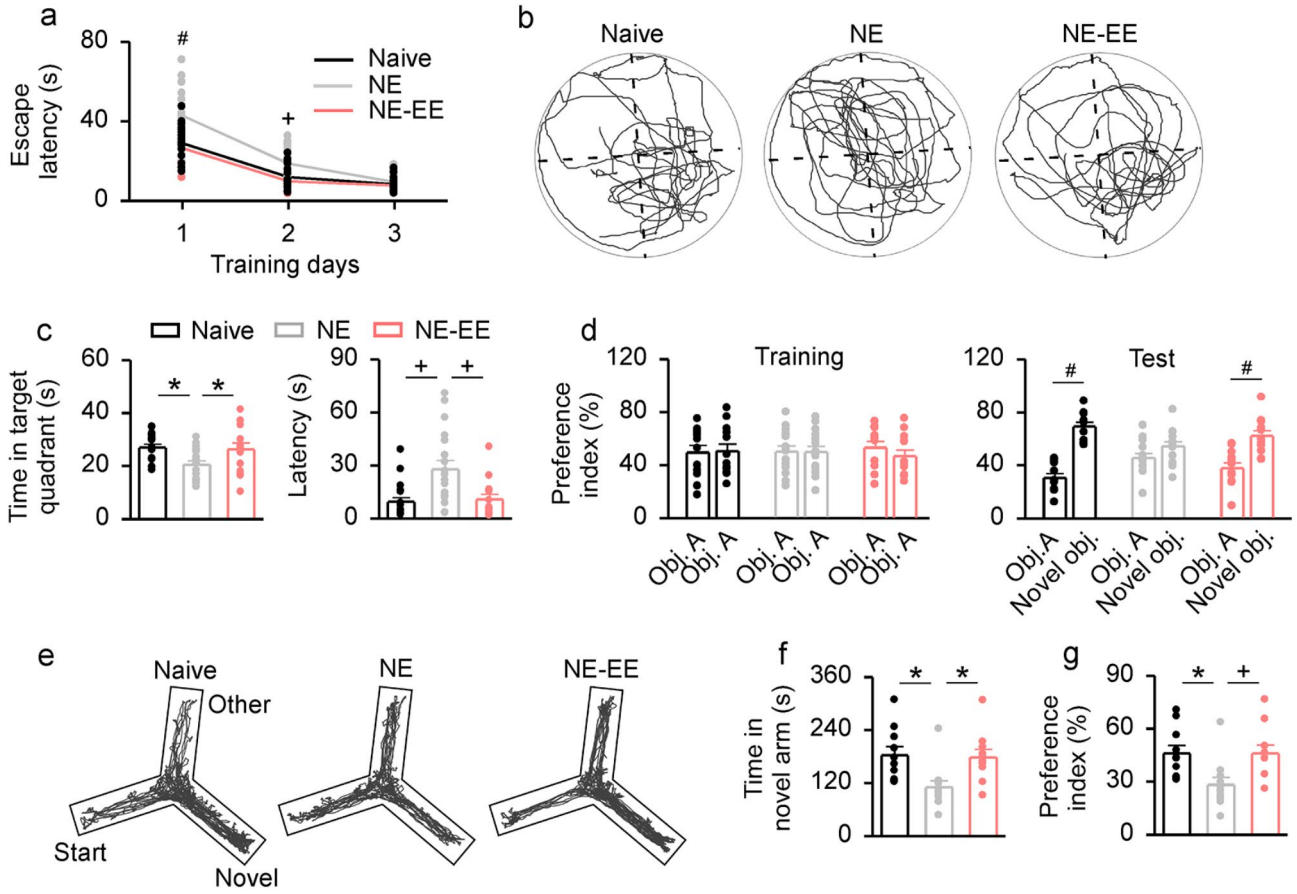

Fig. 2. Learning and memory associated with the hippocampus. (a) Average escape latency to locate the hidden platform during the training phase of the Morris water maze test for the naïve ($n = 19$), NE ($n = 18$), and NE-EE ($n = 14$) rats. Error bars represent SEM. +, $p < 0.01$; #, $p < 0.001$. (b) Sample swim paths recorded during the test phase of the Morris water maze. The platform was previously located in the lower right quadrant but was removed during the test phase. (c) Average time spent in the target quadrant (left) and the latency to the former platform position (right) during the test phase. *, $p < 0.05$. (d) Average preference indices for novel objects during the novel object recognition test for the naïve ($n = 12$), NE ($n = 14$), and NE-EE ($n = 12$) rats. (e) Sample movement traces recorded during the test phase of the Y maze test. (f) Average time spent in the novel arm during the Y maze test for the naïve ($n = 10$), NE ($n = 11$), and NE-EE ($n = 10$) rats. (g) Average preference indices for the novel arm during the Y maze test.

PV + interneurons in the hippocampus

PV + inhibitory interneurons play a crucial role in the regulation of hippocampal function[26–28]. To investigate the cellular changes induced by noise exposure and their potential reversal by EE, we measured the density of PV + interneurons in different hippocampal subregions in the NE, NE-EE, and naïve rats.

Consistent with previous studies[29–31], we found that PV + interneurons were primarily located in the serrations and cones of the cornu ammonis (CA) 1 and CA3 subregions, as well as in the myelin and granule cell layers of the dentate gyrus (DG) (Fig. 3a). As shown in Fig. 3b, we detected decreases in PV + interneuron density of 30.8%, 25.6%, and 33.1% in the CA1, CA3, and DG subregions, respectively, in the NE group relative to the naïve group. Statistical analysis revealed significantly lower densities of PV + interneurons in these subregions for the NE group compared to the naïve group (one-way ANOVA, $F(2,173) = 35.54$, $p < 0.001$ for CA1, $F(2,173) = 32.99$, $p < 0.001$ for CA3, and $F(2,173) = 23.34$, $p < 0.001$ for DG; all post hoc test $p < 0.001$). Moreover, EE exposure significantly increased PV + interneuron densities across all three subregions in the NE-EE group compared to the NE group (all post hoc tests $p < 0.001$), resulting in PV + interneuron densities in the NE-EE group approaching those of the naïve group (post hoc test $p < 0.001$ for CA1, $p = 0.38$ for CA3, and $p = 0.36$ for DG, respectively). These results were further confirmed by additional analysis using the number of animals as the statistical sample size (Fig. 3c). A one-way ANOVA indicated significantly lower PV + interneuron densities in all three subregions for the NE group compared to the naïve group ($F(2,12) = 9.51$, $p = 0.003$ for CA1, $F(2,12) = 18.34$, $p < 0.001$ for CA3, and $F(2,12) = 4.41$, $p = 0.037$ for DG; post hoc test $p = 0.003$ for CA1, $p < 0.001$ for CA3, and $p = 0.037$ for DG, respectively). However, PV + interneuron densities in the NE-EE group were significantly higher than in the NE group (post hoc test $p = 0.025$ for CA1, $p < 0.001$ for CA3, and $p = 0.038$ for DG, respectively), showing values that were close to those of the naïve group (post hoc test $p = 0.10$ for

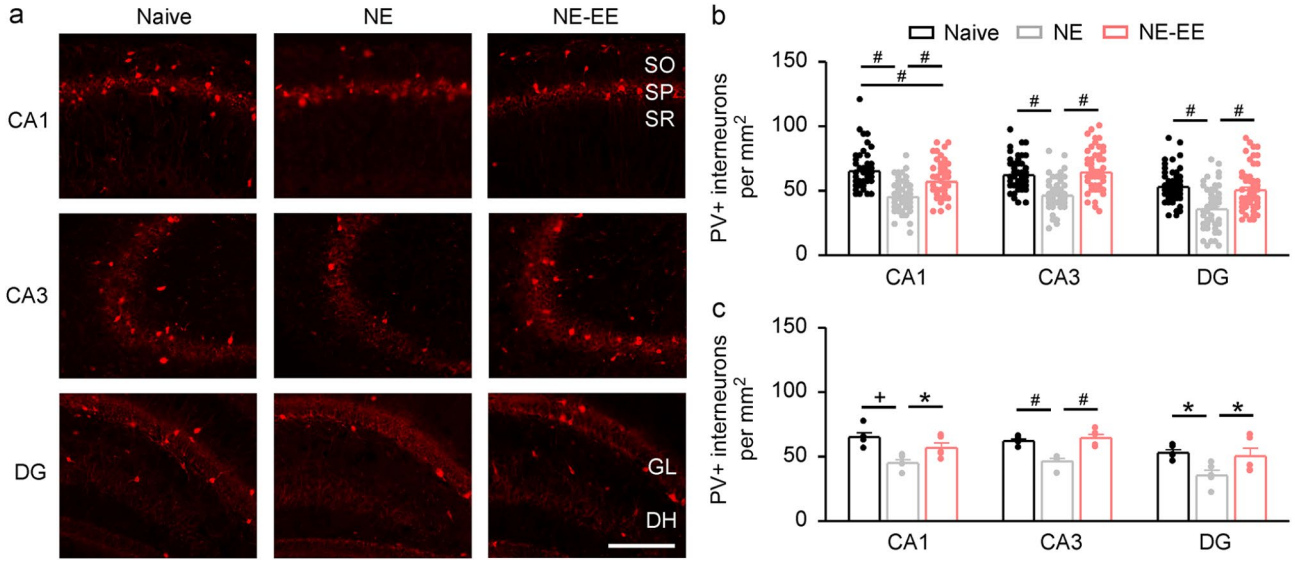

Fig. 3. Distribution of parvalbumin-positive (PV+) interneurons in hippocampal subregions. (a) Representative images of PV + interneurons within the cornu ammonis (CA) 1, CA3, and dentate gyrus (DG) subregions of the naïve, NE, and NE-EE rats. Subfields and layers are labeled as DH (dentate hilus), GL (granule cell layer), SO (stratum oriens), SP (stratum pyramidal), and SR (stratum radiatum). Scale bar = 200 µm. (b) Quantification of PV + interneuron density in the naïve ($n = 60$ from 5 animals), NE ($n = 59$ from 5 animals), and NE-EE ($n = 57$ from 5 animals) groups. Error bars represent SEM. #, $p < 0.001$. (c) PV + interneuron densities presented using the number of animals as the statistical sample size, illustrating group-wise variation. *, $p < 0.05$; +, $p < 0.01$.

CA1, $p = 0.48$ for CA3, and $p = 0.69$ for DG, respectively). These results suggest that noise exposure reduces the PV + interneuron density in the hippocampus and that EE largely reverses this effect.

In vivo hippocampal LTP induction

LTP is known to contribute to learning and memory processing[32–34]. To investigate the synaptic basis of EE-induced behavioral alterations, we assessed the induction of hippocampal LTP in the NE, NE-EE, and naïve rats (Fig. 4a, b). Input-output curves were obtained to determine the stimulus intensity for baseline recording (Fig. 4c). As illustrated in Fig. 4d, LTP was successfully recorded in the DG in all three groups following high-frequency stimulation (HFS) of the perforant path (PP). A two-way ANOVA revealed that both the group ($F(2,324) = 76.58$, $p < 0.001$) and time point ($F(11,324) = 2.59$, $p = 0.004$) had significant effects on the amplitude of the population spike (PS). Remarkably, the NE group exhibited significantly lower PS amplitudes at various time points post-HFS than the naïve group (Fig. 4e, left; all post hoc test $p < 0.016$). In contrast, the NE-EE group had PS amplitudes that were substantially higher than the NE group (all post hoc test $p < 0.012$) and were comparable to the naïve group (all post hoc test $p > 0.53$). These observations were further confirmed by average PS amplitude data recorded 5–60 min post-HFS (Fig. 4e, right). The NE group showed significantly lower amplitudes than the naïve group (one-way ANOVA, $F(2,27) = 7.91$, $p = 0.002$; post hoc test $p = 0.002$), whereas the NE-EE group had higher amplitudes than the NE group (post hoc test $p = 0.007$), and these amplitudes were comparable to the naïve group (post hoc test $p = 0.85$). These results suggest that exposure to noise during early development reduces LTP in PP-DG synapses and that EE substantially restores this loss of LTP.

Enriched environments typically include relatively more social interaction, sensory stimulation, and physical activity[1,2,16–18]. To examine the role that social interaction plays in EE-induced LTP recovery, we recorded the LTP for a separate group of rats that were individually housed in EE cages after the cessation of developmental noise exposure. These animals were referred to as socially isolated NE rats, i.e., Iso-EE rats. The data were then compared with those of the NE-EE, NE, and naïve rats (see experimental timelines in Fig. 5a). The results of a two-way ANOVA revealed that the group ($F(3, 408) = 67.18$, $p < 0.001$) and time point ($F(11,408) = 3.06$, $p < 0.001$) had significant effects on the PS amplitude. The post hoc test showed that the PS amplitudes recorded at different time points post-HFS from the Iso-EE group were lower than those from the NE-EE group (Fig. 5b, left; post hoc test $p < 0.05$ except at 40 min where $p = 0.054$) and closely resembled those from the NE group (all post hoc test $p > 0.55$). Additionally, the PS amplitudes in the Iso-EE group were lower than those in the naïve group (all post hoc test $p < 0.038$). As expected, the average values of the Iso-EE group recorded 5–60 min post-HFS were also lower than those of the NE-EE group (Fig. 5b, right; one-way ANOVA, $F(3,34) = 6.86$, $p < 0.001$; post hoc test $p = 0.02$) but were similar to those of the NE group (post hoc test $p = 0.72$). These results suggest that EE without social interaction has a limited effect on noise-induced LTP impairment in PP-DG synapses.

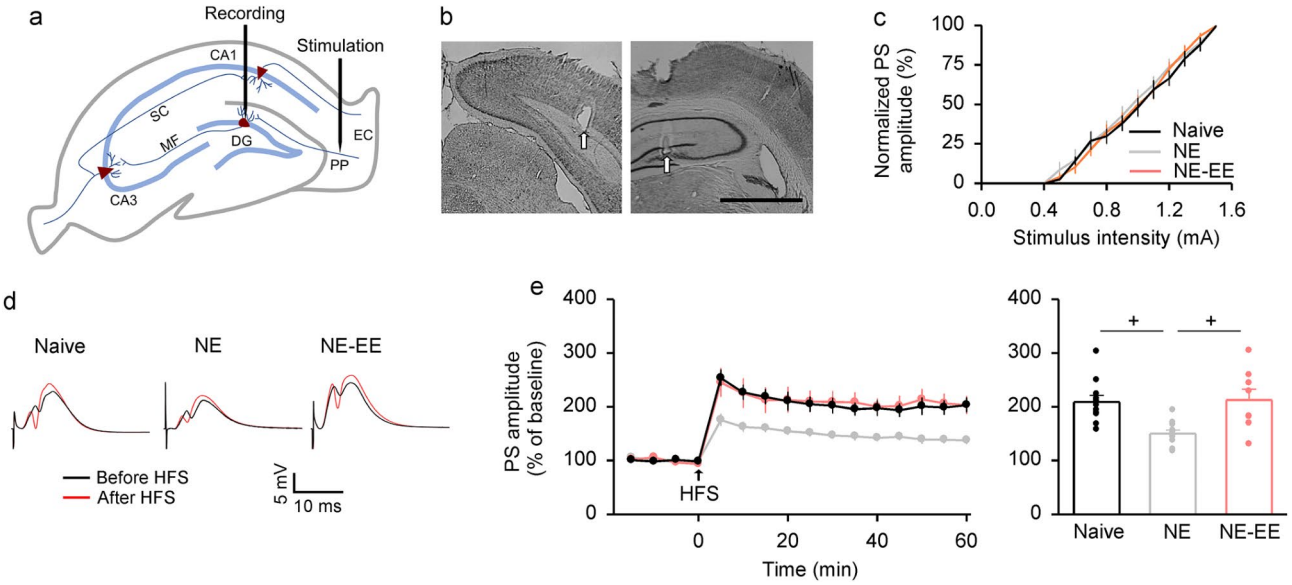

Fig. 4. LTP recorded in the hippocampus. (a) Schematic showing the placement of the stimulating and recording electrodes in the coronal section of the hippocampus. (b) Examples of electrically induced lesions in a naïve rat. The positioning of the stimulating electrode in the perforant path (PP) (arrow, left) and the recording electrode in the DG (arrow, right), which were used to record field potentials, are shown. Scale bar = 2 mm. (c) An input-output curve generated by stimulating the PP to determine the appropriate stimulus intensity. Error bars represent SEM. (d) Representative population spikes (PSs) recorded before and after high-frequency stimulation (HFS) in the naïve, NE, and NE-EE rats. (e) PS amplitudes at different time points post-HFS (left) and average PS amplitudes (right) in the naïve ($n = 11$), NE ($n = 11$), and NE-EE ($n = 8$) rats. +, $p < 0.01$.

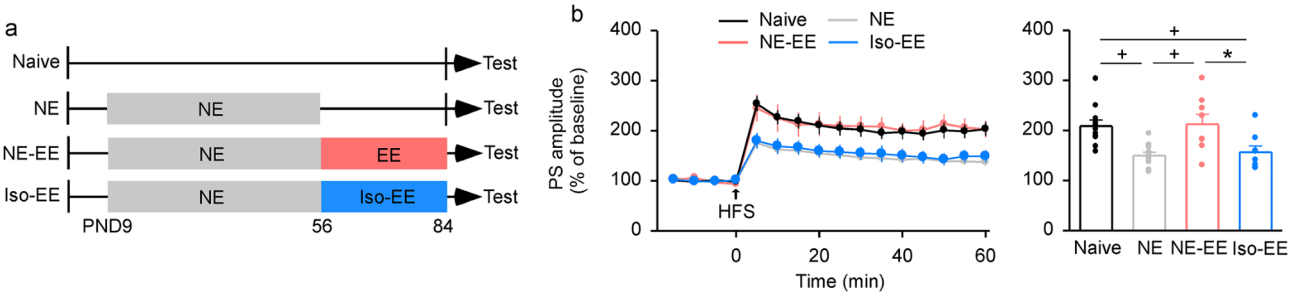

Fig. 5. Role of social interaction in EE effects. (a) Experimental timelines for the different groups of rats, including the Iso-EE rats, which were individually housed in EE cages for four weeks following noise exposure. (b) PS amplitudes at different time points post-HFS (left) and average PS amplitudes (right) in the naïve, NE, NE-EE, and Iso-EE ($n = 8$) rats. Error bars represent SEM. *, $p < 0.05$; +, $p < 0.01$.

Discussion

Previous studies have demonstrated that noise exposure alters hippocampus-related learning and memory, synaptic plasticity, and aminoacidergic neurotransmitters in developing rats and that these noise effects can be substantially prevented by EE rearing[35–37]. In this study, rats were exposed to pulsed noise of a moderate level for 10 h daily during the light phase from PND9 to PND56, a period that included critical stages of auditory system and hippocampal development[38–40]. This noise exposure paradigm was designed to model the environmental noise commonly encountered in modern workplace and living environments. Following noise exposure, the NE rats were housed in enriched conditions for four weeks (PND57-PND84). By PND57, rats are nearing sexual maturity, and their neurological development has surpassed the typical cortical development phase related to learning and memory[40–42]. We showed that noise degraded learning and memory as assessed by the Morris water maze, novel object recognition, and Y maze tests was reversed after EE rearing. These post-EE effects on hippocampus-related behavioral performance were accompanied by reversals of PV + inhibitory interneuron density and the LTP recorded in the hippocampus. Therefore, our results demonstrate that EE applied in postcritical period animals can restore deteriorated hippocampal function that stems from early exposure to

abnormal environmental conditions. They suggest that EE may serve as a viable approach to counteract noise-induced cognitive deficits in older children and adults.

LTP is a critical marker of synaptic transmission efficiency in neuronal circuits and is widely regarded as a key mechanism underlying learning and memory processing[25–27]. Previous animal studies have consistently demonstrated that alterations in learning and memory are often accompanied by changes in LTP induction in the hippocampus. Moreover, experimental manipulations that either facilitate or suppress LTP induction in the hippocampus have been shown to correspondingly improve or impair learning and memory[14,43–45]. These findings underscore the significance of synaptic plasticity, particularly LTP, in the mediation of hippocampus-related behavior. In this study, we found that EE rearing nearly restored to normal the noise-impaired LTP induction in the hippocampus. Consequently, we propose that the EE-induced reversal of LTP, at least in part, contributes to the observed recovery of impaired learning and memory in the NE-EE rats. However, it is important to acknowledge that while the behavioral tests in this study primarily assess hippocampal function, animals may also engage other brain regions, such as the prefrontal cortex[46,47]. Therefore, the potential involvement of EE effects on these additional brain structures in the observed behavioral changes cannot be ruled out. Furthermore, our primary focus in this study was on evaluating alterations in LTP in PP-DG synapses to elucidate the potential synaptic mechanisms responsible for the EE effects. The DG is considered the primary entry point for multisensory information (e.g., vestibular, olfactory, visual, and auditory information) into the hippocampus[48]. It plays a crucial role in various memory processing linked to multisensory inputs and may be particularly sensitive to environmental stimuli. Recent studies have indicated that noise exposure also influences LTP in the Schaffer-CA1 and longitudinal DG-DG networks[49,50]. Thus, the role of plasticity in these other synapses within the hippocampus, particularly in relation to the observed post-EE effects, remains to be investigated.

PV + interneurons are GABAergic, fast-spiking cells that coordinate and synchronize the activity of surrounding excitatory neurons[51,52]. In the hippocampus, these interneurons are crucial for regulating synaptic plasticity[26,28]. In a rat model of multiple sclerosis, for example, abnormal LTP in the CA1 was linked to reduced GABAergic inhibition of excitatory pyramidal neurons because of the loss of PV + interneurons[53]. In addition, we have previously demonstrated that auditory training induced subregion-specific changes in PV + interneuron density in the hippocampus, alongside enhanced hippocampal LTP, in trained rats compared to the naïve control animals[31]. In the current study, we observed a significant decrease in PV + interneuron density within the CA1, CA3, and DG subregions of the NE rats, while the densities in the NE-EE rats were comparable to those in the naïve rats, particularly in the CA3 and DG subregions. These findings indicate that developmental noise exposure impairs hippocampal PV + interneurons and that subsequent EE in adulthood effectively reverses this deficit. Given the critical role of PV + interneurons in regulating synaptic plasticity, our results suggest that altered PV + interneurons may underlie changes in hippocampal LTP induction in the NE rats, and the reversal of these changes in the NE-EE rats. It should be noted, however, that EE only partially reversed the PV + interneurons in the CA1 subregion, as the density recorded in the NE-EE group was significantly lower than in the naïve group. While these results suggest that the CA1 subregion is less responsive to EE-induced plasticity, which effectively restored PV + interneurons in the CA3 and DG subregions, further studies are needed to elucidate the mechanisms underlying the subregion-specific effects of EE on PV + interneurons.

Enriched environments typically involve heightened social interaction, sensory stimulation, and physical activity. Previous studies have suggested that each of these factors selectively influences EE effects in brain regions associated with that factor[1,2,16–18]. For example, our previous studies demonstrated that enriched environments that lacked additional sound exposure had limited effects on noise-impaired spectral processing in the auditory cortex. In contrast, enriched environments with extra sound exposure induced significant auditory cortical plasticity, underscoring the crucial role of sensory stimulation in modulating EE effects on the sensory system[16]. In this study, we identified the role that social interaction plays in EE by comparing the effects induced by enriched rearing with or without social isolation. We found that EE with social isolation had a limited impact on noise-impaired LTP in the hippocampus (i.e., the LTP in the Iso-EE group was similar to the NE group). Thus, our findings indicate that social interaction during EE is critical to reversing noise-induced LTP impairment in the hippocampus. It is noteworthy that the EE protocol used in this study included the presence of a running wheel, which resulted in increased physical activity among the rats housed in the EE cages compared to the naïve controls. Previous studies have shown that the increased levels of physical activity associated with EE can have positive effects on neurogenesis in the DG and hippocampal-related cognition[17]. Hence, the contribution of increased physical activity to the observed EE effects is an important issue that warrants further investigation in future studies.

A recent study on male rats reported that two weeks of EE during adolescence prevented hippocampus-related behavioral alterations induced by early noise exposure, including deficits in habituation memory and exploratory activity[15]. Consistent with these findings, we observed that EE rearing significantly improved spatial learning and recognition memory in noise-exposed female rats. Notably, one concern stemming from this study is that our experiments were conducted exclusively in female animals to investigate the synaptic mechanisms underlying EE-induced changes in learning and memory. Given that Molina et al.[15] assessed similar effects in males, future research should directly compare male and female subjects to elucidate potential sex-specific differences in the impact that EE has on noise-impaired hippocampal function. In addition, we only assessed hippocampal LTP induction in the Iso-EE group to determine the role that social interaction plays in EE effects. Given the well-established role of LTP in learning and memory, our findings suggest that Iso-EE group may exhibit cognitive impairments, though further behavioral studies are needed to confirm this hypothesis. Finally, the PV + interneuron population in the hippocampus of Iso-EE group should be examined in future study to better understand the contribution that social interaction makes to EE-induced effects.

In summary, we found that EE during adulthood nearly restores to normal the developmentally degraded learning and memory associated with the hippocampus, with social interaction emerging as a crucial element in this recovery process. These findings emphasize the importance of social engagement in the EE effects, particularly the restoration of cognitive abilities affected by developmental challenges. Thus, increasing social interaction should be a key consideration when designing enriched environments for animals with cognitive impairments, as well as for humans with cognitive disorders, such as autism and schizophrenia.

Methods

All experimental procedures complied with the ARRIVE guidelines and were approved by the Institutional Animal Care and Use Committee at East China Normal University. Experiments were therefore performed in accordance with these guidelines and regulations.

Noise exposure

Female offspring of timed-pregnant Sprague-Dawley (SD) rats (acquired from Shanghai Slack Laboratory Animal Co., Ltd., China) were cross-fostered on PND1 to lactating SD dams that had given birth within 24 h, ensuring six pups per litter to standardize early postnatal rearing conditions. Each dam and her litter were housed individually in a standard cage (41 × 26 × 20 cm) and placed in a sound-insulated chamber for controlled noise exposure for 10 h each day (8 AM-6 PM), starting on PND9 and continuing until weaning on PND21. After weaning, the pups were regrouped and housed in groups of four per cage (41 × 26 × 20 cm) and exposed to the same noise conditions until PND56. Each day, following the noise exposure, the cages were returned to the standard vivarium environment. During the noise exposure periods, 50 ms noise pulses (with 5 ms rise/fall times) of approximately 65 dB sound pressure level (SPL) were emitted from a speaker placed about 15 cm above the rats, at a rate of six pulses per second (pps). To reduce the adaptation effects, a silent interval (randomly set at either 0.5–1 s) was introduced after every six noise pulses. The pulsed noise stimuli had a broad frequency range, spanning from 0.8 to 30 kHz, with relatively flat energy distribution across this spectrum[14,20,54].

Upon completion of the noise exposure at PND56, the rats were randomly assigned to (1) NE rats that were reared in standard housing, and (2) NE-EE rats that were housed in EE cages. The naïve group consisted of age-matched rats that were never exposed to noise or EE. Both NE and naïve rats were kept in standard housing, in cages measuring 41 × 26 × 20 cm, at four rats per cage. All these rats had unrestricted access to food and water and were maintained on a 12-h light (8 AM-8 PM) /12-h dark (8 PM-8 AM) cycle. To ensure the anonymization of the study, one researcher was responsible for assigning the rats to the groups, while another researcher conducted the experiments.

Enriched environment exposure

As described in previous studies[16,55,56], the EE was consisted of a large cage measuring 90 × 80 × 100 cm equipped with stimulating elements such as running wheels, seesaws, balls, tunnels, cubes, and cone toys. The cage also had stairs, ramps, and platforms inside. To maintain novelty, three differently styled cages, each containing the same enriching elements, were used, and the rats were rotated between these cages every three to four days during the EE phase. The NE-EE rats were housed in the EE cage (eight rats per cage) after the cessation of noise exposure for four weeks (i.e., from PND57 to PND84). Our previous study demonstrated that four weeks of EE (PND38-66) effectively restored degraded behavioral and cortical processing of sound frequency caused by early noise exposure[16].

The Iso-EE rats were housed individually in the EE cages, with each cage placed in a separate room, for four weeks after the noise exposure phase.

Morris water maze test

The Morris water maze test protocol was based on that used in previous studies[57,58] with minor modifications. In briefly, a circular tank measuring 150 cm in diameter and 50 cm in height was used for the test. The apparatus was positioned in a room with geometric shapes on the walls that served as spatial cues. The tank had black interior walls and was filled with water maintained at approximately 25 °C. The water was rendered opaque with black food coloring. An escape platform (diameter: 10 cm) was placed in the center of the southeast quadrant, submerged 2 cm below the water surface.

Each animal had 90 s per trial to locate the platform during the training phases, followed by a 20 s rest period on the platform before the next trial. Four trials were conducted per day over three days. The animals were released from different quadrants in each trial. On the fourth day, a 90 s probe test was administered without the platform. The animals' activities during the training and testing (escape latency, time spent in the target quadrant, and latency to enter the former platform position) were analyzed using Any-maze software (Stoelting, USA).

Novel object recognition test

A nontransparent plastic box measuring 40 × 40 × 40 cm was used to conduct the novel object recognition test, which consisted of three phases conducted over three days. Habituation was performed over the first two days, and the third day involved both training and testing. During the habituation phase, the animals were placed in the empty box, facing the wall, and allowed to explore for 10 min each day. During the training phase, two identical objects were introduced into the box, and the animals explored them for 5 min. Afterward, the animals were returned to their home cages. One hour later, the test phase was conducted: One familiar object from the training phase was presented alongside a novel object for 5 min. Between each session, the box and objects were cleaned using 10% ethanol. The animals' activities were analyzed using Any-maze software (Stoelting, USA). The

preference index was determined by calculating the percentage of time the animals spent exploring each object in relation to the total exploration time.

Y maze test

The Y maze had three identical arms (45 × 15 × 35 cm) positioned 120° apart, designated as the start arm, the other arm, and the novel arm. During the training phase, the animals were placed in the start arm, facing the wall, and allowed to explore the maze for 10 min, with the novel arm blocked off. After spending 1 h in their home cages, the animals returned for the test phase, during which they were given 8 min to explore all three arms. Their movements were analyzed with Any-maze software (Stoelting, USA). The maze was cleaned with 10% ethanol between sessions. The preference for the novel arm was calculated by determining the percentage of time the rats spent in the novel arm compared to the total time spent in all arms.

Immunostaining of PV + interneurons

As previously reported in our studies[31], animals were anesthetized with sodium pentobarbital (100 mg/kg body weight) and perfused with a saline solution, followed by 4% paraformaldehyde in 0.1 M potassium PBS (pH 7.2). The brains were extracted and placed in the same fixative containing 20% sucrose for cryoprotection for 12–24 h. Serial coronal brain section (40 μm thick) were collected using a freezing microtome (Leica CM3050 S, Leica Microsystems, Germany) to ensure even spacing. Every third section spanning the dorsal hippocampus (-1.5 to -4.5 mm from bregma) was selected, resulting in a total of five to six sections per brain. These sections were then processed for fluorescence immunohistochemistry to detect PV + interneuron expression.

In preparation for immunostaining, free-floating sections were first incubated in a blocking solution to prevent nonspecific binding. The sections were subsequently incubated with an anti-PV primary antibody (Sigma, USA) at 4 °C for 12 h and an Alexa Fluor 546-conjugated secondary antibody (Invitrogen, USA) at room temperature for 1.5 h. Samples from different experimental groups were processed together to ensure consistent staining and control for variations in antibody penetration, incubation, and tissue handling.

The immunostained sections were visualized using a TissueFAXS Plus ST epifluorescence imaging system (TissueGnostics, Austria). Digital images were acquired with a 20× objective lens. To ensure consistency across samples, imaging parameters such as exposure time and gain were standardized for all sections. The PV + interneurons in the hippocampal subregions were quantified using ImageJ (NIH, USA), with neurons included only if they displayed a clearly defined soma perimeter and strong contrast from the background. Data from different groups were averaged and statistically compared to assess group differences.

In vivo LTP induction

Animals were anesthetized with sodium pentobarbital (50 mg/kg body weight) and positioned in a stereotaxic frame according to established protocols[14]. Briefly, a midline incision was made on the scalp, and the skull was cleared to expose the sutures. A bipolar stimulating electrode (FHC, USA) was inserted into the PP (AP: -7.8 mm, ML: +4.3 mm, DV: 3.2 mm), while a glass electrode (filled with 2 M NaCl, resistance 1–3 MΩ) was positioned in the granular cell layer of the DG (AP: -3.8 mm, ML: +2.3 mm, DV: 2.7–3.2 mm). Areflexia was maintained with additional doses of dilute pentobarbital (8 mg/mL) during surgery and recording. Body temperature was monitored via rectal probe and maintained at approximately 37 °C using a feedback-controlled heating pad.

Extracellular recordings were made from the DG in response to electrical stimulation of the PP. The amplitude of the elicited PS was calculated as the mean of the amplitudes of the first and second positive peaks relative to the maximal negative peak. Once a stable waveform was recorded, an input-output curve was generated by stimulating the PP to determine the appropriate stimulus intensity. The intensity of the pulse stimuli (0.15 ms in duration at 30 s intervals) was gradually increased from 0.1 mA to 1.5 mA in 0.1 mA increments. The stimulus intensity at 50% of the maximum PS amplitude was used for baseline recording. The PS amplitude was continuously monitored for 20 min to establish a stable baseline. After the baseline recording, HFS was applied, consisting of eight pulses per burst at 100 Hz, repeated at 5 Hz for 10 bursts. To assess LTP, the PS amplitude was measured at each post-HFS time point, normalized to baseline, and expressed as a percentage of the pre-HFS PS amplitude. The PS amplitude was tracked for 60 min post-HFS to evaluate LTP maintenance.

The stimulation was controlled using a Master-8 stimulator (AMPI, Israel), and signals were amplified with a MultiClamp 700B amplifier (Molecular Devices, USA) and recorded for offline analysis using Clampex 9.0 software (Molecular Devices, USA).

At the end of the experiments, the animals were anesthetized with a lethal dose of sodium pentobarbital (100 mg/kg body weight). After confirming a lack of reflexes by paw pinching, the animals were euthanized by decapitation.

Statistical analysis

Data are expressed as mean ± SEM. Statistical analyses were performed using a one- or two-way ANOVA, followed by the Student-Newman-Keuls post hoc test where applicable, to compare multiple group means while maintaining statistical rigor. A p-value of < 0.05 was considered statistically significant.

Data availability

All data supporting the findings of this study are available within the paper.

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Author contributions

Y.S., Y.Z., and X.Z. contributed to the study conception and design. Material preparation, data collection and analysis were performed by Y.S., P.A., Y.C., W.Y., Y.F., H.L., G.Z., Y.S., J.W., and Y.Z. The manuscript was written by Y.S., Y.Z., and X.Z.

Declarations

Competing interests

The authors declare no competing interests.

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