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Effects of Different Training Loads on Emotional State and mRNA and Protein Expressions of N-Methyl-D-Aspartate Receptor Subunits, Postsynaptic Density 95, and Kinesin Family Member 17 in Hippocampus of Rats

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Emotional state can be affected by different training loads. The aim of this study was to explore the changes of rat emotional state, as well as the mRNA and protein expressions of N-methyl-D-aspartate receptors (NMDARs), postsynaptic density 95 (PSD-95), and kinesin family member 17 (KIF-17) in the hippocampus, by long-term moderate-intensity and high-intensity training models in rats.

Material/Methods: The exercise model of SD rats was set up by treadmill running of moderate and high intensities for 4 weeks. The rats in the moderate-intensity training group were given endurance training with increasing intensity, while rats in the high-intensity training group were given high-speed training, and those in the normal control group were also established. The body weights of rats were measured before and after exercise to determine weight reduction. Real-time PCR and Western blotting were used to detect the mRNA and protein expressions of NMDARs, PSD-95, and KIF-17 in hippocampus of rats under different training loads.

Results: Compared with the control group, the rats in the moderate-intensity training group had better body condition and emotional state, while the rats in the high-intensity training group had poor body condition and emotional state. The mRNA and protein expression of PSD-95, KIF-17, and NMDARs in the moderate-intensity training group were significantly elevated ($P<0.05$) while those in the high-intensity training group were suppressed ($P<0.05$).

Conclusions: Different training loads have remarkable influences on the cognition, emotion, and mental status of rats, and can affect the mRNA and protein expressions of NMDARs, PSD-95, and KIF-17 in rats. Appropriate training loads alleviate hypoxia damage to the hippocampus, and also effectively improve hippocampus function.

MeSH Keywords: Cognitive Science • Emotions • Oxidative Stress • Receptors, Ionotropic Glutamate

Abbreviations: **NMDAR** – N-methyl-D-aspartate; **PSD-95** – postsynaptic density 95; **KIF-17** – kinesin family member 17

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Background

Exercise can cause adaptive physical changes and enhance the body's ability to adapt to exercise. Reasonable exercise can promote brain health, enhance emotion regulation [1], improve metabolism, and increase ability to learn and work. However, the excessive stress caused by overload training and a variety of military and sports competitions may cause physical problems, as well as producing certain negative effects on learning, memory, and emotional regulation [2], which are important depressive symptoms. The hippocampus is an important component of the limbic system in coordinating learning and memory, and is also the most sensitive area of the brain to fatigue stress injury [3].

NMDARs are excitatory amino acid receptors that can cause changes in learning, memory, and motion under different intensities of training, and are closely related to the progression of depression and the corresponding specific therapies [4]. NMDA receptor is a heteropolymer consisting of NR1 and NR2 (A or B); it is activated by combining simultaneously with glutamic acid and glycine to play a biological role [5,6]. It is mainly distributed in the postsynaptic membrane of the central nervous system and is expressed at highest levels in forebrain areas such as the hippocampus [7]. PSD-95 is a scaffold protein mainly located in the postsynaptic density area, playing a key role in the signal integration and transduction of glutamate receptor. KIF-17 is a member of the kinesin-2 family; it has a dimer structure composed of kinesin monomer, which is specifically distributed in the nervous system and testicular tissue.

There is a close relationship between NMDA receptor, PSD-95, and KIF-17. PSD-95 is widely distributed in the brain, overlapped with the distribution area of NMDA receptors. NR1-NR2B is connected with PSD-95 at C terminal. NR2B is a major component transported by KIF-17 to cells, so decreased transport function of KIF-17 causes corresponding changes in NR2B expression, leading to various diseases and pathological states. PSD-95 can combine with KIF-17, and when KIF-17 is damaged or inhibited, NR2B cannot be transported. Therefore, the combination of PSD-95 and KIF-17 is particularly critical to synaptic transmission of NMDA receptor.

This study used the method of Bedford et al. [8] to establish a platform exercise model in SD rats with medium- and high-strength continuous training. SD rats learn easily, are sensitive to various stimuli, have a nervous system similar to that of humans, and have been widely used in the study of higher nervous system activity, such as rewards and punishment experiments, maze testing, and research on neurosis and manic-depressive psychosis. After training SD rats for 4 weeks, changes in the NMDA-related receptors PSD-95 and KIF-17 were tested. The present study aimed to explore in depth the influences of different training loads on rat emotional state and expressions of NMDA receptors, PSD-95 and KIF-17 mRNA, and proteins, which are important in alleviating fatigue and improving the emotional state under different training loads, and to provide an experimental basis for scientific training.

Material and Methods

Establishment of laboratory animal model and hippocampal slice preparation

We used 24 healthy, male, SD rats, aged 2 months and weight 214.65±11.24 g, which were provided by Beijing University Health Science Center Department of Laboratory Animal Science (permit number SCXK2002-0001). Rats could eat and drink freely and were kept in an environment of 23±2°C, 40%~60% humidity, and a natural day/night light cycle. A person was specially assigned to be responsible for rat training, which started at 8 AM. The handling of animals in the experiment was in accordance with the Guidance Suggestions for the Care and Use of Laboratory Animals formulated by the Ministry of Science and Technology of the People's Republic of China. After 1 week of adaptation, the 24 rats underwent adaptive treadmill training for 3 weeks (slope gradient 0°, speed 8.2 m/min, and 10 min per day). Then, according to their weights (no distinct differences were observed among the 3 groups), they were randomly assigned into 3 groups: control group, high-intensity training group, and moderate-intensity training group. Following the method of Bedford et al., increasing load training was applied to the moderate-intensity training group with speed starting at 15 m/min and increasing to 3 m/min every 5 min until 20 m/min, at which time the slope gradient of the treadmill was raised to 5° and training lasted for 60 min, with its intensity being 64–76% VO_2max. In the high-intensity training group, rats were trained at the speed of 50 m/min for 6 min, then rested for 5 minutes, and in this pattern the rats were trained altogether for 3 times with training intensity greater than 80% VO_2max. In the process of training, electric stimulation or a hairbrush were used to keep rats in the front one-third of the treadmill track so as to assure steady training intensity. After each training, the rats were tested to determine whether they were injured. If so, they would be given timely treatment and rest for adjustment. The training lasted 4 weeks with 6 training days per week. In control group, the rats were kept in their cages and not given training. The rats were killed instantly after training was completed, and the hippocampus was taken out and put on an ice plate. Then, the hippocampus was weighed after rinsing with cold physiological saline.

General changes in rats

Rat's mental state, fur condition, food intake, drinking, and autonomous activity were observed and recorded during the

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feeding period in normal condition with food and water freely available. Rat mental state at rest and during training were especially observed, and the changes in rat rectal temperature (Tr) and body weight were determined.

Tr was determined immediately after training. A digital thermometer was inserted about 5 cm into the anal sphincter and temperature was recorded after the reading was stable (after about 5 s). Tr was used to represent the core body temperature (Tc) of rats. The rats were weighted immediately after training, and the reduction of body weight was calculated weekly.

Real-time polymerase chain reaction (PCR)

We took hippocampal slices and dissolved them in 1 ml Trizol to extract the total RNA. The RT-PCR reaction was carried out in accordance with the instructions of the EasyScript First-Strand cDNA Synthesis SuperMix and 2xEasyTaq PCR SuperMix. To synthesize cDNA, we used 2 μl of isolated total RNA and a mixture of oligo-dT with random hexamer primers (20 μl) provided in the kit. We applied 2-step real-time PCR with the StepOnePlus™ System (Applied Biosystems) and SYBR Green I dye for monitoring PCR. To prepare samples for real-time PCR, we used FastStart DNA Master SYBR Green I (Roche), following the recommendations of the manufacturer. As a template for real-time PCR, we used 2 μl of 10× diluted cDNA reaction for β-actin, which serves as an internal control. The concentration of primers in each reaction mixture was 1 μl per each specific set of primers. The relative mRNA expression for each target was measured by real-time PCR and was calculated by the comparative CT method (ΔΔCT) (the amount of target, normalized to an endogenous reference (β-actin) and relative to a calibrator) (cDNA from a pooled sample). The primer subsequences were as follows:
NR1:
(forward) 5'-ACCATGCACCTGCTGACATT- 3'
(reverse) 5'-CTTCAGCACCTCGGACAGCA- 3'
NR2A:
(forward) 5'-TCCACCTTCTCCGGCTACAG-3'
(reverse) 5'-GTCGGTGCTGCACTGTCTTG- 3'
NR2B:
(forward) 5'-GGATTCTGCATTGTGAGCTG-3'
(reverse) 5'-TCGCTTGCATATCCACATAA- 3'
PSD-95:
(forward) 5'-ACG ACAAGACCAAGGACTGC- 3'
(reverse) 5'-TGGCCTTTAACCTGGACCAC-3'
KIF-17:
(forward) 5'- AAGGTACCGCGTGTGAACCTGCTTACAA- 3'
(reverse) 5'- AAAAGCTTCCATCGAAGGTGAACTGCTT- 3'

The PCR procedure was as follows: pre-denaturalize the reaction system at 94°C for 5 min, denaturalize at 94°C for 15 s, anneal for 34 s (NR1 at 56°C; NR2A, PSD-95, and β-actin at 58°C; NR2B and KIF-17 at 60°C), and leave it at 72°C for 10 s. Then, the process of denaturalization, annealing, and leaving it alone was repeated 35 times before the system was maintained at 72°C for 10 min. We carried out melting curve analysis (StepOne software) and agarose gel electrophoresis to analyze the amplicons obtained. For a determination of CT (cycle threshold) values, we used StepOne analysis software, which provides automatic evaluation of the data acquired from the StepOnePlus system. The relative mRNA expression for each target was measured by real-time PCR and was calculated by the comparative CT method (ΔΔCT).

Western blotting analyses

We collected 50-μg samples for SDS-PAGE electrophoresis, and then transferred them to PVDF membranes, added 5% skimmed milk powder blocking liquid, and then slowly blocked them on a shaking bed at room temperature for 60 min. Primary antibody was added according to the proportion (1: 1000, Abcam, UK) followed by incubation at 4°C overnight. Horseradish peroxidase (HRP)- labeled goat-anti-rabbit antibody (1: 5000; Abgent, USA) was added and the proteins were incubated at 37°C for 1 h. After applying ECL fluorescence, the X-ray image was developed in the dark, the results were photographed by use of a gel imaging system, and Quantity One V4.40 (Bio-Rad, USA) software was used for quantitative analysis of signal strength of the band.

Statistical analysis

In the present study, all data are presented as the mean ± standard deviation (SD). Statistical differences were determined analysis of variance (ANOVA) followed by the Bonferroni *t* test for post hoc multiple comparisons. A statistical significance level of α=0.05 and P<0.05 was applied to all tests.

Results

Changes in rat body condition and mental state under different training intensities

Long-term observation showed that rat body condition and mental state were obviously changed after training. Compared with the control group, rats in the moderate-intensity training group were healthier and had obviously better mental state, while rats in the high-intensity training group had loss of appetite and appeared depressed (Table 1).

Weight loss of rats after treadmill training with different training intensities.

As compared with the state before training, the body weight loss in the high-intensity training group showed a more

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Table 1. Changes in rat body condition and mental state under different training intensities.

Group	n	Tr	Body condition	Mental state at a normal state	Mental state under training intensities
Control	8	37.18±0.18	Fat, fur normal	Calm, complete feeding	–
Moderate-intensity	8	40.62±0.57*	Strong, fur glossy	Active, complete feeding	Positive
High-intensity	8	39.70±0.21*	Thin, fur not glossy	Apathetic and irritable, reduced feeding	Manic

Data are expressed as mean ±SD (°C). * $P<0.05$, compared to control group.

Table 2. Weight loss of rats after treadmill training.

Grouping	Training time (weeks)			
	1	2	3	4
Moderate intensity	8.4±1.7	7.7±2.1*	9.4±1.5	6.6±2.1*
High intensity	8.1±2.8	9.4±2.2	8.9±2.2	8.2±1.5*

Data are expressed as mean ± SD (g). * $P<0.05$, compared to high-intensity training group.

significant decrease than in the moderate-intensity training group after 4-week training (Table 2).

Relative mRNA expression of NMDAR, PSD-95, and KIF-17

Effects of different training intensities on gene expression of NR2A, NR2B, PSD-95, and KIF-17 were significantly increased in the moderate-intensity training group and decreased in the high-intensity training group as compared with the control group ($P<0.05$). Furthermore, the relative mRNA levels of NR1 showed no significant differences (108.80±8.12% in the moderate-intensity training group *vs.* 100.00±0.00% in the control group) ($P>0.05$) (Figure 1).

The protein expression of NMDAR, PSD-95, and KIF-17

It generally showed that the moderate-intensity continuous training increased the total protein levels of NR2A, NR2B, PSD-95, and KIF-17, while the expression in NMDARs and KIF-17 was reduced in the high-intensity training group as compared with the control group ($P<0.05$) (Figure 2).

As compared with the control group, moderate-intensity continuous training caused no significant difference in NR1 expression (103.71±2.17% in the moderate-intensity training group *vs.* 100.00±1.93%) in the control group) ($P>0.05$). In addition, PSD-95 showed no significant differences (95.41±1.26% in the high-intensity training group and 100.00±0.98% in the control group) ($P>0.05$).

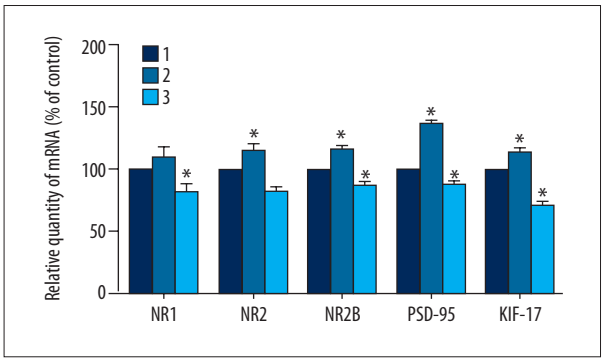

Figure 1. Summary of the mRNA levels of NMDAR subunits (NR1, NR2A, and NR2B), PSD-95, and KIF-17 in the rat hippocampus were calculated and are shown above. The 3 groups (control group, moderate-intensity training group, and high-intensity training group) are labeled as 1, 2, and 3, respectively. Bar graphs represent mean ±SD. * $P<0.05$ as compared with the control group.

Discussion

Influences of different intensities of training load on changes of emotional state in rats

Previous studies have discussed the influences of training loads on cognitive functions in rats by methods like rewards and punishment experiment and maze tests [9,10]. Modern medical research confirmed that different intensities of training loads can affect body condition and mental state. A study has found that reduced emotional capacity is an important depressive symptom [11]. Excessive stress can cause reduction in rat and human emotional abilities. The experimental results

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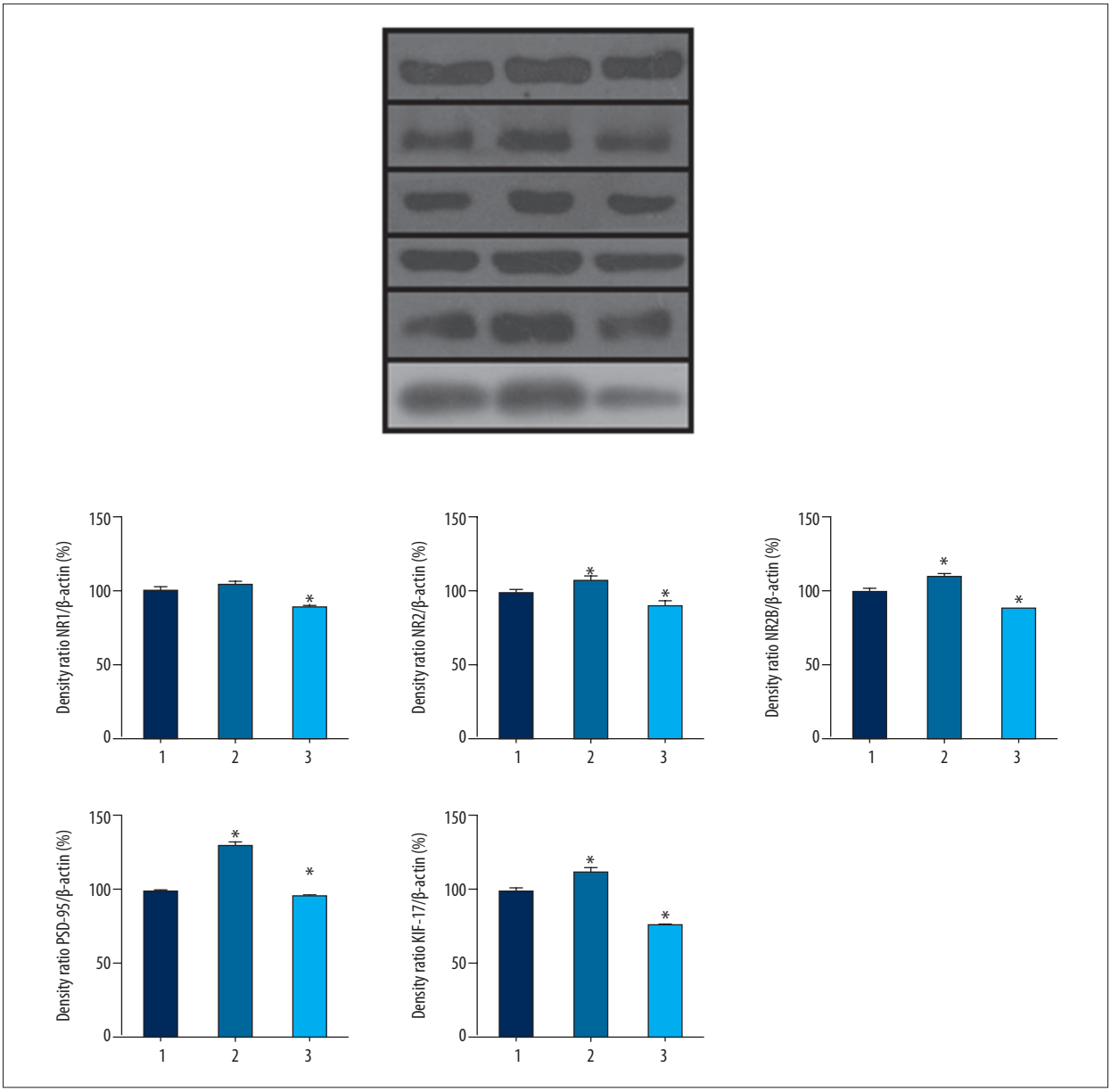

Figure 2. The moderate-intensity continuous training increased total protein expression in NMDAR subunits, PSD-95, and KIF-17 within the hippocampus, and the high-intensity continuous training showed a decreasing trend. The 3 groups (control group, moderate-intensity training group, and high-intensity training group) are labeled as 1, 2, and 3, respectively. Bar graphs represent mean ±SD. * $P<0.05$ as compared with the control group.

showed that training can cause obvious changes in the health and mental state of rats, and the impact of different intensities of training load also had different effects. Appropriate training intensity can help rats maintain physical and mental pleasure, with better training effects, thus promoting the emotional state and to a certain extent alleviating the anxiety behavior of experimental animals. The present study found that high-intensity training can lead to obvious decreased rat body weight, showing significant symptoms of depression, which was consistent with previous research results.

Influences of different intensities of training load on expressions of NMDA receptor, PSD-95, and KIF-17

NR1 is a functional subunit whose disordered expression can cause loss of receptor function, while NR2 is a regulatory subunit that can help the NMDA receptor to form a diversified structure [12]. A recent study found that the density of the dendritic spines was significantly decreased in NR2B knockout mice, and the related functions were also affected [13]. Previous research and results of this experiment suggested that after 4

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weeks of training, the expression level of NMDA receptor in rat hippocampus was changed with the change of training load intensity, and the promotion role of moderate-intensity training on its expression was most significant. Appropriate training can affect the functions of NMDA receptors and facilitate synaptic information transmission by increasing expressions of NR1, NR2A, and NR2B. In addition, the experiment found that the correct amount of training did not significantly enhance the expression of NR1, but the causes and related mechanism still need further research.

A study has shown that when rats are in high-intensity training, NMDA receptors accept regulations of various ions such as Ca^{2+} and PSD to elevate the concentration of Ca^{2+} in brain tissue cells [14]. NR2B, while interacting with PSD-95, also produces excitatory nerve toxic effects when NMDA receptor is activated excessively, leading to excessive in-flow of Na+ and overload of intracellular Ca^{2+}, and activation of downstream Ca^{2+}-dependent proteases (e.g., nNOS) [15], thus producing a large amount of NO and oxygen free radicals, damaging mitochondria, and eventually resulting in necrosis and apoptosis of nerve cells and overall damage to vital organs [16,17]. Results of the experiment suggested that high-intensity platform training did not promote the expression of hippocampal NMDA receptor. High-intensity platform training decreased hippocampal NR1, NR2A, and NR2B expressions, as well as the rat's abnormal performance, which are suspected to be related to the inhibitory effects of free radicals produced by high-intensity training.

In the formation of spatial memory, PSD-95 can be recruited to the corresponding synaptic membrane surface, which helps to cluster and anchor NMDA receptors and increases the efficiency of synaptic transmission in the process of synaptic plasticity [18]. In KIF-17$^{-/-}$ mouse neurons, KIF-17-mediated NR2B transport is blocked, so the transcription of NR2B is greatly reduced [10]. This experiment analyzed the influences of different training intensities on expression of PSD-95 and KIF-17, and found that the expressions of hippocampus PSD-95 and KIF-17 were also affected by the intensity of training, and the changing trend was basically consistent with the NMDA receptors. Thus, it seems that the up-regulated expressions of PSD-95 and KIF-17 are likely to further promote NR2 subunit expression through the enhancement of related NR2 subunit transport after the combination.

Relationship between emotional state and NMDA receptor, PSD-95, and KIF-17

NMDA receptors can be combined with an excitatory neurotransmitter to participate in the development of neurons and synaptic plasticity, especially long-term potentiation (LTP), and is closely related with the emotional state [19]. Kaut et al. confirmed that NR2A is closely associated with severe depression by NMDA receptor methylation detection and related analysis [20]. A study suggested that the increased expression of some specific genes reflects the increased number of neurons and synapses, thereby enhancing the corresponding physiological function [21]. For example, it was found that Mg^{2+} concentration can increase the expression of NMDA receptor, and the downstream signal pathway through phosphorylating the postsynaptic membrane density by calcium/calmodulin dependent protein kinase II, thereby enhancing NMDA receptor-dependent LTP [22,23], and the formation of LTP can promote the expression of NR2B subunits, forming a vicious cycle. LTP is the major factor in hippocampal synaptic plasticity, which can enhance the transmission efficiency of synaptic information, thus affecting the emotional state [24]. PSD-95, combined with KIF-17, plays an important role in synaptic transmission and emotion regulation, brain pathology physiology disorders such as cerebral infarction, and pain by NMDA receptor. In this study, compared with the control group, the moderate-intensity training group had obviously better mental state, and correspondingly increased expressions of NMDA receptor, PSD-95, and KIF-17, and the high-intensity training group showed obvious depressive state and the expressions were inhibited to different degrees. Nevertheless, we still lack a unified understanding of the mechanism by which these 3 indexes are related to cognition and emotion, which needs further research.

Conclusions

Different training modes have different effects on hippocampal function. The mechanism was complex. An appropriate amount of training alleviates hypoxia damage to the hippocampus and more effectively improves the emotional state. However, research on the mechanism of hippocampal function changes caused by training and selective research on training methods and training amount are not systematic and need further work.

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