Neuroscience Letters 514 (2012) 141–146

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Acute footshock-stress increases spatial learning–memory and correlates to increased hippocampal BDNF and VEGF and cell numbers in adolescent male and female rats

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ARTICLE INFO

Article history:
Received 18 November 2011
Received in revised form 22 January 2012
Accepted 14 February 2012

Keywords:
Acute-stress
Footshock
Hippocampus
Learning and memory
Adolescent
BDNF
VEGF

ABSTRACT

It is well known that the acute-stress enhances cognitive functions in adults, but is not known in adolescents. The purpose of this study is to investigate the effects of low and high intensities of acute-stress on hippocampus and spatial memory in the adolescent male and female rats. Thirty-eight days aged rats were subjected to 0.2 and 1.6 mA intensity of footshock-stress for 20 min. Spatial memory performance was assessed in the Morris water maze. Learning had been positively affected in stress groups. Neuron density in the CA1 hippocampal region and the gyrus dentatus as well as VEGF and BDNF levels of hippocampus increased in all stress groups. In females, learning process and BDNF levels increased in low-intensity-stress group than high-intensity-stress group. There was no difference in hippocampal apoptosis among groups.

We conclude that adolescent hippocampus is affected positively from acute-stress; however, while there is no difference in male response with respect to intensity of stress, females are affected more positively from low-intensity of stress.

Stress is an environmental factor that affects our behavior and can cause many disease, and plays an important role in human and animal biology. Stress causes a new regulation for response to stress in the human body. Inadequate regulation to stress may occur depression, panic disorders, drug addiction and cognitive disorders [36].

In mammals, brain development begins in intrauterine period and continues until the end of the adolescence. Many disorders among humans often begin during adolescence. The adolescent period in rats starts at postnatal 38–42 days and continues postnatal 60 days [36]. During the adolescent period, the volume of the rodent hippocampus, the number of cells and the dendrite density undergo development. Learning and memory also develop throughout adolescence [21].

During adolescent period, the daily life-stresses are perceived as larger that in other ages. In human studies, adolescents had a higher stress levels in stressor tasks and increased stressor-induced cortisol levels and increased cardiac reactivity to stressors compared adults [15,37]. Also in animal studies, adolescent animals show more anxious than adults in anxiety tests [16,43]. In our previously study, we have shown that both low and high intensity footshock-stress increased glutathione peroxidase (GPx) enzyme activity, an anti-oxidant enzyme, in the prefrontal cortex of adolescent male rats, while only high intensity stress increased activity of GPx in the same region of adult males [14,40].

It is known that stress is an important regulator for brain functions and cognition. In adults, prolonged and/or severe stress negatively affects learning and memory; acute-stress can affect learning differently, depending on stress duration, severity, type and time. Many studies in adults show that acute-stress affects negatively the hippocampus-related spatial learning [45]; in some studies, positively affects the cognitive functions of the adaptive response to stress [31]. However, effects of acute-stress on cognitive functions in adolescents are unknown.

Acute-stress stimulates the sympathetic nervous system, causing the release of noradrenaline [39] and results in activation of the dopamine (DA) system which are neuromodulators

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doi:10.1016/j.neulet.2012.02.049

[2,30]. Also, acute-stress results in activation of the hypothalamic–pituitary–adrenal (HPA) axis, which regulates the release of glucocorticoids [39]. Acute-stress is essential for adaptation and maintenance of homeostasis. In previous studies, men and female were given different endocrinological response and memory effects to acute-stress [42,44].

The adult hippocampal neurogenesis is regulated by angiotrophic factors such as VEGF and by neurotrophic factors such as BDNF [24,46]. It is known that stress affects both VEGF and BDNF levels in adult hippocampus. Chronic-stress, reduces both the level of these factors [34,35], but how they are affected by acute-stress is not known. Whether effects of acute-stress on hippocampal VEGF and BDNF levels is unknown in adolescents.

The aim of this study is to investigate the effects of acute-footshock-stress on hippocampal cells and VEGF and BDNF levels and spatial learning and memory in adolescent male and female rats.

There are the same stress hormone levels (corticosterone and ACTH) with adults after postnatal 46 days [21]. So that, 38 days old Wistar-Albino female and male rats ($n = 7$) were used. All experiments were performed in accordance with the guidelines provided by the Experimental Animal Laboratory and approved by the Animal Care and Use Committee of the Dokuz Eylul University, School of Medicine. All rats were maintained on a constant 12-h-light/dark cycle at constant room temperature (21 °C), and humidity (60%). The animals were divided into six groups: control-males, 0.2 mA footshock-males (low-intensity), 1.6 mA footshock-males (high-intensity), control-females, 0.2 mA footshock-females, 1.6 mA footshock-females. Rats were exposed to electric foot-shocks of 160 ms duration with a 160 ms interval for 20 min.

One hour after at the end of stress period, all rats were subjected to Morris-water-maze tests [22]. The Morris-water-maze was 140 cm in diameter and 75 cm in height. The water level in the tank was 50 cm, which was 1.0 cm above the height of the escape invisible platform. Each rat was exposed to the task for 4 consecutive days (total 20 trials), and on day 5 a probe trial was run. The learning tests recorded and evaluated with HVS-image video-tracking-system.

After the water maze test at postnatal days 42, all animals were decapitated under ether anesthesia. Brain tissues were removed and half of hemisphere fixed in 10% formalin in phosphate-buffer for histological-examination. Other hemisphere hippocampus was used biochemical-analysis.

The brain was sectioned coronally into sequential 6 μm sections using a microtome (Leica RM2255, Köln, Germany). Each sample was subjected to the estimation of neuron number by taking three coronal sections through the hippocampus that corresponded to plates 21,23,25 in the rat atlas of Paxinos and Watson [25]. All sections were stained by cresyl violet. The images were analyzed by using a computer assisted image analyzer system consisting of a microscope (OlympusBH-2 Tokyo, Japan) equipped with a high-resolution video camera (JVC TK-890E, Japan). The numbers of hippocampal neurons were counted by help of a 6000 μm^2 counting frame viewed through a 20× Nikon-lens at the monitor. The counting frame was placed randomly five times on the image analyzer system monitor and neuron numbers were counted (UTHSCA-Image-Tool for windows version-3.0 software) and the average was taken. The numbers of hippocampal neurons were counted in CA1, CA2, CA3 and gyrus dentatus (GD) regions and neuron density was calculated.

To detect DNA-fragmentation in cell nuclei, terminal deoxynucleotidyl-transferase-mediated dUTP-nick end-labeling (TUNEL) reaction was applied to the paraffin sections by using a kit (G7130-Promega, USA).

The serum corticosterone levels were measured with the radioimmunoassay method using a double antibody kit (ImmuChem, MP-Biomedicals, Orangeburg, NY).

Hippocampus tissue homogenate was analyzed by enzyme immunoassay for BDNF (Catalog Number EK0308, Boster Immunoleader, Wuhan, China) with assay sensitivity <2 pg/ml and range 31.2–2000 pg/ml and VEGF (Catalog Number EK0308, Boster Immunoleader, Wuhan, China) with assay sensitivity <1 pg/ml and range 15.6–1000 pg/ml.

VEGF expression was detected by avidin-biotin-complex method using Santa-Cruz biotechnology (SC-7629) (R&D-Systems) according to the manufacturers. Immunoreactivity was graded as follows: more than 10% of the cells staining were graded as positive. No detectable staining or <10% of cells staining was graded as negative. The qualitative intensity of staining for VEGF was assessed using a scale between 0 and +++. With 0 representing no detectable stain and +++ representing strongest stain.

Difference between the learning days in MWM was analyzed by using GLM-repeated measure post hoc Bonferroni. Differences between the groups were analyzed using two-way-ANOVA post hoc Bonferroni. Results are presented as mean ± S.E.M (significance level was $p \leq 0.05$).

The present study showed that acute-stress significantly improved spatial learning–memory. The mean latency to find the platform declined progressively in all animals ($F_{1,34} = 2.88$, $p < 0.05$). Stressed rats had shorter escape latencies at the second (in stressed males), third (in all stressed groups) and fourth (in all stressed groups) days of training days than controls (Fig. 1A). An effect of sex ($F_{3,33} = 5.48$, $p = 0.004$) and interaction between sex × stress in learning days ($F_{3,33} = 4.73$, $p = 0.008$), but no interaction only stress on subject's learning was observed. In females, low-intensity-stress more decreased escape latency than high-intensity-stress (second-day, $F_{2,17} = 7.95$, $p = 0.004$; third-day, $F_{2,17} = 28.04$, $p = 0.000$, fourth-day, $F_{2,17} = 6.52$, $p = 0.009$). In males, the escape latency was reduced in all stressed-males compared to control-males, but there was not any difference between high and low-intensity-stress groups (second-day, $F_{2,20} = 9.16$, $p = 0.002$; third-day, $F_{2,20} = 6.68$, $p = 0.007$, fourth-day, $F_{2,20} = 9.46$, $p = 0.002$).

In probe trials (quadrant time), time spent in target quadrant was used to evaluate long-term memory. All stressed animals spent more time in the target-quadrant and spent less time in the opposite-quadrant (Fig. 1B), compared to controls (males, target-quadrant, $F_{2,20} = 19.70$, $p = 0.000$, opposite-quadrant, $F_{2,20} = 111.43$, $p = 0.000$; females, target-quadrant, $F_{2,17} = 9.16$, $p = 0.003$, opposite-quadrant, $F_{2,17} = 8.24$, $p = 0.004$). The cell numbers increased in CA1 hippocampal region and the GD (males, CA1, $F_{2,18} = 10.87$, $p = 0.001$, GD, $F_{2,18} = 3.80$, $p < 0.05$; females, CA1, $F_{2,16} = 12.84$, $p = 0.001$, GD, $F_{2,16} = 22.56$, $p = 0.000$) (Fig. 2). Hippocampal VEGF and BDNF levels increased in all stress groups (males, VEGF, $F_{2,14} = 19.70$, $p = 0.000$, BDNF, $F_{2,14} = 6.85$, $p < 0.05$; females, VEGF, $F_{2,14} = 4.22$, $p < 0.05$, BDNF, $F_{2,14} = 6.43$, $p < 0.05$) (Fig. 3). However, BDNF levels of the females showed significant differences between low- and high-intensity of stress. VEGF immune staining and marking were increased in all stress groups. There was a positive correlation between time spent in the target quadrant and cell numbers of CA1 and gyrus dentatus, VEGF and BDNF levels (CA1 cell-numbers, $r = 0.548$, $p = 0.001$; GD cell-numbers, $r = 0.341$, $p = 0.042$; VEGF, $r = 0.423$, $p = 0.020$; BDNF, $r = 0.438$, $p = 0.016$), and a negative correlation between the time spent in the opposite quadrant and cell numbers of CA1 and gyrus dentatus, VEGF and BDNF levels (CA1 cell numbers, $r = -0.643$, $p = 0.000$; GD cell numbers, $r = -0.455$, $p = 0.005$; VEGF, $r = -0.376$, $p = 0.040$; BDNF, $r = -0.388$, $p = 0.034$). Few cells were seen to be TUNEL-positive in both control and stress groups in females and males. There was no statistical difference of hippocampal apoptosis and basal corticosterone levels among groups (5 days after stress).

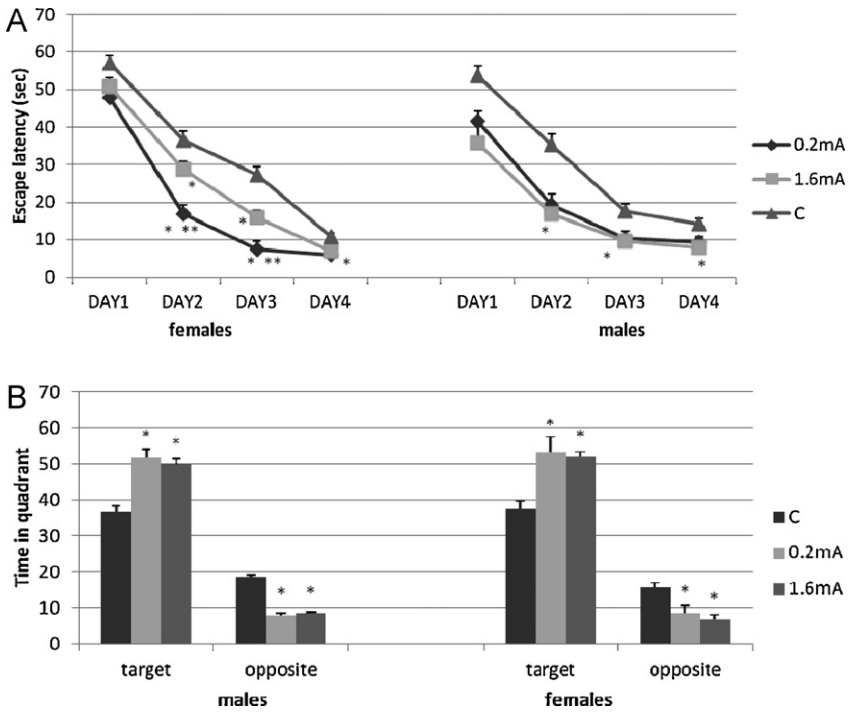

Fig. 1. Effects of acute-stress on Morris water maze performance. (A) Mean daily latencies to escape from the start point onto the hidden platform. (B) The time spent in the target quadrant in the probe trial at the fifth day. $^{*}p < 0.05$ compared with control group of same sex. $^{**}p < 0.05$ compared with 1.6 mA-stress group.

In this study, we found that both low and high intensities of acute stress increased the learning and memory performance and hippocampal cell numbers and VEGF and BDNF levels in adolescent rats. Stressed groups showed shorter escape latency than control groups at second, third and fourth days of learning trials. In the probe trial, the stressed groups spent more time in the correct quadrant and less time in the opposite quadrant compared to controls. The activation of the stress system stimulates the attention, alertness, and motivation (fight or flight) in the organism to increase the chance of survival [39]. The effects of stress and stress hormones on cognitive functions are complex. Some of the studies, acute stress and stress hormones enhanced cognitive functions [48], the negative impact on others in adults [28]. Type, intensity, timing and duration of stress are determining the adaptation to stress-response and may affect positively or negatively. To the best of our knowledge, there is no data about the effects of acute stress on spatial learning and memory in adolescents. During the preadolescent period, acute-noise-stress and footshock-stress impaired learning and memory [17,45]. Footshock-stress for 5-consecutive days (repeated-stress) enhances avoidance learning compared adults [1]. Duration of stress affects memory differently. In adult rats, spatial-memory positively affected met to cat for 2 min [9], if they met for 30 min spatial-memory affected negatively [10]. In this study stress duration is 20 min.

The hippocampus had the highest density of glucocorticoid receptors in the brain and is involved in the regulation of the corticoid and behavioral responses to stress by controlling the activity of dopaminergic neurons [32]. Effect on the dopaminergic system is different depending on the duration of stress; prolonged or repetitive stress reduces DA levels [2], and acute and short-term stress increase DA levels [30]. Also, for 20 min, intermittent 0.2 mA footshock-stress (low-intensity) cause a selectively increased DA metabolism in mesocortical areas, 1.6 mA footshock-stress (high-intensity) increase DA metabolism in mesocorticolimbic areas [8,12]. In this study, for 20 min footshock-stress, which is known to increase nigrostriatal, mesocortical and mesolimbic DA, was applied. Dopamine improves learning and memory formation [19]. Insufficient or excessive DA impairs cognitive functions, whereas medium dosages improve cognition [33]. In our previously study, we found that the 20 min foot-shock stress increased GPx activity which is produced via increased dopamine metabolism in the hippocampus [40]. In this study, high-intensity-stress enhanced

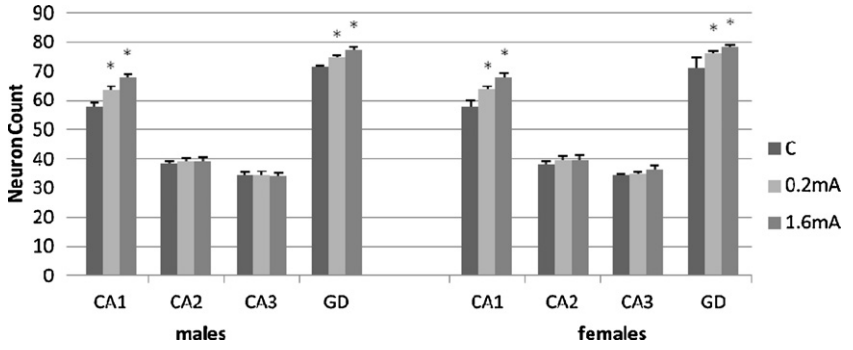

Fig. 2. Quantitative evaluation the effect of acute stress on the neuron numbers in hippocampus. $^{*}p < 0.05$ compared with control group of same sex.

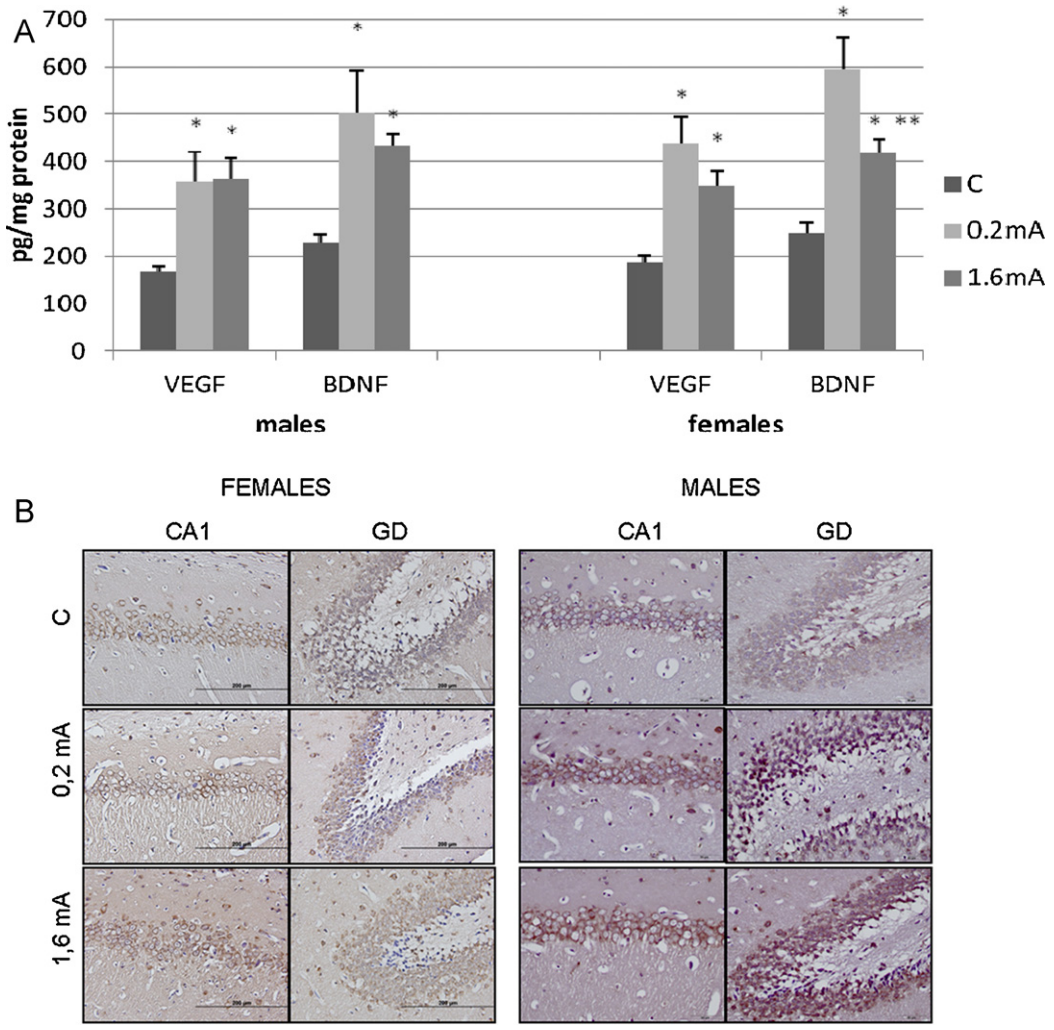

Fig. 3. Hippocampal VEGF and BDNF results. (A) Hippocampal VEGF and BDNF levels. *$p < 0.05$ compared with control group of same sex. **$p < 0.05$ compared with same sex of 0.2 mA group. (B) VEGF+ immune staining cells.

learning less than low-intensity-stress in females. High level of stress may be caused by insufficient dopamine release.

In the MWM test, there is an invisible platform, the test subjects locate the platform using the extra-maze clues [41]. During the learning process, CA3 and GD neurons of hippocampus taking the information and then integrate with the information from the prefrontal cortex. CA3 and GD are prerequisites to find the correct path and the target quadrant in the probe trial [18]. In this study, we found that the number of cells in the GD increased in all stress groups. In addition, we found a strong positive correlation between the time spent on the target quadrant and the cell number of gyrus dentatus.

Hippocampal CA3 region is connected to CA1 region through Schaffer collaterals. CA1 outputs reach subiculum, entorhinal and prefrontal cortex [4]. CA1 takes most of the information from CA3, and a smaller portion from the entorhinal cortex [4,27]. CA1 region works as an error detector: it looks for discordance among the information it receives from cortex, CA3 and entorhinal cortex and corrects the stored information [27]. In this study, the cell number was increased in CA1 regions and less time in the opposite (incorrect) quadrant in all stressed groups. In addition, there was a strong negative correlation between the CA1 cell numbers and the time spent in the opposite quadrant (errors-committed).

Increased neuron number may result from both an increase of cell proliferation or a decrease of cell death. The present experiment showed that high and low intensities of acute stress significantly increase total number of neuron, and did not change apoptosis of young animals. This result indicates that increased neuron number may be resulted from cell proliferation.

The regulation mechanism of the adult hippocampal neurogenesis includes various growth factors. Low BDNF levels may cause neuronal loss and atrophy [11]. The effect of stress on BDNF levels depends on the duration of stress; acute-restraint-stress with 2 h and chronic-stress decreased hippocampal BDNF [38]. However, acute-restraint-stress for 30 min, increased hippocampal BDNF [3]. Shi et al. found that the BDNF levels increased in acute-stress in which 2 months and 22 months rats, and that this increase was higher in 2-months-old rats [34]. Consistent with this study, in our study, the BDNF levels increased with 20 min of footshock-stress in 38 days old rats. Increase in BDNF may be the result of the need for protecting the organism in this stimulated state. BDNF affects the spatial memory positively; spatial learning and memory impaired BDNF-deprived animals [23]. In our study, there was a positive correlation between hippocampal BDNF levels and time in target quadrant in probe trials; and a negative correlation between BDNF levels and time in the opposite quadrant. BDNF has also trophic and modulatory effects on the growth and plasticity of dopaminergic, serotonergic and other neurons. The stimulation of dopamine causes to increase the BDNF-mRNA and protein [20].

In adults, hippocampal changes that due to various factors occur in regions close to blood vessels [46]. The angiogenesis and neurogenesis may be regulated by the same stimulants. This indicates that, the signals regulating the cell proliferation in adults may arise from the endothelial growth factor. The changes in the VEGF concentration or the VEGF receptor expression affected cell proliferation and survival [29]. Corticosteroids are potent inhibitor of angiogenesis; they regulate VEGF and/or expression of VEGF receptor in different cell types [35]. Chronic stress decreased VEGF levels [5]. Acute stress increased VEGF levels in adult rat bladder [6]. In our study, acute stress increased VEGF levels in adolescent rat hippocampus. Spatial memory enhanced in VEGF over expressed rats [26]. Enriched environment increased hippocampal VEGF and enhanced spatial memory [7]. VEGF therefore seems to be a direct mediator of improved cognition in rodents [13]. In our study, there was a positive correlation between hippocampal VEGF levels and time in target quadrant in probe trials; and a negative correlation between VEGF levels and time in the opposite quadrant. In addition, VEGF has protective effect on the dopaminergic neurons [47]. In this study, the increased levels of VEGF and BDNF might have affected the dopaminergic neurons.

Male and female rats differ in neuroendocrine and behavioral parameters, and vulnerability to stress is gender dependent [44]. In both adolescents and adults, females give higher cortisol response to stress, and more affected from stress [42]. In our study, BDNF levels increased less than high-intensity-stress group. But, this little increase of BDNF was not enough to negatively affect the learning process.

In summary, acute-footshock-stress during the adolescent period increased hippocampal VEGF and BDNF levels, cell numbers of CA1 and GD without altering apoptosis, and enhanced spatial learning and memory in males independent of stress level. However, the level of stress seems to be important in adolescent females hippocampus. Future studies are needed to explore the effects of different type, duration and level of stress in the adolescent period.

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