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Neuroprotective And Therapeutic Effects of Exercise in Restraint Stress Induced Depression Like Behavior Albino Rat Model

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ABSTRACT

Background: Major depressive disorder (MDD) is considered to be a chronic high-risk, recurring mental illness affecting individual's feelings, cognition, and behaviors. Exercise may be a promising target for the treatment of depression but the processes underlying this association between mood and exercise intervention are still poorly understood.

Objective: The current work is designed for assessment of beneficial effects of moderate swimming exercise on behavior and neurochemical parameters in a restraint-stress rat model of depression.

Materials and Methods: Depression was induced via placing rats in individually into a cylindrical, transparent restraint tube for 2 h/day for 3 weeks. Swimming exercise training was analyzed for its potential health benefits both before and after a period of chronic restraint stress.

Results: restraint stress induced depression like behavior, increased corticosterone ($p<0.001$), MDA ($p=0.001$) as well as inflammatory markers and decreased hippocampal BDNF ($p=0.001$) and SOD ($p<0.05$). swimming exercise was able to prevent and improve these behavioral and biochemical abnormalities.

Conclusions: exposure to chronic stress induced depression. Swimming exercise training, on the other hand, has a moderate benefit in reducing these damages if it is undertaken after the stress period. This impact, however, is amplified when swimming exercise is conducted prior to then in combination with restraint stress.

Keywords: CRS, Depression, Swimming, BDNF, Corticosterone, Oxidative stress.

INTRODUCTION

Major depressive disorder (MDD) is a high-risk chronic, recurring mental illness that endangers both physical and mental health [1]. Nearly 800,000 people take their own lives each year in the twenty-first century, and this trend appears to be a major contributing factor [2].

The effect that exercise may have on one's mental health is attracting more attention. Exercise is increasingly being used as a non-pharmacological therapy for depression as studies show that reduces depressive symptoms and improves physical function[3].

Although there is substantial evidence linking exercise to improved mood, our understanding of the mechanisms behind this association is still limited[4].

The World Health Organization has declared stress to be a "health epidemic" in the modern era. There is mounting evidence that prolonged emotional stress is a major contributor to the onset of depression; yet, the complex and heterogeneous molecular and cellular pathways implicated in stress-induced brain damage remain poorly understood[4].

Both depression and anxiety have been linked to oxidative stress, according to a number of studies. Also, the hypothalamic-pituitary-adrenal axis (HPA) has been linked to both depression and chronic stress [5].

While the precise cause of depression remains unknown, there is growing evidence to suggest that inflammation and immunological dysregulation play a significant role in the condition[6].

Numerous studies have established a link between neurotrophic factors, particularly BDNF, and emotional distress. Depression's pathophysiology may be facilitated by changes in functional neurotrophic factors, which dampen neuronal plasticity [7].

In the present study, we examined the effect of swimming exercise as a potential non-pharmacological method for prevention and treatment of depression using the chronic restraint stress (CRS) rat model of depression.

MATERIALS AND METHODS

Thirty-five adults male wistar albino rats weighing between 180 – 200 g. were procured from the Zagazig University Faculty of Veterinary Medicine. The animal section of the physiology department in the medical school at Zagazig University provided clean, sanitary environments for these animals. The rodents could eat and drink whenever they wanted.

The rats were acclimated for two weeks before being randomly split into five groups of seven:

Group 1: Sedentary control (Sed-C) intact controls (non-stressed & non-exercised). It will serve to establish basal levels of studied parameters (Behavioral, Pathological, and Biochemical) ; control group. **Group 2: Trained control (Train-C)** (non-Stressed & exercised); swimming exercise only, **Group 3: Sedentary + restraint stress (Sed-RS)** restraint stress only for 3 weeks, **Group 4: Restraint stress + training (RS-Train)** restraint stress for three weeks followed by

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swimming exercise for four weeks and **Group 5: Training followed by restraint stress + training (Train-RS)** swimming exercise for four weeks followed by restraint stress +swimming exercise for three weeks.

Induction of depression:

Restraint stress sessions lasted 2 hours each day from 9:00 am to 11:00 am for 21 days straight (Sed-RS, RS-train, and Train-RS groups) [8]. Rats were placed individually into a cylindrical, transparent, acrylic restraint tube, ventilated by holes (height = 20 cm, diameter = 5 cm).

Exercise protocol:

Training and adaptation are the two halves of the swimming programme. In order to facilitate adaption, the training was phased in over the course of the first week, beginning with 15 minutes on day one and culminating in 60 minutes on week's end. After that, we began our training regimen, which consisted of 60 minutes, five times a day, for a total of four weeks. Regular swimming practices were held in a big water tank maintained at 32°C (100 cm long, 60 cm wide, and 80 cm high) [3].

Behavioral Tests:

Rats were tested for behaviour after they had the CRS surgery and the swimming exercise routine. Anxiety and depression-like behaviours were evaluated using the Forced Swim Test (FST), Open Field Test (OFT), and Novel Object Recognition Test (NORT). All behavioural assessments were conducted in a quiet room between the hours of 8:00 A.M. and 12:00 P.M.

Biochemical studies:

The retro-orbital plexus was pricked to get the blood. Blood serum was extracted via 15 minutes of centrifugation at 3000 rpm. Bioassays for BDNF, corticosterone, lipid peroxide (malondialdehyde, MDA), C-reactive protein (CRP), superoxide dismutase (SOD), interleukin-6 (IL-6), as well as tumor necrosis factor (TNF-α), were performed on the supernatant serum, which had been frozen at -20 ^{o}C.

Tissue samples:

The brains of sacrificed rats were dissected out surgically. Hippocampus is excised and rinsed thoroughly using cold salt water and dividing it in half, one part was preserved in formalin 10% for histopathological examination of paraffin wax sections of 5µ thickness and other part was rapidly frozen at -80°C, for later biochemical determination of BDNF.

Ethical approval:

The Animal Care and Use Committee at Zagazig University and the Physiology Department gave its consent to the experiment (ZU-IACUC). ZU-IACUC/3/F/429/2022 is the number for this authorization.

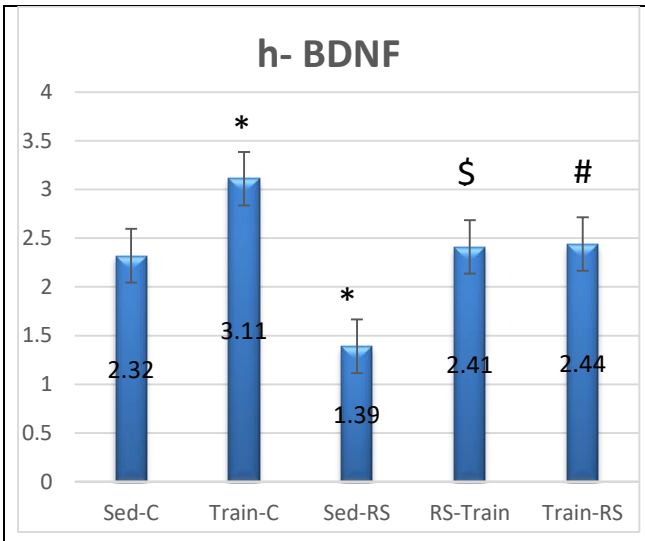
Statistical analysis

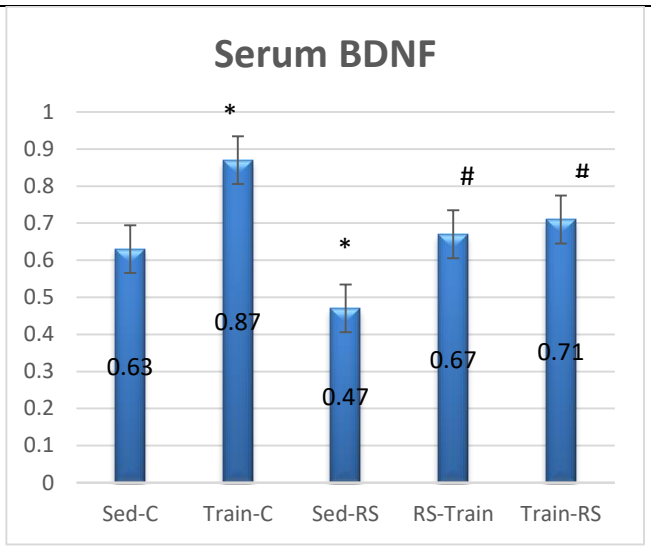
For the purpose of statistical analysis, we employed SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA). Statistics were presented as a mean with standard deviation. Statistical significance was determined using one-way analysis of variance (ANOVA) for parametric data and Kruskal-Wallis for non-parametric data. The significance level was taken to be 0.05 or lower.

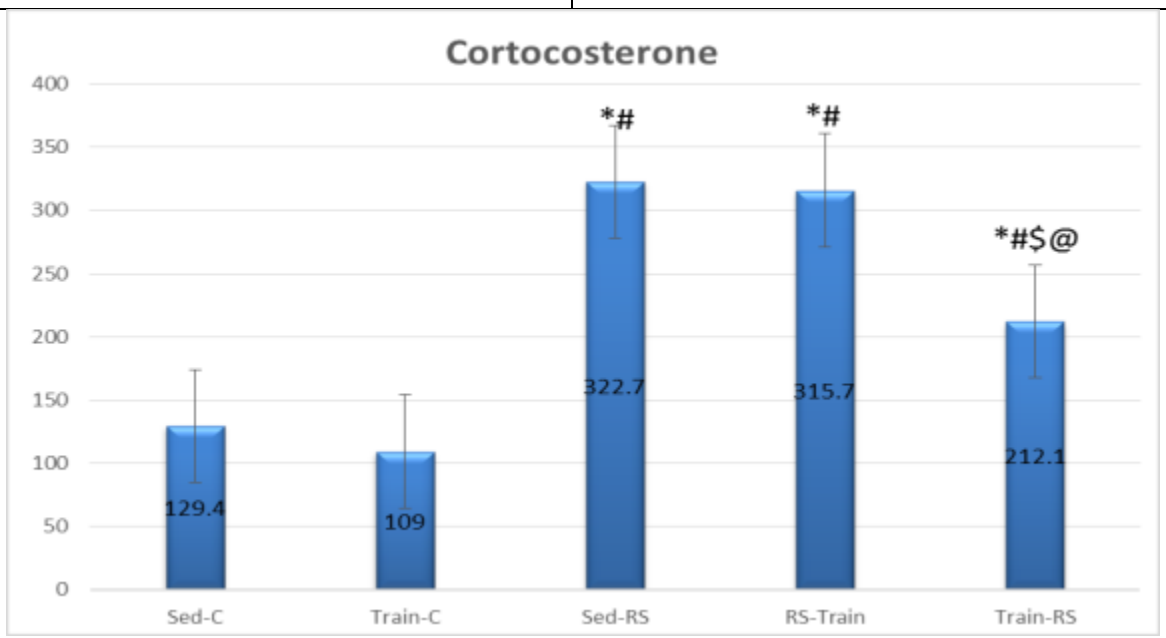
RESULTS

Figure (1) showed that CRS significantly decreased h BDNF **(p =0.001)** and serum BDNF **(p<0.05)** in Sed-RS rats. However, swimming exercise reversed CRS induced reduction in BDNF in RS-Train and Train-RS rats **(P>0.05)** as compared to Sed-C.

The result showed increased serum corticosterone in Sed-RS and RS-Train groups **(p <0.001)** compared to that of Sed-C. Compared to Sed-RS, corticosterone was significantly lower in Train-C and Train-RS **(p <0.001)**







*: significant versus Sed-C #: significant versus Train-C
$: significant versus Sed-RS @**:** significant versus RS-Train

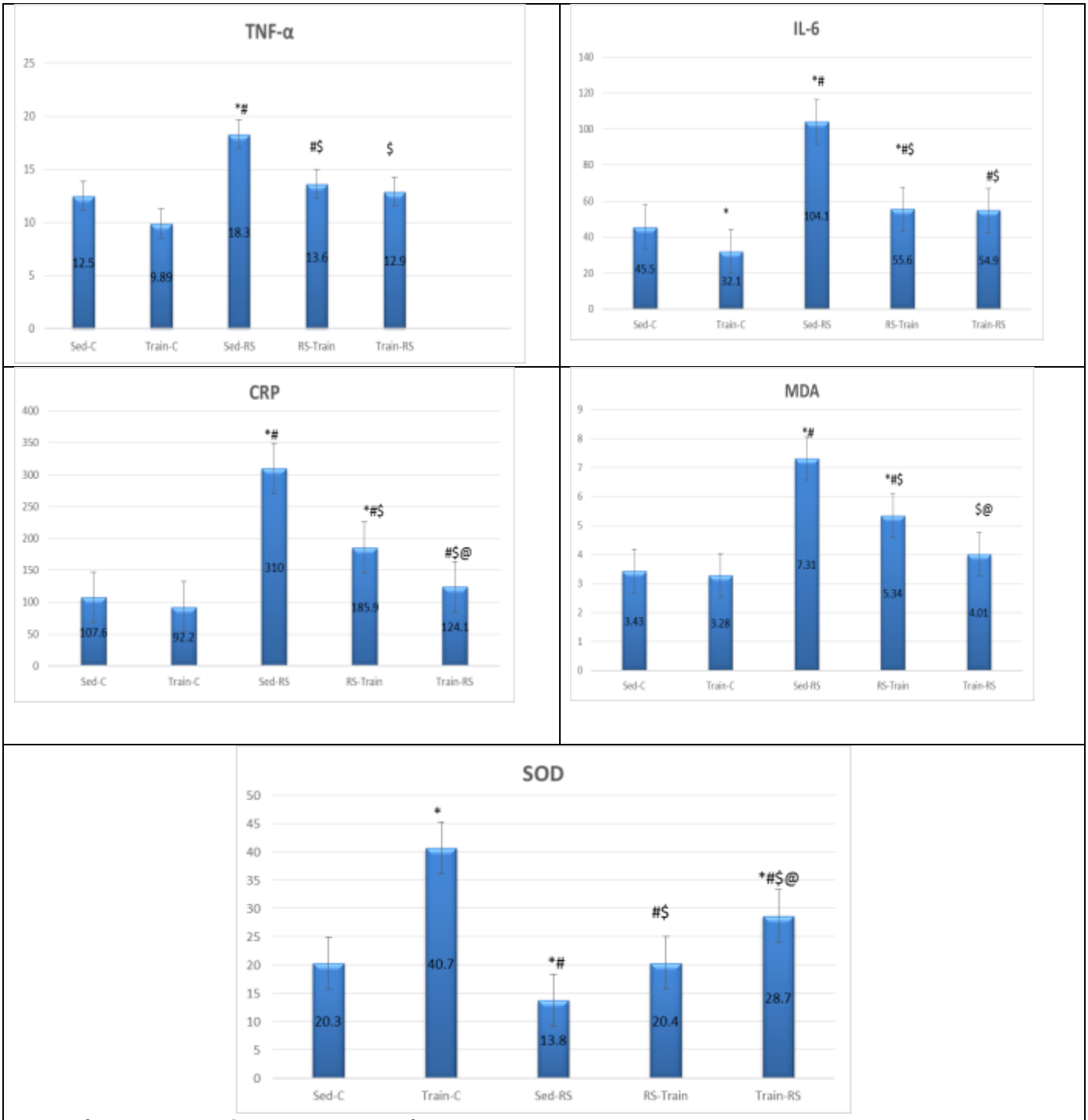
Figure (1): Difference in hippocampal, serum BDNF and corticosterone level (ng/mL) among studied groups.

The analysis of serum inflammatory cytokines Figure (2) revealed that Sed-RS present increased levels of TNF-a **(P=0.001)**, IL-6 **(p <0.001)** and CRP **(P=0.001)**, These values, however, were enhanced in the trained groups (Train-C, RS-train, and Train-RS). Oxidative stress indicators in the blood were also analyzed. Sed-RS and RS-train animals had higher levels of MDA than Sed-C animals (P=0.001). Compared to the Sed-C group, the SOD levels in the Train-C and Train-RS groups were significantly higher after exercise training (p 0.001).

Behavior Assessment showed that Sed-RS group in OFT showed significant increases in latency to move and rear **(p <0.001)** with increased number of fecal boli. There was also significant decrease in number of rear **(p<0.05)** and crossed squares **(P=0.001)** compared to control group Figure (3).

When comparing the Sed-RS group to the control group in the FST, the immobility time was considerably higher and the swimming and climbing times were lower (p0.001). Figure (4).

In NORT Sed-RS significantly decrease preference index **(P=0.001)**, number of visits **(p <0.001)** and exploration time **(p<0.05)** of the novel object compared to control group Figure (5). Exercise training was able to improve depression-like behaviors induced by CRS.



*: significant versus Sed-C. #: significant versus Train-C
$: significant versus Sed-RS. @**:** significant versus RS-Train

Figure (2): Serum TNF-α, IL-6, CRP, MDA and SOD among studied groups.

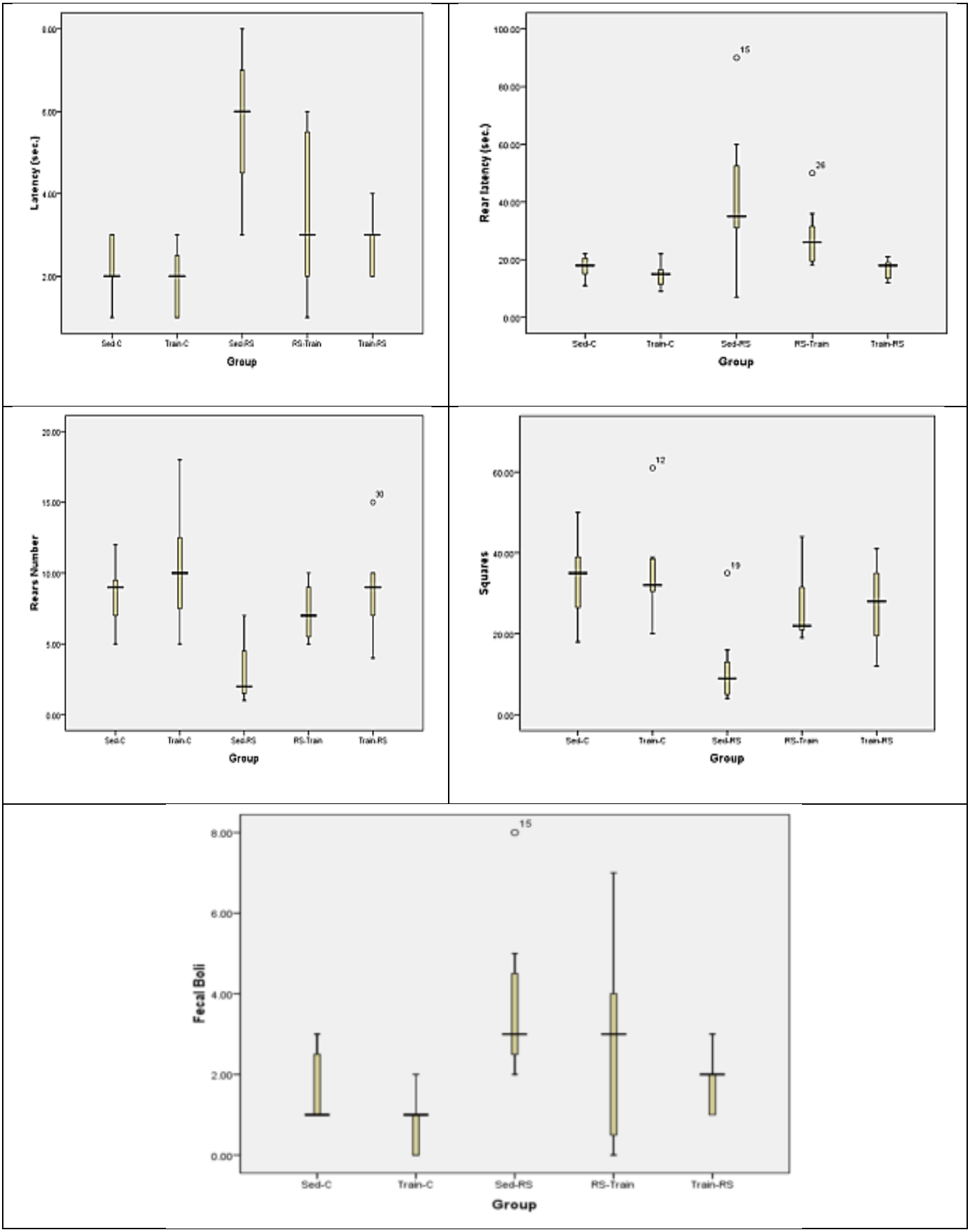


Figure (3): Box-plot analysis of latency, rear latency, rears no, crossed squares no and fecal boli OFT results among studied group.

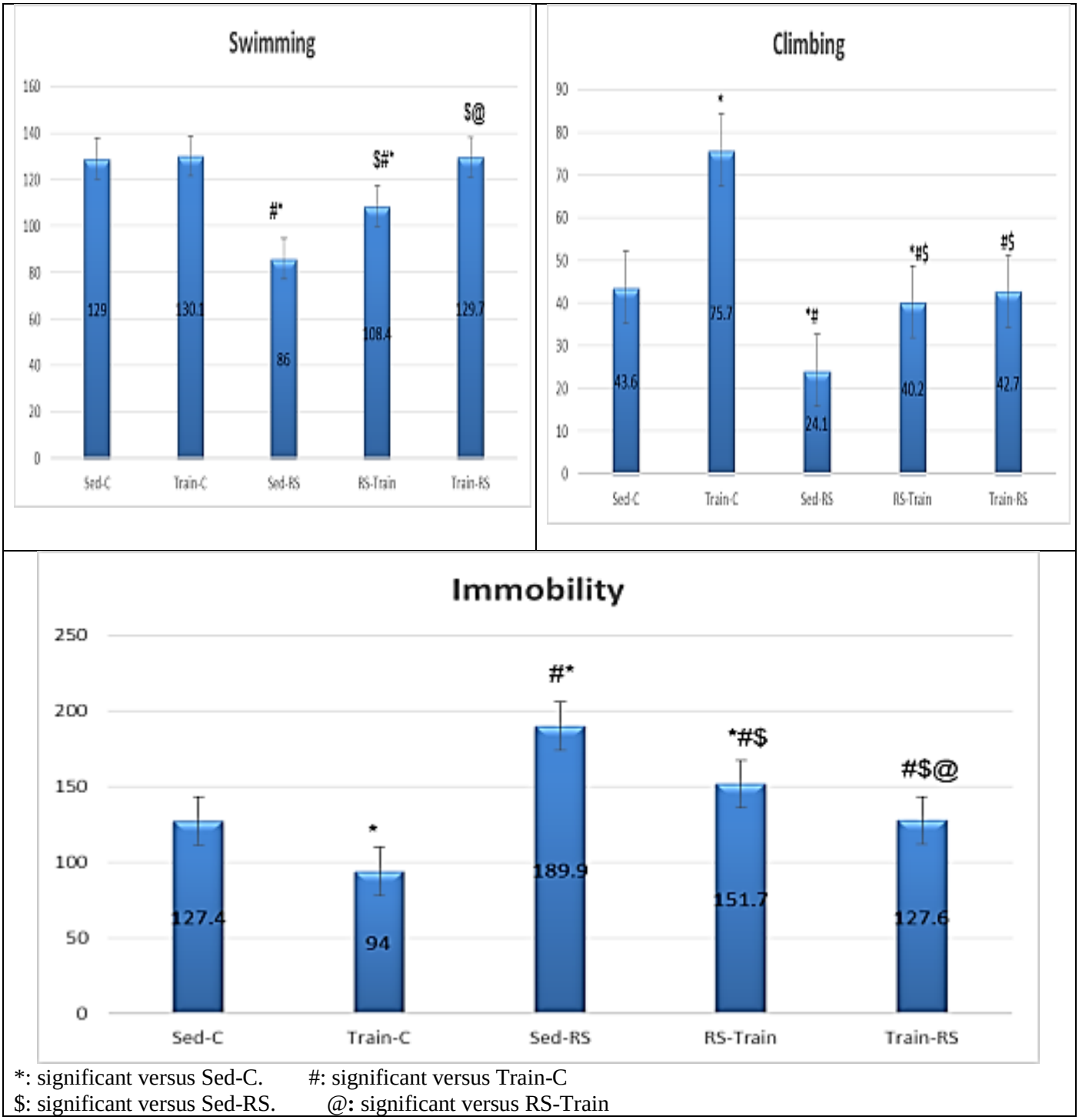


Figure (4): Difference in swimming, immobility and climbing time (seconds) FST results among studied groups.

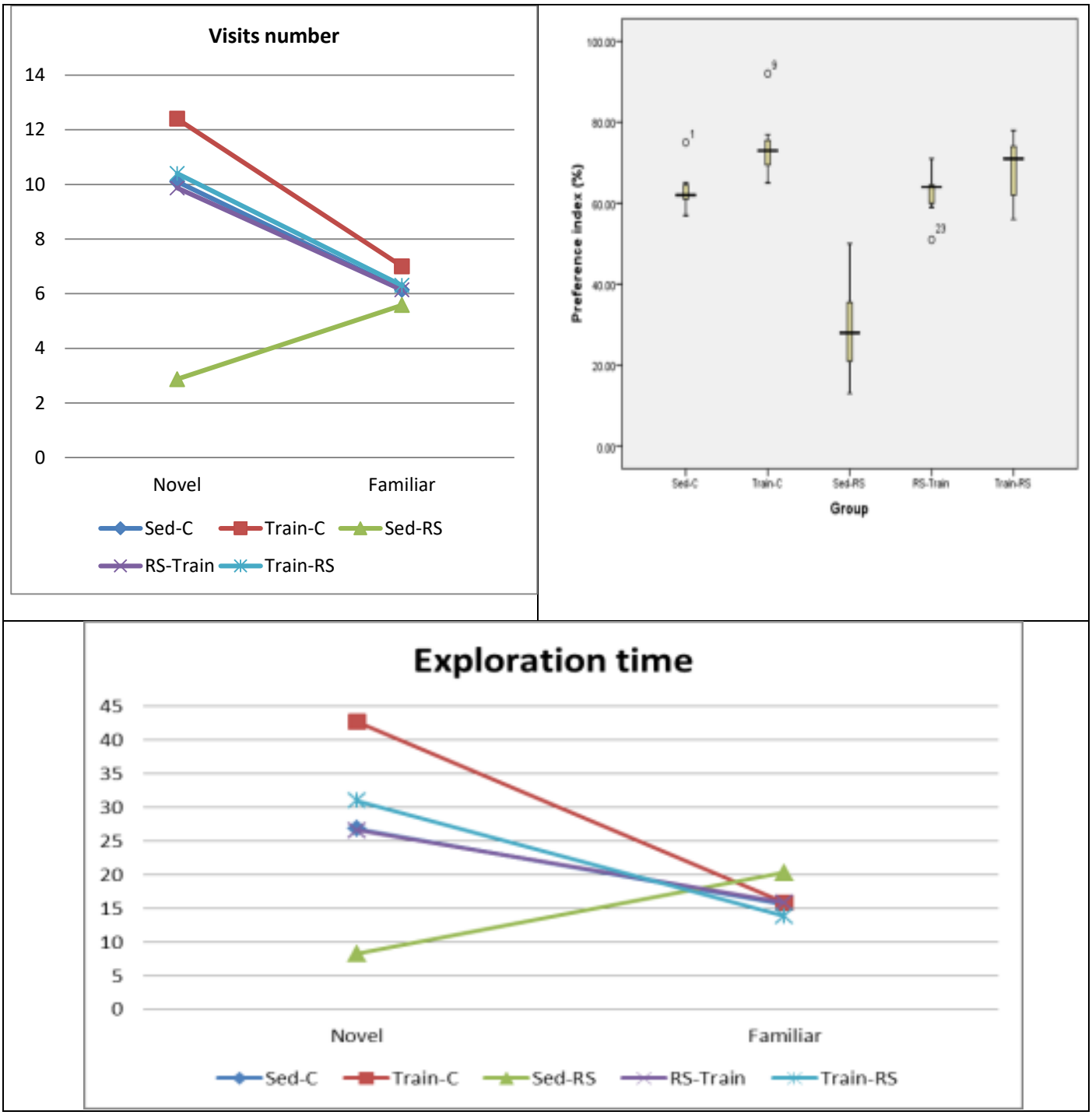
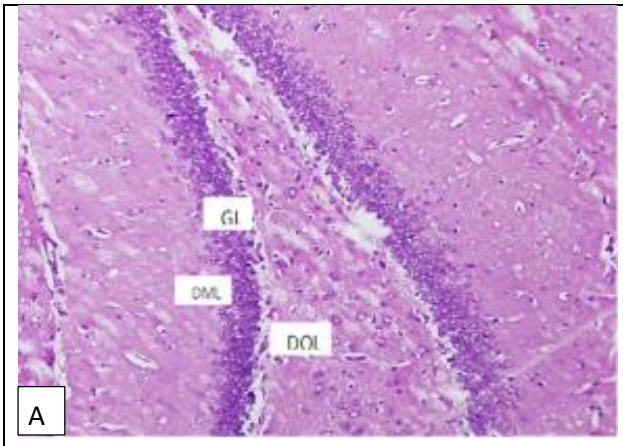
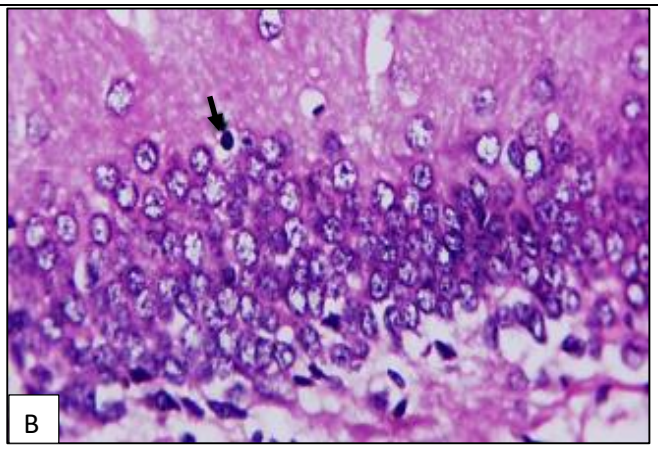


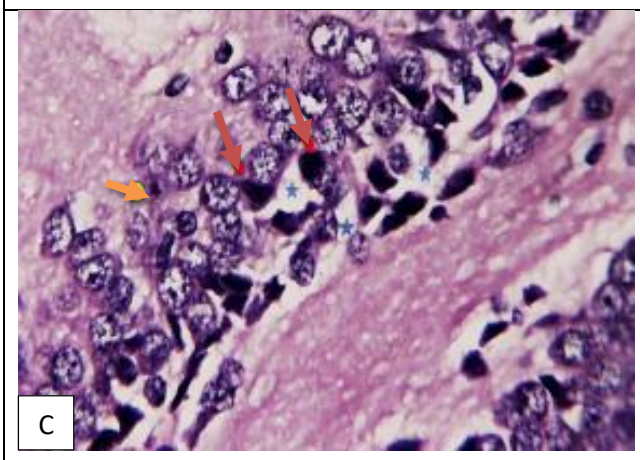
Figure (5): Difference in visits number, preference index and exploration time in NORT among studied groups.



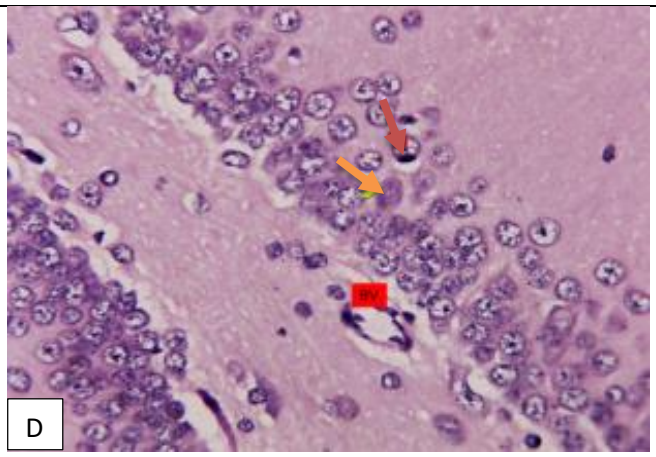
(A) Photomicrographs of a section in Sed-C group. Demonstrate 3 layers (GL=granular layer, DML=molecular layer, DOL=polymorphic layer). Multiple layers of densely packed neurons with ovoid vesicular nuclei make up the GL (X: 200).



B) Photomicrographs of a section in the Train-C group. It shows multiple layers of densely packed neurons with round vesicular nuclei and a few pyknotic (dark-stained) nuclei forming GL (black arrow) (X: 200).



C) Photomicrographs of section of Sed-RS group revealed many dark stained pyknotic nuclei (red arrows), many irregular degenerating neurons with eosinophilic cytoplasm (yellow arrow head) and many vacuolations (blue star) (X: 200).



D) Photomicrographs of section of RS-Train group revealed mild decrease in number of dark stained pyknotic nuclei (red arrows), many irregular degenerating neurons with eosinophilic cytoplasm (yellow arrow head) and many vacuolations (blue star). BV =blood vessel (X: 200).

E) Photomicrographs of section of Train-RS group revealed decrease in number of dark stained pyknotic nuclei (red arrows), and decrease in number of degenerating neurons with eosinophilic cytoplasm (yellow arrow head) and many vacuolations (blue star) (X: 200).

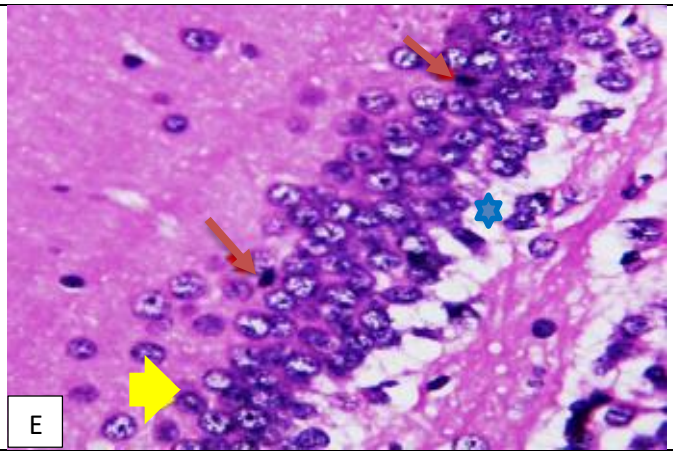


Figure (6): Photomicrographs of Dentate Gyrus (DG) of the hippocampus in all the studied groups stained by Hematoxylin and eosin (X: 200).

DISCUSSION

Despite the progress made in neuroscience, not all of depression's molecular components have been explained. Major challenges in treating depression include the disorder's high relapse rate and treatment's often-limited success [10].

Consequently, there is a rising demand for interventions that aim to prevent this psychiatric condition altogether or at least intervene early. These treatments may eventually focus on the benefits of exercise[11].

Chronic restraint stress (CRS) was utilized to induce depression in the current investigation. CRS is a reliable and inexpensive psychophysical stressor that has been shown to have no negative effects on the animal. It's a form of stress that involves both the body and the mind[12].

In accordance with these findings, rats in the Sed-RS group exhibited more depressive-like behavior when utilizing FST, with a substantial increase in immobility time. By using OFT Sed-RS group showed an increase in anxiety-like behavior with and a significant decrease in locomotor activity. For testing cognition, particularly recognition memory, NORT was used. The rats in the (Sed-RS) group showed a significant reduction in the preference index compared to other groups.

Furthermore, swimming exercise alleviated the chronic restraint stress procedure's results when comparing the (RS-Train) group with the (Sed-RS) group. This suggests the benefits of exercise for anxiety and depression-like behaviors

These data were in agreement with **Safari *et al.*** [13], who reported that swimming training after chronic stress could not reverse depression-like behaviors but only reduce them.

Contrary to **Liu *et al.*** [14] they discovered that depression-like behaviours in mice exposed to chronic unexpected mild stress (CUMS) might be reversed through swimming exercise.

Fascinatingly, swimming exercise prior to then in combination with restraint stress in the (Train-RS) group was able to reverse depression-like behaviors induced CRS. Thus, further evidence is necessary to explain the role of exercise in prevention of depression-like behaviors.

In the present study, the behavioral and cognitive aberrations observed with chronic restraint stress (CRS) were paralleled by biochemical alterations, including hippocampus and serum brain-derived neurotrophic factor (BDNF) levels dropped, but corticosterone, inflammatory markers, and oxidative stress levels all raised up.

The current study showed that (CRS) as a model of depression induction, increased serum corticosterone levels in Sed-RS group. These findings provide credence to the hypothesis that glucocorticoids play a significant role in stress and that chronic stress leads to persistent activation of the hypothalamic-pituitary-adrenal (HPX) axis. The significance of glucocorticoids in the stress response and the pathophysiology of depression is well-established [15].

Stressful events, especially prolonged constraint stress, have been demonstrated in numerous clinical and experimental research to dysregulate the HPA axis by interfering with this axis' negative feedback loop, leading to an excessive spike in blood corticosterone that may exacerbate brain damage[16].

On the other hand, analysis of the current data obtained from trained groups showed that swimming exercise was able to lower basal corticosterone levels in unstressed exercised rats (Train-C) group compared to unstressed unexercised (Sed-C) group.

These results were in accordance with **Koc** [17] who revealed that athletes' pre-exercise cortisol levels were lower than those of sedentary subjects.

The present work showed that moderate swimming exercise after the stress period did not affect serum corticosterone level in (RS-Train) group.

These data were in agreement with **Kwon *et al.*** [18] and **Safari *et al.*** [13], who justified the sustained elevation of corticosterone in (RS-Train) group by the persistence of the effects of the two stressors (CRS and exercise), which lasted for a reasonably long duration.

On the contrary, a study done by **Patki *et al.*** [19] demonstrated that corticosterone levels were significantly lowered but did not return to normal after exercise in a single-prolonged stress rat model. He went on to say that this is because of the disproportionately huge increase in corticosterone caused by stress (more than 100%), which may require more time spent exercising.

Further future research is recommended to clarify why swimming exercise did not lower corticosterone in stressed rats while doing so in unstressed rats.

Beserra *et al.* [20] suggested that differences in sampling times and diurnal cortisol rhythm changes, both of which are known to occur in people with MDD, may account for the conflicting findings.

In the current study, swimming training prior to then in combination with restraint stress in the (Train-RS) group was able to avoid marked stress-induced enhancement in corticosterone levels as compared to the (Sed-RS) group, which was an intriguing new finding from our study suggesting a protective effect of exercise.

This could be explained by the earlier findings showing that the exercise performed prior to stress lowered basal corticosterone level in addition to the longer exercise period in this group may also explain it, implying that the longer the duration of the exercises, the more efficient they are.

These results were in accordance with a study done by **Vollert *et al.*** [21] who reported that prior treadmill exercise prevented sleep deprivation-induced increase in corticosterone levels.

Regarding the effects of CRS on hippocampal BDNF levels, the current study showed that CRS for 21

days caused a significant decrease in hippocampal and serum BDNF in the (Sed-RS) group.

The results matched those of **Kwon *et al.* [18],** who reported downregulation of BDNF during and after CRS in the hippocampus.

There are several possible mechanisms that could explain the downregulation of BDNF by stress. Stress-induced adrenal glucocorticoids and activation of the HPA axis is one aspect of this. Additionally, neuroinflammation impacts the expression of BDNF [22].

Recent research has demonstrated that exercise increases BDNF levels in the hippocampi of experimental animals and in the serum of healthy persons [23].

Consistent with these results, the present investigation demonstrated that exercise swimming was able to elevate serum and hippocampus BDNF in the (Train-C) group.

Furthermore, swimming exercise reversed chronic restraint stress induced alteration in serum and hippocampal BDNF in (RS-Train) group and prevented prevent stress-induced reductions in serum and hippocampal BDNF in (Train-RS) group.

In agreement with **Yakhkeshi *et al.* [24]**, our results showed that, in contrast to hippocampal BDNF, serum BDNF levels were lower. However, the direction of small variations in serum BDNF mirrored those in hippocampal BDNF, as it cannot easily pass the blood brain barrier due to its high molecular weight.

Exercise-induced BDNF production enhances the size of the hippocampus, stimulates the activity of brain regions, and positively regulates neurogenesis-related pathways [25].

When compared to controls, the (Sed-RS) group's serum MDA levels and SOD enzyme activity were significantly reduced after 21 days of CRS, suggesting that chronic restraint stress increases oxidative stress.

In line with these findings, **Bajpai *et al.* [26]** study revealed higher serum MDA and significantly lower SOD in patients with major depression.

According to **Maes *et al.* [27]**, there is a positive correlation between the concentration of peripheral oxidative stress indicators and depression severity and duration.

Contrary to these findings, **Sarandol *et al.* [28]** noted that both serum MDA and SOD activity were considerably greater in the MDD group.

There is mounting evidence that certain diseases, including depression, may be characterized by a vicious and self-reinforcing signaling loop that includes oxidation and inflammation [29].

In the present study, results obtained from trained groups showed that swimming exercise in the Train-C group has been shown to enhance superoxide dismutase (SOD), but no significant differences were observed in MDA between sedentary or exercise only control rats.

In addition, after the stress period, moderate swimming exercise in the RS-Train group decreased MDA and elevated SOD. Demonstrating that exercise training was effective at reducing the oxidative damage that stress causes.

In line with these findings, **Salim *et al.* [30]** looked into the impact of moderate treadmill exercise on buthionine sulfoximine (BSO)-induced oxidative stress in rats found that exercise may have a role in boosting antioxidant enzyme activity and decreasing levels of stress hormones in the brain.

The current work revealed that moderate swimming exercise prior to then in combination with restraint stress prevented CRS-induced oxidative stress in (Train- RS) group suggesting a protective effect of exercise.

By activating the peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a) pathway, exercise protects against stress-induced oxidative damage by boosting the synthesis of antioxidant enzymes. When PGC1 is turned on, a number of processes improve, including mitochondrial biogenesis and fatty acid oxidation [22].

Inflammation is one proposed mechanism connecting prolonged stress to health problems[31]. As regard the effects of chronic restraint stress on inflammatory markers, our data showed increased concentrations of serum TNF-α, CRP and IL-6 in the Sed-RS group compared to other groups.

Parallel evidence demonstrates that Clinical data supports an increased tendency for pro-inflammatory markers in people with depression (increased IL-6, TNF-α, and CRP) compared to controls in the general population [32].

The current work revealed that moderate swimming exercise in stressed animals, reduced serum IL-6, TNF-α, and CRP in RS-Train group.

Supporting this finding, **Li *et al.*[33]** investigated effects of exercise training on serum proinflammatory Cytokines in hypertensive rats and noticed significant reduction in TNF-α, IL-6 after exercise training.

Contrary to these findings, **Schuch *et al.* [34]** observed no significant acute or chronic adaptation on any inflammatory marker in participants with MDD following exercise training.

Exercise's anti-inflammatory benefits may be mediated through a release of IL-6 from contracting skeletal muscle after each acute bout of exercise which has immuno-regulatory functions [35].

In this line, histopathological examination of hippocampus was done for exploring further mechanisms at tissue levels. The result showed signs of neuronal damage in hippocampus of Sed-RS group. These findings confirmed those of **Chandrasekhar *et al.* [35]**, who observed neuronal apoptosis in the hippocampus following CRS.

We could return that to the high levels of glucocorticoids that have been hypothesized to be associated with the hippocampus damage in depression [15].

In present study moderate swimming exercise treatment in the RS-Train group after the stress period partially alleviated this damage but cannot completely reverse it. When compared to the control group, however, damage was uncommon in the Train-RS group.

Suggesting that moderate swimming exercise may help to prevent stress-induced hippocampus damage or at least lessen the effects of already present depression or stress-related hippocampus degeneration.

The positive effects of moderate swimming exercise on hippocampal volume are mediated by BDNF induction, which is connected to hippocampal neurogenesis [23].

CONCLUSION

In conclusion, our results revealed that exposure to chronic stress induced depressive behaviors. Swimming exercise training performed after the stress period, in turn, has a moderate effect in mitigating these damages. This impact, however, is amplified when swimming exercise is conducted prior to then in combination with restraint stress. We can conclude that exercise has a preventative impact against chronic restraint stress induced behavioral and biochemical abnormalities.

Sponsoring financially: Nil.
Competing interests: Nil.

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