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Research Article

Citalopram and physical Exercise for the Prevention of Stress-Induced Dysfunction in Male Wistar Rats

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ABSTRACT

Objectives: Learning is essential for nearly all aspects of human behavior and perception. Among the factors that can disrupt learning and memory, stress is particularly significant, as it interferes with cognitive functioning and overall well-being. The present study aimed to evaluate and compare the effects of citalopram, treadmill-based aerobic exercise, and swimming on learning and memory performance in male Wistar rats exposed to stress.

Methods: To assess these interventions, animals were subjected to immobility stress, moderate-intensity treadmill running, swimming exercise, or citalopram administration (10 mg/kg body weight for four weeks), as well as various combinations of these interventions under stressed and non-stressed conditions, but citalopram was assessed in the presence of stress. The Morris water maze test was used to assess cognitive performance, particularly by measuring the distance traveled to reach the hidden platform.

Results: The results revealed that stress negatively impacted learning and memory. However, both forms of exercise alleviated stress-induced cognitive impairments, with swimming showing especially beneficial effects in enhancing learning and memory among stressed rats.

Conclusion: Contrary to expectations, administration of citalopram did not prevent stress-induced cognitive dysfunction. However, the beneficial effects of both forms of exercise were evident during the acquisition phase. Notably, physical exercise—particularly swimming—may serve as a potential non-pharmacological substitute, as its cognitive effects under stress differed significantly from those of treadmill training in the presence of citalopram.

Keywords: Citalopram; Immobility stress; Learning and Memory; Swimming; Treadmill.

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Introduction

Learning is a fundamental and unavoidable aspect of life, defined as the capacity to modify behavior based on experience and memory. Various forms of stress have been identified as critical factors influencing the processes of acquisition and learning (1). Stress—conceptualized as any threat to an organism's homeostasis—may be either real or perceived, and can stem from physical or psychosocial sources (2). It has been shown to disrupt memory, modulate neural circuitry, and affect both neural replay mechanisms and behavior (3).

Several studies have examined both pharmacological and non-pharmacological approaches to stress management (4), demonstrating that physical activity can effectively alleviate stress-related disorders and enhance mood, cognitive function, and self-concept (5). These findings underscore the rehabilitative role of aerobic exercise in improving learning efficiency and suggest its therapeutic potential for memory-related central nervous system disorders (6).

Chronic stress in animal models has been linked to memory impairment, and physical exercise has shown both preventive and therapeutic effects in mitigating stress-induced cognitive deficits (7). Prior studies have compared the impact of various exercise regimens on learning and cognition, adopting different intensities, durations, and behavioral assessments (8). Notably, recent evidence suggests that moderate-intensity exercise yields the most beneficial effects on memory performance, indicating that high-intensity exertion may not be necessary to achieve measurable cognitive improvement (9).

Findings on the impact of anti-stress and antidepressant medications—particularly Selective Serotonin Reuptake Inhibitors (SSRIs) like citalopram—on learning and memory remain inconclusive. Some studies support the hypothesis that acute administration of SSRIs or citalopram may impair certain forms of learning (10). In contrast, research by Zhang *et al*. revealed that citalopram significantly increased the density of parvalbumin (PV)-positive neurons in the cortex of APP/PS1 transgenic mice, without inducing changes in hippocampal structure. This neural modulation was associated with enhanced behavioral performance, leading the authors to propose that citalopram may be a promising candidate for early intervention in neurodegenerative disorders such as Alzheimer's disease (11).

Given the heterogeneous findings in previous studies, there remains a need for well-controlled investigations to address unresolved questions in this field. Accordingly, the present study aimed to evaluate both the main and interactive effects of pharmacological and non-pharmacological interventions in modulating stress-induced outcomes. Specifically, it compared the impact of citalopram administration, treadmill exercise, and swimming on learning and memory performance in male Wistar rats exposed to stress.

Materials and methods

Ethical Approval

All experimental procedures involving animals were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, revised 1996), and were approved by the Ethics Committee of the Pasteur Institute of Iran.

Animals

Forty-two male Albino Wistar rats (n = 42), weighing between 200 and 250 g, were obtained from the Pasteur Institute of Iran. The animals were housed in groups of five per Plexiglas cage under standard laboratory conditions (temperature: 22 ± 2 °C; humidity: 60–65%) with a 12-hour light/dark cycle (lights on at 7:00 AM). Food and water were provided ad libitum. Prior to the commencement of experimental procedures, all subjects underwent a one-week acclimatization period in the animal facility. To ensure uniform baseline physical activity, rats were housed in polycarbonate containers offering equivalent spatial conditions.

After a one-week acclimatization period in the colony room, all 42 male Wistar rats were randomly assigned to seven experimental groups (n = 6 per group). The groups were categorized as follows: Control (Stress-Free), Stress Only, Treadmill Exercise (No Stress), Swimming Exercise (No Stress), Treadmill Exercise + Stress, Swimming Exercise + Stress, Citalopram Treatment + Stress. This grouping allowed for evaluation of both independent and interactive effects of pharmacological treatment and physical exercise under stressful and non-stressful conditions.

Stress induction

To induce immobility stress, the animals were positioned in an inverted orientation within plastic restraint devices for 2 hours daily for one week. This procedure was designed to activate the hypothalamic-pituitary-adrenal (HPA) axis. Stress exposure continued until the day preceding the onset of the acquisition phase of the Morris water maze test. The acquisition phase commenced on the first day of the eighth week (i.e., day 50 of the experimental timeline).

Treadmill Exercise

A six-lane motorized rodent treadmill was employed for the exercise training protocol. All animals designated for training underwent a two-day acclimation period to the treadmill, running for 10 minutes per day—initially at 5 m/min on the first day and 8 m/min on the second (12). During the first week of training, rats participated in introductory aerobic sessions that included walking

and running on the rotating belt at speeds ranging from 8 to 10 m/min for 10 to 30 minutes. Specifically, all rats began running at 8 m/min for 10 minutes, with the speed and duration gradually increased to 10 m/min for 30 minutes by the end of the week. To minimize additional physiological or psychological stress, a moderate-intensity training regimen was adopted—guided by prior studies emphasizing low to moderate exercise loads in rodents (13). Beginning in the second week, the structured treadmill protocol consisted of three 10-minute segments per session: First 10 min: 10 m/min, second 10 min: 13 m/min, third 10 min: 16 m/min. Training sessions were conducted three times per week over a four-week period. Mild electric shocks were used as a motivator to encourage consistent running behavior. After each session, rats were returned to their home cages with ad libitum access to food and water. Upon completion of the four-week treadmill regimen, the Morris Water Maze test was initiated on day 50 of the study.

Swimming exercise

Water temperature was maintained at 32 ± 2 °C throughout the swimming exercise sessions. During the initial practice session, rats were placed in a water tank for 10 minutes. Over the course of six days, the duration was gradually increased to 60 minutes to promote acclimation. Following this familiarization phase, the main training protocol was implemented across a four-week period. Rats underwent regular swimming sessions three times per week, with each session lasting one hour. Upon completion of the four-week training period, the acquisition phase of the Morris Water Maze test commenced on day 50 of the experimental timeline.

Citalopram Injection

Citalopram Hydrobromide (Novin Kavosh Mamatir Co., Iran) was dissolved in 0.9% (w/v) isotonic saline and administered intraperitoneally (i.p.) at a dosage of 10 mg/kg body weight, as previously described (14). This pharmacological intervention was applied alongside stress exposure for four weeks. On day 50 of the experimental timeline, the acquisition phase of the Morris Water Maze test was initiated to evaluate spatial learning performance. Figure 1 presents a visual overview of the experimental design.

Behavioral tests

The learning ability and memory capacity of each experimental group were assessed using the Morris Water Maze following the completion of the four-week exercise and pharmacological intervention protocols. Behavioral testing was conducted between 9:00 A.M. and 12:00 P.M. to minimize circadian variability.

Morris water maze

The Morris Water Maze (MWM) task was conducted in a circular black tub (diameter: 136 cm; depth: 60 cm) filled with water to a depth of 25 cm, maintained at 20 ± 1 °C. The escape platform consisted of clear Plexiglas (diameter: 10 cm) and was submerged 1.5 cm below the water's surface to remain hidden from view. An infrared camera was mounted centrally above the tank, and each rat was equipped with an infrared LED, enabling automated tracking of movement via computer-based video analysis. Behavioral testing included four trials per day over four consecutive acquisition sessions. In each trial, the rat was placed into the pool facing the tank wall. Starting positions were randomized across four compass directions (north, east, south, and west), with each position used once per session. The hidden platform remained fixed in the southwest quadrant throughout testing. A trial concluded either when the rat successfully located and climbed onto the platform or after 90 seconds had elapsed. Following each successful trial, the rat was permitted to rest on the platform for 20 seconds before being removed and prepared for the subsequent trial.

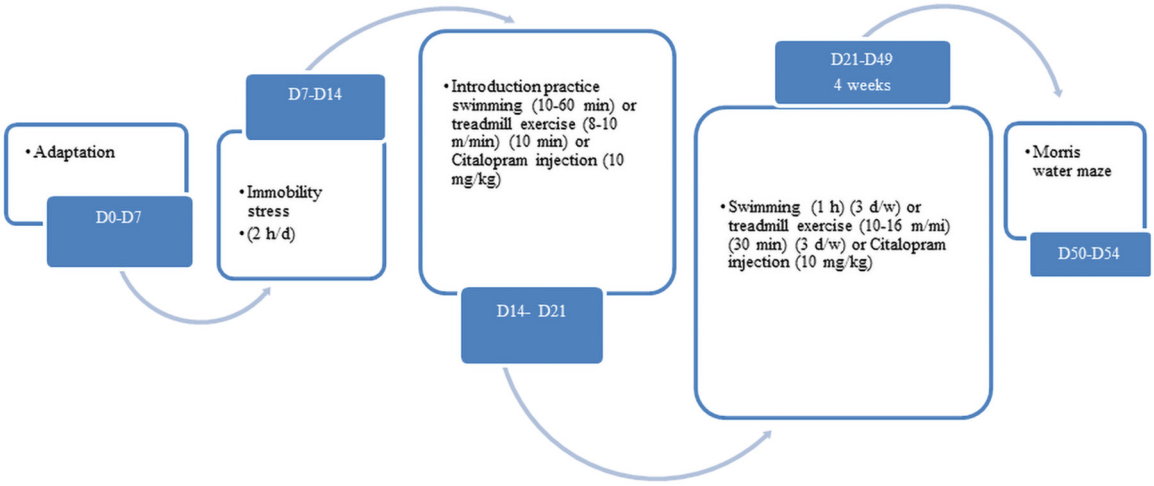

Figure 1. The diagram of all experiment processes.

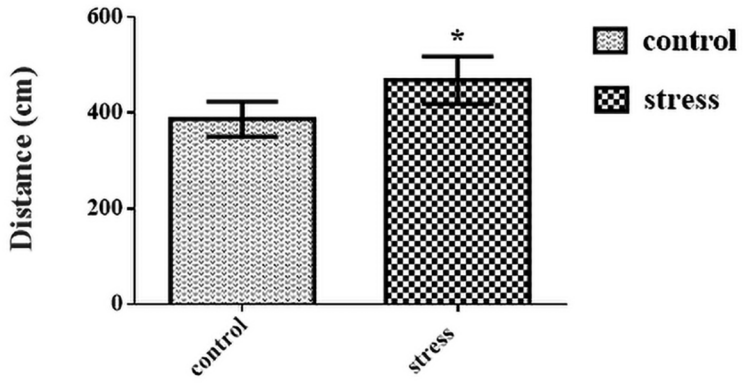

Figure 2. Effect of immobilization stress on MWM performance. (A) Average distance traveled to reach the hidden platform. All data are presented as mean ± standard deviation (SD). $P < 0.05$ indicates a statistically significant difference between the stress group and the control group.

Rats that failed to locate the hidden platform within 90 seconds were gently guided onto the platform by the experimenter and remained there for 20 seconds to reinforce spatial encoding. Following the completion of the fourth trial, each rat was dried with a towel, kept warm for one hour, and then returned to its home cage. The trajectory of each rat during every trial was recorded automatically using a computer-based video-tracking system (EthoVision 1.6; Noldus Information Technology, Wageningen, Netherlands), enabling the analysis of behavioral parameters such as escape latency, path length, and swimming speed. Behavioral assessments were conducted immediately following the four-week intervention period to evaluate spatial learning and memory using the Morris Water Maze. The acquisition phase was carried out over four consecutive days. On day five, a probe test was administered to assess memory retention. During this test, the platform was removed, and rats were allowed to swim freely for 60 seconds. Key metrics evaluated included the time spent in the target quadrant, the number of entries into the target quadrant, and the number of entries into the quadrant opposite the target.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 22). A one-way repeated measures ANOVA was employed to compare learning and memory performance across experimental groups: stress, stress + swimming, stress + treadmill, and stress + citalopram. Additionally, independent samples t-tests were used to evaluate the individual effects of stress exposure, swimming exercise, treadmill training, and citalopram administration on spatial memory outcomes. To examine post hoc differences and interaction effects among the groups, Tukey's Honestly Significant Difference (HSD) test was applied. All statistically significant findings (defined as $P<0.05$) were further analyzed and visualized using GraphPad Prism 10 software. In all figures, error bars represent the mean ± standard deviation (SD).

Results

The effects of inactive stress on learning and memory

Acquisition Test

To evaluate the impact of chronic stress on spatial learning and memory, restraint stress was applied for four weeks prior to behavioral testing using MWM. The stress-exposed group demonstrated a significant increase in the distance traveled to locate the hidden platform compared to the control group, with a 21% increase observed ($P = 0.043$; Fig. 2). This finding suggests that stress impairs spatial navigation efficiency, potentially reflecting deficits in learning and memory performance.

Probe Test

During the probe phase of the MWM task, no statistically significant differences were observed between the control and stress groups across spatial memory parameters ($P > 0.05$, data not shown).

The effects of physical exercise on learning and memory

Acquisition Test

To investigate the effects of physical activity on spatial learning and memory, swimming and treadmill exercise protocols were implemented over a four-week period. Behavioral performance was assessed using the MWM. Following treadmill training, rats exhibited a 31% increase in the average distance traveled to reach the hidden platform compared to controls; however, this change did not reach statistical significance ($P = 0.064$; Fig. 3A). In contrast, swimming exercise unexpectedly impeded spatial learning, as evidenced by a 17% increase in distance traveled, which was statistically significant ($P = 0.046$; Fig. 3B). These findings suggest that, under the specific experimental conditions used in this study, moderate treadmill exercise had no adverse effects, whereas swimming may have transiently slowed acquisition in the MWM task.

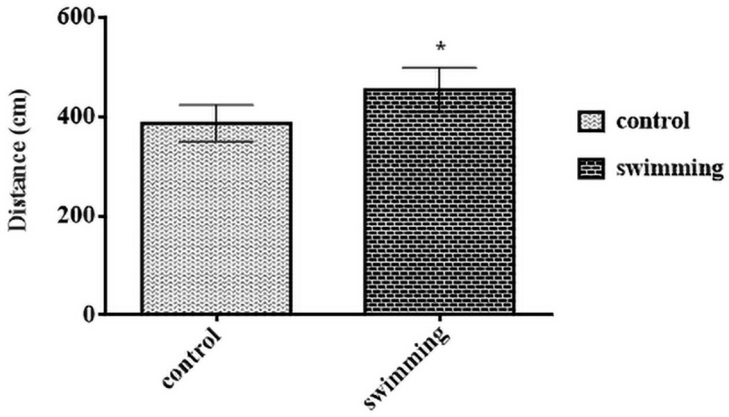

Figure 3. Effects of treadmill and swimming training on MWM performance. (A) Average distance traveled by the treadmill exercise group during the acquisition phase. (B) Average distance traveled by the swimming exercise group during the acquisition phase. Data are presented as mean ± standard deviation (SD). $P < 0.05$ indicates a statistically significant difference between the swimming group and the control group.

Probe test

During the probe phase of the MWM, no significant differences were found between the treadmill or swimming exercise groups and the control group regarding spatial memory measures (data not shown). These findings suggest that, while both exercise modalities may counteract stress-induced impairments during the acquisition phase, they did not produce measurable enhancements in memory retention under non-stress conditions.

The effect of citalopram on learning and memory in rats under stress

Acquisition test

To assess the cognitive effects of pharmacological intervention, citalopram was administered to stressed rats over a four-week period. Our results suggested that citalopram did not effectively counteract stress-induced learning impairments under the conditions of this study.

Probe test

There was no statistically significant difference between the stress-only group and the citalopram-treated group in terms of the percentage of time spent in the target quadrant during the probe trial. The number of entries into both the target quadrant and the quadrant opposite the target did not differ significantly between the two groups ($P > 0.05$). These results suggest that citalopram administration did not produce measurable improvements in spatial memory retention under stress conditions (data not shown).

The effects of citalopram and physical exercise on learning and memory after the application of stress

Acquisition test

Four experimental groups of rats subjected to immobilization stress were assessed for spatial learning and memory performance using the MWM during a four-day acquisition phase following completion of exercise and pharmacological intervention protocols. Results revealed that the swimming training group exhibited a 35% reduction in the distance traveled to reach the hidden platform compared to the stress-only group, a difference that reached statistical significance (Fig. 4A). Additionally, comparison between the citalopram-treated group and the exercise groups demonstrated significantly enhanced performance in the latter: the swimming group showed a 43% reduction and the treadmill group a 27% reduction in travel distance relative to the citalopram group (Fig. 4A). When evaluating the average escape latency under stress conditions, a significant difference was observed only between the stress + swimming group and the stress + citalopram group, suggesting superior spatial learning performance in rats subjected to swimming exercise (Fig. 4B).

Probe test

As shown in Figure 4C, there was no statistically significant difference among the stress-exposed groups in the percentage of time spent in the target quadrant during the probe trial. Similarly, Figure 4D indicates no significant difference in the frequency of entries into the target quadrant or the quadrant opposite the target across groups ($P > 0.05$). These results suggest that, despite variations in intervention protocols, the tested treatments did not yield measurable improvements in memory retention under stress conditions using these specific spatial metrics.

Discussion

Stress on learning and memory

Based on the findings of this study, immobility stress significantly impaired learning performance, as evidenced by increased distance traveled to locate the

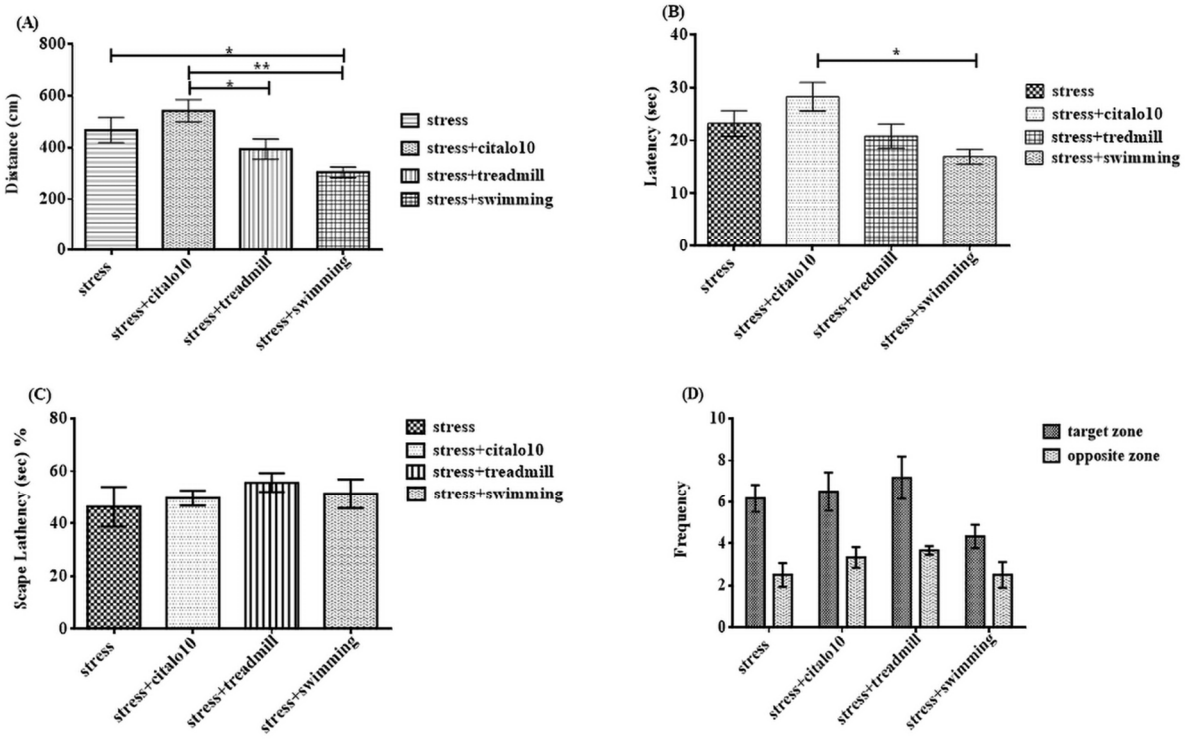

Figure 4. Effects of citalopram administration and physical exercise (swimming and treadmill) on spatial learning and memory performance following stress exposure in rats, as assessed by the MWM. (A) Average distance traveled to reach the hidden platform during acquisition trials. (B) Escape latency (time taken to reach the platform). (C) Percentage of time spent in the target quadrant during the probe trial. (D) Frequency of entries into the target quadrant and the quadrant opposite the target. All data are presented as mean ± standard deviation (SD). $P < 0.001$ indicates a statistically significant difference between the swimming + stress group and the citalopram + stress group. $P < 0.05$ denotes statistically significant differences between the swimming + stress group and: – the stress-only group – the treadmill + stress group – the citalopram + stress group.

hidden platform in the MWM. This behavioral deficit may be attributed to stress-induced changes in brain structure, particularly within the hippocampus, which contains a dense concentration of glucocorticoid receptors. Chronic exposure to adrenal stress hormones has been shown to alter hippocampal architecture—resulting in neurochemical shifts, increased irritability, reduced neurogenesis, disrupted neuronal morphology, and even cellular degeneration (15). Despite this, the literature presents conflicting outcomes regarding the impact of pre-learning stress. Some studies report facilitative effects on learning and memory (16), while others note impairments in hippocampal-dependent functions (17). Brown et al. (2020) recently offered mechanistic insight, suggesting that stress can dysregulate memory control circuitry, disrupt route planning via altered neural replay, and lead to inefficient behavior (3). These findings underscore that stress does not inherently exert beneficial or detrimental effects on cognition; its impact may depend on factors such as duration, severity, and individual susceptibility.

Stress responses involve a complex interplay of physiological mechanisms and mediators, and their impact on spatial learning and memory can vary depending on multiple factors. Numerous studies employing the MWM) have reported divergent effects of chronic stress, often influenced by the nature, duration, and severity of the stressors applied. For instance, prolonged or severe stress—such as five months of unstable maintenance conditions (18), one month of unpredictable stress (19), and restricted mobility for 7 or 21 days (17) — has been shown to impair learning. In contrast, milder or shorter stress exposure — such as 21 days of continuous light (16), 10 days of unexpected stress (20), or a recovery period following stress (19) — has been associated with improved or unaffected learning. Interestingly, chronic motor stress (6 hours/day for 21 days) appeared to have no measurable effect on MWM performance (17), further highlighting the nuanced role of stressor type and intensity. These discrepancies may reflect differences in stress severity; for example, light exposure or short-term restriction might be less effect than long-term confinement or environmental instability. Additionally, strain-specific responses may influence behavioral outcomes. For example, Moosavi et al. (2007) reported learning impairments in Wistar rats after three weeks of immobilization stress (21), whereas studies involving other strains found no such deficits (22). Thus, genetic background likely contributes to variability in stress reactivity and cognitive performance. Therefore,

these inconsistencies point to the multifactorial nature of stress effects on spatial memory.

Physical exercise on learning and memory

In the present study, four weeks of moderate-intensity aerobic exercise using a treadmill did not yield statistically significant improvements in learning and memory performance, as measured by the Morris Water Maze. Contrary to expectations, swimming exercise appeared to attenuate the learning process, reflected by an increased average distance traveled to locate the hidden platform. Furthermore, no significant differences were detected in this group regarding escape latency, swimming speed, or memory retention outcomes during probe trials compared to the control group.

Several studies have reported that both voluntary and compulsory physical exercise enhance synaptic plasticity in the hippocampus and improve spatial learning (8). However, discrepancies among findings may stem from variations in exercise duration, intensity, and protocol design. Moreover, the type of behavioral test used to assess learning and memory also appears to influence results (23). For example, Van Praag *et al*. (1999) observed significant improvements in spatial learning after 2–3 months of voluntary exercise (24), while Anderson et al. (2000) reported enhanced performance in the radial arm maze following 7 weeks of voluntary wheel running (25). Additional research demonstrated improvements in Morris Water Maze performance after just one week of voluntary exercise in younger animals (26). These findings suggest that voluntary exercise, particularly over longer durations, may effectively support learning and memory. In contrast, compulsory exercise—often associated with external stress—has been hypothesized to produce less favorable cognitive outcomes. However, this assumption remains debatable. For instance, gentle treadmill training has been shown to improve spatial learning in aged rodents (27), suggesting that the degree of stress imposed by exercise might modulate its cognitive benefits. A recent systematic review of 107 studies emphasized the rehabilitative effects of aerobic exercise on nervous system function, highlighting its role in improving learning efficiency and in the potential treatment of memory-related disorders in the central nervous system (6). Similarly, Loprinzi and Frith (2019) found that chronic aerobic exercise may exert both preventive and therapeutic effects on stress-related memory impairments in animal models (7). Nonetheless, some studies have reported no significant effects of physical exercise on memory performance (8). These inconsistencies may reflect differences in experimental designs, including the type of cognitive test employed, the age and developmental stage of the subjects, and the intensity and duration of the exercise protocols. Importantly, variations in exercise load may differentially influence neural plasticity and cognitive outcomes (7).

Citalopram on learning and memory

Based on the findings of the present study, citalopram administration did not alleviate stress-induced cognitive deficits and appeared to further slow the learning process. Although the citalopram-treated group exhibited increased average escape latency and distance traveled to reach the hidden platform, these changes were not statistically significant compared to the stress-only group across the full acquisition phase. Notably, a significant difference emerged on the second day of testing, with the citalopram group showing longer escape latencies and greater distances than the stress group. This suggests a transient decline in spatial learning efficiency in response to citalopram treatment under stress conditions.

Previous research on the cognitive effects of anti-stress and antidepressant drugs has yielded inconclusive findings, particularly regarding selective serotonin reuptake inhibitors (SSRIs) such as citalopram and fluoxetine. Some studies have reported that SSRIs can disrupt various forms of learning when administered acutely or via injection (28). For example, acute administration of citalopram was associated with learning deficits in certain behavioral paradigms. In contrast, fluoxetine appeared to have a more nuanced effect. Acute fluoxetine treatment did not impair inhibitory learning, whereas chronic administration resulted in memory impairments in the same task among rats (29). These conflicting outcomes underscore the importance of treatment duration, task type, and experimental model in determining the impact of pharmacological agents on learning and memory.

Citalopram's effects on memory performance appear to vary depending on experimental context and dosage. For instance, Archer *et al*. (1984) reported memory impairments at higher doses (10 and 20 mg/kg) in rats during the active avoidance task (30), while lower doses (1 and 3 mg/kg) showed no such effect in the inhibitory avoidance test. Meanwhile, Zhang *et al*. (2018) demonstrated that citalopram significantly increased the number of PV-positive neurons in the cortex of APP/PS1 mice (31), potentially enhancing behavioral performance without affecting hippocampal structure—suggesting its therapeutic relevance for early-stage Alzheimer's disease. Some studies further support the benefits of low-dose citalopram in ameliorating memory deficits and impaired consciousness (14). These conflicting findings may be attributed to differences in dosage, administration route, species and sex of animals, test design, and experimental conditions. In the present study, however, citalopram administration did not mitigate the cognitive deficits induced by stress. On the contrary, it led to increased escape latency and distance traveled in the Morris Water Maze compared to both swimming + stress and treadmill + stress groups—indicating a statistically significant difference in learning performance. These findings raise concerns

about the potential adverse cognitive side effects of SSRIs, especially in vulnerable populations such as older adults and individuals with neurodegenerative conditions. Careful consideration of dosage, treatment duration, and individual patient profiles is warranted when using SSRIs for mood disorders, stress-related dysfunction, and Alzheimer's disease. Future research should continue to investigate both the neurobiological mechanisms and therapeutic boundaries of citalopram in cognitive modulation.

Physical exercise after stress on learning and memory

In this study, the treadmill-based aerobic exercise group under stress conditions showed a modest reduction in average escape latency and distance traveled to locate the hidden platform during the acquisition phase compared to the stress-only group. However, these differences did not reach statistical significance. Similarly, during the probe trial, although the treadmill group spent more time in the target quadrant, this increase was not statistically significant. In contrast, the swimming training group demonstrated a notable improvement in learning performance. Specifically, this group exhibited a statistically significant reduction in the average distance traveled to reach the platform compared to the stress group during the acquisition phase. Despite an increased duration spent in the target quadrant during the probe test, no significant differences were observed between groups for this measure.

Contrary to the findings of the present study, Kim *et al*. (2011) did not observe a significant difference between stress-only and stress-plus-exercise groups (32). Notably, their exercise protocol involved a longer duration (eight weeks of treadmill running) and higher intensity than the intervention used in this study. This may account for the divergent outcomes, as previous research suggests that the activity of the hypothalamic-pituitary-adrenal (HPA) axis gradually increases with extended training duration—rising notably between 9 and 24 days (33). Thus, elevated corticosterone levels may be linked to the length and intensity of the exercise protocol. Despite these complexities, it appears that restoration of stress-impaired learning and spatial memory may depend on appropriate physical activity. Corticosteroids may act as mediators of exercise's protective effects against stress-related cognitive dysfunction. Additional neurobiological mechanisms proposed include enhanced neurogenesis, increased expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (34), and improved synaptic strength through long-term potentiation (LTP) (24). LTP is broadly considered a key substrate for memory formation and consolidation, potentially involving the remodeling of dendritic spines and neuronal connectivity (35).

Authors' Contributions

NN conceptualized and designed the research. NN and MDS carried out the experimental procedures. Data analysis was performed by MDS, AM, NN, RH, and HGZ. The manuscript was drafted by MDS and AM. All authors reviewed, revised, and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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