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RESEARCH ARTICLE

Swimming exercise on spatial memory performance and hippocampal oxidative stress in colchicine-induced memory-impaired male Long-Evans rats

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Abstract

Background: Spatial memory is one of the necessary components of our typical day-to-day life. Therefore, its impairment should be alleviated or prevented. The purpose of this study was to assess the effects of swimming exercise on spatial memory performance and hippocampal oxidative stress in male Long-Evans rats with colchicine-induced memory impairment.

Methods: Thirty male aged 8 standard deviation (2) weeks; weight 225 (75) gm Long-Evans rats were assigned to normal control, sham control, colchicine control, pre colchicine swimming exercise and post colchicine swimming exercise groups. A memory-impaired rat model was established by administering colchicine intrahippocampally. Swimming exercise was performed before and after spatial memory impairment. For spatial reference and working memory performance evaluation, the Morris water maze test was used. Hippocampal malondialdehyde and glutathione peroxidase were estimated for oxidative stress assessment in all rats.

Results: Intrahippocampal colchicine administration significantly impaired spatial memory, and elevated malondialdehyde, decreased glutathione peroxidase level in the hippocampus of colchicine control rats. In contrast, both pre- and post-treatment with swimming exercise significantly improved learning and spatial memory retention and attenuated oxidative damage to nearly normal levels.

Conclusion: Swimming exercise prevents as well as alleviates colchicine-induced spatial memory impairment along with hippocampal oxidative stress in male Long-Evans rats. Moreover, this swimming exercise schedule is sufficient to reverse these alarming consequences to almost normal.

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Key messages

Intrahippocampal colchicine impaired spatial memory as well as increased hippocampal oxidative stress in male Long-Evans rats. Swimming exercise may be equally effective in preventing and alleviating colchicine-induced spatial memory impairment, along with hippocampal oxidative stress, thereby returning it to nearly normal levels.

Introduction

Memory refers to the processes by which any learned knowledge is encoded, stored, and later retrieved [1]. In it, spatial memory plays a crucial role in helping us navigate and find our way to a specific destination [2]. According to WHO, currently, more than 55 million people have dementia worldwide [3] and spatial memory impairment is one of the critical components of dementia. Physical inactivity, a sedentary lifestyle, and a stressful lifestyle are linked with spatial memory impairment and many clinical conditions [4].

Currently, the long-term memory is known as reference memory (RM) [5]. Here, the information available for solving RM tasks remains constant throughout the trials and is reinforced by repeated training [6]. On the other hand, working memory (WM) is a form of short-term memory that retains information for a short period, usually while an individual plans an action based on it [7]. Both of these memories depend on the hippocampus, the most medial portion of the temporal lobe cortex. Neurodegeneration of the hippocampus can lead to memory impairment, and oxidative stress is one of the proposed mechanisms underlying this neurodegeneration [8]. Oxidative stress is caused by reactive oxygen species, which are part of a group of molecules called free radicals, and leads to cell injury [9]. Malondialdehyde (MDA), an end product of lipid peroxidation, is commonly measured as an indirect index of oxidative stress [10]. Superoxide dismutase, glutathione peroxidase (GPx) play a crucial role against oxidative injury as scavengers [9].

Physical exercises such as swimming exercise (SwE) that use oxygen more efficiently, [11] would be a good alternative for improving memory and reducing oxidative stress [12,13]. Reduction of oxidative stress and neuroinflammation, [14,15] as well as an increase in brain-derived neurotrophic factor [16] and choline acetyltransferase activity [17] in the hippocampus, are the suggested mechanisms for memory improvement by SwE. Therefore, SwE was applied either before [14] or after [18] or during [15] the brain damage in different experimental models. Various time schedules of SwE for 28 or 90 days [14,15,18] were applied in several studies.

The beneficial effects of SwE on memory impairment, as well as oxidative stress, before or after hippocampal damage remained unresolved [18]. However, the volume of information regarding the effects of SwE on memory impairment and oxidative stress is not enough for reaching any final inference. The present study has been designed to examine the effects of SwE on memory performance, as well as hippocampal oxidative stress markers, before and after colchicine-induced spatial memory impairment in male Long-Evans rats.

Methods

The experimental design

This experimental study was conducted at the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March 2023 to February 2024. The sampling technique was purposive. Here, the specified difference between the two means was compared to test the null hypothesis. So the formula, $n = [(u + v)^2 X (\sigma 12 + \sigma 22)] / (\mu 1 - \mu 2)^2$, involving effect size was used to calculate the intended sample size for a group [19]. We used mean and standard deviation of 'escape latency in reference memory' version of the Morris Water Maze test, stated by Raghavendra *et al.* (2013) [20]. Thus, we used 30 rats.

Procurement and maintenance of animals

A total of 30 male Long-Evans rats aged 8 (standard deviation 2) weeks; weight 225 (75) gm were collected from the central animal house of BSMMU and were housed in standard laboratory environments (temperature: 27°C, 12/12 hour light-dark cycle). The rats were provided with free access to standard laboratory food [21] and cooled boiled water ad libitum. All the experiments were conducted according to the 'Guidelines for the Animal Experimentation Ethics Committee (AEEC, 15 May 2023) of the International Centre for Diarrhoeal Disease Research, Bangladesh and the advice of an expert veterinarian. All the experiments were performed during the daytime between 08:00 and 16:00 hours.

Experimental design and dose schedule

Rats were randomly divided into 5 groups (6 rats/group):

- Normal control (NC): No stereotaxic surgery (SS) + no normal saline (NS) + no swimming exercise (no SwE).
- Sham control (SC): SS + hippocampal infusion of 1 µl NS + no SwE.
- Colchicine control (ColC): SS + hippocampal infusion of 15 µg of colchicine in 1µl NS + no SwE.
- Pre colchicine swimming exercise (Pre-SwE Exp): SwE for 28 days followed by SS + hippocampal infusion of 15 µg of colchicine in 1µl NS.
- Post colchicine swimming exercise (Post-SwE Exp): SS + hippocampal infusion of 15 µg of colchicine in 1µl NS followed by SwE for 28 days.

Swimming exercise protocol [14]

SwE was performed in a circular pool (150 cm X 50 cm) for 28 days in rats of Pre-SwE Exp and Post-SwE Exp groups. Treatment was conducted five days a week. During the initial two days, SwE was started at 10 minutes per day and gradually increased by 10 minutes every two days until reaching 1 hour per day by the 12th day. From that moment onward, training continued at a rate of one hour per day until day 26.

Hippocampal colchicine application by SS

According to previous research, [22-24] colchicine (Incepta Pharmaceuticals Ltd, Bangladesh) was administered into the rat hippocampus by SS. Each rat was deeply anesthetised with thiopental sodium (45 mg/kg, i.p.) and positioned in a stereotaxic apparatus (BioMed Easy Technologies Co., Ltd.). The scalp was incised and retracted. The rat was infused through a Hamilton microsyringe with 15 µg of colchicine in 1 µL of NS in each hippocampus. Controls that received the vehicle injection were utilised. The coordinates

were -3.6 mm anterior-posterior, ±2 mm lateral-medial, and -3.4 mm dorso-ventral relative to bregma. All intra-hippocampal applications of colchicine and/or NS were infused very slowly over 1 minute, and the micro syringe was kept in place for the next minute before being slowly withdrawn. Gentamicin (5 mg/kg, i.p.) was administered postoperatively to prevent sepsis.

Spatial memory assessment by MWM test

Test tools and circumstances [25-27]

MWM was a large circular pool (150 cm x 50 cm) filled to a depth of 30 cm with water at 24 to 26 °C. This pool was arbitrarily divided into four quadrants: north-west (NW), north-east (NE), south-east (SE) and south-west (SW). A round platform (15 cm × 28 cm) was placed at the center of one quadrant, with its top 2 cm below the water's surface, and served as the only escape route for the rats from the water. To determine the start locations, eight points —north (N), south (S), east (E), west (W), northeast (NE), northwest (NW), southeast (SE), and southwest (SW) of MWM — were labelled. To prevent visual clues in the pool, the entire inner wall of the pool and platform was painted with a non-toxic black color. The pool was placed in a room containing extra maze cues that rats could use to assist them in navigating. Two distinct testing paradigms were sequentially employed to assess reference and working memory skills, as illustrated in the **Supplementary file**.

Reference memory test

The rats swam without a platform for 3 minutes over three consecutive days to acclimatise and habituate themselves to the reference memory version. Then, during the acquisition phase, all rats underwent four trials each day for six consecutive days, with the platform consistently placed in the NE quadrant. In every trial, the rats were released from different starting points in a predetermined sequence each day and given 60 seconds to locate the platform and climb onto it. A 50-second inter-trial time (20 seconds on the platform and 30 seconds for self-drying) was allowed. The time taken for the rat to find the platform, also known as the mean escape latency (EL), was measured using a stopwatch to assess the rat's learning ability. On the first trial each day, the rats found the platform by chance, which served as the information stage. The subsequent trials necessitated matching to the new position each day, as the platform remained in the same place for 6 days. The average EL of the 5th and 6th acquisition days was measured to assess memory consolidation. Approximately 24 hours after the last trial on day 6, the platform was removed from the pool, and a final spatial probe trial was conducted to assess the strength of learning and retrieval. In this probe trial, rats swam freely for 60 sec during which target crossings (TC; number of passing the quadrant made by rats within 60 sec after the platform was removed) and time spent in target (TT; the time spent in the quadrant from where the platform was removed during the same 60 sec period) were measured [28].

Working memory test

A testing paradigm adapted from Sarihi *et al.* [25] was used to conduct the working memory version of the test approximately 48 hours following the probe trial. Here, the 6-day acquisition phase of the reference memory test was considered as the pre-training phase of the working memory test. Then, a training and test phase was conducted over four consecutive days, with four trials each day. Here, the platform position was altered daily but remained the same for the four trials. However, during the four daily trials, each rat was released from four distinct starting points, all of which were far from the platform position. Rats randomly arrived at the platform on the first trial of each day, which served as the information stage. The following trials needed to be matched to the new position for that day, as the platform was changed daily. The mean escape latency in the training and test phases was recorded as above to assess learning ability and savings (the difference in latency scores between trials 1 and 2, expressed as the percentage of savings increased from trial 1 to trial 2) was measured to assess learning efficiency [28, 29].

Hippocampal oxidative stress marker assessment

Rats were euthanised through decapitation under diethyl ether anesthesia, 24 hours following the final behavioral test [15]. Then the brain tissues were swiftly taken out, and the hippocampal tissues were promptly isolated. They were then carefully rinsed with ice-cold Phosphate-Buffered Saline (PBS) (0.1 M, pH 7.4) to ensure complete removal of excess blood. The tissue pieces were weighed and homogenised in PBS using a glass homogeniser on ice, maintaining a ratio of weight (g) to volume (mL) of 1:4. Next, the homogenate underwent centrifugation at 3500 rpm for 10 minutes to obtain the supernatant. The supernatant was collected for the estimation of MDA and GPx levels by ELISA according to the manufacturer's protocol (Elab Science Biotechnology, USA). If any unintended delay occurred, the supernatant was stored in a laboratory at -20°C.

Statistical analysis

Data were expressed as mean (standard error) of the study variables and statistically analysed using ANOVA followed by the Bonferroni post hoc test (between groups) using SPSS (version 25.0), P <0.05 was considered statistically significant.

Results

Effect of SwE on spatial memory impairment induced by hippocampal colchicine

For reference memory performance

ColC rats showed significantly (P <0.01) higher mean EL than those of SC rats. However, SwE improved learning ability performance, as evidenced by statistically significant (P <0.01) differences in mean EL of our ColC and experimental (Pre-SwE Exp and Post-SwE Exp) rats. Notably, the differences in this variable between experimental and NC rats were found to be statistically non-significant on the last acquisition day. However, the differences of mean EL between Pre-SwE Exp vs Post-SwE Exp rats were found statistically non-significant in all acquisition days **(Table 1)**. These data demonstrated that the learning ability of reference memory was impaired by colchicine, and this impairment was reversed almost to normal by SwE.

Table 1 Mean (standard errors) escape latency, in seconds and average escape latency (5th and 6th acquisition days, in seconds) in the acquisition phase of the Morris water maze test in five groups of rats

Mean escape latency of acquisition day	Groups				
	NC	SC	ColC	Pre-SwE Exp	Post-SwE Exp
Days					
1st	26.2 (2.3)	30.6 (2.4)	60.0 (0.0)[b]	43.2 (1.8)[b]	43.8 (1.6)[b]
2nd	22.6 (1.0)	25.4 (0.6)	58.9 (0.5)[b]	38.6 (2.0)[b]	40.5 (1.2)[b]
3rd	14.5 (1.8)	18.9 (0.4)	56.5 (1.2)[b]	34.2 (1.9)[b]	33.8 (1.0)[b]
4th	13.1 (1.7)	17.5 (0.8)	53.9 (0.7)[b]	35.0 (1.6)[b]	34.9 (1.6)[b]
5th	13.0 (1.2)	15.9 (0.7)	51.7 (2.0)[b]	25.9 (0.7)[b]	27.7 (0.9)[b]
6th	12.2 (1.0)	13.3 (0.4)	49.5 (2.0)[b]	16.8 (1.1)[b]	16.8 (0.8)[b]
Average of acquisition days					
5th and 6th	12.6 (0.2)	14.6 (0.8)	50.6 (0.7)[b]	20.4 (2.1)[a]	22.4 (3.2)[a]

NC indicates normal control; SC, Sham control; ColC, colchicine control; SwE, swimming exercise exposure.
[a]*P* <0.05; [b]*P* <0.01.

The mean value of the average EL on the 5th and 6th acquisition days was significantly (*P* <0.01) higher in ColC rats than in SC rats (Table 1). Moreover, SwE showed significantly (*P* <0.05) lower average EL in both groups of our experimental rats than in the ColC rats. On the contrary, the differences in this variable between our NC and experimental rats, as well as between Pre-SwE Exp and Post-SwE Exp rats, were found to be statistically non-significant. This result indicated that colchicine induced consolidation disability in our ColC rats and SwE improved it similar to normal.

Table 2 Target crossings, in frequency/minute and time spent in target, in seconds/minute in probe trial of Morris water maze test in five groups of rats

Variables in probe trial day	Groups				
	NC	SC	ColC	Pre-SwE Exp	Post-SwE Exp
Target crossings	8.0 (0.3)	7.3 (0.3)	1.7 (0.2)[a]	6.0 (0.3)[a]	5.8 (0.4)[a]
Time spent in target	18.0 (0.4)	16.2 (0.7)	5.8 (0.8)[a]	15.3 (0.7)[a]	15.2 (0.9)[a]

NC indicates normal control; SC, Sham control; ColC, colchicine control; SwE, swimming exercise exposure.
[a]*P* <0.01.

Moreover, ColC rats showed retrieval impairment, as evidenced by significantly lower TC and TT (*P* <0.01) compared to those of SC rats. SwE caused significantly higher TC and TT in our experimental rats compared to ColC rats (*P* <0.01). However, statistical analysis revealed that the differences in these variables between our two experimental groups were not significant. However, when these variables were compared between NC and experimental rats, TC showed a significant difference (*P* <0.01), but TT did not (Table 2). From these findings, we inferred that learning strength (retrieval) was hampered by colchicine and was both prevented and alleviated by our 28-day SwE; however, our exercise schedule was not sufficient to fully utilise the complete retrieval power.

Table 3 Mean (standard deviation) escape latency, (seconds) and savings (%) in training and test phase of Morris water maze test in five groups of rats

Trials	Groups				
	NC	SC	ColC	Pre-SwE Exp	Post-SwE Exp
1	20.8 (0.6)	22.1 (1.8)	41.1 (1.3)[b]	31.9 (1.9)[b]	32.9 (1.8)[a, b]
2	10.9 (0.6)	14.9 (1.7)	37.4 (1.1)[b]	24.9 (2.0)[b]	26.8 (2.5)[b]
3	8.4 (0.5)	9.9 (2.0)	32.8 (1.2)[b]	22.0 (1.4)[b]	21.0 (1.4)[b]
4	7.8 (0.5)	10.4 (1.3)	27.6(1.1)[b]	12.8 (1.2)[b]	13.0 (1.4)[b]
Savings (%)[c]	47.7 (3.0)	33.0 (3.0)	10.0 (0.9)[b]	23.6 (2.7)[b]	18.9 (5.3)[b]

NC indicates normal control; SC, Sham control; ColC, colchicine control; SwE, swimming exercise exposure.
[a]*P* <0.05; [b]*P* <0.01.
[c]The difference in latency scores between trials 1 and 2, expressed as the percentage of savings increased from trial 1 to trial 2

For working memory performance

Here, colchicine caused significantly higher mean EL (*P* <0.01) and lower savings (*P* <0.01) in the training and test phases in ColC rats compared to those in SC rats. However, both of our experimental rats showed significantly lower mean EL [Pre-SwE Exp (*P* <0.01 in trial 1; *P* <0.01 in trial 2, 3 and 4) and Post-SwE Exp (P<0.05in trial 1; *P* <0.01 in trial 2; *P* <0.01 in trial 3 and 4)], but not savings, when compared to those of ColC rats. Moreover, when we compared these variables between our experimental and NC rats, mean EL was found to be statistically non-significant in trial 4, except for savings. Furthermore, no statistically significant difference was observed in any of these variables between Pre-SwE Exp and Post-SwE Exp rats (Table 3). Therefore, based on these findings, it is evident that our 28-day SwE could improve the learning disability of colchicine-induced WM impairment in our rats, although not entirely and efficiently.

Effect of SwE on hippocampal oxidative status induced by colchicine

We observed that our ColC rats showed significantly higher (*P* < 0.01) hippocampal MDA levels and lower GPx levels compared to those of the SC rats. However, SwE caused a significantly lower MDA and higher GPx in Pre-SwE Exp (*P* <0.01) as well as in Post-SwE Exp (*P* <0.01) rats in comparison to those of ColC rats. Strikingly, there were non-significant differences between NC vs Pre-SwE Exp and NC vs Post-SwE Exp as well as Pre-SwE Exp vs Post-SwE Exp rats (Table 4). These data indicate that colchicine causes hippocampal oxidative stress, and our SwE can prevent and alleviate this stress to nearly normal levels.

Discussion

In our research, we examined the effects of SwE on spatial memory and hippocampal oxidative stress in a colchicine-induced memory-impaired rat model. The present study demonstrated that both pretreatment and posttreatment with SwE were able to ameliorate spatial memory impairment and the marked diminution of oxidative stress.

Here, the intrahippocampal colchicine may bind to microtubule-binding proteins (tubulin), depolymerising microtubules and blocking axoplasmic flow, cellular growth, and cellular differentiation, leading to damage to hippocampal granule and pyramidal neurons [22]. Moreover, this microtubule-disrupting agent might also induce direct nitric oxide (NO) production by activation of inducible nitric oxide synthase (iNOS) enzyme [30]. This NO might react rapidly with superoxide anions (a reactive oxygen species, ROS) to form peroxynitrite (ONOO-) (a reactive nitrogen species, RNS), resulting in oxidative stress and hippocampal neuronal death. In addition, this neurotoxic agent may elevate glutamate binding site [22] in α–amino-3-hydroxy-5-methyl-4-

Table 4 Hippocampal malondialdehyde and glutathione peroxidase in five groups of rats

Hippocampal oxidative stress markers	Groups				
	NC	SC	ColC	Pre-SwE Exp	Post-SwE Exp
Malondialdehyde (ng/mg protein)	8.0 (1.4)	8.3 (0.6)	17.3 (2.0)[b]	9.7 (1.4)[b]	11.7 (2.0)[a]
Glutathione peroxidase (pg/mg protein)	316.2 (28.9)	258.3 (14.6)	121.8 (6.4)[b]	308.8 (22.2)[b]	296.0 (26.2)[b]

NC indicates normal control; SC, Sham control; ColC, colchicine control; SwE, swimming exercise exposure.
[a]*P* <0.01; [b]*P* <0.001.

isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors in hippocampal neurons, causing excess Ca2+ influx. This process might be responsible for mitochondrial stress, ROS production, oxidative stress [31] and neuronal death in the hippocampus. Moreover, this marked increase in ROS and RNS might affect the double bonds of polyunsaturated fatty acids in neuronal cell membranes (lipid peroxidation) [9] and elevate hippocampal MDA levels in our memory-impaired rats [24]. In addition, this increase in oxidants may cause an increased consumption of GPx [9] for maintaining oxidative balance and a decreased GPx concentration [24] in hippocampal neurons.

In our study, SwE may cause an increase in brain-derived neurotrophic factor (BDNF), [16] an important marker of memory and cognition [32]. As a consequence, BDNF might activate neurogenesis, [33] synaptogenesis [34] and hippocampal volume increment, [35] to replenish the microtubule-disrupted neuronal death in our experimental rats. Moreover, SwE may reduce glutamate concentration, followed by regulation of Ca2+ influx through the NMDA receptor [18]. In addition, our 28 days SwE might stimulate the hippocampal ROS induced metabolic adaptation, [36, 37] enhancement of the activity of nuclear erythroid 2 – related factor 2/antioxidant response element (Nrf2/ARE) signal transduction pathway and formation of GPx [14, 38-40] in our experimental rats. This increased GPx might mitigate the increased MDA level in both our pre- and post-exercise treated experimental rats.

Limitations

This study was done using manual stereotaxic apparatus and manually operated memory performance tests. Here, only two variables related to reference memory retrieval were measured, and only two oxidative stress markers from the hippocampus were assessed.

Conclusion

Findings of this study suggest that swimming exercise may be equally effective in preventing as well as alleviating colchicine-induced spatial memory impairment, along with hippocampal oxidative stress, in male Long-Evans rats. Moreover, this swimming exercise schedule might be sufficient to reverse these alarming consequences to almost normal.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data and drafting the work: RBA, TA, PB, FA, MSI, KRI. *Drafting the work or reviewing it critically for important intellectual content:* RBA, TA, PB, FA, MSI, KRI. *Final approval of the version to be published:* RBA, TA, PB, FA, MSI, KRI. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* RBA .

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

Yes

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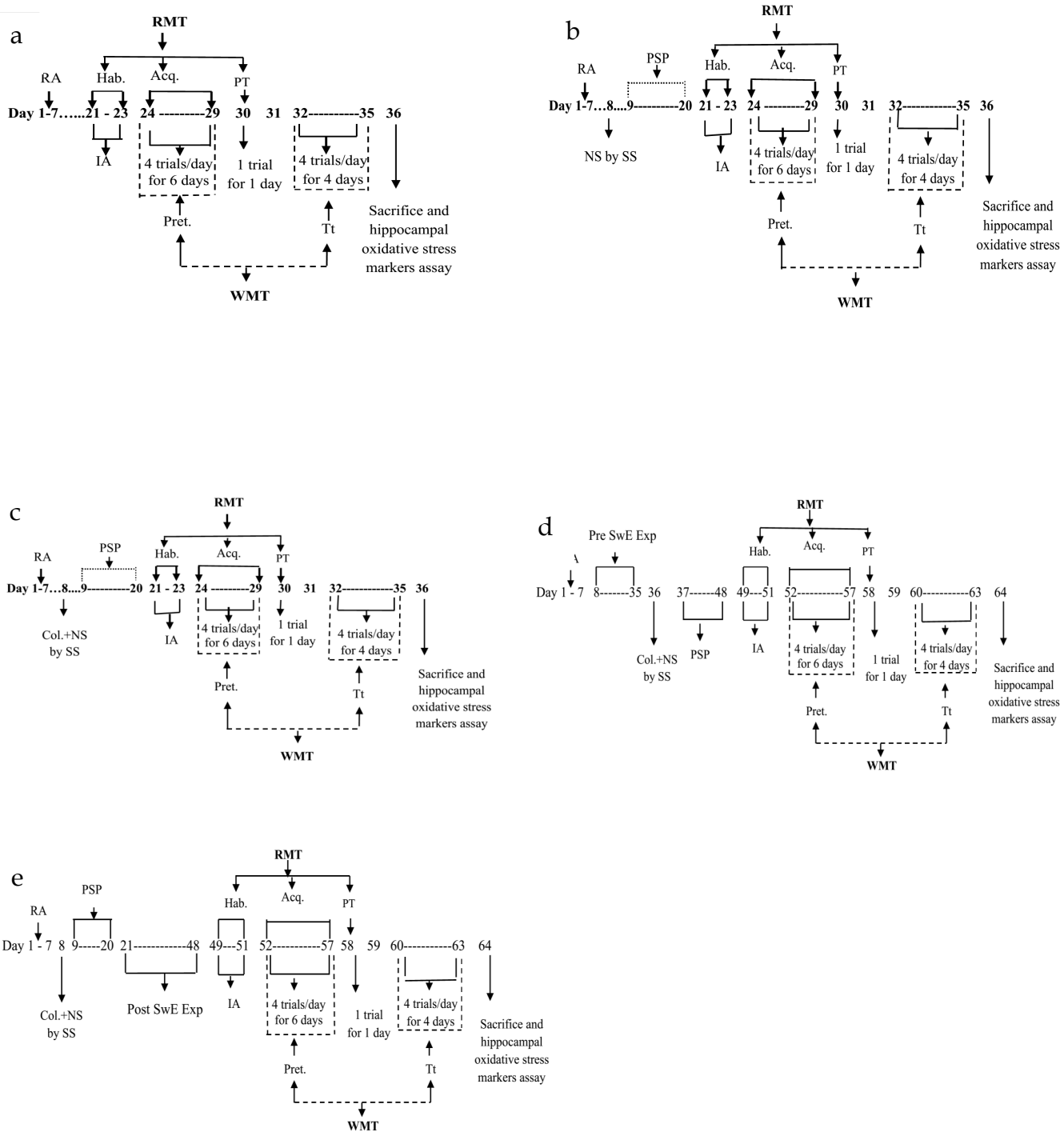
Supplementary file 1 Working plan for rats*



*a) normal control, b) sham control, c) colchicine control, d) Pre colchicine swimming exercise, e) Post colchicine swimming exercise.

RMT: Reference memory test; WMT: Working memory test; RA = Room acclimatization; PSP=Post-surgical period; Hab.=Habituation; Acq.=Acquisition; PT=Probe trial; IA=Instrumental acclimatization; Pret.=Pretraining; Tt=Training and test; NS=Normal saline; SS=Stereotaxic surgery; Col.=Colchicine; Pre SwE Exp=Pre colchicine swimming exercise; Post SwE Exp=Post colchicine swimming exercise.

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