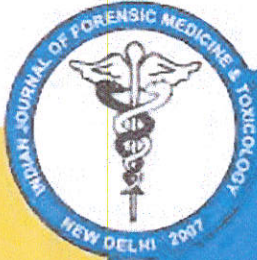


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# Swimming Improves Memory Function and Decreases N-Methyl-D-Aspartate in Ageing Rats

Hanik Badriyah Hidayati<sup>1</sup>, Purwo Sri Rejeki<sup>2</sup>, Lilik Herawati<sup>2</sup>, Susi Wahyuning Asih<sup>3</sup>, Suhartati Suhartati<sup>4</sup>, Siti Khaerunnisa<sup>2</sup>

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## Abstract

A single Memory impairment substantially reduces the quality of life in the elderly. It is associated with the alteration of neurotrophic (NT) factors, such as brain-derived neurotrophic factor (BDNF) and glutamate receptor N-methyl-D-aspartate (NMDA). Exercise is often used to reduce cognitive impairment. Previous studies show that the benefits of aerobic exercises on such impairments are correlated with increasing BDNF and preventing the production of NMDA. However, some results remain controversial. Thus, the association between exercise and Memory was addressed by examining increases in BDNF and the reduction of NMDA in ageing rats. The study used a randomized, post-test-only controlled group of 30 male one-year-old ageing *Rattus norvegicus* divided into three groups, namely, K0 (control) and K1 and K2 (aerobic swimming exercise). K1 and K2 animals differed in the frequency of exercise, which is three and four sessions per week, respectively. Memory was assessed using Y-maze performance. BDNF and NMDA were analyzed using enzyme-linked immunosorbent assays. A significant improvement in memory function and reduction in the NMDA level were observed in K1 and K2 group rats ( $p = 0.001$ ;  $p = 0.041$ ). No significant impact on the BDNF levels was observed ( $p = 0.387$ ). Swimming may boost Memory by reducing the NMDA level but not by increasing BDNF. Swimming is a promising method for preventing or delaying memory loss in degenerative brain diseases. Further investigation is needed to fully understand underlying mechanisms.

**Keywords:** Memory; NMDA; BDNF; ageing rat; swimming

## Introduction

Life expectancy has continuously increased during the last decades, which has led to increasing numbers of elderly individuals<sup>1</sup>. In fact, the elderly are the fastest-growing segment of the United States population<sup>2</sup>. The latest projections suggest that the number of individuals

older than 60 years will increase from 810 million in 2012 to 2 billion by 2050 worldwide (United Nations Department of Economic and Social Affairs, 2012)<sup>1</sup>.

The elderly are at a high risk of developing cognitive impairments<sup>2</sup>. Previous studies show that cognitive impairment is associated with chemotherapy and age<sup>2-4</sup>. Many elderly individuals experience difficulty performing complicated daily tasks<sup>5</sup>. Physical and mental abilities markedly decline with age and hence reduced quality of life<sup>1,6</sup>. Quality of life is an important concern in ageing societies<sup>7</sup>. Various recent studies indicate that cognitive impairment, among degenerative brain diseases, are particularly common for elderly

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individuals<sup>2,6</sup>.

Memory, the accumulated and stored aggregate of an individual's experience, plays an important role in the overall cognitive function<sup>3</sup>. Memory has multiple dimensions, including the ability to store, retain, and retrieve information<sup>2</sup>. Memory problems include a tendency toward misplacing items, difficulty remembering appointments, and forgetting details of conversations and events<sup>2</sup>. These and other memory issues substantially impact the quality of life of afflicted individuals<sup>3</sup>.

The hippocampus, an important brain region for learning and Memory, is the primary site of neurogenesis in adulthood and retains the greatest brain neuroplasticity<sup>3</sup>. Brain-derived neurotrophic factor (BDNF) is expressed ubiquitously in the brain<sup>8</sup>. BDNF, a fundamental neurotrophic factor in learning and Memory<sup>8</sup>, plays a pivotal regulatory role in the development, cognition, and plasticity of the hippocampus<sup>1,3,4,9</sup>. BDNF is key to maintenance, growth, neuronal survival, differentiation, neurotransmitter release, dendritic remodeling, axon growth, the formation of neurons, regulation of hippocampal structure, synaptic transmission, synaptic modulation, promotion of synaptic growth and plasticity<sup>3,8,9</sup>. BDNF exerts neurotrophic anti-apoptotic regulation in neurons by binding with tyrosine receptor kinase B, also known as tropomyosin-related kinase B (TrkB)<sup>3,9</sup>.

BDNF is secreted at pre- and post-synaptic sites. Synaptic BDNF is secreted in response to activities and activates pre- and post-synaptic TrkB receptors. BDNF is important for long-term potentiation (LTP). BDNF mediates the regulation of excitatory synapses during early LTP. Presynaptic BDNF increases the exocytosis of glutamate-containing synaptic vesicles. Post-synaptic BDNF-TrkB signaling induces NMDA receptor (NMDAR) phosphorylation<sup>8</sup>.

A key aspect of quality of life is health<sup>7</sup>. Exercise, a major component of efforts to maintain and improve health, is an effective intervention for addressing degenerative brain diseases<sup>3,7</sup>. Exercise may relieve stress and anxiety that can lead to deteriorating mental

and physical health. Regular exercise is widely reported to help maintain and enhance a cognitive function, activate neurotransmitters, induce gene expression, and promote neuroprotection<sup>3</sup>, but underlying mechanisms are not yet clear. Several studies have concluded that exercise can be a therapeutic strategy to increase the BDNF level and that a sedentary lifestyle may impair BDNF signaling<sup>9</sup>.

BDNF and NMDA play important roles in hippocampal synaptic plasticity<sup>8</sup>. Therefore, the current study aims to determine whether a cognitive impairment, neuroplasticity in the hippocampus.

## Materials and Methods

### Setting

This work was conducted in the animal research laboratory of the Department of Medical Biochemistry of Airlangga University, Surabaya, East Java, Indonesia. This study received approval by the Animal Care and Use Committee, Veterinary Faculty of Airlangga University with certificate number 745-KE.

### Animal

Thirty-one-year-old male rats (*Rattus norvegicus*), with an average weight of  $\pm 300$  g, were used. Animals were acclimatized for one week and allowed free access to food and water *ad libitum*. The exercise period lasted for eight weeks. Behavioral analyses were conducted upon completion of all exercise sessions. Brains (cerebral hemisphere) were removed and homogenized using a sonicator, and BDNF and NMDA were measured using enzyme-linked immunosorbent assays (ELISA)<sup>3</sup>.

### Grouping

The animals were randomly divided into three groups ( $n = 10$ ):

- Group 1 (K0): control group, non-swimming
- Group 2 (K1): swimming exercise sessions three times/week for eight weeks
- Group 3 (K2): swimming exercise sessions five

times/week for eight weeks

### 2.1.3. Exercise Protocol

The rats in Groups 2 and 3 used a pool made for animal exercise sessions. Animals swam for 10 min during the first week, 20 min during the second week, and 30 min in weeks three through eight.

### Y-Maze

The rat performance was assessed in a Y-maze after the exercise period. The performance in the maze measured the willingness of the rats to explore a new environment. The Y-maze allowed only two choices: right and left pathways. Food was placed at the end of one path as an incentive. An animal was placed in the middle of the maze and allowed to choose one of the paths. The rats were guided manually to the target if the food was not found after 90 seconds. A sign was provided in the maze to indicate the location of food. During the memory test, signs were eliminated to test whether the rats recalled the food location. The time of placement in the maze to achieving the target was measured. Re-entry into the path with food was taken as an indication that the animals recalled their previous maze experience. Entry to the path without food was taken as a sign of a

lack of recall.

### Determining the Level of NMDA and BDNF

The samples were collected from the left or right hemispheres of the hippocampus and analyzed using ELISA. The samples were homogenized using a sonicator suspended in a lysis buffer and centrifuged at 15.000 x g for 15 min at 4 °C. Supernatants were retained for the analysis. The samples were immediately frozen at -20 °C. BDNF and NMDA levels were measured using a Rat CREB Kit (category no. E0039Ra, Bioassay Technology Laboratory), Rat NMDA Kit (category no. E0999Ra, Bioassay Technology Laboratory) and Rat BDNF Kit (category no. E0476Ra, Bioassay Technology Laboratory).

### Statistical Analysis

Normally distributed data were analyzed by one-way analysis of variance, followed by the least significant difference tests. Non-normal distributions were analyzed by the Kruskal–Wallis test, followed by Mann–Whitney U test. Statistical significance was set at  $p < 0.05$ . Data analysis using SPSS version 23.

## Results

**Table 1. BDNF, NMDA, and Memory in each group**

Variable	Mean ± SD			p-value
	K0	K1	K2	
BDNF	4.17 ± 0,64	4.68 ± 1.03	4.84 ± 0.87	0.387
NMDA	19.771 ± 1,67	15.59 ± 5.12	16.29 ± 6.15	0.041*
Memory	52.31 ± 22,73	19.85 ± 8.2	20.69 ± 6.69	0.001*

\*Significant with  $p < 0.05$



The BDNF, NMDA, and Memory results for each group are presented in Table 1. The BDNF levels between groups did not differ significantly ( $p = 0.387$ ;  $p > 0.05$ ). The NMDA levels were significantly different between Groups K0 and K1 ( $p = 0.016$ ). Significant differences were not observed between Groups K0 and K2 ( $p = 0.055$ ) and Groups K1 and K2 ( $p = 0.749$ ).

Memory performance from K0 to K2 increased with increasing amounts of exercise. Between Groups K0 and K1 and Groups K0 and K2, significant differences in the maze recall were observed ( $p = 0.001$  and  $p = 0.000$ , respectively). No significant difference was found between Groups K1 and K2 ( $p = 0.962$ ).

### Discussion

In this study, the cognitive function improved in elderly rats after eight weeks of regular exercise. Exercise has been shown to improve Memory at different ages, along with other beneficial effects<sup>1,3,4,10-13</sup>. Physical activity is needed for the elderly in exercising the muscles of the elderly from the condition of movement that tends to reduce function<sup>14</sup>. The treatment of cognitive impairments has emphasized the regulation of maintenance, growth, survival, and formation of neurons. Besides, physical activity is known to increase the BDNF level, which binds TrkB<sup>3,9</sup>, thus inducing an anti-apoptotic state<sup>3</sup>. Some authors have suggested exercise as a treatment for cognitive impairments. At the cellular level, mitochondria endow hippocampal neurons with neuroplasticity in several ways: control of Ca<sup>2+</sup> uptake, redox signaling, developmental and synaptic plasticity, and cell survival and death. Furthermore, mitochondrial permeability transition pores, which are closely related to apoptosis, regulate various physiological functions at the cellular level, and play a key role in learning and synaptic plasticity<sup>3</sup>.

Exercise relieves stress and anxiety and thus augments mental and physical health<sup>3,11</sup>. Physical activity causes brain neuronal and biochemical changes that activate neurotransmitters and induce gene expression, which promotes proliferation and survival of neurons, maintain and improve cognitive function and

confer neuroprotection against brain damage<sup>3</sup>. Exercise has also been associated with enhanced capacity of mitochondria for calcium toleration, with further consequences on the control of mitochondrial-driven apoptotic cell death<sup>12</sup>. Exercise also helps preserve brain function during ageing by enhancing BDNF signaling<sup>4</sup>.

Nagahara et al. found that BDNF treatments can decrease A $\beta$ -mediated cell death, counter cognitive dysfunction, and synapse loss and even retard the cognitive decline in nonhuman primates and APP transgenic mice<sup>9</sup>. The effects of BDNF on neurogenesis, neuronal survival, and synaptic plasticity appear to be mediated by signal transduction pathways involving Akt kinase, Ca<sup>2+</sup>/calmodulin and mitogen-activated protein kinases. The gene targets of BDNF signaling pathways include the anti-apoptotic protein Bcl-2, NMDA glutamate receptor subunits and neuronal nitric oxide synthase<sup>4</sup>. High levels of BDNF correlate with a low risk of developing dementia<sup>1</sup>. BDNF signaling can promote healthy ageing and protect the brain against age-related neurodegenerative disorders<sup>4</sup>.

Erickson et al. (2011) investigated relationships between chronic aerobic physical activity and peripherally assessed concentrations of BDNF, hippocampal volume, aerobic fitness (VO<sub>2</sub> max) and cognitive performance (spatial Memory) in a 1-year RCT with older adults. This study demonstrates that changes in aerobic fitness from pretest to posttest were positively correlated with changes in hippocampal volume and the increase in hippocampal volume experienced in the physical activity group was positively correlated with better spatial memory performance and greater change in BDNF concentration<sup>15</sup>. Umm et al. (2008) demonstrated that treadmill running increases the BDNF level<sup>1</sup>. BDNF signaling is probably the key mechanism for triggering brain neuroplasticity<sup>16,17</sup> and anti-apoptotic cell death that leads to the improvement of cognitive function<sup>4,16</sup>.

In this study, BDNF and NMDA were used to assess changes in brain chemistry associated with improved Memory after regular swimming exercise. BDNF plays

a pivotal role in neurogenesis, neuronal survival and synaptic plasticity in the brain. The lowest BDNF mean level was recorded in the hippocampus of rats in Group K0 ( $4.17 \pm 0.64$ ). This group did not exercise. BDNF gradually increased from Groups K0 to K2 along with the increasing frequency of swimming sessions. However, no statistically significant interaction between exercise and BDNF level was found. A protective effect of exercise against apoptosis demonstrated by the increased BDNF levels in a frequency-dependent manner was not demonstrated by a statistically significant increase in BDNF concentration.

Elderly with exercise swimming can improve their memory function compared to that without exercise. The molecular mechanism is suggested by inhibiting NMDA expression; thus, it could prevent intracellular calcium build up that results in the activation of  $Ca^{2+}$ /calmodulin dependent protein kinase II (CaMKII) and c-AMP response element-binding (CREB) pathway. This pathway related to the maintenance of synaptic plasticity through increased BDNF expression.

BDNF is related to the NMDAR. One BDNF signaling pathway targets the NMDA glutamate receptor subunits<sup>4</sup>. BDNF stimulates NMDAR autophosphorylation. Autophosphorylation and function of CaMKII protect synaptic function. An *in vivo* investigation showed that Met carriers reduced the hippocampal volume and changed synaptic plasticity, especially NMDAR-dependent LTP. These effects resulted in a loss of hippocampal-related Memory<sup>9</sup>.

A meta-analysis found that physical activity positively influences cognitive function in patients with dementia, independent of the clinical diagnosis and frequency of the aerobic exercise program<sup>18</sup>. In this study, swimming stimulated the BDNF levels but showed no significant interaction. The greater the time between the placement of animals into the maze to finding food, the worse the animals' Memory. The slowest time to reach the target was observed in rats in Group K0 ( $52.31 \pm 22.73$  sec) and the quickest in Group K1 ( $19.85 \pm 8.2$  sec). In Group K2, rats were essentially as quick at

solving the maze as Group K1 animals ( $20.69 \pm 6.69$  sec). Thus, exercising either three or five times a week had a similar positive impact on recall. Statistically, the results from Group K0 rats were significantly different and higher than those from animals in Groups K1 and K2 ( $p = 0.001$ ,  $p = 0.000$ , respectively).

The results of the current study are consistent with those of previously published works, which show that exercise can help improve memory and neurodegenerative diseases. Investigators have used various methods and parameters in different settings to assess the impacts of exercise, and outcomes are always similar; that is, exercise improves the cognitive function.

## Conclusions

The results of the current study help confirm that exercise can improve cognitive function and prevent and delay degenerative brain diseases in the elderly. Exercise may produce its effects via inhibiting the excessive increase of NMDA. Additional investigations on the relationship between BDNF and cognitive function are warranted.

## Declarations

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## AVAILABILITY OF DATA AND MATERIALS

All data generated in the present study are included in this article.

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**Conflicts of Interest :** The authors declare that they have no competing interests.

## Ethics Approval and Consent to Participate

This study received approval by the Animal Care

and Use Committee, Veterinary Faculty of Airlangga University with certificate number 761-KE.

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