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Effects of aerobic exercise on memory functions and serum levels of BDNF and TrkB in young adult and older adult male football players☆

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ABSTRACT

Background/Objective: This study aimed to investigate the effect of aerobic exercise on verbal memory (VM) and non-verbal memory (NVM) functions as well as BDNF and TrkB serum levels in young and older adult male football players.

Methods: Twenty-nine male football players voluntarily participated in this study and were divided into two age groups: G1 (young; 19–30 years old, n = 15, football experience 10.6 ± 2.79 years) and G2 (older; 46–71 years old, n = 14, football experience 35.78 ± 9.48 years). Serum BDNF and TrkB levels and performance on the VM and NVM tests were measured before and after a 60-min aerobic exercise session. A 2 (Time) x 2 (Group) mixed-model repeated measures ANOVA test was used to detect the effects of exercise and age differences.

Results: There was a statistically significant time × group interaction of age and exercise on BDNF and TrkB levels ($p < 0.01$, $p < 0.001$; respectively). However, this interaction was not observed for VM and NVM ($p = 0.751$, $p = 0.869$; respectively). There was also a significant effect of the group on BDNF, TrkB, and NVM ($p < 0.001$, $p < 0.001$, $p < 0.01$; respectively), whereas there was not a significant effect on VM ($p = 0.094$). Furthermore, there was a significant effect of time on BDNF, TrkB, and VM ($p < 0.001$, for all); but not on NVM ($p = 0.110$).

Conclusion: Regular football training participation can maintain BDNF levels as a neurotrophin that can improve cognitive functions. Likewise, this neurotrophin and its receptor's response to aerobic exercise in old age suggests the effectiveness of exercise as a preventive strategy against age-related memory loss and neurodegeneration.

1. Introduction

Due to the improved access to healthcare and living standards, life expectancy has risen, leading to a growing aging population.[1] With an increasing number of adults over 65[2], and a rise in age-related cognitive issues, understanding the effects of aging on cognitive functions has become more critical.[3] Prevention of cognitive decline in the elderly is currently one of the priorities of the World Health Organization.[4]

Normal aging is linked to declines in cognitive abilities such as processing speed, memory, and executive function,[5] although the exact causes are not fully understood.[6] Memory changes are widespread among the elderly who tend to perform less efficiently than younger individuals on memory and learning tests. These changes may result from slower processing speed, difficulty ignoring irrelevant information, and challenges in using strategies to enhance memory and learning.[7,8]

Genetics also plays a significant role in age-related cognitive changes, which vary widely among individuals[9]; however, environmental factors can influence or slow the cognitive decline. An active lifestyle and participation in certain activities throughout life are among the factors that can help mitigate these changes.[10]

Regular physical activity and exercise offer greater benefits for cognitive and physical health compared to irregular activity.[11] Research increasingly shows that exercise can positively impact on brain structure and function, with some studies indicating an increased volume in brain

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areas such as the hippocampus and prefrontal cortex in older adults.[12,13]

Exercise activates various molecular signaling pathways in the nervous system, promoting neuroplasticity through neurotrophic mechanisms, although the precise mechanisms remain unclear.[14] One critical factor in the neural network development is brain-derived neurotrophic factor (BDNF),[14] a member of the neurotrophin family that plays a crucial role in neuronal growth and development across various brain regions.[15]

Approximately 75 % of BDNF is secreted in the brain under normal conditions, but it is also released by peripheral tissues such as skeletal muscles, fat, liver, and endothelial cells.[16] Lower circulating levels of BDNF are linked to reduced cognitive functions, impaired learning and memory, and increased anxiety and depression in both animals and humans.[17]

BDNF binds to its specific receptor, tyrosine kinase B (TrkB), which is crucial for synaptic plasticity in the hippocampus.[18] This interaction activates three key intracellular pathways—PI3K/AKT, Ras/MAPK/ERK, and PLCγ/DAG/IP3—promoting neuronal survival, neurogenesis, and neurite outgrowth.[19]

Different sports enhance cognitive processing in unique ways by engaging various brain functions.[20] For example, strategic sports such as football are linked to improved executive functioning, working memory, and cognitive flexibility.[21] Research has shown that football players with higher performance levels have superior cognitive abilities

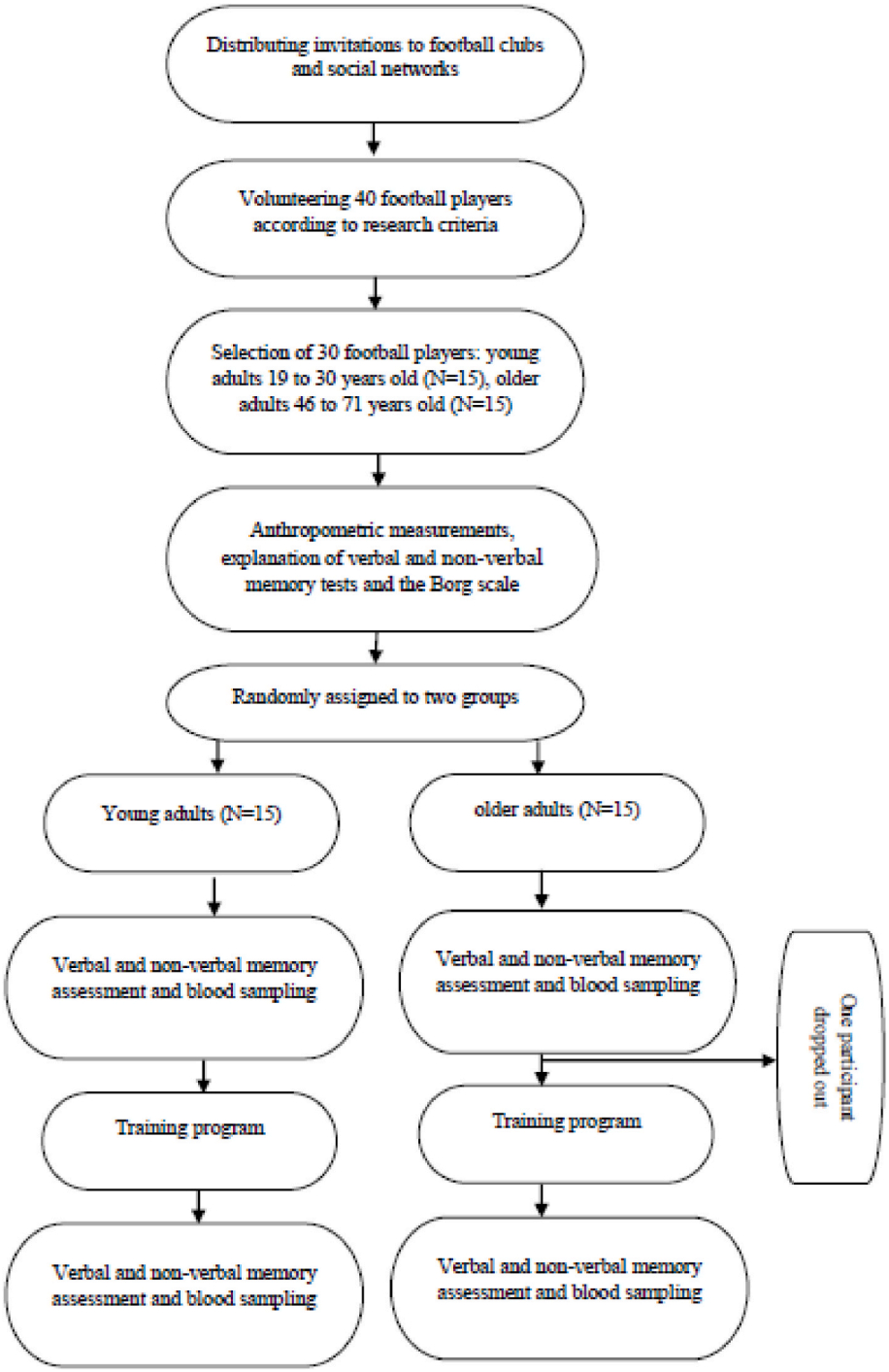

Fig. 1. The flowchart for the study protocol.

compared with their lower-performing peers,[22] and these enhanced cognitive skills are predictive of future success in this sport.[23]

Football as a game-based sport has potential cognitive benefits, while few studies have investigated its specific impacts on cognitive functions.[24] In addition, in previous studies, the positive effects of regular exercise on brain health and cognitive performance in young people and the elderly has been confirmed.[25] However, football players in these two age groups (i.e. young adults and the elderly) have not been compared to determine the effect of staying active (specifically through playing football) into old age on working memory and serum levels of some related variables. Therefore, this study aims to compare baseline verbal memory (VM) and non-verbal memory (NVM) functions, as well as BDNF and TrkB serum levels, and to evaluate the effects of a single bout of moderate-intensity aerobic exercise on these variables in young and older adult male football players.

2. Methods

2.1. Study design and participants

This research employed a semi-experimental, two-group, pre-post-test design. In this study, non-probability convenience sampling was used. For this purpose, invitations for expression of interest were distributed through flyers in community centres and on clubs' notice-boards for three weeks, and 40 male football players aged 19–71 years were enquired about the study. Then, according to the research objectives and inclusion criteria, 15 football players aged 19–30 years (G1: young adults: n = 15, football experience: 10.6 ± 2.79 y) and 15 aged 46–71 years (G2: older adults: n = 15, football experience: 35.78 ± 9.48 y) were selected (Fig. 1). The older adult football players had participated in the domestic football semi-professional championship in the Kurdistan Provincial League, Marivan City, Iran. They have been playing soccer regularly except for cases of illness, when they might have stopped playing for a while until recovery.

The inclusion criteria were regularly participating in football games prior to the implementation of the training protocol, no chronic diseases, no use of medication, and willingness to participate in research. Participants were informed about the benefits and risks involved in this study, read the plain language statements, and provided signed informed consents. This research project was approved by the relevant Human Ethics Committee (approval number: IR.SSRC.REC.1402.281) and was conducted in accordance with the Declaration of Helsinki. During the study, one person from the older adults was excluded from the research process due to his disability.

One day before participating in the training session (first session), the anthropometric (Body composition analyzer, model x-contact 350, brand JAWON, South Korea) assessments were performed (Table 1). The procedure for VM and NVM tests was explained to subjects and research assistants. Furthermore, participants were familiarized with the Borg scale to adjust the intensity of training. At the end of this session, the subjects were given the same breakfast and snack pack to consume on the training day and they were asked to attend the gym the next day to perform the training protocol.

2.2. Training program

On the training day (second session), participants first completed the VM and NVM tests, followed by blood sample collection. During the training session, participants performed a warm-up including jogging at a low to moderate intensity for 10 min followed by a 5-min active stretching of major muscle groups in the lower and upper body. After the warm-up, participants ran for 60 min at an intensity corresponding to 12–13 on the Borg scale. At the end of four 100m lap, participants specified the intensity of exercise using the Borg scale between 6 and 20, and verbal cues were provided to increase, decrease, or maintain the speed of running. This was to ensure the training intensity was maintained at ~12–13 on the Borg scale.[26] Upon completing the 60-min running exercise, in the cool-down stage, the participants performed a 5-min stretching. In the post-training stage, VM and NVM tests were performed, then blood samples were collected from all participants.

In this study, in addition to evaluating baseline levels of working memory and serum levels of BDNF and TrkB between two age groups, the effect of a moderate-intensity aerobic exercise session, as a common exercise among athletes and even active individuals, was evaluated.

2.3. Assessment of VM and NVM functions

In the VM test, there were 8 stages with 2 attempts per stage, the first stage began with 2 digits, and the final stage ended with 9 digits. At each stage, the examiner read the numbers related to each attempt, and the test taker was asked to verbally repeat the numbers with the same number and order. In this test, the test would be stopped at the stage where both 2 attempts were wrong. Grading was done as follows: if the test taker gave a correct answer to one of the 2 attempts in one stage, the score would be 1, if he answered both 2 attempts correctly, the score would be 2, and if he gave a wrong answer to both attempts, he would receive a score of zero.[27]

In the NVM test, there were 8 stages of 2 attempts. The method of implementation was a way that 8 cans were placed in 2 rows of 4 so that each can be assigned a number from 1 to 8 and it was only possible for the examiner to see the numbers. In the first stage, the examiner would touch two cans and the test taker was asked to touch the same cans in order non-verbally, and this continued until the stage of touching 9 cans. In this test, the grading method was similar to the VM test.[27]

2.4. Blood sampling and analysis

Blood samples were collected before and after the intervention from the median antecubital vein. Serum was separated by centrifuging the blood samples at 3000 rpm for 15 min in a refrigerated centrifuge and stored at −80 °C for later analyses. Serum levels of BDNF and TrkB were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (BDNF; sensitivity: 0.063 ng/ml, detection range: 0.312–20 ng/mL; TrkB: sensitivity: 0.063 ng/ml, detection range: 0.16–10 ng/ml, Cusabio, Japan) following protocols supplied alongside the kits. Each sample was measured in duplicate and the mean value was used in subsequent analyses.

2.5. Assessment of the maximum aerobic capacity

In order to prevent excessive fatigue, the subjects' maximum aerobic capacity was assessed 3 days after completing the training protocol. The Bruce treadmill test was used to measure the maximum aerobic capacity. Briefly, the subjects started at a low intensity walking and with the increase in speed and slope they ran on the treadmill to exhaustion. During the test, the speed (km/hr) and grade of slope (%) of the treadmill were

Table 1
The anthropometric variables and maximum aerobic capacity.

Variables	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	P.B.F (%)	W.H.R (cm)	Vo_{2max} (ml/kg/min)
Young Adults	24.54 ± 3.80	76.62 ± 9.89	179.53 ± 5.48	23.87 ± 3.62	16.42 ± 6.63	0.75 ± 0.07	55.26 ± 10.57
Older Adults	58.35 ± 9.77	77.49 ± 10.19	172.78 ± 6.07	26.01 ± 2.7	22.04 ± 3.38	0.87 ± 0.03	46.37 ± 8.99

BMI, Body mass index; P.B.F, Percent body fat; Vo_{2max}, Maximum aerobic capacity; W.H.R, Waist-to-hip ratio.

increased according to the protocol. When the subject was unable to continue the test, the total time was recorded in minutes and seconds. Then, using the following formula, the maximum aerobic capacity was calculated.

$$VO_{2\ max} = 14.8 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$$

In the above formula, 'T' was the total time of the test in minutes and fractions of a minute.[28]

2.6. Statistics

Data were analyzed using SPSS 24.0 (SPSS Inc, Chicago, IL), and the results are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to assess the normality of the data. A 2 (Time) x 2 (Group) mixed-model repeated measures ANOVA test was conducted since in this kind of experimental design subjects serve as their control and assumed two different time points (pre and post-test), while two groups (young adults and older adults) were compared. The P-value was also set at 0.05. Also, partial Eta Squared (η^2) was used to evaluate the effect size, which the value of $\eta^2 = 0.01$ indicates a small effect size, the value of $\eta^2 = 0.06$ indicates a medium effect size, and the value of $\eta^2 = 0.14$ indicates a large effect size.

3. Results

A 2 (Time) x 2 (Group) mixed-model repeated measures ANOVA test was used to detect effects of aerobic exercise and age difference. There was a statistically significant time × group interaction of age and exercise on BDNF, $F(1, 27) = 11.556$, $p < 0.01$, $\eta_P^2 = 0.300$; and TrkB, $F(1, 27) = 20485$, $p < 0.001$, $\eta_P^2 = 0.431$. However, it was not seen for VM, $F(1, 27) = 0.103$, $p = 0.751$, $\eta_P^2 = 0.004$; and NVM, $F(1, 27) = 0.028$, $p = 0.869$, $\eta_P^2 = 0.001$.

There was also a significant effect of age on BDNF, $F(1, 27) = 17.176$, $p < 0.001$, $\eta_P^2 = 0.389$; TrkB, $F(1, 27) = 83.58$, $p < 0.001$, $\eta_P^2 = 0.884$; and NVM, $F(1, 27) = 8.544$, $p < 0.01$, $\eta_P^2 = 0.240$. Where, there was not a significant effect on VM, $F(1, 27) = 3.020$, $p = 0.094$, $\eta_P^2 = 0.101$.

In addition, there was a significant effect of exercise on BDNF, $F(1, 27) = 68.746$, $p < 0.001$, $\eta_P^2 = 0.718$; TrkB, $F(1, 27) = 42.272$, $p < 0.001$, $\eta_P^2 = 0.610$; and VM, $F(1, 27) = 35.161$, $p < 0.001$, $\eta_P^2 = 0.566$; but not on NVM, $F(1, 27) = 2.731$, $p = 0.110$, $\eta_P^2 = 0.092$.

The mean values of BDNF, TrkB, VM, and NVM were illustrated in Table 2.

Table 2
Mean and SD of study variables in pre- and post-time for young adults and older adults.

	Young Adults		Older Adults	
	Before 95 % CI	After 95 % CI	Before 95 % CI	After 95 % CI
BDNF (ng/ml)	7.06 ± 0.44 [6.81–7.31]	8.11 ± 0.79[a] [7.67–5.55]	7.45 ± 0.60 [7.10–7.80]	9.97 ± 1.52[a¥] [9.09–10.85]
TrkB (ng/ml)	1.29 ± 0.22 [1.17–1.41]	1.51 ± 0.24[a] [1.38–1.65]	1.42 ± 0.32 [1.24–1.61]	2.05 ± 0.26[a¥] [1.89–2.21]
VM	8.93 ± 2.05 [7.79–10.06]	10.60 ± 2.06[a] [9.45–11.74]	7.85 ± 1.16 [7.18–8.53]	9.71 ± 1.32[a] [8.94–10.47]
NVM	9.20 ± 1.01 [8.63–9.76]	9.66 ± 1.39 [8.89–10.44]	8.21 ± 1.25 [7.49–8.93]	8.78 ± 1.12 [8.13–9.43]

¥ Significantly different from adult ($p \leq 0.01$; $p \leq 0.001$).
CI, confidence interval.
[a] Significantly different from pre-exercise ($p \leq 0.01$; $p \leq 0.001$).

4. Discussion

This study aimed to compare VM and NVM functions, BDNF and TrkB serum levels, and to investigate the effect of a single bout of acute moderate-intensity aerobic exercise on these variables in young and older adult male football players. At baseline, no significant differences were observed between the two groups in serum BDNF and TrkB levels or VM function. However, young adults performed significantly better on the NVM test. Post-exercise, moderate-intensity aerobic exercise significantly increased BDNF and TrkB levels and VM performance in both groups, whereas NVM performance showed no significant improvement. Notably, BDNF and TrkB serum levels increased significantly more in older adults than in young adults, with no significant differences between the groups in VM or NVM performance.

The repeated-measures ANOVA revealed no significant interaction between age and aerobic exercise on VM and NVM functions. However, aerobic exercise alone significantly improved VM functions. The study found that NVM performance in football players was significantly affected by age. Although studies generally report cognitive improvements from both acute and long-term aerobic exercise, there is limited evidence on the benefits of regular, long-term participation in team sports.[29] Consistent with these findings, Babaei et al. found that athletes aged 45–65 years with over 10 years of sports experience performed better on NVM tests than sedentary ones.[30] Similarly, De la Rosa et al. reported that long-term rugby practice was linked to better memory function, suggesting that prolonged sport participation may help delay age-related memory decline.[29]

The study found that at baseline, the NVM performance of the G1 group was better than that of the G2 group. This difference is likely due to the higher cardiovascular fitness of the G1 group, which tends to decrease with age, as seen in the G2 group. Supporting this, Mekari et al. demonstrated a relationship between cardiorespiratory fitness and cognitive function, highlighting that oxygen delivery to the brain plays a key role in this connection.[31]

Long-term aerobic exercise helps partially counteract the decline in cerebral blood flow that occurs with normal aging.[32] Physical exercise upregulates endothelial nitric oxide synthase activity, a key mechanism for increasing the cerebral blood flow.[33] Additionally, the blood flow in the brain's gray matter is positively correlated with cardiorespiratory fitness and negatively correlated with age, helping to prevent the cognitive decline.[34]

Studies suggest that cardiovascular fitness is linked to the integrity of brain white matter in middle aged people,[35] with aerobic exercise having the most significant effect on brain areas that have experienced substantial functional declines.[12] The lower effect of aerobic exercise in the G1 group compared to the G2 group may be due to the G1 group's cognitive function being normal and less affected by exercise. Long-term participation in football not only benefits physical fitness and cardiovascular health, but also helps maintain the cognitive function and delays its decline with age.

Participation in open-skill sports, which involve multiple stimuli and require an appropriate level of arousal, is more effective for improving the cognitive function.[36] For example, Ottoboni et al. found that team sports with open skills enhance verbal, visuo-spatial, and motor short-term memory.[37] Thus, strategic sports like football may improve working memory and cognitive plasticity.[21]

The study found that both age and aerobic exercise, as well as their interaction, significantly affect BDNF and TrkB levels in football players. BDNF, a key neurotrophin for neurogenesis, binds to its receptor TrkB.[38] After acute exercise, BDNF levels significantly increase compared to resting conditions, and this increase is positively linked to the improved cognitive function in humans.[39] Chronic aerobic exercise not only improves VO2 max but is also associated with a significant increase in BDNF levels.[40] Although serum BDNF levels increase following the aerobic exercise, resting serum BDNF levels appear to decrease after a prolonged (regular) exercise, suggesting an upregulation and efficiency

of BDNF-related pathways.[29,30]

Some studies have reported a significant increase in resting serum BDNF levels in middle-aged individuals compared to young ones, both in sedentary and trained groups.[29] However, most studies have reported a decrease in BDNF resting levels with the increase of age (40 years and later).[41–45] In this study, although the resting BDNF levels were higher in the G2 group, the difference from the G1 group was not significant, suggesting that long-term football practice modulates the BDNF secretion. Exercise may directly activate neuroprotective and neurotrophic pathways downstream of BDNF, influencing the binding of pro-BDNF and BDNF to Trk receptors, which could explain the reduction in resting serum BDNF levels.[46] In this study, resting serum levels of BDNF and TrkB did not differ significantly between the G1 and G2 groups at baseline. This indicates the maintenance of optimal levels of BDNF and TrkB in regular football players (i.e. G2 group). However, the G2 group demonstrated a stronger response to an aerobic exercise session. This response is likely related to the greater tissue demand for BDNF and TrkB in older individuals. In general, athletes have been shown to have improved BDNF and TrkB sensitivity.[47]

Furthermore, the higher response of BDNF and TrkB serum levels to aerobic exercise in the G2 group, along with similar resting levels in both groups, suggests a lower efficiency of this signaling pathway in the G2 group. However, conflicting results on the effect of regular, long-term aerobic exercise on BDNF concentrations highlight the need for further research to clarify these findings.[48]

BDNF expression in the brain and gray matter volume correlates with serum BDNF concentration, and this relationship is commonly used to study the impact of BDNF on memory functions in both normal and pathological conditions.[44,49] The decrease in BDNF levels in older individuals is linked to the reduced activation of the TrkB receptor and increased levels of proBDNF and the p75 neurotrophin receptor (p75NTR), suggesting aging-related disruptions in the BDNF signaling pathway and the conversion of proBDNF to mature BDNF.[44] Therefore, regular football practice may help enhance the efficiency of this pathway.

The expression of the BDNF/TrkB pathway and improvements in learning and memory have been linked to enriched environments.[50] As a form of enriched environment, football practice can activate mechanisms involved in cognitive functions, helping to improve cognitive abilities and moderate the decline in neurotrophin levels associated with aging.[51]

Morphologically, BDNF is considered the strongest stimulus for dendrite growth and development in the hippocampus,[52] leading to an increase in the number of dendritic spines.[53] BDNF-TrkB signaling plays a key role in synaptic development and neuroplasticity across various brain regions.[54] Despite the decline in cognitive functions and changes in BDNF and TrkB serum levels,[44] elderly football players maintain optimal cognitive functions and serum levels of BDNF and TrkB. Notably, the response of these serum levels to aerobic exercise was higher in the G2 group compared to the G1 group.

4.1. Limitations

A limitation of this study is the absence of a comparison group of non-exercising individuals within the same age categories as the young and older groups, which should be addressed in future studies.

5. Conclusion

Playing football as an open-skill activity can be a good option for improving cognitive function. It seems that long-term engagement in football provides the basis for better cognitive functions through BDNF-TrkB signaling in old age. Finally, it seems that one of the positive aspects of long-term sports practice is delaying the onset of physiological memory loss associated with normal aging.

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Declaration of competing interest

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. JESF Editors strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

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