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The Acute Effect of Prolonged Endurance Running on Hippocampal Subregions in Male Athletes

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ABSTRACT

Although the benefits of regular exercise have been known for several organs and systems, the effect on brain health is still under debate during aging. It has been widely accepted that type and duration of exercise play a critical role in the maintenance of cognitive function and memory. Ultramarathon (UM) has become a popular sport in recent years because of its benefits. This study aimed to determine the acute effect of 25 km half-marathon (HM) and 64 km UM on the hippocampus, especially on its subregions that are responsible for cognitive function and memory. A total of 15 healthy male runners aged between 40-60 years were grouped as HM (n=7) and UM (n=8). Brain scans were obtained with 3T magnetic resonance imaging (MRI) before and after the race. Volumetric differences in the subregions of the hippocampus were compared by using a paired-sample t-test in HM and UM groups before and after the race. As a result, the volume of subiculum subregion was increased in both HM and UM groups, whereas volumetric increase in total hippocampus and CA1-3 subregions were observed only in the UM group. The volume of DG remained unchanged in both HM and UM groups after the race. It can be concluded that endurance running causes an increase in hippocampal volume in healthy male runners. However, a certain threshold is needed to stimulate the CA1-3 subregion of the hippocampus. In conclusion, endurance running may prevent age-dependent atrophy in the hippocampus which has a key role in cognitive function and memory.

1. Introduction

Aging has become a major topic in health science in the 21st century as a result of the increased life expectancy of humankind which seems to break the 90-year survival barrier by 2030 [1]. The increased longevity of life creates important public health challenges since aging has adverse effects on all organ systems because of decreased metabolism, impaired immune system, increased oxidative stress, etc. [2-4]. The most profound effect of aging is on the structure and function of the brain, thus cognitive impairment and dementia are widely seen in aging societies [5]. Longitudinal studies reported an annual decrease of 2% in hippocampal volume which correlates with the decline in cognitive function and memory in the elderly [6]. On the other hand, there is a consensus that exercise is an effective form to stimulate the central nervous system to improve the cognitive ability and mental health [7], however, the type and duration for optimal benefit is still argued and remains unclear.

2. Literature Review

Recent studies explicitly propose that moderate exercise reverses and prevents cognitive function and cortical volumetric decrease in individuals with and without dementia [8-10]. Lee et al. (2018) showed that exercise inhibited neuronal apoptosis in the hippocampus. Hippocampus consists of Cornu Ammonus (CA), dentate gyrus (DG) and subiculum and plays a key role in memory and healthy aging [11]. It is a part of the limbic system placed in the medial temporal lobe and is sensitive to several lifestyle habits. Studies have shown that hippocampal volume decline may occur during depression, [12], chronic alcohol consumption [13] and prolonged stress [14]. On the other hand, higher education level, attendance to recreational activities, environmental enrichment, and physical exercise correlates with greater hippocampal volume among individuals suggesting that changing the lifestyle might have a beneficial effect in preventing or reversing the hippocampal atrophy [15,16].

Aerobic exercise triggers cell proliferation and survival in brain tissue, enhances synaptic plasticity which increases hippocampal volume and prevents or slow brain atrophy in the elderly [17]. Moreover, moderate exercise also increases cerebral blood volume in the hippocampus of adults, which is related to enhanced memory function and neurogenesis [18].

Neurological benefit of chronic endurance training attenuates cortical loss and possibly improve neurological function at every age [19]. However, type and intensity of exercise plays an important role in the magnitude of the effect of exercise on hippocampal volume [20]. Animal studies showed that regular moderate exercise attenuates improved newborn cell survival and increased blood vessel density in the hippocampus of chronic stress-induced rat model, whereas high intermittent exercise or strength training did not affect hippocampal volume changes or neurogenesis [21]. Resistance training caused long-term promotion on cognition and white matter volume in older women and triggered hippocampal synaptic plasticity [16]. The study indicated that aerobic exercise lasting eight weeks induced significant cognitive improvement and significantly increased the number of hippocampal neurons in CA and DG sub-regions [22]. Hajisoltani et al. (2011) found that moderate exercise might cause long-term potentiation in DG after 10 days [23], whereas Den Ouden et al. (2018) showed that exercise enhances long term potentiation in CA region of the hippocampus in acute stress-induced rat model [24]. Moreover, it has been hypothesized that low to moderate exercise may activate high-affinity glucocorticoid receptors that enhance memory and learning, whereas higher concentrations of glucocorticoids also activate low-affinity mineralocorticoid receptors, resulting in a lowered long term potentiation (LTP) and may cause memory impairment [25].

Ultramarathons are endurance races longer than a marathon and expose runners to severe physical and mental stress. The ultramarathons have become very popular in recent years with participants at an average age of 45 years [17,26]. Only a few studies have demonstrated positive effect of ultramarathon on volumetric changes in certain brain regions, however, there is only one study so far to our knowledge that has examined the chronic effect of endurance running on hippocampal volume in ultramarathon (UM) runners. Wood et. al (2016) showed that hippocampal volume did not differ between UM runners and their physical active agemates, however, volumetric changes in hippocampal subregions CA, DG and subiculum were not investigated [19]. Therefore, this study aimed to investigate the acute effect of prolonged endurance running on hippocampus subregions CA1-3, DG and subiculum in healthy male UM runners by using 3T MRI scanning and hippocampal segmentation.

3. Method

3.1. Participants

All subjects gave their informed consent form before participation in the study which was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the local University (83/09-10-2019). A priori power analysis was conducted to test the difference between two dependent group means using a two-tailed test, a medium effect size (d= .78), and an alpha of .05. Power analysis revealed that a sample of 15 participants with two equal sized groups of n = 7 was required to achieve a power of .80.

Fifteen healthy male runners aged between 40 and 60 years participated in the study and were grouped as half-marathon (HM) (n=7) or UM (n=8). The participants of the present study were enrollees of the Ultra-Skytrail who were contacted one week before the race and asked for participation in this study. Exclusion criteria were a history of alcohol and/or substance abuse, any neurological or psychiatric condition, metabolic disease, traumatic brain injury, hypertension, traffic accident, depression, any kind of medication and being left-handed.

3.2. Materials

Participants received a medical check-up and examination by physician before pre-race measurements. A questionnaire including personal information, medical conditions, and training and race history was administered to all participants on the day before the race. Weight and height measurements were performed according to standardized procedures [27]. The body-mass index (BMI) was calculated using the weight (kg)/height (m2) formula.

MRI acquisition and processing

MRI scans were performed twice for each athlete by the same radiologist at the National Research and Education City Hospital. Pre-race scanning was performed one day before the race, and postrace scanning immediately after the race. Brain scans were performed with a Siemens 3T MRI (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). The T1-weighted images were obtained at supine position with a 3D sagittal magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence (sagittal, repetition time (TR) = 2300 ms, echo time (TE) = 3.4 ms, field of view (FOV) = 250 mm2, matrix: 256×256, flip angle 7°, slice thickness = 1 mm). All images were examined for possible lesions in the cortex as an exclusion criterion. T1-weighted images were processed by cloud-computing software HIP 3 (http://volbrain.upv.es), which is an advanced automatic pipeline that provides automatic hippocampus subfield segmentation as CA1-3, CA4/DG and subiculum according to Kulaga-Yoskovitz method [28] described in detail elsewhere [29].

3.3. Procedure

All participants were assessed at the same day for pre-teat evaluation before the Erciyes Ultra Sky Trail (https://skyerciyes.com). All runners participated to the 25 km HM and 65 km UM according to their enrolment. Both HM and UM group runners had to pass the check points within a time limit and were free to consume food, water, and hypotonic drinks. The altimetry and distance of HM and UM are given in Figure 1 and 2, respectively.

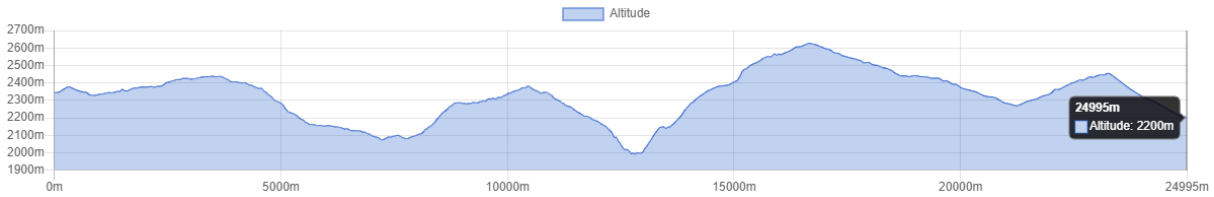

Figure 1. Schematic representation of 25 km HM route with detailed distance and altimetry (https://skyerciyes.com). The race lasted for 6.5 hours and took place between 08.00 am and 14:40 pm.

The HM runners completed a 25km half marathon with a total climbing of 1429 m at an altimetry ranging between 1991 m and 2626 m. The runner of UM group completed a distance of 65 km with a total climbing of 3223 m at an altimetry ranging between 1646 m and 2626 m. Mean temperature (day= 27.03±3.1°C; night=12.75±0.96°C; 12-29°C), humidity (12.2±2,3 %) and wind speed (8.05 km/h) were obtained from AccuWeather (AccuWeather Superior). Wet Bulb Globe Temperature index that is a measure of the heat stress in direct sunlight was calculated as 23.9 °C and heat index as 17.2 °C during the race.

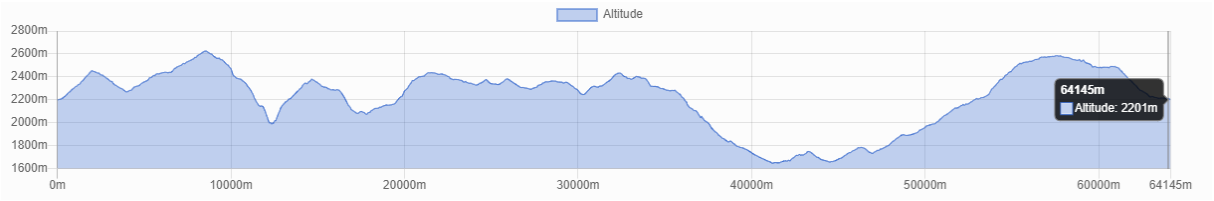

Figure 2. Schematic representation of 64 km UM with detailed distance and altimetry (https://skyerciyes.com). The race started at 05.30 am and finished the next day 07.00 am.

At the end of the race, runners were free to consume 200 gr of carbohydrates (hot pasta) and 200 ml of water during the transportation from mountain to hospital. Post-race MRI scans were performed within 20 minutes by the same radiologist.

Statistical analysis was performed by using the IBM statistical package program (SPSS version 25.0, IBM Corp.: Armonk, NY, USA). Shapiro-Wilk test was used to check the normality of distribution. Differences in the volume of hippocampal subregions CA1-3, CA4/DG and subiculum before and after the race were compared by using the paired-sample t-test in HM and UM groups, separately. The level of statistical significance was set at $p<0.05$. Results were interpreted as mean ± standard deviations from 95% confidence interval (CI).

4. Results

As shown in Table 1, the mean scores of HM and UM groups were nearly identical, regarding their age, height and body weight. BMI was almost the same with no statistical difference between HM and UM groups. Running history was lower in the UM group compared to HM whereas annual running distance was slightly higher in the UM group. Weekly running distance, training speed, and race speed showed no statistically significant difference between HM and UM groups (Table-1).

Table 1. Characteristics of the participants

	HM (n=7) mean±SD (%95 CI)	UM (n=8) mean±SD (%95 CI)
Age (years)	49.29 ± 5.85 (40-60)	46.25 ± 3.37 (40-52)
Height (m)	1.77 ± 0.07 (1.65-1.84)	1.75 ± 0.05 (1.67-1.82)
Weight (kg)	72.86 ± 9.00 (60-86)	71.62 ± 8.12 (63-90)
BMI (kg/m2)	22.04 ± 2.28 (22.04-27)	23. 05 ± 2.12 (22.02-27.41)
Running history (year)	10.29 ± 6.60 (4-20)	8.88 ± 4.64 (6-20)
Running distance (year/km)	3940.00 ±1875.23(1280-6800)	4187.50 ± 1338.91 (1100-5000)
Running distance (week/km)	132.86 ± 69.93 (50-270)	132.50 ± 89.24 (75-340)
Training volume (hours/week)	13.78 ± 4.30 (8-20)	10.75 ± 5.04 (8-21)
Mean training speed (km/h)	5.17 ± 0.62 (4.30-6.04)	5.16 ± 0.58 (4.30-5.80)
Mean race speed (km/h)	6.03 ± 1.37 (5.10-8.98)	5.95 ± 1.32 (4.43-8.2)

BMI: Body mass index

Pre and postrace hippocampal volume differences in the HM group were compared for both HM (Table 2) and UM (Table 3) groups, separately. Paired sample t-test showed a statistically significant increase in the subiculum volume and right subiculum in the HM group, whereas no other statistically significant change was observed in any other subregion of the hippocampus when prerace values were compared to postrace values. (Table 2).

Table 2. Volumetric changes in hippocampus and sub-regional structures in the HM race

Tissue Volume (cm^3)	n	Pre-race mean ± SD	Post-race mean ± SD	t	p
Hippocampus total	7	8.351 ± 0.901	8.440 ± 0.765	-.832	.437
Hippocampus right	7	4.254 ± 0.550	4.277 ± 0.491	-621	.558
Hippocampus left	7	4.099 ± 0.357	4.161 ± 0.285	-895	.405
CA1-3 total	7	5.209 ± 0.620	5.346 ± 0.501	-1,387	.215
CA1-3 right	7	2.694 ± 0.411	2.756 ± 0.359	-1,681	.144
CA1-3 left	7	2.514 ± 0.216	2.591 ± 0.172	-1,242	.260
CA4/DG total	7	0.911 ± 0.162	0.914 ± 0.142	-.108	.918
CA4/DG right	7	0.444 ± 0.082	0.446 ± 0.079	-.152	.884
CA4/DG left	7	0.464 ± 0.086	0.471 ± 0.077	-.267	.798
Subiculum total	7	2.180 ± 0.180	2.233 ± 0.170	-2,632	.039*
Subiculum right	7	1.079 ± 0.071	1.113 ± 0.071	-3,526	.012*
Subiculum left	7	1.117 ± 0.110	1.101 ± 0.114	.755	.479

*p<.05

In the UM group, a statistically significant increase was observed in the volume of total hippocampus, right hippocampus and left hippocampus after the race. Moreover, there was a statistically significant increase in the volume of total CA1-3 subregion and left CA1-3 subregion. UM group runners showed an increase in total subiculum and right subiculum after the race when compared to pre-race volumes. Other volumes of hippocampal regions remained the same when pre-race values were compared to the post-race value in the UM group (Table 3).

Table 3. Volumetric changes in hippocampus and sub-regional structures in the UM race

Tissue Volume (cm^3)	n	Pre-race mean ± SD	Post-race mean ± SD	t	p
Hippocampus total	8	8.153 ± 0.587	8.267 ± 0.579	-5.276	.001*
Hippocampus right	8	4.112 ± 0.323	4.168 ± 0.305	-2.960	.021*
Hippocampus left	8	4.036 ± 0.271	4.104 ± 0.286	-5.169	.001*
CA1-3 total	8	5.115 ± 0.649	5.179 ± 0.622	-2.441	.044*
CA1-3 right	8	2.631 ± 0.366	2.654 ± 0.341	-1.368	.214
CA1-3 left	8	2.484 ± 0.298	2.525 ± 0.294	-3.136	.016*
CA4/DG total	8	0.848 ± 0.105	0.858 ± 0.110	-.966	.366
CA4/DG right	8	0.411 ± 0.062	0.419 ± 0.069	-1.219	.262
CA4/DG left	8	0.439 ± 0.054	0.442 ± 0.054	-.284	.785
Subiculum total	8	2.189 ± 0.163	2.231 ± 0164	-2.753	.028*
Subiculum right	8	1.079 ± 0.071	1.095 ± 0.070	-2.489	.042*
Subiculum left	8	1.114 ± 0.098	1.138 ± 0.109	-1.610	.151

*p<.05

5. Discussion and Conclusion

The main purpose behind conducting this study was to investigate the acute effect of endurance running at different distances on hippocampal volume and its subregions which are suggested to be involved in cognitive functioning, spatial and non-spatial memory. For the first time in literature, as to our knowledge, this study was focused on the effect of UM running in male athletes' hippocampal subregions CA1-3, DG, and subiculum which responded differently to exercise in previous animal studies.

The findings of this study showed that UM running has an acute effect on hippocampal volume and the sub-regions which responded differently to prolonged durations of exercise in HM and UM races. The subiculum subregion increased in volume after HM and UM races in all runners. However, the volume of the total hippocampus and the subregion CA1-3 increased only in the 64 km UM race, whereas the 25 km HM race failed to cause an increase in these regions of the hippocampus. DG remained the same after both HM and UM races. Although hippocampus studies with UM runners are sporadic, the results of this study are in concordance with previous neurology research performed with animals and humans. Animal studies showed that exercise has a site-specific influence [22]. Previous research that examined the hippocampus, thalamus and caudate showed that exercise effect was highly selective, influencing only the anterior hippocampus, but not the thalamus or the caudate nucleus [30]. The results in this study are parallel to our findings since the anterior hippocampus mainly consists of the subiculum and the subregion CA1 [31], which has increased in volume in the endurance runner in the present study.

Subiculum volume has increased in both HM and UM races which are the same type of activity performed in an outdoor environment. This seems consistent with literature since the subiculum is the pivotal structure in spatial information processing and plays a crucial role in organizing hippocampal output [32]. Multiple CA1 place cells converge with one subicular neurons which are activated and consistently modulated by movement-related activity. This place and movement signal combination is assumed to modulate hippocampal spatial information and body movement-related information in the subiculum [33]. Moreover, research performed with rats showed that the visual cortex sends visual information of external landmarks to the subiculum which in turn calibrates head-direction signals

[34]. A study showed that the hippocampus plays a crucial role in navigation, especially in unknown and outdoor environments [35]. Since both groups performed exercise in an outdoor environment and run continuously for several hours in an open area, it not surprising that subiculum might be activated in both groups and underwent a volumetric increase. Moreover, firing pattern of neuronal units in CA1 and subiculum were different in dark and light transition [36,37] which might be a possible explanation for CA1-3 subregion volume increase in the UM group who were running during night (from 05.30 am to the next day 07.00 am), whereas HM group finished the race in day time (between 08.00 am and 2:40 pm).

It might be speculated that increased volume in the subiculum and CA1-3 subregions might correlate with an incline in Brain-Derived Neurotrophic Factor (BDNF) in the hippocampus since previous studies found a strong correlation between hippocampal volume and BDNF-mediated signaling [38-39]. Erickson et.al (2011) found that a volumetric increase in the anterior hippocampus was associated with high BDNF serum levels [30], suggesting that anterior hippocampus is rich in BDNF which may increase with exercise also in humans [40,41]. Furthermore, the increase in the hippocampus volume correlates with BDNF increases within the CA1 subregion in animals [42] which parallels findings of our study that identified volumetric increase in the CA1-3 subregion the UM group.

Barzroodi et. al (2019) showed that prolonged exercise may modulate GABA signaling pathways in the CA1-3 subregion of the rat hippocampus. It was concluded that exercise can cause both the upregulation of GABA receptors in CA3 and down-regulation in CA1 and CA3 subregions in epileptic rats [43]. These findings support the results of the present study that showed increased volume in CA1-3 subregion in the hippocampus of UM runners, but not HM, suggesting that CA1-3 subregions are sensitive to prolonged exercise compared to DG subregion which was unaltered in both HM and UM groups.

Previous literature is in concordance with these findings suggesting that plasticity in animals may show diversity depending on exercise type, duration, speed and intensity as well as age, strain, and sex differences [44,45]. In a longitudinal study, Erikson et.al (2011) demonstrated that stretching exercise could not prevent brain atrophy and caused a 1.4% decline in the elderly, whereas aerobic exercise was effective at increasing hippocampal volume by 2% and preventing hippocampal atrophy [30]. A meta-analysis has demonstrated that acute aerobic exercise increases basal peripheral BDNF concentrations, whereas strength training or intermittent exercise did not affect [46]. Swimming, on the other hand, reversed the decline in BDNF mRNA expressions in stressed rats [47]. Animal studies showed BDNF expression correlated positively with aerobic exercise [48], but not with anaerobic exercise [49,50]. Strength exercise seems to have an adverse effect and attenuates the aerobic exercise-induced BDNF mRNA levels in rats [51]. Meditation, however, had a summative effect on synchronous neuronal responses during physical training [52], suggesting that neuronal activity increase BDNF expression and function [53].

Age is a very critical predictor for adult hippocampal neurogenesis and plasticity during prolonged exercise since previous animal studies strongly agree that exercise may prevent age-dependent atrophy and improve plasticity predominantly in the elderly [54]. This situation was explained by increased blood flow during exercise due to the location of proliferating hippocampal cells near the small capillaries [55]. In contrast to previous studies that identified increased blood flow in animal and human DG subregion after exercise [56], both HM and UM groups did not show any volumetric alteration in the DG subregion. However, greater volume of total hippocampus, subiculum and CA1-3 subregion after UM and subiculum after HM might indicate increased blood flow in both groups, but to a greater extent in the UM group. This result is supported by previous literature that suggests that the duration of learning tasks or training plays a critical role in the survival of new adult-born hippocampal neurons [57]. It has been

accepted that extended engagement in the learning process increases new neuron survival in the hippocampus [58,59]. Furthermore, endurance exercise training promotes angiogenesis in brain tissue [60]. Considering all these findings, it might be concluded that physical training, like cognitive training, should be performed for a certain duration and volume to benefit adult hippocampal neurogenesis.

In this study, it can be speculated that the 25 km distance of HM was not enough to trigger exercise dependent adult hippocampal neurogenesis. This might be explained by shorter exercise duration and lower exercise volume in HM compared to UM. Moreover, the athletes in the HM group were not new starters and had the same fitness level as the UM group since training volume was nearly the same in both groups. It is not surprising that the acute effect of endurance running on the hippocampus was greater in the UM group than the HM group. It can be concluded that there is a threshold of aerobic exercise to stimulate adult hippocampal neurogenesis and this threshold depends on certain factors such as physical fitness level of the athletes, age, sex, genetic variation, etc. [19,61]. This phenomenon is not limited to the brain and is also valid for maximal aerobic capacity (VO2max) and metabolic health [62].In conclusion, this study showed that the volume of subiculum increased after both HM and UM in male endurance runners aged between 40 and 60 years. Moreover, UM was able to cause an increase in the volume of CA1-3 subregion and total hippocampus, whereas HM did not affect these regions suggesting that a certain threshold is needed to trigger hippocampal volume increase. Interestingly, the DG subregion remained the same before and after the race in both groups. It can be concluded that UM has benefits for healthy male runners suggesting that exercise dependent increased volume may prevent age-dependent atrophy in the hippocampus which has a key role in cognitive function and memory.

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