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Human Kinetics
ORIGINAL RESEARCH

Greater Semantic Memory Activation After Exercise Training Cessation in Older Endurance-Trained Athletes

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Purpose: To examine the effects of a 10-day exercise-training cessation on semantic memory functional activation in older distance runners. ***Methods:*** Ten master runners (62.6 ± 7.0 years) with a long-term endurance-training history (29.0 ± 6.0 years) underwent a 10-day training cessation. Before and immediately after the training cessation, semantic memory activation was measured during the famous name recognition task, using functional magnetic resonance imaging. ***Results:*** The 10-day training cessation resulted in greater semantic memory activation in three brain regions, including the left inferior frontal gyrus, parahippocampal gyrus, and inferior semilunar lobule. The 10-day training cessation did not significantly alter famous name recognition task performance. ***Conclusions:*** The findings demonstrate that even a relatively short period without exercise training alters the functional activation patterns of semantic memory–related neural networks. Increased semantic memory activation after training cessation may indicate reduced neural efficiency during successful memory retrieval.

Keywords: aging, brain health, cognition, healthy older adults, fMRI, master athletes

Age-related cognitive decline often begins before 60 years of age in many individuals (Salthouse, 2009), and memory dysfunction is one of the most common hallmarks of age-related cognitive impairment (Grady & Craik, 2000). Age-related memory decline often accompanies hippocampal atrophy (Mega et al., 2002), altered functional connectivity (Beason-Held, Hohman, Venkatraman, An, & Resnick, 2017), and reduced synaptic contacts (Detoledo-Morrell, Geinisman, & Morrell, 1988; Foster, 1999). Severe memory deficits are also a part of the clinical symptomatology of mild cognitive impairment and Alzheimer's disease (AD; Petersen, 2000). Currently, 17% of Americans between the ages of 75 and 84 years, and 32% of those between 80 and 85 years suffer from AD (Alzheimer's Association, 2019), making it one of the nation's greatest public health concerns.

Exercise training serves as a potent and cost-effective intervention to maintain cognitive health in late adulthood (Cotman & Engesser-Cesar, 2002). Several animal studies have suggested that exercise training induces neurogenesis in the hippocampus (Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002), a brain area specifically affected early in the course of AD, and improves hippocampal-dependent learning and memory (Russo-Neustadt, Alejandre, Garcia, Ivy, & Chen, 2004). Among older adults, exercise training results in both greater hippocampal volume and enhanced spatial memory performance (Erickson et al., 2011). Additionally, exercise training in healthy older adults reduces cortical activation during a semantic memory retrieval task (the famous name recognition task [FNT]). This effect occurred in the absence of changes in performance, suggesting improved neural efficiency during semantic memory retrieval (Smith et al., 2013).

Although numerous studies provide support for exercise as an important lifestyle behavior to maintain cognitive health in older adults, it is unknown whether these benefits might be reversed when an individual ceases training. Rodent evidence suggests that stopping exercise may not only reverse exercise-induced neurophysiological adaptations (Radak et al., 2006), but may also decrease the expression of brain-derived neurotrophic factor and impair neurogenesis (Nishijima et al., 2013). In humans, we showed that a 10-day cessation of exercise training in older distance runners reduced cerebral blood flow (CBF) in the bilateral hippocampi, as well as several cortical regions (Alfini et al., 2016). These prior results suggest that even a short-term period without exercise training significantly affects the cerebrovascular system in regions known to be important for cognitive functions, including brain regions critical to memory. In the current study, using neuroimaging data collected in a sample of older men and women endurance runners, we investigated the effects of exercise training cessation on brain network activation during the performance of a well-characterized semantic memory task (Rao et al., 2015; Smith et al., 2013).

The use of a short period of exercise training cessation will provide a unique opportunity to understand the importance of continuous exercise training on brain networks involved in cognition and memory in older adults. Thus, the purpose of the present study was to determine the effects of 10 days of exercise training cessation in older endurance-trained men and women on semantic memory-related brain activation using functional magnetic resonance imaging (fMRI). Considering earlier findings showing that an exercise training intervention resulted in reduced semantic memory-related activation (Smith et al., 2013), we hypothesized that the cessation of exercise training would increase semantic memory-related activation, which would suggest a reduction in neural efficiency. We further explored whether changes in semantic memory-related activation (Δmemory activation) were associated with previous results demonstrating cessation-induced changes in hippocampal CBF (ΔCBF; Alfini et al., 2016) to assess the possible association between the training cessation effects in different metrics of brain function. We hypothesized that increased memory-related neural activation would be associated with decreased hippocampal CBF after the cessation of training.

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Methods

Participants

Twelve master runners (seven women and five men, aged 54–76 years) were recruited from running clubs in the Washington, DC/Baltimore area. The inclusion criteria were: ≥50 years old, ≥15 years of endurance training history, ≥4 hr/week of high-intensity endurance training, body mass index <30kg/m^2, ≥27 (out of 30) of the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), and recent participations in either regional- or national-level endurance competitive events. Individuals were excluded if they reported being a smoker within the past 5 years, history of heart attack, stroke, diabetes, lung disease, chronic obstructive pulmonary disease, peripheral vascular disease, high blood pressure (systolic blood pressure >130 mmHg and diastolic blood pressure >80 mmHg), kidney disease, anemia, left handedness, or MRI contraindications. Female participants who had not been postmenopausal for at least 2 years and had used hormone therapy during the previous year were excluded. The study procedures were approved by the institutional review board at the University of Maryland and were administered according to the Helsinki Declaration of 1975. Written informed consent was obtained from all participants. The data were collected from October 2012 to December 2013.

Training Cessation

The 10-day training cessation began 72 hr after the first MRI scan. During the cessation period, the participants were instructed to refrain from aerobic exercise training and only perform activities of daily living. The participants were called every other day during their training cessation to ensure that they had not performed any exercise. The number of training cessation days (10 days) was chosen to minimize the changes in $\dot{V}O_2$max and body composition (Rogers, King, Hagberg, Ehsani, & Holloszy, 1990). The second MRI session was administered in the morning following the last day with no training.

Blood Pressure, $\dot{V}O_2$max Test, and Body Composition Assessment

After completion of the first MRI scan, the participants' brachial blood pressure was measured. Subsequently, the participants underwent a graded maximal exercise test to measure cardiorespiratory fitness, using indirect calorimetry (Quark; COSMED, Chicago, IL). A Bruce treadmill exercise test (Bruce & Hornsten, 1969) with standard electrocardiogram monitoring (Rogers et al., 1990) was used for the test protocol, and a cardiologist was present for standard electrocardiogram monitoring. The end point of the test was the inability to continue due to volitional exhaustion. The criteria for attainment of maximal effort were a plateau in $\dot{V}O_2$ despite an increase in workload and a respiratory exchange ratio of >1.1. This maximal exercise test protocol has previously been used in master runners (Heath et al., 1983; Seals et al., 1984). Dual-energy X-ray absorptiometry (Prodigy, LUNAR Radiation Corp.) was used to assess body composition.

fMRI Acquisition

Whole-brain, event-related fMRI data were acquired on a 3.0-Tesla Siemens (Munich, Germany) TIM TRIO MR scanner using a 32-channel head coil. A high-resolution T1-weighted anatomical image was acquired for coregistration, with the following sequence parameters: Magnetization Prepared Rapid Acquisition of Gradient Echo, matrix = 256, field of view = 230 mm, voxel size = 0.9 × 0.9 × 0.9 mm, slices = 192 (sagittal plane, acquired right to left), slice thickness = 0.9 mm, repetition time = 1,900 ms, echo time = 2.32 ms, inversion time = 900 ms, flip angle = 9°, and sequence duration = 4:26 min. The FNT event-related data were acquired using the following sequence parameters: single-shot gradient echo planar images, matrix = 64, field of view = 192 mm, voxel size = 3.0 × 3.0 × 3.0 mm, slices = 36, slice thickness = 3.0 mm, repetition time/echo time = 2,000/24 ms, volumes = 175, flip angle = 70°, bandwidth = 2232 Hz/Px, multislice mode = interleaved, and sequence duration = 5:56 min. The fMRI data were acquired between 7:00 AM and 9:00 AM.

fMRI Task

To assess semantic memory-related activation, the FNT was administered electronically using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) during the fMRI acquisition. The fMRI task consisted of 30 famous (e.g., Frank Sinatra) and 30 nonfamous names projected on a screen directly above the participants' face. Only names with a high rate of identification (>90% correct) were selected from an original pool of 784 names (Douville et al., 2005), which has been validated for older adults (Smith et al., 2013; Sugarman et al., 2012; Won et al., 2019). The stimuli were presented for 4 s each, with a randomly interspersed 4-s centrally placed fixation crosshair at an overall 2:1 (names: fixation) ratio. The participants completed the FNT in the scanner using an MRI-compatible button box in their right hand. The participants were instructed to press a button using the index finger of their right hand for famous names and another button using the middle finger of their right hand for nonfamous names. The participants were also instructed to do their best to accurately identify the names. Both accuracy (%correct) and response time (RT in milliseconds) were recorded. Two unique versions of the task were administered in counterbalanced order for each participant.

Image Analysis

Preprocessing. First, both anatomical and functional images were converted into 3D space using the Analysis of Functional NeuroImages (AFNI)'s Dimon program (Cox, 1996). Second, the anatomical images were processed using Freesurfer's (version 5.3.0; Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA) cortical reconstruction process for cortical parcellation and subcortical segmentation (Fischl et al., 2002). Next, the first 3 TRs of each functional time series were manually discarded using AFNI's 3dTcat function to avoid magnetization disequilibrium. The truncated functional data were realigned using Slice-Oriented Motion Correction to reduce motion artifact effects (Beall & Lowe, 2014). The functional time series data were then aligned with the Freesurfer-processed anatomical images using AFNI's Local Pearson Correlation cost function (align_epi_anat.py). The aligned anatomical and functional data were visually inspected for quality assurance and further processed using AFNI's preprocessing program (proc.py). The functional data were despiked, (3dDespike) and each volume of the time series was time-shifted to the beginning of the TR (3dTshift). TRs with excessive motion (outlier fraction >10%) were censored. Nonlinear transformation of the anatomical images to the standard space (AFNI's MNI152_T1_2009c template) was performed (3dQwarp). The resulting nonlinear transformation matrices were used to normalize and resample the functional data. The resolution of the final image was 2 × 2 × 2 mm. There was no difference in the percentage of censored TRs between the before (0.20 ± 0.06%) and after cessation scans (0.22 ± 0.06%) (p = .343), suggesting that the effects of head movement were negligible and did not confound our fMRI data interpretation.

The FNT data processing. Regressors for famous and nonfamous trials were created using only correct trials to isolate semantic memory activation associated with correct FNT performance. We reasoned that investigating error-related processing based on incorrect trial analysis would not be effective using the FNT because the task was designed to produce fewer error trials (>90% of accuracy rate in healthy older adults). Therefore, incorrect trials were not modeled in the analysis. The famous and nonfamous name regressors were created by convolving a square wave (duration [d] = 4 s; amplitude [p] = 1) using AFNI's 3dDeconvolve function. The resulting parametric maps for each participant were used for the group analysis.

Whole-brain voxel-wise group analysis. Semantic memory-related activation was defined where the famous minus nonfamous contrast showed significant differences. The rationale for this subtraction was to reduce the confounding effects of task performance and nonsemantic memory-related activation (e.g., activations in visual cortex while looking at the screen). This method effectively isolates semantic memory-related activation and has been used in previous studies (Smith et al., 2013; Won et al., 2019; Woodard et al., 2009). Second, a gray matter mask was created by combining all participants' gray matter masks based on the voxels identified as gray matter during Freesurfer segmentation. The aggregated group-level gray matter mask was used for the final analysis. Third, using AFNI's paired t-test program (3dttest++), semantic memory-related activation maps (famous minus nonfamous) illustrating the intensity and spatial location of activation were created for before and after training cessation, respectively. Next, AFNI's cluster-thresholding program (3dClustsim) was used to control the whole-brain family-wise error rate (FWER) corrected alpha = .05 by setting an uncorrected voxel-wise threshold of $p < .005$ and minimum cluster size $k \geq 70$ (NN = 1). Then the semantic memory activation maps for before and after training cessation were combined to create a disjunction ("OR") mask (Figure 1). Any significantly activated clusters (famous minus nonfamous contrast) identified before and after the training cessation were included in the disjunction map. The voxels identified in the disjunction map were then applied to each participant's individual functional data to extract the mean activation intensity (β) from each region.

Postscan Recognition Task

The postscan recognition task was administered immediately after the MRI scan outside of the scanner environment. Before each MRI scan, the participants were informed that they would receive a postscan recognition test composed of famous names that were presented during the scan and famous names that were not presented during the scan. The test consisted of a list of 120 famous names, including 60 famous names that were old and had been viewed during the scan and 60 famous names that were new and had not been presented during the scan. The participants were instructed to circle the famous names that had appeared during scan. The postscan recognition task corresponded to the version of the task administered during the scan. The following variables were calculated based on the test results: hit (correct recognition of old name), miss (failure to recognize old name), correct rejection (correctly recognized as a new name), and false alarm (incorrectly indicating a new name as old). We also calculated d prime (the standardized difference between the hit rate and false alarm rate) to measure the participant's discriminability using R psycho package (Makowski, 2018). A higher d prime indicates more accurate discrimination between old and new names.

Statistical Analysis

Paired sample t-tests were used to compare semantic memory-related activation intensity, the FNT, and postscan recognition performance between before and after training cessation. Benjamini–Hochberg false discovery rate (FDR) correction was conducted to control the family-wise error rate for multiple comparisons (Benjamini & Hochberg, 1995). Statistical significance was determined using a two-tailed alpha = .05. We used a nonparametric statistical test (Wilcoxon signed-rank test) to analyze the famous name accuracy data because they were not normally distributed (negative skewness and high kurtosis). We used linear regression to examine the association between changes induced by exercise training cessation in semantic memory activation (Δmemory activation) and CBF (ΔCBF; Alfini et al., 2016). Training cessation-induced changes were computed by subtracting before-cessation values from after-cessation values. All statistical tests were conducted using SPSS (version 21.0, Armonk, NY).

Results

Participant Endurance Training Profile

Ten out of 12 qualified endurance runners were included in the final analysis. Two individuals were excluded due to the following reasons, respectively: irregular electrocardiogram activity during the exercise stress test and failure to achieve $\dot{V}O_2$max during the exercise stress test. On average, their continuous endurance training history was 29 years. At the time of enrollment, each participant had been engaged in high-intensity endurance training at least 4 days/week and, on average, running a distance of 59 km/week. The participants were retired or had sedentary occupations. Collectively, these master runners were highly trained and possessed a level of cardiorespiratory fitness above the 90th percentile for their age and sex (American College of Sports Medicine, 2013). Demographic, physical, and cognitive data for all participants are provided in Table 1.

The FNT and Postscan Recognition Performance

The FNT and postscan recognition test performance data are reported in Table 2. There were no statistically significant differences in FNT performance before compared with after training cessation, including famous name RT, $t(9) = .386$, $p = .709$, $d = 0.121$; nonfamous name RT, $t(9) = -1.530$, $p = .160$, $d = 0.483$; famous name accuracy, $Z = -0.877$, $p = .380$, $d = 0.296$; and nonfamous name accuracy, $t(9) = .176$, $p = .864$, $d = 0.055$. Similarly, none of the postscan recognition test performance measures showed statistically significant differences from before to after training cessation, including hit rate, $t(9) = -.165$, $p = .872$, $d = 0.052$; miss rate, $t(9) = .263$, $p = .798$, $d = 0.083$; correct rejection rate, $t(9) = -.412$, $p = .690$, $d = 0.129$; and false alarm rate, $t(9) = .079$, $p = .938$, $d = 0.025$. There was also no change in d prime between the before and after training cessation, $t(9) = -.051$, $p = .961$, $d = 0.015$. The lack of change in FNT performance during the scan and the consistency of the famous name recognition performance after the scan are consistent with

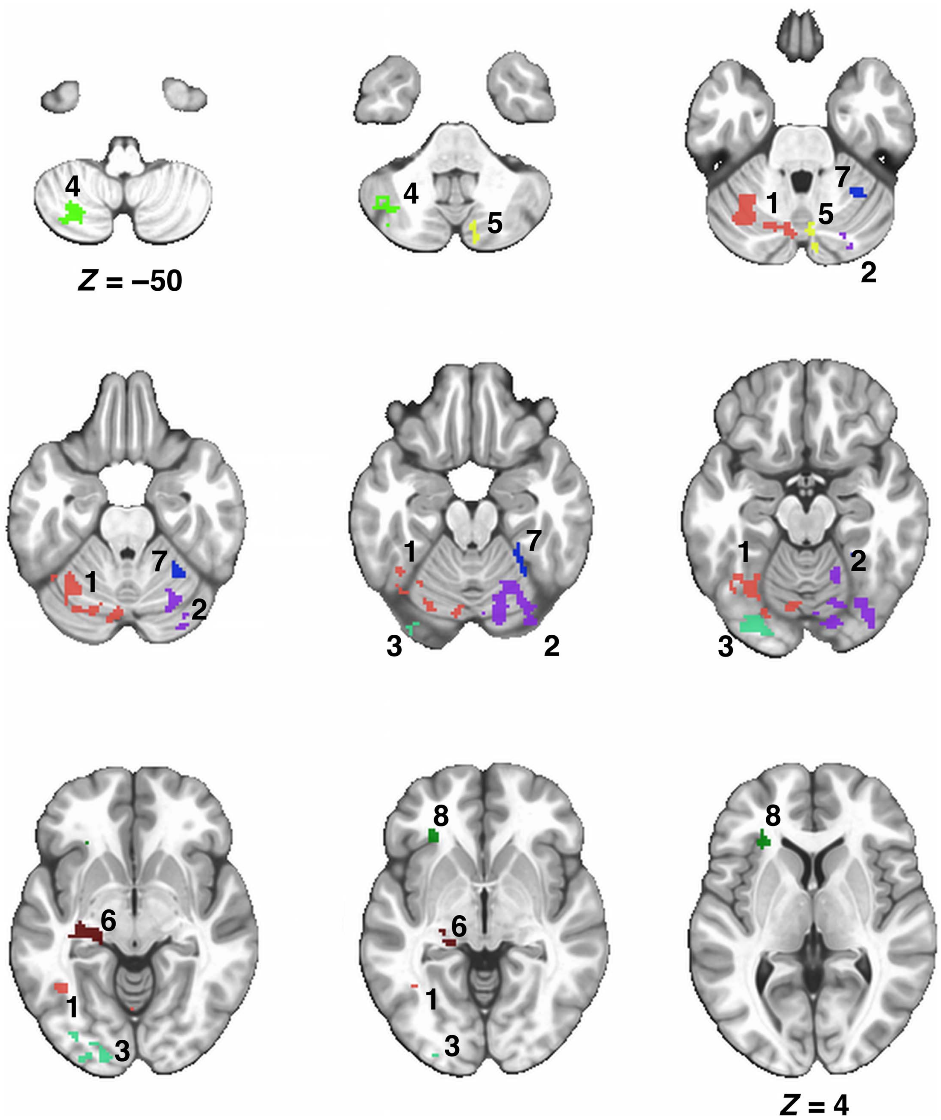

Figure 1 — A montage of axial slices showing eight regions derived from a disjunction (OR) mask activated in both the before and after training cessation. The numerical labels correspond to the region numbers shown in Table 3.

previous studies and are key to the interpretation of the changes in functional activation that were observed.

Semantic Memory fMRI Activation

The disjunction ("OR") mask identified eight regions demonstrating significant semantic memory-related activations for before and after training cessation (Figure 1). The comparison of the activation in each region between before and after training cessation using a paired sample *t* test is presented in Table 3. Three out of eight regions demonstrated significantly greater semantic memory-related activation after training cessation than before training cessation (Figure 2). The regions showing significantly greater activation after training cessation include the left inferior frontal gyrus ($p = .023$; FDR threshold $p = .0062$), parahippocampal gyrus ($p = .033$; FDR threshold $p = .012$), and inferior semilunar lobule ($p = .021$; FDR threshold $p = .018$). While these significant effects did not survive FDR correction for multiple comparisons, the effect sizes were large, and the 95% confidence intervals (CIs) for the effect sizes do not include zero (see Table 3).

Post Hoc Linear Regression Analysis

The hippocampus was chosen as an a priori region of interest in our previous study, and we found that exercise cessation significantly decreased CBF in the left and right hippocampus (Alfini et al., 2016). In the current analysis, we observed greater semantic memory-related activation in the left hippocampal region. While these two results did not directly overlap, they were similar in spatial location. We conducted an exploratory post hoc analysis to determine whether these two effects were related. The association between cessation-induced changes in CBF in the left hippocampus and semantic memory activation in the left parahippocampal gyrus was examined using linear regression. Nine participants whose data were successfully processed in both sessions were included in this analysis. While the association was not statistically significant, there was a moderately strong relationship between increased memory activation and decreased CBF in the left hippocampal area after training cessation, $R^2 = .433$, $F(1, 7) = 5.335$, 95% CI = [−105.5, 1.2], $p = .054$; Figure 3.

Discussion

Our study provides evidence that a 10-day period of endurance training cessation among older distance runners significantly alters semantic memory-related neural networks. In agreement with our hypothesis, there was an increase in the magnitude of semantic memory-related fMRI activation from before to after the training cessation. Importantly, there were no differences between the test sessions in the FNT performance during the scan or the famous name recognition test performance after the scan. This finding is consistent with the prior study that reported no significant changes in cognitive task performance (verbal fluency) from before to after training cessation (Alfini et al., 2016). The increased semantic memory-related activation we observed after the cessation of training, therefore, occurred in the absence of alterations in memory performance. Indeed, 10 days of cessation from exercise training would not be expected to impact overall cognitive or memory function. This leads to a question regarding how to interpret the pattern of activation changes that occurred in light of the fact that cognitive performance was unaltered.

Using the same semantic memory task, there was a significantly reduced semantic memory activation following a 12-week treadmill walking exercise intervention in sedentary older adults that led to an 10% increase in maximal aerobic capacity (Smith et al., 2013). As in the current study, and as expected, the participants demonstrated high accuracy during the FNT, and the performance did not change as a result of the exercise intervention. Thus, it was speculated that neural adaptations following exercise training within the semantic memory network resulted in a reduced neural workload during successful memory performance (i.e., recognition of the names as famous due to retrieval of previously learned semantic information), and this effect was represented by decreased semantic memory-related fMRI activation (Smith et al., 2013). Furthermore, it was reasoned that the reduced activation after exercise training reflected enhanced efficiency and resilience of the neural network and the development of a stronger neural scaffolding within the network (Reuter-Lorenz & Park, 2014).

Extending our hypothesis concerning the relationship between exercise training and semantic memory neural networks, we surmise that training cessation and the relatively brief yet drastic move to a sedentary lifestyle may have, to some limited degree, though not completely, reversed exercise-training–related neural network efficiency. Our sample was small, we did not have a control group that continued to train, nor were we able to demonstrate a restoration of these changes when training was resumed, so our results should be considered with caution. While the statistically significant results did not survive correction for multiple comparisons, the

Table 1 Demographic Information, Physical Characteristics, and Cognitive Function of Study Participants

Variable	Total sample ($n = 10$) Mean (*SD*)
Demographic Information	
Age (years)	63.5 (6.3)
Female (*n*)	6
Training history (years)	29.0 (6.0)
Physical characteristics	
Height (cm)	170.8 (7.9)
Weight (kg)	68.1 (15.7)
BMI (kg/m^2)	23.4 (3.1)
$\dot{V}O_2$max (ml·kg^{-1}·min^{-1})	43.8 (9.0)
Female	40.5 (10.6)
Male	44.9 (7.9)
%Body fat	27.5 (8.2)
Female	30.1 (8.9)
Male	24.4 (6.9)
Blood pressure (mmHg)	
SBP	121.4 (16.3)
DBP	71.8 (7.7)
MAP	88.3 (8.4)
Cognitive function	
MMSE	28.8 (1.3)

Note. BMI = body mass index; $\dot{V}O_2$ max = relative maximal oxygen consumption; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; MMSE, Mini-Mental Status Exam (out of 30).

Table 2 Famous Name Task and Postscan Recognition Task Performance

	Total sample ($n = 10$)		
	Before	After	Time main effect
Semantic Memory Task Performance	Mean (*SD*)	Mean (*SD*)	*p* value (*d*)
FNT			
Famous RT (ms)	1,226.1 (271.1)	1,243.79 (253.8)	.709 (0.12)
Nonfamous RT (ms)	1,639.3 (587.0)	1,519.15 (386.3)	.160 (0.48)
Correct famous (%)	92.0 (9.5)	90.66 (9.5)	.380 (0.29)
Correct nonfamous (%)	95.0 (4.7)	95.33 (5.9)	.864 (0.05)
Postscan recognition performance			
Hit (%)	60.33 (10.3)	59.88 (11.1)	.872 (0.05)
Miss (%)	39.33 (10.8)	40.16 (11.1)	.798 (0.08)
Correct rejection (%)	90.33 (14.7)	90.00 (14.8)	.690 (0.12)
False alarm (%)	9.66 (14.7)	9.83 (14.8)	.938 (0.02)
d prime	1.80 (0.7)	1.81 (0.7)	.961 (0.01)

Note. RT = response time; *d* = Cohen's *d* effect size; d prime = difference between the *z* score of hit and false alarm; FNT = famous name recognition task.

Table 3 Comparison of Semantic Memory-Related Activation (Famous Minus Nonfamous) Between the Pre- and Posttraining Cessation in Eight Brain Regions Derived From a Disjunction Mask

Brain Anatomical Location								Total sample ($n = 10$) Before	After	Time main effect	
Region no.	Side	Region label	BA	*x*	*y*	*z*	Volume (mm^3)	Mean (*SD*)	Mean (*SD*)	*p* value	*d* [95% CI]
Frontal lobes											
8	L	IFG, insula, and claustrum	47	−27	29	−7	584	0.02 (0.06)	0.10 (0.05)	.023	0.864 [0.11, 1.58]
Temporal lobes											
6	L	PHG, HIPP, CD, LTN, and THL	28	−15	−25	−15	840	0.13 (0.16)	0.26 (0.08)	.033	0.791 [0.05, 1.49]
Occipital lobes											
3	L	IOG, MOG, LG, and cuneus	17 and 18	−35	−89	−21	2,048	0.32 (0.30)	0.32 (0.17)	.973	−0.011 [−0.63, 0.60]
Subcortical and cerebellum											
1	L	UV, declive, and FG	19 and 37	−23	−69	−33	4,200	0.09 (0.11)	0.17 (0.07)	.077	0.632 [−0.65, 1.30]
2	R	Declive, LG, and FG	18 and 19	27	−83	−29	3,312	0.20 (0.24)	0.26 (0.07)	.525	0.209 [−0.42, 0.83]
4	L	ISLL, CT, and pyramis		−33	−71	−53	1,736	0.04 (0.07)	0.12 (0.05)	.021	0.878 [0.12, 1.59]
5	R	UV, declive, and pyramis		9	−83	−43	984	0.05 (0.14)	0.13 (0.05)	.182	0.458 [−0.20, 1.10]
7	R	Culmen		31	−51	−33	696	0.07 (0.12)	0.16 (0.06)	.058	0.686 [−0.02, 1.36]

Note. The region numbers correspond to the regions in the brain activation maps identified in Figure 1. Positive, right (*x*), anterior (*y*), and superior (*z*) representing peak activation in Talairach coordinates. BA = Broadmann area; *d* = Cohen's *d* effect size; CI = confidence interval; CD = caudate; CT = cerebellar tonsil; FG = fusiform gyrus; IFG = inferior frontal gyrus; HIPP = hippocampus; IOG = inferior occipital gyrus; ISLL = inferior semilunar lobule; LG = lingual gyrus; LTN = lentiform nucleus; MOG = middle occipital gyrus; PHG = parahippocampal gyrus; THL = thalamus; UV = uvula.

effect sizes were large and the 95% CIs did not overlap with zero. Moreover, although the significant *p* values were greater than the FDR correction threshold, a possible occurrence of Type II error due to overcorrection should be taken into consideration, as we employed a relatively stringent approach during the voxel-wise analysis (i.e., $p < .005$). Nevertheless, our results, which are in line with previous findings in both animal models and studies of older adults, should be replicated in a larger sample.

Prior studies have reported impaired neurogenesis (Nishijima et al., 2013; Nishijima, Kamidozono, Ishiizumi, Amemiya, & Kita, 2017) and reduced brain-derived neurotrophic factor expression (Radak et al., 2006) in the rodent hippocampus after cessation of exercise training. A short-term exercise training cessation has also reverted training-induced adaptations in several physiological systems. For example, 10 days of exercise training cessation was associated with exacerbated insulin-regulated glucose metabolism (Rogers et al., 1990), and a 7-day training cessation impaired the stress response and immune system function (Glass et al., 2004). In summary, studies of this nature consistently suggest that neurophysiological and physiological adaptations induced by exercise training are not permanent and rapidly dissipate in the absence of the training stimulus (Mujika & Padilla, 2000).

Viewed from this perspective, the greater memory-related activation in the present study may indicate the reversibility of the exercise training–induced adaptive process in the neural networks. According to the Scaffolding Theory of Aging and Cognition revised, greater functional activation during a cognitive task may reflect compensatory brain processes aimed at bolstering distressed neural networks and preserving declining cognition in the aging brain (Reuter-Lorenz & Park, 2014). Supporting this theory, Rao et al. (2015) found a steadily increased semantic memory-related functional activation using the FNT over the course of 5 years in healthy older adults, suggesting a gradually increasing compensatory response over time in the aging brain. In line with the Scaffolding Theory of Aging and Cognition revised and the greater neural response over time in older adults, the additional recruitment of neural networks and increased functional activation following a 10-day training cessation may suggest a greater compensatory neural scaffolding that is presumably associated with increased neural workloads, an opposite pattern in response to exercise training.

Exercise training studies consistently show increased CBF compared with the baseline in healthy older adults (Alfini, Weiss, Nielson, Verber, & Smith, 2019; Kleinloog et al., 2019). In contrast, a previous training cessation study examining cerebrovascular blood flow using the same sample reported a significantly reduced cerebral and hippocampal blood flow after this 10-day period of exercise training cessation (Alfini et al., 2016). The previous CBF and our current semantic memory data collectively suggest that exercise training cessation is associated with brain function changes opposite to those elicited by exercise training. Furthermore, although it was not statistically significant ($p = .054$), there was a strong trend toward the association between the reduced CBF and the increased memory activation in the left hippocampal

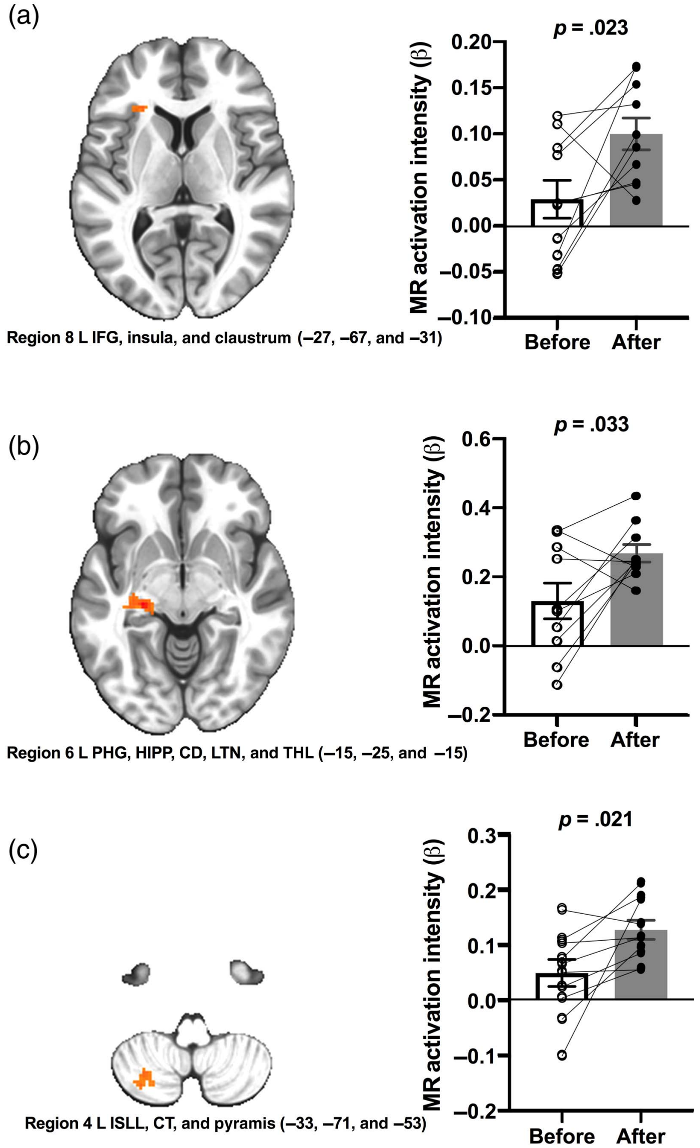

Figure 2 — Axial montages demonstrate brain regions showing significant differences in functional memory activation intensity between before and after exercise training cessation. Brain regions and peak activation in Talairach coordinates (*x*, *y*, and *z*) are included. Adjacent bar graphs illustrate the mean semantic memory activation (±SEM) of each region for the before and after exercise training cessation. *p* values above the bar graphs indicate statistical difference between the time points. L = left; CD = caudate; CT = cerebellar tonsil; IFG = inferior frontal gyrus; HIPP = hippocampus; ISLL = inferior semilunar lobule; LTN = lentiform nucleus; PHG = parahippocampal gyrus; THL = thalamus; MR = magnetic resonance.

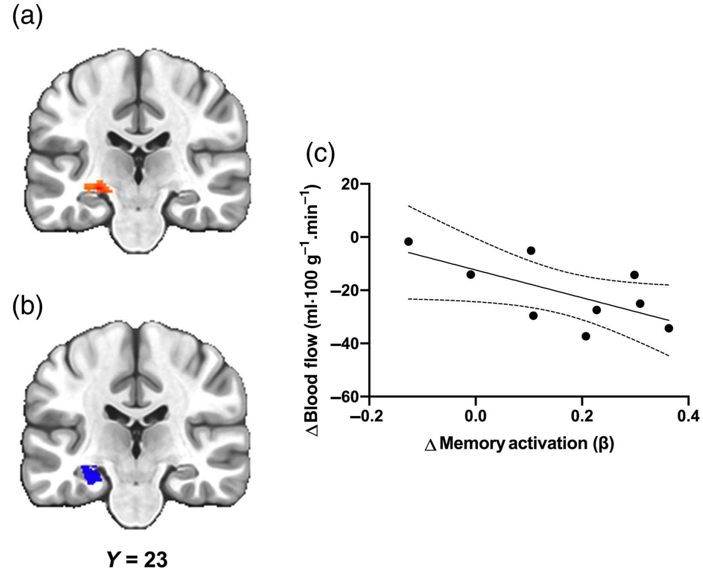

Figure 3 — The exercise-training-cessation–induced increase in semantic memory activation in the left hippocampal area (panel a; Region 6 in Figure 1) was moderately but not significantly associated with a decrease in CBF in the left hippocampus (panel b; from Alfini et al., 2016), $R^2 = .433$, $F(1, 7) = 5.335$, $p = .054$. The panel c represents the correlation map; dotted curves indicate the 95% confidence interval around the mean. Participants whose data were successfully processed in both sessions were included ($n = 9$). CBF = cerebral blood flow.

area after training cessation ($R^2 = .433$, 95% CI [−105.5, 1.239]). This may suggest that the left hippocampus and neighboring area are sensitive to the brain function changes induced by exercise training cessation. The specific mechanisms underlying the relationship between functional memory activation and CBF remains unclear. Nevertheless, this moderately strong association supports the hypothesis that neurophysiological changes elicited by exercise training cessation may concomitantly occur and be represented across different metrics of brain function. However, this interpretation should be viewed with caution since the association failed to reach statistical significance.

Since our fMRI observation is based on a hemodynamic response, and the blood oxygen level-dependent (BOLD) signal contrast depends on the deoxyhemoglobin content of blood (Ogawa, Lee, Kay, & Tank, 1990), one may question whether the decreased CBF reported previously is at odds with the greater BOLD activation after training cessation we reported here. However, because our index of activation is calculated by subtracting the BOLD response to nonfamous name stimuli from the BOLD response to famous name stimuli, this relative difference in the BOLD signal reflects task-driven activation that is independent of any overall changes in resting CBF. Hence, the present study does not conflict with the previous CBF finding and, in fact, complements the prior work using task-related functional activation.

Strengths and Limitations

Our sample does not reflect the profile of typical healthy older adults. The mean age of the older endurance runners was 63.5 years, body mass index was 23.4 kg/m^2, $\dot{V}O_2$max was 43.8 ml·kg^{-1}·min^{-1}, %body fat was 27.5%, and lean mass was 46.3 kg . Importantly, the exercise training intensity and history of our participants were substantially greater and longer, respectively, than older adults who engage in moderate- to vigorous-intensity physical activity. Of note, their $\dot{V}O_2$max classification was above the 90th percentiles for their age and sex (American College of Sports Medicine, 2013), indicating that they were substantially more fit than the vast majority of individuals of their age. These unique characteristics of the participants allowed us to effectively examine whether long-term exercise training–induced adaptation in functional memory network is reversible after a short-term cessation of training.

Another strength of the present study is that the semantic memory task (FNT) is inherently easy to perform. Since the participants acquired semantic knowledge of famous people throughout their daily lives, they were able to effortlessly perform the task. Previous studies employing the FNT consistently demonstrated a high accuracy rate (>80%) across a wide variety of participants, including individuals with a high risk for AD (Seidenberg et al., 2009; Smith et al., 2011) and those diagnosed with mild cognitive impairment (Smith et al., 2013; Woodard et al., 2009). Conversely, episodic memory tasks are typically effortful because the encoding and retrieval phases must be completed in a relatively short period of time. The greater task difficulty often confounds data interpretation, as it is unclear if the observed brain activation was elicited by alterations in the underlying brain function or motivational factors during cognitive performance (Price & Friston, 1999).

There are several limitations to the present study that warrant further exploration in the future. First, the final analysis consisted of only 10 highly fit athletes. Thus, older adults with high cardiorespiratory fitness may represent a distinct cognitive decline trajectory compared with those of the general older population. An important direction for future research is to recruit a larger sample with diverse fitness levels to further assess the effects of training cessation on the aging brain. Further examinations of potential changes in semantic memory circuits after master runners return to their training routine are also needed. Future studies need to administer a variety of cognitive test batteries, such as executive function, to investigate possible alterations in behavioral performance. Finally, $\dot{V}O_2$max and body composition were only assessed at the baseline. It remains to be determined whether physiological changes correspond to those of neurophysiological evidence after training cessation.

Conclusions

In summary, the present study demonstrates that 10 days of exercise training cessation is associated with an increased semantic memory activation compared with before training cessation in older endurance-trained men and women athletes. The greater functional activations during engagement in semantic memory-related retrieval may suggest a decreased neural network efficiency, perhaps as a result of attenuated exercise-training–induced adaptations. Our exploratory analysis further suggests that there was a moderate association between the increased memory activation and decreased blood flow in the left hippocampal area from before to after exercise training cessation. What makes the current results unique is that even a relatively short period of exercise training cessation significantly modulates the semantic memory network in older endurance-trained men and women. Currently, there is a paucity of literature investigating the effects of exercise cessation on brain function. Future aging neuroscience research should assess the relationship between training cessation and brain function by observing other aspects of cognitive function (e.g., executive function) or methods to assess brain health (e.g., functional connectivity or volumetric changes).

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