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Aerobic Fitness and the Brain: Increased *N*-Acetyl-Aspartate and Choline Concentrations in Endurance-Trained Middle-Aged Adults

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Abstract

Engagement in regular aerobic exercise is associated with cognitive benefits, but information on the mechanisms governing these changes in humans is limited. The goal of the current study was to compare neurometabolite concentrations relating to cellular metabolism, structure, and viability in endurance-trained and sedentary middle-aged adults. Twenty-eight endurance-trained and 27 sedentary adults, aged 40–65 years, underwent general health assessment, cardiorespiratory fitness

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measurement, neuropsychological testing, and proton magnetic resonance spectroscopy (^{1}H MRS). ^{1}H MRS was used to examine *N*-acetyl-aspartate (NAA), creatine (Cr), myo-inositol (mI), choline (Cho), and glutamate (Glu) concentrations in frontal and occipitoparietal grey matter. Group differences in concentrations of NAA, Cho, mI, and Glu, calculated as ratios over Cr, were explored using ANOVA. There were no significant differences in global cognitive function, memory, and executive function performance between the groups. In comparison to sedentary adults, the endurance-trained group displayed significantly higher NAA/Cr in the frontal grey matter ($F(1, 53) = 5.367$, $p = 0.024$) and higher Cho/Cr in the occipitoparietal grey matter ($F(1, 53) = 5.138$, $p = 0.028$). Within our middle-aged sample, endurance-trained adults demonstrated higher levels of NAA/Cr in the frontal grey matter and higher Cho/Cr in the occipitoparietal grey matter. Higher levels of NAA may indicate greater neuronal integrity and higher cerebral metabolic efficiency in association with cardiorespiratory fitness, whereas increased Cho may represent increased phospholipid levels secondary to neural plasticity.

Keywords

Aerobic fitness; ^{1}H MRS; *N*-acetyl-aspartate; Choline; Endurance exercise

Introduction

Normal human aging induces pervasive changes in brain morphology such as global mass reduction, ventricle expansion, and loss of myelination (Pakkenberg and Gundersen 1997; Skullerud 1985). Age-related structural changes couple with decrements in cognitive abilities (Park et al. 2001), placing older adults at increased risk for institutionalization and all-cause mortality (St John et al. 2002). Fortunately, the trajectory towards cognitive decline is not immutable as recent research indicates that the simple practice of engaging in regular aerobic exercise lowers the incidence of cognitive impairment and dementia (Barnes et al. 2003; Larson et al. 2006). These findings provide an unprecedented opportunity to enhance our understanding of cognitive aging. Systematic examination of the mechanisms underlying exercise-related cognitive benefits may yield unique insights into the physiological underpinnings of successful cognitive aging, paving the way for new therapeutic interventions.

To date, the majority of research on the impact of fitness on the central nervous system has been conducted using animal models. Within these models, running wheel access robustly increases trophic factors and enhances the number of newly labeled cells within the dentate gyrus of the hippocampus, a brain structure crucial for successful declarative memory performance (Neeper et al. 1996; Van Praag et al. 1999). However, while neurogenesis in rodent studies appears to be restricted to the hippocampal region, the largest cognitive benefits of regular exercise in humans have been noted in the domain of executive function (Colcombe and Kramer 2003), which is not dependent on the hippocampus. Thus, current evidence suggests that the mechanisms driving fitness-related cognitive enhancement in human and non-human animals may be different.

Fortunately, fitness-related changes in the central nervous system can be noninvasively assessed in humans in vivo with the help of magnetic resonance imaging (MRI). In particular, proton magnetic resonance spectroscopy (^{1}H MRS) can provide quantitative measures of neurometabolites relating to cellular metabolism, structure, and viability (Ross and Sachdev 2004), which may shed light on how aerobic exercise alters brain composition in humans. Using a cross-sectional design, neurochemical concentrations were compared between sedentary and endurance-trained middle-aged adults in two voxels of interest, the frontal gray matter, including anterior cingulate gyrus, and occipitoparietal gray matter

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including, posterior cingulate. The frontal area was selected based on substantial evidence of fitness-related increases in brain structure and function in this region (Colcombe et al. 2003b, 2004; Prakash et al. 2010). The posterior region was chosen because neurochemical alterations that relate to cognition in this area are well-documented (Friedman et al. 1999; Kantarci et al. 2000; Griffith et al. 2007). Based on the findings of increased brain volume in association with higher cardiorespiratory fitness (Colcombe et al. 2003a; Gordon et al. 2008) it was hypothesized that higher concentrations of *N*-acetyl-aspartate (NAA), a marker of neuronal viability, would be observed in the endurance-trained adults.

Materials and Methods

Participants

Sedentary and endurance-trained adults between the ages of 40 and 65 years were recruited through flyers and newspaper advertisements. Participants were classified as endurance-trained if they reported cycling and/or running at a moderate or strenuous exercise intensity at least 4 days per week on the International Physical Activity Questionnaire Short Form (Craig et al. 2003). Sedentary participants reported engaging in no regular physical exercise in the past year. Self-reported exercise training status was verified by maximal oxygen consumption (Wilson and Tanaka 2000). The age range of the sample was restricted to middle-age adults in accordance with the World Health Organizations (2005) recommendations for implementing early interventions. All participants were apparently healthy and free of overt coronary artery disease, neurological disease (e.g., stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g. schizophrenia, bipolar disorder), and substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse) as assessed by the medical history questionnaire. All participants were nonsmoking and were not taking any cardiovascular-acting medications. Sixty-two participants completed the initial screen and were enrolled in the study after providing written consent. Seven participants were excluded from analyses due to poor quality MRS data (Cramér-Rao Lower Bounds for NAA/creatine [Cr], myo-inositol [mI]/Cr, choline [Cho]/Cr or glutamate [Glu]/Cr > 12). The removed participants did not differ in age ($p = 0.668$), education ($p = 0.502$), cardiorespiratory fitness ($VO_{2\ max}$) ($p = 0.331$), or sex distribution ($p = 0.677$) from the remaining sample. The final sample consisted of 28 participants in the endurance-trained group and 27 participants in the sedentary group. Participants identified themselves as follows: 83.6 %, Caucasian; 5.5 %, Hispanic; 3.6 %, African American; 1.8 %, Asian; and 5.5 %, Other/Did Not Specify.

Procedures

The study was conducted in accordance with the Helsinki Declaration of 1975 and with approval from the local Institutional Review Board. All volunteers provided written informed consent before enrollment. Participants completed a medical history questionnaire in which medical conditions and treatments were coded as either present or absent based on participants' self-report. Participants then underwent a general health assessment, cardiorespiratory fitness assessment, and neuropsychological/brain imaging assessment. Assessments were conducted on separate days and participants completed the study within 2 months.

General Health Assessment

Participants abstained from caffeine and fasted for at least 12 h prior to the assessment. Body mass in kilograms and height in centimeters were measured on a physician's beam balance scale for the subsequent calculations of body mass index (BMI). BMI was calculated by dividing body mass in kilograms by height in meters squared. Following 15 min of rest, participants sat upright while brachial blood pressure was measured using a

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semi-automated device (VP-2000, Omron Healthcare, Bannockburn, IL). Approximately 3 ml of fasting blood was collected from the antecubital vein by venipuncture. The plasma concentrations of glucose and total-cholesterol were measured using standard enzymatic technique.

Cardiorespiratory Fitness Assessment

Participants abstained from caffeine and physical exercise for 24 h and fasted for at least 4 h prior to the visit. Maximal oxygen consumption ($VO_{2\ max}$) was assessed with a graded treadmill exercise test during a modified Bruce protocol. Following a 5-min warm up period, participants ran or walked at a speed that corresponded to 70–80 % of their age-predicted maximal heart rate. The treadmill slope was increased 2 % every 2 min until volitional exhaustion. Oxygen consumption (indirect calorimetry via respiratory gas measurements; Physio-Dyne, Quogue, NY), heart rate, and ratings of perceived exertion (the original Borg scale) (Borg 1982) were measured throughout the protocol. At the end of each stage, participants rated their perceived exertion using the Borg scale (Borg 1982) and heart rate was recorded. The gas analyzer was calibrated with standard gases of known concentrations before each trial.

Neuropsychological/Brain Imaging Assessment

Participants completed a battery of standard clinical neuropsychological instruments with established reliability and validity (Lezak et al. 2004). In order to reduce the number of multiple comparisons, neuropsychological measures were grouped into one of three domains —global cognition, memory, or executive function. For the domain scores, raw test scores were converted to *z* scores based on the study sample's mean and standard deviation. Timed test scores were multiplied by −1 so that higher scores indicate better performance. Domain scores were calculated for each participant by averaging the *z* scores within the domain as follows: (1) *global*: Mini-Mental Status Exam (Folstein et al. 1975) and Wechsler Test of Adult Reading (2001); (2) *memory*: California Verbal Learning Test II immediate recall, delayed recall, and recognition discrimination (Delis et al. 1987); (3) *executive*: Trail Making Test Parts A and B time to completion (Reitan 1958), Controlled Oral Word Associations Test (Ruff et al. 1996), and Wechsler Adult Intelligence Scale III Digit Span Subtest (1997). All tests were administered and scored by a trained research assistant using standard administration and scoring criteria.

MRS data for each participant were acquired in a single session on a 3T GE Signa Excite MRI scanner equipped with a standard head coil. As described in previous studies (Haley et al. 2010a, b), imaging included single voxel proton MRS performed using the GE pulse sequence PROBE-P, an automated point resolved spectroscopy sequence with chemical shift selected water suppression. Each spectroscopic voxel was prescribed from 3D high-resolution spoiled gradient echo sagittal images (256 × 256 matrix, FOV = 24 × 24 cm^2, 1 mm slice thickness, 0 gap) of the entire brain. ^1H MRS parameters were as follows: echo time/repetition time = 35/3,000 ms, 128 excitations, 5,000 Hz spectral width, volume ~6 cm^3, 15mm × 20 mm × 20 mm from the occipitoparietal gray matter including posterior cingulate and the frontal gray matter including anterior cingulate gyrus (Fig. 1). In order to ensure the quality of the data, a single experimenter localized the voxel placement on all subjects. A digital archive of the placement was saved and reviewed for placement consistency before analysis. The concentrations of five neurochemical were assessed: NAA, a marker of neuronal viability; Cho-containing compounds (phosphocholine and glycerophosphocholine, Cho), an indicator of phospholipid composition; mI, an organic osmolyte and a precursor of inositol triphosphate; Glu, a marker of excitatory neurotransmission; and Cr, an indicator of energy metabolism (Ross and Sachdev 2004). Commercially available software, LCModel, was used to quantify and separate the

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metabolite resonances from the macromolecule background (Provencher 1993) (Fig. 2). The main metabolites were quantified at the following resonance frequencies: NAA, 2.02 ppm; total Cho, 3.26 ppm; Cr, 3.03 ppm; mI, 3.56 ppm; and Glu, 2.34 ppm.

Statistical Analyses

All variable distributions were assessed using the Shapiro–Wilk test of normality recommended for small samples. Group differences in demographic and physiological variables were assessed using non-parametric χ^2 or Mann–Whitney U tests since many physiological variables have naturally skewed distributions. Group differences for the cognitive domain scores were assessed with ANOVA. In line with standard protocols (Kantarci et al. 2000; Staffen et al. 2005), the concentrations of NAA, Cho, mI, and Glu were reported as ratios relative to Cr. Group differences in neurometabolite ratios (NAA/Cr, Cho/Cr, mI/Cr, and Glu/Cr) were assessed using ANOVA in each voxel regions. Regression was used to explore the relationship between cardiorespiratory fitness ($VO_{2\ max}$) and neurochemical concentrations with significant group differences (NAA/Cr in the frontal grey matter and Cho/Cr in the occipitoparietal grey matter), controlling for age. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL). An α level of 0.05 was set as the criterion for statistical significance.

Results

Descriptive Statistics

Means and standard deviations of the demographic and physiological variables for each group are reported in Table 1. As expected, the two groups differed significantly for $VO_{2\ max}$ (Table 1). The groups also differed in BMI, and there was a near significant effect for total cholesterol. However, there were no significant group differences in gender (sex) distribution, age, years of education, systolic and diastolic blood pressure, and fasting blood glucose concentration (Table 1). Cognitive domain scores are reported in Table 2. There were no significant differences in global cognitive function, memory, and executive function scores between endurance-trained and sedentary groups (Table 2).

Cerebral Metabolism in the Frontal Grey Matter and Cardiorespiratory Fitness

Analysis of variance revealed that endurance-trained adults had significantly higher NAA/Cr in the frontal grey matter ($F(1, 53) = 5.367$, $p = 0.024$) (Fig. 3). Endurance-trained and sedentary adults did not significantly differ for frontal grey matter Glu/Cr ($F(1, 53) = 0.247$, $p = 0.621$), mI/Cr ($F(1, 53) = 0.073$, $p = 0.787$) or Cho/Cr ($F(1, 53) = 1.539$, $p = 0.220$) levels. The means and standard deviations of neurochemical concentrations for each group are presented in Table 3.

Cerebral Metabolism in the Occipitoparietal Grey Matter and Cardiorespiratory Fitness

Analysis of variance indicated that endurance-trained had significantly higher Cho/Cr in the occipitoparietal grey matter ($F(1, 53) = 5.138$, $p = 0.028$) (Fig. 4). The groups did not differ significantly for NAA/Cr ($F(1, 53) = 1.848$, $p = 0.180$), Glu/Cr ($F(1, 53) = 2.172$, $p = 0.146$), or mI/Cr ($F(1, 52) = 1.069$, $p = 0.306$) occipitoparietal grey matter levels. The means and standard deviations of neurochemical concentrations for each group are presented in Table 3.

Cerebral Metabolism and $VO_{2\ max}$

Independent of age, $VO_{2\ max}$ successfully predicted NAA/Cr in the frontal grey matter (adjusted $R^2 = 0.107$, $\beta = 0.338$, $p = 0.044$) and Cho/Cr in the occipitoparietal grey matter (adjusted $R^2 = 0.227$, $\beta = 0.452$, $p = 0.001$).

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Discussion

To our knowledge, this is the first study to examine neurochemical differences in endurance-trained and sedentary middle-aged adults. We found that endurance-trained adults displayed higher NAA/Cr in frontal grey matter and higher Cho/Cr in occipitoparietal grey matter. Additionally, $VO_{2\ max}$ successfully predicted NAA/Cr in frontal grey matter and Cho/Cr in occipitoparietal grey matter independent of age. These findings significantly extend knowledge based on animal models where the majority of exercise-related changes have been restricted to the hippocampus (Neeper et al. 1996; Van Praag et al. 1999). Additionally, they support a prior study, which found that higher $VO_{2\ max}$ was associated with increased right frontal cortex NAA/Cr in a sample of older, sedentary adults (Erickson et al. 2012). Our results indicate that aerobic fitness may have distinctive effects on the human brain, preferentially affecting neuronal viability in the frontal brain regions and cellular membrane composition in the posterior regions. The observed pattern of results is consistent with the cognitive literature documenting the largest exercise-related benefits in humans in the frontally-mediated executive function domain (Colcombe and Kramer 2003).

NAA is found almost exclusively within neurons (Unger et al. 1991), leading to the suggestion that NAA concentrations may be directly reflective of neuronal number (Cheng et al. 2002). Moreover, NAA levels decrease in conditions associated with neuronal loss such as healthy aging (Angelie et al. 2001) and Alzheimer's disease (Kantarci et al. 2000). Extensive evidence from the animal literature indicates that aerobic exercise is neuroprotective. In rodents, exposure to running wheel access enhances the number of newly labeled cells in the dentate gyrus of the hippocampus (Van Praag et al. 1999). The exercise-induced neurogenesis is believed to be secondary to the upregulation of brain-derived neurotrophic factor (BDNF) (Neeper et al. 1996), which supports the growth and differentiation of neurons. While evidence is more limited in humans, higher cardiorespiratory fitness was associated with attenuated age-related declines in frontal and parietal grey matter volumes (Colcombe et al. 2003). Moreover, a 6-month aerobic exercise intervention was found sufficient to increase brain volume in several regions including the dorsal anterior cingulate, the supplementary motor cortex, the frontal gyrus, and the superior temporal lobe (Colcombe et al. 2006). Therefore, the higher frontal grey matter NAA in endurance-trained adults that we observed may be a reflection of greater neuronal integrity in the response to enhanced cardiorespiratory fitness.

Alternatively, higher NAA/Cr levels may indicate mitochondrial health and metabolic efficiency secondary to cardiorespiratory fitness. NAA is synthesized from acetyl-coA and aspartate within the mitochondria and is therefore, directly related to mitochondrial viability (Clark 1998). NAA levels are known to diminish in response to pharmacological mitochondrial damage (Demougeot et al. 2001) and recover upon restoration of cerebral energy balance (Signoretti et al. 2008). With advancing age, mitochondria in the brain show reductions in oxidation capabilities and higher reactive oxygen species production (Navarro and Boveris 2007). In contrast, habitual exercise has been shown to improve mitochondrial oxidative capacity and reduce oxidative stress levels in the brain (Navarro et al. 2004). Thus, higher NAA/Cr levels in endurance-trained adults may reflect enhanced mitochondrial functioning and potential exercise-related protection from age-related declines in cerebral metabolic efficiency.

While higher NAA in endurance-trained adults was an anticipated result, the outcome of higher Cho/Cr in the occipitoparietal region was an unexpected and intriguing finding. The Cho peak in the MR spectrum is largely comprised of the phospholipids phosphocholine and glycerophosphocholine (Ross and Sachdev 2004). Phosphocholine is a precursor for phosphatidylcholine, the most ubiquitous phospholipid component of cell membranes,

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whereas glycerophosphocholine is a by-product of phosphatidylcholine breakdown (Klein 2000). Therefore, higher Cho/Cr is often interpreted as either enhanced phospholipid membrane synthesis or heighted membrane turnover and breakdown. For example, higher Cho/Cr levels are documented in demyelinating diseases (Inglese et al. 2003) as well as in conditions of enhanced cellular growth such as tumors (Herminghaus et al. 2002).

In relation to aerobic fitness, higher Cho levels are more likely to represent upregulation of phospholipids secondary to dendritic and axonal growth. Phosphocholine is significantly enhanced during periods of rapid neuritic growth such as in the developing brain (Pettegrew et al. 1999). Additionally, surges in phosphatidylcholine synthesis are observed when axonal growth is stimulated by nerve growth factor (Araki and Wurtman 1997). Supplementation of the phosphatidylcholine precursor, citicoline, increases cerebral levels of phosphatidylcholine (Adibhatla et al. 2001) and improves functional outcomes after stroke by increasing neurogenesis, promoting dendritic spine growth, and enhancing the expression of synaptic proteins (Gutiérrez-Fernández et al. 2011; Hurtado et al. 2007). With ^{1}H MRS, higher Cho levels have been observed in the rat hippocampus following electroconvulsive shock treatment (Sartorius et al. 2003), a procedure associated with neurogenesis (Madsen et al. 2000). Additionally, frontal grey matter Cho levels have been found to positively correlate with greater overall cortical, frontal, and temporal gray matter volumes in patients with HIV (Cohen et al. 2010). Interestingly, many structural brain changes reflecting increased neuroplasticity have been observed in association with regular aerobic exercise. In addition to neurogenesis (Gutiérrez-Fernández et al. 2011; Hurtado et al. 2007), habitual exercise upregulates the synaptic protein, synapsin I (Vaynman et al. 2004) and enhances dendritic arborization and spinal density in the dentate gyrus and entorhinal cortex (Redila and Christie 2006; Stranahan et al. 2007). Thus, higher Cho/Cr levels in endurance-trained adults may represent enhanced neural plasticity stimulated by the upregulation of neurotrophic factors such as BDNF. However, this hypothesis will need verification from future studies of fitness and neurochemical concentrations, particularly those combined with histological examination.

Given that different neurometabolites were elevated in association with fitness in the frontal and occipitoparietal areas, it appears that impact of cardiorespiratory fitness may show regional influence. In particular, aerobic fitness may have a larger impact on neuronal viability in the frontal regions and greater implications for phospholipid composition in the posterior regions. Regional variability of the impact of fitness is supported by the finding that aerobic fitness has the greatest cognitive benefit for frontally-mediated executive function tasks (Redila and Christie 2006; Stranahan et al. 2007). Similarly, a structural MRI study found that higher aerobic fitness was associated with greater frontal, temporal, and parietal grey matter volumes, but had no relation with volumetry in the occipital regions (Colcombe et al. 2003).

The findings in our present study are limited by the cross-sectional study design. It is possible that individuals who choose to engage in regular aerobic exercise may have other fundamental differences that account for the results. However, the fact that the groups did not differ in terms of age, education, and global cognitive ability helps to minimize this possibility. Importantly, longitudinal studies will be critical for determining if exercise interventions can alter neurometabolite concentrations. Given that reductions in NAA are reversible in other conditions (Signoretti et al. 2008), aerobic exercise interventions may be capable of enhancing NAA levels in previously sedentary adults. Another limitation was the ^{1}H MRS methodology, which does not enable tissue segmentation for grey matter, white matter, and cerebrospinal fluid. Finally, future studies with larger sample sizes should assess the influence of other cardioprotective factors (e.g. low BMI, high HDL-cholesterol levels) on the relationship between cardiorespiratory fitness and neurochemical concentrations.

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In summary, we found that endurance-trained adults displayed higher levels of NAA/Cr in the frontal grey matter and higher Cho/Cr in the occipitoparietal grey matter than sedentary controls. Higher levels of NAA could be indicative of greater neuronal integrity and higher cerebral metabolic efficiency in association with cardiorespiratory fitness, whereas increased Cho may represent enhanced phospholipid levels secondary to neural plasticity. Our results support a growing body of literature suggesting that engagement in regular aerobic exercise may influence central nervous system structure and function, which may ultimately help to preserve cognitive functioning throughout the lifespan.

Acknowledgments

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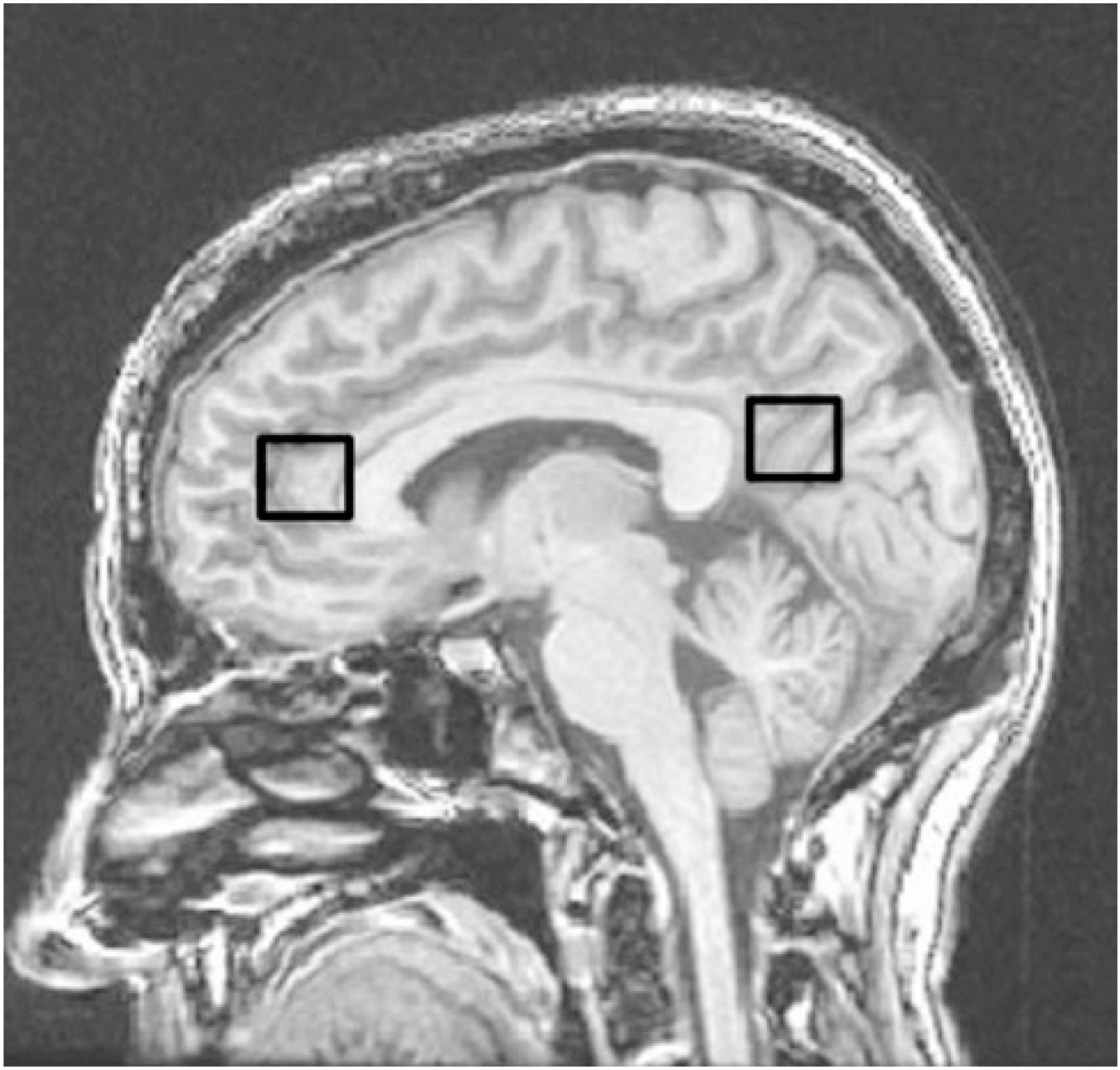

Fig. 1.
Anatomical *image* with superimposed voxel outlines indicating MRS volumes in the frontal and occipitoparietal gray matter

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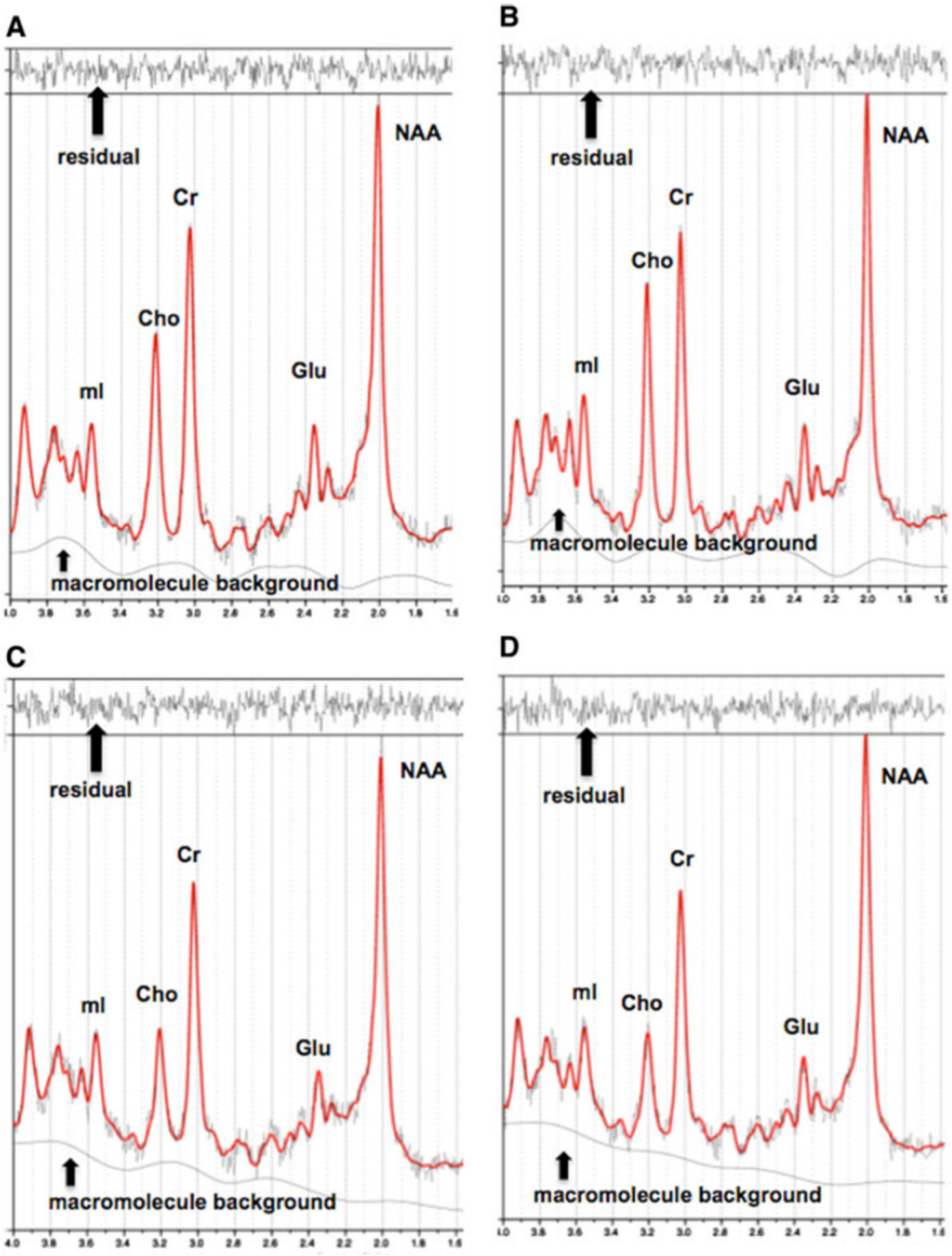

Fig. 2.

NAA N-acetyl-aspartate, *Glu* glutamate, *Cr* creatine + phosphocreatine, *Cho* = choline + phosphocholine, *mI myo*-inositol. **a** Representative ^{1}H MRS spectrum from the frontal grey matter in the sedentary group. **b** Representative ^{1}H MRS spectrum from the frontal grey matter in the endurance-trained group. **c** Representative ^{1}H MRS spectrum from the occipitoparietal grey matter in the sedentary group. **d** Representative ^{1}H MRS spectrum from the occipitoparietal grey matter in the endurance-trained group

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Fig. 3.

Bar graph with standard errors showing significantly higher frontal grey matter NAA/Cr in the endurance-trained group as compared with sedentary controls

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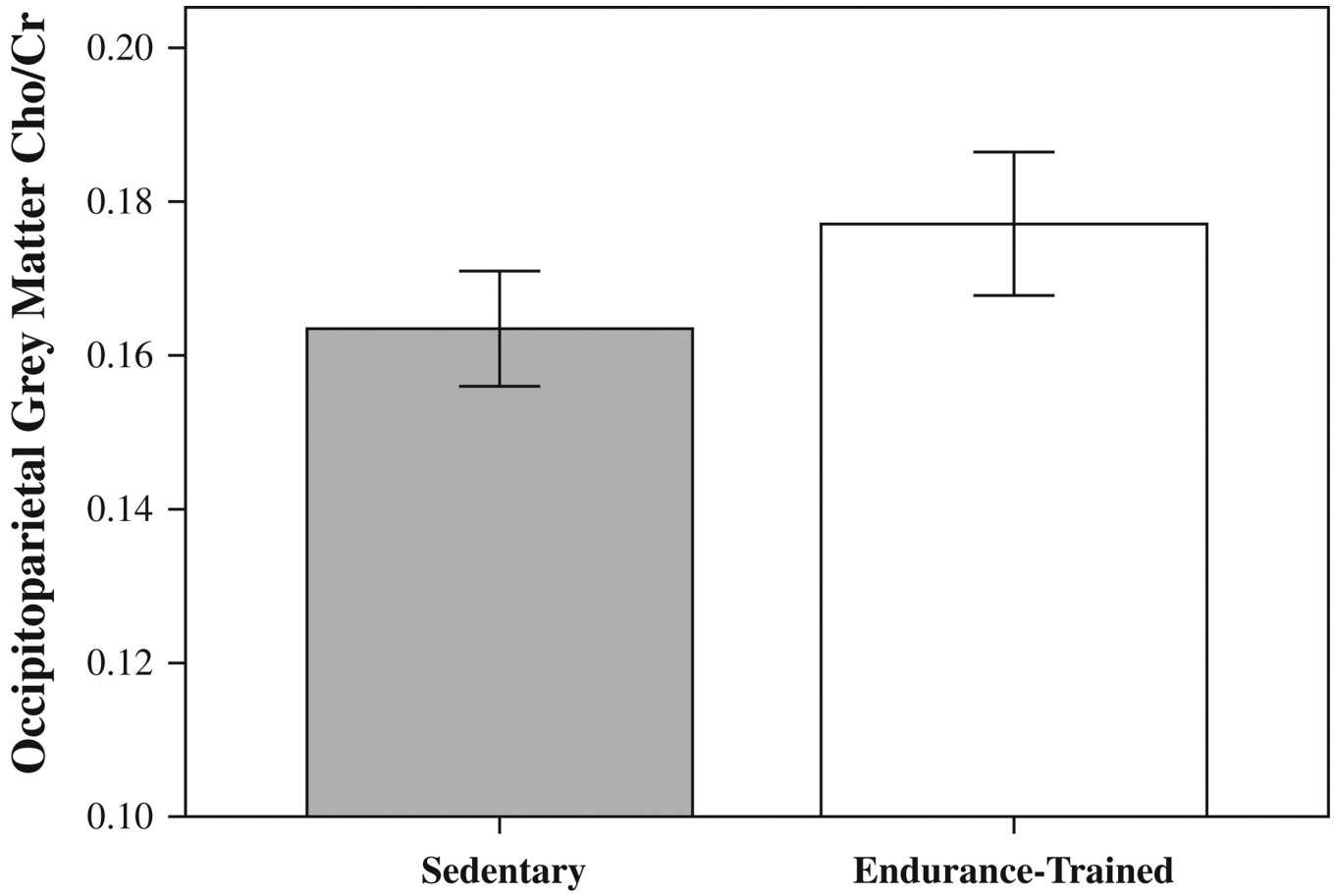

Fig. 4.

Bar graph with standard errors showing significantly higher occipitoparietal grey matter Cho/Cr in the endurance-trained group as compared with sedentary controls

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Table 1

Selected demographic and physiological characteristics

	Sedentary ***N*** **= 27**	**Endurance-trained** ***N*** **= 28**	***p*** **Value**
Male/Female	6/21	12/16	0.103
Education (years)	16.4 ± 2.0	17.2 ± 2.1	0.250
Age (years)	53.1 ± 5.6	51.3 ± 5.4	0.252
BMI (kg/m^2)	26.2 ± 4.9	23.6 ± 2.8	0.021
Systolic blood pressure (mmHg)	120 ± 13	123 ± 12	0.411
Diastolic blood pressure (mmHg)	73 ± 96	72 ± 7	0.924
Total cholesterol (mg/dl)	203.3 ± 31.3	188.0 ± 36.3	0.051
Blood glucose (mg/dl)	90.5 ± 13.0	89.9 ± 7.9	0.678
$VO_{2\ max}$ (ml/kg/min)	26.5 ± 5.1	45.4 ± 8.3	<0.001

VO2 max maximal oxygen consumption

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Table 2

Cognitive domain *z* scores

Cognitive domain	Sedentary *N* = 27	Endurance-trained *N* = 28	*p* Value
Global	−0.006 ± 0.83	0.006 ± 0.58	0.948
Memory	−0.18 ± 1.12	0.15 ± 0.63	0.193
Executive function	−0.08 ± 0.69	0.08 ± 0.62	0.360

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Table 3

Neurochemical concentrations

Neurochemical	Sedentary *N* = 27	Endurance-trained *N* = 28	*p* Value
mI/Cr (frontal)	0.83 ± 0.12	0.84 ± 0.12	0.787
Glu/Cr (frontal)	1.50 ± 0.13	1.52 ± 0.17	0.621
Cho/Cr (frontal)	0.29 ± 0.04	0.30 ± 0.05	0.220
NAA/Cr (frontal)	1.25 ± 0.12	1.32 ± 0.10	0.024 *
mI/Cr (occipitoparietal)	0.65 ± 0.09	0.67 ± 0.08	0.306
Glu/Cr (occipitoparietal)	1.41 ± 0.15	1.47 ± 0.15	0.146
Cho/Cr (occipitoparietal)	0.16 ± 0.02	0.18 ± 0.02	0.028 *
NAA/Cr (occipitoparietal)	1.47 ± 0.13	1.51 ± 0.08	0.180

* $p < 0.05$