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Voluntary Exercise Regionally Augments Rates of Cerebral Protein Synthesis

Jeffrey Nadel, Tianjian Huang, Zengyan Xia, Thomas Burlin, Alan Zametkin, and Carolyn Beebe Smith*

Section on Neuroadaptation and Protein Metabolism, National Institute of Mental Health, United States Public Health Service, Department of Health and Human Services, 10 Center Drive, Bethesda, Maryland 20892, United States of America

Abstract

Exercise is a natural form of neurophysiologic stimulation that has known benefits for mental health, maintenance of cerebral function, and stress reduction. Exercise is known to induce an upregulation of brain-derived neurotrophic factor and this is thought to be involved in associated increases in neural plasticity. Protein synthesis is also an essential component of adaptive plasticity. We hypothesized that exercise may stimulate changes in brain protein synthesis as part of its effects on plasticity. Here, we applied the quantitative autoradiographic L-[1-¹⁴C] leucine method to the *in vivo* determination of regional rates of cerebral protein synthesis (rCPS) in adult rats following a seven day period of voluntary wheel-running and their sedentary counterparts. In four of 21 brain regions examined, the mean values of rCPS in the exercised rats were statistically significantly higher than in sedentary controls; regions affected were paraventricular hypothalamic nucleus, ventral hippocampus as a whole, CA1 pyramidal cell layer in ventral hippocampus, and frontal cortex. Increases in rCPS approached statistical significance in dentate gyrus of the ventral hippocampus. Our results affirm the value of exercise in encouraging hippocampal and possibly cortical neuroplasticity, and also suggest that exercise may modulate stimulation of stress-response pathways. Ultimately, our study indicates that measurement of rCPS with PET might be used as a marker of brain response to exercise in human subjects.

Keywords

protein synthesis; exercise; synaptic plasticity; hippocampus; paraventricular nucleus; frontal cortex

*Corresponding Author: Carolyn Beebe Smith, 10 Center Drive, MSC 1298, Bethesda, Maryland, 20892, United States, Phone: (301) 402-3120, Fax: (301) 480-1668, beebe@mail.nih.gov.

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1. Introduction

The positive effects of exercise on mental health and maintenance of cerebral function are well established. In addition to promoting longevity, physical exercise reduces risk of anxiety and depression, and is used clinically for their management. Physical exercise also may stave off the effects of cognitive impairments in old age (Gremeaux et al., 2012; Nelson et al., 2007). Additionally, through its relationship with brain-derived neurotrophic factor (BDNF), exercise has been implicated in stress-pathway modulation, adult neurogenesis, neuronal regeneration, and synaptic strengthening (Kohman et al., 2012; Marlatt et al., 2012; van Praag et al., 1999). BDNF, a neurotrophin, is involved in various forms of neural plasticity such as axonal and dendritic extension and synaptic strengthening (Cotman et al., 2007; McAllister et al., 1999), and is an essential component of late-phase long-term potentiation (LTP) (Martinez-Moreno et al., 2011). Its expression is activity-dependent. Thus, electrical stimulation via induced seizures, direct electrical stimulation *in vitro*, and physical exercise *in vivo* produce robust increases in both BDNF mRNA expression and BDNF protein concentration in the hippocampus and cortex, suggesting a role in higher-level cognitive functioning such as learning and memory (Cotman and Berchtold, 2002; Cotman et al., 2007; Kornblum et al., 1997; Nawa et al., 1995; Neeper et al., 1996).

It is well documented that protein synthesis plays an essential role in adaptive neural plasticity throughout the brain. Activity-dependent upregulation of mRNA expression (Frey et al., 1996) and protein synthesis (Frey et al., 1988) are necessary features of late-phase LTP, and accordingly, protein synthesis inhibition prevents long-term memory storage (Agranoff, 1981). Consequently, how exercise alters overall brain protein synthesis is of significance, since exercise may serve as a natural and readily accessible means to encourage neural plasticity and stave off cognitive decline due to aging (Nagamatsu et al., 2013).

Given the important role of protein synthesis for memory and neural plasticity, we asked if voluntary exercise in adult rats produces an increase in *in vivo* regional rates of cerebral protein synthesis (rCPS). We used the quantitative autoradiographic L-[1-¹⁴C]leucine method (Smith et al., 1988) to evaluate *in vivo* changes in rCPS in young adult rats selected for a voluntary seven day exercise regimen. We chose to study animals after seven days of exercise because of the known changes in BDNF mRNA that take place in the brain following two to seven days of exercise (Neeper et al., 1996). We focused our analysis on 21 brain regions including some regions in which changes in BDNF and other mRNAs are known to occur (e.g., hippocampus and cortex), some regions involved in stress and emotional responses (e.g., amygdala, cingulate cortex, and hypothalamus), and some regions in which we did not expect to find a change (e.g., corpus callosum and caudate nucleus). We report statistically significant increases in rCPS in the ventral hippocampus as a whole, the CA1 pyramidal cell layer of the ventral hippocampus, frontal cortex, and paraventricular hypothalamic nucleus (PVN). Our results affirm the value of exercise to encourage neuroplasticity, modulate stress pathways, and maintain proper cerebral function.

2. Results

2.1. Running Behavior

Rats that underwent voluntary exercise were permitted to exercise *ad libitum*. In the 11 exercised rats, we found that running behavior mirrored their natural circadian cycle (Figure 1), i.e., all rats were more active during the dark phase of the circadian cycle and tended to be quiescent during the light phase. Running distances, however, varied widely among the animals. Animals that ran more did so over the entire duration of the study, and rats that ran less did so consistently. Consequently, the total distance run over the 7-day exercise period varied among the 11 rats. Some weight loss (14.9 ± 11.6 g, mean $\pm$ SD) was observed during the first three days of exercise in ten of the eleven exercised rats. As the exercise period progressed, all exercised rats gained weight, and at the time of rCPS determination, the weight of exercised rats did not differ significantly from that of sedentary rats (Table 1).

2.2. Effects of Exercise on Cerebral Protein Synthesis

At the time of rCPS determination, the exercised and sedentary groups were well-matched with respect to the physiological variables measured (Table 1). The effects of exercise on rCPS were determined in 21 regions of the brain (Table 2), and results were analyzed by means of repeated measure analysis of variance (RM ANOVA) with condition (sedentary, exercised) as the between subjects factor and regions as the within subjects factor. The region $\times$ condition interaction was statistically significant ($F_{(4,20, 54.56)}=2.60$; $p<0.05$), so we proceeded with pairwise comparisons. We found statistically significant ($p < 0.05$) increases in rCPS in the exercised rats in four regions: ventral hippocampus as a whole (11.1% effect), CA1 pyramidal cell layer of the ventral hippocampus (9.5% effect), frontal cortex (8.4 % effect), PVN (29.8% effect) (Figure 2). Increases approached statistical significance ($0.05 < p < 0.11$) in dentate gyrus of the ventral hippocampus (6.5% effect).

Among the exercised rats, rCPS did not appear to vary with distance run. Pearson's correlations were computed between total distance run and rCPS in all 21 regions analyzed. Results revealed no significant relationship between the distance run in the 7-day exercise period and rCPS ($0.26 < p < 0.95$). An additional analysis was conducted in which rats that exercised were divided into two subgroups—a low running distance group and high running distance group. Rats that ran more than 6,000 meters during their 7-day exercise period were in the high running distance group, while those that ran less than 6,000 meters were in the low running distance group. There were 5 rats that ran less than 6,000 meters (range: 2,022 – 5,655 meters; mean $\pm$ SD: 3835 ± 1323) and 6 rats that ran more than 6,000 meters (range: 6,238 – 9,607 meters; mean $\pm$ SD: 7968 ± 1213). Two-tailed Student's *t*-tests revealed no statistically significant difference between the low and high distance groups in rCPS in any region.

3. Discussion

The results of our study indicate that following a seven day voluntary exercise regimen in young adult rats, synthesis of tissue proteins is augmented in some areas of brain. Most notably, rCPS were significantly enhanced in the ventral hippocampus, frontal cortex, and

the PVN. We propose that augmented rCPS in these areas may be part of enhanced plasticity thought to accompany exercise. Our study adds validity to the idea that an exercise regimen may serve to enhance neuroplasticity, modulate stress responses, and possibly also to stave off the involuntal effects of aging (Nagamatsu et al, 2013).

We considered alternative explanations for the effects on rCPS. One possibility is that experimental stress is responsible for the changes in rCPS. It has been reported that certain stressors increase rCPS in rats (Giaume et al., 1995). Apart from the exercise manipulation, the two groups of rats were subjected to the same experimental procedures. All animals were singly housed, recovered from surgical implantation of catheters and acclimated to their experimental environment for four hours prior to rCPS quantification. Furthermore, all rats were allowed to move freely during the experimental procedure, and aside from arterial blood sampling, were not subjected to any known stressors during the experiment. We expected that methodological stress would affect both groups equally. There is the possibility that stress decreases rCPS (contrary to the report of Giaume et al., 1995) and that this response was modulated in the exercised rats by the effects of the exercise itself. We cannot discount this possibility, but we think it unlikely.

Our measurements of rCPS are average or global rates of incorporation across all tissue proteins. Measured rates encompass proteins turning over with short, long and intermediate half-lives. The relative contribution of an individual protein to the overall rCPS will be weighted by both its fractional contribution to total tissue protein and its half-life in the tissue. Our study addresses a single time point after seven days of exercise. Our choice of this time point was based on reports in the literature that other biochemical changes in brain tissue occur as quickly as two days after commencement of exercise and are sustained for between seven days and several weeks of exercise (Cotman et al., 2002; Neeper et al., 1996). It is likely that structural and behavioral plasticity (that underlie increases in white matter and changes in cognition, respectively) may require even longer exercise regimens. We cannot rule out the possibility that changes in rCPS may be more robust at other times during the exercise regimen. This question awaits further studies.

Of the 21 regions analyzed in our study, the means of the two groups were similar in 16. Our data indicate that effects of exercise on rCPS were not detectable in the dorsal hippocampus, amygdala, caudate nucleus, white matter and parietal and cingulate cortex. Only the hypothalamic nuclei, ventral hippocampus and frontal cortex showed any indication of differences between the groups. We analyzed the hippocampus in some detail because of observed effects of exercise in this region on BDNF expression and neurogenesis (Kohman et al., 2012; Neeper et al., 1996; van Praag et al., 1999). Consistent with findings of increased BDNF expression (Cotman and Berchtold, 2002; Cotman et al., 2007; Neeper et al., 1996), rCPS were significantly elevated in the ventral hippocampal formation as a whole and in particular in the CA1 pyramidal cell region. Increased rCPS may reflect an increase in the synthesis of various plasticity-related proteins (Cotman et al., 2007; Martinez-Moreno et al., 2011; McAllister et al., 1999).

We observed that increases in rCPS were localized to portions of the ventral and not the dorsal hippocampus. The ventral hippocampus is associated with stress, affect, and emotion,

whereas dorsal hippocampus is primarily involved in learning and memory associated with navigation and locomotion (reviewed by Fanselow and Dong, 2010). Our finding of effects on rCPS in the ventral, but not the dorsal, hippocampus is consistent with work in human subjects following a chronic exercise regimen in which increases in volume were found in the anterior, but not the posterior, hippocampus (Erickson et al., 2011). In primate brain, anterior and posterior portions of hippocampus are analogous to ventral and dorsal hippocampus, respectively in rodent brain (Fanselow and Dong, 2010). Intrinsic wiring in both parts of the hippocampus is similar, but extrinsic connections are quite distinct. The ventral portion connects with hypothalamus via the prefrontal cortex and amygdala, whereas the dorsal portion connects with mammillary bodies, septal and anterior thalamic nuclei. Post-exercise increases in rCPS in ventral hippocampus are in accord with known effects of exercise on stress reduction and mood elevation.

In light of the known stress-alleviating and emotional effects of voluntary physical exercise, we included analysis of cingulate cortex, amygaloid nuclei, and stria terminalis, but rCPS was unchanged in these regions. Exercise-induced increases in hormone expression, particularly CRH and vasopressin prompted us to include paraventricular and supraoptic hypothalamic nuclei. The greatest increase (30%) in rCPS was observed in the PVN. Physical exercise is a known activator the hypothalamic-pituitary-adrenal (HPA) axis (Chennaoui et al., 2002; Luger et al., 1987; Pacak, 2000). This exercise-induced HPA axis activation results in the hypothalamic production of CRH and vasopressin to promote a downstream stress response (Luger et al., 1987; Smoak et al., 1991). Given that the primary function of cells in the PVN and SON is the production and subsequent secretion of peptide hormones from preprohormones, it is likely that observed increases in rCPS in these regions are attributable in part to synthesis of the preprohormones of CRH and vasopressin. It is also noteworthy that the rCPS signal is the highest in a region that serves to synthesize peptide hormones.

We looked at rCPS in frontal association cortex and caudate nucleus because in these regions upregulated BDNF expression is correlated with augmented cognitive function and improved learning and memory (Greybiel, 2005). We found increased rCPS in frontal cortex but not in the caudate nucleus. Our finding of no effect in the caudate nucleus is consistent with a lack of an effect on caudate volume in human subjects following chronic exercise (Erickson et al., 2011). The increased rCPS in frontal cortex is in accord with the increases in BDNF mRNA reported after two days of voluntary exercise in rats (Neeper et al., 1996).

Corpus callosum and parietal cortex were analyzed as control structures, in which we hypothesized no change in rCPS after exercise, and these two regions were not affected by the exercise regimen. It is likely that other regions of the brain not analyzed in our study may also have detectable changes in rCPS due to exercise, as we have not surveyed the entire brain.

Our findings are consistent with the benefits of voluntary exercise on neuroplasticity, cerebral maintenance, and mental and physical health considered in light of known exercise-induced neurotrophic protein upregulation in the hippocampus, hypothalamus, and cortex (Cotman and Berchtold, 2002; Neeper et al., 1996; Oliff et al., 1998), the beneficial effects

of exercise on cognition and memory for children and adults alike (Chaddock et al., 2012; Hindin and Zelinski, 2012), and the advantages of acute, exercise-induced HPA axis activation (Bayatti and Behl, 2005; Mastorakos et al., 2005). Given the link between increased cerebral activity and augmented expression of various neuroprotective and otherwise advantageous protein species, measurement of rCPS may serve as a tool for the examination of the effects of exercise interventions on aging and age-related diseases in human subjects. The L-[1-¹⁴C]leucine autoradiographic method employed in this study has been adapted for use in human subjects with L-[1-¹¹C]leucine as tracer and positron emission tomography (Schmidt et al., 2005; Smith et al., 2005). Application of this methodology to the study of the effects of exercise in human subjects may provide us with a unique tool for future examination of the effects of exercise interventions on rCPS in aging populations and those with age-related diseases.

4. Experimental Procedure

4.1. Chemicals

Chemicals were obtained from the following vendors: L-[1-¹⁴C]leucine from Moravsek Radiochemicals (Crea, CA), and L-norleucine and 5-sulfosalicylic acid from Fluka (Buchs, Switzerland).

4.2. Animals

All experiments were conducted in accordance with the National Institutes of Health *Guidelines for the Care and Use of Animals* under an animal study protocol approved by the National Institute of Mental Health Animal Care and Use Committee. Adult (90 days of age; N= 22) male Sprague-Dawley rats (Taconic Farms, Albany, NY) were individually housed in a central facility with controlled humidity and temperature on a 12:12 light to dark circadian cycle. Standard food and water were provided *ad libitum*.

4.3. Physical Exercise

Rats were randomized to two groups: with or without voluntary wheel running (N=11 per group). Animals acclimated to the central facility for a minimum of 7 days in standard cages, housed two to a cage, with no running wheel. Following the acclimation period, rats randomized to the physical exercise group were housed in standard cages with stainless steel running wheels (35.5 cm diameter × 10.9 cm width, 1.10 meters/revolution) attached (Activity Wheel and Living Chamber, Lafayette Instruments, Lafayette, IN). Sedentary rats were housed in standard cages without running wheels, but supplemented with a cylindrical tube for enrichment. Those randomized for physical exercise were permitted to exercise *ad libitum* for 7 days, and voluntary wheel rotations were electronically recorded with Activity Wheel Monitoring System software (Lafayette Instruments, Lafayette, IN). Data were recorded every 10 minutes during the active hours of the rat's circadian cycle, and every 90 minutes during the inactive circadian period. Rats were weighed each day. Wheel running remained voluntary to reduce additional, variable stressors (Farmer et al., 2004; Leasure and Jones, 2008).

4.4. Surgical Preparation

Surgical catheterization as preparation for determination of rCPS began immediately following the conclusion of the 7th night of exercise. Rats, under light isoflurane anesthesia, were prepared for studies by insertion of polyethylene catheters (PE-50) into the right femoral artery and right femoral vein. Catheters were tunneled under the skin and exited at the nape of the neck to prevent the animals from gaining access to the tubing (Smith and Kang, 2000). During a four hour recovery period, rats were allowed to move freely in standard cages with access to water *ad libitum*.

4.5. Measurement of Physiological Variables

The following physiological variables were monitored during the recovery and experimental periods to assess the physiological state of the animals: mean arterial blood pressure, arterial blood hematocrit, and arterial plasma glucose concentration.

4.6. Determination of rCPS

rCPS was determined *in vivo* by labeling with L-[1-¹⁴C]leucine as tracer and quantitative autoradiography to spatially localize newly synthesized protein in the brain (Smith et al., 1988). Rates were calculated using the operational equation of the method as follows:

$$R_i = \frac{P_i^*(T)}{\lambda_i \int_0^T \left[\frac{C_p^*(t)}{C_p} dt \right]}$$

where R_i is the rate of leucine incorporation into protein in tissue i ; $P_i^*(T)$ is the concentration of ¹⁴C fixed in tissue i at any time, T , after tracer introduction into circulation; λ_i is the fraction of leucine in the precursor pool for protein synthesis in tissue i that is derived from plasma; $C_p^*(t)$ and C_p are the concentrations of labeled and unlabeled leucine in the arterial plasma, respectively; and t is time. Determination of λ_i was performed separately in a series of experiments that measured the steady-state ratio of leucine specific activity in the tissue tRNA-bound pool to that of the arterial plasma (Smith et al., 1988).

Determination of rCPS was initiated by the intravenous injection of a pulse of L-[1-¹⁴C]leucine (100 μ Ci/kg body weight) contained in approximately 0.5 cc of physiological saline. Arterial blood was drawn continuously over the first minute and subsequently at decreasing intervals for 60 minutes to measure the time course of the specific activity of the [¹⁴C]-labeled leucine in the plasma as previously described (Smith et al, 1988). Blood samples were immediately centrifuged to separate plasma from red blood cells, plasma was deproteinized, and concentrations of labeled and unlabeled leucine in the acid-soluble fractions were analyzed by liquid scintillation counting and amino acid analysis, respectively. At 60 minutes, animals were euthanized with an intravenous injection of sodium pentobarbital (40 μ l/kg; MWI, Meridian, ID) and brains were quickly removed and frozen on dry ice. Brain sections 20 μ m in thickness were prepared for quantitative autoradiography as previously described (Smith and Kang, 2000).

Autoradiograms were digitized with a 12-bit Qicam Scientific Digital Camera (QImaging, Surrey, BC, Canada) and a spatial resolution of 11 pixels per 100 μm . Each image was analyzed with MCID Elite image processing software (Imaging Research, St. Catharine's, Ontario, Canada). The concentration of ^{14}C in each region of interest was determined by comparison with calibrated [^{14}C]methylmethacrylate standards, and rCPS was calculated from the operational equation of the method above. Each region of interest was identified by referencing a rat brain atlas (Paxinos and Watson, 1986). Twenty-one regions of interest were quantified (Table 2).

4.7. Statistical Analyses

Comparisons between sedentary and exercised animals for the physiological data were made by means of Student's *t*-tests. The rCPS data were analyzed by means of RM ANOVA with condition (sedentary, exercised) as the between-subjects factor and brain region as a within-subjects factor. We used the Huynh-Feldt epsilon correction of degrees of freedom. *Post hoc* pair-wise comparisons were further conducted with Bonferroni *t*-tests. The significance level was set at $p = 0.05$. All analyses were conducted with the statistical software package SPSS Statistics 17.0 (SPSS, Chicago, IL).

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Abbreviations

BDNF	brain-derived neurotrophic factor
LTP	long-term potentiation
rCPS	rates of cerebral protein synthesis
PVN	paraventricular hypothalamic nucleus
SON	supraoptic hypothalamic nucleus
CRH	corticotropin releasing hormone
HPA	hypothalamic-pituitary-adrenal
RM ANOVA	repeated measures analysis of variance

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Highlights

- Seven days of voluntary exercise in rats
- Rates of cerebral protein synthesis (rCPS) were determined after exercise
- rCPS increased in frontal cortex, PVN, CA1 and whole ventral hippocampus
- Affirm value of exercise for neural plasticity
- Affirm value of exercise in affecting stress-responses

Figure 1. Distance run in meters in 90 min intervals by two representative rats over a 48 hour period. During their 7 day exercise period, Rat A ran 2,022 meters and Rat B ran 8,735 meters. The bar below the graph indicates the light-dark cycle for all rats. The blackened portion of the bar indicates lights out time, and the white portion of the bar indicates lights on time in the facility.

Figure 2.

Digitized autoradiograms of coronal sections at the level of the anterior hypothalamus. Images are from representative sedentary (**A**) and exercised (**B**) rats. Images have been colorcoded for rCPS according to the color bar shown on the right. The color bar (right) provides the calibration scale for the range of rCPS in nanomoles per gram per minute for each color. Scale bar (in **B**) represents 1.0 mm and applies to both images. In **A–B**, dorsal is up and the left side of the brain is on the left.

Table 1

Physiological variables in studies of rCPS

Physiological variable	Exercised (11)	Sedentary (11)
Age (days)	103 $\pm$ 1	104 $\pm$ 1
Body weight (g)	377 $\pm$ 6	386 $\pm$ 7
Hematocrit (%)	50.9 $\pm$ 0.7	52.5 $\pm$ 0.7
Arterial blood pressure (mm Hg)	116 $\pm$ 2	113 $\pm$ 2
Arterial plasma glucose concentration (mM)	6.31 $\pm$ 0.57	6.77 $\pm$ 0.24
Arterial plasma leucine concentration (μ M)	155.6 $\pm$ 34.4	167.6 $\pm$ 32.2

Values are the means $\pm$ SEM for the number of rats indicated in parentheses. There were no significant between-group differences. Results were analyzed by means of two-tailed Students t-tests.

Table 2

Effects of voluntary exercise on rCPS

Region	rCPS (nmol · g ⁻¹ · min ⁻¹)		% Effect
	Sedentary (11)	Exercised (11)	
Cortex			
Frontal	5.13 ± 0.15	5.56 ± 0.17*	8.4
Parietal	5.50 ± 0.11	5.56 ± 0.20	1.1
Cingulate	5.48 ± 0.11	5.48 ± 0.20	0
Dorsal hippocampal formation			
Pyramidal cell layer, CA1	8.68 ± 0.25	9.22 ± 0.28	6.2
Pyramidal cell layer, CA3	11.61 ± 0.38	12.05 ± 0.38	3.8
Stratum radiatum	2.08 ± 0.05	2.14 ± 0.07	2.9
Dentate gyrus, granular layer	9.92 ± 0.34	10.23 ± 0.34	3.1
Whole formation	3.91 ± 0.12	3.96 ± 0.13	1.3
Ventral hippocampal formation			
Pyramidal cell layer, CA1	9.45 ± 0.15	10.35 ± 0.35*	9.5
Pyramidal cell layer, CA3	11.36 ± 0.29	12.07 ± 0.40	6.3
Dentate gyrus, granular layer	9.64 ± 0.28	10.27 ± 0.36	6.5
Whole formation	3.61 ± 0.11	4.01 ± 0.17*	11.1
Amygdaloid complex			
Anterior nucleus	7.31 ± 0.27	7.30 ± 0.29	0.1
Central nucleus	4.80 ± 0.25	4.87 ± 0.29	1.5
Medial nucleus	4.59 ± 0.20	4.61 ± 0.21	0.4
Basolateral nucleus	5.60 ± 0.25	5.65 ± 0.18	0.9
Hypothalamus			
Paraventricular nucleus	10.41 ± 0.32	13.51 ± 0.90*	29.8
Supraoptic nucleus	14.86 ± 0.43	16.97 ± 1.03	14.2
Basal Ganglia			
Caudate nucleus	3.75 ± 0.08	3.82 ± 0.09	1.9
White matter			
Corpus callosum	2.49 ± 0.05	2.45 ± 0.08	1.6
Stria terminalis	3.69 ± 0.15	3.75 ± 0.18	1.6

Values are the means ± SEM for the number of rats indicated in parentheses. Results were analyzed by means of RM ANOVA, followed by pair-wise comparisons with Bonferroni t-tests. The 2-way interaction (condition x region) was statistically significant ($F(4,20, 54.56)=2.60, p<0.05$).

Post-hoc comparisons: Statistically significantly different from sedentary,

*, 0.01 P 0.05.