The Effect of Acute Exercise on Serum Brain-Derived Neurotrophic Factor Levels and Cognitive Function

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ABSTRACT

FERRIS, L. T., J. S. WILLIAMS, and C.-L. SHEN. The Effect of Acute Exercise on Serum Brain-Derived Neurotrophic Factor Levels and Cognitive Function. *Med. Sci. Sports Exerc.*, Vol. 39, No. 4, pp. 728–734, 2007. Brain-derived neurotrophic factor (BDNF) is one of a family of neurotrophic factors that participates in neuronal transmission, modulation and plasticity. Previous studies using animals have demonstrated that acute and chronic exercise leads to increases in BDNF in various brain regions. **Purpose:** To determine the effects of acute exercise on serum BDNF levels in humans, and to determine the relationship between exercise intensity and BDNF responses. Additionally, the relationship between changes in BDNF and cognitive function was examined. **Methods:** Fifteen subjects (25.4 ± 1.01 yr; 11 male, 4 female) performed a graded exercise test (GXT) for the determination of $\dot{V}O_{2max}$ and ventilatory threshold (V_{Th}) on a cycle ergometer. On separate days, two subsequent 30-min endurance rides were performed at 20% below the V_{Th} (V_{Th} − 20) and at 10% above the V_{Th} (V_{Th} + 10). Serum BDNF and cognitive function were determined before and after the GXT and endurance rides with an enzyme-linked immunosorbent assay (ELISA) and the Stroop tests, respectively. **Results:** The mean $\dot{V}O_{2max}$ was 2805.8 ± 164.3 $mL \cdot min^{-1}$ (104.2 ± 7.0% pred). BDNF values ($pg \cdot mL^{-1}$) increased from baseline ($P < 0.05$) after exercise at the V_{Th} + 10 (13%) and the GXT (30%). There was no significant change in BDNF from baseline after the V_{Th} − 20. Changes in BDNF did not correlate with $\dot{V}O_{2max}$ during the GXT, but they did correlate with changes in lactate ($r = 0.57$; $P < 0.05$). Cognitive function scores improved after all exercise conditions, but they did not correlate with BDNF changes. **Conclusion:** BDNF levels in humans are significantly elevated in response to exercise, and the magnitude of increase is exercise intensity dependent. Given that BDNF can transit the blood–brain barrier in both directions, the intensity-dependent findings may aid in designing exercise prescriptions for maintaining or improving neurological health. **Key Words:** GRADED EXERCISE TEST, ENDURANCE, NEUROTROPHIN, STROOP TEST

Physical inactivity has many known deleterious effects on the body. Heart disease, stroke, and metabolic diseases such as type 2 diabetes are just a few examples of the consequences of a sedentary lifestyle (2). As such, exercise interventions could prove beneficial in combating these and other conditions. It is becoming increasingly evident that exercise also is beneficial to the brain and nervous system. An endogenous substance that plays a central role in the health of neurons is brain-derived neurotrophic factor (BDNF). BDNF is a 27.0-kDa homodimer of two 13.5-kDa subunits linked by noncovalent interactions (26). BDNF acts via its tyrosine kinase receptor, TrkB, to promote neuronal differentiation and survival (5). Exercise studies with rodents have shown that treadmill running increased hippocampal BDNF (21) and have implicated BDNF as one of the central influences on brain plasticity (20).

In the rodent spinal cord injury (SCI) model, Hutchinson et al. (9) have shown that animals that underwent SCI and remained sedentary experienced significant drops in BDNF mRNA in the spinal cord and soleus muscle relative to a control group. SCI rats that underwent treadmill training recovered from allodynia, an associated condition of sensory dysfunction, and BDNF mRNA in the spinal cord and soleus muscle were not significantly different than control group levels. Using human subjects, Colcombe and colleagues (4) reported that among an older adult population, there was a reduction in the age-based decline in tissue density in the frontal, parietal, and temporal cortices as a function of cardiovascular fitness. These exercise-associated outcomes

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would be consistent with the neurotrophic (5) and/or neurogenic (31) actions of BDNF. Assays for BDNF or other markers of brain health, however, were not performed.

Indeed, comparatively fewer studies have examined the response of BDNF to exercise in humans. A study by Gold et al. (6) has reported increases in serum BDNF in healthy controls and multiple sclerosis patients in response to acute exercise, but only one exercise intensity was selected. To date, the present study is the only study to examine systemic BDNF responses to acute exercise in humans while incorporating varying exercise intensities.

Physical activity also has been shown to effect cognitive function. Vaynman et al. (32) report that animals that exercised for a short period outperformed their sedentary counterparts on a measure of learning and recall, the Morris water maze test. BDNF mRNA levels were also examined (as were the levels of mRNA of cAMP response–element binding protein, CREB, an associated molecular effector). The animals that were the fastest learners and that had the best recall also had the highest expression of BDNF and CREB mRNA. Human-based studies also have shown that exercise has a positive effect on measures of cognitive performance. Khatri et al. (14) examined the effects of exercise training on cognitive function in a group of depressed older individuals. They report that individuals who participated in aerobic exercises demonstrated greater increases in certain cognitive processes (memory, executive functioning) compared with participants taking antidepressant medication. Relative to rodent-based investigations, however, studies involving human participants have largely not examined possible biochemical effectors involved in the exercise-induced improvements in cognitive function.

The potential impact of exercise on the nervous system is significant; if exercise in humans can lead to BDNF-mediated maintenance or improvement of neural tissue, then exercise may become a potent weapon in combating neuromuscular disorders and the diseases of affect and cognition that correlate with a sedentary lifestyle. The purpose of this study was to determine the effects of acute exercise on serum BDNF levels in humans and the relationship between exercise intensity and BDNF responses. Additionally, the relationship between the change in serum BDNF and the change in cognitive function scores after an acute exercise bout was examined. We hypothesized that an acute exercise bout would result in an increase in serum BDNF and that the increase would be exercise intensity dependent. We further hypothesized that the change in BDNF would directly correlate with the change in cognitive function scores.

METHODS

Subjects. The study population consisted of 15 subjects (11 male, 4 female; age 25.4 ± 1.0 yr; height 174.7 ± 1.9 cm; weight 71.0 ± 3.1 kg; BMI 23.1 ± 0.6 $kg \cdot m^{-2}$; mean ± SE) who were physically active (i.e., involved in collegiate intramural activities) and, therefore, of adequate health to participate in the exercise protocols, but not engaged in competitive sports. According to a detailed medical history questionnaire, all subjects were free of cardiopulmonary, metabolic, or musculoskeletal disease, mental disorders, and were nonsmokers. All subjects signed an informed consent form, and the institutional review board approved the study.

General testing procedures. Participation in the study required three visits to the exercise physiology laboratory. During the first visit, the subjects performed a graded exercise test (GXT) on a stationary cycle. The second and third visits consisted of 30-min endurance rides at fixed intensity levels performed in a randomized fashion. For each endurance ride, data from the individual's GXT was used to determine the work rate that corresponded to the target intensity. Participants were instructed to forgo strenuous exercise for 24 h before each exercise bout, and food, caffeine, and alcohol intake were prohibited for 3 h before each ride. All females who participated were in the follicular phase of their menstrual cycle, to control for time-dependent variations in estrogen levels. Additionally, all testing was performed at the same time of day to control for circadian influences.

GXT. During the first visit, the subjects became familiarized with the exercise testing equipment and then performed a GXT on a cycle ergometer (Lode, Corival) to volitional fatigue. Cardiopulmonary and metabolic parameters (maximal work rate, maximal oxygen consumption ($\dot{V}O_{2max}$), maximal heart rate, and respiratory exchange ratio (RER)) were determined on a breath-by-breath basis with samples averaged for 30-s intervals (MedGraphics, CPX/D). Blood pressure was determined before, during, and after the GXT via auscultation. Heart rate and rhythm were monitored during the GXT via electrocardiography (Quinton Instruments, Model 4000). The ventilatory threshold (V_{Th}) was determined by the V-slope method (33).

Endurance rides. The subjects performed two 30-min exercise bouts in a randomized fashion on the cycle ergometer at a power output that corresponded to the V_{Th} plus 10% (high intensity) or minus 20% (low intensity) as determined for each individual from the GXT. Metabolic, ventilatory, and heart rate parameters were collected at 10-min intervals during the rides and were averaged as described above. There was a minimal rest period of 48 h between the GXT and the first endurance ride, and there was a similar rest period between the first and second endurance rides.

Blood sampling and analysis. A 10-mL blood withdrawal via aseptic technique from the antecubital vein was taken before and after the GXT and endurance rides for the determination of blood lactate and serum BDNF levels. Blood lactate was measured with an Accusport portable lactate analyzer (Mannheim Boehringer) that was calibrated to the manufacturer's specifications before each test. The blood was allowed to clot (BD Vacutainer Plus SST) and

was then centrifuged (Eppendorf Centrifuge 5804) for 12 min at 1300 relative centrifugal force. The supernatant was decanted and stored in a −80°C freezer until analysis. Serum BDNF was assayed using a Chemikine BDNF sandwich enzyme-linked immunosorbent assay (ELISA) kit. The sensitivity as reported in the ELISA kit literature was 7.8 $pg \cdot mL^{-1}$. The reported intraassay and interassay variations were ± 3.7 and ± 8.5%, respectively.

Cognitive function tests. A cognitive function assessment, the Stroop color and word test (7,27), was administered pre- and postexercise for the GXT and the two endurance rides. The Stroop color and word test consists of three sections, all of which are variations of the same theme; subjects are required to read out loud, as quickly and accurately as possible, from a list of items for 45 s. Test 1, the word test, requires that subjects read from a page containing three printed words: red, green, or blue. The words are printed in black ink and are listed in random fashion in five columns of 20 words each. No word is allowed to follow itself in a column. Test 2, the color test, similarly consists of 100 items that are all written as XXXX and printed either in red, green, or blue ink. The subject states the color of the ink for each of the series of four X's. Test 3, the color–word test, consists of the same 100 words (red, green, or blue) as the first test, but printed in colored ink, and the color of the ink and the printed word are never the same (for example, the word "blue" could be printed in red or green ink, but never blue ink). The subject is required to say the color of the ink that the word is printed in, not the printed word itself. For the three tests, a higher score reflects a better performance. Subjects performed a practice session to become familiar with the Stroop test before it was initially administered pre-GXT.

Statistical analysis. Postexercise performance parameters from the endurance rides and serum BDNF and Stroop scores from the GXT were analyzed with paired *t*-tests. The serum BDNF and Stroop scores from the endurance rides were analyzed with a two-way repeated-measures ANOVA with main effects examined for condition (V_{Th} − 20 and V_{Th} + 10) and time (before and after exercise). Significant main effects were further analyzed with Student–Newman *post hoc* tests. Results are presented as means (± SE). The relationships between the pre- to postexercise changes in serum BDNF and blood lactate, and the changes in serum BDNF and Stroop scores, were examined with the Pearson product–moment correlation. A P value of < 0.05 was considered significant. Statistical analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, SPSS Inc., Chicago, IL).

TABLE 1. Graded exercise test: maximal exercise values (N = 15).

	Mean	SE
WR_{max} (W)	293.47	17.65
$\dot{V}O_{2max}$ ($mL \cdot min^{-1}$)	2805.80	164.31
HR_{max} (bpm)	175.67	3.19
% pred HR_{max}	90.31	1.75
RER	1.27	0.02
Lactate (mM)	10.67	0.66

TABLE 2. Comparisons of physiological values for the two endurance rides.

	V_{Th} − 20		V_{Th} + 10	
	Mean	SE	Mean	SE
Work rate (W)	109.85	9.70	155.35*	12.55
VO_2 ($mL \cdot min^{-1}$)	1571.97	110.42	2107.61*	142.64
% $\dot{V}O_{2max}$	55.95	1.82	75.22*	2.27
HR (bpm)	121.86	2.54	150.25*	3.64
% HR_{max}	69.72	1.97	85.83*	2.43
RER	0.97	0.01	1.02*	0.01
Lactate (mM)	2.80	0.26	4.98*	0.44

V_{Th} − 20, endurance ride performed at 20% below ventilatory threshold; V_{Th} + 10, endurance ride performed at 10% above ventilatory threshold. * Significantly different from V_{Th} − 20 condition ($P < 0.001$).

RESULTS

Graded exercise and endurance ride responses. Table 1 lists maximal values from the GXT for six measured variables. The values for RER and lactate meet accepted criteria for a true maximal effort (RER > 1.1 and lactate >8 mM) (1). The mean V_{Th} occurred at 57.6 ± 2.3% $\dot{V}O_{2max}$. Table 2 compares indicators of exercise intensity between the two endurance ride conditions. All variables were significantly greater at the V_{Th} + 10 condition relative to the V_{Th} − 20 condition ($P < 0.001$; P value smaller than that required from Bonferroni correction).

Serum BDNF responses. The intraassay variation between duplicate samples was 1.653%. The GXT yielded a significant elevation in the postride serum BDNF (Fig. 1) relative to baseline (30% increase) ($P < 0.001$). Additionally, there was a significant correlation between the change in blood lactate and the change in serum BDNF responses from the GXT (Fig. 2). For the endurance rides, an ANOVA for repeated measures on BDNF levels revealed a significant effect of time ($F_{1,14} = 13.09$; $P < 0.01$), whereas neither condition nor the interaction of the factors was significant. The V_{Th} + 10 endurance ride

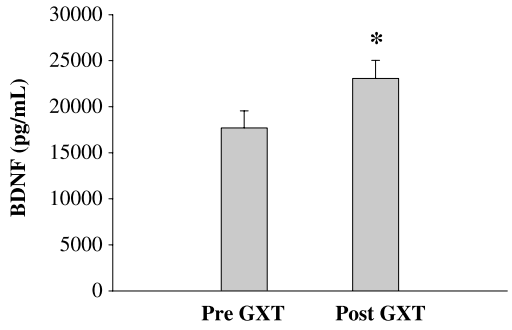

FIGURE 1—Serum BDNF values before and after the GXT. Data are means (± SE). * Significantly different from baseline ($P < 0.001$).

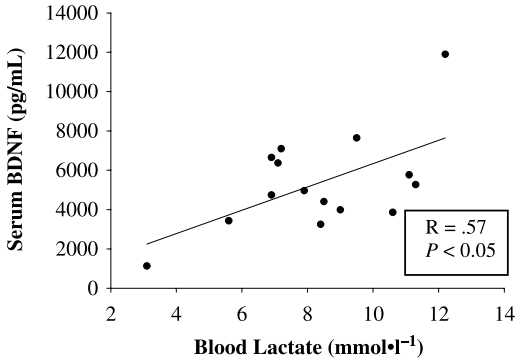

FIGURE 2—Relationship between serum BDNF and blood lactate values immediately after the GXT.

resulted in a significant increase in serum BDNF (Fig. 3) relative to baseline (13% increase) ($P < 0.05$, Student–Newman–Keuls *post hoc* test), whereas the $V_{Th} - 20$ ride did not yield a significant postexercise increase. There were no significant correlations between the pre–post changes of serum BDNF and blood lactate for either the $V_{Th} - 20$ or $V_{Th} + 10$.

Cognitive assessments. The results from the Stroop word and color tests, but not the color–word test, were significantly greater post-GXT compared with their respective pre-GXT scores ($P < 0.05$) (Fig. 4). For the endurance rides, an ANOVA for repeated measures on the Stroop word and color tests revealed a significant effect of time ($F_{1,14} = 9.76$; $P < 0.01$ and $F_{1,14} = 33.72$; $P < 0.001$, respectively), whereas neither condition nor the interaction of factors was significant for either test. An ANOVA for repeated measures on the Stroop color–word test revealed a significant effect of time ($F_{1,14} = 7.16$; $P < 0.05$). The $V_{Th} + 10$ resulted in a significant increase in the color–word score ($P < 0.05$, Student–Newman–Keuls *post hoc* test) (Fig. 5), whereas the $V_{Th} - 20$ ride did not yield a significant postexercise increase. Additionally, the color–word test from the endurance rides yielded the only significant interaction between condition and time ($F_{1,14} = 6.45$; $P < 0.05$). There were no significant correlations between change in the Stroop word, color, or color–word scores and change in BDNF for the GXT, $V_{Th} - 20$, or $V_{Th} + 10$.

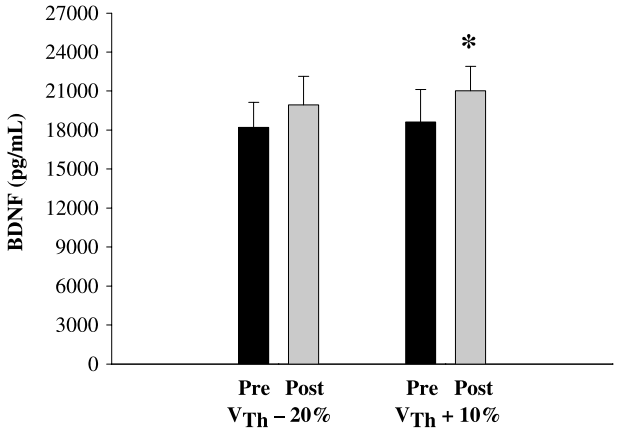

FIGURE 3—Serum BDNF values before and after the $V_{Th} - 20$ and $V_{Th} + 10$ endurance rides. Data are means (± SE). * Significantly different from baseline ($P < 0.05$).

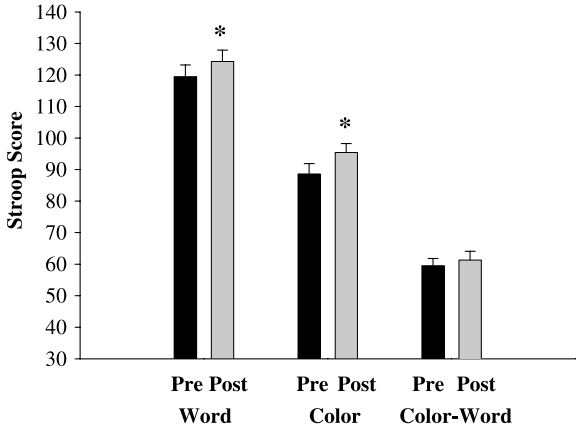

FIGURE 4—Stroop scores before and after the GXT. Values reported are raw scores for each test. Data are means (± SE). * Significantly different from baseline ($P < 0.05$).

DISCUSSION

The present study examined how acute exercise bouts at different intensities affected serum levels of BDNF and assessments of cognitive function. The intensity at the end of the GXT is rarely, if ever, encountered by an individual during recreational activities and fitness training. However, assessments of BDNF and cognitive function were made before and after the GXT, yielding, along with measurements from the endurance rides, a collection of data from exercise bouts of disparate intensities. Target work rates of $V_{Th} - 20\%$ and $V_{Th} + 10\%$ were selected for the fixed-intensity endurance rides because the V_{Th} corresponds to the work rate at which exercise becomes difficult (25). The $V_{Th} + 10$ was characterized as being between somewhat hard and hard according to the Borg scale of perceived exertion (14.2 ± 0.4; mean Borg rating of perceived exertion (RPE) ± SE), whereas the $V_{Th} - 20$ was described as light (10.8 ± 0.4; mean RPE ± SE). Given the disparate intensities between the two fixed-intensity exercise conditions, as determined by both subjective responses and physiological measurements, we feel that this protocol provided valuable insight into an intensity-dependent response of a 30-min exercise bout to yield an increase in BDNF.

Reported average serum BDNF values for healthy subjects seem to vary between studies and may reflect methodological differences. The preexercise average serum BDNF value of this protocol (18,168 ± 1193 pg·mL^{-1} (mean ± SE)) falls approximately halfway between the reported averages (of healthy controls) from two published psychiatric studies (12,29) and is comparable with the reported median value of healthy adults (22,600 pg·mL^{-1}) from a recent study notable for its large sample size ($N = 140$) (19). Thus, we feel that the average preexercise serum BDNF values presented in

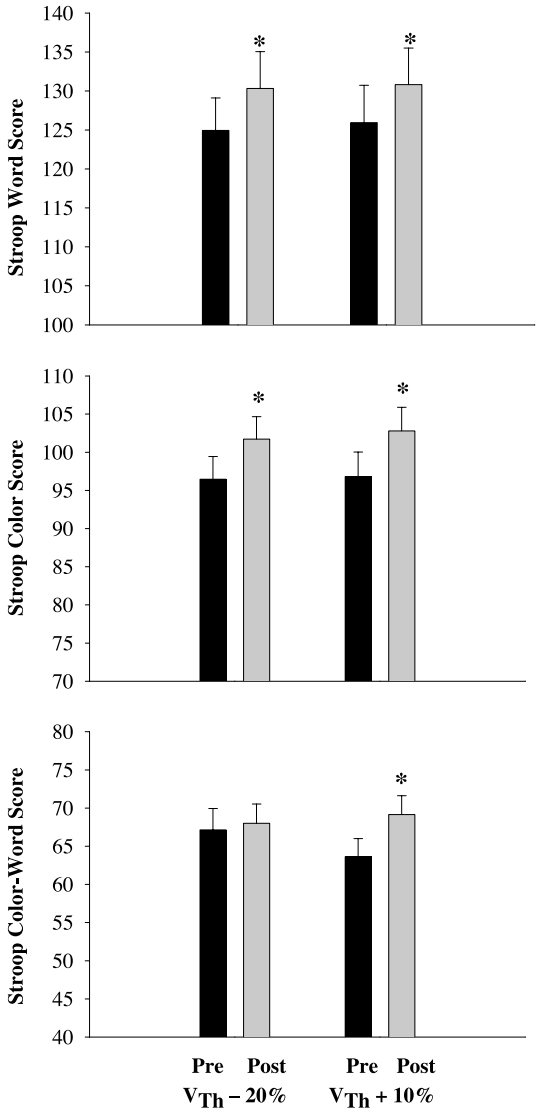

FIGURE 5—Stroop word (*top panel*), color (*middle panel*), and color–word (*bottom panel*) scores before and after the V_{Th} − 20 and V_{Th} + 10 endurance rides. Data are means (± SE). * Significantly different from baseline ($P < 0.05$).

this study are consistent with resting serum BDNF levels in the established literature and provide a valid resting baseline for the examination of the effects of acute exercise on the serum levels of this neurotrophin.

The GXT and the V_{Th} + 10 yielded significant increases in serum BDNF levels relative to baseline. The relative magnitude of the pre- to postexercise percent increases were as follows: V_{Th} − 20 (10%) < V_{Th} + 10 (13%) < GXT (30%), thus indicating an intensity-dependent induction of serum BDNF. To the best of our knowledge, we are the first to report an exercise intensity–dependent induction of serum BDNF in human participants. The change in blood lactate did correlate with the change in BDNF, but only for the GXT.

The intensities of the V_{Th} − 20 and the V_{Th} + 10 endurance rides employed in this study corresponded to 55.9 and 75.2% $\dot{V}O_{2max}$, respectively. The V_{Th} − 20 did not yield a significant pre- to postexercise increase in the serum BDNF concentration, whereas the higher-intensity V_{Th} + 10 did result in significantly elevated BDNF relative to baseline. These results are consistent with the results of Gold et al. (6), who reported significant increases in serum BDNF for multiple sclerosis patients and healthy controls after a 30-min cycle ride at 60% $\dot{V}O_{2max}$, which, according to their pre- and postexercise lactate measurements, exceeded the anaerobic threshold. Exercise of sufficient intensity and/or duration may increase the serum BDNF concentration via onset of acidosis relative to the resting state.

BDNF is a neurotrophin; it is integral in the maintenance of the healthy neuronal phenotype. Additionally, BDNF has been shown to acutely modulate presynaptic neurotransmitter release (10) and evoked excitatory postsynaptic currents via TrkB receptors (17) and to directly induce neuronal depolarization (11). It is becoming widely recognized that exercise is directly beneficial to brain health and function, probably via a BDNF-mediated mechanism. BDNF is found and made in many locations throughout the body (18,34) in addition to its namesake source of production, the brain. In this study, we assayed for peripheral serum BDNF levels via a blood withdrawal from the antecubital vein. We view it as likely that, in accordance with rodent studies, exercise in humans also results in elevated BDNF levels in the brain, because in rats there is a strong correlation between serum and cortical BDNF levels ($r = 0.81$) (13), and it has been reported that BDNF undergoes bidirectional transport across the blood–brain barrier (22,23). Although this study did not directly assess brain levels of BDNF, it seems plausible that BDNF in the brain increased because of onsite production, transport from the periphery, or both. Given this speculation, it is especially heartening that the subjects were able to bring about a serum BDNF increase after the V_{Th} + 10, which was a submaximal exercise bout characterized as falling between somewhat hard and hard according to the Borg scale (3), and that all participants were able to perform for 30 min. Exercise prescriptions for the purpose of neurological health could, conceivably, be of an intensity that would discourage few from participating because of the level of difficulty.

Adequate BDNF levels are essential for cognitive function (30). Previous studies have reported post–acute exercise bout Stroop score improvements (8,15). Therefore, pre- and postexercise Stroop tests were administered, and the relationship between those results and BDNF changes was examined. The GXT word and color scores increased significantly relative to baseline, whereas the color–word score did not. The post–endurance ride word and color test scores increased relative to baseline for the V_{Th} – 20 and V_{Th} + 10, whereas an increase in the color–word score occurred only after the V_{Th} + 10. The process of cognitive interference is associated specifically with the

Stroop color–word task, and the anterior cingulate has been cited as a pivotal brain structure involved in its execution (24). Although rodent BDNF exercise studies have focused to a large extent on hippocampal BDNF responses, BDNF is found in many brain regions, including the anterior cingulate (28). Therefore, we felt that the color–word results also warranted analysis as we examined possible associations between pre- to postexercise changes in BDNF and the Stroop color and word test. It is worthwhile to note that the V_{Th} + 10, as opposed to the V_{Th} − 20, yielded increases in both BDNF and the Stroop color–word score. However, the increase in the V_{Th} + 10 Stroop color–word performance could be attributed to an increase in activation and attention after the higher-intensity exercise (8); it is not necessarily related to the exercise-induced BDNF increase. Indeed, in all five instances where there was a significant BDNF and Stroop increase (GXT: word, color; V_{Th} + 10: word, color, color–word), examination of the coefficient of correlation when comparing the pre- to postexercise BDNF changes with the Stroop changes did not yield significant results. The pre- to postexercise increases in BDNF, where significant, occurred in most participants (15/15 for GXT, 14/15 for V_{Th} + 10), whereas the Stroop scores, even where significant increases occurred, were not as uniform (i.e., for the Stroop word test from the V_{Th} + 10, 11/15 increased relative to baseline, two individuals' scores did not change, and two scores decreased). Likely, this greater variability of change in Stroop scores precluded significant associations with the changes in BDNF values. Future investigations with a larger sample size may result in significant correlations between BDNF and Stroop responses.

This study examined the response of serum BDNF and cognitive function to acute bouts of exercise at varied intensities. Chronic physical activity in humans has been shown to benefit cognitive processes (16) and brain health (4). It is tempting to speculate that repeated pulses of exercise-induced BDNF are key phenomena in the neurological and cognitive improvements that occur as a function of regular chronic exercise. Future studies should examine the effect of chronic exercise training on the interplay between cardiovascular fitness, resting levels of BDNF, and cognitive function in human subjects. Further, investigations into the response of BDNF to an acute exercise bout before and after chronic training might shed additional light on the relationship between cardiovascular fitness, circulating BDNF levels, and cognitive and neurological function.

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