

Research article

## The Effects of Aerobic Exercise Intensity and Duration on Levels of Brain-Derived Neurotrophic Factor in Healthy Men

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### Abstract

This study examined the combined effects of aerobic exercise intensity and duration on serum brain-derived neurotrophic factor (sBDNF) levels in healthy human adult males aged 18-25 years. Forty five participants were randomly assigned to one of six exercise conditions based on varying intensity (80% or 60% of heart rate reserve, or control) and duration (20 or 40 min). Vigorous (80% heart rate reserve, "Vig") and moderate (60% heart rate reserve, "Mod") exercise was carried out on cycle ergometers. Control subjects remained seated and at rest during the exercise period. Pre- and post-exercise blood draws were conducted and sBDNF measured. Physical exercise caused an average ~ 32% increase in sBDNF levels relative to baseline that resulted in concentrations that were 45% higher than control conditions. Comparing the six conditions, sBDNF levels rose consistently among the four exercise conditions (Vig20 = 26.38 ± 34.89%, Vig40 = 28.48 ± 19.11%, Mod20 = 41.23 ± 59.65%, Mod40 = 30.16 ± 72.11%) and decreased consistently among the controls (Con20 = -14.48 ± 16.50, Con40 = -10.51 ± 26.78). Vig conditions had the highest proportion of subjects that experienced a significant (≥10%) increase in sBDNF levels, followed by Mod and control conditions. An analysis of modeled sBDNF integrals (area under the curve) demonstrated substantially greater values for Vig40 and Mod40 conditions compared to Vig20 and Mod20 conditions. Collectively, these results demonstrate that neither duration (20 vs. 40 min) nor intensity (60 vs. 80% HR reserve) significantly affects the benefits of exercise if only the sBDNF increase at a single post-exercise time point is considered. However, when comparing either the probability of achieving a significant BDNF gain or the integral (i.e. the volume of circulating BDNF over time) the Vig40 condition offers maximal benefits. Thus, we conclude that the future study of aerobic exercise effects on BDNF-mediated neuroprotection should take the volume of BDNF release over time into account.

**Key words:** Aerobic, brain-derived neurotrophic factor (BDNF), exercise, human, neurotrophins.

### Introduction

Brain-derived neurotrophic factor (BDNF) has been recognized as an important tropic hormone in the regulation of neuron morphology and survival. Endogenous BDNF is known to be involved in cellular development and growth, mood regulation, and cognitive functions such as learning and memory. Low circulating BDNF levels have been associated with a wide range of neuropsychiatric disorders including depression (Karege et al., 2002), bipolar disorder (Cunha et al., 2006), schizophrenia (Zhang

et al., 2007) and neurodegenerative diseases (Yu et al., 2008), although no causal relationship has yet been established. Research over the past decade has investigated the factors that can acutely and chronically elevate brain levels of BDNF in animals and circulating levels of BDNF in humans, based on the assumption that elevated BDNF levels can lead to improved brain health.

Research has consistently shown that chronic aerobic exercise can elevate baseline BDNF levels in the hippocampus, striatum, and various cortical regions in laboratory animals (Ding et al., 2004; Neeper et al., 1996; Oliff et al., 1998; Rasmussen et al., 2009; Vaynman et al., 2004a; Widenfalk et al., 1999), and Suijo et al. (2013) have recently demonstrated that resistance exercise can also elevate BDNF levels in the hippocampus. Encouragingly, BDNF transcription can be induced in the rat hippocampus after only three consecutive days of aerobic exercise. Also, unlike other neurotrophic factors which showed tolerance to chronic exercise, BDNF levels remained upregulated in the rat hippocampus after 28 consecutive days of wheel running (Molteni et al., 2002). In animal models of disease, chronic exercise has provided BDNF benefits such as cell survival (Ang et al., 2003), decreased depressive symptoms (Marais et al., 2009), and cellular protection and functional recovery after traumatic brain injury (Griesbach et al., 2004). Furthermore, chronic aerobic exercise seems to have a robust effect on cognition, as various intensities and durations of voluntary and forced exercise have consistently improved learning and memory in healthy laboratory animals, whether assessed by Morris water maze (Adlard et al., 2004; Huang et al., 2006; Vaynman et al., 2004b), radial arm maze (Anderson et al., 2000), Y-maze (Van der Borght et al., 2007), object recognition tasks (O'Callaghan et al., 2007), or pain avoidance training (Liu et al., 2008; Radak et al., 2006). In each of these studies, an increase in BDNF mRNA or protein levels was positively associated with performance enhancement.

In humans, chronic aerobic exercise has been tested for its ability to raise baseline circulating BDNF levels. Several chronic exercise studies suggest that aerobic training can increase resting levels of circulating BDNF (Seifert et al., 2010; Zoladz et al., 2008). However, the majority of chronic exercise studies, especially those not using aerobic exercise training, have not observed increased basal circulating BDNF levels (Goekint et al., 2010; Griffin et al., 2011; Levinger et al., 2008; Schiffer et al., 2009).

While the impact of chronic exercise on BDNF has been extensively tested, particularly in animal studies, much less is known about the effects of a single bout of aerobic exercise on brain BDNF levels. Several animal studies have demonstrated significantly increased BDNF mRNA levels in the rat hippocampus after a single bout of six hours voluntary wheel running (Chen and Russo-Neustadt, 2009; Oliff et al., 1998). Huang et al., (2006) also reported a strong BDNF response in the hippocampus (~50% increase) of rodents after a single bout of aerobic exercise, with no difference between moderate or intense exercise. However, Klintsova et al. (2004) did not find an effect of acute moderate intensity aerobic exercise on BDNF levels in the cerebellum or motor cortex of rats; BDNF levels were elevated in the cerebellum only after five days of training and in the motor cortex after 14 days.

Human research investigating the effect of acute single-bout aerobic exercise has focused on two areas in particular, either characterizing the change in serum BDNF (sBDNF) levels after one exercise session, or identifying the effects of exercise intensity on these post-exercise sBDNF levels. The acute effect of exercise on human sBDNF levels is characterized as a transient, moderate (~20-40%) increase (Gold et al., 2003; Rojas Vega et al., 2006; Tang et al., 2008). Serum BDNF levels rise during aerobic exercise, and quickly return to baseline levels upon exercise cessation, approximately 10-15 minutes after exercise offset (Rojas Vega et al., 2006; Tang et al., 2008). High intensity exhaustive aerobic exercise for a short duration (Rojas Vega et al., 2006), or sustained moderate intensity exercise (Gold et al., 2003) appear sufficient to increase sBDNF levels. Encouragingly, as little as 15 minutes of moderate intensity exercise has significantly elevated sBDNF levels in healthy human subjects (Tang et al., 2008). Ferris et al. (2007) clearly demonstrated an effect of aerobic exercise intensity on sBDNF levels using a within subjects counterbalanced design. Their report suggested that low intensity exercise was insufficient to elevate BDNF levels relative to baseline, while high intensity exercise for a comparable duration significantly elevated sBDNF levels (Ferris et al., 2007).

Human studies to date have not systematically varied exercise duration across acute aerobic conditions, and only several studies have examined the impact of exercise intensity. Therefore, the present study was designed to assess for the first time the combined effects of exercise intensity and duration on sBDNF levels in young healthy adult humans and to assess the extent to which sBDNF levels can be elevated in relation to sedentary controls.

## Methods

### Participants

Healthy adult males aged 18-25 years were recruited from introductory psychology courses at Weber State University through informational postings and classroom announcements. This study was limited to male subjects to reduce variability in BDNF levels that vary across gender and vary with menstrual cycle status in females (e.g. Be-

gliomini et al., 2007). A follow-up study is currently underway to assess the impact of physical exercise on BDNF in women, while accounting for menstrual cycle status and estrogen levels. All postings and announcements contained information regarding the experimental procedure, exclusion criteria, instructions for dress and eating schedules, as well as times and meeting locations. Participant recruitment and experimental procedures were approved by an IRB committee and were implemented in accordance with the Declaration of Helsinki. Prior to participation, subjects were required to complete an informed consent document, emergency contacts form, demographics survey, and an exercise readiness assessment (a modified version of the Physical Activity Readiness Questionnaire or PAR-Q published by the American College of Sports Medicine). The exercise readiness assessment was reviewed just prior to exercise; subjects' responses were used to determine qualification for the study, and to identify subjects with medical contraindications to exercise. Participant exclusions based on self report included: past or present cardio-pulmonary diseases or joint or muscle disease, current tendon or bone damage, metabolic disease, blood borne pathogens, symptoms of illness, or noncompliance with the request to abstain from eating and consuming caffeinated beverages 2 hours prior to the study.

Subjects provided information on their average weekly exercise patterns via self-report, first by estimating the "number of hours exercised in the past week" and the "average number of hours exercised, per week, over the past six months," and then by listing the average number of hours attributed to individual sports or physical routines (e.g. basketball, cycling, martial arts, soccer, swimming, weight lifting, etc.). Subjects were asked to correct discrepancies between the initial overall estimate and the more detailed sport/routine estimates. Regular exercise patterns played no role in subject recruitment and, as expected, the final subject pool included those that exercised regularly and those that did not.

During study sessions, 50 subjects were randomly assigned to one of six exercise conditions based on exercise intensity (vigorous, moderate, or sedentary control), and duration (20 or 40 min), using quota sampling. Conditions are referred to as Vig20, Vig40, Mod20, Mod40, Con20, and Con40, respectively.

Participants were asked to exercise at the proper intensity and durations of exercise. Subject data were not included without proper adherence to assigned exercise conditions. Three subjects were excluded due to incorrect completion of exercise condition (one from Vig20, two from Mod20). Additional subjects were recruited to meet quota sampling. Baseline sBDNF levels are known to be extremely variable in the human population (Knaepen et al., 2010). To reduce the impact of outliers, subject data were excluded from the reported analyses if the baseline sBDNF level was  $\geq$  the 99th percentile, or  $\leq$  the 1st percentile (i.e. 2.33 S.D. above or below the mean baseline sBDNF,  $n = 47$ ). Two subjects were excluded from the Mod20 condition due to elevated baseline sBDNF levels. Final sample sizes per condition were as follows: Vig20  $n = 9$ , Vig40  $n = 9$ , Mod20  $n = 9$ , Mod40  $n = 8$ , Con20  $n =$

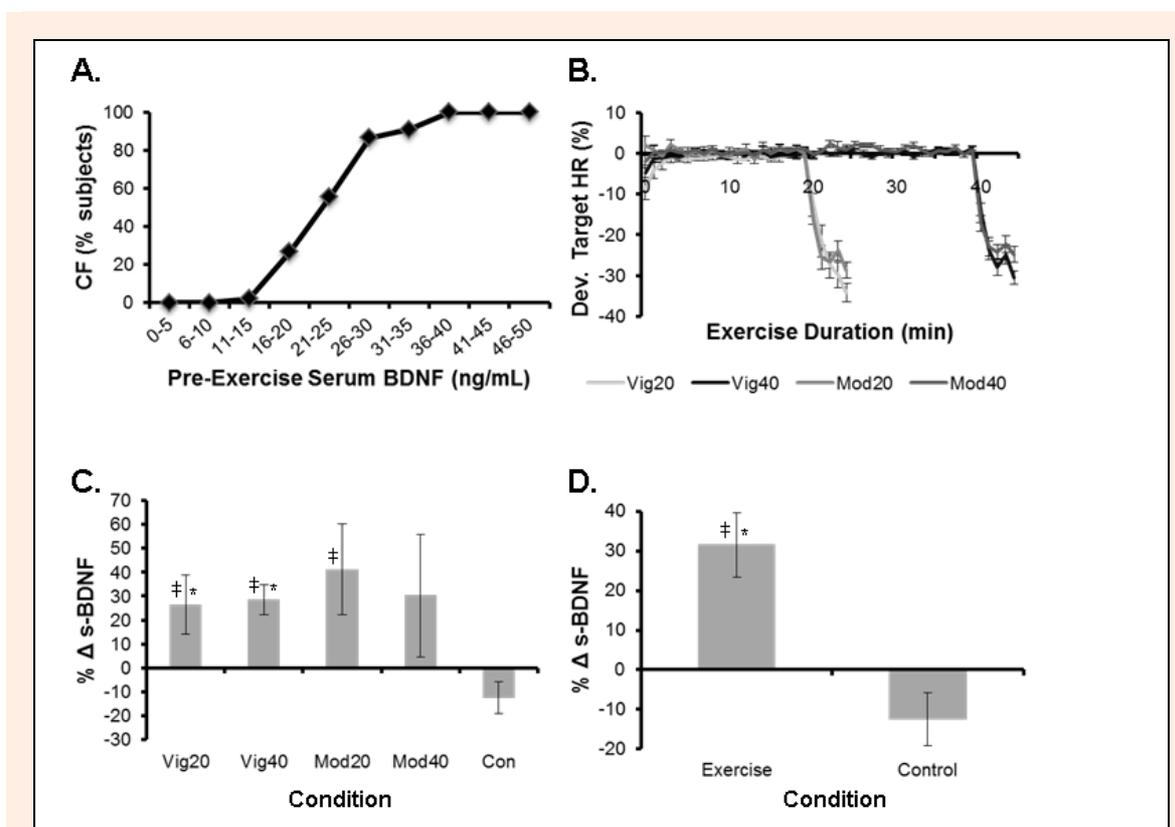
5, Con40 n = 5.

### Exercise Conditions

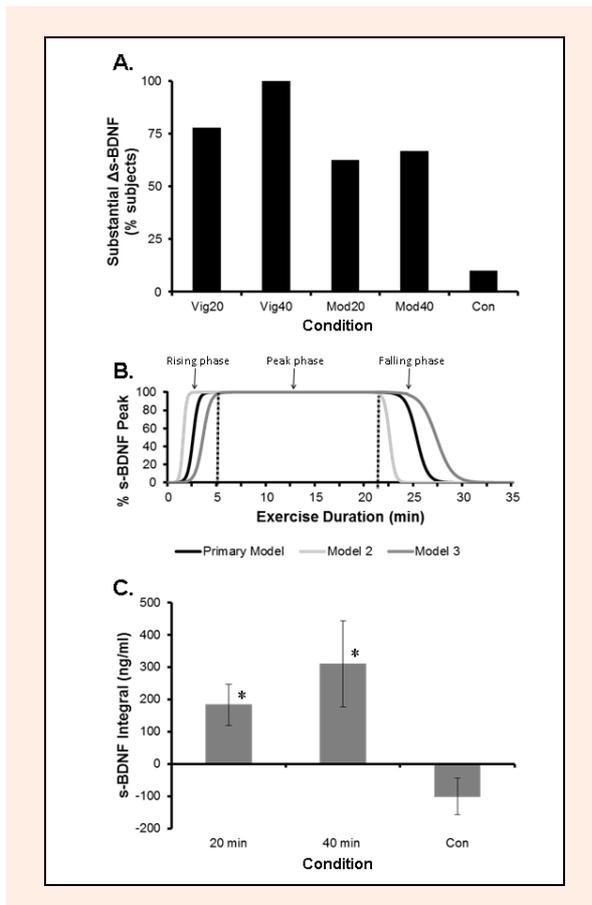
All study sessions were carried out between 14:00 and 18:00 hours to limit circadian and other time-of-day effects on sBDNF levels. All data collection was conducted with ambient temperature at 22° C and normal humidity.

Vigorous (80% heart rate reserve) and moderate (60% heart rate reserve) exercise was carried out on cycle ergometers (Life Fitness LifeCycle 9100, Schiller Park, IL, USA) in the Weber State University Exercise Biochemistry Laboratory. Heart rate (HR) reserve was used as a subject normalized measure of exercise intensity, and was calculated as  $220 - \text{resting HR} - \text{age}$  (Baker et al., 2010; Thompson et al., 2010). Blood pressure and resting

HR were first measured by automatic calculation (Nonin 2120 Vital Signs Monitor, Nonin Medical Inc., Minneapolis, MN) while subjects were seated. After a ~20 min sedentary rest period during which they completed the consent form and demographic surveys, subjects were fitted with heart rate monitors (Polar Vantage XL, Polar Electro Inc., Lake Success, NY). HR was measured once per minute during a baseline period and during exercise to verify compliance with the exercise regimen. To be included in data analysis, subjects' actual HR could not be more than  $\pm 5\%$  of their calculated target HR for more than three consecutive minutes, with the exception of the first three minutes of exercise. Any subject that fell out of this compliance threshold was excluded from the study (see Figure 1B).



**Figure 1.** Baseline sBDNF levels, heart rate during exercise, and change in sBDNF levels due to physical exercise. (A) The cumulative frequency distribution for baseline sBDNF levels for all subjects (n=45). Note that baseline BDNF levels show substantial variability (10.84 ng/ml to 39.01 ng/ml) even in this intentionally homogenous subject sample. (B) To ensure subject compliance to the assigned experimental condition (Vig20, Vig40, Mod20, or Mod40), heart rate (HR) was sampled for each subject during and just after the exercise period. HR data for each subject was transformed to a percentage of the target HR for that subject during exercise and deviation scores (expressed in %) were then calculated. The vast majority of subjects were able to quickly reach, and then maintain, their target HR for the 20 or 40 min period they were assigned. To be included in data analysis, subjects' actual HR could not be more than  $\pm 5\%$  of their calculated target HR for more than three consecutive minutes, with the exception of the first three minutes of exercise. Due to experimenter error, two participants exercised for an additional two minutes. Blood draws were time-locked at 2 minutes post-exercise and, therefore, their heart rate data was frame shifted to the left by two minutes to match exercise cessation and blood draw times within and between regimens. (C) The percent of change in sBDNF levels post-exercise. A 2X2 between factors ANOVA revealed no significant difference between the four exercise conditions when considering either the Intensity or Duration main effect, or the Intensity x Duration interaction. However, the average sBDNF level was greater in three of the conditions compared to baseline and two of the conditions compared to the control condition. (D) Because there was no significant difference between exercise conditions or control conditions, data was collapsed across conditions to allow for an exercise to control comparison of the percent change in sBDNF levels. Exercisers experienced an ~30% increase in sBDNF relative to basal values, which represents a concentration that was nearly 45% greater than controls immediately post-exercise. Panels B, C, and D show mean  $\pm$  SEM. \* indicates significantly different relative to control ( $p < 0.05$ ); ‡ indicates significant increase relative to baseline ( $p < 0.05$ ).



**Figure 2.** Probability of substantial sBDNF increase, and integral assumptions and values. **(A)** The percentage of participants that experienced a significant ( $\geq 10\%$ ) increase in sBDNF levels comparing post-exercise to pre-exercise values. Note that subjects in the Vig40 condition were most likely to show significant BDNF gains. Subjects in the Mod conditions and Vig20 condition had a 60-70% chance of showing a significant gain while the probability of a BDNF elevation in the sedentary control condition was 10%. **(B)** Graphical representation of sBDNF integral assumptions for a 20 min exercise duration and two models with alternative assumptions. The model can be divided into three distinct phases: the rise phase (which corresponds to beginning of exercise when heart rate is increasing), the peak phase (which corresponds to the portion of exercise when heart rate is maintained at the assigned level), and the falling phase (which corresponds to the post exercise return of heart rate to resting baseline levels). The primary model assumes a rise phase of 5 min, a peak phase of 15 or 35 min, depending on 20 or 40 min exercise assignment, respectively, and a 10 min falling phase. Model 2 assumes a rise phase of 7 min, a peak phase of 13 min or 33 min, depending on exercise assignment, respectively, and a falling phase of 15 min. Model 3 assumes a rise phase of 3 min, a peak phase of 17 or 37 min depending on 20 or 40 min exercise assignment, respectively, and a falling phase of 5 min. **(C)** As there were no significant differences between Vig20 and Vig40 conditions, between Mod20 and Mod40 conditions, nor control conditions, integral data was collapsed to allow for a comparison between 40 min, 20 min and control conditions. There were no significant differences between the collapsed 40 and 20 min conditions; however, integrals were significantly greater in both exercise conditions than in the control condition. Panel C shows mean  $\pm$  SEM. \* indicates significantly different from control ( $p < 0.05$ ).

### Blood draw and serum extraction

Pre- and post-exercise venous blood draws of 5 ml were collected from the median antecubital vein or adjacent veins by a certified phlebotomist using 21 gauge needles into BD Vacutainer Serum Plus Blood Collection Tubes (BD, Franklin Lakes, NJ, USA). Blood was drawn  $\sim 5$  minutes before exercise and 2 minutes post-exercise. Control subjects received identical “pre” and “post” venous blood draws but were sedentary, watching others exercise for a 20 min or 40 min duration. Whole blood was clotted at room temperature for one hour and then centrifuged (Eppendorf Centrifuge 5810, Hamburg, Germany) for 10 min at 3000 rpm. Upon supernatant extraction, serum was immediately frozen at  $-80^{\circ}\text{C}$ , and later packed and shipped on dry ice. Analysis of sBDNF concentration by sensitive enzyme-linked immunosorbent assay (ELISA) was conducted by Millipore Corporation, USA, according to their published protocol (Luminex<sup>®</sup>-based MILLIPLEX<sup>™</sup> MAP Human Neurodegenerative Disease Panel 3 kit 96 well plate assay). This protocol has been validated for human serum and is reported to have no crossreactivity with other neurotrophins, an intra-assay and inter-assay variability of 4.8% and 13.0% respectively, and a minimum sensitivity of  $0.3 \text{ ng}\cdot\text{ml}^{-1}$ .

### Modeled BDNF integral calculation

The pre- and post-exercise sBDNF levels were used for each subject to calculate a set of modeled BDNF integrals; i.e. the area under the curve for the BDNF vs. time plot. While no published study yet provides a detailed examination of BDNF kinetics in response to exercise, a number of studies support an exponential or sigmoidal rise and/or decay in the concentration of circulating hormones during and after exercise, respectively (e.g. human growth hormone; Lassarre et al., 1974; Raastad et al., 2000; Vanhelder et al., 1984). Thus, the following assumptions were used to calculate the mean sBDNF integral. First, the rise in sBDNF follows a logistic model, which is characterized by a sigmoidal rise that proceeds exponentially from a lower asymptote then decelerates exponentially as BDNF levels reach an upper asymptote. Second, the rise to a steady-rate BDNF level (i.e. asymptote) takes 5 minutes to achieve (1-2 minutes after the target HR was achieved, see Figure 1B). This assumption is supported by Rojas Vega et al. (2006) who found a  $\sim 20\%$  increase in sBDNF levels after  $\sim 7$  min of exercise. Third, the assumption was made that once reached, asymptote BDNF levels are maintained throughout the remainder of exercise. Finally, the return from asymptote value to baseline value after exercise cessation also follows a logistic model and takes 10 minutes to achieve (see Figure 2B). The authors believe this to be a reasonable estimate considering that Rojas Vega et al. (2006) found that BDNF levels had returned to baseline after approximately 10 min, though other reports suggest that the sBDNF rise may last longer than 10 min (Tang et al., 2008).

Integrals in this study represent a model of the amount of sBDNF circulated above baseline during and just after exercise. For this reason, we shifted the curve down on the y axis so that at time zero sBDNF levels

were no different than baseline, making the lower asymptote 0. Our assumptions and axial shifts allowed us to utilize the following equations, where the first was used to solve for slope of the rising or falling phase (i.e. just after exercise began or just after exercise ended, respectively) and the second was used to calculate area under the curve of the rising or falling phase:

In order to solve equation 1 to find the value of  $r$ , the value of  $y$  at one interim time had to be determined. Therefore, we assigned  $y$  to be one-half  $\Delta$  sBDNF, where  $t$  equals half of the time needed to reach asymptote. For example, if it takes 5 min to elevate sBDNF  $10 \text{ ng}\cdot\text{ml}^{-1}$  over baseline, then the difference between baseline and asymptote sBDNF levels at  $t = 2.5 \text{ min}$  is  $5 \text{ ng}\cdot\text{ml}^{-1}$ .

$$y = \frac{Ky_0}{y_0 + (K - y_0)e^{-rt}} \quad \text{Equation 1}$$

$$A = \frac{K}{r} [\ln(y_0 e^{tr} + K - y_0) - \ln(K)] \quad \text{Equation 2}$$

In both equations, symbols are as follows:  $K$  is the difference between asymptote BDNF and baseline levels;  $y_0$  is the level of sBDNF at time-zero;  $r$  is the rate of BDNF increase;  $i$  is the time necessary to reach asymptote or to return to baseline, and;  $t$  is time. It is important to note that by shifting the whole model down by several points on the  $y$  axis, the area under the curve was not altered. The same procedure was used to calculate the sBDNF integral for the falling phase, post-exercise. The area of the asymptote phase is that of a rectangle ( $1 \times w$ ) where length is the exercise duration – rising phase period (e.g. 20 min duration – 5 min rising phase) and width is  $= K$ . For example, if a subject in a 20 minute condition had a baseline BDNF value of  $15 \text{ ng}\cdot\text{ml}^{-1}$  and a post-exercise BDNF of  $25 \text{ ng}\cdot\text{ml}^{-1}$ , assuming  $i = 5 \text{ min}$  for the rising phase and  $i = 10$  for the falling phase, the values for the three areas would be 25 (rising phase), 150 (asymptote phase), and 50 (falling phase); the integral would be  $225 \text{ ng}\cdot\text{ml}^{-1}$ .

### Statistical analysis

To simplify and standardize comparisons between the six groups, a pre-post percentage change in sBDNF ( $\Delta$  % sBDNF) was calculated for each subject. Planned com-

parisons were carried out using mixed model multivariate ANOVAs and Bonferroni corrected t-tests on  $\Delta$  % sBDNF values and, where appropriate, on raw sBDNF values. Pearson correlations were conducted between pre-exercise measurements and baseline sBDNF levels, and between baseline sBDNF levels and the pre-post exercise change in sBDNF levels. Chi square analyses were conducted for all non-parametric data, to test for inter-group differences in the proportion of subjects that showed a significant increase in sBDNF. All statistical analyses were conducted using SPSS 16 for windows, and graphical representation was conducted using Microsoft Windows Excel. Statistical significance was defined as  $p < 0.05$ . Except where noted, data are presented as mean  $\pm$  standard deviation (S.D.).

### Results

The mean baseline sBDNF level for the 45 subjects included in this study ranged from  $10.85$  to  $39.01 \text{ ng}\cdot\text{ml}^{-1}$ ,  $M = 24.95 \pm 7.28 \text{ ng}\cdot\text{ml}^{-1}$  (see Figure 1A). The effectiveness of random subject assignment was verified by one-way ANOVAs, which revealed no significant differences between conditions in the following key baseline (pre-exercise) variables: basal sBDNF level, age, self-reported weekly exercise (in the past week or on average over the past six months), resting heart rate, systolic and diastolic blood pressure, height, weight, hours of sleep per day, or caffeine intake (see Table 1). Combining subjects in all conditions, the average self-reported weekly exercise over the prior six months was  $7.7 \pm 5.9$  hours ( $n = 43$ ) and for those subjects that correctly completed the list of hours per specific physical activity, 62% was attributed to exercise scored aerobic (e.g. jogging, cycling), 26% to exercise scored resistance/strength training (e.g. weightlifting), and 12% to exercise scored “mixed activities” (e.g. baseball, martial arts) ( $n = 38$ ).

Conformity to exercise protocol was assessed and was consistently maintained by participants throughout exercise. Figure 1B shows group conformity to exercise procedures based on heart rate and exercise duration.

### Post-exercise BDNF levels

A  $2 \times 2 \times 3$  mixed model ANOVA on sBDNF levels

**Table 1. Baseline (pre-exercise) characteristics of subjects (N = 45) by group. Values shown are means ( $\pm$  SD).**

	Vig 40 (n = 9)	Vig 20 (n = 9)	Mod 40 (n = 8)	Mod 20 (n = 9)	Control (n = 10)	rB
Basal sBDNF Levels ( $\text{ng}\cdot\text{ml}^{-1}$ )	23.0 (6.6)	24.8 (6.4)	23.9 (8.6)	28.6 (4.4)	21.9 (4.2)	-
Age (years)	21.6 (2.6)	20.9 (2.4)	21.1 (2.6)	21.1 (2.9)	20.4 (2.0)	.09
Weekly Exercise (hours in last week)	7.3 (6.4)	8.1 (7.9)	3.9 (4.3)	4.8 (4.1)	9.7 (8.0)	.01
Weekly Exercise (hours/week/6 months)	9.3 (7.6)	5.8 (2.6)	4.7 (3.7)	8.3 (5.0)	11.6 (8.3)	-.05
Resting HR (bpm)	72 (9)	69 (10)	78 (14)	69 (12)	67 (11)	-.17
Systolic BP (mm hg)	125.9 (12.6)	127.6 (11.8)	131.6 (12.0)	137.6 (14.1)	135.0 (13.8)	.13
Diastolic BP (mm hg)	69.2 (4.4)	67.4 (7.1)	71.8 (3.3)	71.1 (6.4)	71.2 (9.2)	.11
Weight (kg)	76.8 (11.9)	76.4 (11.0)	75.2 (11.4)	83.6 (18.7)	81.0 (10.6)	-.01
Height (m)	1.80 (.04)	1.76 (.05)	1.80 (.07)	1.81 (.07)	1.77 (.06)	-.03
Sleep (hours/day)	7.3 (.9)	7.5 (.7)	7.4 (.9)	7.1 (.1)	7.1 (1.2)	.04
Caffeine intake (drinks/day)	.33 (1.0)	.13 (.35)	.50 (.76)	.69 (.70)	.55 (.90)	-.07

Significant differences between groups were assessed via independent-samples One-Way ANOVA and t-tests. Note that no significant differences between groups were found for the given variables. The last column gives the Pearson correlation coefficient for correlation between baseline BDNF (rB) and the variable indicated in the row for all subjects ( $n=45$ ). None of the correlations were significant. Note that the self-reported measures of weekly exercise are likely an overestimate due to social desirability bias. BP: blood pressure; HR: heart rate.

revealed significant effects for the within-subjects factor Time (pre vs. post;  $F = 5.22$ ,  $p < 0.05$ ) and the between subjects factor Intensity (Vigorous vs. Moderate vs. Control;  $F = 4.89$ ,  $p < 0.05$ ); the between subjects factor Duration (20 min vs. 40 min) was not significant ( $F = 0.90$ ,  $p = 0.35$ ). The Time X Intensity interaction was significant ( $F = 3.63$ ,  $p < 0.05$ ). As predicted, physical exercise did lead to a significant increase in serum BDNF levels. As shown in Figure 1C, the average pre-post percentage change in sBDNF ( $\Delta\%$  sBDNF) was 25-30% in three of the exercise conditions (Vig20 =  $26.38 \pm 34.89$ , Vig40 =  $28.48 \pm 19.11$ , Mod40 =  $30.16 \pm 72.11$ ), and was numerically, though not statistically, higher in the fourth condition (Mod20 min =  $41.23 \pm 59.65\%$ ). Interestingly, the  $\Delta\%$  sBDNF actually decreased on average in both control conditions, (Con20 =  $-14.48 \pm 16.50$ , Con40 =  $-10.51 \pm 26.78$ ); there was no significant difference between the average  $\Delta\%$  sBDNF values for the two control groups ( $t(8) = 0.173$ ,  $p = 0.87$ ). Therefore, data were collapsed across exercise conditions, and across control conditions to allow for an exercise to non-exercise comparison of the  $\Delta\%$  sBDNF (Figure 1D). Analysis of the collapsed data demonstrated a significant 44.10% increase in  $\Delta\%$  sBDNF relative to control (exercise =  $31.60 \pm 48.11$ , control =  $-12.50 \pm 21.07$ ), and significantly elevated sBDNF levels relative to baseline ( $t(34) = 3.89$ ,  $p < 0.001$ ). Eight out of ten control subjects showed a decrease in sBDNF levels (comparing post to pre values) although the average decrease just failed to attain significance ( $t(9) = -2.133$ ,  $p = 0.06$ ).

A two-way ANOVA for the four exercise conditions demonstrated no main effect for Exercise Intensity on  $\Delta\%$  sBDNF (Vig =  $27.43 \pm 27.31$  and Mod =  $36.02 \pm 63.93$ ,  $F(1, 31) < 0.001$ ,  $p = 0.99$ ). In addition, neither the main effect of Duration (20 min =  $33.81 \pm 48.02$  vs. 40 min =  $29.27 \pm 49.58$ ,  $F(1, 31) = 0.10$ ,  $p = 0.74$ ) nor the interaction of Intensity x Duration ( $F(1, 31) = 0.47$ ,  $p = 0.50$ ) proved significant. Both Vig intensity conditions and the Mod20 condition demonstrated significantly increased  $\Delta\%$  sBDNF relative to the combined control condition ( $t(16) = 4.18$ ,  $p < 0.01$ ,  $t(16) = 3.15$ ,  $p < 0.01$ ,  $t(17) = 2.96$ ,  $p < 0.01$ ), while the Mod40 condition showed a trend towards significance ( $t(16) = 2.51$ ,  $p = 0.06$ ). No others between group comparisons were significant.

### Probability of BDNF increase

We conducted an analysis of the portion of subjects in each condition that experienced an increase in  $\Delta$  sBDNF levels post-exercise equal to or greater than a statistically significant cutoff. A one sample t-test using the experimental sample size ( $n = 35$ ) and standard deviation

(48.11) demonstrated that the cutoff for a significant change in sBDNF was 13.8% above the control value of -12.5%, or +1.3%. To be conservative, we set the cutoff at +10.0%, which is significant at the  $p = 0.01$  level,  $t = 2.76$ . Subjects who exercised at Vig intensities were more likely than Mod intensity exercisers to show a significant sBDNF increase. Furthermore, subjects who remained sedentary were not likely to show significantly increased sBDNF levels (see Figure 2A). A two-way chi square analysis of the portion of subjects experiencing  $\geq 10\%$  increases in BDNF levels was significant (Vig40 = 100%, Vig20 = 77.8%, Mod40 = 62.5%, Mod20 = 66.7%, Con40 = 20%, Con20 = 0%,  $\chi^2(5) = 18.49$ ,  $p < 0.01$ ).

### Modeled BDNF integral

In addition to the pre-post sBDNF level change, the sBDNF integral, a measure of total circulated BDNF above baseline over time, was modeled for each subject and compared across groups. Figure 2B provides a graphical summary of integral assumptions.

The mean sBDNF integrals for Vig40 ( $292.69 \pm 302.77$  ng·ml<sup>-1</sup>) and Mod40 ( $285.71 \pm 730.91$  ng·ml<sup>-1</sup>) conditions were substantially greater than the means of the Vig20 ( $113.21 \pm 160.29$  ng·ml<sup>-1</sup>) and Mod20 ( $206.58 \pm 730.91$  ng·ml<sup>-1</sup>) conditions. However, a two-way ANOVA for exercise groups showed no significance for the main effects of Intensity ( $F(1,30) = 0.04$ ,  $p = 0.90$ ) or Duration ( $F(1, 30) = 0.70$ ,  $p = 0.40$ ), or the interaction of Intensity x Duration ( $F(1, 30) = 0.236$ ,  $p = 0.60$ ). Data were collapsed across durations to allow for a numerical comparison between 20 to 40 min conditions. Data were also collapsed across control conditions after verifying that there were no significant differences between the two control conditions ( $p > 0.05$ ). A one-way ANOVA of the collapsed integral data demonstrated a significant difference between groups ( $F(2, 42) = 3.40$ ,  $p < 0.05$ ). The numerical difference between the collapsed 20 ( $183.09 \pm 261.24$  ng·ml<sup>-1</sup>) and collapsed 40 min ( $310.23 \pm 567.89$  ng·ml<sup>-1</sup>) conditions was not statistically significant ( $t(33) = 1.14$ ,  $p = 0.40$ ). There were significant elevations in sBDNF integrals for collapsed 20 and 40 min conditions relative to control ( $-100.94 \pm 178.70$  ng·ml<sup>-1</sup>,  $p < 0.05$ ) (see Figure 2C).

It is worth noting that the assumptions made in our BDNF integral models have not been fully validated experimentally. However, the results of the integral analysis are largely unaffected by changes to the assumptions (e.g. we tested models with the BDNF rise to asymptote at 3 or 7 minutes rather than 5, and the fall to baseline at 5 minutes or 15 minutes, rather than 10). Several of these permutations are demonstrated in Figure 2B, and the results of these alternative analyses are shown in Table 2.

**Table 2. Integral model comparisons. Data are means ( $\pm$ SD).**

	Primary Model	Model 2	Model 3
40 min	289.40 (528.75)	273.31 (497.64)	317.43 (580.18)
20 min	159.89 (227.64)	142.16 (201.52)	191.06 (272.07)
Con	-92.18 (166.10)	-85.68 (156.92)	-104.35 (183.47)

Primary model is based on 5 min rising phase and a 10 min return to baseline. Model 2 is based on 7 min rising phase, and a 15 min return to baseline. Model 3 is based on 3 min rising phase and a 5 min return to baseline. All values represent the change in sBDNF occurring within the model (in ng·ml<sup>-1</sup>).

## Discussion

Comparison of baseline sBDNF levels between studies is complicated by differences in blood clotting procedures and high variability within healthy populations. However, the mean baseline sBDNF level for the 45 subjects included in this study ( $24.95 \pm 7.28 \text{ ng}\cdot\text{ml}^{-1}$ ) was within reported ranges (7.17 to  $30.9 \text{ ng}\cdot\text{ml}^{-1}$ ; Currie et al., 2009; Nofuji et al., 2008; Tang et al., 2008) for healthy, human subjects (see Figure 1A).

As expected, based on previously reported research, we found elevations in human sBDNF levels after physical exercise. On average, subjects in the exercise conditions experienced an approximate 30% increase in sBDNF levels compared to baseline. This magnitude of change is comparable to other studies reporting acute-exercise induced increases in sBDNF on the order of 10% (Tang et al., 2008) to just over 30% (Rojas Vega et al., 2006). Having sedentary controls within the laboratory setting proved to be an important approach in this study, as there was an unexpected but consistent pre-post decrease in sBDNF levels among controls on the order of 13%. Thus, subjects in the exercise condition actually demonstrated an approximate 45% increase in sBDNF levels relative to sedentary controls. This decrease in control sBDNF levels could be the result of short term fluctuations in sBDNF levels due to circadian rhythms or, we believe far more likely, increased physiological arousal due to the blood draws and observation of the ongoing experimental procedures (blood draws of other subjects; moderate and vigorous physical exercise). Studies have shown that elevated stress, exogenous cortisol application, or glucocorticoid receptor agonism can lead to reduced BDNF levels (see Pluchino et al., 2013 for review).

One of the primary objectives of this research was to evaluate, for the first time, the combined effects of exercise intensity and duration on post-exercise sBDNF levels. Contrary to our predictions and expectations based on previous research where high intensity exercise was compared to low intensity exercise (Ferris et al., 2007), neither exercise intensity (60% HR reserve versus 80% HR reserve) nor duration (20 versus 40 minutes) had a significant impact upon pre-post sBDNF values. The Intensity x Duration interaction was also not significant. This might suggest that exercise parameters (within a certain range) have no influence on BDNF benefits, but that is only the case when the data analysis is limited to mean pre-post sBDNF levels. When we considered either the *probability* of achieving a significant BDNF rise ( $\geq 10\%$ ) during exercise or the volume of BDNF circulating over time (i.e. the *integral*) key differences among the groups emerged.

In this and other studies (e.g. Tang et al., 2008), physical exercise caused no change in sBDNF levels in some participants and an actual decrease in sBDNF in several. Individuals who exercised at a vigorous intensity for 40 min were most likely to experience significant increases in sBDNF levels, followed by those in the Vig20 condition, and then those in the moderate intensity conditions (see Figure 2A). This suggests that individuals

who exercise at sustained vigorous intensity could increase their likelihood for significant changes in BDNF levels and, thereby, increase the likelihood for improved brain functioning and neural protection. Such findings may be meaningful to clinical research, as subjects who experienced unchanged or even decreased sBDNF levels may represent a subpopulation that is resistant to some of the beneficial effects of exercise; i.e. those that are known to be BDNF-mediated (e.g. see Rojas Vega et al., 2008).

Comparing integrals for the two vigorous intensity conditions, subjects in the 40 min period showed an increase in the volume of BDNF circulated that was 2.7 times greater than that seen in the 20 min period group; the moderate intensity 40 min group showed an increase that was 1.4 times greater than the 20 min group. Future studies should seek to characterize the rise in sBDNF levels, the timing of the BDNF asymptote, and any potential fluctuations in sBDNF levels during exercise. Such investigations would allow for more accurate estimations of the increased volumes of BDNF circulated during exercise and the volume increase necessary to achieve enhanced brain functioning. It is presumed that BDNF levels are critical for improving brain functioning, and preventing and treating neuropsychiatric diseases; it follows that the volume of circulating BDNF over time (measured with the integral) is a more important indicator of BDNF function than is the magnitude of peak BDNF concentration at one fixed time point.

Human studies investigating the acute effects of single-bout aerobic exercise have consistently reported transient elevations in sBDNF levels, and similar elevations may result from acute bouts of resistance training (Yarrow et al., 2010; but see Goekint et al. 2010). However, details on the necessary factors (i.e. duration, intensity, frequency, etc.) that can increase resting levels of circulating BDNF are unknown. Correlation studies investigating ongoing, self-regulated, or unmodified levels of locomotion, frequency of sports activities, or current level of cardio-respiratory fitness have suggested that high levels of physical activity and aerobic fitness are negatively associated with basal sBDNF levels (Chan et al., 2008; Currie et al., 2009; Gold et al., 2003; Nofuji et al., 2008; Rojas Vega et al., 2006). In line with these findings, physiological markers of sedentary lifestyle have been associated with increased levels of plasma BDNF (Levinger et al., 2008). When considering the effect of regimented fitness programs on circulating BDNF levels, it has become clear that chronic strength training has little if any significant effect on basal circulating BDNF levels (Goekint et al., 2010; Levinger et al., 2008; Schiffer et al., 2009), and aerobic training may not improve baseline BDNF levels in healthy subjects (Griffin et al., 2011), nor in patients with mild cognitive impairment (Baker et al., 2010). To our knowledge, there is only one report of increased basal plasma BDNF levels following aerobic exercise training. This study involved healthy young males engaged in rigorous aerobic exercise several times a week, for 5 weeks (Zoladz et al., 2008).

While chronic aerobic exercise may lead to a decline in basal BDNF levels, evidence suggests that long term training can alter the way BDNF responds to acute

bouts of aerobic exercise, both enhancing the peak response (Griffin et al., 2011; Zoladz et al., 2008), and potentially elevating the ratio of arterial to venous pBDNF across the brain (Seifert et al., 2010). Chronic resistance training may also enhance the effects of acute exercise on sBDNF levels (Yarrow et al., 2010). Chronic exercise could also enhance the use of systemic BDNF after acute exercise, as seen when comparing sedentary individuals to those that are physically active (Nofuji et al., 2012). Altered BDNF circulation may have a role in cognition and brain protection through the integration of BDNF during and just after single exercise sessions, as well as across the exercise training periods.

The use of more regimented exercise programs, increased control of extraneous variables (e.g. nutrition, stress levels, etc.), and integration of single-bout factors may be necessary to understand how chronic exercise can be used to enhance brain functioning and protection. For example, Baker et al (2010) had males and females with mild cognitive impairment exercise 4 days per week, for 6 months, using a single bout intensity and duration (~80% of HR reserve for 45-60 min·d<sup>-1</sup>) nearly identical to that used in the Vig40 condition in the current study. Our results and integral modeling (using the primary model for integral calculation, see Figure 2) suggest that the average subject in the Baker et al. (2010) study could have experienced a transient ~28% increase in BDNF levels (post-pre) and an increased volume of approximately 300 ng·ml<sup>-1</sup> of BDNF, 4 days/week, for 6 months. Patients with depression (Karege et al., 2002), attention deficit-hyperactivity disorder (Shim et al., 2008), bipolar disorder (Cunha et al., 2006), and schizophrenia (Zhang et al., 2007), which have all been linked to alterations in circulating BDNF, may benefit from exercise in a similar fashion, either through enhanced baseline BDNF levels or repeated transient increases in BDNF.

## Conclusion

In summary, this study tested the impact of both exercise intensity and duration upon sBDNF levels in healthy adult males. Under the conditions set, neither factor (intensity nor duration) influenced the degree of BDNF increase resulting from exercise. However, these factors did play a role in both the *probability* of an individual subject achieving a significant BDNF increase and in the *integral* (i.e. the volume of circulating BDNF). Future studies should evaluate these factors in the context of acute and chronic exercise in other sub-populations such as patients with neuropsychiatric disease.

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### Key points

- Aerobic exercise caused a ~32% increase in serum BDNF in adult human males while serum BDNF decreased 13% in sedentary control subjects.
- Vigorous intensity (80% heart rate reserve), long duration (40 min) exercise offered the greatest probability of a significant BDNF elevation.
- Long duration exercise offered the greatest numerical benefits in terms of BDNF integral.
- Neither intensity nor duration affected the mean elevation in BDNF amplitude caused by exercise.

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