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Joshua T. Reycraft[1], Hashim Islam[2,3], Logan K. Townsend[2,4], Grant C. Hayward[1], Tom J. Hazell[2], Rebecca E.K. MacPherson[1]

[1]Department of Health Sciences, Brock University, St. Catharines, ON, Canada; [2]Department of Kinesiology and Physical Education, Wilfrid Laurier University, Waterloo, ON, Canada; [3]School of Kinesiology and Health Studies, Queen's University, Kingston, ON, Canada; [4]Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON, Canada

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Joshua T. Reycraft[1], Hashim Islam[2,3], Logan K. Townsend[2,4], Grant C. Hayward[1],Tom J. Hazell[2], Rebecca E.K. MacPherson[1]

[1] Department of Health Sciences, Brock University, St. Catharines, ON, Canada

[2] Department of Kinesiology and Physical Education, Wilfrid Laurier University, Waterloo, ON, Canada

[3]School of Kinesiology and Health Studies, Queen's University, Kingston ON, Canada

[4]Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, CANADA

Corresponding Author:

Rebecca EK MacPherson

Assistant Professor

Department of Health Sciences

Brock University

St. Catharines, Ontario, Canada

905.688.5550 x6620

rmacpherson@brocku.ca

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Abstract

Introduction: BDNF is an exercise-induced neurotropin mediating neuroprotection and synaptic plasticity. Although exercise intensity is implicated as a potentially important mediator of BNDF release following exercise, the optimal exercise stimulus (interval versus continuous) and intensity (sub- versus supra-maximal) for augmenting circulating BDNF levels remains unknown. Irisin, an exercise-driven myokine, may also contribute to neuroprotection by upregulating BDNF. **Purpose:** to examine the response and recovery of plasma BDNF and irisin following acute exercise of differing intensities. **Methods:** Eight males (23.1±3.0 years of age; VO_{2max} 51.2±4.4 $mL \cdot kg^{-1} \cdot min^{-1}$) completed four acute exercise sessions: 1) moderate-intensity continuous training (MICT, 65% VO_{2max}); 2) vigorous-intensity continuous training (VICT, 85% VO_{2max}); 3) sprint interval training (SIT, "all out"); and 4) no exercise (CTRL). Blood was collected pre-exercise as well as immediately, 30 min, and 90 minutes post-exercise. Plasma BDNF and irisin were assessed with commercially available ELISA kits. **Results:** Plasma BDNF levels increased immediately following exercise in the SIT group ($p<0.0001$) with plasma concentrations recovering 30 and 90 min post-exercise. BDNF levels following MICT were reduced 30 min post-exercise compared to immediately post-exercise ($p=0.0189$), with no other changes across time points in MICT and VICT groups. Plasma BDNF AUC in SIT was significantly higher compared to CTRL, MICT, and VICT ($p=0.0020$). No changes in plasma irisin across exercise groups and time points were found ($p>0.9999$). **Conclusions:** Plasma BDNF levels increased in an intensity-dependent manner with SIT eliciting the highest BDNF concentration immediately post-exercise. These results identify SIT as a time-efficient exercise modality to promote brain health through BDNF release.

Keywords: sprint interval training; high-intensity interval training; aerobic exercise; BDNF; lactate; irisin

Introduction

Characterized by the progressive deterioration of cognitive and functional ability beyond that of normal aging, dementia is now the 7th leading cause of death worldwide with Alzheimer's disease (AD) making up 60-70% of cases (1). Physical inactivity shows a greater population attributable risk for AD development compared to midlife obesity and other related morbidities combined (hypertension, diabetes mellitus) (2). Although exercise training is an effective treatment method for obesity and metabolic dysfunction, the augmented effect size of physical inactivity in AD risk reveals a direct mechanism by which exercise offers neuroprotective effects. Given the health benefits of physical activity and its wide accessibility at any age, determining how exercise can be used as medicine to sustain cognition during aging would have enormous societal and economic impact.

The transient short-term functional improvements and long-term neuroprotective benefits of exercise have been attributed to the activity-induced expression and release of the neurotrophin family member brain-derived neurotrophic factor (BDNF) (3). At a neuronal level, BDNF release promotes synaptogenesis which in turn directly mediates cognitive processes such as memory, learning, and emotion (4, 5). Interestingly, BDNF is able to cross the blood-brain barrier (BBB) and cross-species studies show that whole blood BDNF concentrations reflect BDNF levels in the brain (6, 7). Further, it is known that basal levels of plasma BDNF decline with age (8) and that reduced circulating BDNF has been demonstrated in patients with major depression, obesity, and type 2 diabetes (9, 10). In addition, reduced circulating BDNF has been implicated with a faster cognitive decline in patients with AD compared to patients with a slower

cognitive decline (11). The prominence of reduced plasma BDNF in AD and populations at greater risk for AD (e.g., obesity, T2DM, aging) demonstrate the importance of examining interventions that increase BDNF and preserve brain health.

Aerobic exercise training is known to elevate resting plasma BDNF (12, 13), demonstrating the potential of regular exercise to increase circulating BDNF. Acutely, it has been reported that the brain contributes 70-80% of the circulating BDNF post-exercise (14). This increase in circulating BDNF post-exercise has been demonstrated across ages, sex, and within patient populations (panic disorder, AD, major depressive disorder) (15–18). A recent meta-analysis found that there is a relationship between exercise duration and BDNF in serum and plasma of healthy adults, however the majority of evidence points towards a stronger intensity dependent relationship, with higher intensities provoking greater circulating BDNF concentrations (15, 19–22). Yet, the optimal exercise intensity to provoke the highest and longest lasting circulating BDNF remains unknown. Given the relationship between BDNF release and exercise intentisy, sprint interval training (SIT) may provide a time efficient exercise that optimally increases BDNF.

In addition to the peak BDNF elicited by exercise, it is important to establish which exercise will elicit the longest increase in BDNF post-exercise. Studies examining the BDNF recovery profile following high-intensity acute exercise have reported inconsistent results. For example, following the completion of a graded exercise test to volitional fatigue serum and plasma BDNF recovered by 30 and 60 min, respetively (23). However, a running-based HIIT protocol at maximal intensity (100% VO_{2peak}) demonstrated serum BDNF recovery within 60

min, though no earlier blood draws were collected (22). As studies to date have neither demonstrated intensity-dependent BDNF response in plasma nor post-exercise BDNF changes following SIT, the effect of exercise intensity and SIT on plasma BDNF recovery is unknown.

Interestingly, recent *in vivo* rodent and *in vitro* cell culture studies have suggested a novel mechanism by which skeletal muscle contraction secretes myokines into the circulation, which may readily cross the BBB and induce central *Bdnf* expression. One potential candidate is circulating irisin and its membrane-bound form fibronectin type III domain-containing protein 5 (FNDC5) (24). Mediated through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), *in vivo* and *in vitro* models show *Bdnf* expression to be dependent on FNDC5 (24). Furthermore, adenoviral vector administration of FNDC5 into the liver of mice transiently increased circulating irisin and enhanced hippocampal *Bdnf* expression (24).

This study tested the hypothesis that exercise intensity is an important mediator of changes in plasma BDNF levels in healthly male adults. Specifically this study aimed to examine: 1) the intensity-dependent plasma BDNF response and recovery profile following different exercise protocols across an intensity continuum; and 2) investigate exercise-induced changes in circulating irisin as a candidate modulator of BDNF expression in response to running-based exercise. Results from this investigation will help to identify the optimal exercise intensity for promoting brain health.

Methods

Participants

Eight active young males participated in this study and all experimental sessions were conducted at Wilfrid Laurier University for a previously published study (see Islam et al., 2017). Participants were non-smokers and determined healthy through the PAR-Q+ health questionnaire prior to study enrolment. All participants were physically active (<3 weekly exercise sessions) and not involved in any systemic training program for at least 6 months prior to study participation. Participants were instructed to refrain from any dietary supplements at the time of the study and refrain from any physical activity, alcohol, or caffeine for >24 hours prior to experimental sessions. Experimental details were fully explained to all participants and all provided written informed consent prior to any data collection. This study was approved by the Research Ethics Board at Wilfrid Laurier University in accordance with the 1964 Declaration of Helsinki.

Experimental Design

The experimental design has been described previously (Islam et al. 2017). Briefly, each participant completed four different experimental sessions, with each session taking place >1 week apart using a systemic rotational order using a counterbalanced Latin square design. Experimental interventions consisted of a resting control session (CTRL; no exercise) in addition to three running-based exercise protocols: 1) moderate-intensity continuous training (MICT, 65% of maximal oxygen uptake [VO_{2max}]); 2) vigorous-intensity continuous training (VICT, 85% VO_{2max}); and 3) sprint interval training (SIT, four 30-sec bouts of "all-out" running interspersed with 4-min rest periods). Blood draws were obtained at four time-points throughout

each three-hour experimental session. Blood draws for the immediately post-exercise samples were taken within 30 seconds of completing the 5-min cool-down for all participants. Participant's energy intake was recorded over a three-day period and participants were asked to replicate their dietary intake for 24 hours prior to each experimental session.

Pre-experimental Procedures

One week prior to the first experimental session all participants completed a familiarization session in which participants were introduced to testing procedures and equipment. During the familiarization session, participants' VO_{2max} was determined through a graded exercise test to exhaustion on a motorized treadmill (4Front, Woodway, WI) as described previously (Islam et al. 2017). Oxygen consumption and carbon dioxide production (VO_2 and VCO_2, respectively) were measured continuously using an online breath-by-breath gas collection system calibrated using known gas concentrations and a 3-L syringe for flow. To ensure comfort and accurate gas measurement recordings, participants wore a fitted silicon facemask. Participant's heart rate (HR) was recorded beat-to-beat using an integrated HR monitor.

Determination of VO_{2max} consisted of a 5-min treadmill warm-up followed by participants running at a self-selected pace (5-7 mph) maintained throughout the test. Incremental increases in workload (2% grade) were applied every 2 min until volitional fatigue was achieved. VO_{2max} was defined by as the greatest 30-second average at which VO_2 values plateaued (increase < 1.35 $mL \cdot kg^{-1} \cdot min^{-1}$) despite increases in workload, or two of the following criteria: 1) respiratory exchange ratio (RER) value >1.10; 2) maximal HR (within 10 bpm of age-predicted maximum [220-age]) and/or; 3) voluntary exhaustion. All participants met the RER

and HR criteria used for the determination of VO_{2max}, while six of the eight participants also achieved a plateau in VO_2 values. Following a short 5-min treadmill cool-down and 20-min rest period, the running speed/grade required to elicit the appropriate workloads for MICT (65% VO_{2max}) and VICT (85% VO_{2max}) were determined. Participants began by jogging at moderate pace (5 mph) with incremental increases in speed (1-2 mph) applied every 3-min until the speed corresponding to the appropriate workload was achieved and recorded.

Experimental Sessions

Participants arrived at the laboratory at 0800 h following an overnight fast and the experimental session was completed over a 3 h period (Figure 1). Once arrived, participants were given a standardized test meal consisting of a Chocolate Chip Clif Bar (7 kcal/kg body mass) and water, which was provided ad libitum throughout the session. Participants were given 15-min to consume the test meal, followed by a 30-min sitting rest. Following the rest, exercise commenced at 0850 h consisting of a 5 min standardized warm-up (3.5 mph) on a motorized treadmill, followed by a 30-min running based exercise protocol (MICT or VICT), and a 5-min standardized cool-down. To match exercise protocol duration between exercise groups, SIT sessions were allocated an additional 12-min of rest prior to warm-up, followed by the required 18-min for the SIT exercise protocol (four, 30-sec "all out" running efforts interspersed with 4-min recovery). Participants in the SIT group ran on a specialized self-propelled treadmill (HiTrainer Pro, QC, Canada). Gas exchange and HR were measured continuously throughout the exercise component of the experimental session. Upon completing the running-based exercise protocol, participants remained in the laboratory until 1100 h for an additional 90-min rest period. The experimental protocol within the CTRL sessions was similar, with time allocated

towards running-based protocol (0850-0930 h) replaced with quiet rest. Venous blood samples were collected from participants at 0845 h (pre-exercise), 0930 h (immediately post-exercise), 1000 h (30-min post-exercise), and 1100 h (90-min post-exercise). Specifically, blood samples collected immediately post-exercise were drawn from participants within 30 seconds of cessation of the standardized cool-down.

Blood Processing and Biochemical Analysis

All blood samples were collected by venipuncture from the antecubital vein while lying in a supine position. Two samples of blood (3 mL of whole blood each) were collected into separate pre-chilled Vacutainer tubes coated with K2 EDTA (5.4 mg) at each time point. Tubes were inverted ten times, centrifuged at 3000 g for 10-min and the plasma supernatant was then dispended into Eppendorf tubes. Plasma samples were stored at -80˚C until subsequent plasma-parameter analysis. To measure blood lactate, a blood droplet was collected from one of the Vacutainer tubes and placed on a lactate strip using a hand-held analyzer (Accutrend lactate; Roche Diagnostics, Mannheim, Germany). Commercially available enzyme-linked immunosorbent assay kits were used to determine plasma concentrations of BDNF (Cat. # CYT306, EMD Millipore BDNF ELISA) and Irisin (Cat. # EK-067-29, Phoenix Pharmaceuticals Inc.). The BDNF ELISA kit was specific to human BDNF with no significant cross-reactivity with other members of the neurotrophin family (NGF, NT 4/5 or NT3). All samples were run in duplicate.

Statistical Analysis

All participant data was analyzed using GraphPad Prism Version 6 (La Jolla, CA). To account for individual variability within participants in absolute protein concentrations, protein concentration changes at each time point were expressed relative to the group's average protein concentration at baseline. Area under the curve (AUC) for plasma BDNF and Irisin fluctuations across the experiment session was calculated using the change in each variable relative to baseline. One-way repeated measures analysis of variance (ANOVA) was used to compare plasma BDNF and Irisin AUC values across sessions. Two-way repeated-measures ANOVA (session x time) was used to compare differences in plasma BDNF and Irisin between experimental sessions at each time point. Post hoc analysis using Tukey's multiple comparisons test was used when necessary. To estimate effect sizes for between-protocol differences in changes in BDNF, Cohen's D calculation was used. Significance was set at $p < 0.05$. All data are presented as means ± standard error.

Results

Participant Characteristics

As previously published (Islam et al. 2017), participants were male (n=8), 23.1 ± 3.0 years of age, and had a mean VO_{2max} of 51.2 ± 4.4 $mL \cdot kg^{-1} \cdot min^{-1}$ (4.1 ± 0.27 L/min). Additionally, participants had a mean height of 178.2 ± 2.7 cm; weight of 78.7 ± 8.1 kg; and BMI of 24.8 ± 2.3 kg/m^2 (Table 1).

Brain-Derived Neurotrophic Factor (BDNF)

Plasma BDNF was determined across four exercise groups (CTRL, MICT, VICT, SIT), and four time points (PRE, POST, 30-POST, and 90-POST). At baseline, there were no differences ($P > 0.19$) in absolute BDNF plasma concentrations between groups (CTRL: 4934 ± 1048 pg/ml; MICT: 4775 ± 1095 pg/ml; VICT: 5470 ± 1535 pg/ml; SIT: 3168 ± 420 pg/mL). Immediately post-exercise, the SIT group had significant increases in BDNF compared to CTRL *(*p = 0.0002; d = 1.24*),* MICT *(*p = 0.0134; d = 1.12*),* and VICT *(*p = 0.0120; d = 1.23*)* (Figure 2A). Within the SIT group, BDNF levels increased immediately post-exercise compared to pre- *(*p < 0.0001). BDNF returned to levels similar to baseline at 30-min *(*p = 0.1481*)* and 90-min post-exercise *(*p = 0.7222*).* Furthermore, a significant reduction in BDNF was observed within the MICT group at 30-min post- compared to immediately post-exercise *(*p = 0.0189*;* Figure 2A). No other changes were observed.

When examining the area under the curve (AUC), plasma BDNF levels were increased across the experimental session in the SIT group compared to CTRL *(*p = 0.0020*),* MICT *(*p = 0.0477*),* and VICT *(*p = 0.0279*).* No significant differences were revealed between continuous exercise groups (MICT and VICT) and CTRL *(*p = 0.7877; Figure 2B). Changes in plasma BDNF concentrations from pre- to immediately post-exercise were also analyzed. Both SIT and VICT increased immediately following exercise compared to pre- *(*p = 0.0001 and p = 0.0274, respectively; Figure 2C) and CTRL levels (p = 0.0002 and p = 0.0053, respectively). MICT post-exercise plasma BDNF was no different to pre-exercise levels and CTRL *(*p = 0.0567 and p = 0.0713, respectively). Lastly, we examined the changes in plasma BDNF concentration immediately following exercise session relative to baseline. Plasma BDNF significantly

increased post exercise in the SIT group compared to CTRL *(*p= 0.0277*),* with no other changes observed in continuous exercise groups (MICT and VICT) compared to CTRL *(*p = 0.2030 and p = 0.2255, respectively*;* Figure 2D).

Irisin

In addition to BDNF, plasma irisin levels were determined across exercise groups and time points. At baseline, there was no difference between any of the groups (p>0.9999; Figure 3A). Further, no significant differences in CTRL, MICT, and SIT groups, at any time points, or when comparing groups within the same time point, were observed (p>0.05). Irisin in the VICT group however, did increase 30-min post-exercise compared to immediately post- *(*p = 0.0357). There were also no significant changes in plasma irisin AUC levels (p= 0.1732; Figure 3B), irisin from pre- to immediately post- (p=0.4026; Figure 3C), and irisin immediately following exercise compared to baseline levels (p=0.1167; Figure 3D).

Correlational Results

As recent research demonstrates elevated blood lactate levels induce brain BDNF expression in exercise *in vivo*, correlational analysis was completed between blood lactate and plasma BDNF. Correlational analysis between the peak plasma BDNF immediately post-exercise (~5.5 min following the intervention, incuding the 5-min cool down) and lactate as well as Irisin were completed. Past literature demonstrates a peak in blood lactate 6 minutes following exercise cessation {Gass, 1981 #2572}, therefore it is likely that peak lactate levels were obtained following SIT, however this may not be the case for MICT or VICT. For this original analysis, we used previously reported lactate results from Islam et al., 2017. A significant weak/moderate

positive correlation was discovered between the changes in lactate and BDNF ($r=0.3906$, $p=0.03$; Figure 4A).

Discussion

The present study provides novel results demonstrating SIT to be more effective in elevating plasma BDNF compared to moderate- and vigorous-intensity continuous exercise modalities. We further demonstrate that the elevated post-exercise plasma BDNF profile was short-lived, recovering within 30-min of exercise cessation. Interestingly, while no changes in plasma irisin were observed in response to exercise, a significant positive correlation between blood lactate and BDNF was found, further supporting the relationship between exercise intensity and BDNF. These results provide valuable information in the design of running-based exercise prescription for brain health through provoking a neuroprotective BDNF response.

In the present study, we demonstrate elevated plasma BDNF following 30-min of continuous running at vigorous-intensity (85% VO_{2max}), however only an upward trend following the same duration of moderate-intensity (65% VO_{2max}) running. Moreover, SIT consisting of four 30-sec bouts of all-out sprinting on a manual treadmill elicited a significantly higher post-exercise plasma BDNF response compared to both 30-min of moderate- and vigorous-intensity continuous exercise. These findings are in line with the intensity-dependent relationship observed in exercise-induced increase in serum BDNF. Following aerobic exercise where high-intensity endurance exercise at a VO_2 10% over the ventilatory threshold (V_{Th}) or where exercise at ~75% VO_{2max} increased post-exercise serum BDNF compared to low-intensity exercise which was 20% below the ventilatory threshold or ~45% VO_{2max} of the same duration

(20). Moreover, a study utilizing a 20 min HIIT protocol (1-min cycling at 90% work rate max (W_{max}) interspersed with 1-min active rest periods of active rest) demonstrated a slightly greater post-exercise serum BDNF response compared to 20-min of high-intensity continuous cycling at 70% W_{max} (21). In the present study SIT, designed to reach intensities equal to or greater than $VO_{2max/peak}$, elicited a robust increase in plasma BDNF compared to vigorous-intensity continuous running. These results demonstrate that exercise protocols eliciting maximal effort/intensity result in the largest BDNF response.

It is important to note the post-exercise plasma BDNF recovery profile in investigating the optimal exercise modality to facilitate a BDNF response. Our results demonstrate a rapid recovery of post-exercise elevated plasma BDNF, which returned talmost to baseline levels by 30-min following exercise cessation. As BDNF is readily able to cross the blood-brain barrier in a bi-directional manner and peripheral levels in the blood reflect that of the brain, exercise modalities that elicit a longer duration of elevated BDNF in circulation would have prolonged effects in the brain (6, 7). Interestingly, time required for BDNF recovery following acute exercise has been shown to be dependent on the blood component analyzed. Specifically, serum BDNF was shown to recovery more quickly as compared to plasma BDNF (30 vs 60-min) following the completion of an incremental graded exercise test (23). The present study is the first to examine plasma BDNF recovery following SIT. Given the short plasmatic BDNF recovery profile, our results suggest that SIT does not offer any beneficial effect in maintaining post-exercise augmented BDNF, nor might post-exercise plasma BDNF have a prolonged recovery and more closely align with that of serum.

Irisin, a muscle-derived myokine has recently been shown to be released by skeletal muscle in exercise and up-regulate central BDNF in an endocrine manner (24, 25). Therefore, a second aim of this study was to examine the effects of exercise intensity and recovery on plasma irisin. Given the myokines' role in increasing energy expenditure and thus a potential target for treatment in obesity, a number of studies have investigated and found increased circulating irisin in response to acute exercise in a wide range of modalities (26), although this myokine is highly contentious with other papers being unable to detect any effect of acute exercise on circulating levels. Our results show no change in plasma irisin in response to running-based exercise and no correlation with BDNF. In contrast, studies have demonstrated both 45-min of MICT (70% VO_{2max}) and 16 min of HIIT (4 x 4 min at 95% HR_{max} separated by 5 x 4 min active recovery) elicit an increase in plasma irisin in healthy adults (27, 28). As this is the first study to investigate both irisin and BDNF levels following acute exercise in healthy adults, and both have been shown to increase in response to acute exercise, further studies examining a correlation between irisin and BDNF following acute exercise are required. However, given the lack of response in circulating irisin in the present study, it is unlikely that elevated plasma BDNF and exercise-induced BDNF content as in the present study can be attributed to peripherally-derived irisin.

In support of our findings that the higher intensity exercise, SIT, elicited the highest BDNF response, our results further show a significant correlation of moderate strength between changes in plasma BDNF post-exercise and blood lactate. In addition to the exercise intensity related relationship between BDNF and lactate, recent work has demonstrated that acute exercise *in vivo* generated a lactate-induced hippocampal *Bdnf* expression (30). Specifically, augmented lactate levels in the brain during exercise elevate intraneuronal NAD^+ levels, which in turn

activate SIRT1 and induce the PGC1α pathway promoting FNDC5/irisin, which has been shown to induce *Bdnf* expression (30, 31). Indeed, the BBB is permeable to lactate and exercise further up regulates expression of lactate transporter MCT1 at the BBB (32). Moreover, treatment of exercised mice with an MCT1 inhibitor rendering the BBB impermeable to lactate abolishes exercise-induced *Bdnf* expression (30). Therefore, we propose that lactate induced by high intensity exercise, such as SIT, may be a driving factor in stimulating brain *Bdnf* expression which over time may increase neuronal BDNF content for release with subsequent exercise bouts. One study has previously demonstrated a correlation between serum BDNF and lactate, however this is the first study to show a significant positive correlation between change in lactate and BDNF in the plasma (20).

Irisin's role as a peripheral messenger in organ cross talk has been criticised due to ambiguity regarding the appropriate measure of the biologically functional FNDC5 cleavage product (33). In fact, studies reporting irisin levels in circulation have reported a large range from 24 $pg \cdot mL^{-1}$ – $2e^{+6}$ $pg \cdot mL^{-1}$ and a normal range of irisin in circulation has yet to be established (34). Although three irisin ELISA kits have been validated as accurate and reliable in measuring concentration changes, reported irisin concentrations are still largely dependent on the commercially available kit used (34). Of the three, the kit by Phoenix Pharmaceuticals used in the present study is considered the current gold standard, with levels consistently falling in the linear range of the curve. Our reported values of plasma irisin ranging from 11.44 – 40.95 ng/mL align with recent studies utilizing the same ELISA kit and showing no exercise-induced irisin change in the plasma (35, 36). Given irisin levels are equated between plasma and serum, it is unlikely our results were affected by portion of blood analyzed (37).

In interpreting the results of the correlational analysis between blood lactate and plasma BDNF following exercise, it is important to note that measurements of the candidate peripheral modulators immediately post-exercise (5.5 minutes following the particular intervention) were used. Previous work has demonstrated that blood lactate concentrations increase approximately 6 minutes post-high intensity exercise and demonstrate no difference between the 4^{th}, 5^{th}, and 6^{th} minute following exercise cessation {Gass, 1981 #2572}, therefore we believe that the timing of our post-exercise blood lactate measurement (~5.5 min after completion of the last sprint) was a valid approximation of blood lactate responses after SIT. However, we acknowledge that this timing may not have been optimal for the measurement of blood lactate after other protocols (e.g. MICT, VICT), therefore the correlational analyses presented for BDNF and lactate must be interpreted with the possibility that the peak blood lactate levels may have been missed.

Studies investigating basal BDNF levels in circulation following a long-term exercise-training program demonstrate increased resting levels. Using HIIT over a 3-month period demonstrated increased resting BDNF in active young healthy adults (38). Rodent studies have indicated the exercise-induced BDNF mediated brain benefits to be transient during acute exercise as increased hippocampal and cortical BDNF content returns to baseline 4 hours following exercise cessation (12). With the scope of identifying the most robust form of acute exercise to integrate into long-term exercise training and optimize BDNF levels in circulation, our results show SIT to be of most use. This is important considering HIIT and SIT have recently become popular exercise modalities in both recreation and clinical settings and routinely demonstrate benefits to body composition and markers of cardiorespiratory health and performance such as peak oxygen consumption (VO_{2peak}) and anaerobic tolerance (38).

Moreover, higher intensity exercise of shorter durations has shown to be an effective intervention in symptom management and improving outcomes in patients with mental disorders like depression and schizophrenia (39, 40). The overarching purpose of the present study in healthy young male adults was to identify the optimal exercise modality in elevating plasma BDNF levels post-exercise for exercise design in obtaining neuroprotective benefit. As lifestyle can play a crucial factor in the development of AD and normal age-related cognitive decline, the present study provides rationale for the use of SIT in provoking the most robust BDNF response compared to CNTRL modalities of lesser intensity in the prevention of brain illness throughout the aging process.

In conclusion, the present study demonstrates changes in plasma BDNF response following acute running-based exercise to be dependent on exercise intensity. Our results demonstrate sprint-interval training to be a superior exercise modality in increasing BDNF levels in circulation compared to prolonged continuous exercise of lower intensity. Moreover, the present study provides valuable information in targeting exercise modalities that elicit a greater blood lactate response in the design of exercise prescription optimizing for brain health through provoking a neuroprotective BDNF response.

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Conflict of Interest

No conflicts of interest to disclose

The present study do not constitute endorsement by ACSM

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Figure Legends

Figure 1: Timeline of three-hour experimental exercise session.

Figure 2. Changes in plasma BDNF concentration across exercise sessions and blood draw time points. A. Changes in plasma BDNF at time points in each experimental session relative to baseline. [a,b,c] SIT significantly different from POST CTRL, VICT and MICT, respectively, $P < 0.05$. [#]SIT POST significantly different from SIT PRE, 30-POST, and 90-POST ($P < 0.01$). B. Plasma BDNF area under the curve (AUC) across all time points in each experimental session relative to baseline. C. Changes in absolute plasma BDNF concentration between pre-exercise to immediately post-exercise. D. Change in plasma BDNF concentration immediately following exercise session relative to baseline. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$. All data are presented as means ± standard error.

Figure 3. Changes in plasma irisin concentration across each exercise group and blood draw time points. **A.** Changes in plasma irisin across time points in each experimental session relative to baseline ($n = 8$). [a]30-POST VICT is significantly greater than POST. **B.** Plasma irisin area under the curve (AUC) across all time points in each experimental session relative to baseline, no changes observed. **C.** Absolute plasma irisin concentrations pre-exercise and post-exercise in each experimental session. No changes were observed. **D.** Change in plasma irisin concentration immediately following exercise session relative to baseline. No changes were observed. All data are presented as means ± standard error.

Figure 4. Correlational results between change in plasma BDNF (pg/mL) concentrations and **A.** change in Lactate (mmol/L) **B.** change in plasma irisin (ng/mL). Significance set to $p<0.05$. All data are presented as means ± standard error.

Figure 1

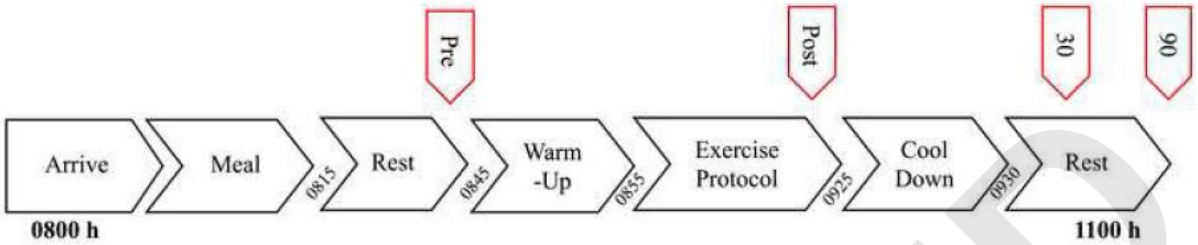

Figure 2

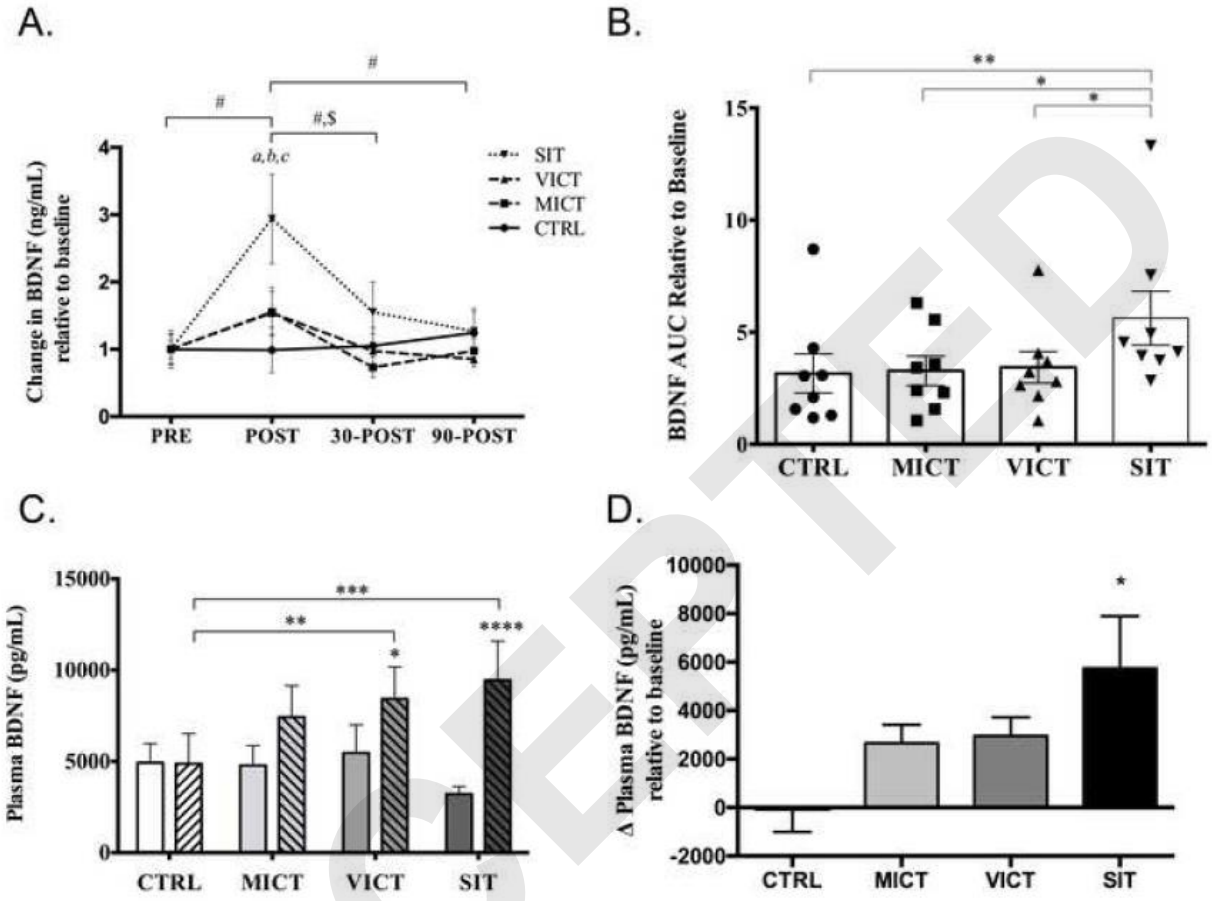

Figure 3

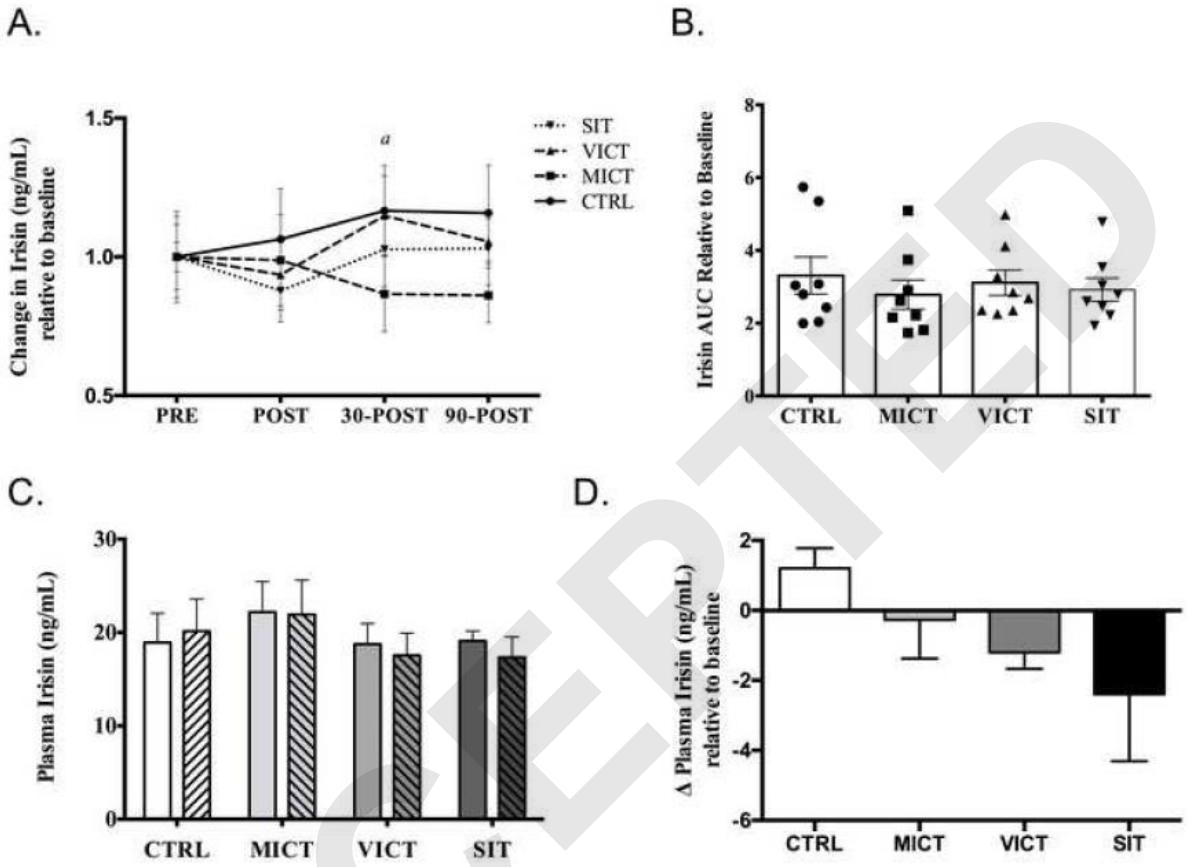

Figure 4

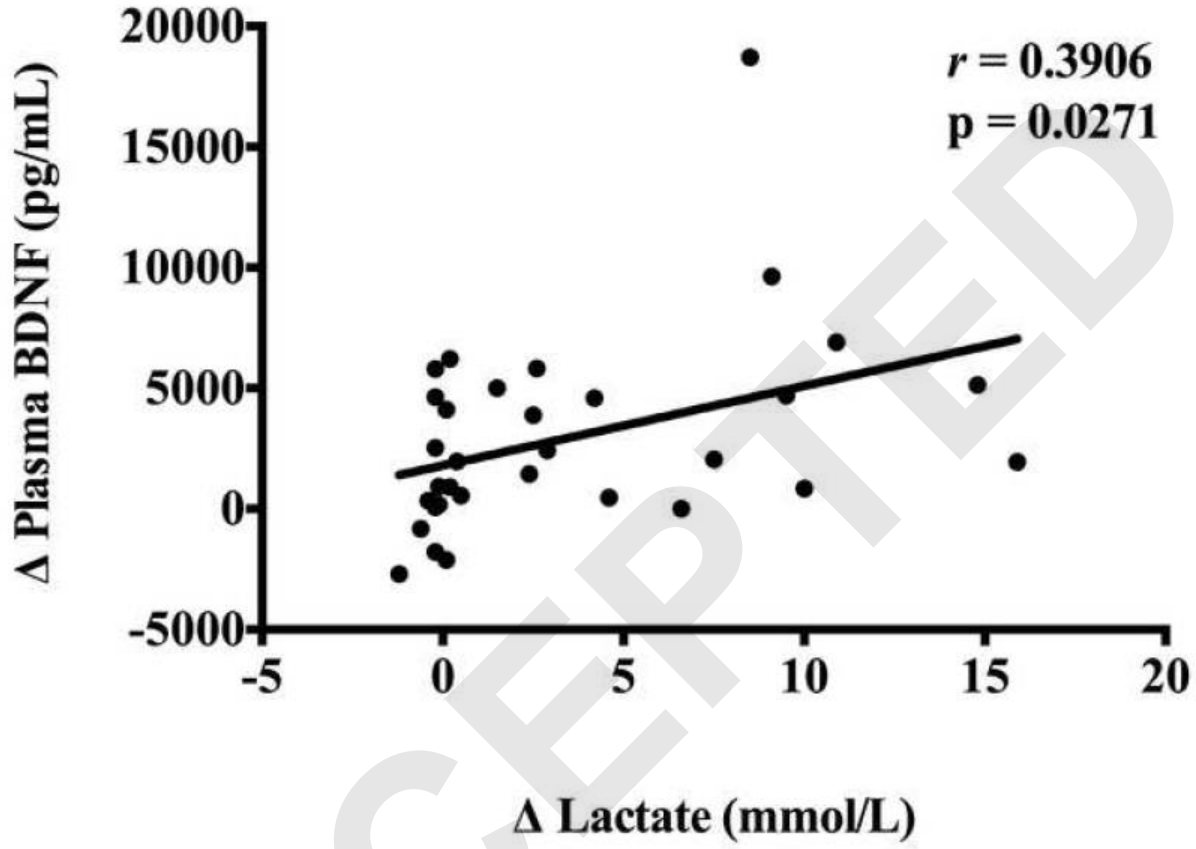

Table 1.

Participant Characteristics	
Age	23.1 ± 3.0 years
Mean VO_{2max}	51.2 ± 4.4 $mL \cdot kg^{-1} \cdot min^{-1}$ (4.1 ± 0.3 $L \cdot min^{-1}$)
Height	178.2 ± 2.7 cm
Weight	78.7 ± 8.1 kg
Body mass index (BMI)	24.8 ± 2.3 kg/m^2