Physiology & Behavior 160 (2016) 26–34

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Repeated high-intensity interval exercise shortens the positive effect on executive function during post-exercise recovery in healthy young males

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HIGHLIGHTS

- The effect of different lactate accumulation on executive function (EF) was examined.
- Lactate accumulation decreased with repeated high-intensity interval exercise (HIIE).
- Repeated HIIE was accompanied by a shorter positive effect on EF.
- A potential link between lactate accumulation and EF should be further elucidated.

ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form 25 March 2016
Accepted 25 March 2016
Available online xxxx

Keywords:
Brain
Cognitive function
Glycogen depletion
Neuronal activation
Psychological arousal

ABSTRACT

A single bout of aerobic exercise improves executive function (EF), but only for a short period. Compared with a single bout of aerobic exercise, we recently found that high-intensity interval exercise (HIIE) could maintain a longer improvement in EF. However, the mechanism underlying the effect of different exercise modes on the modifications of EF remains unclear. The purpose of the current investigation was to test our hypothesis that the amount of exercise-induced lactate production and its accumulation affects human brain function during and after exercise, thereby affecting post-exercise EF. Ten healthy male subjects performed cycle ergometer exercise. The HIIE protocol consisted of four 4-min bouts at 90% peak VO_2 with a 3-min active recovery period at 60% peak VO_2. The amount of lactate produced during exercise was manipulated by repeating the HIIE twice with a resting period of 60 min between the 1st HIIE and 2nd HIIE. To evaluate EF, a color-word Stroop task was performed, and reverse-Stroop interference scores were obtained. EF immediately after the 1st HIIE was significantly improved compared to that before exercise, and the improved EF was sustained during 40 min of the post-exercise recovery. However, for the 2nd HIIE, the improved EF was sustained for only 10 min of the post-exercise recovery period, despite the performance of the same exercise. In addition, during and following HIIE, the glucose and lactate accumulation induced by the 2nd HIIE was significantly lower than that induced by the 1st HIIE. Furthermore, there was an inverse relationship between lactate and EF by plotting the changes in lactate levels against changes in EF from pre-exercise during the late phase of post-exercise recovery. These findings suggested the possibility that repeated bouts of HIIE, which decreases lactate accumulation, may dampen the positive effect of exercise on EF during the post-exercise recovery.

1. Introduction

During exercise, lactate, a glycolytic product, is formed in contracting skeletal muscle and utilized continuously in diverse cells under fully aerobic conditions. Lactate exchange occurs not only between white glycolytic and red oxidative fibers within a working muscle bed but also between working skeletal muscle and the heart, liver, kidneys, and brain as oxidative and gluconeogenic substrates [1]. During prolonged exercise, muscle metabolism (e.g., lactate kinetics) and brain cognitive function change [1–5]. In light of the fact that systemic lactate is an energy source for the brain [6], there might be an unexplored association between muscle metabolism and the function of the brain. Given its reliance on lactate as a fuel, particularly as lactate concentrations rise, variations in lactate concentration in the blood likely impact cognitive function in the peri-exercise period.

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http://dx.doi.org/10.1016/j.physbeh.2016.03.029

During prolonged dynamic exercise, cerebral blood flow gradually decreases towards resting values in association with hyperventilation [7,8]. Similar to the decrease in cerebral blood flow (CBF), the exercise-induced facilitation of cognitive function disappears during such prolonged exercise [9]. We previously hypothesized that cognitive function might be impaired during prolonged exercise and could be restored by an increase in CBF. However, this hypothesis was not validated by our finding that cognitive function was not impaired during prolonged exercise, despite a conflict between an increase in cerebral metabolism and a decrease in CBF [10]. In addition, hypercapnia-induced increases in CBF did not improve cognitive function [10]. Soya and colleagues reported that improved EF after acute aerobic exercise was associated with increased left-dorsolateral prefrontal cortex (L-DLPFC) activity in the brain [11,12]. Moreover, their recent study showed that improved EF after exercise correlated with enhanced psychological arousal levels [11]. These findings suggest that improved cognitive function during exercise may be due to the augmented cerebral neuronal activation and metabolism associated with exercise, rather than cerebral perfusion [10].

Previous studies have demonstrated that during heavy exercise, compensatory increases in the uptake (the difference between arterial and venous concentration (a–v difference)) of lactate, glucose and oxygen support elevated brain neuronal activity and metabolism [13]. When arterial lactate is elevated during exhaustive physical exercise, the brain takes up lactate in amounts that may supersede the uptake of glucose [14]. Furthermore, the arterial lactate concentration increased several-fold during exercise, and the reduced oxygen-to-carbohydrate ratio (cerebral metabolic ratio: CMR) during recovery was associated with relatively high lactate uptake by the brain [15,16]. In addition, increased lactate availability through intravenous lactate infusion increased lactate utilization by the brain [6]. These results suggest that lactate fuels the human brain during and after exercise to satisfy the augmented cerebral neuronal activation and metabolic demand, thereby affecting cognitive function. Indeed, lactate has emerged as a central player in the maintenance of neuronal function and long-term memory [17]. For example, albeit in animals, the administration of a glycogen phosphorylase inhibitor in rat hippocampus resulted in abolished extracellular lactate accumulation and long-term memory, whereas exogenous L-lactate administration rescued memory loss [18]. In addition, intracerebroventricular or intravenous injection of lactate has been shown to exert a neuroprotective effect during experimentally induced hypoglycemia or cerebral ischemia [19–21]. Furthermore, the intravenous infusion of 100 mM L-lactate improved cognitive recovery by preserving cerebral ATP generation following traumatic brain injury (TBI) in rats [22]. Recently, George Brooks' group has examined the advantages of using inorganic and organic lactate salts, esters and other compounds in TBI patients [23–25]. The authors compared dextrose + insulin treatment to exogenous lactate infusion in TBI patients with intact hepatic and renal functions, demonstrating that the latter results in normal glycemia and provides nutritive support to the injured brain [23–26]. However, no previous studies have investigated the effect of exercise-induced lactate production on cognitive function.

High-intensity interval exercise (HIIE) training is emerging as an effective alternative to current health-related exercise guidelines [27]. It has been reported that long-term HIIE was more effective at increasing exercise capacity and metabolic and cardiovascular health compared to long-term moderate-intensity continuous exercise in healthy individuals [3,4,28]. Importantly, the effectiveness of HIIE has been demonstrated in older individuals and patients with chronic diseases such as diabetes [29,30], chronic obstructive pulmonary disease [31], and heart failure [32,33]. In addition, Rognmo et al. [34] reported that the adaptation of HIIE for cardiac rehabilitation had a low risk of acute adverse cardiovascular events in a large population. Thus, in regard to ethical issues, it is well known that HIIE can be safely applied to various populations. However, few studies to date have examined the impact of HIIE on the cerebrovasculature and corresponding implications for cognitive function [27]. Recently, we found that HIIE-induced improvements in cognitive function (especially EF) after exercise were sustained for significantly longer periods than after moderate-intensity continuous exercise [35]. However, it is unclear whether the higher production of lactate induced by HIIE compared to that induced by moderate-intensity continuous exercise could sustain EF for a longer time period.

Lactate is produced continuously even under fully aerobic conditions, especially during exercise, when rates of glycogenolysis and glycolysis are elevated [36]; decreased muscle glycogen during and/or following prolonged exercise attenuates lactate production [3,4]. With this knowledge, we hypothesized that repeated high intensity exercise (e.g., first bout of HIIE) would reduce muscle glycogen and hence result in low lactate production and low lactate availability during and after second bout of HIIE and that in addition, this low lactate production/accumulation would affect EF. To test our hypothesis, we examined lactate production and EF in response to the first (1st HIIE) and second (2nd HIIE) rounds of HIIE. In this protocol, it was expected that lactate production and hence EF would be lower following the 2nd HIIE than following the 1st HIIE, although exercise workload (i.e., exercise volume: intensity × duration) between 1st and 2nd bout of HIIE is identical.

2. Methods

2.1. Subjects

Ten healthy, male subjects (mean ± SEM, age: 22.9 ± 0.6 yr, height: 171.4 ± 1.6 cm, weight: 67.5 ± 2.3 kg, peak oxygen uptake (peak VO_2): 46.8 ± 2.1 ml/min/kg) participated in this study. The subjects were informed of the experimental procedures and potential risks and provided written consent to participate in the study. All subjects were right-hand dominant and free of any known neurological, cardiovascular, and pulmonary disorders as well as color-blindness and abnormal vision. All procedures were approved by the Ethics Committee of Ritsumeikan University (BKC-IRB-2015-005). Subjects were instructed to avoid strenuous physical activity in the 24 h prior to each experimental session. Each subject also abstained from food (overnight fasting), caffeine, and alcohol for 12 h prior to each experiment.

2.2. Experimental procedure

Before the day of the experiment, subjects were familiarized with the EF test using the color-word Stroop task (CWST) [37] on their first visit to our laboratory. The CWST was practiced until the subject achieved consistent scores. Subsequently, peak VO_2 was measured to calculate the exercise intensity required for the exercise protocols.

On the day of the experiment, subjects ate a breakfast of approximately 580 kcal 2 h before the 1st exercise (8:00 a.m.). Thereafter, the subject rested until approximately 20 min before the 1st exercise and practiced the CWST for at least 10 min before pre-exercise data were recorded to prevent the learning effect. Next, the subjects rested for 5 min before undergoing measurements of cardiovascular and psychological parameters and the collection of fingertip blood samples for the pre-exercise data, which was concluded within 5 min. Ten min after the practice CWST was conducted, the subjects performed the pre-exercise CWST. Subsequently, the subjects performed the HIIE protocol (1st HIIE). The post-exercise recovery period was set to 60 min, during which the CWST was measured six times at 10-min intervals, including immediately after exercise (i.e., 0 min, 10 min, 20 min, 30 min, 40 min, and 50 min after exercise, Post 0, 10, 20, 30, 40, and 50, respectively). The subjects drank 50 ml of water while resting after the CWST. Shortly thereafter, the subjects performed the same HIIE (2nd HIIE) and post-exercise recovery protocol again.

2.3. Experimental conditions

The experimental protocol used in this study is presented in Fig. 1.

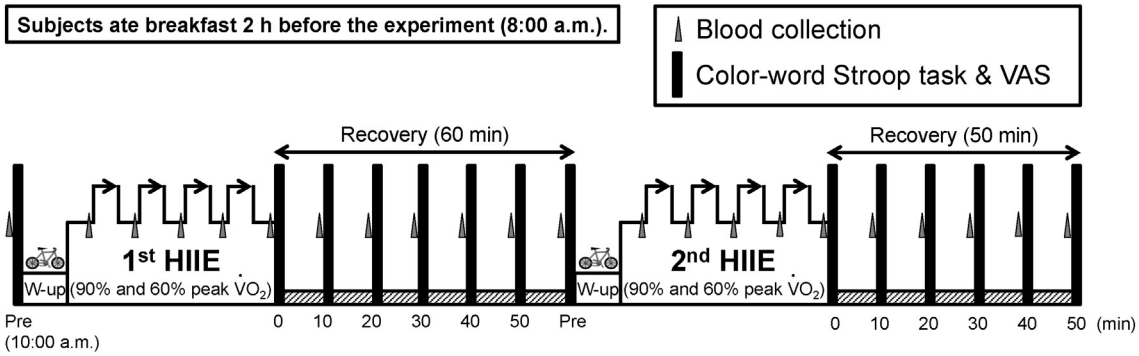

Fig. 1. Overview of the experimental protocol. Subject performed repeated high-intensity interval exercise (HIIE) twice, with a resting period of 60 min between the 1st HIIE and 2nd HIIE sessions. Blood was collected at the time points marked by triangles. The evaluation of executive function (EF) using a CWST was performed pre-exercise (Pre) and during the 60 min post-exercise recovery period (five times with 10-min intervals). Psychological parameters were measured at the same time points. These time points are denoted by the black bar.

All subjects completed cycle ergometer exercise in both HIIE protocols (1st and 2nd). Both protocols were performed following a warm-up at 100 W for 3 min. After the warm-up period, the HIIE protocol was initially carried out at 60% peak VO_2 for 5 min, followed by four 4 min bouts at 90% peak VO_2 with 3 min of active recovery at 60% peak VO_2 for a total exercise period of 33 min. The mean heart rate (HR) at the end of the four 4-min bouts at 90% peak VO_2 in the 1st and 2nd HIIE were 175.8 ± 2.8 and 181.3 ± 2.7, respectively, which was approximately 90% of the age-predicted maximum in healthy adults, calculated as [208 − 0.7 × age] [38]. The subjects were instructed to maintain a cadence of 60 rpm, which was carefully checked by an examiner. The exercise volumes between the 1st and 2nd HIIE protocols were identical (354 ± 10 kJ vs. 354 ± 10 kJ; n.s.).

2.4. Ramp-incremental exercise test

During the first visit, all subjects performed a maximal incremental exercise test to determine peak VO_2 on a cycle ergometer. Initially, subjects performed baseline cycling for 3 min at 30 W, after which the workload was incrementally increased at a rate of 30 W/min until the subjects could not maintain a cadence of 60 rpm. During the incremental exercise test, breath-by-breath pulmonary gas-exchange data were collected and averaged every 10 s (AE-310S; Minato Medical Science, Osaka, Japan). HR was measured continuously via telemetry (RS 400; Polar Electro Japan, Tokyo, Japan). The peak VO_2 was determined as the highest 30-s mean value attained prior to exhaustion. Exhaustion was assessed to be the maximum when three of the following criteria were obtained: 1) a plateau in the VO_2 despite increasing workload, 2) a respiratory exchange ratio above 1.10, 3) an HR above 90% of the age-predicted maximum, and 4) task failure of the pedaling rate of at least 55 rpm over 5 s despite maximal effort.

2.5. Measurements

Measurement of the following parameters was carried out before the pre-exercise CWST, during exercise at the end of each active recovery period, immediately before completion of the exercise, and during the 60-min post-exercise recovery period (five 10-min intervals).

2.6. Cardiovascular parameters

During the experimental sessions, HR was measured continuously via telemetry. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a mercury manometer (FC-110ST; Focal, Chiba, Japan). MAP was calculated as [(SBP − DBP) / 3 + DBP].

2.7. Psychological parameters

The felt arousal scale (FAS) and rating of perceived exertion (RPE) were recorded to evaluate psychological responses.

FAS—The FAS was measured to assess arousal level. This is a six-item scale ranging from 1 (low arousal) to 6 (high arousal), and subjects were asked to report how they felt before CWST during pre- and post-exercise. For example, a high arousal level represents "excitement," and a low arousal level represents "relaxation" [39].

RPE—The RPE was measured to assess the effort expended during exercise. This scale ranges from 6 (no exertion) to 20 (maximal exertion) [40].

VAS—The visual analog scale (VAS) for the CWST consisted of questions of three psychological types that assessed mental fatigue, the ability to concentrate, and motivation about CWST. Each VAS was labeled from 0 mm (i.e., not at all) to 100 mm (i.e., extremely). The subjects drew lines to indicate their responses.

2.8. Blood glucose and lactate levels

Fingertip blood samples were collected in capillary tubes to determine the glucose levels and lactate concentrations. The blood glucose levels were measured using a glucose analyzer (Medisafe FIT Blood Glucose Meter; Terumo, Tokyo, Japan). The blood lactate concentrations were measured using a lactate analyzer (Lactate Pro 2; Arkray, Kyoto, Japan).

2.9. EF

The evaluation of EF in this study was performed using the CWST [37], which is a well-known paradigm for investigating aspects of cognitive performance that depend on EF, specifically, the selective attention to specific information and the inhibition of prepotent responses during decision-making tasks involving stimuli and responses [41]. The CWST was adopted in an event-related design [10], and this CWST was programmed by modifying an Excel Visual Basic for Applications from our previous study. We measured both reaction time (RT) and response accuracy using the CWST. The following instruction was given to the subjects: "You must perform as accurately and quickly as possible." The stimulus words were four color names ("RED", "YELLOW", "GREEN" and "BLUE"), and they were presented on a 98-in. display. All words were written in Japanese for our Japanese subjects. We prepared a color-labeled ten-key keyboard: number 1 key was labeled red, number 2 key was labeled yellow, number 3 key was labeled green, and number 4 key was labeled blue. The subjects were required to press the color-labeled key that corresponded to the text meaning of the stimulus word. The subjects performed three types of CWST. The congruent task, which is a facilitated (dummy) task, displayed the color names

presented in the same-colored text. The neutral task, which is a control task, displayed the color names presented in black text. The incongruent task, which is an interference task, displayed the color names presented in a differently colored text. The words for each type of task were presented in a random order. One trial of each task consisted of 24 stimulus words and was repeated for three trials. To evaluate EF, reverse-Stroop interference scores were calculated as [(RT of incongruent task − RT of neutral task) /RT of neutral task × 100] [42]. In addition, we calculated relative values (pre-exercise = 1).

2.10. Statistical analysis

The data are expressed as the mean ± SEM. Blood sample data were used to calculate the incremental or decremental area under the curve during exercise and following exercise and were compared using a paired *t*-test (1st vs. 2nd HIIE). Other all data were analyzed using a two-way (time × 1st or 2nd HIIE) repeated-measures analysis of variance after normal distributions were confirmed. Specific differences were identified with a Bonferroni *post-hoc* test. The statistical significance level was defined at $P < 0.05$. A linear regression was performed to test the relationship between changes in blood glucose or lactate concentrations and changes in reverse-Stroop interference scores (i.e., EF) at post-exercise recovery (Post 0, 10, 20, 30, 40, and 50). All statistical analyses were conducted using IBM SPSS software (version 19.0; International Business Machines Corp, NY, USA).

3. Results

3.1. Exercise parameters

The exercise parameters are shown in Table 1.

The HR values before and during every active recovery at 60% peak VO_2 for the 2nd HIIE were significantly higher than those of corresponding time points for the 1st HIIE, and the HR values in both HIIEs gradually increased towards just before the end of each HIIE (described as "pre-recovery" in Table 1). MAP values during exercise did not significantly differ between the 1st and 2nd HIIE. The pre-exercise tympanic temperature near the brain for the 2nd HIIE was significantly higher than for the 1st HIIE, while during HIIE there were no significant differences in tympanic temperature between the 1st and 2nd HIIE.

With regard to psychological responses, RPE values for the 2nd HIIE during active recovery at the 1st, 2nd, and 3rd points were significantly higher than those of the 1st HIIE. However, FAS values did not differ significantly between the 1st and 2nd HIIE.

3.2. Blood sample data

The blood glucose and lactate concentrations as well as their increased or decreased areas under the curve (AUCs: response compared with the pre-exercise phase) during and after exercise are shown in Fig. 2. The glucose and lactate accumulated during and after the 2nd HIIE were significantly lower than those during and after the 1st HIIE. The time effects for blood glucose and lactate concentrations are summarized in Supplemental Table 1.

3.3. EF and psychological parameters

The RT and response accuracy during the CWST for the 1st and 2nd HIIE are shown in Table 2.

The RT of the congruent tasks did not differ significantly between the 1st and 2nd HIIE protocols throughout the experimental sessions. For the neutral tasks, the RT after 10 min of post-exercise recovery following the 1st HIIE was significantly shorter than that at the same time point following the 2nd HIIE. For the incongruent tasks, the RT prior to the 2nd HIIE was significantly shorter than that prior to the 1st HIIE. However, the RT after 40 min of post-exercise recovery following the 1st HIIE was significantly shorter than that at the same time point following the 2nd HIIE. Additionally, the RT for the incongruent tasks after 30 and 40 min of post-exercise recovery following the 2nd HIIE was significantly shorter than that immediately after the exercise. Furthermore, the RT for incongruent tasks immediately after both HIIEs was significantly shorter than those prior to exercise, and this shortened RT was sustained during the 50 min post-exercise recovery following the 1st HIIE, whereas it returned to pre-exercise levels for the 2nd HIIE after 30 min of post-exercise recovery following the 2nd HIIE. The response accuracy for all tasks did not differ significantly between the

Table 1
Exercise parameters in healthy male participants.

	Pre-exercise	During exercise (active recovery)				
		1st point	2nd point	3rd point	4th point	Pre-recovery
HR, bpm						
1st HIIE	69.7 ± 2.6	136.5 ± 2.9††	150.9 ± 2.6^{††,aa}	156.8 ± 3.4^{††,aa}	158.9 ± 4.0^{††,aa}	158.8 ± 4.2^{††,a}
2nd HIIE	78.6 ± 2.7**	148.2 ± 2.8**,††	159.8 ± 2.7^{**,††,aa}	162.3 ± 2.2^{*,††,aa}	164.9 ± 3.1^{*,††,aa}	165.8 ± 2.6^{*,††,aa}
MAP, mm Hg						
1st HIIE	95.2 ± 4.2	109.6 ± 4.0†	112.8 ± 3.5†	108.7 ± 3.6†	105.9 ± 3.4	104.5 ± 3.4
2nd HIIE	92.3 ± 2.5	106.6 ± 4.0†	111.8 ± 3.5††	108.3 ± 3.4††	105.9 ± 3.6^{††,bb}	104.2 ± 3.8^{†,b,c}
RPE						
1st HIIE	–	12.3 ± 0.2	14.3 ± 0.4^{a}	15.3 ± 0.4^{aa}	16.2 ± 0.6^{aa,b}	16.1 ± 0.5^{aa,b,c}
2nd HIIE	–	13.6 ± 0.4 *	15.5 ± 0.4^{*,a}	16.3 ± 0.5^{*,aa}	16.8 ± 0.3^{aa}	16.1 ± 0.4^{aa}
FAS						
1st HIIE	2.2 ± 0.2	3.3 ± 0.3	4.3 ± 0.4^{†,a}	4.6 ± 0.4^{†,a}	4.6 ± 0.5^{†,a}	4.5 ± 0.4†
2nd HIIE	2.8 ± 0.2	3.7 ± 0.2	4.4 ± 0.3	4.6 ± 0.5	4.5 ± 0.5	4.6 ± 0.4
Tympanic temperature, °C						
1st HIIE	36.0 ± 0.1	36.3 ± 0.1	36.3 ± 0.1	36.6 ± 0.2	36.8 ± 0.2^{†,a}	36.8 ± 0.2†
2nd HIIE	36.3 ± 0.1*	36.5 ± 0.2	36.5 ± 0.2	36.6 ± 0.2	36.8 ± 0.2^{a,bb}	36.8 ± 0.2^{a,b}

Values are presented as means ± SEM. HIIE; high-intensity interval exercise, HR; heart rate, MAP; mean arterial pressure, RPE; rate of perceived exertion, FAS; felt arousal scale.
HR [Condition $F_{1,9} = 36.61$, $P < 0.01$; Time $F_{5,45} = 364.85$, $P < 0.01$; Condition × Time $F_{5,45} = 1.51$, $P = 0.21$], MAP [Condition $F_{1,9} = 0.60$, $P = 0.46$; Time $F_{5,45} = 17.49$, $P < 0.01$; Condition × Time $F_{5,45} = 0.50$, $P = 0.78$], RPE [Condition $F_{1,9} = 6.13$, $P < 0.05$; Time $F_{4,36} = 50.35$, $P < 0.01$; Condition × Time $F_{4,36} = 1.86$, $P = 0.14$], FAS [Condition $F_{1,9} = 1.42$, $P = 0.26$; Time $F_{5,45} = 12.66$, $P < 0.01$; Condition × Time $F_{5,45} = 1.88$, $P = 0.12$], Tympanic temperature [Condition $F_{1,9} = 2.78$, $P = 0.13$; Time $F_{5,45} = 17.79$, $P < 0.01$; Condition × Time $F_{5,45} = 1.16$, $P = 0.35$].
*, ** $P < 0.05$, 0.01 vs. 1st HIIE, †, †† $P < 0.05$, 0.01 vs. pre-exercise, ^{a}, ^{aa} $P < 0.05$, 0.01 vs. 1st point, ^{b}, ^{bb} $P < 0.05$, 0.01 vs. 2nd point, ^{c} $P < 0.05$ vs. 3rd point.

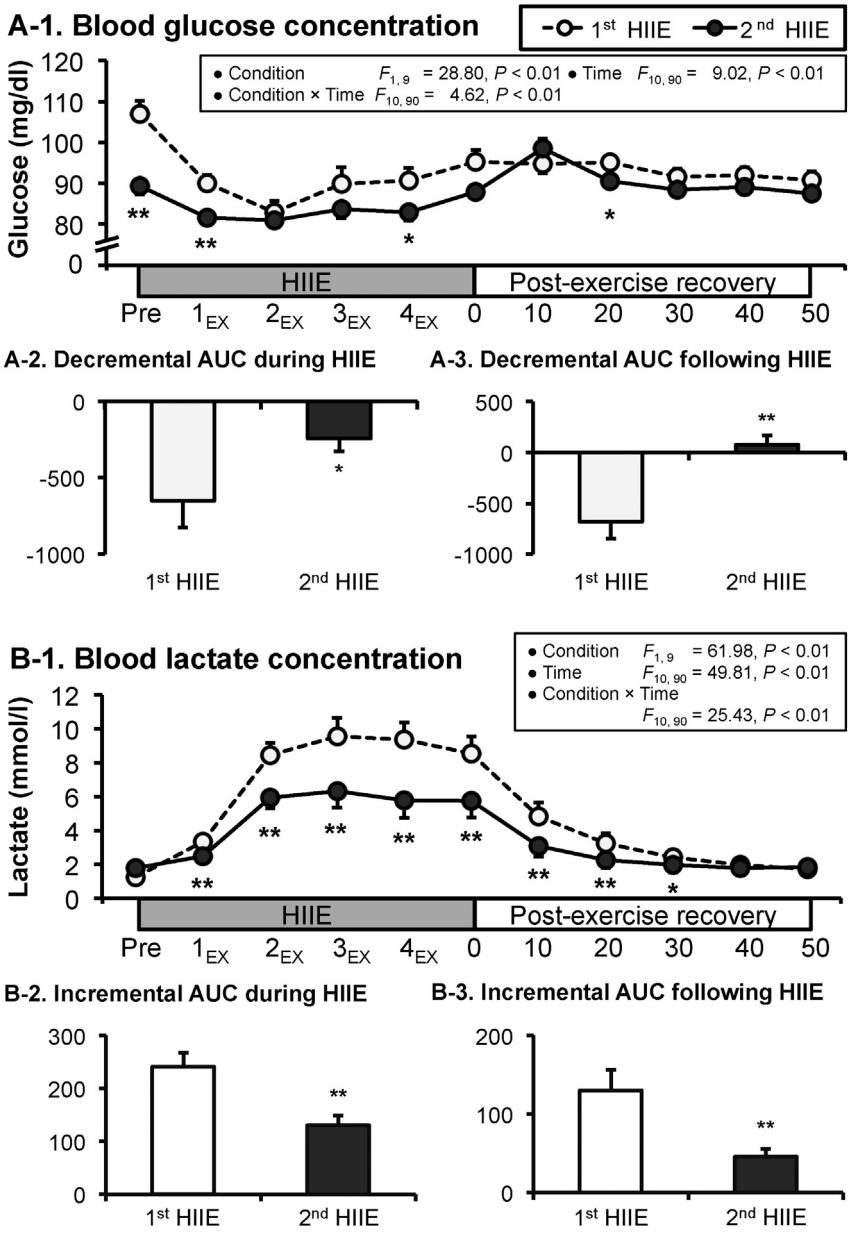

Fig. 2. Changes in blood glucose and lactate concentrations. The panels illustrate the changes in blood glucose (A) and lactate (B) concentrations for the 1st HIIE (open circles) and 2nd HIIE (solid circles). The histogram represents increased or decreased blood glucose (A-2 and A-3) and lactate (B-2 and B-3) areas under the curve (AUCs) during (A-2 and B-2) and following (A-3 and B-3) HIIE. The values are expressed as the mean ± SEM. *, ** $P < 0.05$, 0.01 vs. 1st HIIE.

1st and 2nd HIIE protocols throughout the experimental sessions and did not differ significantly among all time points.

The changes in EF evaluated using the reverse-Stroop interference score for the 1st and 2nd HIIE sessions are shown in Fig. 3.

The reverse-Stroop interference scores immediately after the 1st HIIE were significantly reduced, indicating that EF was improved compared to the pre-exercise scores; the improved EF was sustained for 40 min during the post-exercise recovery period. However, after the 2nd HIIE EF was transiently improved after 10 min of post-exercise recovery compared with the pre-exercise EF, and it returned to pre-exercise levels after 20 min of post-exercise recovery. Notably, the EF after 40 min post-exercise recovery after the 2nd HIIE was significantly lower than that for the 1st HIIE.

Fig. 4 shows the relationship between lactate and EF by plotting the changes in lactate levels against changes in EF from pre-exercise at each time point during the post-exercise periods. There was an inverse relationship at Post 20 ($r = -0.48$, $P < 0.05$), Post 30 ($r = -0.46$, $P < 0.05$), Post 40 ($r = -0.63$, $P < 0.01$), and Post 50 ($r = -0.58$, $P < 0.01$), between the two parameters, indicating that higher lactate levels were associated with a lower interference score (i.e., better EF) during post-exercise recovery (Fig. 4). These relationships were not observed against glucose (Supplemental Fig. 1).

The changes in felt arousal level, mental fatigue, ability to concentrate, and motivation for the CWST following both HIIE protocols are shown in Fig. 5.

Mental fatigue was significantly increased immediately after both HIIE sessions. Increased mental fatigue was sustained after 20 min post-exercise recovery after the 1st HIIE. The ability to concentrate during post-exercise recovery (at 0 and 30 min) was significantly higher after the 2nd HIIE than the 1st HIIE. Motivation during post-exercise recovery (at 30 min) was significantly higher after the 2nd HIIE than the 1st HIIE.

Table 2
Changes in reaction time and response accuracy in the color-word Stroop task.

	Pre-exercise	Post-exercise					
		0 min	10 min	20 min	30 min	40 min	50 min
Reaction time (ms)							
Congruent task							
1st HIIE	8814 ± 599	8207 ± 490	8478 ± 512	8645 ± 567	8841 ± 660	8805 ± 626	8728 ± 580
2nd HIIE	8940 ± 629	7988 ± 555	8538 ± 592	8513 ± 574	8999 ± 686‡	9044 ± 566‡	8968 ± 661
Neutral task							
1st HIIE	9303 ± 607	8665 ± 578	8931 ± 576	9144 ± 652	9248 ± 634	9132 ± 607	9039 ± 597
2nd HIIE	9176 ± 642	8682 ± 593	9277 ± 628*	9140 ± 602	9153 ± 559	9192 ± 651	9239 ± 656
Incongruent task							
1st HIIE	10,592 ± 697	9336 ± 620†	9500 ± 616††	9702 ± 679††	9902 ± 688†	9888 ± 678†	9766 ± 666†
2nd HIIE	10,146 ± 711*	9218 ± 653††	9727 ± 654	9758 ± 622	9904 ± 658‡‡	10,318 ± 711*,‡‡,§§	10,243 ± 736‡
Response accuracy (%)							
Congruent task							
1st HIIE	98.7 ± 0.5	96.8 ± 0.8	96.7 ± 1.3	98.5 ± 0.4	96.9 ± 0.5	97.9 ± 0.4	97.3 ± 0.5
2nd HIIE	98.4 ± 0.5	98.4 ± 0.5	97.5 ± 0.8	97.6 ± 0.6	97.3 ± 0.7	96.8 ± 0.9	97.8 ± 0.9
Neutral task							
1st HIIE	97.3 ± 0.8	97.6 ± 0.7	97.4 ± 0.8	98.1 ± 0.7	97.8 ± 0.9	98.7 ± 0.6	97.9 ± 0.7
2nd HIIE	97.6 ± 1.3	98.2 ± 0.6	98.2 ± 0.5	98.0 ± 0.4	97.9 ± 1.0	98.4 ± 0.5	96.7 ± 0.6
Incongruent task							
1st HIIE	96.7 ± 1.1	96.7 ± 0.9	97.8 ± 1.0	97.4 ± 0.8	97.5 ± 0.8	97.8 ± 0.7	97.3 ± 0.6
2nd HIIE	97.8 ± 0.4	97.1 ± 0.7	96.7 ± 1.0	98.3 ± 0.6	97.7 ± 0.5	98.1 ± 0.7	98.5 ± 0.6

Values are presented as means ± SEM.
Congruent task (Reaction time [Condition $F_{1,9} = 0.36$, $P = 0.56$; Time $F_{6,54} = 6.36$, $P < 0.01$; Condition × Time $F_{6,54} = 0.64$, $P = 0.70$], Response accuracy [Condition $F_{1,9} = 1.10$, $P = 0.32$; Time $F_{6,54} = 1.40$, $P = 0.23$; Condition × Time $F_{6,54} = 1.28$, $P = 0.28$]), Neutral task (Reaction time [Condition $F_{1,9} = 0.68$, $P = 0.43$; Time $F_{6,54} = 7.42$, $P < 0.01$; Condition × Time $F_{6,54} = 1.42$, $P = 0.23$], Response accuracy [Condition $F_{1,9} = 0.00$, $P = 1.00$; Time $F_{6,54} = 1.24$, $P = 0.30$; Condition × Time $F_{6,54} = 0.71$, $P = 0.65$]), Incongruent task (Reaction time [Condition $F_{1,9} = 0.53$, $P = 0.49$; Time $F_{6,54} = 16.00$, $P < 0.01$; Condition × Time $F_{6,54} = 4.77$, $P < 0.01$], Response accuracy [Condition $F_{1,9} = 0.58$, $P = 0.47$; Time $F_{6,54} = 1.07$, $P = 0.39$; Condition × Time $F_{6,54} = 0.98$, $P = 0.45$]).
* $P < 0.05$ vs. 1st HIIE, †, †† $P < 0.05$, 0.01 vs. pre-exercise, ‡, ‡‡ $P < 0.05$, 0.01 vs. 0 min, §§ $P < 0.01$ vs. 10 min.

4. Discussion

Cognitive function involves various brain functions, including general intellect, memory function, language function, perceptual function and EF. Of these, EF is specifically involved in working memory, reasoning, task flexibility and problem solving [43]. Previous studies have demonstrated that moderate-intensity continuous exercise can acutely improve EF in various populations [12,44,45]. More recently, we have found that the HIIE-induced improvement in EF was sustained for a significantly longer period after exercise than with moderate-intensity continuous exercise. Additionally we suggested that brain lactate metabolism might have an important influence on post-exercise EF [35] because Rasmussen et al. [46] suggested that the acceleration of lactate metabolism in the brain during and after exercise is induced by blood lactate levels ≥2 mM or 2–4 mM, respectively, and the mean values of blood lactate levels at 30 min post-exercise recovery after HIIE were found to be ≥2 mM. However, it is still unclear whether the increased production of lactate induced by HIIE compared to moderate-intensity continuous exercise could sustain high EF for longer. Therefore, the initial challenge of the present study was to examine the effects of different concentrations of blood lactate during and after HIIE following the same exercise procedure on EF. Lactate can accumulate during exercise, particularly when rates of glycogenolysis and glycolysis are elevated [36], probably due to 1) increased lactate production with speeded metabolism, 2) increased recruitment of fast-twitch fibers with intense exercise, 3) decreased removal of blood; hence, decreased muscle glycogen during and/or following prolonged exercise attenuates blood lactate production and accumulation [3,4]. Lower lactate production would be expected in response to the second session of HIIE (2nd HIIE) if muscle glycogen was diminished by the first session of HIIE (1st HIIE). Confirming our hypothesis, in the present study, we found that blood lactate concentration during and after the 2nd HIIE was lower than that during and after the 1st HIIE, even when implementing the same exercise procedure. This finding also allowed us to examine whether repeated HIIE, in which exercise increased lactate concentrations, but that increase was lower in the second HIIE bout, affected post-exercise EF.

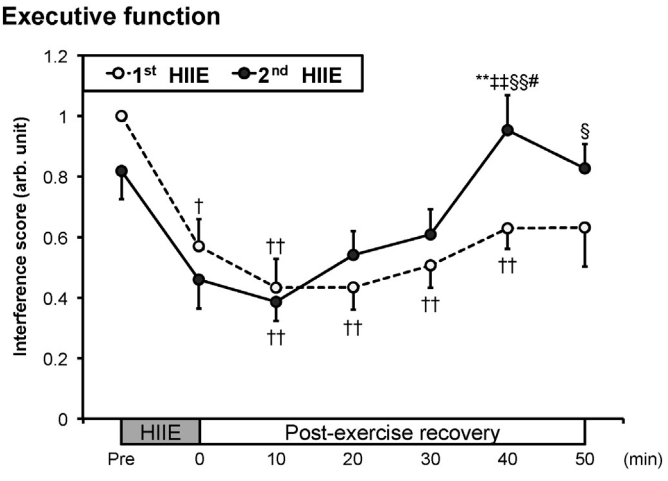

Fig. 3. Changes in EF. The panel illustrates the changes in reverse-Stroop interference score, which is an indicator of executive function (EF), for the 1st HIIE (open circles) and 2nd HIIE (solid circles). The values are expressed as the mean ± SEM. ** $P < 0.01$ vs. 1st HIIE, †, †† $P < 0.05$, 0.01 vs. Pre, ‡‡ $P < 0.01$ vs. Post 0, §§ $P < 0.01$ vs. Post 10, # $P < 0.05$ vs. Post 20.

Other novel findings of the present study were that EF increased after the 1st HIIE and that the improvement was sustained for 40 min, whereas the 2nd HIIE, during which blood lactate concentration was lowered, failed to produce a sustained improvement in EF. In addition, there was an inverse relationship at Post 20 ($r = -0.48$, $P < 0.05$), Post 30 ($r = -0.46$, $P < 0.05$), Post 40 ($r = -0.63$, $P < 0.01$), and Post 50 ($r = -0.58$, $P < 0.01$), between changes in lactate and EF, indicating that higher lactate levels were associated with a lower interference score (i.e., better EF) during post-exercise recovery (Fig. 4). These relationships were not observed against glucose (Supplemental Fig. 1). These findings suggested the possibility that repeated bouts of HIIE, which decreases lactate accumulation, may dampen the positive effect

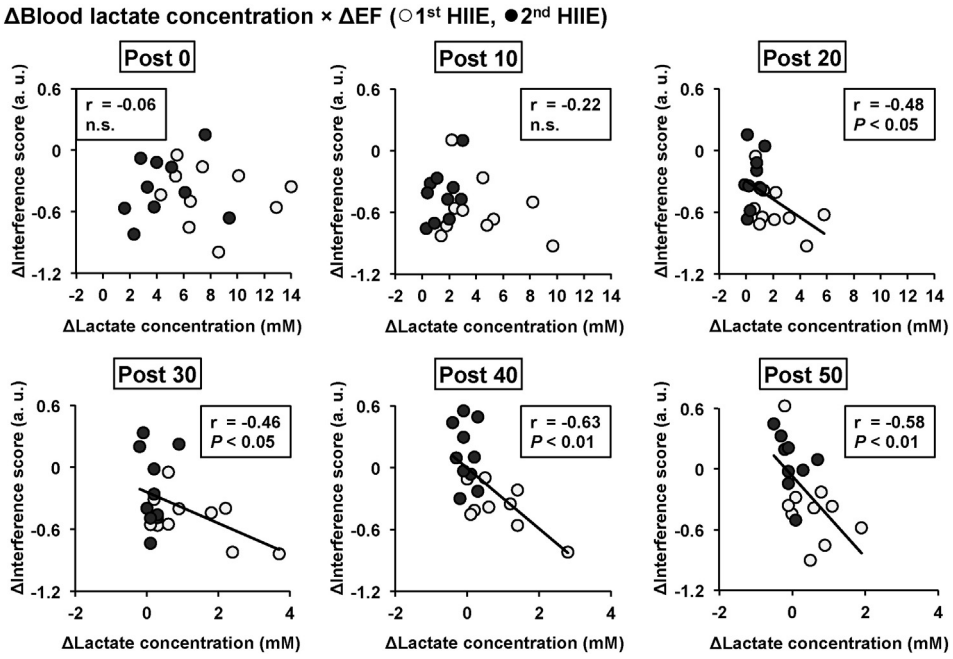

Fig. 4. Relationship between lactate and EF by plotting the changes in lactate levels against changes in EF (a.u., arbitrary unit) from pre-exercise at each time point during the post-exercise periods. The open circles indicate the 1st HIIE response, and the solid circles indicate the 2nd HIIE response. There were inverse relationships at Post 20 ($r = -0.48$, $P < 0.05$), Post 30 ($r = -0.46$, $P < 0.05$), Post 40 ($r = -0.63$, $P < 0.01$), and Post 50 ($r = -0.58$, $P < 0.01$), between the two parameters. n.s., not significant.

of exercise on EF, at least during the late phase of post-exercise recovery.

Previous studies have posited that the aerobic exercise-induced improvement in EF might be related to increased psychological responses, possibly through increases in neuronal activity in the brain. For example, Soya and co-workers reported that improved EF after acute aerobic exercise was associated with increased L-DLPFC activity in the brain [11,12]. Moreover, their recent study showed that improved EF after exercise was correlated with enhanced psychological arousal levels [11]. However, the results of the present study demonstrated that felt arousal level did not differ between the post-exercise recovery periods after each round of HIIE. Additionally, after exercise, some psychological parameters such as concentration and motivation tended to be higher for the 2nd HIIE than for the 1st HIIE, indicating that psychological responses may not be sufficient to explain the lack of prolonged exercise-induced improvements in EF following the 2nd HIIE.

We previously suggested that improved cognitive function during exercise may be due to the augmented cerebral neuronal activation and metabolism associated with exercise rather than cerebral perfusion [10]. It has been demonstrated that during high-intensity exercise, compensatory increases in the uptake (a–v difference) of lactate, glucose and oxygen support elevated brain neuronal activity and metabolism [13]. In the present study, both the absolute glucose and lactate concentrations decreased, although the decreased level of glucose to the pre-exercise phase was lower, during and following the 2nd HIIE in comparison to the 1st HIIE. Notably, however, at rest, the brain mainly relies on

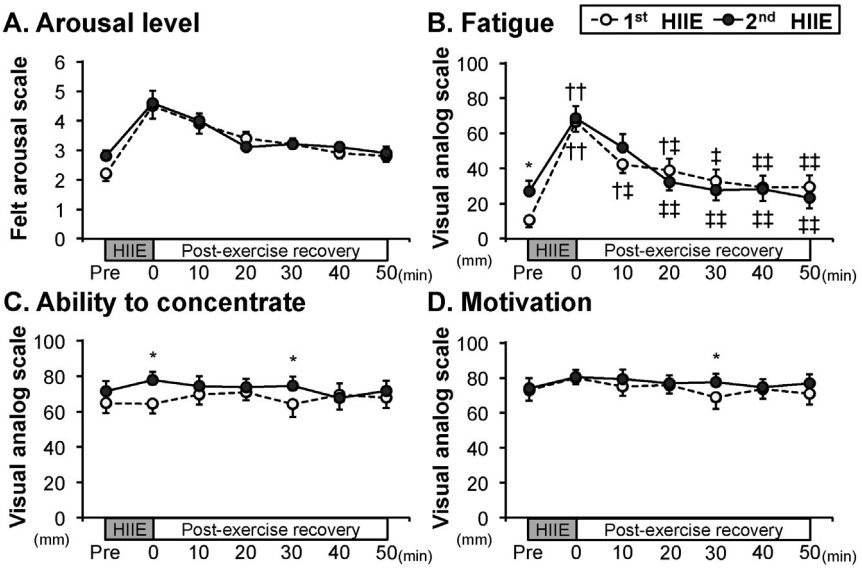

Fig. 5. Changes in psychological parameters for the CWST. The panels illustrate the changes in felt arousal level (A), mental fatigue (B), ability to concentrate (C), and motivation (D) for the 1st HIIE (open circles) and 2nd HIIE (solid circles). The arousal level was evaluated using a felt arousal scale. Mental fatigue, ability to concentrate, and motivation were evaluated using the visual analog scale. The values are expressed as the mean ± SEM. * $P < 0.05$ vs. 1st HIIE, †, †† $P < 0.05$, 0.01 vs. Pre, ‡, ‡‡ $P < 0.05$, 0.01 vs. Post 0.

glucose, whereas during high-intensity exercise, glucose uptake significantly decreases with increased blood lactate levels [47]. Interestingly, due to the compensatory action of decreased glucose uptake, the main energy source in the brain switches to lactate [6]. Rasmussen et al. [46] suggested that the acceleration of lactate metabolism in the brain is induced by blood lactate levels ≥2 mM. These findings suggest that lactate fuels the human brain during and after exercise to satisfy augmented cerebral neuronal activation and metabolic demand. Conversely, there is a possibility that lowered lactate concentration/production during and after the 2nd HIIE compared to the 1st HIIE might fail to adequately support elevated brain neuronal activity and metabolism, thereby affecting improved EF following the 2nd HIIE.

Previously, Kamijo et al. [48] indicated that greater attentional resources were allocated to the flanker task after moderate-intensity exercise, but not after high-intensity exercise, and suggested that EF a few minutes after exercise may change in an inverted-U fashion relative to exercise intensity. On the other hand, Chang et al. [49] reviewed the effects of acute exercise on cognitive function (including EF) in a meta-analysis, indicating the importance of exercise intensity and the specific timing of the administration of cognitive tests in influencing the size of the effect. The authors of this previous report noted that when the cognitive test is administered following a delay after exercise, more intense exercise produces the strongest effects. Although the identification of the mechanism regulating this relationship may be difficult owing to confounding factors involved in intense exercise, we have shown that the lower production/accumulation of lactate without decreased psychological responses diminished the size of the effect in terms of prolonged EF after exercise in the present study. Thus, exercise-induced lactate might, at least partially, affect EF following a delay after exercise. To support this interpretation, we revisited the data obtained in our recently published study [35] and found that there were inverse relationships between EF and lactate as assessed by plotting the changes in lactate levels against changes in EF from pre-exercise at each time point during the post-exercise periods at Post 20 ($r = -0.36$, $P < 0.05$) and Post 30 ($r = -0.52$, $P < 0.01$) following HIIE, which was similarly performed in the current study or workload-matched moderate-intensity continuous exercise (Supplemental Fig. 2). However, there was no relationship between EF and glucose (Supplemental Fig. 3). These findings provide further support the possibility that the improvement in EF with HIIE is linked to lactate levels. Nevertheless, it should be noted that we did not demonstrate the cause and effect relationship between lactate and post-exercise EF such that it is merely a possibility that lactate is involved in the improved EF (i.e., the results being merely co-relational and thus possibly merely coinciding and possibly caused by other shared or non-shared mechanisms). Thus, a potential direct link between lactate accumulation and post-exercise EF should be further elucidated.

4.1. Limitations

The arterial lactate concentration increased several-fold during exercise, and the reduced oxygen-to-carbohydrate ratio (cerebral metabolic ratio: CMR) during recovery was associated with a relatively large lactate uptake by the brain [15,16]. We postulated that the acceleration of lactate metabolism in the brain during and after HIIE could be associated with augmented neuronal activity, and hence improvement in post-exercise EF; however, we did not measure lactate metabolism and neuronal activity in the brain. To test our hypothesis, further studies are needed to assess the relationship between the exercise-induced enhancement of neuronal activity as well as lactate metabolism in the brain and EF. In addition, we did not examine the effect of repeated HIIE on EF compared to control conditions such as sedentary, the same experiments performed later during the day, or repeated very light-intensity interval exercise which would not be accompanied by less lactate accumulation in the second bout of exercise. Furthermore, many physiological factors that could influence lactate metabolism and hence EF might be altered in the 2nd HIIE. For example, O_2 uptake kinetics might be faster, which could contribute to less lactate accumulation (less production, more removal). Alternatively, it would be needed to add lactate infusion to the 2nd HIIE to see if simply increasing the lactate concentration causes EF to return.

Furthermore, with repeated bouts of exercise, there might also be a possibility that fatigue (e.g., central fatigue), which may not be evident from the obtained subjective measures, results in the lack of attention in the subsequent tests. Neurohumoral and metabolite responses, including their precursors, such as serotonin, tryptophan, dopamine, and the depletion of brain glycogen stores, could be related to exercise-induced central fatigue [14,16,50–52]. One may argue that there was likely to be neurotransmitter quantitative and qualitative changes occurring and there was a possibility of neural accommodation occurring during the 2nd HIIE, reducing the effectiveness of the neurotransmitters released. In addition, interactions between excitatory and inhibitory pathways might influence the responses. Further studies are needed to determine the association between neurohumoral and metabolite responses and brain function during and after exercise.

Finally, we did not identify the interrelationship between changes in lactate levels and EF at Post 0 and Post 10 following HIIE, suggesting that many other factors might affect EF, at least shortly after post-exercise recovery. VAS analyses revealed that the arousal level tended to increase immediately after each round of HIIE. In addition, the concentration tended to be higher for the 2nd HIIE than for the 1st HIIE at Post 0. However, we cannot discount the possibility that these psychological factors affected the interrelationship between changes in the lactate levels and EF shortly after post-exercise recovery. As previously described, direct evidence of lactate infusion to the 2nd HIIE to determine whether simply increasing the lactate concentration causes EF to improve is warranted.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.physbeh.2016.03.029.

Disclosure

The authors for this manuscript have nothing to disclose.

Acknowledgements

We thank all of the subjects who participated in the study. This work was supported by the Ministry of Education, Culture, Sports, Science and Technology - Grant-in-Aid for Young Scientists (A) for TH (no. 26702029); Grant-in-Aid for Exploratory Research for TH (no. 25560344).

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