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Executive function after exhaustive exercise

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1 23 **Abstract (240)**

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3 24 **Purpose:** Findings concerning the effects of exhaustive exercise on cognitive function are
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6 25 somewhat equivocal. The purpose of this study was to identify physiological factors that
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8 26 determine **executive** function after exhaustive exercise. **Methods:** **Thirty-two participants**
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11 27 completed the cognitive tasks before and after an incremental exercise until exhaustion
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13 28 **(Exercise group: N = 18)** or resting period **(Control group N =14)**. The cognitive task was a
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16 29 combination of a Spatial Delayed-Response (Spatial DR) task and a Go/No-Go task, which
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18 30 requires executive function. Cerebral oxygenation and skin blood flow were monitored during
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21 31 the cognitive task over the prefrontal cortex. Venous blood samples were collected before and
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24 32 after the exercise or resting period, and blood catecholamines, serum brain-derived
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26 33 neurotrophic factor, insulin-like growth hormone factor 1, and blood lactate concentrations
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29 34 were analyzed. **Results:** In the Exercise group, exhaustive exercise did not alter reaction time
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31 35 (RT) in the Go/No-Go task (Pre: 861 ± 299 ms vs. Post: 775 ± 168 ms) and the number of error
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34 36 trials **in the Go/No-Go task (Pre: 0.9 ± 0.7 vs. Post: 1.8 ± 1.8) and the spatial DR task (Pre: 0.3**
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36 37 **± 0.5 vs. Post: 0.8 ± 1.2).** However, Δ RT was negatively correlated with Δ cerebral oxygenation
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39 38 ($r = -0.64$, $P = 0.004$). Other physiological parameters were not correlated with cognitive
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42 39 performance. **Venous blood samples were not directly associated with cognitive function after**
43
44 40 **exhaustive exercise. Conclusion:** The present results suggest that recovery of regional cerebral
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47 41 oxygenation affects **executive** function after exhaustive exercise.

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49 42 **Key Words:** executive function, reaction time, cerebral oxygenation, brain
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1	44	Abbreviations:	
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3	45	BDNF	Brain-derived neurotrophic factor
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5	46	DBP	Diastolic blood pressure
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8	47	Deoxy-Hb	Deoxyhemoglobin
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11	48	DR	Delayed-Response
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13	49	IGF-1	Insulin-like growth hormone factor 1
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16	50	NIRS	Near-infrared spectroscopy
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18	51	NTS	Nucleus tractus solitarii
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21	52	Oxy-Hb	Oxyhemoglobin
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24	53	RPE	Ratings of perceived exertion
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26	54	RT	Reaction time
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29	55	SBP	Systolic blood pressure
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31	56	SD	Standard deviation
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34	57	Total-Hb	Total hemoglobin
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59 Introduction

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61 Cognitive function is one of the major determinants of performance in sports and may be
62 impaired under exhaustive conditions. Recent studies summarized the effects of exhaustive
63 exercise on cognitive function, but the findings are somewhat equivocal (Chang et al. 2012;
64 McMorris 2016a). Exercise has many physiological effects on the human brain (Ide and Secher
65 2000; Nybo and Secher 2004; Ogoh and Ainslie 2009). Thus, several physiological factors are
66 likely to be related to interaction between cognitive function and exhaustive exercise. In the
67 present study, we attempted to determine physiological factors that affect cognitive function
68 under exhaustive conditions. To this end, cognitive function was assessed after exhaustive
69 exercise since it is difficult to complete a cognitive task that lasts for a long time during
70 exhaustive exercise.

71 Cerebral oxygenation reflects the balance between oxygen availability and utilization (Boushel
72 et al. 2001). During incremental exercise, cerebral oxygenation measured from the prefrontal
73 cortex increases up to moderate to hard intensities, then decreases at very hard intensity near
74 exhaustion (Rooks et al. 2010). In contrast, cerebral oxygenation quickly recovers after
75 exhaustive exercise (Ando et al. 2010; Gonzalez-Alonso et al. 2004). Provided that oxygen
76 availability could be compromised under exhaustive condition, the degree of recovery of
77 cerebral oxygenation may be crucial for cognitive function after exhaustive exercise. Therefore,
78 in the present study, we first hypothesized that recovery of cerebral oxygenation is associated
79 with cognitive function after exhaustive exercise.

80 Exercise affects brain circuits involving neurotransmitters including dopamine, noradrenaline,
81 serotonin, adrenocorticotrophic hormone, and cortisol (Dietrich and Audiffren 2011; McMorris
82 2016a; Meeusen and De Meirleir 1995; Nybo and Secher 2004). Some of these physiological

1 83 changes are potential candidates that affect cognitive function (Brisswalter et al. 2002; Chmura
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3 84 et al. 1994; McMorris 2016a). Exhaustive exercise substantially increases circulating
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5 85 catecholamine concentrations (Chmura et al. 1994; Gonzalez-Alonso et al. 2004). Given that
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7 86 catecholamine does not readily cross the blood-brain barrier (Cornford et al. 1982), venous
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9 87 blood catecholamine concentrations are almost entirely the result of peripheral activity
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11 88 (McMorris 2016a). However, increases in circulating adrenaline and noradrenaline activate
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13 89 β -adrenoceptors on the afferent vagus nerve (McGaugh et al. 1996; Miyashita and Williams
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15 90 2006), which terminates in the nucleus tractus solitarii (NTS) within the blood-brain barrier
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17 91 (McMorris 2016b). Noradrenergic cells in the NTS project to the locus coeruleus (LC) and
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19 92 stimulate noradrenaline synthesis and release to other parts of the brain (McMorris 2016a).
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21 93 Thus, increases in circulating catecholamines induced by exhaustive exercise may be critical to
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23 94 cognitive performance. Therefore, it is worth investigating whether cognitive performance
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25 95 after exhaustive exercise is associated with alterations in venous blood catecholamine
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27 96 concentrations. Furthermore, alternations in brain-derived neurotrophic factor (BDNF) (Lee et
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29 97 al. 2014; Piepmeier and Etnier 2015; Winter et al. 2007), insulin-like growth hormone factor 1
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31 98 (IGF-1) (Cassilhas et al. 2012; Cotman and Berchtold 2002; Ding et al. 2006), and blood
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33 99 lactate (Tsukamoto et al. 2016) may be contributing factors that affect cognitive function after
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35 100 exercise. We also examined whether alterations in BDNF, IGF-I, and blood lactate are
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37 101 associated with cognitive function after exhaustive exercise.
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41 102 The purpose of this study was to examine the effects of exhaustive exercise on cognitive
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43 103 function and to identify physiological factors that determine cognitive function. The findings
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45 104 from the present study extend our prior knowledge and may help to develop methods to prevent
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47 105 impairments in cognitive performance under exhaustive conditions.
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107 **Materials and Methods**

109 *Participants*

110 Thirty-four healthy male participants were recruited in this study. However, two participants
111 were not able to complete cognitive task after exhaustive exercise due to total exhaustion. Thus,
112 thirty-two healthy male participants completed the cognitive tasks [Exercise group: N = 18, age
113 = 23.2 ± 2.1 yr; height = 1.71 ± 0.06 m; body mass = 66.8 ± 5.9 kg; peak oxygen uptake
114 ($\dot{V}O_{2\text{peak}}$) = 48.2 ± 6.6 ml/kg/min, Control group: N = 14, age = 22.3 ± 2.3 yr; height = $1.70 \pm$
115 0.06 m; body mass = 64.4 ± 9.5 kg; $\dot{V}O_{2\text{peak}}$ = 47.7 ± 7.4 ml/kg/min]. The participants were
116 physically active and did not have any history of cardiovascular, cerebrovascular, or respiratory
117 disease. All participants gave written informed consent to participation. This study was
118 approved by the ethics committee of Fukuoka University and was in accordance with the
119 Declaration of Helsinki.

121 *Cognitive task*

122 Cognitive task was a combination of Spatial Delayed Response (Spatial DR) and Go/No-Go
123 tasks (Harada et al. 2004; Komiyama et al. 2015). The Spatial DR task required working
124 memory, and the Go/No-Go task required response inhibition and executive control. Hence, the
125 present cognitive task required executive function. The details of the cognitive task were
126 previously described (Komiyama et al. 2015). Figure 1 summarizes the present cognitive task.
127 In the Spatial DR task, a visual stimulus was presented in one of the eight locations
128 surrounding a fixation point. The participants were asked to remember the location where the
129 visual stimulus was presented. Then, the Go/No-Go task was started. On each trial, one of a
130 pair of figures was presented at the center of the computer display. One figure was identified at

1 131 the outset as the target. On any given trial, if the presented figure was the target (“Go trial”),
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3 132 participants released a shift key as quickly as possible. If the figure was not the target (“No-Go
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5 133 trial”), participants continued holding the shift key down. After the Go/No-Go task,
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8 134 participants continued with the Spatial DR task. Visual stimuli were presented at eight
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11 135 locations surrounding the fixation point. The participants pressed the button on a portable
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13 136 ten-key pad to indicate the location they remembered. The portable ten-key pad and computer
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16 137 keyboards were horizontally situated above both sides of the ergometer’s handlebars. The
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18 138 participants pressed the ten-key pad with their right index finger (Spatial DR task) and pressed
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21 139 the shift button on the keyboard with their left index finger (Go/No-Go task).
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23 140 *After the participants had completed four or five successive trials (pseudo randomly*
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26 141 *determined) in the Go/No-Go task, the other figure became the target. After the next four or*
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29 142 *five successive trials were completed, a new pair of figures was presented. The participants did*
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31 143 *not know when the correct response and the figure would be reversed or when the new pair of*
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34 144 *figures would be presented.* The cognitive tasks continued until the participants had completed
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36 145 20 trials of each task. To assess cognitive function, we used reaction time (RT) of the Go trial in
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39 146 the Go/No-Go task and number of error trials of each task. In the Go/No-Go task, error trials
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41 147 were defined as omitting the response in the Go trial, or an incorrect response in the No-Go
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44 148 trial. For calculation of number of error trials, we excluded trials immediately after the
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47 149 relationship between correct response and figure was reversed or one of a new pair of figures
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49 150 was presented. In the Spatial DR task, error trials were defined as incorrect responses to the
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52 151 remembered location.

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57 153 *----- Insert Figure 1 about here -----*
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1 155 *Experimental procedure*

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3 156 A few days before the experiment, the participants completed practice blocks of the cognitive
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6 157 task at rest and during cycling until RT decreased within three SD from the mean. On the day of
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8 158 the experiment, the participants arrived at the laboratory at least 1 hour before the experiment.
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11 159 At the beginning of the experiment, venous blood sample was collected from the antecubital
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13 160 vein. The left earlobe was pricked with a safety lancet and 2 μ L capillary blood was collected.
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16 161 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured from the
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18 162 right arm in a sitting position. Then, the participants performed the cognitive task at rest sitting
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21 163 on a cycle ergometer (75XLII, COMBI Wellness, Tokyo, Japan). After the cognitive task,
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23 164 ratings of perceived exertion (RPE; 6-20 Borg scale) (Borg 1975) was recorded. In the Exercise
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26 165 group, the participants started an incremental exercise test until exhaustion. Following a
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29 166 warm-up period at 10 W for 1 min, the maximal exercise test was initiated with 20 W
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31 167 increments every minute in a ramp manner. The pedaling rate was freely chosen **over 50**
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34 168 **revolution per minute (rpm)** by each participant. The maximal exercise test was stopped when
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36 169 the participants were no longer able to maintain a pedaling rate of 50 **rpm**. We measured
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39 170 ventilatory parameters using a gas analysis system (ARCO-2000, ARCO System, Chiba,
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41 171 Japan), and peak oxygen uptake was determined as the highest oxygen uptake attained. RPE
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44 172 was recorded after the cessation of exercise. The participants performed the cognitive task 2
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46 173 min after the maximal exercise test. Then, venous and capillary blood sample was collected,
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49 174 followed by blood pressure measurement. In the Control group, the participants completed the
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52 175 measurement in the same manner except for exercise. We used the average time (16 min 1 sec)
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54 176 of the maximal exercise in the Exercise group as the duration of resting period in the Control
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57 177 group. Thus, the experiments in the Control group were conducted after all experiments in the
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59 178 Exercise group had completed. The participants in the Control group also performed the
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1 179 incremental exercise test until exhaustion within a week after the main experiment and
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3 180 confirmed that $\dot{V}O_{2\text{peak}}$ was not different between groups ($P = 0.86$, *two-sample t-test*).

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5 181 Throughout the experiment, the ambient temperature was maintained at 22 °C and the relative
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8 182 humidity was controlled approximately at 50%.

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11 184 *Measurement*

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13 185 Cerebral oxygenation was continuously monitored over the prefrontal cortex with a
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16 186 near-infrared spectroscopy (NIRS) (BOM-L1 TRW, Omegawave, Tokyo, Japan), as previously
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19 187 described (Ando et al. 2010). A probe holder contained one light source probe and two
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22 188 detectors placed at 2 cm (detector 1) and a 4 cm (detector 2) from the source. The probe holder
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25 189 was attached at the right side of the forehead so that midpoint of the detectors cover the Fp2
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28 190 position of the international electroencephalographic 10–20 system. We used positions of Fpz
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31 191 and F8 as landmarks. The source generated three wavelengths of near-infrared light (780, 810,
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34 192 and 830 nm). Based on the modified Beer-Lambert law, continuous measurement of
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36 193 concentration changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb), and
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39 194 tissue scattering and attenuation coefficients were measured with the three wavelengths of
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42 195 near-infrared light. After movement artifacts were removed, hemoglobin concentrations were
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44 196 calculated using near-infrared light received by each detector without detrend. Total
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47 197 hemoglobin (total-Hb) is calculated as the sum of oxy-Hb and deoxy-Hb. Cerebral oxygenation
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49 198 is expressed as $\text{oxy-Hb}/\text{total-Hb} \times 100$ (i.e., as a percentage). Hence, cerebral oxygenation
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52 199 reflects proportion of oxy-Hb, and the definition of cerebral oxygenation is different from other
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54 200 studies using different devices (e.g. Tobias et al. 2008). We assessed relative changes in
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57 201 cerebral oxygenation from the baseline in response to exhaustive exercise and the cognitive
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59 202 tasks. In the present study, the hemoglobin concentrations received by detector 1 were
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1 203 subtracted from those received by detector 2, which allowed us to reduce effects of
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3 204 near-surface blood flow on hemoglobin concentrations in the cortical tissue (see also limitation
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6 205 in the Discussion).

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8 206 Skin blood flow was monitored from the right side of the forehead with a laser Doppler flow
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11 207 probe (FLO-C1, Omegawave, Tokyo, Japan). The probe of skin blood flow were placed side by
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13 208 side with the probe of NIRS, and both probe holders were wrapped by a black cloth to shield
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16 209 them from the light. Before the experiment, we confirmed that there was no cross-talk when we
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18 210 measured cerebral oxygenation and skin blood flow simultaneously. Before the cognitive task
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21 211 at rest, we measured averaged oxy-Hb, deoxy-Hb, total-Hb, cerebral oxygenation and skin
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23 212 blood flow for 30 second as a baseline while sitting on the ergometer. Oxy-Hb, deoxy-Hb,
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26 213 total-Hb and cerebral oxygenation during the cognitive tasks were averaged and expressed
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28 214 relative to the baseline. Relative changes in skin blood flow were expressed as a percentage.
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31 215 Plasma samples were obtained from heparinized blood samples at centrifugation at 3,000 rpm
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34 216 for 15 min and stored at -80°C until analysis. Plasma adrenaline, noradrenaline and dopamine
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36 217 concentrations were determined using a high-performance liquid chromatography system
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39 218 (Shimadzu, Kyoto, Japan). Relative changes in adrenaline, noradrenaline, and dopamine were
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41 219 expressed as a percentage. Serum samples were obtained from venous blood by centrifugation
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44 220 and were stored until analysis. Serum BDNF concentration was measured using the Quantikine
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46 221 Human BDNF Immunoassay (R&D systems, Minneapolis, USA). For BDNF analysis, data
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49 222 from one participant in the Control group were excluded due to technical problem. Serum
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52 223 IGF-1 concentration was determined using an immunoradiometric assay (IGF-1 IRMA Daiichi,
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54 224 TFB, Tokyo, Japan) and a Wallac 1460 Gamma Counter (Wallac, Turku, Finland). Blood
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57 225 lactate concentration was determined by the lactate oxidase method, using an automated
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59 226 analyzer (Lactate Pro, Arkray, Kyoto, Japan).
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3 228 *Data and statistical analysis*4
5 229 Two-way analysis of variance (ANOVA) with Time (pre and post) as the within-subject factor6
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8 230 and Group as the between-subject factor was performed. When an interaction was observed,9
10 231 we performed a paired t-test with Bonferroni correction. Sample size was calculated from our11
12 232 preliminary results and we observed that, at least, thirteen participants would be needed. We13
14 233 performed the Shapiro-Wilk test before correlation analysis to test if data are normally15
16 234 distributed. Pearson's correlation test was used to establish a correlation between alterations in17
18 235 cognitive performance and physiological parameters when data are normally distributed.19
20 236 Spearman's correlation test was used when data are not normally distributed. For correlation21
22 237 analysis, provided p-values were corrected with false discovery rate correction (Glickman et al.23
24 238 2014) for each physiological variable. All data are expressed as mean \pm SD. The significance25
26 239 level was set at $P < 0.05$.27
28 24029
30 241 **Results**31
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34 243 *Cognitive function*35
36 244 Figure 2 illustrates RT in the Go/No-Go task (A), number of error trials in the Go/No-Go (B)37
38 245 and the Spatial DR (C) tasks. We observed no significant main effects of Time [$F(1,30) = 1.33$,39
40 246 $P = 0.26$, $\eta_p^2 = 0.04$] and Group [$F(1,30) = 0.02$, $P = 0.88$, $\eta_p^2 = 0.001$] on RT. No interaction41
42 247 was observed between Time and Group [$F(1,30) = 1.02$, $P = 0.32$, $\eta_p^2 = 0.03$]. These results43
44 248 indicate that RT did not change in the Exercise (Pre: 861 ± 299 ms vs. Post: 775 ± 168 ms) and45
46 249 Control (Pre: 833 ± 234 ms vs. Post: 827 ± 221 ms) groups. In contrast, we found a significant47
48 250 interaction between Time and Group on number of error trials in the Go/No-Go task [$F(1,30) =$ 49
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251 7.43, $P = 0.01$, $\eta_p^2 = 0.20$]. The difference in number of error trials in the Go/No-Go task was
 252 not significant in the Exercise (Pre: 0.9 ± 0.7 vs. Post: 1.8 ± 1.8 , $P = 0.04$) and Control (Pre: 1.0
 253 ± 0.8 vs. Post: 0.6 ± 0.6 , $P = 0.06$) groups after Bonferroni correction. Error trials in the Spatial
 254 DR task was affected by neither Time [$F(1,30) = 1.44$, $P = 0.24$, $\eta_p^2 = 0.05$] nor Group [$F(1,30)$
 255 $= 3.13$, $P = 0.09$, $\eta_p^2 = 0.09$], which indicates that accuracy of the Spatial DR task was not
 256 altered in both groups.

----- Insert Figures 2 & 3 about here -----

260 *Physiological parameters*

261 Figure 3 illustrates an example of alterations in cerebral oxygenation and skin blood flow in the
 262 Exercise group. Cerebral oxygenation gradually increased during low to moderate exercise,
 263 then decreased until exhaustion. Nevertheless, cerebral oxygenation quickly recovered after
 264 the cessation of exercise, and recovered to the baseline level during the cognitive task. In
 265 contrast, skin blood flow increased during incremental exercise until exhaustion, and remained
 266 elevated after exercise.

267 Table 1 summarizes the results of physiological parameters. In the Exercise group, we found no
 268 differences in oxy-Hb, deoxy-Hb, total-Hb, and cerebral oxygenation between pre and post
 269 values. In contrast, skin blood flow increased after exercise ($P = 0.003$), showing that skin
 270 blood flow remained elevated during the cognitive task after exhaustive exercise. Plasma
 271 adrenaline, noradrenaline, and dopamine concentrations significantly increased after exercise
 272 ($P = 0.03$, $P < 0.001$, and $P < 0.001$). Serum BDNF did not change after exercise, whereas
 273 serum IGF-1 significantly increased after exercise ($P < 0.001$). Blood lactate concentration and
 274 RPE significantly increased after exercise ($P < 0.001$ and $P < 0.001$). DBP slightly but

1 275 significantly decreased after exercise ($P = 0.02$). In the Control group, we found no alterations
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 3 276 in physiological parameters between the measurements.
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 8 278 ----- Insert Table 1 about here -----
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 13 280 *Correlation analysis*
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 16 281 In the Exercise condition, Δ RT was not correlated with Δ number of error trials in the
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18 282 Go/No-Go task ($r = -0.03$, $P = 0.90$), showing that there was no speed-accuracy tradeoff.
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21 283 Table 2 summarizes the results of correlation analysis between cognitive performance and
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23 284 physiological parameters. In the Exercise group, we observed that Δ RT was negatively
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25 285 correlated with Δ cerebral oxygenation ($r = -0.64$, $P = 0.004$, Figure 4). Alterations in other
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28 286 physiological parameters were not correlated with cognitive performance in the Exercise and
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31 287 Control groups (all P s > 0.05).
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 34 288 In the Exercise group, Δ skin blood flow was not correlated with Δ oxy-Hb ($r = 0.43$, $P = 0.08$),
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36 289 Δ deoxy-Hb ($r = 0.19$, $P = 0.44$), Δ total-Hb ($r = 0.38$, $P = 0.12$), and Δ cerebral oxygenation ($r =$
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39 290 0.20 , $P = 0.44$). In the Control group, Δ skin blood flow was not correlated with Δ oxy-Hb ($r =$
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41 291 0.09 , $P = 0.76$), Δ deoxy-Hb ($r = -0.01$, $P = 0.99$), Δ total-Hb ($r = 0.05$, $P = 0.86$), and Δ cerebral
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44 292 oxygenation ($r = -0.01$, $P = 0.97$). These results indicate that alterations in skin blood flow was
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46 293 not associated with alterations in oxy-Hb, deoxy-Hb, total-Hb, and cerebral oxygenation.
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 52 295 ----- Insert Table 2 & Figure 4 about here -----
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 57 297 **Discussion**
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1 299 The major findings of this study were: 1) Δ RT was negatively correlated with Δ cerebral
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3 300 oxygenation; 2) alterations in BDNF, IGF-1, and blood lactate concentrations were not
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5 301 correlated with cognitive function after exhaustive exercise. These results suggest that
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8 302 recovery of cerebral oxygenation affects speed of response in the cognitive task after
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11 303 exhaustive exercise. Venous blood samples were not directly associated with cognitive
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13 304 function after exhaustive exercise. **The present results suggest that recovery of prefrontal**
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16 305 **oxygenation affects executive function after exhaustive exercise.**

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18 306 A previous study indicated that decreases in cerebral oxygenation was not related to cognitive
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21 307 impairments during strenuous exercise (Ando et al. 2011). Another study also reported that
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23 308 inhibitory control was maintained despite decrease in cerebral oxygenation during exercise
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26 309 near exhaustion (Schmit et al. 2015). In contrast, impaired cognitive performance during heavy
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29 310 exercise was associated with decrease in cerebral oxygenation (Mekari et al. 2015). The
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31 311 discrepancies are probably due to the differences in exercise intensity, duration, and physical
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34 312 fitness of participants. In the present study, we observed that Δ RT was negatively correlated
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36 313 with Δ cerebral oxygenation after exhaustive exercise, which indicates that recovery of
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39 314 prefrontal oxygenation affected cognitive function after exhaustive exercise. Exercise may
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42 315 facilitate implicit information by enhanced noradrenergic and dopaminergic systems (Dietrich
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44 316 and Audiffren 2011). This implies that brain neurotransmitters could play a key role in
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47 317 alterations in speed of response during and after exercise. At the cellular level, the turnover of
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49 318 several neurotransmitters seems to be altered under hypoxia (Raichle and Hornbein 2001). This
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52 319 means that oxygen availability is critical for the turnover of neurotransmitters. In the case that
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54 320 oxygen availability was compromised in the brain areas under exhaustive condition, it can be
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57 321 speculated that reduced oxygen availability affected neurotransmitters turnover and impaired
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59 322 speed of response in the cognitive task. In contrast, sufficient recovery of oxygen availability
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1 323 would impair less speed of response even after exhaustive exercise. Therefore, it is plausible
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3 324 that degree of cerebral oxygenation recovery affected RT after exhaustive exercise. The present
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5 325 findings may suggest that the maintenance and recovery of cerebral oxygenation is a key
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8 326 determinant of cognitive performance in sports under exhaustive situations. However, it should
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10
11 327 be noted that substantial decrease in cerebral oxygenation did not impair cognitive function
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13 328 during moderate exercise under hypoxia (Ando et al. 2013; Komiyama et al. 2015). Given that
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15
16 329 cerebral blood flow does not match the metabolic demand during heavy exercise (Ogoh and
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18
19 330 Ainslie 2009), the present association between cognitive function and cerebral oxygenation
20
21 331 may be limited to the exhaustive condition where regional cerebral metabolism could be
22
23
24 332 compromised.

25
26 333 Moderate exercise has been suggested to increase arousal level to an optimal level and improve
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28
29 334 cognitive function (Brisswalter et al. 2002; Chang et al. 2012; Lambourne and Tomporowski
30
31 335 2010). However, further increases in arousal level (i.e. over-arousal) may produce neural noise
32
33
34 336 and impair cognitive performance (McMorris 2016a). Since the original hypothesis by Cooper
35
36 337 (Cooper 1973), the association between arousal level and catecholamines has been implicated
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38
39 338 (Chmura et al. 1994; McMorris 2016a). Indeed, one would expect that increases in
40
41
42 339 catecholamine concentrations lead to over-arousal and have negative effects on cognitive
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44 340 function following heavy exercise (McMorris 2016a). In the present study, however, we
45
46 341 observed no relationships between alterations in cognitive function and circulating
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48
49 342 catecholamines. These results indicate that circulating catecholamines were not directly
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51
52 343 associated with cognitive function after exhaustive exercise. Hence, the present study may
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54 344 suggest that cognitive performance is not predictable from circulating blood catecholamines
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57 345 after exhaustive exercise.

58
59 346 It has been suggested that upregulation of BDNF expression is associated with neuroplasticity
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1 347 (Cotman and Berchtold 2002; Voss et al. 2013). In contrast, less is known how alterations in
2
3 348 BDNF affect cognitive function after acute exercise. In the present study, there was no
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5 349 association between cognitive function and serum BDNF after exhaustive exercise, suggesting
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7
8 350 that alterations in peripheral BDNF are not related to cognitive function after exhaustive
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11 351 exercise. Given that peripheral BDNF is merely indicative of central concentration, the real
12
13 352 effects of BDNF on cognitive function are probably downstream of synthesis and release
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15
16 353 (McMorris 2016a). Alternatively, a recent review summarized that peripheral BDNF is closely
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18 354 related to memory task and is not implicated more broadly in explaining the effects of acute
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20
21 355 exercise on other types of cognitive performance (Piepmeier and Etnier 2015). Thus, another
22
23 356 possible explanation for the absence of the association between alterations in serum BDNF and
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25
26 357 cognitive function may be that executive function was assessed in the present study.

27
28 358 IGF-1 has multipotent neuroprotective effects and has been demonstrated as a potent mediator
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30
31 359 of the multi-beneficial effects of exercise on the brain (Nishijima et al. 2016). Previous studies
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34 360 using both human and rodent models have suggested that serum IGF-1 increases following
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36 361 acute resistance exercise or resistance exercise training (Borst et al. 2001; Cassilhas et al. 2012;
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38
39 362 Cassilhas et al. 2007; Tsai et al. 2014). In the present study, serum IGF-1 significantly
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41 363 increased after exhaustive exercise. We used the maximal exercise test, which is thought to
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44 364 recruit motor units containing fast fibers to a greater extent. Thus, it is reasonable that serum
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46 365 IGF-1 concentration increased after the exercise until exhaustion. It has been suggested that
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49 366 increases in serum IGF-1 after resistance exercise may contribute to cognitive improvements
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51
52 367 (Cassilhas et al. 2012; Cotman and Berchtold 2002; Ding et al. 2006). However, in the present
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54 368 study, alterations in cognitive performance were not correlated with increases in serum IGF-1.
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57 369 Hence, this result suggests that alterations in serum IGF-1 are not directly associated with
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59 370 cognitive function after exhaustive exercise. Nonetheless, it is less clear whether alterations in
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1 371 IGF-1 are associated with cognitive function after acute exercise. Further studies are needed to
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3 372 examine whether increases in IGF-1 may be responsible for alterations in cognitive function
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6 373 after acute exercise.

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8 374 A recent study suggested that blood lactate may play a key role in improvements in cognitive
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11 375 function after high-intensity exercise (Tsukamoto et al. 2016). In the present study, blood
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13 376 lactate concentration substantially increased after exhaustive exercise. However, alterations in
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16 377 cognitive performance were not correlated with increases in blood lactate concentration. This
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19 378 result suggests that increases in blood lactate are not directly associated with cognitive function
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21 379 after exhaustive exercise. Rather, lactate is well known to be taken up in the brain, which serves
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24 380 as an energy fuel (Quistorff et al. 2008; van Hall 2010). Hence, in the present study, it is likely
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26 381 that lactate served as an energy fuel in the brain areas after exhaustive exercise.

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28
29 382 We have to acknowledge limitations in the present study. First, although we proposed several
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31 383 candidates that affect cognitive function, many physiological alterations occur simultaneously
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33
34 384 in response to acute exercise. Changes in cerebral circulation, blood catecholamines, and
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36 385 growth and neurotrophic factors were not isolated with other physiological changes induced by
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39 386 acute exercise. Hence, we cannot exclude confounding factors, and sophisticated protocols are
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41
42 387 still necessary to reveal contribution of each physiological change. **In the present study, we**
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44 388 **focused on how alterations in physiological variables affect executive function. In that sense,**
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46
47 389 **the present perspective may be more homeostatic than allostatic. However, given that research**
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49
50 390 **investigating activity and relationship among the multiple regulatory loops would be helpful to**
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52 391 **understand physiological regulatory systems (Ramsay and Woods 2014), further study should**
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54 392 **focus on the integration and contribution of different systems (e.g. Ekkekakis et al. 2016).**

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57 393 Second, recent studies challenged the validity and/or reliability of the measurement using
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60 394 NIRS (Sorensen et al. 2012; Takahashi et al. 2011). In particular, concerns raised by recent
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1 395 criticisms are the contamination of skin blood flow. However, even if it might be difficult to
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3 396 exclude the effects of extracranial blood flow completely, we expected that the effects of
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5 397 near-surface blood flow on cerebral oxygenation were reduced by subtraction of data from
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7
8 398 different source-detector distances. The subtraction was performed based on the assumption
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11 399 that NIRS signals is primarily originated from skin blood flow when distance between the
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13 400 source and the detector were 20 mm. Takahashi et al. suggested that NIRS signals primarily
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16 401 reflect skin blood flow even when distance between optodes were 30 mm (Takahashi et al.
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18 402 2011). Furthermore, we observed that oxy-Hb detected at channel 1 was significantly
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21 403 correlated with skin blood flow ($r = 0.61$, $P = 0.007$), suggesting that NIRS signals are affected
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23 404 by skin blood flow in the present study. Hence, we expected that subtraction reduced the effects
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26 405 of near-surface blood flow. Nevertheless, we have to admit that further evaluation using the
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29 406 state-of-the-art method (e.g. Yucel et al. 2015) is needed to understand how exhaustive exercise
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31 407 alters cerebral oxygenation.
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34 408 Finally, the present study was not a randomized cross-over study and number of participants
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36 409 was not equal, which may limit the impact of the study. Given that psychological as well as
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39 410 physiological factors determine endurance performance (e.g. attentional strategies, Bertollo et
40
41 411 al. 2015), further studies are required to examine the effects of exhaustive exercise on cognitive
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44 412 performance in a randomized cross-over design.
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49 414 **Conclusion**

51 415 We examined executive function after exhaustive exercise and attempted to identify
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54 416 physiological factors that determine executive function. The present results indicate that
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57 417 recovery of prefrontal oxygenation affects cognitive function after exhaustive exercise. In
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59 418 many sports, players are required to make decisions quickly and accurately even after
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1 419 exhaustive intermittent exercise. The present findings suggest that quick recovery of cerebral
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3 420 oxygenation may play a key role in cognitive performance in such a situation. In the present
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6 421 study, we focused on how physiological factors affect executive function. However, the effects
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8 422 of exhaustive exercise are multifaceted. Multimodal and multidisciplinary perspective is
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10
11 423 necessary to understand the issue. In addition to measurements used in the present study,
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13 424 integration and contribution of different systems should be further investigated.
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16 425
17
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19
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24 428
25
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29 430
30
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33 432 cognitive function.
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41 435 accordance with the ethical standards of the institutional and/or national research committee
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43 436 and with the 1964 Helsinki declaration and its later amendments or comparable ethical
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45 437 standards.”
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49 438 50 51 439 **Figure Legends** 52

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56 441 **Figure 1:** Spatial delayed response (Spatial DR) task and Go/No-Go task. At the beginning of
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58 442 the Spatial DR task, a visual cue was presented at one of the eight locations. The participants
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1 443 remembered the location during the Go/No-Go task. After the Go/No-Go task, participants
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3 444 responded by pressing the button of the ten-key corresponding to the remembered location. In
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6 445 this case, participants had to press the number 6.

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11 447 Figure 2: Reaction time (A) and number of error trials in the Go/No-Go (B) and Spatial DR
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13 448 tasks (C) in the Exercise and Control groups.

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18 450 Figure 3: An example of alterations in cerebral oxygenation (A) and skin blood flow (B).
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21 451 Black bars show the duration of the cognitive task. Gray bars show the duration of the
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23 452 incremental exercise. Horizontal dashed lines indicate the respective baselines. Note that data
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26 453 were resampled for clarification.

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31 455 Figure 4: Relationship between Δ cerebral oxygenation and Δ RT (A) and between Δ adrenaline
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33 456 and Δ RT (B).

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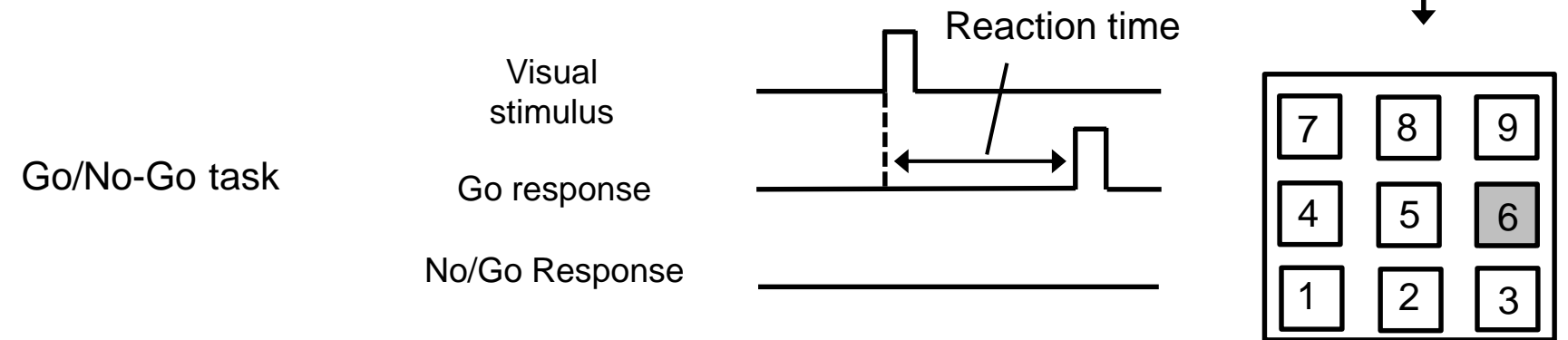
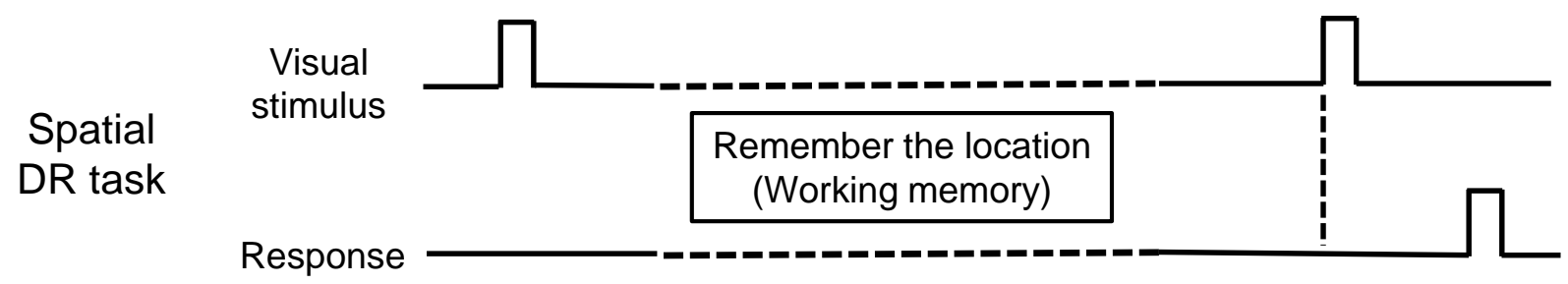
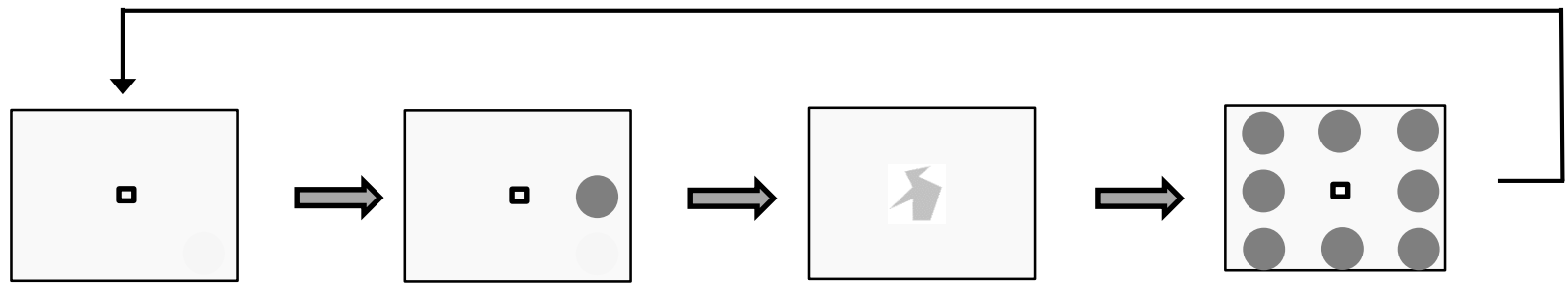
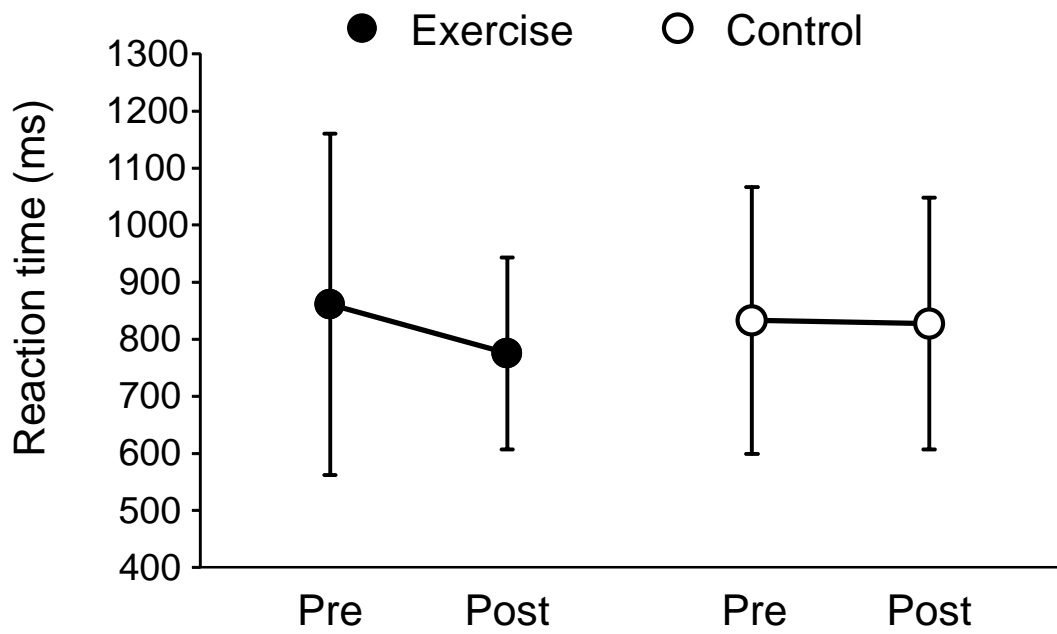
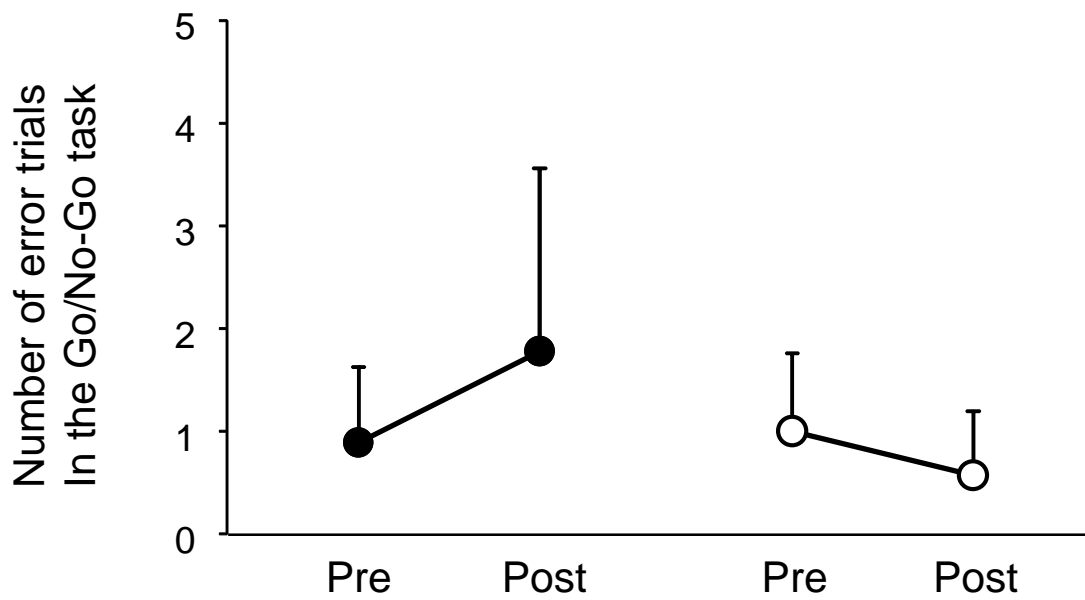


Figure 2

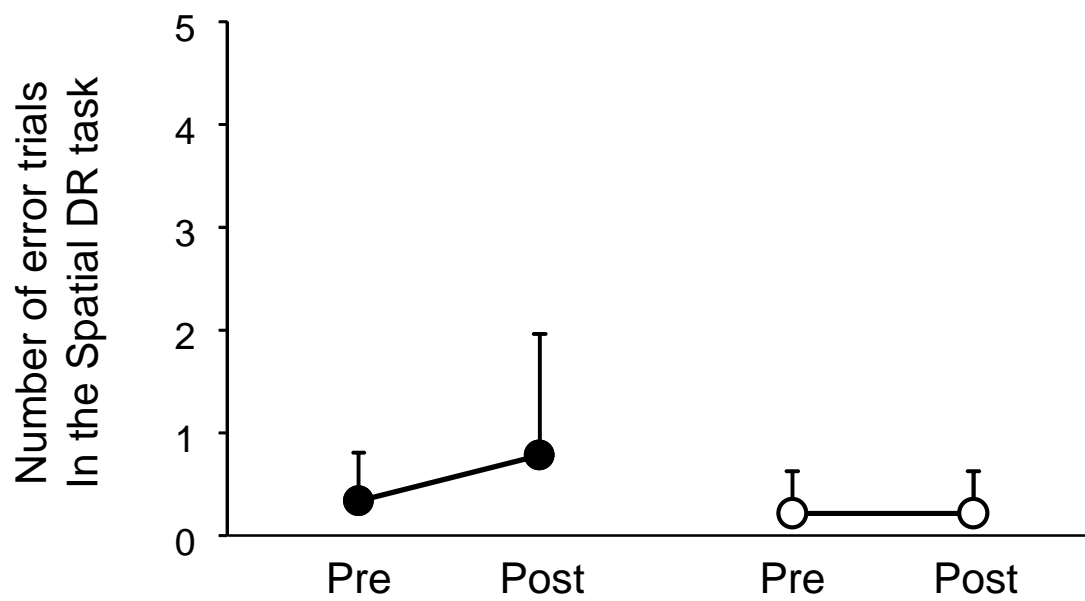
A



B



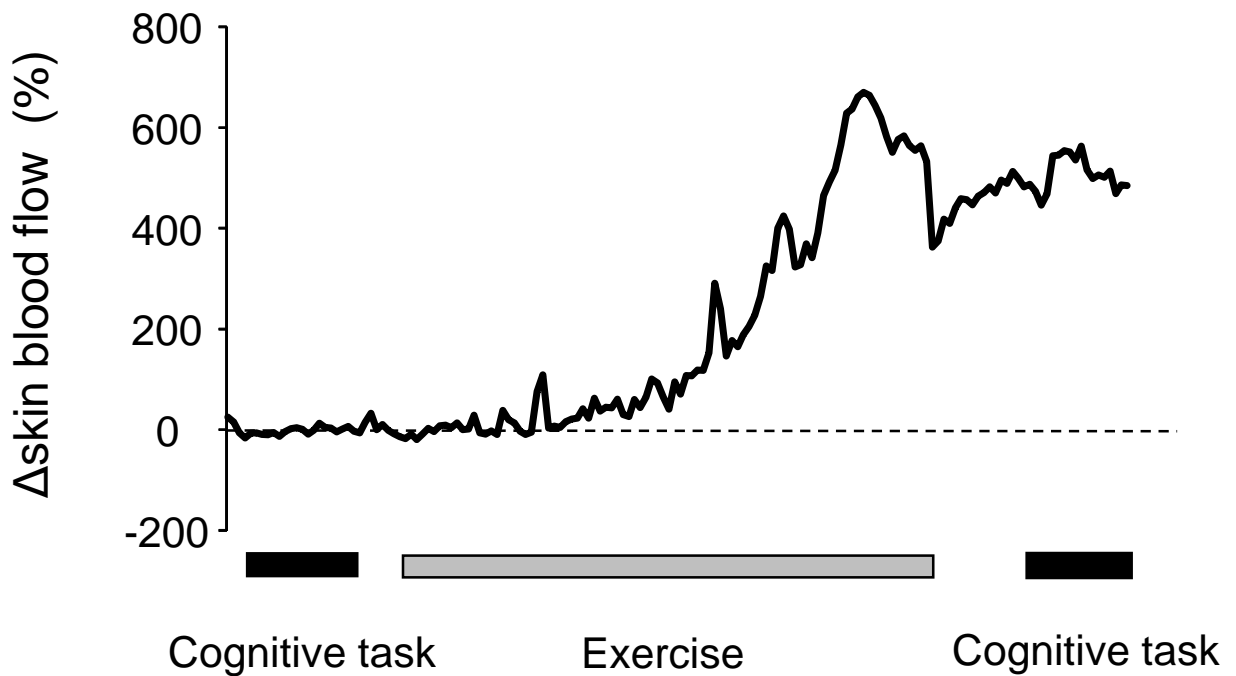
C



A



B



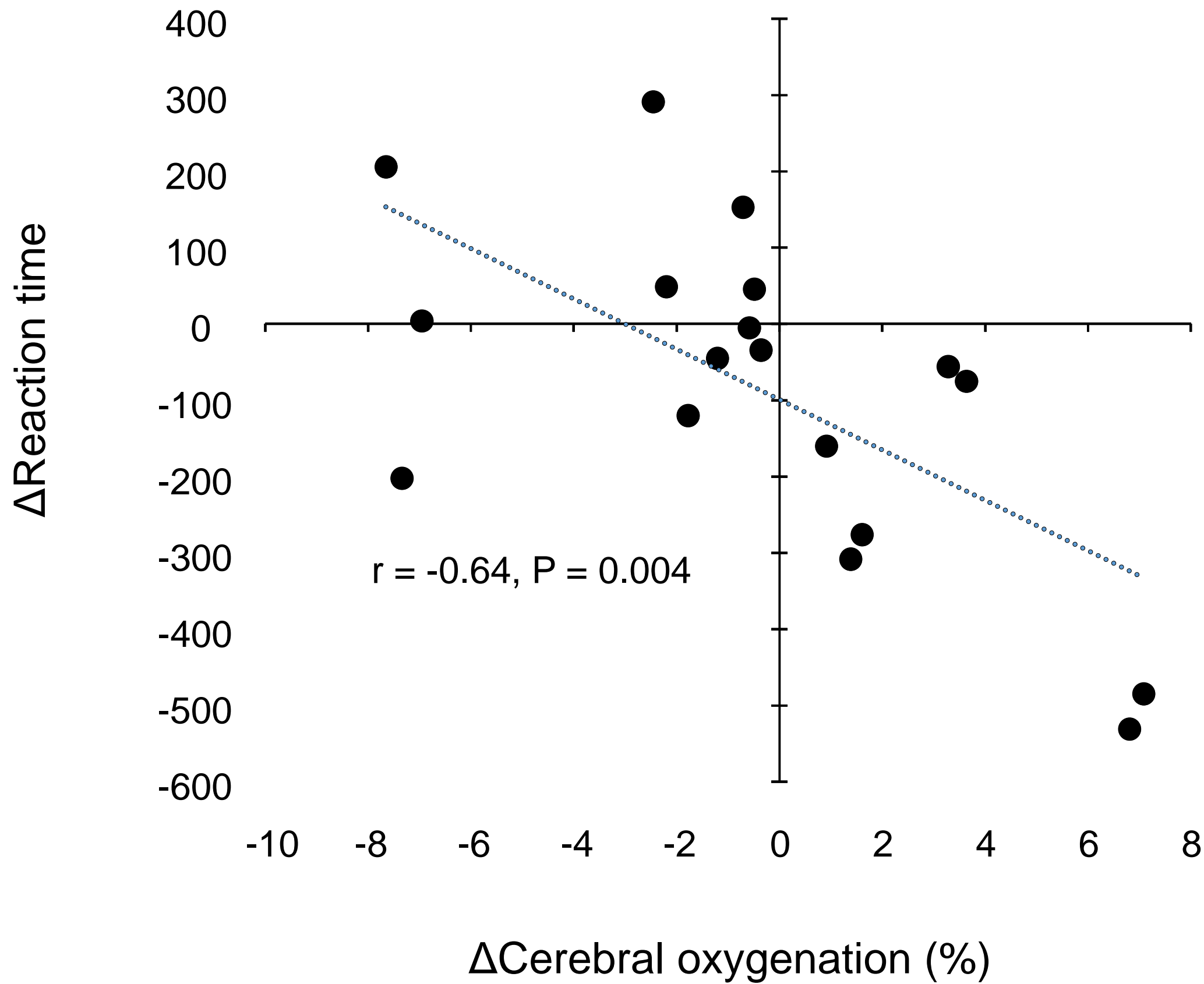


Table 1. Physiological parameters in the Exercise and Control groups.

Variable	Exercise group		Control group		P value		
	Pre	Post	Pre	Post	Main effect		Interaction
					Group	Time	
Oxy-Hb. a.u.	0.02 ± 0.08	0.01 ± 0.18	-0.02 ± 0.13	0.00 ± 0.14	P = 0.52	P = 0.70	P = 0.69
Deoxy-Hb, a.u.	-0.06 ± 0.07	-0.05 ± 0.16	-0.06 ± 0.12	-0.01 ± 0.13	P = 0.56	P = 0.15	P = 0.32
Total-Hb, a.u.	-0.05 ± 0.14	-0.04 ± 0.30	-0.08 ± 0.25	-0.01 ± 0.27	P = 0.97	P = 0.33	P = 0.44
Cerebral oxygenation, %	2.06 ± 1.61	1.53 ± 4.21	1.62 ± 1.80	0.22 ± 2.08	P = 0.25	P = 0.13	P = 0.49
Skin blood flow, %	3.9 ± 13.5	97.5 ± 112.84 **	6.8 ± 16.8	2.9 ± 18.6	P = 0.006	P = 0.007	P = 0.003
Adrenaline, pg/ml	50 ± 24	166 ± 209 *	69 ± 41	51 ± 28	P < 0.001	P = 0.09	P = 0.02
Noradrenaline, pg/ml	426 ± 156	1333 ± 489 ****	305 ± 98	344 ± 70	P < 0.001	P < 0.001	P < 0.001
Dopamine, pg/ml	9 ± 3	39 ± 16 ****	8 ± 2	8 ± 2	P < 0.001	P < 0.001	P < 0.001
BDNF, pg/ml	26906 ± 7133	24556 ± 7101	24649 ± 6001	22263 ± 6020	P = 0.37	P = 0.14	P = 0.99
IGF-1, ng/ml	186 ± 42	204 ± 45 ****	192 ± 51	197 ± 50	P = 0.97	P < 0.001	P = 0.03
Blood lactate concentration, mmol/l	1.0 ± 0.3	9.1 ± 2.2 ****	0.9 ± 0.2	0.9 ± 0.2	P < 0.001	P < 0.001	P < 0.001
RPE	6.8 ± 1.0	18.3 ± 1.6 ****	6.9 ± 1.9	7.3 ± 2.1	P < 0.001	P < 0.001	P < 0.001
SBP, mmHg	123 ± 9	121 ± 11	123 ± 7	123 ± 12	P = 0.67	P = 0.43	P = 0.53
DBP, mmHg	72 ± 7	67 ± 9 *	73 ± 5	74 ± 7	P = 0.13	P = 0.14	P = 0.03

Values are mean ± SD. ****p < 0.001, **p < 0.01, *p < 0.05, vs. Pre.

Table 2 Correlation coefficient between cognitive performance and physiological parameters.

Variable	Exercise group			Control group		
	Δ RT	Δ Number of error trials		Δ RT	Δ Number of error trials	
		GNG task	Spatial DR task		GNG task	Spatial DR task
Δ Oxy-Hb	-0.25	-0.19	-0.26	-0.11	0.12	0.50
Δ Deoxy-Hb	0.34	-0.02	-0.24	-0.12	0.06	0.40
Δ Total-Hb	0.01	-0.13	-0.29	-0.12	0.11	0.56
Δ Skin blood flow	-0.08	-0.36	0.05	0.00	-0.07	0.27
Δ Cerebral oxygenation	-0.64 *	-0.05	0.23	0.14	0.04	-0.20
Δ BDNF	0.08	0.22	-0.42	-0.23	-0.02	0.02
Δ IGF-1	0.34	-0.09	-0.07	0.29	0.23	-0.03
Δ Blood lactate concentration	-0.20	-0.06	0.05	0.26	0.39	0.32
Δ RPE	-0.31	0.41	0.30	-0.11	-0.14	0.00
Δ Adrenaline	0.35	0.04	-0.20	0.24	0.05	0.30
Δ Noradrenaline	0.24	-0.38	-0.33	0.17	-0.01	0.07
Δ Dopamine	0.43	-0.50	-0.40	0.10	0.29	0.50

*significant after false discovery rate correction.