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Abstract

Introduction: An increased perception of effort and subjective fatigue are thought to be central to decreased exercise performance observed following disrupted sleep. However, there is limited understanding of the mechanisms which underpin these phenomena. We investigated the role of interleukin-6 (IL-6), the soluble interleukin-6 receptor (sIL-6R)) and neuroendocrine factors (cortisol, adrenaline, noradrenaline and brain derived neurotropic factor (BDNF)) in mediating these responses at rest and during exercise. **Methods:** In a randomized order ten healthy active males completed 3 experimental trials following different sleep conditions; a single night of sleep deprivation (DEP), partial sleep deprivation equivalent to 4-hrs of sleep (PART) and normal sleep (CON). The experimental sessions consisted of physiological and perceptual measurements of exercise intensity throughout 45-min moderate intensity and 15-min maximal effort cycling. Cytokine and neuroendocrine factors were assessed at rest and in response to exercise. **Results:** Sleep deprivation resulted in increased resting IL-6, lower blood glucose, increased perceived fatigue and perception of effort, lower free-living energy expenditure, and reduced maximal exercise performance. In contrast, sleep deprivation did not alter physiological, cytokine or neuroendocrine responses to exercise. Variations in the resting concentration of IL-6 were associated with lowered blood glucose, an increased perception of effort, and impaired exercise performance. Resting concentrations of cortisol, adrenaline, noradrenaline, and BDNF showed subtle interactions with specific aspects of mood status, and performance but were not impacted by sleep deprivation. There were minimal effects of partial sleep deprivation. **Conclusions:** These findings demonstrate that cytokine and neuroendocrine responses to exercise are not altered by sleep deprivation but that changes in the resting concentration of IL-6 may play a role in altered perception of effort in this context.

Key Words: Sleep deprivation; fatigue; mood; exercise; BDNF; IL-6

1. Introduction

It is widely recognised that poor sleep can have a negative impact upon a wide array of psychological and physiological functions (1). Numerous studies have also investigated the impact of acute sleep deprivation on physical performance, and while there is a broad consensus that physiological responses to exercise remain largely unchanged, an elevation in rate of perceived exertion (RPE) is thought to be a crucial factor mediating impaired exercise performance (2). Interestingly, there is evidence that increased perception of task difficulty is a major factor in impaired performance of not only physical (3) but also cognitive tasks (4), and yet the underpinning biological mechanisms involved in these phenomena remain poorly understood. An improved understanding of the mechanisms involved in these processes may lead to improved management of or countermeasures to the negative effects of poor sleep.

There is a growing interest in the role of cytokines and neuroendocrine signalling factors (e.g. cortisol, adrenaline, noradrenaline and brain derived neurotrophic factor (BDNF)) and their relationship to changes in mood and sensation of fatigue (5). Mechanistic studies are often difficult in humans, yet there is good evidence that at least some of these signalling factors can readily cross the blood brain barrier and that even a small change in the circulating concentration can have signalling effects within the brain (6). Indeed, recent evidence suggests that the circulating concentration of BDNF is positively related to mood and cognition (7), while a negative relationship has been observed between IL-6 and mood (8). This is particularly important given that impaired mood status and wellbeing are some of the most consistently reported psychological effects of sleep deprivation (9,10), and it is plausible that impairments in

athletic performance may be mediated in part by alterations in mood brought about by changes in cytokine or neuroendocrine signalling.

Recent evidence has also documented a relationship between IL-6 and BDNF following disrupted sleep (11,12). Reports of lower circulating concentrations of BDNF are primarily from epidemiological studies and could therefore be confounded by other factors (e.g. diet or levels of physical activity) (11). Previous well conducted studies have shown that sleep deprivation can cause an elevation in IL-6 in response to acute sleep deprivation (12), however, there is limited study of sIL-6R in this context. The effects of IL-6 on the brain likely extend beyond mood and may impact upon the sensation of fatigue which could have important consequences for exercise performance (13). This may be important considering that recent evidence suggests that some of the fatigue inducing effects of IL-6 may be related to ‘trans-signalling’ through sIL-6R (14).

Our group recently provided novel evidence that aspects of interleukin-6 ‘trans-signalling’ through the soluble IL-6 receptor (sIL-6R) was related to measures of sleep, mood and perception of fatigue in elite athletes during a prolonged training period (15). However, this study only examined resting measures and was limited in terms of the breadth of the analysis. In fact, the majority of studies have focussed on resting concentrations of cytokine and neuroendocrine responses following sleep deprivation, while there is considerably less research assessing partial sleep deprivation which may be more similar what is experienced in the real world. Further to this very few studies have investigated any potential divergent responses to exercise. Therefore, the aim of the current study was to (a) characterise the effects of partial and complete sleep deprivation on selected cytokine and neuroendocrine responses both at rest and in

response to exercise and (b) to investigate their relationship with subjective fatigue and effort perception.

2. Methods

Prior to commencement of the study the University Health Sciences Research Ethics Committee granted ethical approval (project code SH16170020-R) for all methods and ensured that the study conformed to the declaration of Helsinki. All participants gave written informed consent to participate in the study.

2.1. Participants

Participants comprised of ten recreationally active males. Their age, height, weight and $\text{VO}_{2\text{max}}$ were as follows (mean \pm SD): 27 ± 6 years, 182 ± 8 cm, 88 ± 8 kg, 43 ± 7 ml.kg.min⁻¹. As part of the screening procedures participants completed in departmental health screening and physical activity questionnaires and the Pittsburgh Sleep Quality Index (PSQI) (16). In order to take part in the study, participants needed to declare themselves free from injury and illness for a minimum of 2 weeks prior to commencement of the study and be identified as having normal sleep pattern based upon a Global PSQI score <5 (16). Participants were required to not be taking any medication known to interfere with normal inflammatory responses (e.g. NSAIDs etc).

2.2. Study design

This study comprised a randomised, repeated measures crossover design. Participants completed preliminary testing in order to ascertain a measurement of aerobic fitness ($\text{VO}_{2\text{max}}$) and were

provided with an actigraph, (Actiheart, Version 2.2, CamNTEch Ltd., Cambridge, UK) which was worn throughout the study and used to assess sleep and activity patterns throughout the study. Energy expenditure was calculated for the 24-hr period before each test session, the 12-hrs on the same day of each test session and in the 24-hr period the day following each test in order to assess activity patterns before and after each condition. In these conditions energy expenditure was measured using an actiheart which integrates accelerometer and heart rate (17).

Participants also completed a sleep diary, estimating the quality of their sleep on a 5-point scale, and the time at which they went to sleep and awoke the day prior to each test session. Following at least 3 days rest, participants completed 3 further experimental trials with manipulated sleep routines in a randomised and counterbalanced order with a further 7 days between each subsequent experimental trial. In order to account for the known effects of time of day on hypothalamic pituitary adrenal (HPA) axis, sympathetic nervous system (SNS), mood and inflammatory signalling, experimental test sessions were completed at the same time of day on each occasion (between 7:00-9:00am). The experimental trials consisted of a control condition (CON), partial sleep deprivation (PART) and a night of no sleep (DEP) which was equivalent to 24-hrs of sleep deprivation. Prior to CON, participants obtained a normal nights sleep (7-9 hrs) in their own bed. For PART and DEP, participants arrived at the laboratory the evening prior to testing and remained under the supervision of the researchers until testing was completed the following day. For PART, participants were allowed a 4-hr sleep opportunity in a prepared bedroom, commencing at their normal bedtime and were then awoken 4-hr later. Once awake, participants remained under the supervision of the researchers at all times, in order to ensure that participants remained awake throughout the trial. Participants carried out sedentary activities

such as, watching films, reading and talking to the researchers. Throughout this period participants were permitted to drink water *ad libitum*, but were instructed to abstain from food for 12-hrs prior to the commencement of each test session and to replicate their diet in between conditions.

During each experimental trial (detailed below) participants initially completed questionnaires for the assessments of mood states and a sleep diary. Following a brief rest, participants then completed an aerobic exercise bout comprising 45-min of standardised submaximal exercise, immediately followed by 15-min self-paced maximal effort time-trial where participants were encouraged to cycle as far as possible. Blood samples were taken at rest, at the end of the submaximal exercise, immediately following the completion of maximal exercise and following 30 minutes of recovery. Blood samples were then later used for the assessment of circulating concentrations of specific cytokines and immune-endocrine markers. A schematic representation of the experimental testing is provided in figure 1.

xxx Insert Figure 1 here xxx

2.3. Preliminary Testing

Participants completed an incremental exercise test on an electromagnetically braked cycle ergometer (Lode Excalibur, Groningen, Netherlands). Expired gases were continuously measured using an online gas analysis system (Cortex Biophysik Metalyzer, Germany), while heart rate (HR) was measured via a short-range telemetric HR monitor (RS400, Polar Electro, Finland). The protocol consisted of 3-min stages, starting at 100W and increased incrementally

by 30W each stage, until volitional exhaustion. Participants were instructed to maintain a pedal cadence of 80 rpm throughout the test. Maximal oxygen uptake ($\text{VO}_{2\text{max}}$) was recorded as the highest 30-s period of oxygen consumption. Oxygen consumption values obtained throughout each participant's test were used to plot a linear regression of power output versus oxygen consumption and the resultant equation was then used to determine standardised power outputs for subsequent test sessions. Following the maximal test participants were then familiarised with tests to be conducted in subsequent sessions.

2.4. Experimental procedures

2.4.1. Subjective fatigue and mood states

Participants completed a modified and shortened version of the profile of mood states (POMS) questionnaire (18) to assess their subjective level of fatigue and mood status. Participants scored themselves on a 1-5 scale in the following categories: tense, miserable, angry, lively fatigued and confused. Prior to completing the questionnaire, participants were provided with a full explanation of each question. Questionnaires of this type have been shown to be reliable and valid for assessing fatigue in sporting contexts (19).

2.4.2. Aerobic exercise session

The aerobic exercise session consisted of a 45-min of submaximal cycling at a constant power output equivalent to 60% of the individuals $\text{VO}_{2\text{max}}$. This was immediately proceeded by a 15-min maximal effort self-paced time-trial, whereby participants were instructed to cycle as far as possible in the given time. This allowed for the comparison of physiological and biochemical responses to both standardised submaximal exercise and maximal exercise within the same

experimental protocol. Distance travelled was calculated and expressed as a percentage of the distance that individual achieved in the control condition. Respiratory gases and HR were measured continuously throughout each trial and expressed as a percentage of individual's maximum value measured during the maximal incremental test. Every 5-min RPE (20), blood lactate and glucose were measured. Lactate and glucose were measured using an automated benchtop analyser (Biosen C-Line Clinic, EKF-diagnostic GmbH, Barleben, Germany) from capillary blood samples, obtained in the final 30-s of each 5-min period.

2.5. Blood collection and analysis

A cannula (Becton, Dickson & Company, Oxford, UK) was inserted into the antecubital vein of the arm. Whole blood (10 mL per time point) samples were collected into K₃EDTA vacutainers (Greiner Bio-one; Frickenhausen, Germany) at rest (PRE), in the final 3-min of the submaximal portion of the exercise trial (DUR), at cessation of the maximal exercise (POST) and 30-min into recovery (30 MIN). Samples were then centrifuged at 4 °C, 3000 g for 10-min and the resultant plasma was separated into aliquots and stored at -80 °C, until subsequent analysis. Commercially available ELISA kits (Biotechne, Abingdon, UK) were used to quantify the concentration of IL-6, sIL-6R, cortisol, BDNF, adrenaline and noradrenaline. All samples were analysed in duplicate and the manufacturer's instructions were adhered to at all times. In order to produce concentrations that were within the dynamic range of each assay, plasma samples were diluted with a commercially available diluent (DY997, R&D Systems Ltd) prior to analysis of sIL-6R (1:100), cortisol, BDNF, adrenaline and noradrenaline (all 1:20). To minimise variation between assays, all samples from an individual participant were analysed in the same assay. In our hands the intra-assay coefficient of variation (CV) for these assays were as follows: IL-6- 4.1

$\pm 2.6\%$, sIL-6R- $2.1 \pm 1.8\%$, cortisol- $6.4 \pm 4.7\%$, BDNF- $3.2 \pm 2.2\%$, adrenaline- $4.0 \pm 2.5\%$ and noradrenaline- $4.0 \pm 4.1\%$. The concentration of each analyte was determined in relation to a 4-parameter standard curve (GraphPad Prism, San Diego, Calif., USA) and were corrected for changes in plasma volume based upon established criteria (21).

2.6. Statistical Analysis

The Shapiro Wilk test was used to test for normality in scale data. For resting and summary data, one-way repeated measures ANOVAs or non-parametric Friedman test were used where appropriate. A two-way repeated measures ANOVA (sleep condition x time) was used to assess the effect of sleep condition on the exercise induced responses for IL-6, sIL-6R, cortisol, BDNF, adrenaline and noradrenaline. When data was non-normally distributed, log-transformations were performed prior to analysis and the respective data was then back transformed for ease of presentation in figures. When main effects were identified, post-hoc analysis was performed using simple pairwise comparisons with Bonferroni adjustment or Dunn's test where appropriate. Pearson correlation and Spearman rank were used to assess the relationship between parametric and non-parametric data respectively. Effect sizes for main effects are presented as η^2 (η^2). Statistical analyses were undertaken using GraphPad Prism and SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). All data are presented as mean \pm standard deviation unless otherwise stated and statistical significance was set at $p < 0.05$.

3. Results

3.1. Sleep and energy expenditure

Participants reported sleeping significantly more (467 ± 42 min) for CON than PART (217.5 ± 21 min) and DEP (0 ± 0) respectively ($F=674.9$, $P<0.001$, $\eta^2=0.98$), with participants falling asleep later prior to PART than CON ($P=0.039$, mean difference 19 min, 95% CI 0.9 to -38 min). Sleep quality was significantly better for CON (3.3 ± 0.8) than PART (2.60 ± 0.7) and DEP (0 ± 0) ($F=98.35$, $P<0.001$, $\eta^2=0.92$). There was no significant difference in total energy expenditure in the 24-hrs before the test (CON= 2533 Kcal vs PART= 2542 Kcal vs CON 2761, $P>0.05$). Energy expenditure in the 12-hrs following the experimental trials showed a main effect of condition ($F=5.2$, $P=0.018$, $\eta^2=0.39$), and was significantly lower in DEP than CON (mean differences -208 Kcal, 95% CI (CI) -404 to -13 Kcal) and PART (mean difference -200 Kcal, -396 to -5 Kcal). But were not significantly different in the 24-hr period the day following each trial (CON= 2681 ± 361 Kcal, PART= 2697 ± 514 Kcal, DEP= 2547 Kcal).

3.2. Resting measurements

The results of subjective fatigue and mood status following each of the sleep conditions are summarized in Table 1. Participants reported being significantly more miserable ($P=0.006$) and confused ($P=0.019$) following DEP than CON, while also feeling less lively ($P=0.019$). Participants reported being significantly more fatigued following PART and DEP than CON ($P=0.001$).

xxx Insert Table 1 here xxx

There were no significant differences in the resting concentration of sIL-6R, cortisol, BDNF, adrenaline or noradrenaline between CON, PART and DEP. There was a significant effect of condition on resting IL-6 ($F=5.6$, $P=0.012$, $\eta^2=0.39$), and blood glucose ($F=4.2$, $P=0.032$, $\eta^2=0.31$) (Fig 2A and 2B respectively). Post-hoc testing revealed significantly higher IL-6 following DEP (0.95 ± 0.37 pg/ml) Vs CON (0.62 ± 0.22 pg/ml), mean difference -0.33 pg/ml (95% CI $-0.59 - 0.06$ pg/ml), and a significant decrease in blood glucose (DEP: 4.2 ± 0.3 Vs CON: 4.6 ± 0.5 mmol/L, mean difference 0.44 mmol/L, 95% CI $0.01 - 0.88$ mmol/L). Correlation analysis revealed a significant negative relationship between resting IL-6 and blood glucose ($P=0.02$, $r=-0.44$, 95% CI -0.7 to -0.07) (See figure 2 for a summary). Subjective fatigue at rest was negatively correlated to the total energy expenditure in the 12-hrs following the exercise ($P=0.01$, $r=-0.46$, 95% CI -0.75 to -0.04). Resting concentrations of IL-6 and sIL-6R were negatively related ($P=0.01$, $r=-0.48$, 95% CI -0.72 to -0.12). Adrenaline was negatively related to subjective perception of fatigue at rest ($P=0.027$, $r=-0.43$, 95% CI -0.7 to -0.06), while noradrenaline was positively related to perceived 'tension' ($P=0.027$, $r=0.49$, 95% CI 0.07 to 0.77). BDNF was negatively related to perceived rating of 'miserableness' ($P=0.02$, $r=-0.46$, 95% CI -0.72 to -0.09), and positively related to perceived 'liveliness' ($P=0.025$, $r=0.44$, 95% CI 0.06 to 0.71).

xxx Insert Figure 2 here xxx

3.3. Physiological and perceptual responses to exercise

Physiological and perceptual responses to exercise are summarised in table 2, while figure 3 provides a graphical demonstration of the differences between key physiological and perceptual

responses to the different sleep conditions. There were no significant differences between any of the physiological responses (mean VO_2 , HR, respiratory exchange ratio (RER) or lactate) between the three experimental conditions during the 45-min constant load portion of the exercise, while perception of effort (as measured by mean RPE) was significantly higher in DEP (13.4 ± 1.9) than CON (11.8 ± 1.6) ($P=0.03$).

Physiological responses to maximal exercise were significantly different between CON and DEP. There was a main effect of condition on mean VO_2 ($F=3.3$, $P=0.038$, $\eta^2=0.3$), which was significantly higher following CON ($85.4 \pm 5.5\%$) than DEP ($78.5 \pm 11.4\%$), mean difference 7.7% (95% CI 0.3 - 14.9%). Similarly, there was a main effect of condition on distance travelled ($F=4.1$, $P=0.026$, $\eta^2=0.23$), with significantly less distance travelled in DEP than CON (mean difference 11.4%, 95% CI 1.2 to 21.6 %) (Fig 3C). Mean RPE during submaximal exercise was positively related to subjective fatigue at rest ($P<0.001$, $r=0.63$, 95% CI 0.33 - 0.81) and negatively related to the mean VO_2 achieved during the maximal exercise ($P=0.03$, $r=-0.39$, 95% CI -0.66 to -0.04), and distance travelled ($P=0.006$, $r=-0.49$, 95% CI -0.72 to -0.16). Subjective fatigue at rest was negatively related to mean VO_2 ($P=0.003$, $r=-0.56$, 95% CI -0.77 to -0.22) and the distance travelled during maximal exercise ($P<0.001$, $r=-0.7$, 95% CI -0.86 to -0.44). In contrast, distance travelled during maximal exercise was positively related to feeling of 'liveliness' at rest ($P<0.001$, $r=0.66$, 95% CI 0.37 - 0.83).

There was a main effect of condition on mean HR ($F=5.0$, $P=0.014$, $\eta^2=0.27$), which was significantly higher following CON ($93.2 \pm 2.2\%$) than DEP ($87.7 \pm 6.1\%$), mean difference 5.4% (95% CI 0.9 - 9.8%). There was a main effect of condition on mean RER ($F=6.1$, $P=0.009$,

$\eta^2 = 0.4$), which was significantly higher following CON ($85.4 \pm 5.5\%$) than DEP ($78.5 \pm 11.4\%$), mean difference 7.7% (95% CI 0.3 - 14.9%). There was a main effect of condition on mean blood lactate ($F=3.8$, $P=0.039$, $\eta^2 = 0.3$), which was significantly higher following CON (5.4 ± 0.7 mmol/L) than DEP (4.3 ± 1.5 mmol/L), mean difference 1.1 mmol/L (95% CI 0.05 - 2.1 mmol/L). In contrast to submaximal exercise, there was no effect of condition on mean RPE during the maximal exercise.

xxx Insert Table 2 here xxx

xxx Insert Figure 3 here xxx

3.4. Cytokine and neuroendocrine responses to exercise

Exercise induced changes in plasma concentration of IL-6, sIL-6R, adrenaline, noradrenaline, cortisol and BDNF are reported in Figure 4. For IL-6 there was a main effect of time ($F=84.1$, $P<0.0001$, $\eta^2 = 0.9$), but no effect of condition ($F=1.2$, $P=0.3$, $\eta^2 = 0.05$) (Fig. 4A). IL-6 was significantly elevated immediately following the constant load portion of all exercise trials ($P=0.027$, mean difference 0.17 pg/ml, 95% CI 0.018 - 0.32 pg/ml), continued to increase following the time trial ($P<0.0001$, mean difference 0.40 pg/ml, 95% CI 0.032 - 0.49 pg/ml), and remained elevated 30-min after cessation of the exercise. IL-6 concentration at rest was positively correlated with the mean RPE during the constant load portion of the exercise ($P=0.03$, $r=0.4$, 95% CI 0.04 - 0.67), but was negatively related to the mean VO_2 achieved during maximal exercise ($P=0.029$, $r=-0.41$, 95% CI -0.67 to -0.05) and distance travelled during maximal

exercise ($P=0.035$, $r=-0.39$, 95% CI -0.66 to -0.01). In contrast distance cycled was positively related to post exercise adrenaline concentration ($P=0.038$, $r=0.39$, 95% CI 0.023 - 0.66).

The change in IL-6 from CON accounted for 25% of the variance in the mean VO_2 achieved during maximal exercise and 22% of the distance cycled. sIL-6R showed a main effect of time ($F=5.8$, $P=0.005$, $\eta^2=0.46$), with no main effect of condition ($F=1.6$, $P=0.23$, $\eta^2=0.19$). There was a trend for elevated sIL-6R following the time-trial and 30-min into recovery, however neither reached statistical significance ($P=0.11$ and $P=0.08$ respectively) (Fig 4B). sIL-6R concentration at rest was negatively correlated with the mean RPE during the constant load portion of the exercise ($P=0.009$, $r=-0.49$, 95% CI -0.73 to -0.14). Adrenaline showed a significant main effect of time ($F=14.9$, $P<0.0001$, $\eta^2=0.15$), with no main effect of condition ($F=0.4$, $P=0.67$, $\eta^2=0.03$) (Fig.4C). Adrenaline was significantly increased at each time point compared to rest, peaking immediately post the time-trial ($P=0.001$, mean difference 0.72 ng/ml, 95% CI 0.4 - 1.0 ng/ml). Noradrenaline showed a significant main effect of time ($F=30.7$, $P<0.0001$, $\eta^2=0.39$), with no main effect of condition ($F=0.6$, $P=0.5$, $\eta^2=0.01$) (Fig 4D). Post-hoc tests revealed noradrenaline was increased from rest at each time point, peaking immediately post time-trial ($P<0.0001$, mean difference 2.2 ng/ml, 95% CI 1.5 - 2.8 ng/ml). The resting concentration of noradrenaline was negatively correlated with the mean RPE during the constant load portion of the exercise ($P=0.04$, $r=-0.46$, 95% CI -0.75 to -0.02). BDNF showed a significant main effect of time ($F=23.2$, $P<0.0001$, $\eta^2=0.22$), with no effect of condition ($F=0.02$, $P=0.98$, $\eta^2=0.008$). BDNF was significantly elevated at each time point post exercise, peaking immediately post time-trial ($P=0.002$, mean difference 3090 pg/ml, 95% CI 1210 - 4970 pg/ml). Cortisol displayed significant main effects of time ($F=6.2$, $P=0.002$, $\eta^2=0.41$) and

condition ($F=3.8$, $P=0.04$, $\eta^2=0.29$) (Fig 4E). However, following a correction for multiple comparisons there were no clear patterns to the variation of the data. Cortisol concentration at rest was positively correlated with the mean RPE during the constant load portion of the exercise ($P=0.002$, $r=0.56$, 95% CI 0.24 - 0.77).

xxx Insert Figure 4 here xxx

4. Discussion

This study investigated the role of selected cytokine and neuroendocrine factors in altered physiological and perceptual responses to exercise following partial and complete sleep deprivation. A single night of sleep deprivation led to an increased perception of fatigue, impaired maximal exercise performance, decreased blood glucose, elevated IL-6 at rest and a reduction in physical activity in the 12-hrs after sleep deprivation. This increase in IL-6 may be mediated in part by altered glucose homeostasis. Neither partial nor complete sleep deprivation altered cytokine or neuroendocrine responses to exercise. However, perception of effort was significantly increased following 24-hrs of sleep deprivation, which was also associated with variations in the resting plasma concentrations of IL-6, sIL-6R, cortisol and noradrenaline. Maximal exercise performance was impaired, likely through an increased perception of effort, which may be mediated in part by an increase in resting IL-6 concentration (Fig 2A). With the exception of subjective fatigue and resting blood glucose, partial sleep deprivation had minimal effects on the responses measured in the current study, however, these findings should not be extrapolated to scenarios of chronic partial sleep deprivation. Taken together these findings

provide novel insights into the mechanisms that may contribute to an increased perception of effort and ultimately impaired exercise performance following sleep deprivation.

In accordance with previous studies, we have demonstrated that perception of effort, but not physiological responses to intensity matched submaximal exercise, were affected by sleep deprivation; and that subsequent maximal aerobic exercise performance was impaired and coincided with significantly lower physiological responses (see Fig 3A) (3,22,23). These responses were also preceded by disruptions in mood and particularly subjective perception of fatigue (Table 1), which have routinely been observed in the context of impaired sleep (9). Interestingly, subjective fatigue prior to exercise and perception of effort during the submaximal exercise were both related to the mean VO_2 and distance cycled during maximal exercise, providing further evidence of their importance in exercise performance. Importantly, sleep deprivation induced elevations in IL-6 were associated with an increased perception of effort during exercise and exercise performance and the mean VO_2 achieved during maximal exercise. Perhaps the most convincing evidence from the current study is that 22% of the variance in performance between conditions was accounted for by the change in resting IL-6 between conditions. Notably, when we examined the IL-6 response to exercise there was no relationship to performance or the detrimental effects of sleep deprivation, this appears to be yet another example of the subtle and context dependent nature of IL-6 signalling. This is a significant result given the highly complex and multifactoral nature of exercise performance. As such, it appears that IL-6 may play a role in impaired exercise performance following sleep deprivation, potentially mediated via an increased perception of effort. Previous studies have shown that sleep deprivation induced increases in IL-6 are associated with an increased

perception of pain (24). Given the link between perception of effort and pain perception, it is highly plausible that the two phenomena may be linked or interact. It is feasible that perceived effort is increased in part by the pain sensitizing effect of IL-6, however this is somewhat speculative and further work is required to investigate the potentially subtle role of IL-6 in mediating these responses. Further to this, we demonstrated that resting blood glucose was lowered following both partial and complete sleep deprivation (Fig 2B), which was positively related to the increase in IL-6 (Fig 2C). Given the established role of IL-6 in glucose metabolism (25), it is highly plausible that alterations in glucose metabolism are partly responsible for the increase in IL-6. The source of the increased plasma IL-6 following sleep deprivation remains poorly understood, however, it is feasible that skeletal muscle may be the source of additional IL-6 in this context given that IL-6 production by skeletal muscle is influenced by muscle glycogen content (26), which has been shown to be reduced following sleep deprivation (27).

With the exception of the aforementioned results for IL-6, the effects of sleep deprivation on sIL-6R and neuroendocrine factors measured in the current study were minimal. Contrary to findings from a recent epidemiological study (11), we found that the plasma concentration of BDNF was not reduced following sleep deprivation, but that lower concentrations of BDNF were related to negative changes in mood. As such, it is possible that sleep deprivation *per se* is not the direct cause of reduced BDNF reported in insomnia sufferers or those with impaired sleep, and it is more likely that the accumulated psychological stress associated with insomnia results in decreased BDNF (7). Sleep deprivation had no discernible impact on sIL-6R, and this finding is interesting considering the extremely limited and somewhat conflicting available evidence regarding the impact of sleep on sIL-6R. Dimitrov and colleagues (28) previously reported that sleep

deprivation abolished the sleep induced increase in sIL-6R, while in a longitudinal setting our group previously reported that sIL-6R was positively related to subjectively reported sleep quality (15). Interestingly, recent evidence suggests that the relationship may be bi-directional in that sleep can also be impacted by IL-6 trans-signalling through sIL-6R mediated responses within the brain (29); this complex interaction warrants further research in those with chronic sleep conditions.

We found a main effect of sleep condition on plasma cortisol which accounted for 29% of the variance in the resting values, with cortisol appearing higher following both partial and complete sleep deprivation (Fig. 4E), however post hoc comparisons were not statistically significant. This appears somewhat reflective of previous studies as the effect of sleep deprivation on cortisol remain largely unclear, with studies having reported no effect (30), increased (31) and decreased (32) plasma cortisol concentration. However, in the current study we observed a positive relationship between resting cortisol concentration and RPE ($r=0.56$), which is very similar to the correlation reported ($r=0.551$) in a previous longitudinal study which assessed the relationship between cortisol and session RPE (33). As such, cortisol responses to sleep deprivation remain unclear, but our results further emphasise the role of cortisol in effort perception.

Similarly, we found no effect of sleep condition on the resting concentration of adrenaline or noradrenaline, which does appear in accordance with the apparent consensus (34). However, resting adrenaline concentration was negatively related to perception of fatigue at rest while post exercise adrenaline concentration was positively related to exercise performance. These findings

would appear in line with the established role of adrenaline in facilitating physical activity, but highlight the importance subjective fatigue in this relationship.

Similarly to IL-6, resting cortisol concentration was positively correlated to perception of effort during exercise. Taken together, it may be that while adrenaline, noradrenaline and cortisol are not impacted by sleep deprivation *per se*, they do play a role in alterations of mood and effort perception during exercise. Further than this, it appears that differences in exercise induced adrenaline concentration also account for some variation in performance. This is important when considering recent evidence that individual differences in anxiety and psychological stress play a role in immune responses to exercise (35). Any interactions between sleep, mood and immune-endocrine responses are likely to be complex and interdependent and future studies should be carefully designed in order to examine potential interactions and investigate the direction of effects.

It is well documented that sleep and physical activity share a bi-directional relationship (36) and can also be involved in development of chronic health conditions such as diabetes or obesity (37). In this regard, we found that free-living energy expenditure was reduced in the 12-hrs after sleep deprivation and was negatively related to the level subjective fatigue reported by participants in the morning prior to exercise. It may be that an increased perception of fatigue, as a result of impaired sleep, may make exercise a less attractive prospect, therefore resulting in reduced levels of physical activity. If repeated this could have important negative consequences for long term health. However, it is important to stress that the current study examined responses to single night sleep deprivation and while this is similar to the quantity of sleep occasionally

experienced by athletes prior to competition (2) or the sleep deprivation experienced by night shift workers (38), it is not necessarily representative of more prolonged sleep deprivation or chronic partial sleep deprivation. Given the increased prevalence of sleep deprivation and physical inactivity in modern society, this is an important finding and highlights the importance of subjective fatigue in the context of physical activity. Physical activity levels were not significantly different in the 24 hr period the day after the trial, suggesting that physical activity levels return to normal following one complete sleep cycle. As such, it is important to emphasise that the current study focused specifically on acute sleep disturbance and that these findings should not be extrapolated to circumstances of chronic partial sleep deprivation, which may indeed be a more common scenario. In this regard, future studies are required to further investigate chronic partial sleep loss.

In the current study, exercise induced changes in cytokine and neuroendocrine factors were largely maintained following partial and complete sleep deprivation. This is important considering that exercise induced changes in IL-6 and BDNF (amongst a range of other factors) appear important for exercise induced adaptations in insulin sensitivity, lipolysis (39,40) and improved cognition and mood status (41). Further to this, there is evidence from animal studies that chronic exercise training can negate the increase in circulating IL-6, which is induced by sleep deprivation (42), suggesting that exercise training may in fact prevent some of the negative effects of sleep deprivation via anti-inflammatory mechanisms. It is also possible that exercise induced elevations in BDNF, may help to mitigate some of the deleterious effects that sleep deprivation can have on mood status and perceived wellbeing. It is important to emphasise that the effects observed in our study are likely multifactorial and highly complex, and as such, there

are undoubtedly a wide range of additional signalling factors which may also contribute to the observed responses. In this regard, we encourage further study in order to further explain variations in perceived fatigue and mood disturbance, as a better mechanistic understanding may well lead to improved management of or countermeasures to sleep deprivation.

In conclusion, the current study shows elevated circulating concentrations of IL-6 at rest appear to play a role in the well-established impairments in mood, perception of effort and exercise performance experienced following sleep deprivation. In contrast, cortisol, adrenaline, noradrenaline and BDNF were not impacted by sleep deprivation but do appear to account for subtle variations in mood and effort perception. Neither partial nor 24-hrs of sleep deprivation impact the cytokine and neuroendocrine responses to exercise measured in this study. Further to this, we found that free-living energy expenditure was reduced following 24-hrs of sleep deprivation and that the level of subjective fatigue at rest explained a significant proportion of the variance. Taken together, these findings highlight the importance of IL-6 in the perception of effort and fatigue, which is an important finding given the increasing prevalence of sleep deprivation and physical inactivity in modern society.

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Conflicts of interest

The authors report no conflicts of interest in this work.

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Figure Legends

Figure 1. A schematic representation of the experimental trial.

Figure 2. Resting concentration of IL-6 (A) and blood glucose (B) following three different sleep conditions. Sleep conditions comprised normal night of 7-9-hrs sleep (CON), to a 4-hr sleep opportunity at the start of the night (PART) and a single night of sleep deprivation (DEP). Correlation between resting IL-6 and blood glucose (C). *= significantly different to CON.

Figure 3. The mean oxygen uptake (A) and perception of effort (B) during 45-min submaximal constant load cycling exercise and a 15-min self-paced maximal effort time-trial following three experimental sleep conditions. Figure (C) depicts the distance travelled in the 15-min self-paced maximal effort time-trial (relative to the distance each person travelled in the control condition). *= a significant difference between CON and DEP. VO_2 , oxygen uptake; RPE, rating of perceived exertion.

Figure 4. Plasma IL-6 (A), sIL-6R (B), adrenaline (C), noradrenaline (D), cortisol (E) and BDNF (F) responses to exercise following three different sleep conditions.

a=significantly different to PRE

b= significantly different to DUR

c= significantly different to POST

d= significantly different to 30 MIN

Figure 1

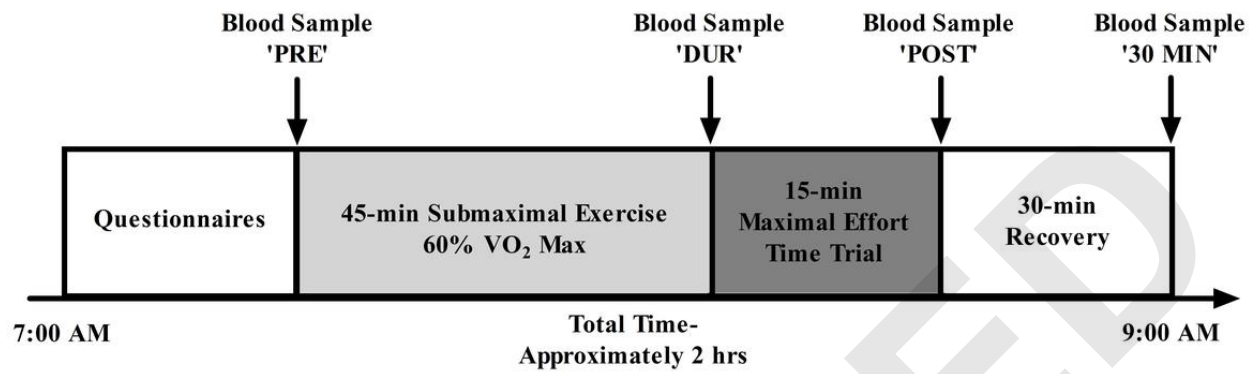


Figure 2

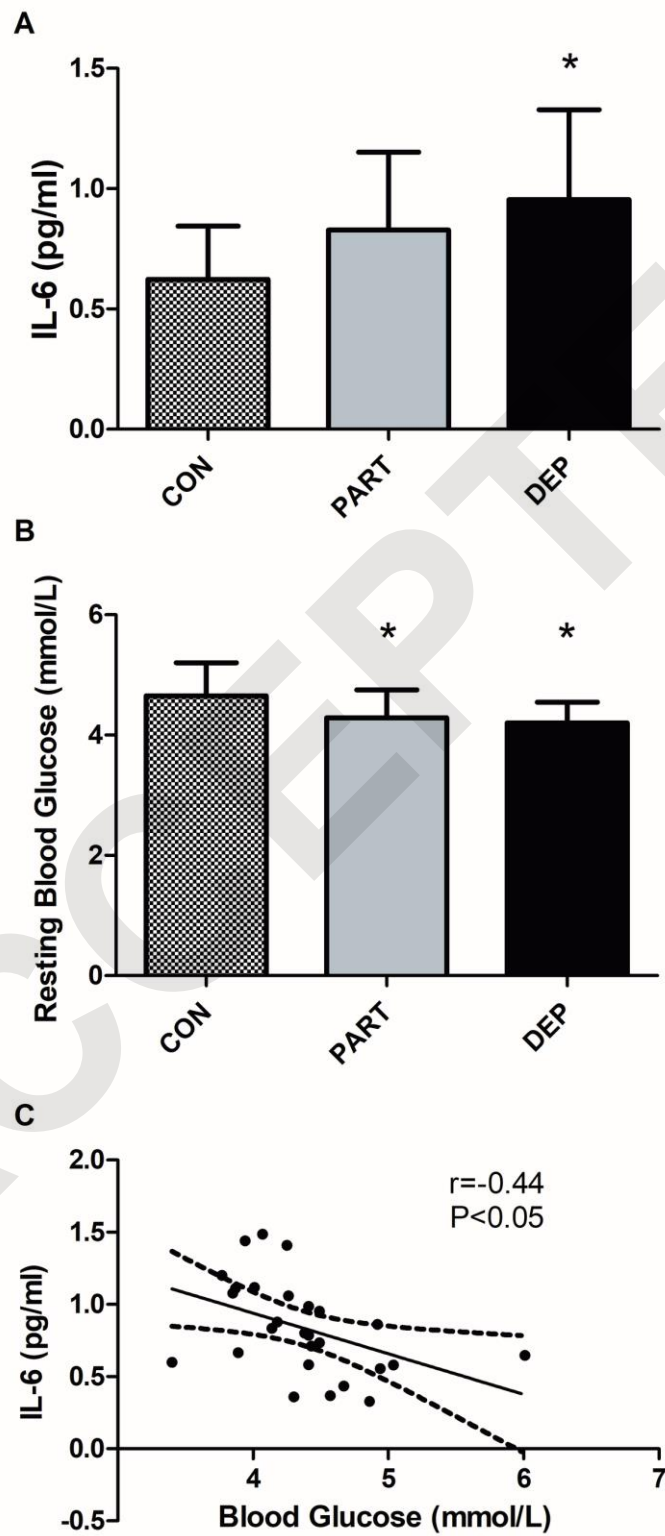


Figure 3

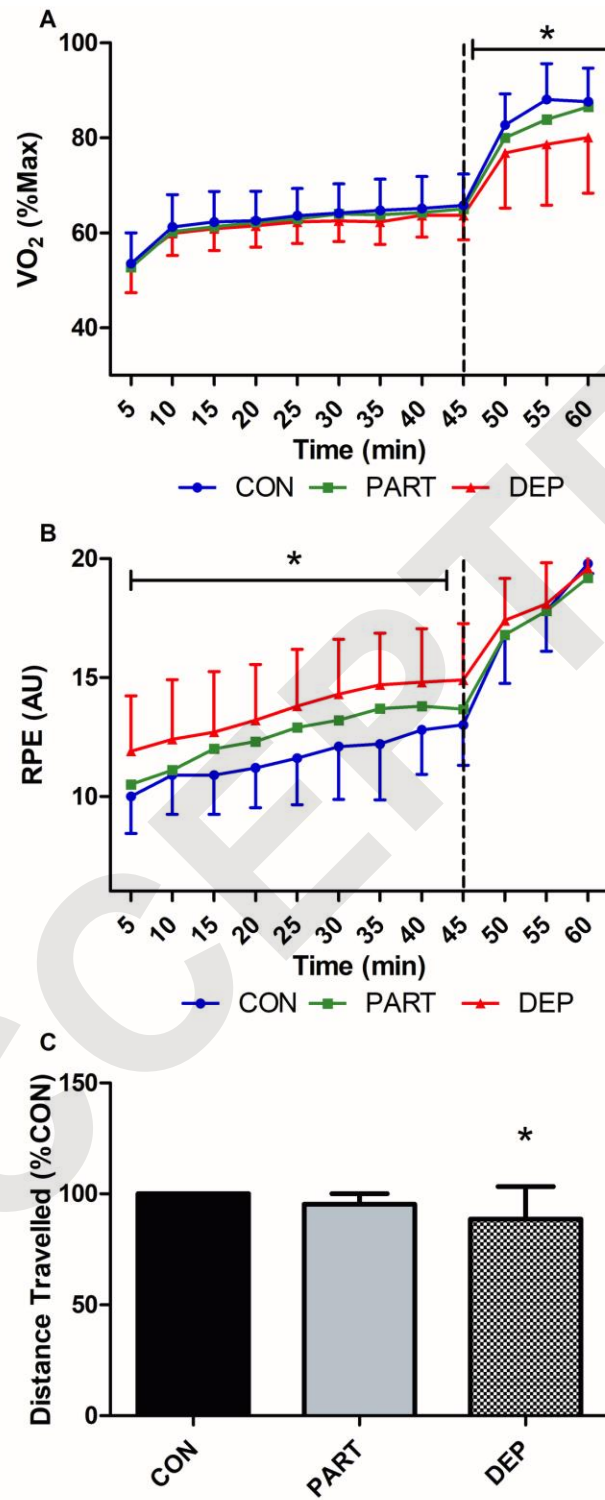


Figure 4

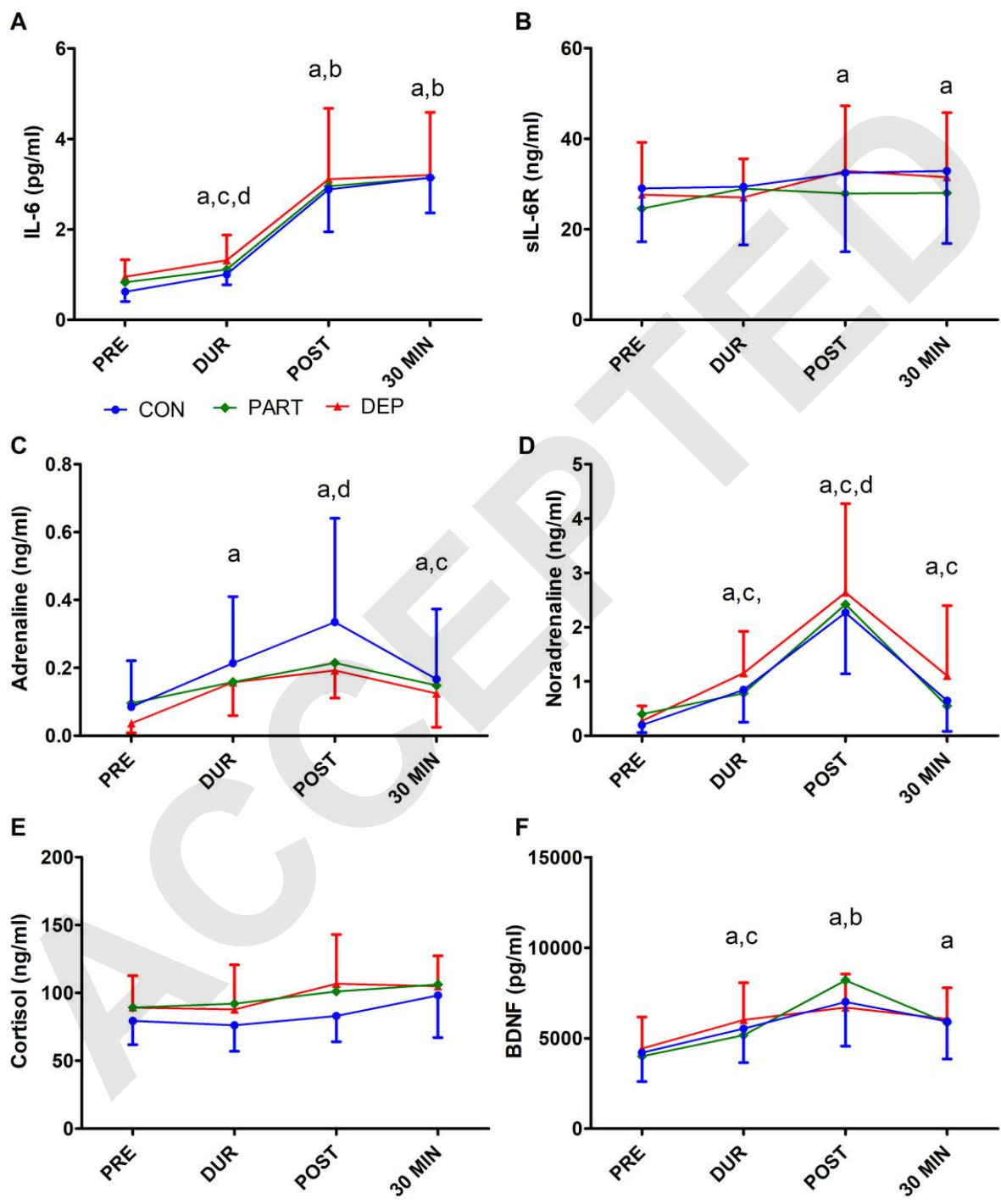


Table 1. Comparisons of fatigue and mood state following the three different sleep conditions.

Sleep conditions comprised normal night of 7-9-hrs sleep (CON), to a 4-hr sleep opportunity at the start of the night (PART) and a single night of sleep deprivation (DEP).

	CON	PART	DEP
Tense	0.7 ± 0.7	1.1 ± 0.9	1.1 ± 0.9
Miserable	0.0 ± 0.0	0.2 ± 0.4	1.1 ± 1.3*
Angry	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.6
Lively	1.9 ± 1.0	1.5 ± 0.7	0.6 ± 0.8*
Fatigued	0.7 ± 0.5	2.0 ± 0.7*	2.7 ± 1.5*
Confused	0.1 ± 0.3	0.5 ± 0.7	1.3 ± 1.6*

*= Significantly different to Control (P<0.05)

Table 2. Summary of physiological and perceptual responses to 45-minute submaximal constant load cycling exercise and a 15-min self-paced maximal effort time-trial following three separate sleep conditions.

Submaximal Exercise	CON	PART	DEP
Mean VO₂ (%Max)	62.5 ± 5.8	61.8 ± 5.7	61.1 ± 4.4
Mean HR (%Max)	73.9 ± 3.8	73.9 ± 3.8	72.5 ± 4.3
Mean RER	0.89 ± 0.03	0.88 ± 0.04	0.87 ± 0.03
Mean Lactate (mmol/L)	2.0 ± 0.7	1.9 ± 0.7	1.8 ± 0.6
Mean RPE (A/U)	11.8 ± 1.6	12.6 ± 0.9	13.4 ± 1.9*
Maximal Exercise			
Mean VO₂ (%Max)	85.4 ± 6.5	83.4 ± 6.2	78.5 ± 11.4*
Mean HR (%Max)	93.2 ± 2.2	91.5 ± 1.8	87.7 ± 6.1*
Mean RER	0.96 ± 0.02	0.95 ± 0.03	0.92 ± 0.05*
Mean Lactate (mmol/L)	5.4 ± 0.7	4.9 ± 1.1	4.3 ± 1.5*
Mean RPE (A/U)	18.1 ± 1.3	17.9 ± 0.9	18.5 ± 1.1

*= Significantly different to Control (P<0.05)

VO₂, oxygen uptake; HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion.