OPEN

Sleep Deprivation: Cytokine and Neuroendocrine Effects on Perception of Effort

TOM CULLEN[1,2], GAVIN THOMAS[2], and ALEX J. WADLEY[3,4]

[1]Centre for Sport Exercise and Life Sciences, Coventry University, Priory Street, Coventry, UNITED KINGDOM; [2]School of Sport and Exercise Science, University of Worcester, Henwick Grove, Worcester, UNITED KINGDOM; [3]National Centre for Sport and Exercise Medicine, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UNITED KINGDOM; and [4]University Hospitals of Leicester NHS Trust, Infirmary Square, Leicester, UNITED KINGDOM

ABSTRACT

CULLEN, T., G. THOMAS, and A. J. WADLEY. Sleep Deprivation: Cytokine and Neuroendocrine Effects on Perception of Effort. *Med. Sci. Sports Exerc.*, Vol. 52, No. 4, pp. 909–918, 2020. **Introduction:** An increased perception of effort and subjective fatigue are thought to be central to decreased exercise performance observed after disrupted sleep. However, there is limited understanding of mechanisms that underpin these phenomena. We investigated the role of interleukin-6 (IL-6), the soluble IL-6 receptor, and neuroendocrine factors (cortisol, adrenaline, noradrenaline, and brain-derived neurotropic factor) in mediating these responses at rest and during exercise. **Methods:** In a randomized order, 10 healthy active men completed three experimental trials following different sleep conditions: a single night of sleep deprivation, partial sleep deprivation equivalent to 4 h of sleep, and normal sleep. 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 BNDF showed subtle interactions with specific aspects of mood status and performance but were not affected 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

It is widely recognized that poor sleep can have a negative effect on a wide array of psychological and physiological functions (1). Numerous studies have also investigated the effect of acute sleep deprivation on physical performance, and although there is a broad consensus that physiological responses to exercise remain largely unchanged, an elevation in RPE is thought 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 signaling factors (e.g., cortisol, adrenaline, noradrenaline, and brain-derived neurotropic 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 signaling factors can readily cross the blood–brain barrier and that even a small change in the circulating concentration can have signaling effects within the brain (6). Indeed, recent evidence suggests that the circulating concentration of BDNF is positively related to mood and cognition (7), whereas a negative relationship has been observed between interleukin-6 (IL-6) and mood (8). This is particularly important given that impaired mood status and well-being 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 signaling.

Recent evidence has also documented a relationship between IL-6 and BDNF after disrupted sleep (11,12). Reports

Address for correspondence: Tom Cullen, Ph.D., Centre for Sport, Exercise and Life Sciences, Coventry University, Priory Street, Coventry CV1 5FB, United Kingdom; E-mail: ad0189@coventry.ac.uk.
Submitted for publication July 2019.
Accepted for publication October 2019.

0195-9131/20/5204-0909/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002207

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 a limited study of soluble IL-6 receptor (sIL-6R) in this context. The effects of IL-6 on the brain likely extend beyond mood and may affect 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-signaling" through sIL-6R (14).

Our group recently provided novel evidence that aspects of IL-6 "trans-signaling" through the sIL-6R were 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 focused on resting concentrations of cytokine and neuroendocrine responses after sleep deprivation, whereas there is considerably less research assessing partial sleep deprivation, which may be more similar to what is experienced in the real world. Furthermore, very few studies have investigated any potential divergent responses to exercise. Therefore, the aim of the current study was to (a) characterize 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.

METHODS

Before 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.

Participants

Participants comprised 10 recreationally active men. Their age, height, weight, and maximal oxygen uptake were as follows (mean ± SD): 27 ± 6 yr, 182 ± 8 cm, 88 ± 8 kg, and 43 ± 7 $mL \cdot kg^{-1} \cdot min^{-1}$. As part of the screening procedures, participants completed departmental health screening and physical activity questionnaires and the Pittsburgh Sleep Quality Index (16). To take part in the study, participants needed to declare themselves free from injury and illness for a minimum of 2 wk before commencement of the study and be identified as having normal sleep pattern based on a Global Pittsburgh Sleep Quality Index score <5 (16). Participants were required to not be taking any medication known to interfere with normal inflammatory responses (e.g., nonsteroidal anti-inflammatory drugs, etc.).

Study Design

This study comprised a randomized, repeated-measures crossover design. Participants completed preliminary testing to ascertain a measurement of aerobic fitness (maximal oxygen uptake ($\dot{V}O_{2max}$)) and were provided with an actigraph (Actiheart, Version 2.2; CamNTech Ltd., Cambridge, United Kingdom), which was worn throughout the study and used to assess sleep and activity patterns throughout. Energy expenditure was calculated in the 24-h period before each test session, the 12 h on the same day of each test session, and the 24-h period the day after each test 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 (HR) data (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 before each test session. After at least a 3-d rest, participants completed three further experimental trials with manipulated sleep routines in a randomized and counterbalanced order with a further 7 d between each subsequent experimental trial. To account for the known effects of time of day on hypothalamic–pituitary–adrenal axis, sympathetic nervous system, mood, and inflammatory signaling, experimental test sessions were completed at the same time of day on each occasion (between 7:00 and 9:00 AM). 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 h of sleep deprivation. Before CON, participants obtained a normal night sleep (7–9 h) in their own bed. For PART and DEP, participants arrived at the laboratory the evening before testing and remained under the supervision of the researchers until testing was completed the following day. For PART, participants were allowed a 4-h sleep opportunity in a prepared bedroom, commencing at their normal bedtime, and were then awoken 4 h later. Once awake, participants remained under the supervision of the researchers at all times, 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 h before the commencement of each test session and to replicate their diet in between conditions.

During each experimental trial (detailed hereinafter), participants initially completed questionnaires for the assessments of mood states and a sleep diary. After a brief rest, participants then completed an aerobic exercise bout comprising 45 min of standardized 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 after the completion of maximal exercise, and after 30 min 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.

Preliminary Testing

Participants completed an incremental exercise test on an electromagnetically braked cycle ergometer (Lode Excalibur,

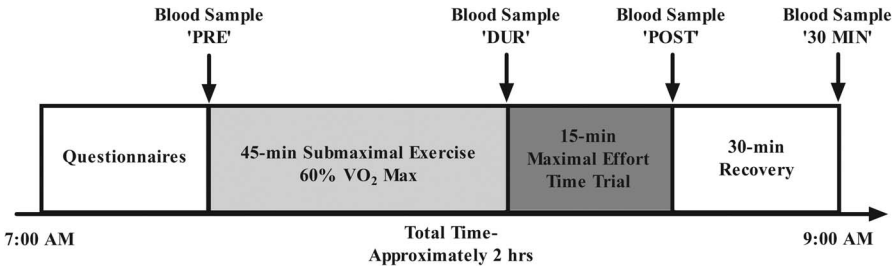

FIGURE 1—A schematic representation of the experimental trial.

Groningen, the Netherlands). Expired gases were continuously measured using an online gas analysis system (Cortex Biophysik Metalyzer, Leipzig, Germany), whereas HR was measured via a short-range telemetric HR monitor (RS400; Polar Electro, Espoo, Finland). The protocol consisted of 3-min stages, starting at 100 W and increased incrementally by 30 W each stage, until volitional exhaustion. Participants were instructed to maintain a pedal cadence of 80 rpm throughout the test. $\dot{V}O_{2max}$ 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 standardized power outputs for subsequent test sessions. After the maximal test, participants were then familiarized with tests to be conducted in subsequent sessions.

Experimental Procedures

Subjective fatigue and mood states. Participants completed a modified and shortened version of the Profile of Mood States 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. Before 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).

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 $\dot{V}O_{2max}$. 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 standardized submaximal exercise and maximal exercise within the same experimental protocol. Distance traveled 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 analyzer (Biosen C-Line Clinic; EKF-diagnostic GmbH, Barleben, Germany) from capillary blood samples, obtained in the final 30 s of each 5-min period.

Blood Collection and Analysis

A cannula (Becton, Dickson & Company, Oxford, United Kingdom) was inserted into the antecubital vein of the arm. Whole blood (10 mL per time point) samples were collected into K_3EDTA 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 enzyme-linked immunosorbent assay kits (Biotechne, Abingdon, United Kingdom) were used to quantify the concentration of IL-6, sIL-6R, cortisol, BDF, adrenaline, and noradrenaline. All samples were analyzed in duplicate, and the manufacturer's instructions were adhered to at all times. 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) before analysis of sIL-6R (1:100), cortisol, BDNF, adrenaline, and noradrenaline (all, 1:20). To minimize variation between assays, all samples from an individual participant were analyzed in the same assay. In our hands, the intra-assay coefficients of variation for these assays were as follows: IL-6, 4.1% ± 2.6%; sIL-6R, 2.1% ± 1.8%; cortisol, 6.4% ± 4.7%; BDNF, 3.2% ± 2.2%; adrenaline, 4.0% ± 2.5%; and noradrenaline, 4.0% ± 4.1%. The concentration of each analyte was determined in relation to a four-parameter standard curve (GraphPad Prism, San Diego, CA) and were corrected for changes in plasma volume based on established criteria (21).

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 nonparametric Friedman test was used where appropriate. A two-way repeated-measures ANOVA (sleep condition–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 were nonnormally distributed, log transformations were performed before analysis, and the respective data were 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 nonparametric data, respectively. Effect sizes for main effects are presented as η^2. Statistical analyses were undertaken using GraphPad Prism and SPSS (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY). All data are presented as mean ± SD unless otherwise stated, and statistical significance was set at $P < 0.05$.

RESULTS

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 before PART than CON ($P = 0.039$; mean difference, 19 min; 95% confidence interval (CI), 0.9 to −38 min). Sleep quality was significantly better for CON (3.3 ± 0.8) than for PART (2.6 0 ± 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 h before the test (2533 kcal for CON vs 2542 kcal for PART vs 2761 kcal for CON, $P > 0.05$). Energy expenditure in the 12 h after 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 in CON (mean differences, −208 kcal; 95% CI, −404 to −13 kcal) and PART (mean difference, −200 kcal; −396 to −5 kcal), but were not significantly different in the 24-h period the day after each trial (2681 ± 361 kcal for CON, 2697 ± 514 kcal for PART, 2547 kcal for DEP).

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

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 ($F = 4.2$, $P = 0.032$, $\eta^2 = 0.31$; Figs. 2A, B, respectively). *Post hoc* testing revealed significantly higher IL-6 after DEP (0.95 ± 0.37 pg·mL^{-1}) versus CON (0.62 ± 0.22 pg·mL^{-1}; mean difference, −0.33 pg·mL^{-1}; 95% CI, −0.59 to 0.06 pg·mL^{-1}) and a significant decrease in blood glucose (4.2 ± 0.3 mmol·L^{-1} for DEP vs 4.6 ± 0.5 mmol·L^{-1} for CON; mean difference, 0.44 mmol·L^{-1}; 95% CI, 0.01–0.88 mmol·L^{-1}). Correlation analysis revealed

TABLE 1. Comparisons of fatigue and mood state after the three different sleep conditions.

	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*

Sleep conditions comprised normal night of 7- to 9-h sleep (CON), a 4-h sleep opportunity at the start of the night (PART), and a single night of sleep deprivation (DEP).
*Significantly different from control ($P < 0.05$).

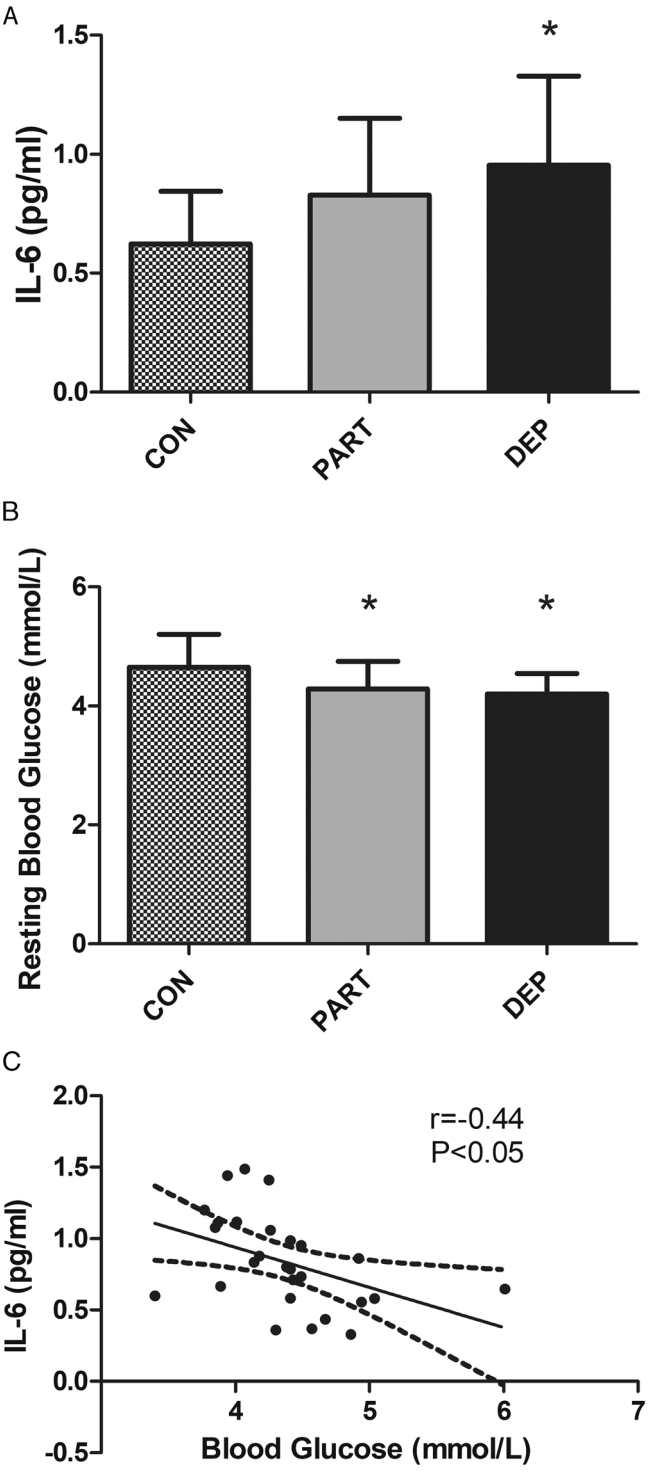

FIGURE 2—Resting concentration of IL-6 (A) and blood glucose (B) after three different sleep conditions. Sleep conditions comprised normal night of 7- to 9-h sleep (CON), a 4-h sleep opportunity at the start of the night (PART), and a single night of sleep deprivation (DEP). C, Correlation between resting IL-6 and blood glucose. *Significantly different from CON.

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

Submaximal Exercise	CON	PART	DEP
Mean $\dot{V}O_2$, %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^{-1}	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 $\dot{V}O_2$, %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^{-1}	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 from control ($P < 0.05$).

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 Fig. 2 for a summary). Subjective fatigue at rest was negatively correlated with the total energy expenditure in the 12 h after 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), whereas noradrenaline was positively related to perceived "tension" ($P = 0.027$, $r = 0.49$; 95% CI, 0.07–0.77). 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, 0.06–0.71).

Physiological and perceptual responses to exercise. Physiological and perceptual responses to exercise are summarized in Table 2, whereas 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 oxygen uptake ($\dot{V}O_2$), HR, RER, or lactate) between the three experimental conditions during the 45-min constant load portion of the exercise, whereas perception of effort (as measured by mean RPE) was significantly higher in DEP (13.4 ± 1.9) than in 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 $\dot{V}O_2$ ($F = 3.3$, $P = 0.038$, $\eta^2 = 0.3$), which was significantly higher after CON (85.4% ± 5.5%) than DEP (78.5% ± 11.4%; mean difference, 7.7%; 95% CI, 0.3%–14.9%). Similarly, there was a main effect of condition on distance traveled ($F = 4.1$, $P = 0.026$, $\eta^2 = 0.23$), with significantly less distance traveled in DEP than in CON (mean difference, 11.4%; 95% CI, 1.2%–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 $\dot{V}O_2$ achieved during the maximal exercise ($P = 0.03$, $r = -0.39$; 95% CI, −0.66 to −0.04) and distance traveled ($P = 0.006$, $r = -0.49$; 95% CI, −0.72 to −0.16). Subjective fatigue at rest was negatively related to mean $\dot{V}O_2$ ($P = 0.003$, $r = -0.56$; 95% CI, −0.77 to −0.22) and the distance traveled during maximal exercise

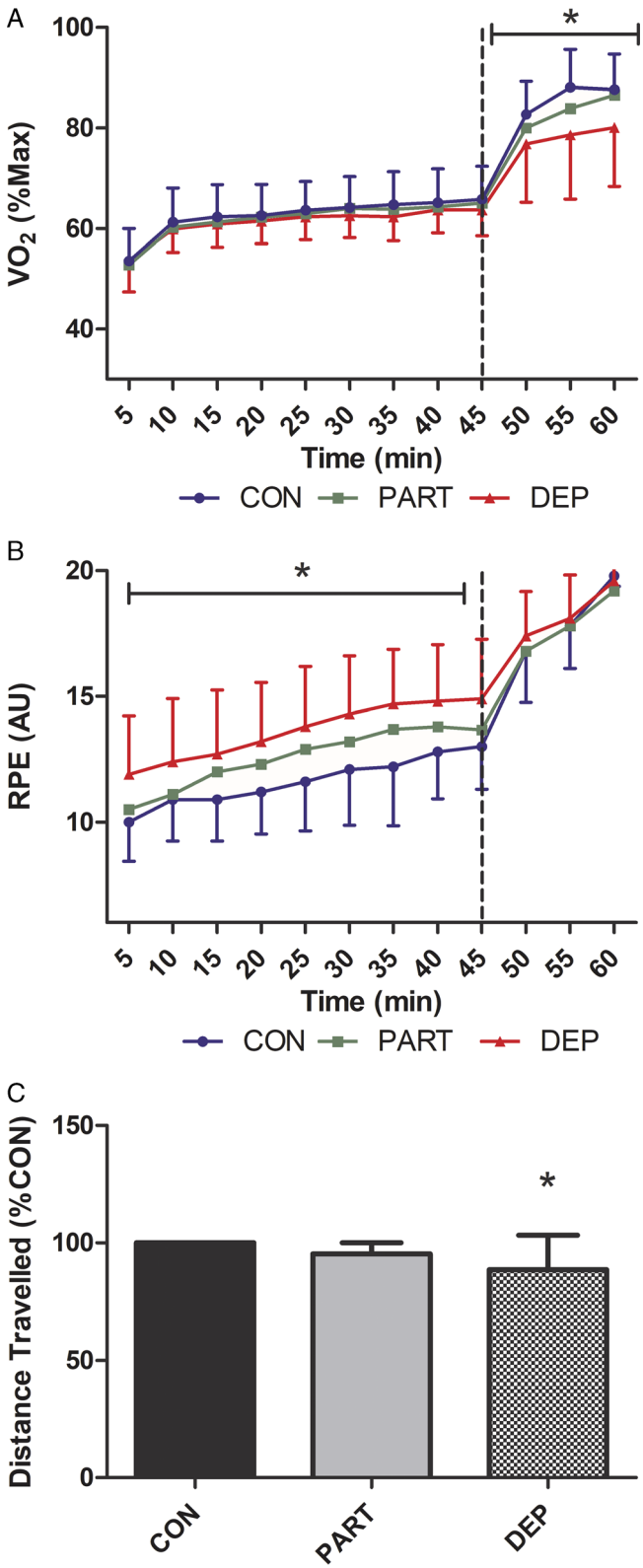

FIGURE 3—The mean oxygen uptake (A) and perception of effort (B) during a 45-min submaximal constant load cycling exercise and a 15-min self-paced maximal effort time trial after three experimental sleep conditions. C, Distance traveled in the 15-min self-paced maximal effort time trial (relative to the distance each person traveled in the control condition). *A significant difference between CON and DEP.

($P < 0.001$, $r = -0.7$; 95% CI, −0.86 to −0.44). In contrast, distance traveled 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 after CON (93.2% ± 2.2%) than DEP (87.7% ± 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 after CON (85.4% ± 5.5%) than DEP (78.5% ± 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 after CON (5.4 ± 0.7 mmol·L^{-1}) than DEP (4.3 ± 1.5 mmol·L^{-1}; mean difference, 1.1 mmol·L^{-1}; 95% CI, 0.05–2.1 mmol·L^{-1}). In contrast to submaximal exercise, there was no effect of condition on mean RPE during the maximal exercise.

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 after the constant load portion of all exercise trials ($P = 0.027$; mean difference, 0.17 pg·mL^{-1}; 95% CI, 0.018–0.32 pg·mL^{-1}), continued to increase after the time trial ($P < 0.0001$; mean difference, 0.40 pg·mL^{-1}; 95% CI, 0.032–0.49 pg·mL^{-1}), 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 $\dot{V}O_2$ achieved during maximal exercise ($P = 0.029$, $r = -041$; 95% CI, −0.67 to −0.05) and distance traveled during maximal exercise ($P = 0.035$, $r = -0.39$; 95% CI, −0.66 to −0.01). In contrast distance cycled

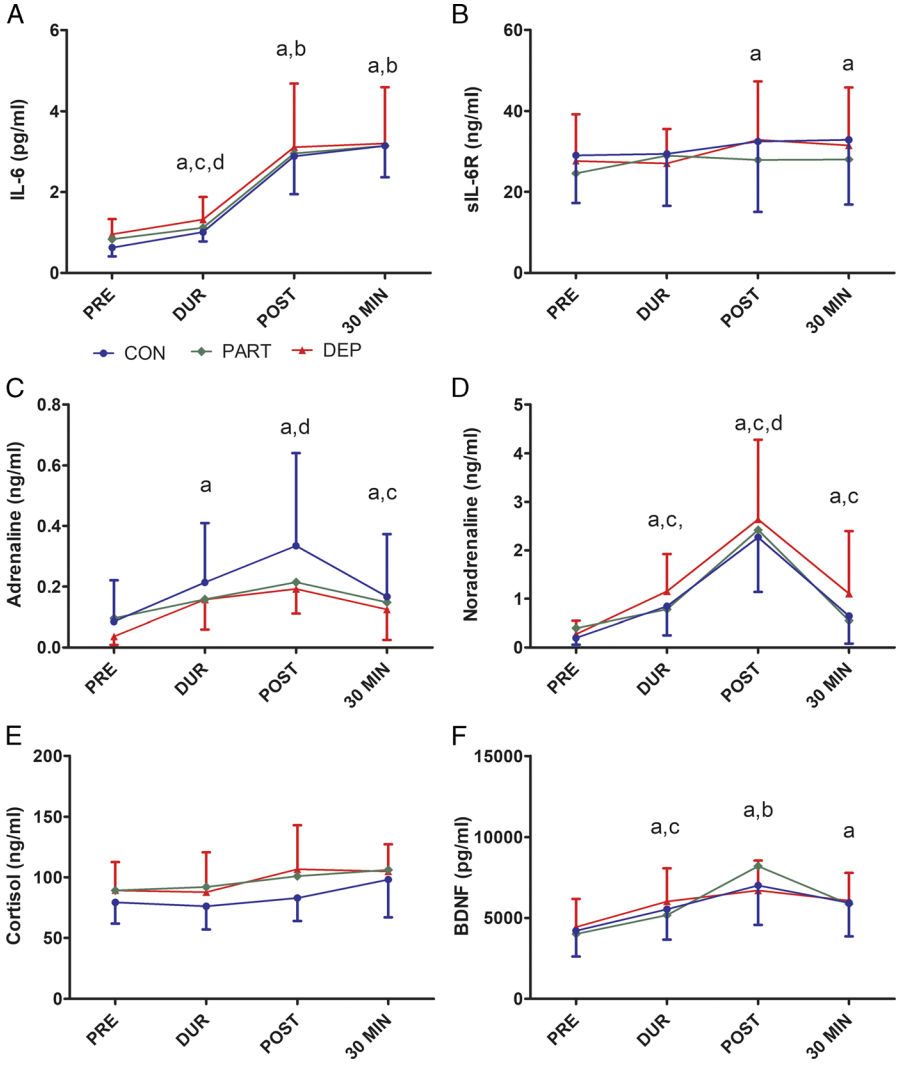

FIGURE 4—Plasma IL-6 (A), sIL-6R (B), adrenaline (C), noradrenaline (D), cortisol (E), and BDNF (F) responses to exercise after three different sleep conditions. [a]Significantly different from PRE. [b]Significantly different from DUR. [c]Significantly different from POST. [d]Significantly different from 30 MIN.

was positively related to postexercise 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 $\dot{V}O_2$ 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 after the time trial and 30 MIN; 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 with rest, peaking immediately after the time trial ($P = 0.001$; mean difference, 0.72 ng·mL^{-1}; 95% CI, 0.4–1.0 ng·mL^{-1}). 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 that noradrenaline was increased from rest at each time point, peaking immediately after time trial ($P < 0.0001$; mean difference, 2.2 ng·mL^{-1}; 95% CI, 1.5–2.8 ng·mL^{-1}). 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 after exercise, peaking immediately after time trial ($P = 0.002$; mean difference, 3090 pg·mL^{-1}; 95% CI, 1210–4970 pg·mL^{-1}). 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, after 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).

DISCUSSION

This study investigated the role of selected cytokine and neuroendocrine factors in altered physiological and perceptual responses to exercise after 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 h 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 after 24 h 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 after sleep deprivation.

In accordance with previous studies, we have demonstrated that perception of effort, but not physiological responses to intensity matched submaximal exercise, was affected by sleep deprivation, and that subsequent maximal aerobic exercise performance was impaired and coincided with significantly lower physiological responses (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 before exercise and perception of effort during the submaximal exercise were both related to the mean $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 seems to be yet another example of the subtle and context-dependent nature of IL-6 signaling. This is a significant result given the highly complex and multifactorial nature of exercise performance. As such, it seems that IL-6 may play a role in impaired exercise performance after 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. Furthermore, we demonstrated that resting blood glucose was lowered after 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 after 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 after 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 after 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 suffers 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 effect on sIL-6R, and this finding is interesting considering the extremely limited and somewhat conflicting available evidence regarding the effect of sleep on sIL-6R. Dimitrov and colleagues (28) previously reported that sleep deprivation abolished the sleep-induced increase in sIL-6R, whereas 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 bidirectional in that sleep can also be affected by IL-6 trans-signaling 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 after both partial and complete sleep deprivation (Fig. 4E); however, *post hoc* comparisons were not statistically significant. This seems 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 that assessed the relationship between cortisol and session RPE (33). As such, cortisol responses to sleep deprivation remain unclear, but our results further emphasize 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, whereas postexercise 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 of subjective fatigue in this relationship.

Similarly to IL-6, resting cortisol concentration was positively correlated with perception of effort during exercise. Taken together, it may be that, although adrenaline, noradrenaline, and cortisol are not affected by sleep deprivation *per se*, they do play a role in alterations of mood and effort perception during exercise. Furthermore, it seems 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 to examine potential interactions and investigate the direction of effects.

It is well documented that sleep and physical activity share a bidirectional 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 h after sleep deprivation and was negatively related to the level of subjective fatigue reported by participants in the morning before 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 although this is similar to the quantity of sleep occasionally experienced by athletes before 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-h period the day after the trial, suggesting that physical activity levels return to normal after one complete sleep cycle. As such, it is important to emphasize 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 after partial and complete sleep deprivation. This is important considering that exercise-induced changes in IL-6 and BDNF (among a range of other factors) seem important for exercise-induced adaptations in insulin sensitivity, lipolysis (39,40), and improved cognition and mood status (41). Furthermore, 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 well-being. It is important to emphasize that the effects observed in our study are likely multifactorial and highly complex, and as such, there are undoubtedly a wide

range of additional signaling factors that may also contribute to the observed responses. In this regard, we encourage further study 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 that elevated circulating concentrations of IL-6 at rest seem to play a role in the well-established impairments in mood, perception of effort, and exercise performance experienced after sleep deprivation. In contrast, cortisol, adrenaline, noradrenaline, and BDNF were not affected by sleep deprivation but do seem to account for subtle variations in mood and effort perception. Neither partial nor 24 h of sleep deprivation affects the cytokine and neuroendocrine responses to exercise measured in this study. Furthermore, we found that free-living energy expenditure was reduced after 24 h 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.

The authors would like to wholeheartedly thank the participants for their considerable efforts throughout the study. They would also like to thank Dr. Matthew Cook and Karolis Kvasas for their assistance with data collection. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the study do not constitute endorsement by the American College of Sports Medicine.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This research was supported by the National Institute for Health Research Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

The authors report no conflicts of interest in this work.

REFERENCES

1. Goel N, Basner M, Rao H, Dinges DF. Circadian rhythms, sleep deprivation, and human performance. *Prog Mol Biol Transl Sci*. 2013; 119:155–90.
2. Fullagar HH, Skorski S, Duffield R, Hammes D, Coutts AJ, Meyer T. Sleep and athletic performance: the effects of sleep loss on exercise performance, and physiological and cognitive responses to exercise. *Sport Med*. 2015;45(2):161–86.
3. Oliver SJ, Costa RJ, Laing SJ, Bilzon JL, Walsh NP. One night of sleep deprivation decreases treadmill endurance performance. *Eur J Appl Physiol*. 2009;107(2):155–61.
4. Engle-Friedman M, Mathew GM, Martinova A, Armstrong F, Konstantinov V. The role of sleep deprivation and fatigue in the perception of task difficulty and use of heuristics. *Sleep Sci*. 2018;11(2): 74–84.
5. Proschinger S, Freese J. Neuroimmunological and neuroenergetic aspects in exercise-induced fatigue. *Exerc Immunol Rev*. 2019;25:8–19.
6. Pollmächer T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines—do they affect human brain functions? *Brain Behav Immun*. 2002;16(5):525–32.
7. Giese M, Unternaehrer E, Brand S, Calabrese P, Holsboer-Trachsler E, Eckert A. The interplay of stress and sleep impacts BDNF level. *PLoS One*. 2013;8(10):e76050.
8. Main LC, Dawson B, Heel K, Grove JR, Landers GJ, Goodman C. Relationship between inflammatory cytokines and self-report measures of training overload. *Res Sports Med*. 2010;18(2):127–39.
9. Pilcher JJ, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. *Sleep*. 1996;19(4):318–26.
10. Keramidas ME, Gadefors M, Nilsson L-O, Eiken O. Physiological and psychological determinants of whole-body endurance exercise following short-term sustained operations with partial sleep deprivation. *Eur J Appl Physiol*. 2018 Jul 23;118(7):1373–84.
11. Schmitt K, Holsboer-Trachsler E, Eckert A. BDNF in sleep, insomnia, and sleep deprivation. *Ann Med*. 2016;48(1–2):42–51.
12. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol*. 2001; 107(1):165–70.
13. Vargas NT, Marino F. A neuroinflammatory model for acute fatigue during exercise. *Sports Med*. 2014;44(11):1479–87.
14. Robson-Ansley P, Cockburn E, Walshe I, Stevenson E, Nimmo M. The effect of exercise on plasma soluble IL-6 receptor concentration: a dichotomous response. *Exerc Immunol Rev*. 2010;16:56–76.
15. Cullen T, Thomas AW, Webb R, Phillips T, Hughes MG. sIL-6R is related to weekly training mileage and psychological well-being in athletes. *Med Sci Sports Exerc*. 2017;49(6):1176–83.
16. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
17. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. *Eur J Clin Nutr*. 2005;59(4):561–70.
18. Curran SL, Andrykowski MA, Studts JL. Short Form of the Profile of Mood States (POMS-SF): psychometric information. *Psychol Assess*. 1995;7(1):80–3.
19. McLean BD, Coutts AJ, Kelly V, McGuigan MR, Cormack SJ. Neuromuscular, endocrine, and perceptual fatigue responses during different length between-match microcycles in professional rugby league players. *Int J Sports Physiol Perform*. 2010;5(3):367–83.
20. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *Eur J Appl Physiol Occup Physiol*. 1987;56(6):679–85.
21. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol*. 1974;37(2):247–8.
22. Myles WS. Sleep deprivation, physical fatigue, and the perception of exercise intensity. *Med Sci Sports Exerc*. 1985;17(5):580–4.
23. Temesi J, Arnal PJ, Davranche K, et al. Does central fatigue explain reduced cycling after complete sleep deprivation? *Med Sci Sports Exerc*. 2013;45(12):2243–53.
24. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007;30(9): 1145–52.
25. Glund S, Deshmukh A, Long YC, et al. Interleukin-6 directly increases glucose metabolism in resting human skeletal muscle. *Diabetes*. 2007; 56(6):1630–7.
26. Steensberg A, Febbraio MA, Osada T, et al. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol*. 2001;537(Pt 2):633–9.
27. Skein M, Duffield R, Edge J, Short MJ, Mundel T. Intermittent-sprint performance and muscle glycogen after 30 h of sleep deprivation. *Med Sci Sports Exerc*. 2011;43(7):1301–11.
28. Dimitrov S, Lange T, Benedict C, et al. Sleep enhances IL-6 transsignaling in humans. *FASEB J*. 2006;20(12):2174–6.

29. Oyanedel CN, Kelemen E, Scheller J, Born J, Rose-John S. Peripheral and central blockade of interleukin-6 trans-signaling differentially affects sleep architecture. *Brain Behav Immun*. 2015;50:178–85.
30. Dimitrov S, Lange T, Tieken S, Fehm HL, Born J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain Behav Immun*. 2004;18(4):341–8.
31. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354(9188):1435–9.
32. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic–pituitary–adrenal and growth axes: potential clinical implications. *Clin Endocrinol (Oxf)*. 1999;51(2):205–15.
33. Balsalobre-Fernańdez C, Tejero-Gonzaĺez CM, Del Campo-Vecino J. Relationships between training load, salivary cortisol responses and performance during season training in middle and long distance runners. *PLoS One*. 2014;9(8):e106066.
34. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis*. 2009;51(4):294–302.
35. Edwards JP, Walsh NP, Diment PC, Roberts R. Anxiety and perceived psychological stress play an important role in the immune response after exercise. *Exerc Immunol Rev*. 2018;24:26–34.
36. Kline CE. The bidirectional relationship between exercise and sleep: implications for exercise adherence and sleep improvement. *Am J Lifestyle Med*. 2014;8(6):375–9.
37. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev*. 2007;11(3):163–78.
38. Vallières A, Azaiez A, Moreau V, LeBlanc M, Morin CM. Insomnia in shift work. *Sleep Med*. 2014;15(12):1440–8.
39. Wedell-Neergaard AS, Lang Lehrskov L, Christensen RH, et al. Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: a randomized controlled trial. *Cell Metab*. 2019;29(4):844–55.
40. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol*. 2012;8(8):457–65.
41. Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N, Brusco A. Aerobic exercise upregulates the BDNF–serotonin systems and improves the cognitive function in rats. *Neurobiol Learn Mem*. 2018;155:528–42.
42. Chennaoui M, Gomez-Merino D, Drogou C, et al. Effects of exercise on brain and peripheral inflammatory biomarkers induced by total sleep deprivation in rats. *J Inflamm (Lond)*. 2015;12(1):56.