Sports Med
DOI 10.1007/s40279-013-0030-4

REVIEW ARTICLE

Neurophysiological Determinants of Theoretical Concepts and Mechanisms Involved in Pacing

Bart Roelands · Jos de Koning · Carl Foster · Floor Hettinga · Romain Meeusen

Abstract Fatigue during prolonged exercise is often described as an acute impairment of exercise performance that leads to an inability to produce or maintain a desired power output. In the past few decades, interest in how athletes experience fatigue during competition has grown enormously. Research has evolved from a dominant focus on peripheral causes of fatigue towards a complex interplay between peripheral and central limitations of performance. Apparently, both feedforward and feedback mechanisms, based on the principle of teleoanticipation, regulate power output (e.g. speed) during a performance. This concept is called 'pacing' and represents the use of energetic resources during exercise, in a way such that all energy stores are used before finishing a race, but not so far from the end of a race that a meaningful slowdown can occur.

It is believed that the pacing selected by athletes is largely dependent on the anticipated exercise duration and on the presence of an experientially developed performance template. Most studies investigating pacing during prolonged exercise in ambient temperatures, have observed a fast start, followed by an even pace strategy in the middle of the event with an end sprint in the final minutes of the race. A reduction in pace observed at commencement of the event is often more evident during exercise in hot environmental conditions. Further, reductions in power output and muscle activation occur before critical core temperatures are reached, indicating that subjects can anticipate the exercise intensity and heat stress they will be exposed to, resulting in a tactical adjustment of the power output. Recent research has shown that not only climatic stress but also pharmacological manipulation of the central nervous system has the ability to cause changes in endurance performance. Subjects seem to adapt their strategy specifically in the early phases of an exercise task. In high-ambient temperatures, dopaminergic manipulations clearly improve performance. The distribution of the power output reveals that after dopamine reuptake inhibition, subjects are able to maintain a higher power output compared with placebo. Manipulations of serotonin and, especially, noradrenaline, have the opposite effect and force subjects to decrease power output early in the time trial. Interestingly, after manipulation of brain serotonin, subjects are often unable to perform an end sprint, indicating an absence of a reserve capacity or motivation to increase power output. Taken together, it appears that many factors, such as ambient conditions and manipulation of brain neurotransmitters, have the potential to influence power output during exercise, and might thus be involved as regulatory mechanisms in the complex skill of pacing.

B. Roelands · R. Meeusen (✉)
Department of Human Physiology, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium
e-mail: rmeeusen@vub.ac.be

B. Roelands
Fund for Scientific Research Flanders (FWO), Brussels, Belgium

J. de Koning · C. Foster
Research Institute MOVE, Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands

J. de Koning · C. Foster
Department of Exercise and Sport Science, University of Wisconsin, La Crosse, USA

F. Hettinga
University of Groningen, University Medical Center Groningen, Center of Human Movement Sciences, Groningen, The Netherlands

Published online: 02 March 2013

1 Introduction

Fatigue has traditionally been defined as an acute impairment of exercise performance, leading to an inability to produce a desired force or power output. Despite the focus of early studies, fatigue apparently does not occur primarily at the peripheral level. There is abundant evidence that mechanisms within the central nervous system are implicated in the genesis of fatigue [1]. Central projections of thin fibre afferents appear to provide inhibitory feedback to the central nervous system and influence the magnitude of the central drive [2]. Further, cerebral metabolism and neurohumoral/neurotransmitter responses during exercise can be disturbed, leading to either an acceleration or delay of the onset of fatigue [3]. It therefore appears that many parameters affect the capacity to 'perform' during exercise and each will depend on the type of exercise, the duration of exercise and environmental factors [1, 3–5].

Research starting over half a century ago suggested that athletes tailor their performance based on their sentiment [6]. Studies from the 1990s [7, 8] evaluated the ideal 'tactics' to complete a race in the best possible time. Foster et al. [9] reviewed a large number of essentially observational studies of the spontaneous pattern of pacing during various athletic events. In general, a U-shaped curve (fast start—slower middle part—end sprint) was most commonly described for events ranging from approximately 2 min to several hours. Events lasting less than 2 min, however, tended to show an all-out pacing strategy, meaning that the power output or speed starts high and progressively declines with time, with little evidence of the end sprint seen in longer events [9]. Obviously, in tactical events, as seen in athletics and some cycling races, pacing strategy is often quite simple; after a slow race, perhaps with some tactical accelerations designed to remove the weaker competitors, the athlete who can produce the fastest sprint takes home the victory. However, in events where competition is against the clock or where the athlete is not in close physical proximity to their competitors (cycling time trials, swimming, rowing, pursuit cycling, speed skating) the pacing pattern has to be focused on producing the optimal individual performance. There is a vast amount of literature available on pacing strategies in temperate climatic circumstances, while evidence of responses in more challenging environments has grown over the last years. The first goal of the present paper is to briefly review the literature on existing pacing strategies in different climatic circumstances. Second, we report on the effects of manipulation of different neurotransmitter systems on pacing strategies in both 18 and 30 °C. With this approach, we want to demonstrate how neurophysiological mechanisms can underlie pacing behaviour. A literature search was conducted from 2004 to 2012 through the PubMed and Web of Knowledge databases, using specific key words 'pacing', 'strategy', 'anticipatory regulation', 'performance', 'time trial', 'rating of perceived' 'exertion', 'heat'. Studies were selected based on the study protocol applied and the number of subjects incorporated.

2 What is Pacing?

Pacing is optimized when energetic resources are used efficiently during exercise, so that all energy stores are used before finishing a race, but not so far from the end of a race that a meaningful slowdown can occur [7, 10]. An important distinction has to be made between the terms 'pacing' and 'pacing strategy/pattern'. 'Pacing' is the distribution of speed, power output or energetic reserves, which can obviously be influenced by a number of factors including central and peripheral fatigue development, while 'pacing strategy' is the self-selected strategy or tactics that the athletes adopt, basically from the beginning of an event. Three basic pacing profiles (positive, negative and even pacing) have been identified, all depending on the duration of the event and the consequences of slowing down [11]. According to de Koning et al. [12], it appears that intramuscular substrate/metabolic changes are more likely to be determinative of changes in muscular power output in shorter-duration events (1–30 min), while core temperature elevation is more central in mid-duration events (20–120 min) and the availability of carbohydrates as a substrate being critical in long-term events (>90 min). Paterson and Marino [13] showed that athletes paced themselves consistently during an exercise bout based on what their pacing strategy, and associated metabolic activity, had been in a previous exercise bout. They further suggested the presence of an 'exercise template' in the brain that is updated by previous exercise bouts and that regulates exercise intensity in future exercise bouts [14]. A component that appears to integrate many variables during whole-body exercise is the rating of perceived exertion (RPE) [15]. This representation of the 'sensation of fatigue' is seen as an instrument for evaluating the perception of whole-body exertion during exercise; essentially, the articulated expression of a somatosensory experience [16]. St Clair Gibson and Noakes [17] stated that exercise activity is controlled as part of a pacing strategy involving active neural calculations in the brain, thereby integrating internal sensory signals and information from the environment. Craig [18] suggested a direct link between the RPE and the brain. It seems that humans create a cortical image of homeostatic afferent activity (located in the dorsal posterior insula) reflecting the physiological condition of the body [18]. In the right anterior insula a meta-representation of the primary interoceptive activity is

represented, causing a 'feeling' based on the homeostatic condition of the individual. This feeling apparently enables athletes to choose the right pace during exercise [19]. Recently, Tucker [20] proposed that changes in homeostasis, reflected by changes in the momentary RPE, allow alterations in the pacing in both an anticipatory and responsive manner, and are based on both pre-exercise expectations and peripheral feedback [12]. Indeed, it appears that athletes are continuously modifying their pace in order to maintain matching between the momentary RPE and the expected RPE at a given point during the race [9]. de Koning et al. [12] have proposed a simple index, representing the 'hazard' of a competitive collapse faced by the athlete. This index, the Hazard Score, is the product of the momentary RPE and the fraction of the event remaining at the same point [12], and has been shown to predict both mid-race deceleration and end-race acceleration.

The question "how do we fatigue during exercise?" has received considerable attention over the last century. In an excellent review Abbiss and Laursen [21] described nine different models describing the mechanism of fatigue from their own unique point of view: cardiovascular/anaerobic; energy supply/depletion; neuromuscular; muscle trauma; biomechanical; thermoregulatory; psychological/motivational; central governor; and a recently developed complex systems model. Already in the 1920s, Hill and his coworkers [22] developed the concept of peripheral fatigue, ascribing termination of exercise to metabolic changes that occur due to failure of the working muscles or the cardiovascular system. This is also known as the cardiovascular/anaerobic/catastrophic model of fatigue. A more recent theory suggests that the brain regulates, both consciously and unconsciously, exercise intensity, based on afferent feedback from the periphery. This model is constituted from the concept of teleoanticipation [23], which means that during exercise, afferent sensory feedback originating from a number of sources, such as partial pressure of respiratory gasses, hydrogen ion concentration, intra- and extracellular electrolyte concentrations, muscle contractile properties, perceived exertion and thermal sensation, causes a continuous regulation/modulation of central motor drive [2]. This complex, regulatory system adapts the work rate in order to optimize performance and to prevent potentially harmful (e.g. catastrophic) changes to homeostasis [17, 20, 24, 25]. An important prediction of this 'central governor' model is that all exercise performances are submaximal because they terminate before there is a catastrophic metabolic or cardiorespiratory failure [24].

Amann [2] proposed the existence of an individual critical threshold of peripheral locomotor muscle fatigue. The exercise-induced levels of certain metabolites known to be associated with peripheral fatigue are usually very similar at exhaustion, independent of the exercise regimen [2]. Interestingly, this critical threshold does not represent the muscles' ultimate limit [26] (e.g. the magnitude of homeostatic disturbance at the point of failure of isolated, stimulated muscle contraction), suggesting that exercise is regulated to retain a muscular 'reserve capacity', even at exhaustion [2, 27]. Furthermore, it has been hypothesized that metabosensitive group III/IV muscle afferents relate exercise-induced metabolic perturbations within the working muscle to the central nervous system and that this neural feedback may cause reductions (or increases) in central motor drive [2, 28]. In a series of experiments Amann et al. [29–31] confirmed the critical role of locomotor muscle afferents in regulating pacing strategy. After fentanyl (opioid analgesic) injection, that blocked the central projection of ascending sensory pathways without affecting motor nerve activity or maximal force output, the subject started a 5-km time trial at a substantially higher power output [31], suggesting that the central nervous system 'tolerated' an exercise-induced development of peripheral locomotor fatigue at a level that was drastically beyond levels as observed with an intact neural feedback system [31]. A logical extension of this study is that manipulations of the central nervous system can indeed affect performance or at least influence the pacing pattern during exercise. This suggests that manipulation of different neurotransmitter systems can cause changes in the central motor drive, which will influence the onset of fatigue [3]. It is very unlikely that a single neurotransmitter system is responsible for the appearance of central fatigue [3]. The present work aims at reviewing recent work on how neurophysiological interferences influence pacing or even pacing strategies.

To summarize, throughout the past few decades scientists have provided different ideas regarding the mechanisms of fatigue during prolonged exercise. Much of the early research focused on peripheral fatigue. More recent research has recognized the importance of central aspects of fatigue and has led to the concept of teleoanticipation [23, 25], which predicts a pacing pattern whereby the rate of energy expenditure is regulated in a way that allows them to complete a task in the minimal time, while controlling the magnitude of homeostatic disturbance [9]. The 'language' of this regulation appears to be the RPE, arguing that fatigue appears to be a sensory perception rather than a physical phenomenon, as suggested by early studies of peripheral fatigue [17, 32]. Accordingly, it is clear that athletes continually change their pace to match the experienced RPE versus that expected for that point in a race.

3 Pacing Strategies in Temperate-Ambient Conditions

Pacing strategies where no additional external stress is provided (such as temperature, oxygen level), primarily

depend on the anticipated exercise duration. During events lasting more than 4 min pacing becomes more even [33]. Athletes typically choose a starting velocity that is substantially higher than the mean velocity of the race, followed by a gradual reduction in the middle part of the trial and a significant increase in velocity near the end. The end spurt is an interesting phenomenon, which provides evidence that the central nervous system is able to override the inhibitory feedback from the muscle afferents [2, 17]. As the endpoint of the race approaches and the chance of premature fatigue declines, the end-spurt reflects the considered reserve that the athlete maintains for the majority of the race in order to reduce the hazard of catastrophic collapse [34].

There is a large body of recent research demonstrating the influence of different pacing strategies during exercise in temperate-ambient conditions. Studies applied different strategies, such as the benefits or drawbacks of a slower versus a faster start, in order to find the optimal pacing. Surprisingly, depending on the study design, considerable discrepancies were found. Renfree et al. [35] asked subjects to perform two 20-km cycle time trials. Pace during the initial 90 % of the time trials was constant, with an end sprint in the final 10 % of the trial. When the slower trial was compared with the faster trial, it became obvious that average power output during the initial 90 % was increased in the fast trials, but the power output of the end sprint remained similar [35]. Thomas et al. [34] had subjects repeat a 20-km time trial three times and concluded that although the overall pacing strategy was broadly similar amongst the trials, there was a high degree of variability at the start and end of the trial. There was a trend for a progressively blunted start on the repeat trials, indicating that information gained from the first trial is utilized to modify the exercise template (either consciously or subconsciously) during subsequent exercise bouts [34]. This contrasts with the findings of Swart et al. [27] who showed that, over the course of several 40-km cycle time trials, subjects consciously adopted more 'aggressive' pacing strategies, resulting in a higher power output in the initial phases leading to improved performances [27]. This was also found by Garland [36] and Lima-Silva et al. [37]. Garland [36] examined pacing strategies during a 2000-m rowing race. The authors observed that the first 500 m was rowed at a higher pace than the subsequent sections. Lima-Silva et al. [37] compared the 10-km running performance in a group of slow performers with a group of fast performers. Both studies found the same pacing profile, meaning a fast start, followed by an even-pace middle part and an end sprint in the final lap. Hettinga et al. [19] had subjects perform four 1,500-m cycling time trials. The slowest and fastest trials were compared, and it became clear that a fast-start strategy resulted in a better performance [19]. In contrast with most of the literature, Mattern et al. [38] and Hausswirth et al. [39] demonstrated that even-paced and fast-start strategies were not as effective as a strategy whereby power output or speed were initially below the average for the entire trial. This would be explained by the higher values for oxygen uptake, ventilation, heart rate and blood lactate in the beginning of the trial. Furthermore, Hettinga et al. [40] showed that experienced speed skaters seem to possess a well-developed performance template, and that changing pacing strategy towards a theoretically optimal fast-start protocol did not result in better performance. Earlier fatigue seemed to affect technique; changes in the timing and direction of the push off (e.g. gross efficiency) crucial for optimal speed-skating performance during a 1,500-m speed skating trial [40].

Recent studies performed in our laboratory have used a preliminary fatiguing task (60 min at 55 % of the maximal power output before the start of a time trial in 18 °C (predetermined amount of work equal to 30 min at 75 % of the maximal Wattage (W_{max}). During the time trial, subjects were free to change their resistance as desired from the onset [41–46]. The average performance time over 37 trials of $30' 42'' \pm 2' 01''$ (mean ± standard deviation (SD)) indicates that this protocol is very reliable. The pacing profile applied by the subjects was consistent with the strategy most commonly displayed in literature: an initial fast start over the first 10–15 % of the trial, followed by a slight reduction in power output with an even pace until the final 10 % of the time trial, where there is an end-spurt in which the power output returns to the initial values.

These data, as well as studies in literature, show that pacing in temperate conditions is quite straightforward, primarily depending on exercise duration and the developed performance template [40]. Most studies investigating longer-duration events find a fast start that is followed by an even pace strategy in the middle part and an end sprint in the final minutes of the race.

4 Pacing Strategies in the Heat

Exercise in hot environmental conditions typically induces hyperthermia, a rise in core and skin temperature. During exercise in the heat, the redistribution of blood from the body core to the skin decreases available muscular blood flow but may still be inadequate to control core temperature. The consequences are a physiological strain on the body, and an impaired exercise capacity [3]. Galloway and Maughan [47], Parkin et al. [48] and Tatterson et al. [49] showed that exercise time to fatigue was reduced when exercise was undertaken in the heat, compared with temperate- and low-ambient temperatures. It is, however,

important to emphasize potential differences in protocol. In the past, most endurance performance tests have been performed at a constant power output until exhaustion. However, Jeukendrup et al. [50] reported a poor reproducibility of this type of protocol (coefficient of variation 26.6 %). On the other hand, endurance performance tests with a known endpoint (a certain target amount of work or time), such as the time trial protocols, appear to be highly reproducible [50, 51].

Data collected from studies in our laboratory [41–46, 52, 53] confirm that subjects need significantly more time to complete a time trial in the heat compared with temperate-ambient conditions. In 30 °C subjects require ~7 min longer to complete the same time trial as in 18 °C [41–46, 52, 53]. In 18 °C, peripheral muscle fatigue and associated inhibitory feedback appear to determine central motor drive [2]. However, the relative importance of this inhibitory feedback seems to vanish in the face of a direct threat (such as a change in the environment) [2].

Recently Cheung [54] described how hyperthermia can induce fatigue. During exercise in the heat, fatigue seems to occur upon the attainment of a critical core/brain temperature of ~40.0 °C [55–57]. This critical core temperature serves as a protective mechanism preventing potential damage to body tissues by limiting further heat production [54]. Supportive evidence comes from studies that have manipulated initial core temperatures, heat storage rate and skin temperature, and reported similar final core temperatures [55, 56, 58]. Tucker et al. [5] showed that, during self-paced cycling time trials in hot conditions (35 °C), power output and muscle activation were reduced before significant changes in core temperature occurred. Abbiss et al. [59] came to the same conclusion after comparing a 100-km time trial in 10 °C with a 100-km time trial in 34 °C. Complex feedforward and feedback mechanisms appear to regulate fatigue. Humans seem to be able to anticipate the intensity of heat stress they will be exposed to, and seek to regulate their workload to minimize heat storage and prevent catastrophic outcomes [3]. Cheung [54] suggested that the theories of a critical core temperature and teleoanticipation are complementary. Indeed, it seems reasonable that the human organism has two protective systems in place: an anticipatory one to prevent excessive heat build-up as much as possible and a safety feedback mechanism to terminate exercise before catastrophic collapse [54].

A consistent finding in literature examining pacing profiles during exercise in the heat is that subjects initiate exercise at a relatively high pace followed by a rapid reduction in pace. At this point power output is most often drastically decreased. Ely et al. [60] had subjects perform two 15–min time trials, one in 21 °C and one in 40 °C. A significant decline in performance in the heat was found. Subjects started the time trial in the heat at a pace they were unable to maintain, resulting in a marked decrease in power output, only to recover in the final stage of the time trial. Abbiss et al. [61] also concluded that subjects tended to self-select an aggressive early pacing strategy for a 20-km time trial in the heat (32.7 °C). A decrease in power output during the middle part indicates that subjects reduced power output in anticipation of the final effort. The authors state that it is plausible that subjects learned a pacing strategy in the familiarization trial (20 °C), which was not modified despite an increase in ambient temperature. Barwood et al. [62] studied the effects of early change in thermal perception during exercise in the heat. Subjects' thermal sensation was altered prior to three 40-km time trials in 32 °C through the application of cold-receptor activating menthol spray, a control spray and no spray. The authors [62] showed that, despite an altered thermal state and perception during exercise in the heat, the self-selected power output was not different between any of the test conditions (control, control spray, L-menthol spray) and remained tightly regulated. A second observation was that the rate of rise in skin temperature was not a driver of early pacing. Levels et al. [63] also showed that skin temperature does not affect the selection and modulation of exercise intensity in a 7.5-km cycling time trial. Despite apparent differences in thermal comfort and perception, RPE was not different between trials, indicating that RPE may be a primary regulator of pacing [62]. These data are in agreement with the data found by Crewe et al. [64] who found that the rise of RPE accurately predicts the duration of fixed-intensity exercise in different ambient conditions (cool trials: 15 °C, 65 and 70 % peak power output; warm trials: 35 °C, 55, 60 and 65 % peak power output). It was suggested that the subconscious brain must be able to forecast the duration of exercise and then set the rate of increase in RPE at greater levels in hot conditions, and with higher intensities, so that fatigue occurs before the body temperature can rise excessively [64]. Tucker et al. [65] asked subjects to perform cycling exercise at a fixed RPE of 16 in cool (15 °C), warm (25 °C) and hot (35 °C) conditions. Exercise was stopped only when power output fell under 70 % of the starting power output for three consecutive minutes. The participants self-selected a lower power output during exercise in the heat, resulting in similar rates of heat storage in all conditions [65]. Recent studies from our laboratory [41–46, 52, 53] showed that, compared with 18 °C, subjects decreased their power output early during the time trial in 30 °C (Fig. 1). This decrease in performance persisted until 35 % of the time trial was completed. From then until 85 % of the time trial was finished, power output remained constant. The final 15–20 % of the time trial was characterized by an end-spurt (Fig. 1). These results indicate that, in the heat even

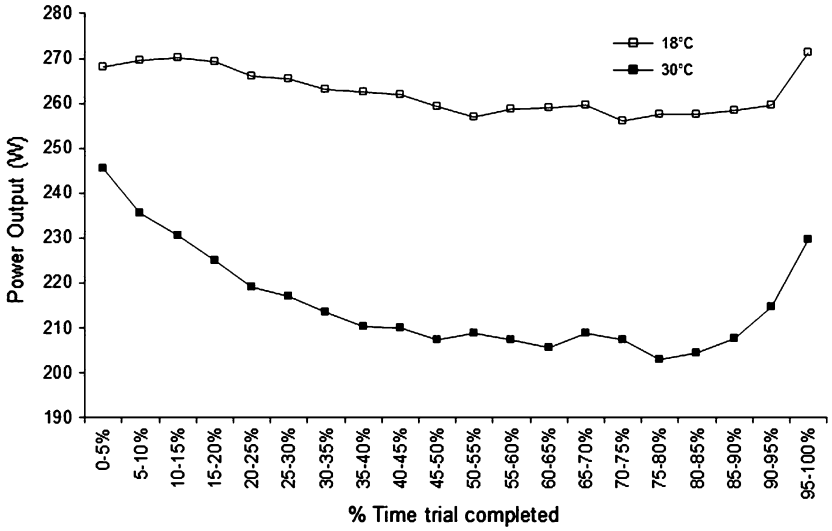

Fig. 1 Average power output in 5 % intervals during placebo time trials in 18 and 30 °C

more than in 18 °C, subjects 'exercise with reserve'. Skein and Duffield [66] showed that fluid ingestion did not influence intermittent sprint performance; however, it did affect pacing with a greater reduction in distance covered during self-paced exercise during the no-fluid trial [66]. Abbiss et al. [61] found no differences in 20-km time trial performance in the heat after having started a time trial 10 % above or below that of a self-paced trial. Furthermore, no differences in core temperature, rate of heat development, perceived pain, thermal sensation or average heart rate were found. This contradicts the findings of Mattern et al. [38] after 20-km time trials in temperate conditions, indicating that the climatic setting clearly influences pacing.

In summary, performance capacity in the heat is decreased compared with performance in temperate- or low-ambient temperatures. Different hypotheses have been put forward to explain the mechanisms of this negative effect on performance. The literature has shown that fatigue seems to occur upon the attainment of a critical core/brain temperature, which may serve as a protective mechanism for the body. Furthermore, it has been shown that during exercise in the heat, a reduction in power output and muscle activation occurs long before these critical core temperatures are reached, indicating that subjects can anticipate the exercise intensity and heat stress they will be exposed to.

5 Which Neurotransmitter Systems are Capable of Influencing Pacing Strategies?

Pacing can be influenced by a wide range of variables. During competitive events defined by placing, race tactics will often depend on the opponents [9]. Corbett et al. [67] showed that the thought of racing against another competitor in a head-to-head race enables subjects to complete a 2,000 m cycling time trial faster. This occurred primarily via an increased anaerobic energy yield, which seems to be centrally mediated, and is consequent with the concept of a physiological reserve [67]. Recently, interest in the role of neurophysiological processes in both pacing and pacing strategy has grown. Selective blocking of the central projection of ascending sensory pathways, without affecting motor nerve activity or maximal force output (using fentanyl, an opioid analgesic), resulted in attenuation of the central inhibitory effect [2]. In this study by Amann et al. [31], subjects had to perform a 5-km cycle time trial. During the fentanyl trial a higher central motor drive resulted in a substantially higher power output during the first half of the race, indicating that the central nervous system 'allowed' subjects to obtain levels of peripheral fatigue beyond normal levels of fatigue observed during the same exercise [2]. The absence of afferent feedback caused the removal of a central safety brake, causing ambulatory problems following the exercise bout [2]. It has been argued that this could also be due to central effects of fentanyl (such as sickness, confusion and impaired movement coordination) [68]. Pharmacological interventions can also induce changes in performance [3]. The brain neurotransmitters dopamine, noradrenaline and serotonin play a key role in the signal transduction between neurons and have all been implicated in the control of thermoregulatory responses, particularly since their neurons innervate areas of the hypothalamus, among which are the pre-optic and anterior hypothalamus [69]. It can be expected that a shift in the concentrations of these neurotransmitters contributes to changes in thermal regulation and consequently to fatigue, specifically when exercise is undertaken in hot environmental conditions [3].

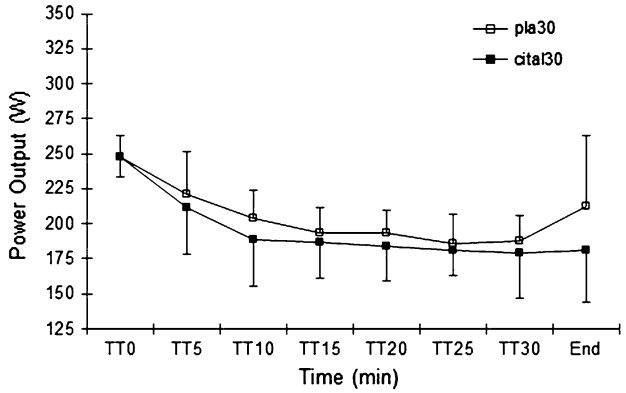

Fig. 2 Power output during placebo and citalopram time trials in 30 °C (mean ± SD). Reproduced from Roelands et al. [44], with permission. *Cital30* citalopram trial in 30 °C, *Pla30* placebo trial in 30 °C, *TT* time trial

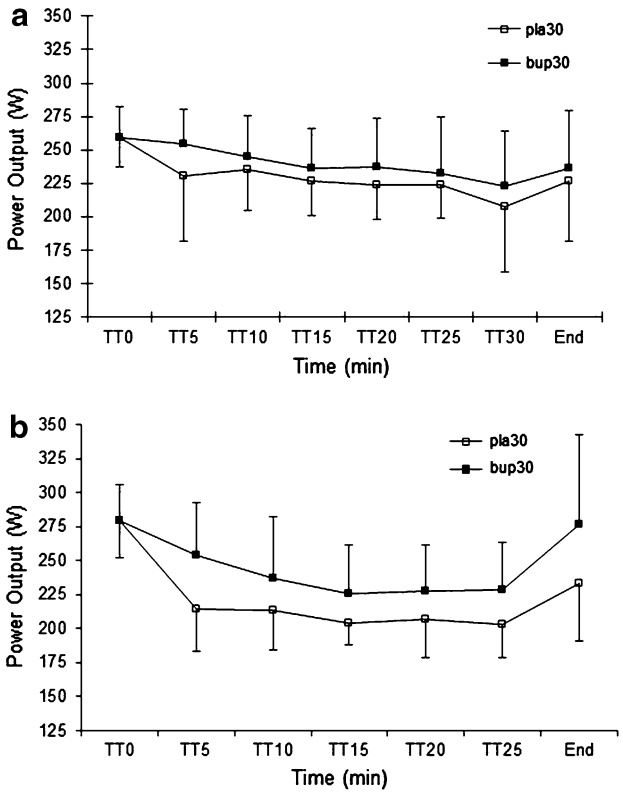

Fig. 3 **a** Power output during placebo and bupropion time trials in 30°C (mean ± SD) [53]. *Bup30* bupropion trial in 30 °C, *Pla30* placebo trial in 30 °C, *TT* time trial. **b** Power output during placebo and bupropion time trials in 30 °C (mean ± SD). Reproduced from Watson et al. [41], with permission. *Bup30* bupropion trial in 30 °C, *Pla30* placebo trial in 30 °C, *TT* time trial

In order to study the mechanism of centrally mediated fatigue, these neurotransmitter systems have been pharmacologically manipulated before the start of exercise in high-ambient temperature (30 °C). As was already put forward by Tucker [20], performance enhancing or retarding effects of central nervous system drugs, acting on these neurotransmitters are reflected by tactical adaptations in the chosen pacing strategy.

Serotonin, the only neurotransmitter implicated in the original central fatigue hypothesis, has not yielded conclusive results in human studies [3]. Although a recent study in our laboratory was not able to detect any significant change on a 30-min time trial after administration of a serotonin reuptake inhibitor (citalopram), subjects needed 2.3 min longer to complete the same amount of work versus placebo, in 30 °C [44]. Studying the pacing strategy employed, two interesting trends could be distinguished. First, during the initial 10 min of exercise, power output declined more in the citalopram trial (Fig. 2); second, subjects were unable to produce an end sprint in the citalopram trial, indicating that despite the lower mid-trial power output, they did not possess the drive and/or motivation to augment power output when approaching the endpoint. Two possibilities arise from these results. First, it is plausible that, at this time, subjects have already depleted their reserve capacity in order to reach this timepoint as fast as possible [27]. Second, increased serotonergic activity in the brain may block access to the reserve capacity. RPE at the start of the time trial was similar between the citalopram trial and the placebo trial. In both trials RPE rose progressively, but no differences were observed. From both options it is likely that brain serotonin is indeed involved in the onset of fatigue.

The link between exercise performance and dopaminergic activity becomes clear when we consider that dopamine plays an important role in motivation, memory, reward and attention [1]. Bridge et al. [70] had subjects cycle until exhaustion in 35 °C after administration of buspirone (serotonin agonist, dopamine antagonist), with or without pretreatment with pindolol (serotonin antagonist) and concluded that there is evidence that high levels of dopamine activity in the hypothalamus were associated with an increased tolerance to exercise in the heat. Watson et al. [41] and a very recent study from our laboratory [53] confirmed this finding. After administration of bupropion, a dopamine/noradrenaline reuptake inhibitor, subjects cycled significantly faster on a preloaded 30-min time trial in the heat. The initial decrease in power output was much smaller in the bupropion condition (Fig. 3a, b). This ergogenic effect was apparent without any change in the subjective feelings of exertion and heat stress [41, 53]. We [42] showed that administration of a dopamine reuptake inhibitor, methylphenidate, significantly improved performance on a preloaded 30-min cycling time trial in the heat (>7 min or 16 % performance improvement). During the time trial subjects were able to maintain a higher output and sustain higher metabolic heat production through an increased drive and motivation [42]. The pacing strategy employed

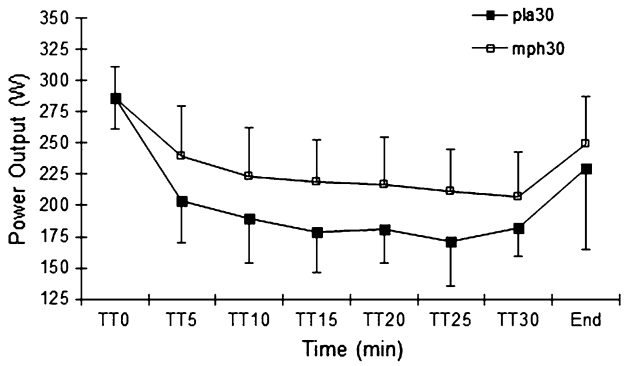

Fig. 4 Power output during placebo and methylphenidate time trials in 30 °C (mean ± SD) [42]. *Mph30* methylphenidate trial in 30 °C, *Pla30* placebo trial in 30 °C, *TT* time trial

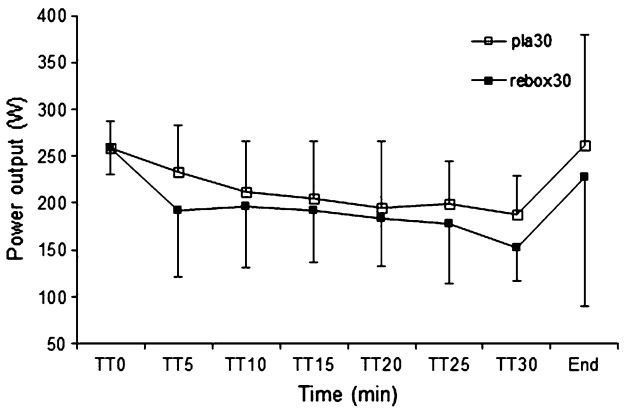

Fig. 5 Power output during placebo and reboxetine time trials in 30 °C (mean ± SD) [43]. *Rebox30* reboxetine trial in 30 °C, *Pla30* placebo trial in 30 °C, *TT* time trial

was very similar to the acute bupropion studies [41, 53]. The major difference between the drug and placebo condition was the decrease of power output observed after 5 min of exercise. In the placebo trial, power output decreased by 29 % of a fixed starting value, while in the methylphenidate trial the decrease was only 16 % (Fig. 4). After this early decrease, a similar even pacing is maintained, followed by an end-spurt in both conditions. The increase of the end-spurt in the placebo condition was larger (35 %) compared with the methylphenidate trial (21 %), suggesting that the subjects saved more energy during the drug trial. The absolute power output after dopamine reuptake inhibition, however, remained higher compared with the placebo (Fig. 4). No differences were observed in the RPE and heat stress scales between conditions. Swart et al. [27] had subjects cycle (until power output fell under 70 % of the starting value) at a fixed RPE, with or without methylphenidate in temperate-ambient conditions. The authors concluded that methylphenidate allowed subjects to sustain higher work rates and greater levels of metabolic and cardiovascular stress for longer, while perceiving the exercise stress to be identical. This indicates that the subjects terminated the placebo trial with a metabolic and cardiorespiratory reserve not accessible without a drug [27]. From these studies, it seems fair to suggest that drugs acting to enhance brain dopamine would change the initial anticipatory setting of work rate by elevating arousal and motivational levels. RPE would be reduced, resulting in a mismatch between the actual and template RPE. Consequently, this would lead to an increased work rate and heat production, until the conscious RPE returns to anticipated levels for the time trial in the heat [20].

Noradrenergic neurons seem to be involved in the regulation of attention, arousal and sleep–awake cycles, as well as learning and memory, anxiety, pain, mood and brain metabolism [71]. Research looking into the effects of noradrenaline on exercise performance is scarce. Two studies from our laboratory manipulated brain noradrenaline concentration. Piacentini et al. [72] found a trend towards a decrease in performance during a 90-min time trial in 18 °C after the administration of the noradrenaline reuptake inhibitor (reboxetine). A higher dose of the same drug significantly decreased a 30–min time trial performance in both 18 and 30 °C [43]. Power output during the reboxetine trials decreased more from the outset of exercise compared with placebo, was equal during the middle part of the time trial and remained lower during the end-spurt (Fig. 5). This result indicated that an increase in brain noradrenaline concentration, in contrast to dopamine, has detrimental effects on power output and thus exercise performance. Despite the lower power output in the reboxetine condition, RPE between conditions was similar.

Taken together, it appears that performance-enhancing or retarding effects of central nervous system drugs on endurance performance are reflected by tactical changes in pacing strategy. In the presence of larger climatic stress, subjects seem to adapt their strategy specifically in the earlier phases of exercise. Dopaminergic manipulations show that during the placebo condition, subjects exercise with reserve. Manipulations of serotonin and, especially, noradrenaline, have the opposite effect and force subjects to decrease power output early in the trial. After manipulation of brain serotonin, subjects are unable to perform an end-spurt, indicating that, at this time, there is either no reserve capacity or reduced motivation to increase power output. Another interesting finding is that RPE is not influenced by the drug treatments indicating that subjects maintain the same RPE, regardless of the power output produced or the core temperature achieved.

6 Conclusion

Athletes tailor their performance based on their sentiment and the knowledge of the time or distance remaining.

Historically, fatigue has been ascribed only to peripheral factors. But in the last decades it became clear that there is an critical role for the central nervous system. An interesting feedforward and feedback mechanism, based on the principle of teleoanticipation, might regulate power output or speed during a performance event. Indeed, it seems that athletes continuously match their pace in order to maintain the ratio between the momentary RPE and the expected RPE at a given point within the race. It is well-known that performance capacity is decreased in higher environmental temperatures. Recent literature showed that during exercise in the heat, a reduction in power output and muscle activation occurs before a critical core temperature is reached, indicating that subjects can anticipate the exercise intensity and heat stress they will be exposed to; thereby preventing catastrophic outcomes. Research performed in recent years has shown that central nervous system drugs affect endurance performance and that this is reflected by changes in pacing. Manipulating time trial performance in research can lead to important information about how pacing strategies are regulated, determining actual underlying neurophysiological mechanisms in the context of theoretical concepts on regulatory mechanisms in pacing. Dopaminergic drugs appear to override a safety switch and allow athletes to use a reserve capacity that is 'off-limits' in a normal (placebo) situation. Serotonergic and noradrenergic manipulations on the other hand decrease the ability of the athlete to produce power, beginning during the early stages of exercise. Taken together, it appears that factors such as ambient condition and manipulation of brain neurotransmitters have the potential to influence power output during exercise, and might thus be involved as regulating mechanisms in the complex skill of pacing.

Acknowledgments **Funding:** Bart Roelands is a postdoctoral fellow of the Research Fund of Flanders (FWO). We want to acknowledge funding through the Vrije Universiteit Brussel (OZR 607, 990, 1235).

Conflict of interest The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF. Central fatigue: the serotonin hypothesis and beyond. Sports Med. 2006;36(10):881–909.
2. Amann M. Central and peripheral fatigue: interaction during cycling exercise in humans. Med Sci Sports Exerc. 2011;43(11):2039–45.
3. Roelands B, Meeusen R. Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. Sports Med. 2010;40(3):229–46.
4. St Clair Gibson A, Lambert EV, Rauch LH, Tucker R, Baden DA, Foster C, et al. The role of information processing between the brain and peripheral physiological systems in pacing and perception of effort. Sports Med. 2006;36(8):705–22.
5. Tucker R, Rauch L, Harley YX, Noakes TD. Impaired exercise performance in the heat is associated with an anticipatory reduction in skeletal muscle recruitment. Pflugers Arch. 2004;448(4):422–30.
6. Robinson S, Robinson DL, Mountjoy RJ, Bullard RW. Influence of fatigue on the efficiency of men during exhausting runs. J Appl Physiol. 1958;12(2):197–201.
7. Foster C, Snyder AC, Thompson NN, Green MA, Foley M, Schrager M. Effect of pacing strategy on cycle time trial performance. Med Sci Sports Exerc. 1993;25(3):383–8.
8. Foster C, Schrager M, Snyder AC, Thompson NN. Pacing strategy and athletic performance. Sports Med. 1994;17(2):77–85.
9. Foster C, de Koning J, BIschel S, Casolino E, Malterer K, O'Brien K, et al. Pacing Strategies for Endurance Performance. In: Mujika I, editor. Endurance training, science and practice. 1 ed. Vitoria-Gasteiz: Inigo Mujika S.L.U.; 2012.
10. Tucker R, Noakes TD. The physiological regulation of pacing strategy during exercise: a critical review. Br J Sports Med. 2009;43(6):e1.
11. Abbiss CR, Laursen PB. Describing and understanding pacing strategies during athletic competition. Sports Med. 2008;38(3):239–52.
12. de Koning JJ, Foster C, Bakkum A, Kloppenburg S, Thiel C, Joseph T, et al. Regulation of pacing strategy during athletic competition. PLoS One. 2011;6(1):e15863.
13. Paterson S, Marino FE. Effect of deception of distance on prolonged cycling performance. Percept Mot Skills. 2004;98(3 Pt 1):1017–26.
14. St Clair Gibson A, Goedecke JH, Harley YX, Myers LJ, Lambert MI, Noakes TD, et al. Metabolic setpoint control mechanisms in different physiological systems at rest and during exercise. J Theor Biol. 2005;236(1):60–72.
15. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.
16. Hampson DB, St Clair Gibson A, Lambert MI, Noakes TD. The influence of sensory cues on the perception of exertion during exercise and central regulation of exercise performance. Sports Med. 2001;31(13):935–52.
17. St Clair Gibson A, Noakes TD. Evidence for complex system integration and dynamic neural regulation of skeletal muscle recruitment during exercise in humans. Br J Sports Med. 2004;38(6):797–806.
18. Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol. 2003;13(4):500–5.
19. Hettinga FJ, de Koning JJ, Hulleman M, Foster C. Relative importance of pacing strategy and mean power output in 1500-m self-paced cycling. Br J Sports Med. 2012;46(1):30–5.
20. Tucker R. The anticipatory regulation of performance: the physiological basis for pacing strategies and the development of a perception-based model for exercise performance. Br J Sports Med. 2009;43(6):392–400.
21. Abbiss CR, Laursen PB. Models to explain fatigue during prolonged endurance cycling. Sports Med. 2005;35(10):865–98.
22. Hill AV. Muscular activity and carbohydrate metabolism. Science. 1924;60(1562):505–14.
23. Ulmer HV. Concept of an extracellular regulation of muscular metabolic rate during heavy exercise in humans by psychophysiological feedback. Experientia. 1996;52(5):416–20.
24. Noakes TD, St Clair Gibson A, Lambert EV. From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans: summary and conclusions. Br J Sports Med. 2005;39(2):120–4.

25. Noakes TD. 1996 J.B. Wolffe Memorial Lecture. Challenging beliefs: ex Africa semper aliquid novi. Med Sci Sports Exerc. 1997;29(5):571–90.
26. Reid C. The mechanism of voluntary muscular fatigue. Br Med J. 1927;2(3481):545–6.
27. Swart J, Lamberts RP, Lambert MI, Gibson ASC, Lambert EV, Skowno J, et al. Exercising with reserve: evidence that the central nervous system regulates prolonged exercise performance. Br J Sports Med. 2009;43(10):782–8.
28. Kaufman MP, Hayes SG, Adreani CM, Pickar JG. Discharge properties of group III and IV muscle afferents. Adv Exp Med Biol. 2002;508:25–32.
29. Amann M, Proctor LT, Sebranek JJ, Eldridge MW, Pegelow DF, Dempsey JA. Somatosensory feedback from the limbs exerts inhibitory influences on central neural drive during whole body endurance exercise. J Appl Physiol. 2008;105(6):1714–24.
30. Amann M, Dempsey JA. Locomotor muscle fatigue modifies central motor drive in healthy humans and imposes a limitation to exercise performance. J Physiol. 2008;586(1):161–73.
31. Amann M, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA. Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. J Physiol. 2009;587(Pt 1):271–83.
32. Lambert EV, St Clair Gibson A, Noakes TD. Complex systems model of fatigue: integrative homoeostatic control of peripheral physiological systems during exercise in humans. Br J Sports Med. 2005;39(1):52–62.
33. de Koning JJ, Bobbert MF, Foster C. Determination of optimal pacing strategy in track cycling with an energy flow model. J Sci Med Sport. 1999;2(3):266–77.
34. Thomas K, Stone MR, Thompson KG, St Clair Gibson A, Ansley L. Reproducibility of pacing strategy during simulated 20-km cycling time trials in well-trained cyclists. Eur J Appl Physiol. 2012;112(1):223–9.
35. Renfree A, West J, Corbett M, Rhoden C, St Clair Gibson A. Complex interplay between determinants of pacing and performance during 20 km cycle time trials. Int J Sports Physiol Perform. 2012;7:121–9.
36. Garland SW. An analysis of the pacing strategy adopted by elite competitors in 2000 m rowing. Br J Sports Med. 2005;39(1):39–42.
37. Lima-Silva AE, Bertuzzi RC, Pires FO, Barros RV, Gagliardi JF, Hammond J, et al. Effect of performance level on pacing strategy during a 10-km running race. Eur J Appl Physiol. 2010;108(5):1045–53.
38. Mattern CO, Kenefick RW, Kertzer R, Quinn TJ. Impact of starting strategy on cycling performance. Int J Sports Med. 2001;22(5):350–5.
39. Hausswirth C, Le Meur Y, Bieuzen F, Brisswalter J, Bernard T. Pacing strategy during the initial phase of the run in triathlon: influence on overall performance. Eur J Appl Physiol. 2010;108(6):1115–23.
40. Hettinga FJ, De Koning JJ, Schmidt LJ, Wind NA, Macintosh BR, Foster C. Optimal pacing strategy: from theoretical modelling to reality in 1500-m speed skating. Br J Sports Med. 2011;45(1):30–5.
41. Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R, Meeusen R. Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions. J Physiol. 2005;565(Pt 3):873–83.
42. Roelands B, Hasegawa H, Watson P, Piacentini MF, Buyse L, De Schutter G, et al. The effects of acute dopamine reuptake inhibition on performance. Med Sci Sports Exerc. 2008;40(5):879–85.
43. Roelands B, Goekint M, Heyman E, Piacentini MF, Watson P, Hasegawa H, et al. Acute norepinephrine reuptake inhibition decreases performance in normal and high ambient temperature. J Appl Physiol. 2008;105(1):206–12.
44. Roelands B, Goekint M, Buyse L, Pauwels F, De Schutter G, Piacentini F, et al. Time trial performance in normal and high ambient temperature: is there a role for 5-HT? Eur J Appl Physiol. 2009;107(1):119–26.
45. Roelands B, Hasegawa H, Watson P, Piacentini MF, Buyse L, De Schutter G, et al. Performance and thermoregulatory effects of chronic bupropion administration in the heat. Eur J Appl Physiol. 2009;105(3):493–8.
46. Roelands B, Buyse L, Pauwels F, Delbeke F, Deventer K, Meeusen R. No effect of caffeine on exercise performance in high ambient temperature. Eur J Appl Physiol. 2011;111(12):3089–95.
47. Galloway SD, Maughan RJ. Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. Med Sci Sports Exerc. 1997;29(9):1240–9.
48. Parkin JM, Carey MF, Zhao S, Febbraio MA. Effect of ambient temperature on human skeletal muscle metabolism during fatiguing submaximal exercise. J Appl Physiol. 1999;86(3):902–8.
49. Tatterson AJ, Hahn AG, Martin DT, Febbraio MA. Effects of heat stress on physiological responses and exercise performance in elite cyclists. J Sci Med Sport. 2000;3(2):186–93.
50. Jeukendrup A, Saris WH, Brouns F, Kester AD. A new validated endurance performance test. Med Sci Sports Exerc. 1996;28(2):266–70.
51. Hickey MS, Costill DL, McConell GK, Widrick JJ, Tanaka H. Day to day variation in time trial cycling performance. Int J Sports Med. 1992;13(6):467–70.
52. Klass M, Roelands B, Levenez M, Fontenelle V, Pattyn N, Meeusen R, et al. Effects of noradrenaline and dopamine on supraspinal fatigue in well-trained men. Med Sci Sports Exerc. 2012;44(12):2299–308.
53. Roelands B, Watson P, Cordery P, Decoster S, Debaste E, Maughan R, et al. A dopamine/noradrenaline reuptake inhibitor improves performance in the heat, but only at the maximum therapeutic dose. Scand J Med Sci Sports. 2012;22(5):e93–8.
54. Cheung SS. Hyperthermia and voluntary exhaustion: integrating models and future challenges. Appl Physiol Nutr Metab. 2007;32(4):808–17.
55. Gonzalez-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldig T, Nielsen B. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol. 1999;86(3):1032–9.
56. Walters TJ, Ryan KL, Tate LM, Mason PA. Exercise in the heat is limited by a critical internal temperature. J Appl Physiol. 2000;89(2):799–806.
57. Nybo L, Nielsen B. Hyperthermia and central fatigue during prolonged exercise in humans. J Appl Physiol. 2001;91(3):1055–60.
58. Fuller A, Carter RN, Mitchell D. Brain and abdominal temperatures at fatigue in rats exercising in the heat. J Appl Physiol. 1998;84(3):877–83.
59. Abbiss CR, Burnett A, Nosaka K, Green JP, Foster JK, Laursen PB. Effect of hot versus cold climates on power output, muscle activation, and perceived fatigue during a dynamic 100-km cycling trial. J Sports Sci. 2010;28(2):117–25.
60. Ely BR, Cheuvront SN, Kenefick RW, Sawka MN. Aerobic performance is degraded, despite modest hyperthermia, hot environments. Med Sci Sports Exerc. 2010;42(1):135–41.
61. Abbiss C, Peiffer J, Wall B, Martin D, Laursen P. Influence of starting strategy on cycling time trial performance in the heat. Int J Sports Med. 2009;30(03):188–93.
62. Barwood MJ, Corbett J, White D, James J. Early change in thermal perception is not a driver of anticipatory exercise pacing in the heat. Br J Sports Med. 2012;46:936–42.

63. Levels K, de Koning JJ, Foster C, Daanen HA. The effect of skin temperature on performance during a 7.5-km cycling time trial. Eur J Appl Physiol. 2012;112:3387–95.
64. Crewe H, Tucker R, Noakes TD. The rate of increase in rating of perceived exertion predicts the duration of exercise to fatigue at a fixed power output in different environmental conditions. Eur J Appl Physiol. 2008;103(5):569–77.
65. Tucker R, Marle T, Lambert EV, Noakes TD. The rate of heat storage mediates an anticipatory reduction in exercise intensity during cycling at a fixed rating of perceived exertion. J Physiol. 2006;574(Pt 3):905–15.
66. Skein M, Duffield R. The effects of fluid ingestion on free-paced intermittent-sprint performance and pacing strategies in the heat. J Sports Sci. 2010;28(3):299–307.
67. Corbett J, Barwood MJ, Ouzounoglou A, Thelwell R, Dicks M. Influence of competition on performance and pacing during cycling exercise. Med Sci Sports Exerc. 2012;44(3):509–15.
68. Impellizzeri FM. Psychobiological factors are more important than central fatigue in limiting endurance performance. J Appl Physiol. 2010;108(2):459 (author reply 69).
69. Meeusen R, Roelands B. Central fatigue and neurotransmitters, can thermoregulation be manipulated? Scand J Med Sci Sports. 2010;20(Suppl 3):19–28.
70. Bridge MW, Weller AS, Rayson M, Jones DA. Responses to exercise in the heat related to measures of hypothalamic serotonergic and dopaminergic function. Eur J Appl Physiol. 2003;89(5):451–9.
71. Cooper BR, Wang CM, Cox RF, Norton R, Shea V, Ferris RM. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. Neuropsychopharmacology. 1994;11(2):133–41.
72. Piacentini MF, Meeusen R, Buyse L, De Schutter G, Kempenaers F, Van Nijvel J, et al. No effect of a noradrenergic reuptake inhibitor on performance in trained cyclists. Med Sci Sports Exerc. 2002;34(7):1189–93.