Bangor University

DOCTOR OF PHILOSOPHY

Mind over muscle? Psychobiolgy of exercise tolerance

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Award date:
2013

Awarding institution:
Bangor University

Mind over muscle?
Psychobiology of exercise tolerance

by

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Thesis submitted to Bangor University
in fulfilment of the requirements of the degree of
DOCTOR OF PHILOSOPHY

2013

This thesis was supervised by Samuele Marcora of the School of Sport and Exercise Science (University of Kent) and John Parkinson of the School of Psychology (Bangor University).

SUMMARY

It has always been of great interest for scientists to study human performance and fatigue in order to better understand the limiting factors and determinants, which ultimately rule exercise tolerance in humans. In the last decades, the focus has moved to study fatigue and human performance not only from a physiological point of view but also to integrate it with psychophysiological mechanisms in order to reach a fuller understanding of fatigue processes and its implications on exercise performance. The aim of this thesis was to analyse the most prominent models of exercise tolerance and delineate psychological and physiological factors determining and/or limiting exercise performance. Moreover, the role of "effort" and its implications for exercise tolerance has been defined and elucidated.

In chapter 2, it has been shown that maximal voluntary cycling power measured before and immediately after exhaustive cycling exercise does not decrease below the constant power at which participants were cycling at exhaustion. Such decrease in power, therefore, does not explain and challenge the traditional assumptions that in high intensity aerobic exercise muscle fatigue causes exhaustion, which occurs when the power generated from the muscles does not match any longer the power required by the task. Moreover, this study suggests the implication of other psychobiological variables such as rating of perceived exertion as important determinant and main limiting factor of exercise tolerance

In chapter 3 has been tested the hypothesis that rating of perceived exertion and naturally occurring muscle pain, the two main perceptual determinants influencing physical performance have a different impact on physical performance. Muscle pain unpleasantness (Cook`s scale) and rating of perceived exertion (RPE) (Borg`s scale) were rated during a high intensity aerobic cycling test. During the cycling task, a constant increase in RPE was reported until subjects withdrew exercise while naturally occurring muscle pain rating increased at a moderate level without reaching the maximal rating. These findings suggest a high correlation between rating of perceived exertion and high intensity cycling at exhaustion and minimize the impact of naturally occurring muscle pain as limiting factor in aerobic performance.

In chapter 4 it has been tested the validity and efficacy of a novel protocol to measure neural correlates of rating of perceived exertion using functional magnetic resonance imaging (fMRI). By comparing two different conditions: Fatigued leg vs. Non fatigued Leg, nine participants performed a series of leg extensions tasks alternating both legs. During this task, brain activation was measured using a 3 Tesla fMRI scanner and rating of perceived exertion has been recorded. Main results have shown an increase in rating of perceived exertion concomitantly to an increase in central motor command across the series of leg extension task performed and a significant activation of the cingulate gyrus and insular cortex has been detected when comparing higher ratings of effort compared to lower ones. These new findings may help the understanding of the neurobiology of perceived exertion and the brain areas and neural processes implicated with an increase of the rating of perceived exertion. Moreover, it elucidates the role of effort-based decision-making mechanisms related with perceived exertion.

Overall, our findings showed the validity of a more psychophysiological approach to study complex processes of fatigue and to delineate main determinants involved in human performance with particular attention to the rating of perceived exertion. It redefined the role and the impact of exercise-related muscle pain in endurance performance. Finally, it proposes new neurophysiological insights into the origin and development of perceptions of effort in the brain.

Acknowledgments

I would like to thank Samuele Marcora and John Parkinson, my two supervisors for the great opportunity they gave me to work with them during these fantastic years. I have always felt so lucky to have the chance to work in a topic I find so interested in and which is also so related to my personal life.

It was a great pleasure to study and doing research in such an interdisciplinary way by approaching problems or discussing ideas and point of views from so many different angles. Such experience gave me the opportunity to develop an open perspective and a knowledge, which is not confined in one single sector or subject, but rather it spaces out across different disciplines with no limit and one single purpose: a better, more complete and functional understanding of the phenomena around us.

I could have not been happier of the support and guidance that both my supervisors gave me during those years. I have always found challenging being in the middle of physiologists and psychologists at the same time and try to understand all I could learn from them, their strength and weaknesses and use an eclectic approach to best face any new challenge.

It was (and still is in many ways) an unforgettable experience. Thanks a lot Samuele and John!

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List of publications of parts of this thesis

Publications in peer-reviewed journals

- Marcora Sm, Staiano W. (2010) The Limit To Exercise Tolerance In Humans: Mind Over Muscle? Eur J Appl Physiol. Jul; 109(4):763-70.

Manuscripts in preparation

- Staiano W, Marcora Sm. Perceptual limits to exercise tolerance in healthy humans: pain or effort?
- Staiano W, Parkinson J, Marcora Sm. Neural correlates of perception of effort: An fMRI study.

CHAPTER ONE

GENERAL INTRODUCTION

Overview

It has always been of interest to exercise physiologists to fully to comprehend all perspectives of fatigue and its effects on physical performance (McKenna and Hargreaves, 2007). Multiple studies for over a century have been conducted with the aim of finding out determinant factors influencing performance either limiting or enhancing it. It is in scientist's nature always to try to test hypotheses in order to develop theories. In particular, it is in human nature always to seek the ultimate theory or the cardinal factor, which may answer our scientific questions.

However, fatigue is a complex phenomenon and, as such, it needs to be explored in all its facets and forms. For the purpose of this thesis fatigue has been defined as an "exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained"(Gandevia, 2001).

Moreover, peripheral fatigue is defined as the inability of the skeletal muscle to produce force and can be caused by biochemical changes occurring in the muscle cells. Increase of lactate concentration, changes in pH or Ca2+ sensitivity are some of the mechanisms that can lead to peripheral fatigue (Fitts, 2008; Allen et al., 2008). Central fatigue, on the other hand, is defined as the inability of the Central Nervous System (CNS) voluntarily to maximally recruit all the motor units to produce force. This phenomenon can occur at spinal and/or supraspinal level (Gandevia, 2001, Taylor and Gandevia, 2008) and can be triggered by different causes such as neurotransmission disruption (Meeusen et al., 2006), brain temperature (Nybo and Secher, 2004) and inhibitory sensory feedback from fatigued locomotor muscles, which can decrease central neural drive during submaximal dynamic contraction (Amann and Dempsey, 2008b).

In the last decades there has been the need to study fatigue and human performance not only from its physiological point of view as it was for most of the last century, but also to integrate it with psychophysiological mechanisms in order to reach a full understanding of fatigue processes and its implications for exercise performance (Kayser, 2003). As Hargreaves (2008) cited "*integrative physiology at its finest!*

As the research on fatigue and determinants of performance goes forward and moves its attention to brain processes so different models have been developed in order to explain fatigue and task failure. Those models move away from traditional peripheral fatigue models (Fitts, 2008, Fitts, 2006, Allen et al., 2008) to more innovative ones focused on central aspects of fatigue (Amann, 2010; Amann and Dempsey, 2008b; Amann and Dempsey, 2008a; Gandevia, 2001; Marcora and Staiano, 2010; Marcora and Staiano, 2009; Taylor and Gandevia, 2008)

Bigland - Ritchie (1981) proposed a list of the major potential sites of muscle dysfunction induced by exercise. They are as shown in figure 1:

1) Central mechanisms

- Excitatory input to higher motor centres
- Excitatory drive to lower motor neurons
- Motor neuron excitability
- Neuromuscular transmission

2) Peripheral mechanisms

- Sarcolemma excitability
- Excitation-contraction coupling
- Contractile mechanism
- Metabolic energy supply/metabolic accumulation

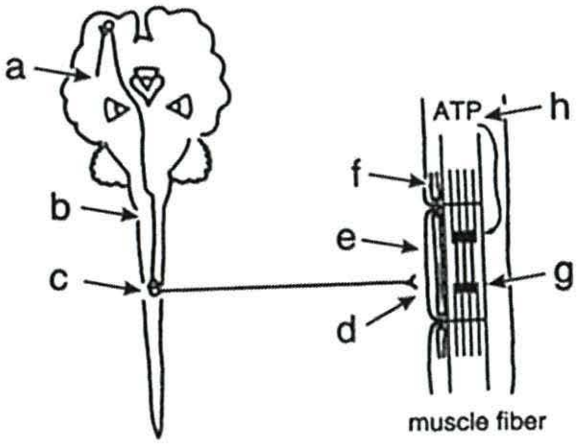


Figure 1

Potential sites of fatigue (a) excitatory input to the motor cortex, (b) excitatory drive to lower motoneuron, (c) motoneuron excitability, (d) neuromuscular transmission, (e) sarcolemma excitability, (f) excitation-contraction coupling, (g) contractile mechanism, (h) metabolic energy supply. From (Bigland-Ritchie, 1981).

Bligand – Ritchie`s list (1981) represents the chain of motor command and any perturbation at each of its ring can produce a change in muscle contraction, force/power output and thus in exercise performance.

Several models have been presented in the literature to explain the limits or major determinants of exercise performance. For the purpose of this thesis, we will discuss the following two:

1. The muscle fatigue model of exercise tolerance, which encompasses peripheral fatigue, central fatigue and inhibitory afferent feedback.

2. The psychobiological model of exercise tolerance, which uses a multidisciplinary approach across physiology, psychology and neurophysiology and consider movement and any related task as a behavioural variable.

Muscle fatigue model of exercise tolerance

For practical reason and clarity, in the muscle fatigue model have been classified both central and peripheral mechanisms, which eventually lead to an involuntary reduction in muscle force and power output. This model of performance assumes that, in well-motivated subjects, exercise terminates when the neuromuscular system is no longer able to produce the force/power required, a point known as exhaustion or task failure. Failure can consist in maintaining the minimum cadence (when on cycle ergometer) or speed or when there is the inability to produce the minimum force required by the task. This model assumes that muscle fatigue is the direct cause of exhaustion (Allen et al., 2008; Jones et al., 2008).

The first researchers interested in studying the mechanisms that lead to fatigue during exercise are dated back more than 100 years ago. Two renowned researchers in this area were Archibald Vivian Hill and Angelo Mosso. Hill and his colleagues performed experiments on isolated muscles mainly, and they concluded that substances called "poisonous" (muscle metabolites) produced by the muscles during exercise were the main factor leading to fatigue (Hill et al., 1924; Hill et Lupton, 1923). Based on those experiments, A.V Hill proposed a model predicting that just before the cessation of maximal exercise the oxygen demands of the exercising muscles surpassed the myocardial capacity to provide such oxygen. According to this model the heart was the solely factor determining human performance and as Noakes (1997) stated the idea that A.V Hill developed was that the main limiting factor to exercise was the inability of the cardiovascular system to provide enough oxygen to active. This model became one of the most prominent model of exercise tolerance for the last 90 years. Mosso, in its turn, developed experiments taking in consideration the presence of the central nervous system (Di Giulio, 2006). While Mosso shared similar ideas to those of Hill's on the presence of "poisonous" substances leading to fatigue and therefore the cessation of exercise, he took an important step in this study, showing that the brain has great

influence on the fatigue process. In one of his studies, he showed how mental fatigue due to hours of teaching lectures in the university had a detrimental effect on a consequent repeated exercise of finger flexion (Di Giulio, 2006).
Although A. V. Hill`s model of exercise has influenced many physiologists in the last century, it has been often object of criticism for his lack of considering brain mechanisms which might determine exercise tolerance. However, most exercise physiologists spent the majority of the twentieth century focusing on fatigue studies in which they did not consider the brain as the protagonist. However, studies such as Noakes (1988, 1997, 2000) Kayser (2003) and Noakes and St Clair Gibson (2004) challenged this model and presented evidence to support the theory that the brain is responsible for limiting the exercise, and not a critical level of the cardiovascular system or any other peripheral bodily system. Thus, new ideas regarding the limitation of physical activity emerged, in which fatigue began to be seen not as a physical event, but as a sensory one, and greater attention began to be given to the sensations during exercise (Jones and Killian, 2000; Noakes et al., 2004).

Noakes and colleagues (St Clair Gibson and Noakes, 2004, Noakes et al., 2004) have proposed a more complex central governor model in which afferent sensory feedback coming from many different organs (e.g., skeletal muscles, heart, lungs, skin, and the brain itself) is processed at subconscious level by an intelligent system located in a not yet identified part of the brain. Central to this model is the hypothesis that exercise duration or intensity (depending upon the type of performance test) is set in anticipation by the CNS in order to avoid failure of homeostasis. Moreover, this central governor in the brain controls pacing strategy in response to afferent feedback from different physiological systems. This is a feed-forward homeostatic mechanism because the extent of locomotor muscle recruitment is controlled in order to complete the exercise task within the physiological limits of the body, i.e. to avoid catastrophic homeostatic failure (Noakes, 2012). I

Based on the similar concept of the inhibitory sensory feedback, Amann and Dempsey (2008b) explain task failure during constant-power tests and time trials by an inhibitory afferent feedback system. Such system will serve as a protective mechanisms and prevent peripheral muscle fatigue to develop beyond a critical threshold, which may lead to potential damage to the muscle (Amann, 2007, Amann and Dempsey, 2008b). Afferent feedback from type III and IV afferent nerve fibres, located in the muscles and stimulated by the accumulation of metabolites such as H + or inorganic phosphate, are supposed to mediate the inhibition of the central motor output (see Figure 2 in Amann and Dempsey 2009).

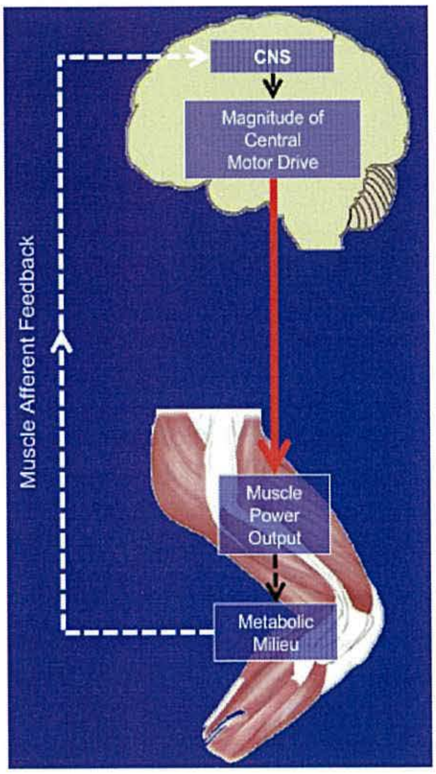


Figure 2

Schematic illustration of the afferent feedback loop mechanism proposed by Amann and Dempsey (Image and caption extracted from Amann and Dempsey (2009).

"The solid line indicates central motor command (CMD) to the locomotor muscle; the dashed line indicates neural feedback mediated by thin-fiber muscle afferents. This regulatory mechanism suggests that muscle afferents exert inhibitory feedback effects on the determination of the magnitude of CMD during high-intensity whole-body endurance exercise. The magnitude of CMD determines power output of the locomotor muscles, which determines the metabolic milieu within the working muscles. The metabolic milieu determines the magnitude of the inhibitory afferent feedback. On the basis of existing data, this feedback loop restricts peripheral locomotor muscle fatigue and associated sensory feedback to an individual threshold and/or sensory tolerance limit that is never exceeded during whole-body endurance exercise".

Pain

As part of the afferent feedback mechanism, it is worth discussing the role of pain and in particular exercise - related pain, and its implications in exercise performance. Pain has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". As underlined in the definition, pain is defined on a multidimensional level. Therefore, it is possible to delineate the physiological mechanisms of peripheral nociception and signal transmission through the spinal cord relating to tissue damage. Further, there is the perceptual experience of pain, which is subjective, and is processed and modulated in the cortical and subcortical brain areas.

Cabanac proposed (1979) that any sensation possess three dimensions:

1. Qualitative dimension which delineates the nature of the stimulus: pressure, burning, stubbing and others

2. Quantitative dimension which delineates the intensity of the stimulus

3. Affective (or Hedonic) dimension which determines the affective valence of how pleasant or unpleasant a stimulus is.

Recently the use of neuroscientific measures such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been able to detect the area involved in the cognitive aspect of pain (O`Connor and Cook, 1999). The major areas that have been highlighted are sensory cortex, prefrontal cortex, parietal cortex, thalamus and anterior cingulate cortex (we will return to this area later in this thesis for the integration of signals of perception of effort).

Exercise – related pain or naturally occurring muscle pain (NOMP) refers to the pain due to repetitive muscular contraction and accumulation of muscle metabolites (O`Connor and Cook 1999). Several methods have been developed to measure muscle pain. Cook et al. (1997) developed a category ratio scale on 10 points (from 0 to 10). With this scale both intensity (quantitative dimension) and unpleasantness (affective/hedonic dimension) can be assessed and such ratings have proved to be valid and highly reliable (O`Connor and Cook, 2001) (See Appendix II).

For many years, in the field of elite sport athletes and coaches has always thought muscle pain to be an important limiting factor in performance, in particular endurance. The motto: "*no pain no gain*" expresses the belief that the ability to tolerate pain was an important factor determining success of an athlete. However, there is very little in research up to date, which underlines the prominent role of muscle pain (natural occurring muscle pain) on physical performance. Interestingly, Cook et al. (1997) reported in a study measuring maximal performance on a cycle ergometer that the main cause of stopping exercise was not muscle pain in the lower limbs but what they defined as leg fatigue.

It is possible that, historically, misunderstandings in the field of fatigue have resulted from the incorrect use of perceptual measures when applied to physical activity. This may have occurred when perceptual measures such as pain and the rating of perceived exertion

(RPE) are not properly used and thus they will lose their validity and reliability. Researchers often confuse muscle pain and RPE in their studies. The main reasons for this may be multiple:

A lack of uniformity in defining and naming the variable to assess may lead to a not valid measure. As matter of fact, defining and taking a measure of RPE as purely how heavy and strenuous exercise is, may differ in terms of values from asking the participant to rate leg discomfort as in the discomfort are encompassed as well a variety of other feeling arising from muscle, joints, hips, saddle discomfort and heat discomfort. Moreover, it is necessary to consider the multidimensionality of pain as intensity and affective dimensions of pain may differ to each other even during the same task. Thus, it is indispensable to determine which measure the researcher is interested in and be sure the participants are fully aware of its definition and scale usage. Finally, limitations of the protocol can have a determinant impact on the outcome of study as a non-single and double blind protocol may alter profoundly the results due to placebo effect, which may result in a complete misunderstanding of the findings in particular in studies using pain rating as main outcome.

In 2011, Marcora clarified the importance of proper definition of those two main perceptual measures of physical exercise:

- Rating of perceived exertion is defined as the conscious sensation of how hard, heavy, and strenuous exercise is (Marcora, 2011).

- Muscle pain refers to an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, 1979).

Psychobiological model of exercise tolerance

The psychobiological model of exercise tolerance proposed by Marcora et al., 2008 and 2009) has been conceived with the idea to explain complex phenomena related to exercise tolerance, using a complete and more integrated scientific approach across the areas of physiology and psychology. Therefore, this model has been developed with the purpose to explain not only physiological mechanisms behind the exercise performance but also to clarify a vast number of psychological factors, which are closely linked to performance, and yet are left unexplained or not considered by the majority of models. To cite some examples of psychological factors implicated in performance and often not considered, we can mention:

- End spurt as the increase in central motor drive/power-output measured at the end of intense time trials despite a very high concentration of fatigue-inducing metabolites (Amann et al.,2008c). Such a variable has been always dismissed and traditional physiological model of exercise performance such as AV Hill`s model did not have a plausible explanation for it.
- Social facilitation or presence of a competitor (Wilmore, 1976) which can increase the motivation of the participant in performing the task.

- Monetary rewards (Cabanac, 1986) which can boost the extrinsic motivation of the participant.

The psychobiological model is based on three assumptions:

1. Physical performance as movement can be considered as a voluntary behaviour and not only as physiological results of a machine. As such many psychological constructs may be apply to such a behaviour. As a conscious behaviour, exercise starts in the brain as conscious decision and it end in the brain as conscious choice of disengaging from the task.

2. Voluntary behaviours, including exercise, can be explained using psychological constructs and theories. This assumption constitutes **the psychological level of explanation** of this model.

3. Our mind is ultimately generated by neuron activity in the brain, and it can be affected by physiological factors. This assumption constitutes **the biological level of explanation** of this model.

The psychobiological model is based on Brehm's motivational intensity theory (Brehm`s and Self, 1989; Wright, 2008). According to the psychobiological model, exercise performance is a variable ultimately regulated by two factors:

1. **Potential motivation** defined as the maximum effort an individual would be willing to exert in a physical task.
2. **Perception of Effort** defined as the conscious sensation of how hard, heavy, and strenuous exercise is (Marcora, 2010).

The model described above is based on tasks where the only possible form of self-regulation is to stop or to keep going, such as time to exhaustion tasks. In physical tasks where a higher level of self-regulation (pacing) is possible (Time trial task), effort can be regulated more precisely. In this type of task, there are five factors that can affect pacing and performance: (1) perception of effort; (2) potential motivation; (3) knowledge of the distance/duration to cover; (4) knowledge of the distance/duration covered/remaining; and (5) previous experience/memory of perceived exertion during exercise of varying intensity and duration (Marcora, 2010).

Disengagement from the physical task occurs when:

- Success seems to be impossible to achieve
- Success seems to call for more effort than would be warranted

According to this model, well-motivated subjects voluntarily terminate any form of submaximal endurance exercise when perception of effort reaches an intolerable level so that they decide to withdraw from the physical task. When expressing in terms of physical performance, withdrawing from a physical task can be interpreted as:

- Decreasing in speed
- Changing of cadence
- Changing of gears
- Inability to sustain the intensity required

People engage in a task until the effort required reaches the maximum level of effort they are willing to invest for succeeding in the task (the so-called potential motivation, Figure 3 A and B) or when the task is perceived as impossible despite very high potential motivation (Figure 3 C; Wright, 2008).

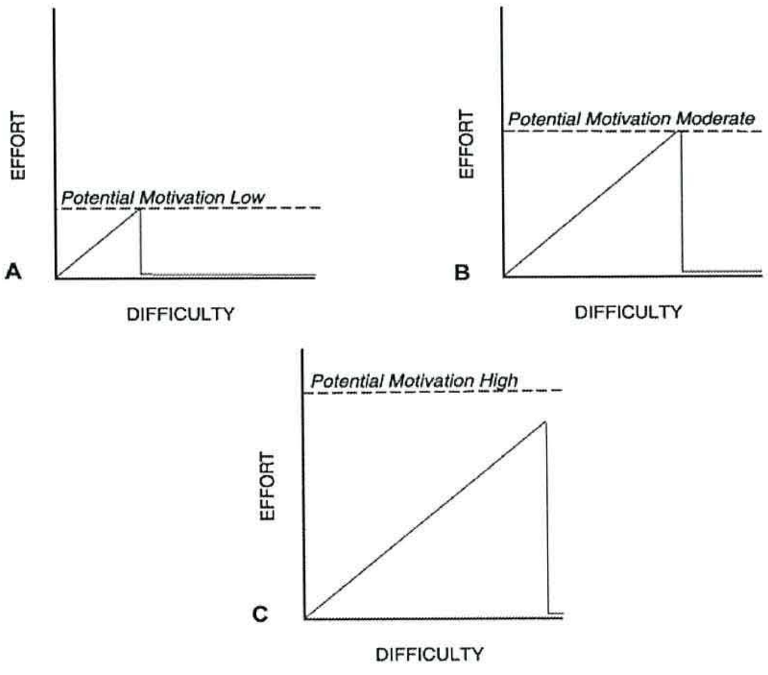


Figure 3

Effort as function of challenge difficulty at low, moderate and high intensity levels of potential motivations (Wright, 2008).

Amann and Calbet (2008) proposed a model relating to convective O2 transport and exercise performance through its effects on fatigue. This selective model does not account for psychological factors at. In contrast, a series of seminal studies were conducted on the effects of different motivational strategies on endurance performance, which suggest the important role of this variable in physical performance. For example, Cabanac (1986) demonstrated how monetary incentives increased the duration on an isometric exercise task. Moreover, he found a high correlation ($r = 0.989$) between the monetary prize offered and the duration in minutes of the exercise. Similarly, Wilmore (1968) noted how the presence of a competitor increased the duration on a time to exhaustion test on cycle ergometer and he demonstrated how social facilitation could affect human performance.

Mosso (in Di Giulio, 2006) and more recently, Marcora et al. (2009) demonstrated how cognitive states such as mental fatigue produce a significant impairment in performance and an increase in perception of effort irrespective of any changes on physiological variables such as ventilation, heart rate, oxygen consumption, blood lactate and cardiac output.

Ikai and Steinhaus (1961) stated more than 50 years ago: "Psychology is a special phase of brain physiology". This sentence encompassed a completely new perspective of considering physiology and psychology as they were traditionally studied. It proposed to overcome the ancient and obsolete dualism body/ mind and suggest the multidisciplinary approach as a successful method of research. It appears almost as an elegant invitation to remember that behind any psychological construct there is a neurological base that can be studied not only qualitatively but also quantitatively.

Definition of perception of effort

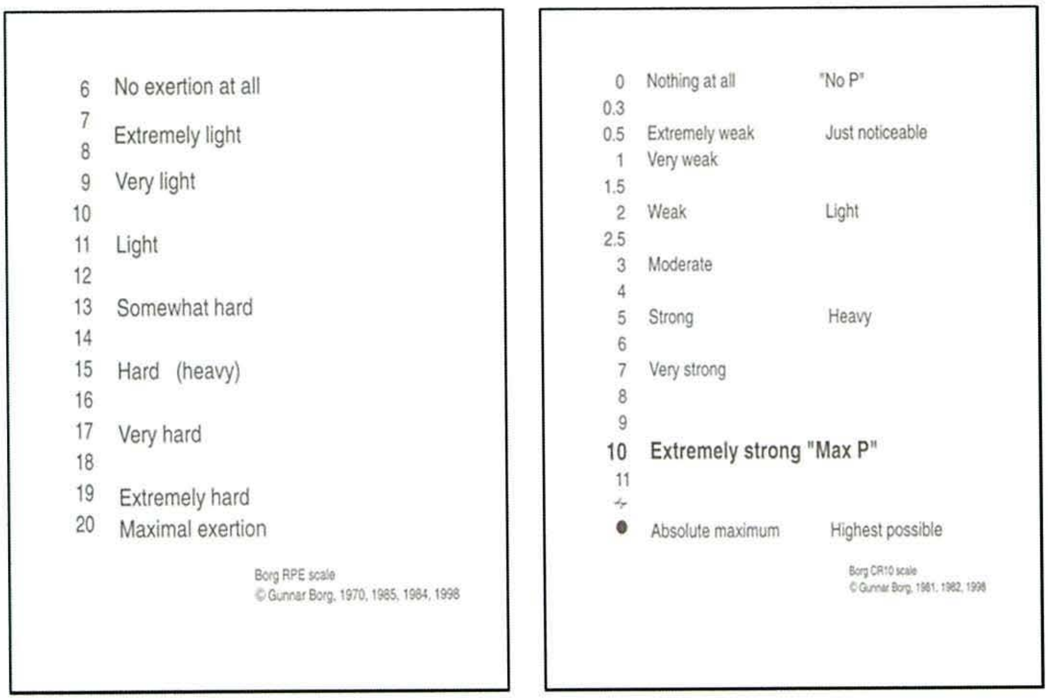
The first definition of perception of effort (or perceived exertion) was provided by Gunnar Borg as "the feeling of how heavy and strenuous a physical task is" (Borg, 1970, 1998). This definition, developed specifically for physical tasks can be in reality applied to any physical or cognitive task. We experience effort not only during physical exertion, but also during mental concentration and self-restraint. As for physical activity, this sensation is mainly related to the active limbs and heavy breathing.

Measuring perception of effort

Perception of effort is commonly measured with the Borg rating of perceived exertion (RPE) scale, which was introduced by Gunnar Borg in the 1960's (Borg, 1970) or with the category-ratio (CR10) scale introduced some years later in 1982 (Borg, 1982). Both scales are presented in Figure 4. The 15-point Borg RPE scale is an equidistant interval scale and the ratings grow linearly with exercise intensity, heart rate, and oxygen uptake

(Borg, 1998). In fact, the scales goes from 6 to 20 so that the rating corresponds on average to the heart rate divided by 10.

The Borg CR10 scale is a category-ratio scale that can be used for rating effort, but also for rating other perceptual intensities, such as pain. The CR10 scale was created to enable direct estimation of intensity levels for inter-individual comparisons. The rating on this scale increases in a nonlinear and positively accelerating manner (Borg, 1982). Moreover, a black dot at the bottom of the scale is used to rate values higher than 10 and so it makes the scale an open scale and thus avoids mechanisms such as "ceiling" effects. Both the 15-point RPE scale and the CR10 scale have been shown to be valid and reliable tools as long as all standardised procedures are correctly executed (Borg, 1998). Standardised procedures for administration of the scale include a clear understanding of the participant about the definition and the nature of the measure and the instructions of the scale. An important factor is the Anchoring of the words of the scale referring as verbal anchoring and the consequent link with the actual number, which is the measure we will collect. Moreover, it is important to have at least one session of familiarization using the scale during a physical task. This familiarization will help the participant to learn how not to over or underestimate the scale in relation of his/her perception. In addition to it, a familiarization can be used to anchor the highest and lowest value the participant perceived. Such method will increase the precision of the measure when used in the following session (Noble and Robertson, 1996)



6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Borg RPE scale
© Gunnar Borg, 1970, 1985, 1984, 1998

0	Nothing at all	"No P"
0.3		
0.5	Extremely weak	Just noticeable
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	**Extremely strong "Max P"**	
11		
⁓		
●	Absolute maximum	Highest possible

Borg CR10 scale
© Gunnar Borg, 1981, 1982, 1998

Figure 4

Borg's RPE scale (left) and CR10 scale (right). From Borg (1998).

Factors influencing perception of effort

Perception of effort is influenced by several physiological and psychological factors.

Perceived exertion increases as workload increases in an incremental task and reflects the relative exercise intensity. Perception of effort also increases with time-on-task when the same exercise intensity is sustained for a prolonged period of time (Hunter et al., 2004; Pincivero et al., 2004; Robertson et al., 2003; Smith et al., 2007; Søgaard et al. 2006). This increase in effort with time-on-task is often considered a sign of muscle fatigue. However, there are several other factors that might underlie the increase in perception of effort over time. A mismatch has been shown between the increase in perception of effort and the loss in muscle strength during sustained low-force contractions (Smith et al., 2007; Søgaard et al., 2006). One possible explanation for this mismatch is that perception of effort might have a cognitive component. This would fit with recent findings that mental fatigue causes an increase in perception of effort during constant-workload cycling in the absence of physiological changes (Marcora et al., 2009).

Perception of effort correlates with a variety of physiological factors. First of all Borg`s original scale (6-20) actually follows variables such as heart rate and oxygen uptake (Borg, 1970). Furthermore metabolic changes such as blood lactate or level of muscle glycogen (Baldwin et al. 2003) have an effect on the perception of effort. Environmental changes such as in temperature or altitude (hypoxia) also have an impact on perceived exertion by increasing RPE at the same workload of exercise when comparing high temperature to lower one and hypoxia with normoxia environment in which participant are performing the physical task (Romer, 2007a).

The subjective nature of (ratings of) effort makes that it can also be affected by psychological and social factors, although it has been pointed out that these factors might be more salient at light and moderate exercise intensities than at high exercise intensities (Noble & Robertson, 1996). Psychological factors that have been shown to influence perception of effort include personality, mood, self-efficacy, and locus of control (Morgan, 1994; Robertson & Noble, 1997). That social factors can influence (ratings of) effort, is shown, for example, by a study where participants rated lower effort together with a coactor than when tested alone (Hardy et al., 1986; Hall & Prestholdt, 1986). Moreover, It has been shown that male participants report significantly lower perceived effort during cycling when the experimenter is female than when the experimenter is male (Boutcher et al., 1988).

Very interestingly, Marcora and colleagues, in a series of studies (Marcora et al. 2008, 2009, Marcora and Staiano, 2010), demonstrated how perception of effort was more than an epiphenomenon correlated with physiological variables. They actually assumed that perception of effort is the primary variable to strictly correlate with endurance performance in such a way that any changes in RPE always reflected changes in task performance. They demonstrated this assumption by isolating RPE from physiological variables such as muscle fatigue, blood lactate concentration, ventilation, heart rate, maximal oxygen consumption and stroke volume.

Biological bases of perception of effort: Afferent sensory dependent or centrally generated?

Up to now, the perception of effort has mainly been investigated from a psychological perspective, mostly related to physical activity. Although it is possible to delineate its correlations with several psychophysiological variables, its actual "origin" in the brain is still unclear. Proposed at first as a sensation, effort has been treated like other sensations such as pain. So it has been thought that the sensation of effort would be generated from physical stimuli (different afferent sensory inputs such as proprioception, pain, thermal discomfort), and that these stimuli are processed in perceptual areas in the brain.

The significant correlations between RPE and multiple physiological markers would support this theory. However, it is important to acknowledge that correlation between two variables does not always mean causation. In fact, there are several studies using spinal blockades such as lidocaine and epidural anaesthesia aimed to block the afferent input (from muscle spindles and Golgi tendon organs and type III and IV afferent fibres) that have shown no effect on RPE (Galbo et al., 1987, Gallagher et al., 2001, Kjaer et al. 1999). A possible explanation is that perception of effort is centrally generated by forwarding neural signals (corollary discharges) from motor to sensory areas of the cerebral cortex. Corollary discharge describes "internal signals that arise from centrifugal motor commands and that influence perception" (McCloskey, 1981, p. 1415). Central motor commands can be defined as "a discharge or pattern of discharge that is generated within the central nervous system and that leads to the excitation of spinal α-motoneurons" (McCloskey, 1981, p. 1421).

Corollary discharges are thought to have perceptual consequences in two distinct ways (McCloskey, 1981). On the one hand, they are thought to modify the processing of incoming sensory information, for example to enable the discrimination between self-generated and external stimuli. Several corollary discharge circuits of this type have now been uncovered across the animal kingdom (Crapse & Sommer, 2008; Poulet & Hedwig, 2007). On the other hand, corollary discharges may give rise to sensations of various kinds in their own right (McCloskey, 1981). This is the type of corollary discharge pathway that is thought to be involved in perception of effort.

Evidence for an important role of corollary discharges in perception of effort comes from experiments that were based on the prediction that conditions in which the central motor command, necessary to achieve a given muscular performance is increased, should lead to increased perception of effort and that conditions in which central motor command is decreased, should lead to decreased perception of effort (McCloskey et al., 1983).

For example, during muscle fatigue a higher than usual central motor command is necessary to produce a certain force. Indeed, the increase in central motor command caused by muscle fatigue was shown to lead to an increase in perception of effort (McCloskey et al., 1974). The same effect was found during partial paralysis induced by injection of a paralysing agent (D-tubocurarine or decamethonium) into the forearm (Gandevia & McCloskey, 1977a, 1977b), and in patients with hemiparesis (Gandevia & McCloskey, 1977a). Another way of changing the central motor command to a muscle (group) is by tendon vibration. Vibration of a tendon leads to excitation of the primary afferents of the muscle spindles. This leads to reflex inhibition in the antagonists and reflex excitation in the agonists (Goodwin et al. 1972). Therefore, when a force needs to be held constant, tendon vibration of the antagonist should lead to an increase in central motor command, and consequently an increase in perception of effort. On the contrary, tendon vibration of the agonist should lead to a decrease in central motor command, and therefore a decrease in perception of effort. Exactly this has been shown to occur when biceps and triceps tendons are vibrated during force matching with biceps contractions (McCloskey et al., 1974).

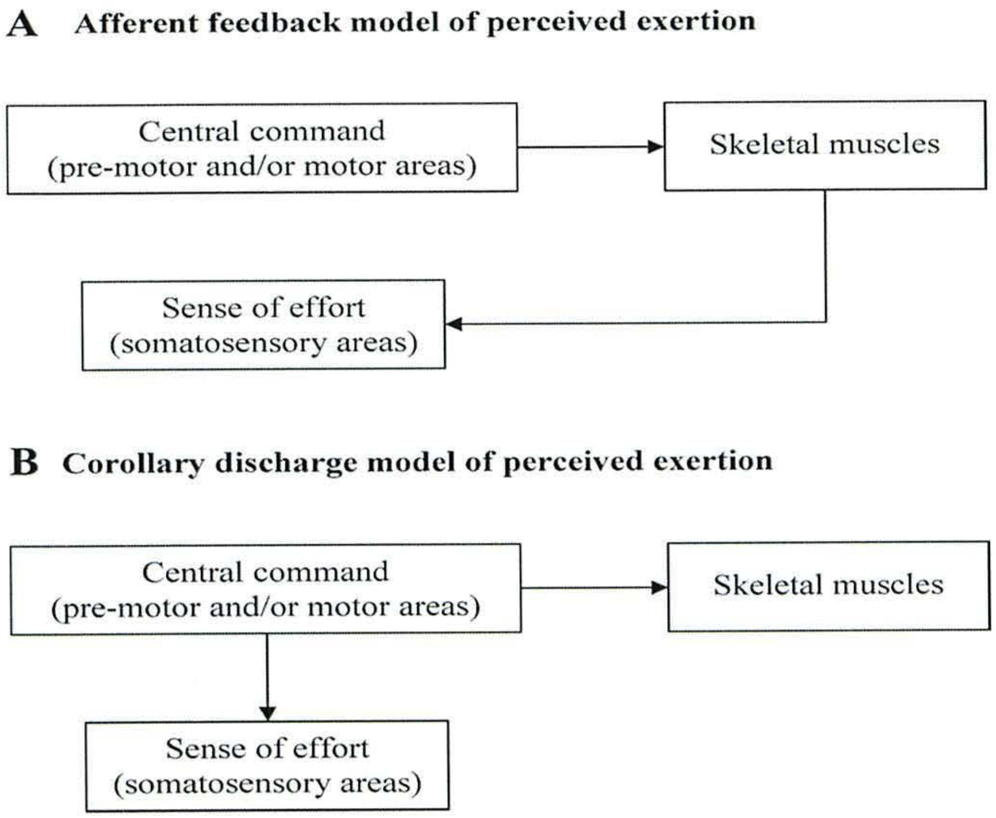


Figure 5

Simplified afferent feedback (A) and corollary discharge (B) models of perceived exertion (Marcora, 2009 with permission).

Neurophysiology of perception of effort

The neurophysiology of the perception of effort is poorly understood. Few studies have been conducted to date which neurophysiologically measure perception of effort. Williamson and colleagues have carried out several experiments using hypnosis to experimentally manipulate perception of effort (Williamson et al, 2006).

For their studies, they have used single-photon-emission computed tomography (SPECT) to measure regional cerebral blood flow (rCBF) distribution in several cerebral cortical areas. They showed that, compared to a control condition, participants rate their effort significantly higher for constant-workload cycling under the hypnotic suggestion that they are cycling uphill, and they are rating their effort significantly lower when under the hypnotic suggestion that they are cycling downhill (Williamson et al., 2001). The uphill condition elicited a significant increase in rCBF distribution to the right thalamic region and right insular cortex, whereas the downhill condition elicited a significant decrease in rCBF distribution to the anterior cingulate cortex and the left insular cortex.

The second study compared RPE and rCBF during actual and imagined (by hypnotic suggestion) handgrip exercise (Williamson et al., 2002). In this case, a group of participants with high hypnotizability was compared with a group of participants with low hypnotizability. It appeared that, during the imagined exercise condition, the high hypnotizability group gave significantly higher ratings of perceived exertion compared with the low hypnotizability group. There was no significant increase in RPE in the low hypnotizability group during the course of the 3 min of imagined handgrip exercise. Significant between-group differences were found in rCBF distribution change scores between actual and imagined exercise conditions in the anterior cingulate cortex, the right inferior insular cortex, and the left inferior insular cortex. Together, these studies suggest that medial prefrontal region (anterior cingulate cortex), insular cortex, and possibly the thalamus are brain areas that might be involved in perception of effort.

Recently, Fontes and colleagues have assessed which brain areas are activated during effortful cycling exercise, by using functional magnetic resonance imaging (fMRI) during cycling on an MRI compatible cycle ergometer (Fontes et al., 2013). They found that the primary motor cortex, primary somatosensory cortex, and cerebellar vermis were significantly more activated during cycling than during rest. Moreover, they compared cycling that was perceived as "hard" (RPE > 15 on 6-20 scale) with cycling that was perceived as less than "hard" (RPE ≤ 15). These preliminary analyses (based on the data of four participants) suggest that the posterior cingulate cortex and the precuneus are involved in perception of effort.

Aim of the thesis

The general aim of the thesis was to investigate the rating of perceived exertion (RPE) as main determinant and limiting factor in exercise tolerance. It has been explored the RPE definition, its neurophysiological and psychological nature and its role as perceptual measure through the most prominent models of exercise tolerance. The second aim of the thesis was to introduce a novel model of exercise tolerance, the psychobiological model of exercise performance and to explore its validity as model to explain exercise tolerance and performance in humans.

Outline of the thesis

Apart from the general introduction and the general discussion, this thesis consists of three manuscripts (chapters 2-4), which have been written as stand-alone papers with the purpose of publication in peer-reviewed journals. All manuscripts are written as independent papers, so at times there is a necessary overlap in the contents.

The aim of the first manuscript (chapter 2) was to provide evidence that muscle fatigue does not limit high intensity aerobic exercise. It has been tested the hypothesis that power expressed on a cycling task does not drop, immediately after a cycling test at exhaustion, below the power required to continue the cycling task. Moreover, it has been tested the hypothesis the decrease in muscle force is not a linear but rather hyperbolic with a plateau which never reached the complete exhaustion.

The aim of the second manuscript (chapter 3) was to define and elucidate the role of perceptual responses such as naturally occurring muscle pain (NOMP) during a physical performance. It has been tested the hypothesis that RPE and NOMP does not have the same impact on high intensity aerobic cycling test. RPE and Pain rating has been measured to assess this hypothesis during a time to exhaustion test.

The aim of the third manuscript (chapter 4) was to test the validity and efficacy of a new protocol, never employed before, to measure muscle fatigue (using big muscle groups such as femoral quadriceps) and perception of effort use functional magnetic resonance imaging. This was an explorative study aimed to test the hypothesis that RPE correlates with an increased in the central motor command expressed and increased in activation of the primary and supplementary cortical areas. The second aim of this study was to test the hypothesis that higher rating of perceived exertion correlate with the activation of cingulate gyrus and insular cortex areas, which are deputy for emotional control and the effort-based decision-making processe

CHAPTER TWO

THE LIMIT TO EXERCISE TOLERANCE IN HUMANS: MIND OVER MUSCLE?

Abstract

In exercise physiology, it has been traditionally assumed that high-intensity aerobic exercise stops at the point commonly called exhaustion because fatigued subjects are no longer able to generate the power output required by the task despite their maximal voluntary effort. We tested the validity of this assumption by measuring maximal voluntary cycling power before (mean ± SD, 1,075 ± 214 W) and immediately after (731 ± 206 W) ($P < 0.001$) exhaustive cycling exercise at 242 ± 24 W (80% of peak work rate measured during a preliminary incremental exercise test) in ten fit male human subjects. Perceived exertion during exhaustive cycling exercise was strongly correlated ($r = -0.82$, $P = 0.003$) with time to exhaustion (10.5 ± 2.1 min). These results challenge the long-standing assumption that muscle fatigue causes exhaustion during high-intensity aerobic exercise, and suggest that exercise tolerance in highly motivated subjects is ultimately limited by perception of effort.

Introduction

The capacity to sustain aerobic exercise (exercise tolerance) is very important for endurance athletes (Coyle et al. 1988), and poor exercise tolerance is strongly associated with disability, risk of cardiovascular disease, and mortality in the general population (Gulati et al. 2005; Myers et al. 2002; Newman et al. 2006). Because of these important implications, the mechanisms determining exercise tolerance have been intensely investigated for over a century (McKenna and Hargreaves 2008). Most of this research has been based on the assumption that, in highly motivated subjects, the tolerable duration of aerobic exercise is limited by central and/or peripheral muscle fatigue (Fig. 6) (Allen et al. 2008; Amann and Calbet 2008; Burnley and Jones 2007; Noakes and St Clair Gibson 2004; Secher et al. 2008; Walsh 2000). In other words, it is assumed that aerobic exercise stops at the point commonly called exhaustion because fatigued subjects are no longer able to generate the power output required by the task despite their maximal voluntary effort. Indeed, task failure/exhaustion is often referred to as the "point of fatigue" (Barry and Enoka 2007).

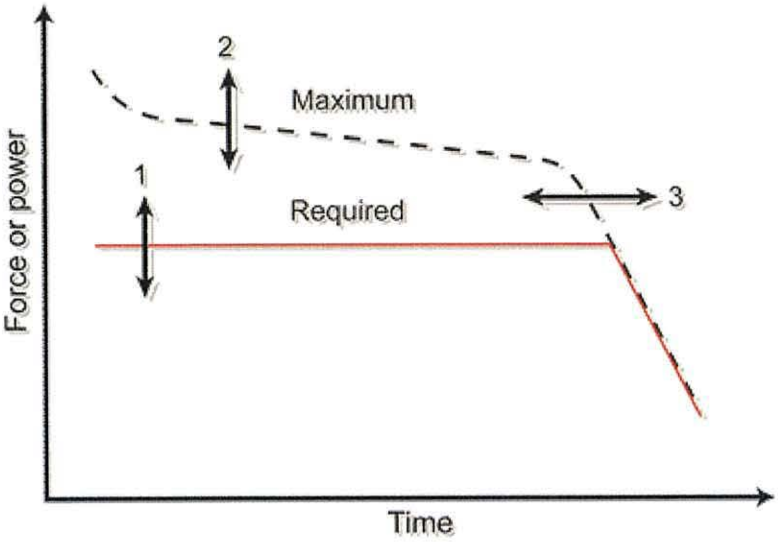


Figure 6

Schematic to illustrate different mechanisms leading to exhaustion. Dashed line shows how the maximum force (or power) declines during repeated tetani. Solid red line indicates a submaximal force required for a particular activity. Exhaustion (failure to produce the required force) occurs at the intersection of the two lines. Increases and decreases in the required force (arrow 1) will cause earlier and later onset of exhaustion, respectively. Increases and decreases in the maximum force that the muscle can produce (arrow 2) will also change the time to exhaustion. Finally, changes in the intrinsic fatigability of the muscle (arrow 3) will also change the time to exhaustion. Reprinted with permission from Allen et al. (2008) (color figure online).

As a result, research into the mechanisms determining exercise tolerance has focused on the cardiovascular, respiratory, metabolic, and neuromuscular mechanisms of muscle fatigue (McKenna and Hargreaves 2008). These physiological mechanisms include limited oxygen delivery (Amann and Calbet 2008; Burnley and Jones 2007), metabolic and ionic changes within the active muscles (Fitts 2008; McKenna et al. 2008), supraspinal reflex inhibition from muscle afferents sensitive to these changes (Amann and Calbet 2008), and altered cerebral blood flow and metabolism (Secher et al. 2008). However, to the best of our knowledge, nobody has ever tested the basic assumption that exhaustion during high-intensity aerobic exercise occurs because fatigued subjects are no longer able to generate the power output required by the task despite their maximal voluntary effort. Therefore, in spite of its long-standing recognition in the field of exercise physiology (Noakes and St Clair Gibson 2004), the validity of the muscle fatigue model of exercise tolerance is unclear.

The primary aim of our study was to test the basic assumption of the muscle fatigue model of exercise tolerance by measuring maximal voluntary cycling power (MVCP) immediately after a time to exhaustion test performed on a cycle ergometer. The secondary aim of the present investigation was to describe the time-course of muscle fatigue induced by high-intensity aerobic exercise.

Methods

Participants

Ten healthy male human subjects were recruited from Bangor University's rugby league team. Their characteristics were age 22 ± 2 years, height

182 ± 7 cm, body mass 81.6 ± 14.0 kg, peak oxygen uptake ($\dot{V}O_{2peak}$) 50.2 ± 6.3 ml/kg/min). All subjects signed an informed consent form describing the study protocol, which was approved by the Ethics Committee of the School of Sport, Health and Exercise Sciences, Bangor University, according to the standards set by the Declaration of Helsinki.

Procedures

Visit 1

Participants visited the Physiology Laboratory on five different occasions with a minimum of 48 h between visits. All visits were completed within a period of 2 weeks. Environmental conditions in the laboratory were kept between 18 and 22°C for temperature and 45 and 60% for humidity.

During the first visit, subjects performed a preliminary incremental exercise test (2 min at 50 + 50 W increments every 2 min) until exhaustion [operationally defined as a pedal frequency of <60 revolutions/min (RPM) for more than 5 s despite strong verbal encouragement] on an electromagnetically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands) to measure their $\dot{V}O_{2peak}$ and peak work rate. Oxygen uptake was measured breath-by-breath using a computerized metabolic gas analysis system (MetaLyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany) connected to an oro-(mouth) mask (7600 series, Hans Rudolph Inc., Kansas City, MO, USA). The highest 1 min average was taken as $\dot{V}O_{2peak}$. Before each test, the system was calibrated using certified gases of known concentration (11.5% O_2 and 5.1% CO_2) and a 3.0 l calibration syringe (Series 5530, Hans Rudolph Inc., Kansas City, MO, USA). Peak work rate was calculated according to the equation of Kuipers et al. (1985). The cycle ergometer was set in hyperbolic mode, which allows the power output to be set independently of the freely chosen pedal frequency over the range of 40–120 RPM. Before the incremental exercise test, the position on the cycle ergometer was adjusted for each subject, and settings were recorded so that they could be reproduced at each subsequent visit. Participants were also given standard instructions for overall rating of perceived exertion (RPE) using the 15-point scale developed by Borg (1998). During the incremental exercise test, the scale low (7 extremely light) and high (19 extremely hard/heavy) anchor points were established as previously described (Noble and Robertson 1996).

Furthermore during the first visit, participants were familiarized with the MVCP test. This test is very similar to the standard Wingate Test but lasts only a few seconds. Subjects were instructed to sit on the ergometer and cycle as fast and as hard as possible for the entire duration of the test (7–8 s in total). After an unloaded (i.e., zero resistance) phase of 2–3 s to reach a high RPM, a resistance corresponding to 7.5% of body mass was generated for 5 s by the electromagnetically braked cycle ergometer which was set in the RPM-dependent linear mode. MVCP was operationally defined as the average power output calculated by the Lode Wingate software package (version 1.09, Groningen, The Netherlands) during the loaded phase of the test. Strong verbal encouragement was provided during all MVCP tests.

Visit 2

During the second visit, subjects cycled for 10 min at 40% of peak work rate with the ergometer set in hyperbolic mode. As soon as participants stopped this warm-up, one operator immediately exited the manually controlled hyperbolic mode (1 s), and subjects started the unloaded phase of the MVCP test. In the meantime, another operator entered the computer-controlled linear mode to start the loaded phase of the MVCP test. This time-point was defined as 0% of time to exhaustion.

After 30 min of rest, participants were asked to perform the time to exhaustion test. This high-intensity aerobic exercise test consisted of a 3-min warm-up at 40% of peak work rate followed immediately by a workload corresponding to 80% of peak work rate. Both power outputs were generated with the cycle ergometer set in hyperbolic mode. Time to exhaustion was measured from the end of warm-up until the pedal frequency was <40 RPM for more than 5 s despite strong verbal encouragement. Such a low RPM was selected to operationally define exhaustion in order to induce as much physiological and muscular strain as possible (Deschenes et al. 2000).

Immediately after exhaustion, subjects performed the MVCP test as described above. This time-point was defined as 100% of time to exhaustion. In order to motivate the participants to cycle for as long as possible during the time to exhaustion test, monetary rewards were given for the three best performances (£50, £30, £10). In order to stimulate competition and with all participants prior consent, a rank with all individual times to exhaustion was circulated at the end of the study. During the time to exhaustion test, RPE was recorded in the last 15 s of each minute.

Visits 3, 4, 5

In the following three visits, subjects were asked to repeat, in a random order, three more bouts of high-intensity aerobic exercise using the same procedures of the time to exhaustion test. However, in these three occasions, participants were stopped at 25, 50 or 75% of time to exhaustion measured during the second visit. Immediately after stoppage, subjects performed the MVCP test as described above.

General procedures

Heart rate (Polar S610i, Polar Electro OY, Kempele, Finland) and RPE were recorded in the last 15 s of each exercise bout (0, 25, 50, 75, and 100% time to exhaustion). Furthermore, immediately after each MVCP test, a 5 μl sample of whole fresh blood was taken from the right earlobe and analysed for lactate concentration using a portable analyser (Lactate Pro LT-1710, Arkray, Shiga, Japan).

All participants were given written instructions to drink 35 ml of water per kilogram of body weight, sleep for at least 7 h, refrain from the consumption of alcohol, and avoid any vigorous exercise the day before each visit. Participants were also instructed to avoid any caffeine and nicotine for at least 3 h before testing. At each visit to the lab, subjects were asked to complete a pre-test checklist to ascertain that they had complied with the instructions given to them. Participants were also asked to declare if they had taken any medication/drug or had any acute illness, injury, or infection.

Data analysis

Data were explored for normality and homogeneity of variance, and are presented as mean ± SD unless noted otherwise. The effects of exercise duration (0, 25, 50, 75, and 100% of time to exhaustion) on MVCP, heart rate, blood lactate concentration, and RPE were tested using one-way repeated measures ANOVAs. If the assumption of sphericity was violated, the Greenhouse–Geisser correction was employed. In such cases, the uncorrected degrees of freedom are reported between square brackets in conjunction with the respective epsilon values. The correlation between RPE at isotime (the highest common exercise duration achieved by all subjects during the time to exhaustion test) and time to exhaustion was assessed by Pearson product-moment correlation coefficient. The difference between MVCP measured immediately after exhaustion and the power output required by the time to exhaustion test was tested using a paired-samples t test. Significance was set at 0.05 (two-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 14.

Results

During the preliminary incremental exercise test, subject reached a peak work rate of 302 ± 30 W. Therefore, in the subsequent time to exhaustion test, subjects cycled at 242 ± 24 W until exhaustion which occurred after 10.5 ± 2.1 min. During this test, the average pedal frequency was 75 ± 10 RPM.

Repeated measures ANOVAs show that heart rate [F(4) = 152.20, P < 0.001] (Fig. 7a), blood lactate concentration [F(4) = 26.92, P < 0.001] (Fig. 7b), and RPE [F(4) = 82.32, P < 0.001] (Fig. 7c) increased significantly with increasing exercise duration reaching high values at exhaustion (heart rate 183 ± 10 beats/min; blood lactate concentration 10.4 ± 1.9 mmol/l; RPE 19.6 ± 0.7). These physiological and perceptual responses to aerobic exercise confirm that the time to exhaustion test was very intense, and that participants were highly motivated to cycle for as long as possible.

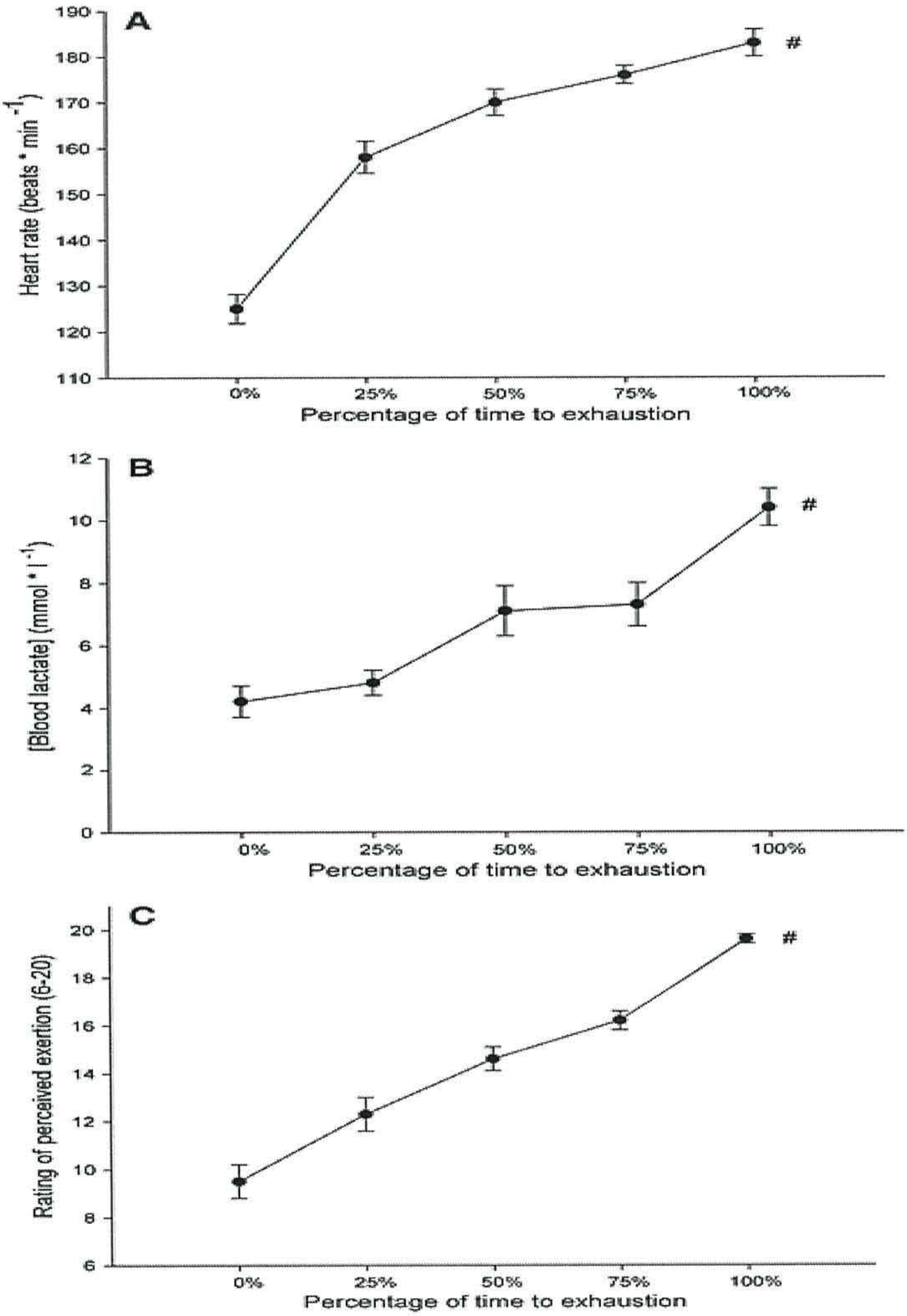


Figure 7

Effects of exercise duration on physiological and perceptual responses to high-intensity aerobic exercise. $^{\#}$Significant main effect of time ($P < 0.05$). Data are presented as mean ± SEM.

High-intensity aerobic exercise significantly reduced MVCP from its initial value of 1,075 ± 214 W [F(4) = 35.98, ε = 0.42, $P < 0.001$) (upper line in Fig. 8). Follow-up tests with Bonferroni correction revealed a significant reduction in MVCP between 0 and 25% of time to exhaustion ($P = 0.001$), and again between 75 and 100% of time to exhaustion ($P = 0.027$). No significant differences were observed between 25 and 50% of time to exhaustion ($P = 1.000$), and between 50 and 75% of time to exhaustion ($P = 0.209$). Pedal frequency during the five MVCP tests was, on average, 137 ± 13 RPM.

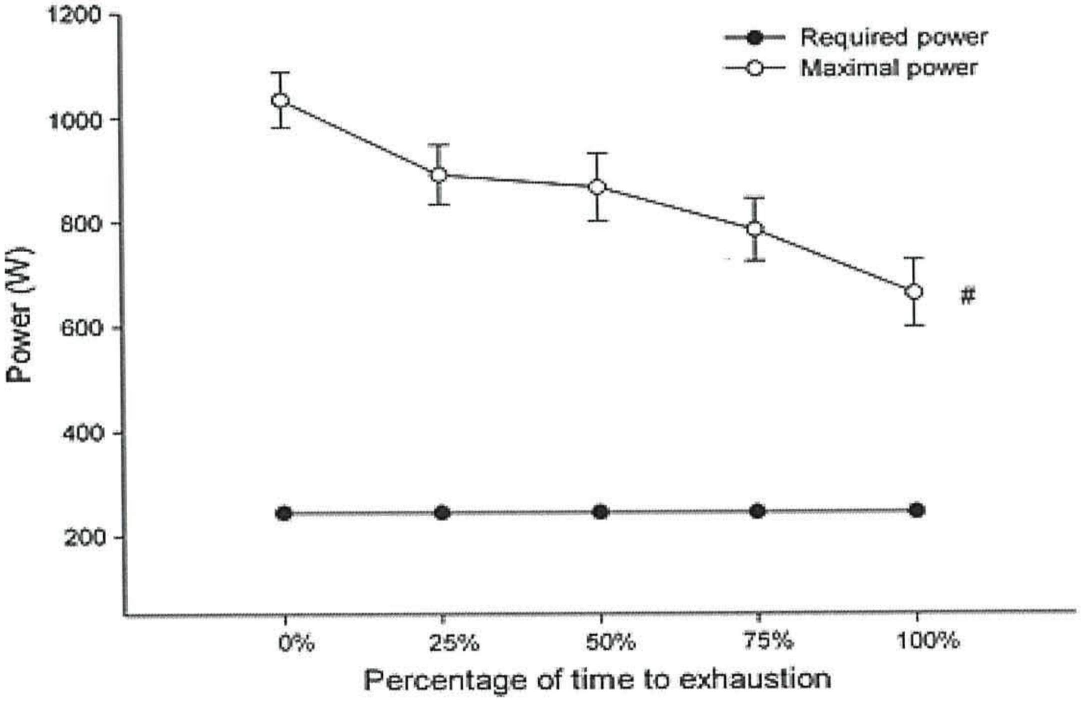


Figure 8

Effect of exercise duration on maximal voluntary cycling power (upper line) and the power output required by the time to exhaustion test (lower line). $^{\#}$Significant main effect of time ($P < 0.05$). Data are presented as mean ± SEM.

Crucially, MVCP measured immediately after exhaustion (731 ± 206 W) was three times the power output required by the time to exhaustion test (lower line in Fig. 8) [t (9) = 7.89, P < 0.001]. Individual results are shown in Fig. 9. In all ten participants, MVCP measured immediately after exhaustion was well above the power output required by the time to exhaustion test.

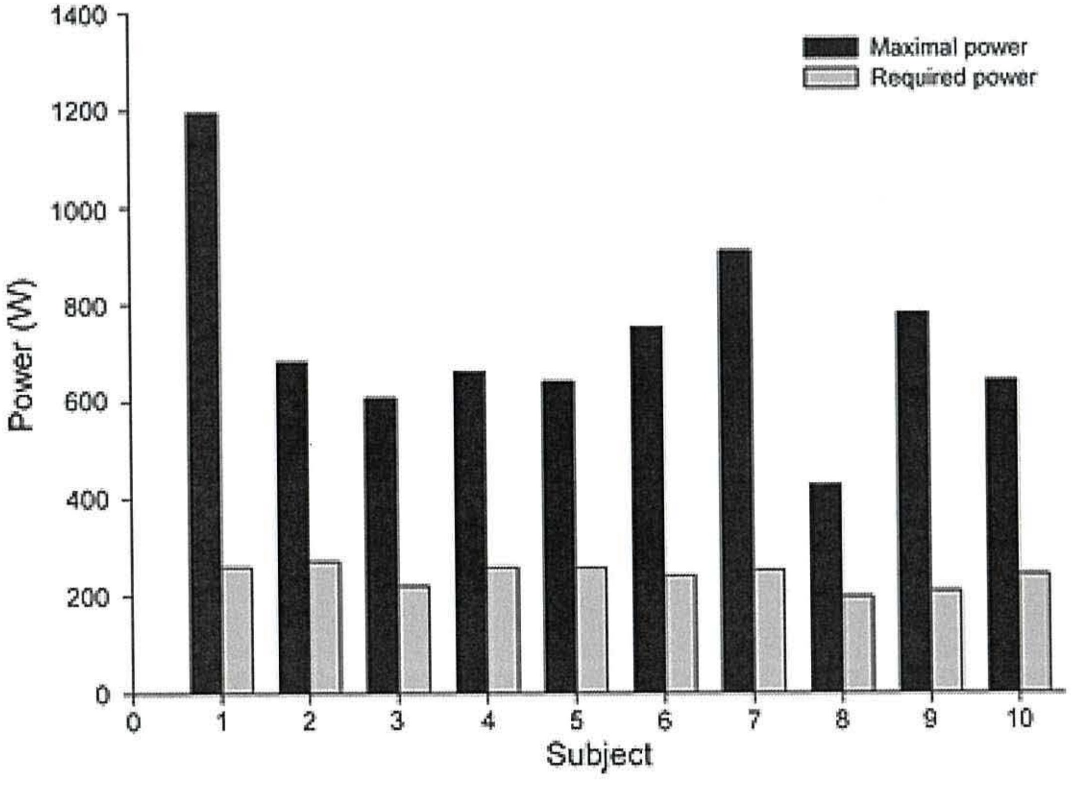


Figure 9

Individual maximal voluntary cycling power measured immediately after exhaustion and the power output required by the time to exhaustion test.

The negative correlation between RPE at isotime (8 min of the time to exhaustion test) and time to exhaustion was highly significant (r = −0.82, P = 0.003) (Fig. 10).

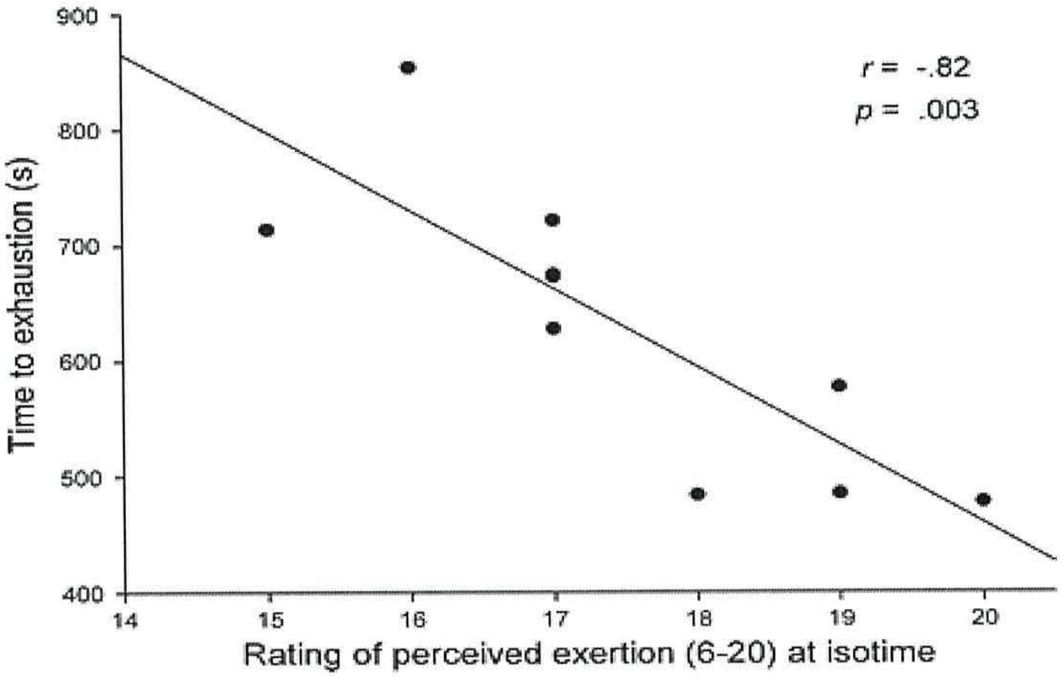


Figure 10

Correlation between rating of perceived exertion at isotime (8 min of the time to exhaustion test) and time to exhaustion.

High-intensity aerobic exercise and muscle fatigue

As expected, high-intensity aerobic exercise induced significant muscle fatigue defined as any exercise-induced decrease in maximal voluntary force or power produced by a muscle or muscle group (Gandevia 2001) (Fig. 8). In fact, MVCP was reduced by 32% immediately after the time to exhaustion test. A 25% reduction in MVCP has been previously reported after 6 min of aerobic cycling exercise at an intensity (80–90% $\dot{V}O_{2peak}$) similar to that of our time to exhaustion test which lasted, on average, more than 10 min (Beelen and Sargeant 1991; Yano et al. 2001). The lower degree of muscle fatigue compared to our study can be explained by the shorter duration of the non-exhaustive cycling tasks used in these investigations.

Interestingly, the time-course of muscle fatigue measured in our study employing maximal voluntary contractions (MVC) in humans is similar to the one observed in studies of electrically stimulated muscle fibres: an early reduction, a plateau, and a late reduction (Fig. 6) (Allen et al. 2008). However, this similarity may be purely coincidental. The early reduction in MVCP followed by a plateau has been observed before (Sargeant and Dolan 1987), and may be caused by metabolic stress in a relatively small population of fast fatigue-sensitive muscle fibres (peripheral fatigue)

(Sargeant 2007). On the other hand, the late reduction in MVCP may be due to reduced CNS capacity to drive the muscles fully (central fatigue) (Amann and Calbet 2008; Secher et al. 2008). Unfortunately, at present, there are no valid methods to differentiate between central and peripheral muscle fatigue during a MVCP test. However, studies using isometric muscle function tests with magnetic and/or electric stimulation suggest that both neural and muscular mechanisms contribute to the muscle fatigue induced by high-intensity aerobic exercise (Amann et al. 2006; Lepers et al. 2001; Romer et al. 2007; Sidhu et al. 2009; Taylor and Romer 2008).

Muscle fatigue and exhaustion during high-intensity aerobic exercise

From a functional point of view, however, differentiation between central and peripheral fatigue is irrelevant; what matters is overall muscle fatigue, i.e., the exercise-induced decrease in MVCP. It is traditionally assumed that exhaustion during high-intensity aerobic exercise occurs because fatigued subjects are no longer able to generate the power output required by the task despite their maximal voluntary effort. Therefore, MVCP measured immediately after exhaustive high-intensity aerobic exercise should not be significantly different from the power output required by the time to exhaustion test. We have demonstrated for the first time that this is not the case. In fact, immediately after exhaustive high-intensity aerobic exercise, subjects could produce a MVCP that was, on average, three times the power output required by the time to exhaustion test (Fig. 8). This significant finding was highly reproducible across all participants who had considerable neuromuscular reserve immediately after exhaustion (Fig. 9).

It may be argued that the capacity of the neuromuscular system to produce power increased from <242 to 731 W in the 3–4 s period (1 s rest + 2–3 s of maximal unloaded cycling) between exhaustion and the loaded phase of the MVCP test. However, the occurrence of such large and fast neuromuscular recovery is unlikely given current evidence that MVCP after high-intensity aerobic exercise recovers with a half-time of ~32 s (Sargeant and Dolan1987). Furthermore, several studies employing constant-power cycling tests of similar intensity and duration have measured significant peripheral locomotor muscle fatigue several minutes after exhaustion (Amann et al. 2006,2007; Romer et al. 2007; Taylor and Romer 2008). Similarly, central fatigue persists long after termination of high-intensity locomotor exercise as recently demonstrated by Sidhu et al. (2009). Therefore, an exceptionally quick recovery of peripheral and/or central fatigue can be excluded.

It may also be argued that physiological differences between the two tasks (e.g., motor unit recruitment and energy substrates) could explain the large difference between MVCP immediately after exhaustion and the power output required by the time to exhaustion test. However, this is irrelevant to the aims of our study. In fact, even in fatigued subjects, there is a hyperbolic relationship between power output and tolerable exercise duration (Ferguson et al.2007). Therefore, if our subjects were able to voluntarily produce 731 W for 5 s immediately after exhaustion, they must have been physiologically able to produce 242 W for much longer.

The most likely explanation for the very high MVCP produced immediately after exhaustion is psychological. Subjects knew that the final MVCP test was going to last only 5 s, and such knowledge motivated them to exert further effort after the time to exhaustion test which had a longer and unknown duration. The effect of expected test duration on effort mobilization has been recently investigated (Wittekind et al. 2009), and the results support our hypothesis: people exert their true MVCP only when expected test duration is <30 s. Therefore, the very high MVCP measured immediately after exhaustion provide strong evidence against the long-standing assumption that exhaustion during high-intensity aerobic exercise occurs when fatigued subjects are no longer able to generate the power output required by the task despite their maximal voluntary effort.

Perception of effort and exhaustion during high-intensity aerobic exercise

So if muscle fatigue does not limit exercise tolerance in humans, what does? According to the psychobiological model of exercise tolerance (Marcora 2008; Marcora et al. 2008, 2009) based on motivational intensity theory (Brehm and Self 1989; Wright 2008), exhaustion is a form of task disengagement rather than task failure. In other words, our participants decided to "give up" (i.e., disengage from the task) either because the effort required by the time to exhaustion test exceeded the greatest effort they were willing to exert in order to succeed in the task (the so-called potential motivation), or because effort was so high that cycling for much longer seemed beyond their perceived ability (Wright 1998). This proposal is supported by the finding that RPE in our highly motivated subjects was nearly maximal at the end of the time to exhaustion test (19.6 on a 6–20 scale). This finding is common across a variety of exercise tasks, physiological and environmental conditions, and experimental manipulations (e.g., Amann et al. 2006; Crewe et al. 2008; Eston et al. 2007; Jacobs and Bell 2004; Marcora et al. 2008, 2009; Martin 1981; Romer et al. 2007; Taylor and Gandevia 2008), and suggests that perception of effort may be the cardinal "exercise stopper" physiologists have searched for over a century among the cardiovascular, respiratory, metabolic, and neuromuscular mechanisms of muscle fatigue (Gandevia 2001; Gandevia et al. 2000).

Furthermore, we have found a strong negative correlation between RPE at isotime (8 min of the time to exhaustion test) and time to exhaustion (Fig. 10). Again, this is not a novel finding; previous studies have consistently shown that RPE is a strong predictor of exercise tolerance (Crewe et al. 2008; Eston et al. 2007; Horstman et al. 1979; Nakamura et al. 2008; Noakes 2008). In addition to this correlative evidence, support to the proposal that perception of effort and potential motivation are the key-determinants of exercise tolerance comes from experiments in which these two parameters have been manipulated independently from the cardiovascular, respiratory, metabolic and neuromuscular mechanisms of muscle fatigue thought to determine exercise tolerance (Burnley and Jones 2007; McKenna and Hargreaves 2008). In these experimental studies, mental fatigue (Marcora et al. 2009), sleep deprivation (Martin 1981), a psychostimulant (Jacobs and Bell 2004), the presence of a competitor

(Wilmore 1968), and monetary reward (Cabanac 1986) had a significant effect on time to exhaustion.

Importantly, the psychobiological model of exercise tolerance can explain the negative effect of experimental locomotor muscle fatigue on time to exhaustion (Gagnon et al. 2009; Marcora et al. 2008) which, in the light of the present results and discussion, may seem paradoxical. On the contrary, this finding can be explained by the significant effect of experimental muscle fatigue on perception of effort. In fact, cycling at a given power output with pre-fatigued locomotor muscles requires higher than normal effort as reflected by higher RPE compared to the control condition (Gagnon et al. 2009; Marcora et al. 2008). Because perception of effort increased over time in both conditions, subjects in the experimental locomotor muscle fatigue condition reached the same high RPE and disengaged from the time to exhaustion test earlier than in the control condition despite having considerable neuromuscular reserve (Gagnon et al. 2009; Marcora et al. 2008).

Muscle fatigue, perception of effort and exhaustion during other forms of exercise

We are the first to demonstrate that muscle fatigue does not cause exhaustion during high-intensity aerobic exercise. However, a similar phenomenon has been described by other authors during isometric tasks performed with isolated muscle groups at a relative exercise intensity (20% of MVC) (Hunter et al. 2004, 2008; Yoon et al. 2007) similar to that of our study (23 ± 3% MVCP). In these studies, despite significant muscle fatigue, the MVC measured after "task failure" was well above the force required by these isometric tasks (Hunter et al. 2004, 2008; Yoon et al. 2007). Again it is clear that fatigue of the principal muscles can not explain why exercise is terminated (Enoka and Duchateau 2008). As in our study, task disengagement during these isometric tasks was associated with high RPE (Hunter et al. 2004, 2008; Yoon et al. 2007). This finding provides further support to the psychobiological model of exercise tolerance, and extends it to low-intensity isometric tasks performed with isolated muscle groups. Muscle fatigue seems to cause task failure only when submaximal exercise requires more intense muscle contractions (80% MVC) (Yoon et al. 2007). Examples of such activities would be resistance training or certain activities of daily living in sedentary old adults (Hortobagyi et al. 2003).

Conclusions

The results of the present study challenge the long-standing assumption that central and/or peripheral muscle fatigue causes exhaustion during high-intensity aerobic exercise (Amann and Calbet 2008; Burnley and Jones 2007; Noakes and St Clair Gibson 2004; Secher et al. 2008; Walsh 2000), and suggest that exercise tolerance in highly motivated subjects is limited by perception of effort as postulated by the psychobiological model based on motivational intensity theory (Brehm and Self 1989; Marcora 2008; Marcora et al. 2008, 2009; Wright 2008). Future research should test further the validity of the psychobiological model of exercise tolerance, and investigate the neural correlates of psychological constructs relevant to exercise tolerance such as perceived exertion (Marcora 2009; Williamson et al. 2001) and potential motivation (Pessiglione et al. 2007).

CHAPTER THREE

PERCEPTUAL LIMITS TO EXERCISE TOLERANCE IN HEALTHY HUMANS: PAIN OR EFFORT?

Abstract

Rating of perceived exertion (RPE) and naturally occurring muscle pain (NOMP) are thought to be the main perceptual factors influencing physical performance, in particular endurance. RPE is defined as conscious sensation of how heavy and strenuous a physical activity is (Marcora, 2010). NOMP refers to the muscle pain induced by physical exercise. Although extensively studied, it remains unclear their impact on endurance performance and the relationship between the two mechanisms. We tested the hypothesis that during high intensity cycling performance RPE and NOMP are distinct sensations and that the effect of NOMP of performance is minimal. 12 subjects, after familiarisation, undertook two tests: cold pressor test (CPT) and a cycling test at constant load (80% of peak power output) to exhaustion (TTE). Pain unpleasantness (Cook`s scale, 0-10) and perceived exertion (RPE) (Borg`s scale, 6-20) were rated. Using the CPT as anchoring test for pain, results in the cycling task showed a constant increase in RPE until subjects withdrew exercise while NOMP rating stopped at a moderate level without reaching the maximal rating. Those results suggest that a subjective distinction exists between the NOMP and RPE and the higher rate of RPE at exhaustion compared with the NOMP support the hypothesis that NOMP does not have a significant impact on endurance cycling performance while highest rates of RPE are strongly correlated with exhaustion during high intensity cycling aerobic power.

Introduction

In the last decades, perceptual processes occurring in the brain have become of crucial interest in our understanding of the limits of exercise tolerance in humans. Several studies (Cook et al. 1997; O`Connor and Cook 1999; Hollander et al. 2003; Marcora et al. 2009; Marcora and Staiano, 2010; Amann et al. 2009, 2010; Mauger et al. 2010. Noakes 2011) highlight the relationship between exercise performance and perceptual mechanisms of pain and effort and they underline the role of sensory perceptual processes as determinants of exercise performance.

Perception of effort is defined as "the conscious sensation of how hard, heavy and strenuous a physical task is" (Marcora, 2010) and thus it does not refer to either muscle pain or general discomfort. Pain, instead, is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Associations for Study of Pain", 1979).

Although these sensory constructs have gained scientific importance, it is still debated the conceptualisation of these terms and their neurophysiological basis. For several years, naturally occurring muscle pain (NOMP), which refers to exercise-related pain, has been considered a limiting factor during sport competition, contributing to the belief that pain tolerance would predict successful outcome in a competition, in particular endurance performance (Anschel & Russel, 1994). However, scientific evidence in support of this theory is unclear and results from several studies conducted on the relationship between pain and performance have shown controversial outcomes (Cook et al. 1997, O`Connor and Cook 1999; Cook 2006; Maugher et al. 2010; Amann 2009, 2010).

Two main limitations can be identified in the studies conducted so far on the role of pain in endurance performance: The first is a conceptual issue as pain has been interpreted as a mono dimensional variable while, as Cabanac suggested (1979), it may reflect a tridimensional characteristic (quantity, quality and affective valance of pain). Such tridimensionality is demonstrated as well neurophysiologically as different brain areas seems to generates different pain dimensions (Peyron et al., 2000). Therefore, researchers should carefully administer perceptual measures in order to collect valid and reliable data (Marcora, 2011). While quality of pain depends upon the type of pain stimulus utilized, the intensity reflect a quantitative measure of a certain stimulus provided, however, it is the valence (how noxious and unpleasant) of such stimulus, which delineates the impact it has on any behaviour (Anderson and Sobel, 2003; Arana et al., 2003; Rainville, 2002; Small et al., 2003).

The second is a technical issue, as most of the studies proposed to measure NOMP do not employ a valid anchoring technique to account for minimum and maximal values of NOMP rating. A correct anchoring renders perceptual measures valid and reliable across trials (Noble and Robertson, 1996).

The aim of the current study was to measure the rating of NOMP unpleasantness, which represent the affective dimension of muscle pain related to exercise and the RPE during a high intensity constant load endurance task and furthermore to compare the impact that both perceptions have on endurance performance. We test the experimental hypothesis that during high intensity constant load exercise RPE will increase and reach its highest rate at the cycling exhaustion and the rate of NOMP, instead, would not reach its maximal value.

We used the cold pressor test (CPT) as a method to induce experimental pain prior to the physical task and we will ask the participants to rate their Pain unpleasantness in order to generate a valid and reliable anchoring for the subjects in the following cycling task (Lovallo, 1975). Moreover, by measuring unpleasantness of the two different stimuli we will be able to normalize the rating of experimental pain produced by the CPT (unpleasantness due to the CPT test) with the NOMP rating produced during the cycling task (unpleasantness due to the NOMP during the cycling test). The anchoring of the CPT test prior the cycling exercise may help participants to produce a more valid rate of NOMP and thus to better quantify the impact of NOMP and RPE during a high intensity cycling performance. .

Methods

Participants

Twelve healthy volunteers were recruited (eight males and four females). Their characteristics were age (mean ± standard deviation) 26 ± 2 years, height 174 ± 7 cm, body mass 74.6 ± 11.0 kg, peak oxygen uptake ($\dot{V}O_{2peak}$) 65.2 ± 6.3 ml/kg/min). Eligibility criteria were being between 18 and 44 yr old, being involved in intense aerobic training, being free of any known disease, and not taking any medication with the exception of contraceptives. All subjects were highly trained endurance athletes of either cycling or triathlon. All subjects signed an informed consent form describing the study protocol, which was approved by the Ethics Committee of the School of Sport, Health and Exercise Sciences, Bangor University, according to the standards set by the Declaration of Helsinki.

Design and Procedures

Participants visited the physiology laboratory on two different occasions with a minimum of 48 h between visits. All visits were completed within a period of 1 week. Environmental conditions in the laboratory were kept between 18 and 22°C for temperature and 45 and 60% for humidity through air condition system.

Familiarisation visit

Participants were familiarised with the (CPT). Participants sat comfortably and were asked to immerse the hand up to the wrist in ice water and to keep it there until it felt too uncomfortable to continue. Participants were instructed that they could move the hand or keep it still as they wanted, and that maximum possible tolerance time limit was set by the researchers to 10 minutes, at which point they would be asked to remove the hand from the water (Mitchell 2004). Pain was measured every 30 seconds using the CR 0-10 category-ratio pain scale (Cook et al.1997). During the CPT the scale low (0.5 very faint pain) and high (10 extremely intense pain) anchor points were established (Noble and Robertson, 1996).

After the CPT was concluded, subjects had a break of 30 min and then they performed a preliminary incremental exercise test (2 min at 50 + 50 W increments every 2 min) until exhaustion [operationally defined as a pedal frequency of <60 revolutions/min (RPM) for more than 5 s despite strong verbal encouragement] on an electromagnetically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands) to measure their $\dot{V}O_{2peak}$ and peak aerobic power. Oxygen uptake was measured breath-by-breath using a computerized metabolic gas analysis system (MetaLyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany) connected to an oro-(mouth) mask (7600 series, Hans Rudolph Inc., Kansas City, MO, USA). The highest 1 min average was taken as VO_{2peak}. Before each test, the system was calibrated using certified gases of known concentration (11.5% O_2 and 5.1% CO_2) and a 3.0 l calibration syringe (Series 5530, Hans Rudolph Inc., Kansas City, MO, USA). Peak aerobic power was calculated according to the equation of Kuipers et al. (1985). The cycle ergometer was set in hyperbolic mode, which allows the power output to be set independently of the freely chosen pedal frequency over the range of 40–120 RPM. Before the incremental exercise test the position on the cycle ergometer was adjusted for each subject, and settings were recorded so that they could be reproduced at the subsequent visit. Participants were also given standard instructions for overall rating of perceived exertion (RPE) using the 15-point scale developed by Borg (1970). During the incremental exercise test, the scale low (7 extremely light) and high (19 extremely hard/heavy) anchor points were established as previously described (Noble and Robertson, 1996).

Main visit

During the main visit participants firstly were asked to perform the CPT as previously described. After 30 min of rest, they were asked to perform a time to exhaustion test. This high-intensity aerobic exercise test consisted of a 3-min warm-up at 40% of peak aerobic power followed immediately by a workload corresponding to 80% of peak aerobic power measured during the incremental exercise at exhaustion in the familiarisation visit. Both power outputs were generated with the cycle ergometer set in hyperbolic mode. Time to exhaustion was measured from the end of warm-up until the pedal frequency was <60 RPM for more than 5 s despite strong verbal encouragement. Heart rate (Polar S610i, Polar Electro OY, Kempele, Finland), RPE and Pain were recorded in the last 15 s of each minute. Pain and RPE scales were administrated in a randomized sequence in order to avoid any order effect. Furthermore, immediately after exhaustion a 5 µl sample of whole fresh blood was taken from the right earlobe and analysed for lactate concentration using a portable analyser (Lactate Pro LT-1710, Arkray, Shiga, Japan).

Before each visit all participants were given written instructions to drink 35 ml of water per kilogram of body mass, sleep for at least 7 h, refrain from the consumption of alcohol, and avoid any vigorous exercise the day before each visit. Participants were also instructed to avoid any caffeine and nicotine for at least 3 h before testing. At each visit to the lab, subjects were asked to complete a pre-test checklist to ascertain that they had complied with the instructions given to them. Participants were also asked to declare if they had taken any medication/drug or had any acute illness, injury, or infection.

Apparatus for cold pressor stimulus

A 48-quart cooler was used as the cold pressor stimulus. The cooler was filled with ice and water. A cylindrical metal grate was used to keep the ice on one side of the cooler in order to avoid any contact of the participant's hand directly with the ice. Temperature of the water was measured using a thermistor immersed in the water directly in the centre of the cooler (YSI temperature probe, Henleys Medical, Hertforshire, UK) and connected to a temperature monitor (YSI Precision 4000, Henleys Medical, Hertforshire).

Temperature was constantly kept between 0.1° and 0.3° C by adding more ice in the cooler if necessary.

Psychological measures

Pain rating

CR 0-10 Pain scale (Cook et al., 1997) was used to assess unpleasantness of pain (affective dimension) perceived during the CPT and TTE test. By measuring the affective dimension, it is possible to compare two or more pain perceptions even if the quality and the intensity of the stimuli is different (Cabanac, 1979). Participants were asked to rate the pain in terms of unpleasantness of pain experienced during the CPT and the high intensity cycling task.

Rating of perceived exertion

The 6-20 RPE scale (Borg, 1970) was used to assess the effort participants perceived during the exercise. As described in Cook at al. (1997) we used the 6-20 scale to minimize the possible effect to obtain similar ratings of RPE and NOMP only due to the similarity of the two scales. Participant were instructed to rate how hard they needed to drive their legs and the overall sensation of how strenuous exercise is. Moreover, they were reminded not to include in this rating any sensation depending on muscle pain, i.e. the aching and burning sensation in your leg or arm muscles.

Data analysis

Data were explored for normality and homogeneity of variance, and are presented as mean ± SD unless noted otherwise. The effect of exercise duration, measured as Isotime in percentage of each participant`s TTE at 25, 50, 75, and 100%, was tested on pain rating and RPE using one-way repeated measures ANOVA. If the assumption of sphericity was violated, the Greenhouse–Geisser correction was employed. Data of Pain unpleasantness and RPE during the exhaustion cycling test were normalized by using piecewise linear interpolation for curve approximation in order to compare both rates to each other. This method is widely used and preserved the relationship among the original data values when transformation occurs from a linear scale to an exponential one (Hamman and Chen, 1994). The correlation between CPT time and TTE at 80% time was assessed by Pearson product-moment correlation coefficient. The difference between pain rating measured at the end of CPT and TTE was tested using a paired-samples *t* test. Significance was set at 0.05 (two-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 18.

Results

During the CPT test, subjects remained with the hand in the cooler for 6.7 ± 3.2 min. With the exception of one subject, who reached the cut-off time of ten minutes, all subjects terminated the CPT when they could not tolerate the pain any longer.

During the time to exhaustion test, subjects cycled at 267 ± 21 W until exhaustion, which occurred after 12.5 ± 3.1 min. Blood lactate concentration at the end of the TTE was 9.7±1.7 mmol/l. Heart rate was 186±10 beats/min.

T-test revealed that pain rating during the TTE (4.8±0.7) was significant lower than the one during the CPT (9.7 ± 0.4) (*$p < 0.001$*) as shown in fig. 11.

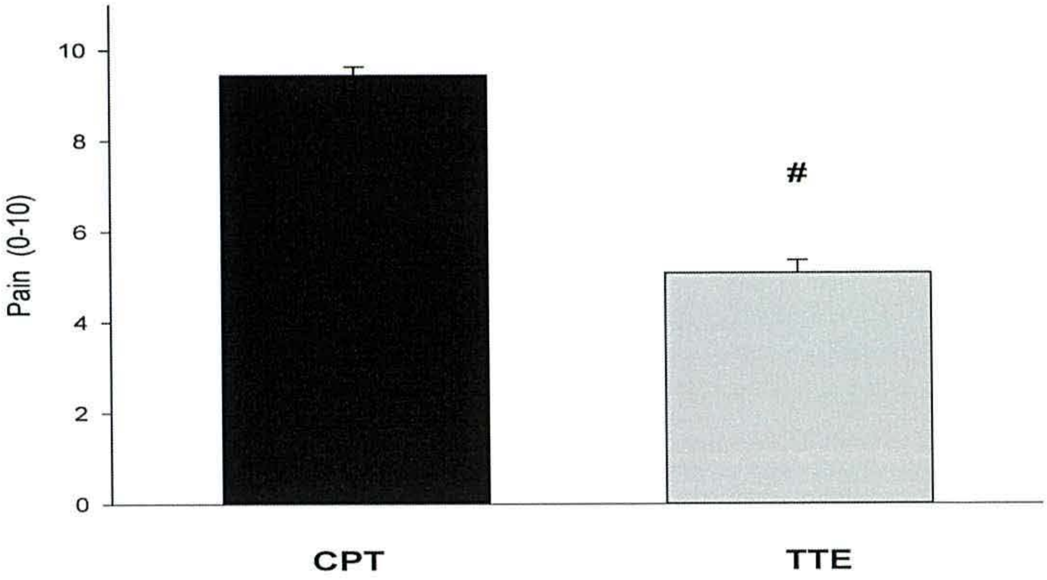


Figure 11

Pain rating at the end of CPT on the left (black bar) and at exhaustion after the TTE cycling test on the right (grey bar). # Significant effect of condition (*$p < 0.001$*). Data are presented as means ± SD.

Repeated measures ANOVA showed a significant main effect of time for both pain rating and RPE (*p < 0.001*). RPE and Pain increased similarly, but RPE (19.6±0.2) increased up to reaching the maximal rating of the 6-20 scale, while pain rating stop at 4.8±0.7 of the 0-10 Cook`s pain scale.

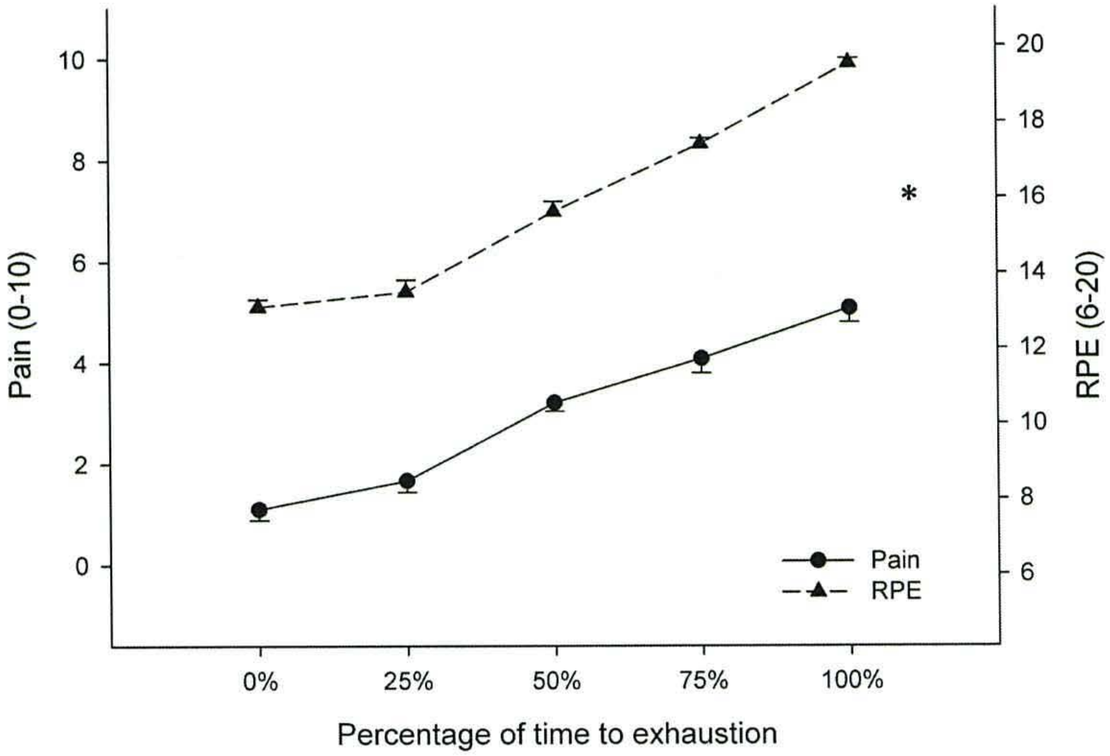


Figure 12

Perceptual responses of pain on the left Y axes and perceived exertion on the right Y axes during the time to exhaustion cycling exercise. * Significant main effect over time. 0% represents the first minute of TTE test. Data are presented as mean ± SD.

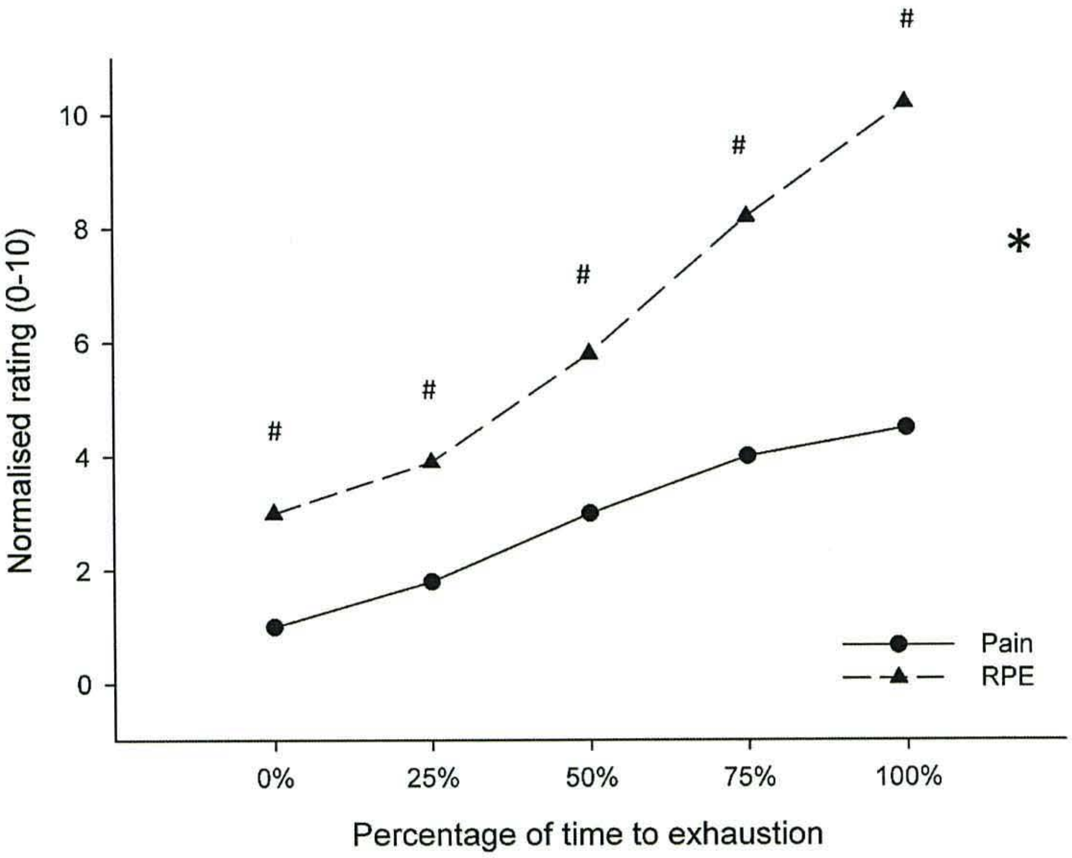


Figure 13

Normalised perceptual responses of pain and perceived exertion (Y-axes) during time to exhaustion cycling test (X-axes). * Significant main effect over time ($p<.001$). # Significant main effect of condition ($p=.02$). 0% represents the first minute of TTE test. Data are presented as normalised means.

Pearson product moment analysis did not show any significant correlation (r = .28) (*p* = .932) between the duration of the CPT and the time at exhaustion during the exercise. (Fig. 4).

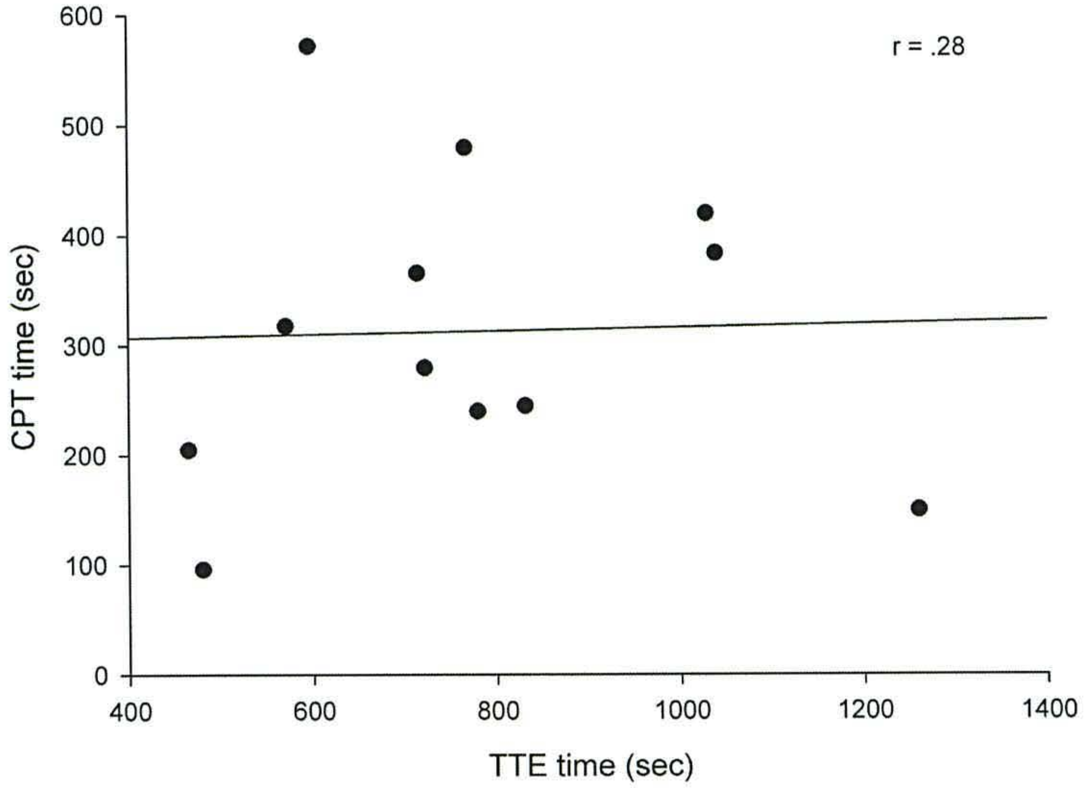


Figure 14

Scatterplot with best-fit line showing the correlation between the time obtained by the participants during the CPT test and at exhaustion after the cycling test.

Discussion

During the time to exhaustion test, physiological responses of heart rate and blood lactate at exhaustion confirmed that participants cycled at very high intensity and that they were highly motivated to cycle for as long as possible.

Pain rating vs. NOMP rating

As expected, we found a significant difference between the rating of unpleasantness of pain during the CPT and during the TTE cycling test. The CPT is a test used mainly to experimentally induce pain and thus it measures pain tolerance at exhaustion (Mitchell et al. 2004). Therefore, participants reached the highest rating of pain unpleasantness when they took the hand out of the water (9.7 CR 0-10 Cook`s pain scale).

However, during the cycling to exhaustion, participants, who were instructed to provide how unpleasant the pain was, reached a far lower score on the pain scale. An average of 4.8 (CR 0-10 Cook`s pain scale) was the rating recorded at exhaustion after the cycling task.

This demonstrates that the pain experienced during the cycling task was lower than the one they perceived during the CPT. It could be argued that the stimuli were different and not comparable though. However, we normalized the quality of the stimuli by comparing the affective dimension of pain (unpleasantness) of such a stimuli, which quantify the effective impact of the pain on the participant behaviour expressed in this case as the cycling task (Rainville, 2002). In previous studies (Rainville et al. 1999) it has been shown that it was possible to hypnotically manipulate pain unpleasantness without changing pain intensity in individuals. Such results suggest the important role of unpleasantness dimension as determinant of behaviour (in our case exercise) instead of pain intensity.

Furthermore, we anchored the pain rating during the cycling task by using the CPT prior to the physical task. This has given us a more valid measure in order to suggest that pain perception (when referring to naturally occurring muscle pain) did not result so unpleasant during the endurance-cycling task (Noble and Robertson, 1996).

In support of this theory, there are several studies underlining the powerful analgesic effect of exercise on pain stimuli, also known as exercise-induced analgesia (EIA) (Cook & Koltyn, 2000). In addition, neurophysiological studies (Peyron et al., 2000) have shown the role of the brain region of Anterior Cingulate Cortex (ACC), in particular as modulator in decoding valence of noxious stimuli in contrast with primary and secondary somatic regions, which are involved in intensity of pain sensation. Given the low rating of unpleasantness produced by the participants during the high intensity TTE test as shown in this study and considering the analgesic effect of repetitive exercise on pain tolerance, it is possible to argue against the major role that NOMP can have as limiting factor of endurance performance.

NOMP rating vs. RPE

Results in figures 2 and 3 comparing the trend of NOMP rating and RPE are in line with results previously published by Hollander et al. (2003) and O`Connor & Cook (1999). The increase of the pain rating and RPE is similar in terms of trend although RPE increment is higher up to reaching the top of the scale (10.2) while pain stopped at a lower rate (4.80), (data normalized as described in fig 3).

Although data showed a similar pattern as described in previous research, in this study the margin of difference between pain rating and RPE was even higher. This result may be due to the protocol used in which we asked subjects to rate how unpleasant the pain stimulus was during the cycling task. Therefore, it may be possible to propose that despite the intensity at which a painful stimulus is perceived, what really has an impact on cycling performance (and more in general to any motivated behaviour) is how subjectively pleasant or unpleasant a stimulus is perceived (Rainville et al., 1999; Vogt, 2005). Therefore, these data support the hypothesis that impact of natural occurring muscle pain on a cycling endurance performance task is minimal compared to the effect of RPE.

Correlation between pain tolerance and duration of exercise

Results in figure 4 showed a very low correlation between the ability of the subjects to sustain pain during the CPT compared to the duration of the cycling at exhaustion. Despite the unproven belief that pain tolerance plays a major role in exercise performance, this result suggests this is not the case and supports the hypothesis that no direct correlation exists between pain tolerance and the ability to perform in an endurance task. Furthermore, all subjects were highly trained cyclists so it could not be argued that the type of sport practised by the subjects would limit the use of this correlation.

Conclusion

The results of the present study aimed to elucidate the role of perceptual responses such as NOMP and RPE during a high intensity aerobic task. The outcome of this research suggest a lower impact of NOMP in the exercise performance as the data show while it underlines the high correlation between higher ratings of effort approaching the exhaustion. The multidimensional approach and the use of the anchoring for pain constitute the novelty of this study and may provide a more valid approach to measure perceptual variables. More studies are needed to validate this protocol and to provide more data for a reliability test. However, data provided in this study suggests and supports even further the concept of RPE as main limiting factors during high intensity prolonged exercise performance.

CHAPTER FOUR

NEURAL CORRELATES OF PERCETPION OF EFFORT: AN FMRI STUDY

Abstract

Perception of effort (PE) is the conscious sensation of how heavy and strenuous a physical task is. Despite its importance for exercise performance, the neurophysiological basis of PE remains poorly understood and strongly disputed (Marcora, 2009). One theory is that PE is generated by central processing of sensory signals (called corollary discharges) related to central motor command (CMD) to the active muscles. This theory has been recently supported by de Morree at al. (2012) who found a significant correlation between CMD during movement execution and rating of perceived exertion (RPE) whilst lifting submaximal weights with fatigued and non-fatigued arm muscles. The aim of the present study is to investigate the location of this brain activity using functional magnetic resonance imaging (fMRI).

Nine subjects were brain scanned using a 3 T Phillips scanner and were asked to lift a submaximal weight alternating between right and leg using a leg extension MR-compatible device. Prior to scanning, muscle fatigue (MF) was induced in one leg using an eccentric exercise protocol aimed to reduce muscle force without producing metabolic stress and related afferent feedback in the active muscles (fatigued leg, FL). The other leg served as control (non-fatigue leg, NFL). After a familiarization visit, participants performed in the scanner 20 runs, alternatively 10 with the FL and ten with the NFL. Each run lasted 128 seconds and consisted of 16s. of isometric contraction followed by 16s. at rest. At the end of each run RPE was measured (Borg`s scale CR-10). Data analysis was conducted using Brain Voyager 2.0 . Contrast FL vs. NFL has been analysed. RPE was measured using 2 X 2 repeated measure ANOVA with time (PRE vs. POST) and MF (NFL vs. FL) as factors.

MF protocol decreased muscle strength in the FL by 17 % ($p < 0.001$). As a result, RPE when lifting the same submaximal weight was significantly higher in the FL compared to

the NFL (p<0.001). fMRI analysis showed higher activity in motor cortex areas and anterior cingulate cortex (ACC) when comparing FL vs. NFL condition (p<0.001).

Introduction

Perception of effort has been defined as conscious sensation of how heavy and strenuous a physical task is (Marcora, 2010). Several studies have demonstrated the importance of perception of effort as a determinant of physical performance in humans (Enoka and Stuart, 1992) and underlined its impact on quality of life in patients affected by different disorders such as chronic fatigue syndrome (Marcora et al. 2009; Marcora et al. 2010).

Despite the importance of this phenomenon, the neurobiological bases of perception of effort remain poorly understood. Given that particular attention has arisen around the neurobiological nature of perception of effort (Fontes et al, 2013), broadening the knowledge relating to its neurophysiology can provide new insight into the role and impact of perception of effort during physical task. It has been argued that perception of effort is independent from afferent feedback from skeletal muscle, heart and lungs (Marcora, 2009). There is also strong evidence in support of its central nature in the sense of central command towards the muscles (Enoka and Stuart. 1992) and as "internal signals that arise from centrifugal motor commands and that influence perception" (McCloskey. 1981). If the Corollary discharge is a valid theory then the perception of effort may reflect central motor command output.

De Morree et al. (2012) used movement-related cortical potentials and demonstrated that perception of effort correlates with central motor commands during movement execution. However, there have been few studies that explored fatigue and, in particular, perception of effort with neurophysiologic measures such as functional magnetic resonance imaging (fMRI). There are several issues related with the use of fMRI and muscle movements, which limit the employment of such a measure. Mehta et al. (2009) described the importance of range of motion of the head during the data acquisition. If head motion during scanning session is greater than 1 mm in each of its axes and planes, a lack of validity and consistency in the data can be found which falsify the outcome of the results. Head motion is too large or not properly corrected it may lead to false positive and false negative outcome of neural activity (Friston et al., 1996). For this reason, many studies conducted so far aiming at investigating motor function, used either small joint such as ankle and wrist, investigated anticipation and preparation of movement, or employed hypnotical manipulation (Ciccarelli et al., 2005; Sahyoun et al., 2004; Williamson et al., 2001).

Williamson and colleagues conducted several studies using hypnosis to alter perception of effort in order to dissociating perception of effort from afferent feedback influences on cardiovascular control during exercise (Williamson et al. 2006). They measured regional cerebral blood flow (rCBF) in the brain cortical areas using single-photon-emission computed tomography. Results suggest that medial prefrontal region (anterior cingulate cortex), insular cortex, and possibly the thalamus are brain areas possibly linked with perception of effort.

In a recent study by Fontes and colleagues, using cycling exercise during fMRI results highlighted that the primary motor cortex, primary somatosensory cortex, and cerebellar vermis were significantly activated compared to baseline during cycling. Moreover, contrast analysis between cycling at an RPE perceived as "hard" (RPE > 15 on 6-20 scale) with cycling with RPE perceived as less than "hard" (RPE ≤ 15) showed significant activation of posterior cingulate cortex and the precuneus.

The aim of this study was to employ functional magnetic resonance imaging (fMRI) to investigate cortical areas related to changes in rating of perception of effort (RPE) during an exercise of leg extension. To dissociate RPE from afferent sensory signals we used the same fatiguing protocol as reported in De Morree et al. (2012) aimed to reduce muscle strengths in the femoral quadriceps. We tested the hypothesis that RPE across the scanning sessions will highly correlate with an increased in cortical activation from the primary motor cortex. Moreover, we test the hypothesis that at higher rating of perceived exertion a significant cortical activation of cingulate gyrus and insular cortex, brain areas involved in the emotion control and decision- making process will be highlighted. In addition, we tested the hypothesis that primary somatosensory will be activated at higher rating of perceived exertion, which may reflect corollary discharge of central motor command.

Methods

Participants

We tested 9 active male volunteers Their characteristics were age (mean ± standard deviation) 29 ± 3 years, height 177 ± 5 cm, body mass 78.6 ± 10.0 kg. Participants were all right foot and had no known neurological or psychiatric disorders. All gave written informed consent prior to testing. All experimental procedures were approved by the ethics committees of the School of Sport, Health and Exercise Sciences and the School of Psychology of Bangor University, and conformed to the standards set by the Declaration of Helsinki.

Experimental Design

Our research group used a crossover design previously employed by DeMorree et al. (2012) in their study with electroencephalogram (EEG) and adapted in this study for fMRI purposes. The volunteers visited the laboratory on three occasions. The first visit was a familiarization session, and the other two visits were the experimental sessions. Our dependent variables were RPE and neural activation. We used one experimental manipulations that is known to increase perception of effort. This variable was muscle fatigue, defined as an exercise-induced reduction in the ability to produce force with a muscle or muscle group during a maximal voluntary contraction (Enoka & Duchateau, 2008).

Most fatiguing muscle contractions not only cause a reduction in maximal voluntary force, but also this is usually accompanied by the accumulation of metabolites such as lactic acid (Fitts, 1994). In order to exclude any potential confounding effect due to sensory feedback from group III and IV muscle afferents on perception of effort we decided to control it experimentally by keeping the sensory feedback from these muscle afferents constant between conditions.

To achieve this we fatigued one leg and we compared this leg with the non fatigued leg, using a fatiguing protocol originally developed by Skurvydas, Jascaninas, and Zachovajevas (2000). This protocol consists of repeated eccentric contractions separated by a 20-s recovery, to avoid the build-up of metabolic byproducts in the muscles (Nielsen, Madsen, Jorgensen, & Sahlin, 2005). Moreover, as we know from animal studies, eccentric exercise does not affect the sensitivity of group III and IV afferents to metabolic stimuli (Taguchi, Sato, & Mizumura, 2005). In order to avoid increased sensitivity of group III and IV muscle afferents to mechanical stimuli, we tested the participants as soon as possible after the eccentric fatiguing protocol to ensure a maximal strength loss in the absence of delayed onset muscle soreness. Furthermore, we used the pressure pain threshold (PPT) test to confirm that there was no difference in muscle soreness between the two legs at the time of testing (Barlas, Walsh, Baxter, & Allen, 2000; Nussbaum & Downes, 1998), and to make sure that the sensitivity of the group III and IV muscle afferents to mechanical stimuli was unchanged, because pressure pain sensation is mainly dependent on these afferents (Graven-Nielsen, Mense, & Arendt-Nielsen, 2004).

Participants repeated the session twice. One time to fatigue the right leg and the other time to fatigue the left one in a counterbalanced randomized order. This procedure is necessary to compare the same brain regions from the same hemisphere and to avoid the problem of laterality (Toga and Thompson, 2003). Therefore, given the difference in baselines it would not be possible to compare two areas of the brain that belong to different hemispheres.

Procedures

Familiarisation session

During the first visit, we explained the procedures and the participants gave written informed consent. Subsequently, we familiarized the participants with the PPT test. Participants laid down on a portable table with their legs exposed. The skin overlying three points on the belly of the Vastus laterali, vastus medialis and rectus was marked with indelible ink. We asked the participants to report as soon as the sensation of pressure changed to a sensation of pain. The rubber footplate (diameter 1 cm) of the algometer (Force Ten FDX 50, Wagner Instruments, Greenwich, CT) was held perpendicular to the muscle belly with the display turned away from the participant. We increased the pressure to the muscle until pain was reported. The pressure was then released and the peak value read from the display. The PPT measurement was repeated three times on each leg, alternating between the legs. The average of the two nearest values for each leg was recorded as the PPT.

After the PPT familiarization, we gave the participants standardized instructions about a modified CR10 scale for rating of perceived effort (Borg, 1970). This scale ranges from 0 (no effort at all) to 10 (maximal effort), and includes standard verbal anchors of perception of effort, such as light, moderate, and hard (heavy) for intermediate values. In the instructions, we emphasized that the rating should be based exclusively on effort and not on any burning. We defined effort to the participants as how heavy and strenuous is to hold the weight (Borg, 1998).

Subsequently, to determine the weight to lift for leg extension we let the subject choose the weight correspondent to an RPE of 3 – 4 (Borg`s CR 0-10), which allow them to correctly perform and complete the whole let-extension protocol. During the familiarization test, participants were familiarized with the position on scanner bed and the scaffold that support the weights were set for participant's height.

Experimental session

All participants were given written instructions to avoid intense exercise and alcohol consumption, to maintain their usual diet, and to drink 40 ml of water per kg body weight during the 24 h preceding the experimental session. Moreover, they were asked to have a good night's sleep (at least 7 h) prior to the test, and were instructed to avoid smoking and caffeine consumption at least 3 h before the test and have a light meal about 2 h before the test.

The experimental session took place at least 3 days after the familiarization session to ensure full recovery. This session started with a PPT test as described for the first visit. Subsequently, a 5 μl sample of whole fresh blood was taken from the right earlobe and was analyzed for blood lactate concentration using a portable analyser (Lactate Pro LT-1710, Arkray Inc., Shiga, Japan). Participants were randomly (counterbalanced) assigned to have first either their right or their left leg fatigued with a bout of eccentric exercise, and they moved to the isokinetic dynamometer (Humac Norm, CSMi, Stoughton, MA). Both legs were tested for isometric maximal voluntary contraction torque (MVC) of the quadriceps muscle, starting with the control leg. Participants lay in a supine position with their knees bent and their feet on the bed. Their position was secured with straps over the hips and chest. After three submaximal warm-up and familiarization trials (25%, 50%, and 75% of maximal effort, separated by a 30-s rest), we asked the participants to maximally contract three times for 5 s. Between these MVC trials, 1-min rest periods were observed. We provided strong verbal encouragement during the trials. The average of the two nearest torque values produced during the maximal attempts was recorded as the MVC.

After completing the MVC trials with both legs, the participants performed eccentric contractions of the leg muscle with the leg selected for the fatiguing protocol. Participants were required to maximally resist leg flexion generated by the dynamometer. Movement started and when participants' leg reached full extension, they were instructed to relax their leg. This process was repeated every 20 s. We constantly encouraged the participants to maintain maximal torque levels throughout each contraction. All participants started with one block of 60 contractions, after which the 3 MVC trials for the fatigued leg were repeated. We aimed for a 20% strength loss. Participants were required to perform additional sets of 30 eccentric contractions with 3 MVCs after each set until this strength loss was reached or until no further strength loss occurred. On average, participants performed 102 ± 14 maximal eccentric contractions.

After the last 3 MVC trials with the fatigued leg, MVC trials with the no fatigued leg were repeated (including warm-up trials). After that, the PPT test was repeated and another capillary blood sample was taken and analyzed for blood lactate concentration. Furthermore, we measured self-reported muscle soreness using a 7-point likert scale of muscle soreness (Vicker, 2001) before, after the eccentric protocol, and after the scanner session for both legs.

At this point, participants were immediately transferred to the scanner laboratory, to minimize the time between the eccentric fatiguing protocol and the weight lifting task. Participant were strapped on the MRI bed with four big straps, which precluded any movement from legs, hips and chest. This was to prevent any head motion, one of the main causes of data invalidity. Using a block design, participants were required to lift the same absolute weight with the fatigued leg and the non-fatigued leg, across twenty runs: 10 with fatigued leg and 10 with non-fatigued leg. The order to initiate the run (either right or left) was randomly assigned. RPE was recorded at the end of each run. Each run lasted 128 sec and consisted in repeatedly extend, hold and release the leg. Every run generated four blocks (one block = 16 sec holding phase + 16 sec rest for a total of 32 sec). The holding phase lasted for 16 sec in order to generate a 16 sec on and off block design, which is statistically considered the most robust protocol (Friston et al., 2007). Every run generated four blocks, every run was separated by a rest period of one min. After completion of the protocol, the PPT test was repeated for the last time and self-report muscle soreness scale was completed.

Neuroimaging recording

Participants performed in the scanner twenty runs, alternatively ten with the fatigued leg and ten with the non-fatigued leg. At the end of each run, RPE was measured using the Borg scale (CR 0-10). Two MRI compatible scaffolds with weights were used to enable the leg extension protocol for both legs, which allow a range of motion of 15 degrees from flexion to complete extension. The imaging data was acquired on a Phillips 3 T scanner. For the functional scans we used a voxel size of $3.0 \times 3.0 \times 3.0$ mm^3. We scanned whole brain, using a TR of 2 s. T1 weighted structural images were acquired using a voxel size of $1 \times 1 \times 1$ mm^3. Data were analysed use Brain Voyager QX 2.0 software. The functional images were processed using Brain Voyager QX version (Brain Innovation, Maastricht, the Netherlands) which was used to perform all pre-processing, Talairach normalisation, whole brain co-registration and whole-brain analysis. Intra-session image alignment to correct for motion across runs was performed using, as the reference image, the first image of the functional run that was acquired immediately before the coplanar T1-weighted image. Interslice timing differences due to slice acquisition order were adjusted using linear interpolation. The T1 images were used to register the functional dataset to the participants' own three-dimensional image, and the resulting aligned dataset was transformed into Talairach space. The group-level anatomical image was an arithmetical average of the participants' structural images.

Statistical Analysis

Unless noted otherwise, data are presented as mean ± SD. MVCs were analyzed using a two-way repeated measures analysis of variance (ANOVA) with factors time (before vs. after the eccentric fatiguing protocol) and leg (fatigued vs. nonfatigued leg). PPT was analyzed with the same test, with 3 levels for the factor time (before, after the eccentric fatiguing protocol, and at the end of the weight lifting task). RPE data were analyzed using two-way fully repeated measures ANOVAs with muscle fatigue (fatigued vs. nonfatigued) over the percentage of the run completed (25, 50, 75 and 100%). The Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. When comparing two means, or when following up a significant two-way interaction, paired t tests were used adjusted for Bonferroni correction.

Results

During the preliminary test the eccentric fatiguing protocol induced a significant 17% reduction in maximal torque in the fatigued leg (MVC fatigued pre: 201±17 Nm and MVC fatigued post: 165±9 Nm [p<0.001]), but not in the non-fatigued leg. Therefore, during the subsequent weight lifting task, the fatigued leg could exert on average 17% less force than the non-fatigued leg. Participants did not report any significant pain in their fatigued leg. This result was confirmed by the fact that PPT and muscle soreness scale was not significantly different between the legs and across all the three different muscles assessed, at any time during the test. We did not find a significant main effect of muscle fatigue for this variable.

Blood lactate concentration was also not affected by the eccentric fatiguing protocol (lactate pre, 0.8 ± 0.2 mmol·l−1 and lactate post, 1.0 ± 0.3mmol·l−1 [$p = 0.498$]). As expected, the type of eccentric protocol with rest in between sessions did not produce any metabolic accumulation at the end of the fatiguing protocol. During the weight lifting task, rating of perceived effort increased significantly during the scanning session across the runs and increased even higher in the fatigued leg compared to the non-fatigue leg (Significant interaction at $p = 0.01$) as shown in Figure 15.

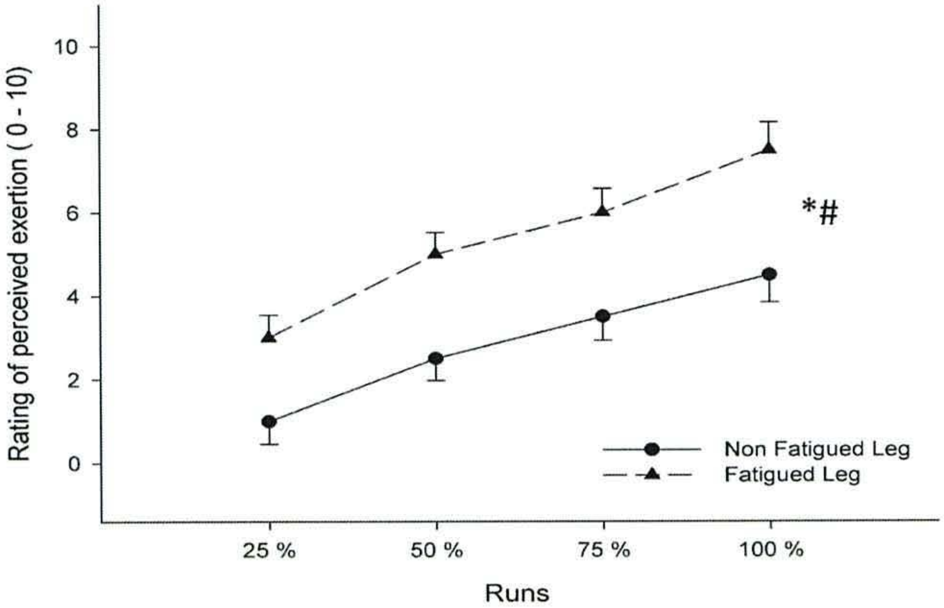


Figure 15

RPE responses across the runs expressed in percentage of the total number of runs completed. * Significant main effects. # Significant interaction. Data are presented as mean ± SD.

fMRI measures

A multiparticipant analysis of contrasts has been employed to compare the three different predictors of this study: Rest, exercise with fatigued leg and exercise with non-fatigue leg. There was a significant difference in percentage of regional hemodynamic BOLD signal (rHBS) compared to baseline in the primary motor cortex, supplementary motor area and in the cerebellum area when comparing movement (FL +NFL) vs. rest ($p<0.0001$), as expected from previous results. Moreover an increase in activation in the primary motor cortex has been observed when comparing the first 4 runs and the last 4 ones of each condition (FL and NFL) against rest (Significant interaction at $p<0.001$) as shown in figure 16 and 17. A positive significant correlation ($r = 0.75$) ($p = 0.02$). has been found between the increase of RPE and the magnitude of brain activation in the primary motor cortex area (Fig.16).

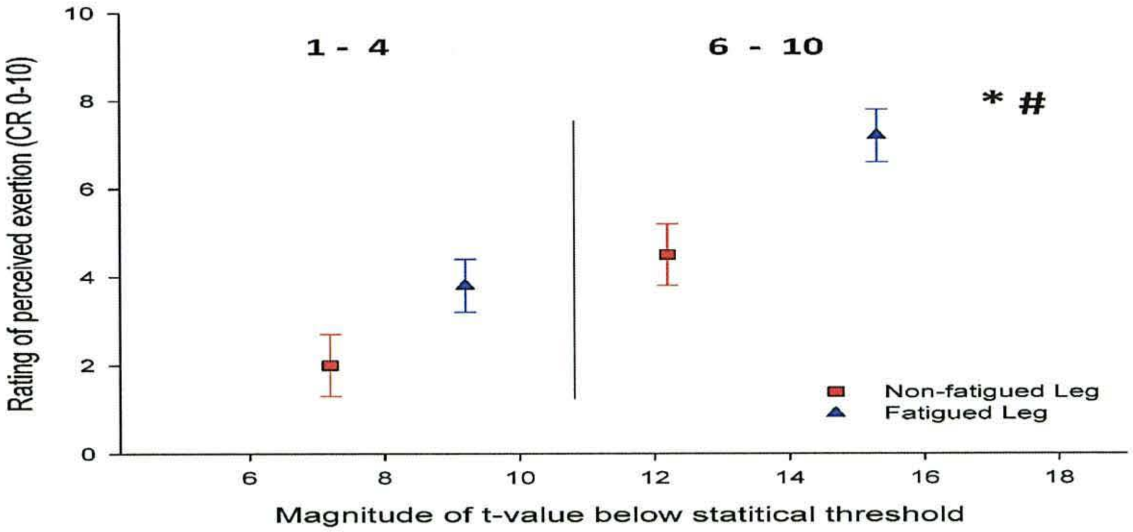
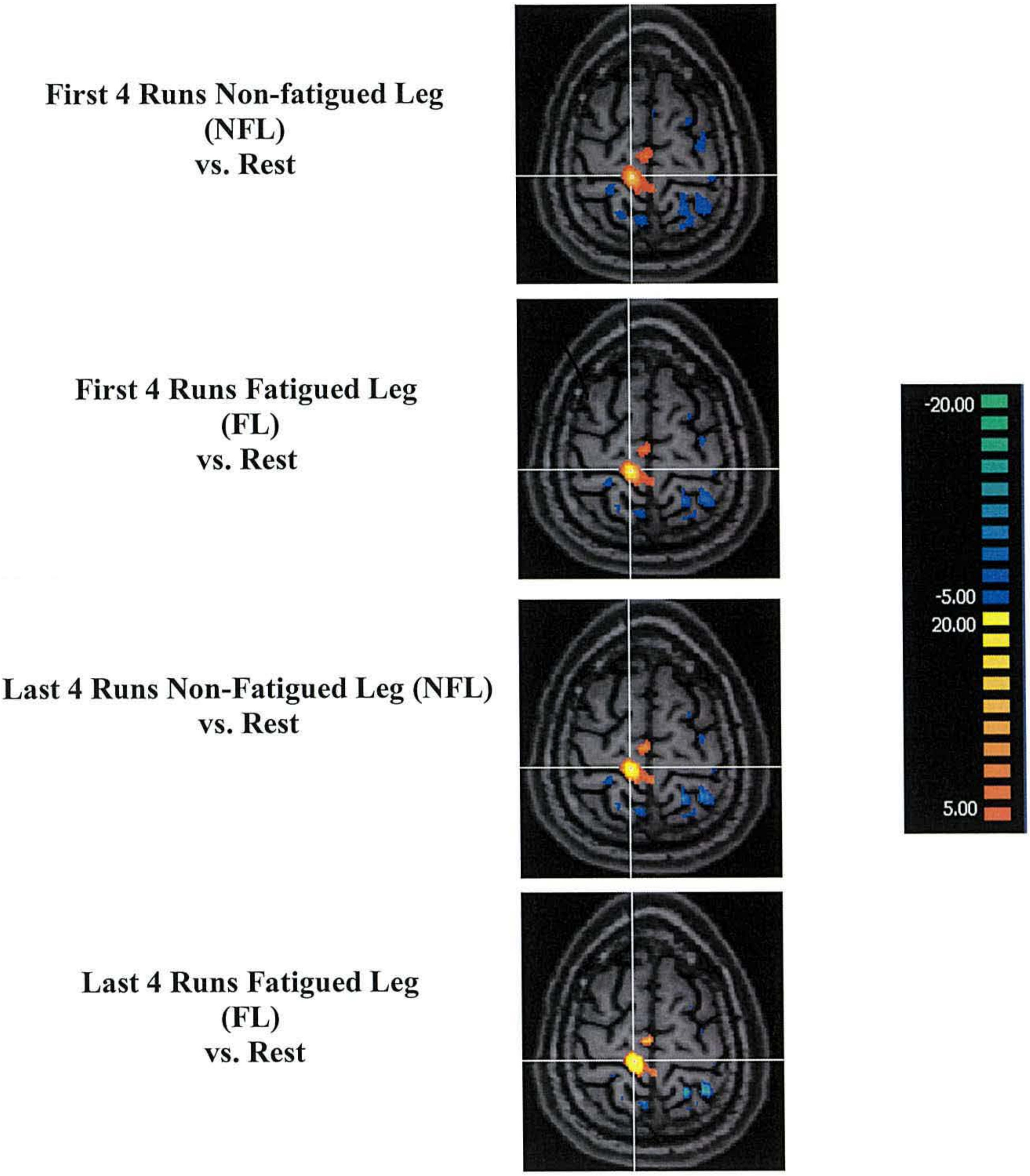


Figure 16

Within-subject correlation between rating of perceived effort and average magnitude of t-value below statistical threshold for primary motor cortex activation. Each data point represents the means ± standard errors for one of the four conditions. * Significant main effects. # Significant interaction. The correlation coefficient was r = 0.75 (*p* =0.02).



First 4 Runs Non-fatigued Leg (NFL) vs. Rest

First 4 Runs Fatigued Leg (FL) vs. Rest

Last 4 Runs Non-Fatigued Leg (NFL) vs. Rest

Last 4 Runs Fatigued Leg (FL) vs. Rest

Figure 17

Topographical maps of functional magnetic resonance imaging for the two weightlifting conditions against rest over time. In the multi-subject contrasts, rHBS activation is expressed as magnitude of t-value resulted below statistical significant threshold.

A significant difference in magnitude of rHBS has been detected in the primary motor cortex, supplementary motor area, cerebellar vermis and primary somatosensory sensory cortex area when comparing FL vs. NFL across the runs ($p < 0.001$) as shown in figure 18.

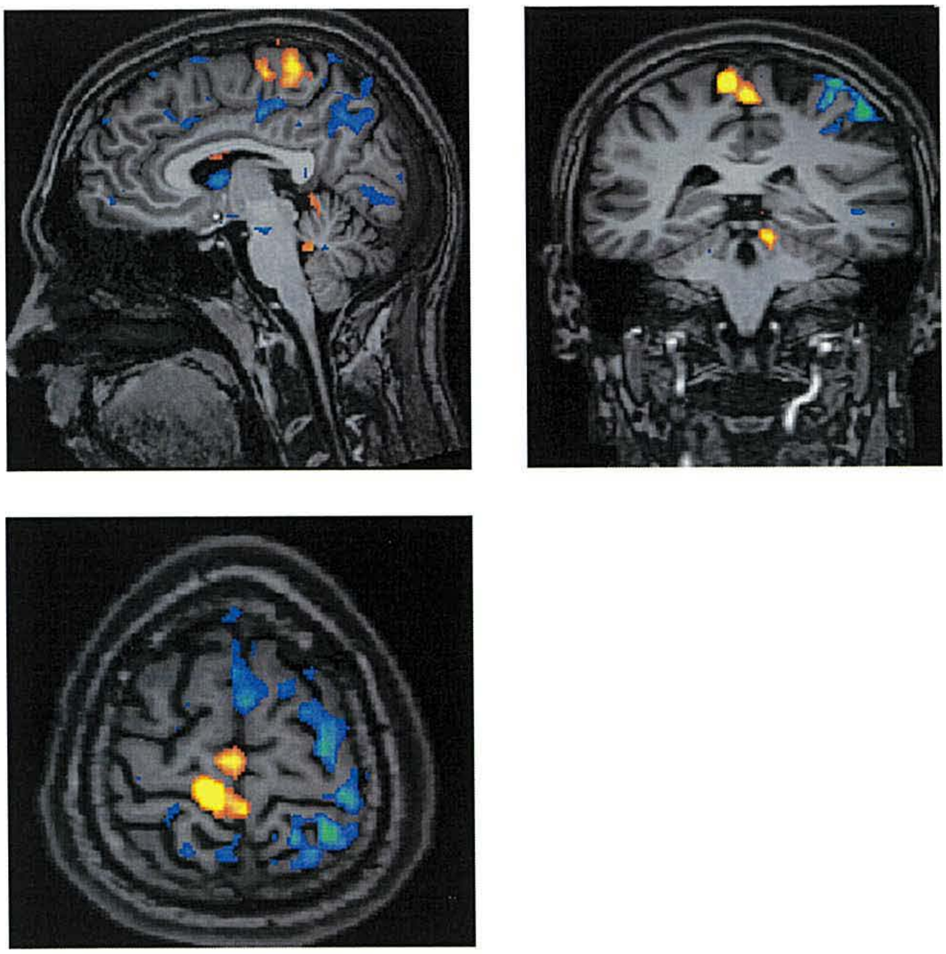


Figure 18

Topographical maps of functional magnetic resonance imaging for the contrast FL vs. NFL. In the contrasts, rHBS activation is expressed as magnitude of t-value resulted below statistical significant threshold.

Moreover by FL vs. NFL during the last 4 runs, we found, along with an increase in motor cortex area and cerebellum, a weak but significant activation of Anterior Cingulate cortex (ACC) (p= 0.002) and (see fig. 19).

Figure 19

Topographical maps of functional magnetic resonance imaging for FL vs. NFL in the last 4 runs. In the contrasts, rHBS activation is expressed as magnitude of t-value resulted below statistical significant threshold. Anterior cingulate cortex area is highlighted in green.

Finally, as shown in figure 20 the average head motion across all the runs for all participants is presented. It is expressed in millimetres and shows all axes of movement. The average motion artefact below 1 mm confirms the validity of the data.

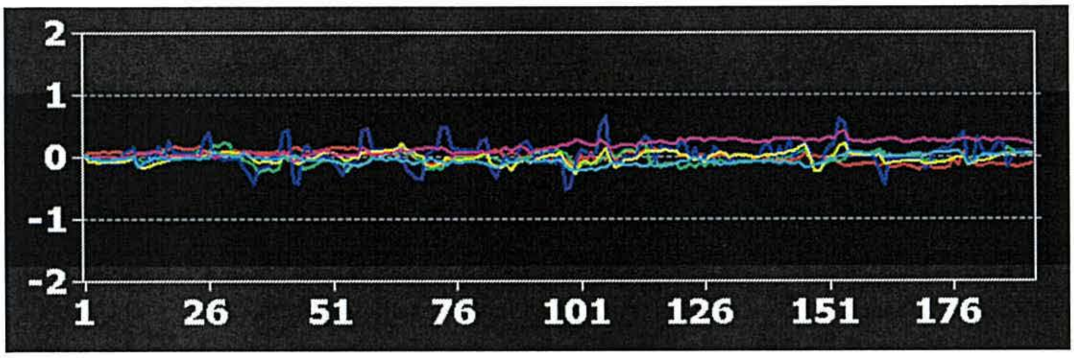


Figure 20

3D motion correction showing average of head of motion across all subjects during the number of runs completed. Six colour lines indicates the different axes and planes in which the head can move or rotate. Y-axis indicates motion in millimetres.

Discussion

The main aim of this study was to test a novel paradigm to use big muscle masses with a neurophysiological measure such as fMRI and measure brain activity correlating with rating of perceived exertion. Lower-limb motion best reflects the real world and can be applied as model to explain brain activation during locomotor-like movement such as cycling (Mehta, 2009). Moreover we employed a protocol aiming at minimize the afferent sensory feedback coming from the muscle. The eccentric protocol for muscle fatigue was successful to reduce muscle force and to minimize the confounding effect of pain dependent on group III and IV afferents (Graven-Nielsen, 2004). As previously reported by O`Connor et al (1999) and Quintero (2013) there are particular cortical area that may be involving in both pain and RPE modulation.

PPT, blood lactate and self-reported muscle soreness may suggest that no muscle pain and no delayed onset muscle soreness was present during the physical task in the scanner (Barlas et al., 2000). However, such measures could not be taken during the actual scan but only before and after the full set of runs. Such a limitation has to be considered as participants may have experienced some pain during the concentric contraction while in the scanner, which were not reported.

The head motion, one of the most critical issues for the present study (Bullmore et al., 1999; Friston, 1996), has been successfully kept at a lower standard: less than 1 mm, which allow us a confident analysis of the data and a more genuine interpretation of the results. Such head motion resulted even lower than the one reported by Fontes et al. (2013) which was less than 3 mm. However, they were using a cycling protocol while we used a static leg extension with a strict range of motion (15 degrees). Those studies constitute a novelty in the use of fMRI measures in exercise science by broadening the possibilities to research more in the specific central mechanisms of fatigue, effort and more in general any psychological feature relevant for human performance (i.e. motivational factors).

The muscle fatigue induced by the eccentric protocol resulted in a significant effect on RPE as reported in figure 15. Subjects with the fatigued legs perceived more effort in order to hold the weight. As RPE increased, it has been noted an increase in rHBS in the motor cortex areas when comparing the first 4 runs with the last 4 ones in the two conditions (Fig. 16 and 17). This result suggests a correlation between the increase of RPE and the concomitant augmentation of central motor command activity. These results are in line with the ones proposed by De Morree et al. (2012) which found a similar result using movement-related cortical potentials and support the theory that perception of effort is a discharge of the central motor command activity. In addition, activation of primary sensory cortex in the contrast between FL vs. NFL are in support of the RPE as corollary discharge of motor cortex in the somatosensory area.

Comparison between the last 4 runs of FL cv. NFL highlighted a small but significant percentage of cortical activation of the anterior cingulate cortex (ACC). Fontes et al. (2013) in their pilot study using a cycling protocol and the fMRI, reported an activation of the ACC when comparing the neural activation at the RPE below 15 compared to the one above 15 (Borg`s 6-20 scale). Those results fully reflect our findings, given that the difference between the first and the last trials is reported as an RPE of 2-3 for the former and 6-7 (Borg`s CR 0-10 scale) for the latter. Moreover Williamson et al. (2011) reported as well a similar activation of ACC when comparing the downhill perception to the uphill.

The ACC is an area implicated in several functions including modulation of pain stimuli (Reiman, 1989), attention (Corbetta et al. 1991) and decision-making processes (Botvinick, 2007; Schweimer, 2006). ACC modulates all those decisions based on a cost-benefit extent. A large number of studies on animals highlight the importance of the ACC as brain structure deputed to modulate the decisions in relationship to a specific obtainable reward and they underline the role of dopamine in those cortical area in altering the decision making process under certain circumstances (Kurniawan, 2011; Walton et al. 2002; Croxon et al, 2009).

Those results may suggest the implication of ACC as modulator of perception of effort in effort-based decision processes during a given physical task. Indeed, those results support the psychobiological model of endurance performance that interprets physical exercise as a task engagement and exhaustion as a conscious task disengagement. As such, decision to withdraw from task or carry on may be closely related to cortical activity of the ACC, which has been pointed by Marcora (2009) as possible mechanism of perception of effort.

In the contrast of FL vs. NFL across the runs and comparing the first 4 runs with the last ones, a large activation of the cerebellum has been detected. Such results, in line with previous results by Fontes and Colleagues (2013), suggest the implication of the cerebellar area in effort-based motion perception. Cerebellum is thought to be implicated in motor coordination and planning motor adaptation to several different situations (Kawato, 1999). Increased activation of cerebellum may suggest a link with central motor command as previously proposed by Kawato (1999) as cerebellum may receive efferent copies from both central motor command and sensory afference. Therefore, an increase in the central motor command as demonstrated in the study in this chapter may well support the significant activation of the cerebellar area.

Moreover if we consider the contrast between FL vs. NFL, the activation of the cerebellar area refers not to the planning and movement coordination of the leg extension, which is present in both condition, but it is may represent the increase in the efferent copy coming from the central motor command or the somatosensory cortex. Indeed, a recent study published by Bhanmpury and colleagues (2012) demonstrates the important role of the cerebellum in the active force perception. According to Bhampury et al. (2012), patients with cerebellar impairment have difficulties in weight perception of objects they try to move and problem with discrimination of heaviness perception. Such results can explain the difficulty of such patients to perform self-generated movements, in particular moving objects in the space due to the inability to perceive their weight and thus to determine the force to use. More interestingly, those outcomes may suggest the implication of cerebellar area in developing the perception of effort, defined originally as conscious sensation of how heavy and hard is to accomplish a task (Borg, 1979).

However, a potential limitation due to the nature of the use of PPT and self-reported pain scale to measure pain in the fatigued leg may render of difficult interpretation the results regarding the ACC and somatosensory areas. It was not possible to measure pain during the scanning sessions so we do not have a pain assessment ongoing during each contraction, but only before and after. Due to such a limitation, it is clearly difficult to rule out the role of pain perception. Therefore, any hypothesis that can be postulated on the role of somatosensory cortex and ACC cannot completely exclude the afferent role of the somatosensory area related to sensory afferences from group III and IV and the role that ACC also have as modulator of pain perception and more in general of emotions (O`Connor, 1999, Rainville et al., 1997).

Conclusion

This study has contributed to the novel and still in early stage research on the neurophysiological bases of RPE. The aim of this study was to isolate the perceived exertion by using a muscle fatiguing protocol and to explore its neural correlates primarily in the primary motor cortex and secondly in other areas such as cingulate gyrus, cerebellum and sensory cortex. These findings confirms and strengthens previous results on the correlation between RPE and central motor command and it may suggest the role of the brain centres related to the effort - based decision -making mechanisms such as ACC and the Cerebellum in the develop of the perception of effort.

CHAPTER FIVE

GENERAL DISCUSSION

The aim of this general discussion is to summarize and compare the main findings across all three studies on the effects of muscle fatigue and the impact and nature of perceptual responses on exercise tolerance. In the conclusion, these two aspects are integrated to discuss their role in exercise tolerance.

It may result helpful to clarify two operational concepts before continuing into the discussion: limiting factor refers to any variable "acting as a limit". Limit means "the point, edge, or line beyond which something cannot or may not proceed". Therefore, it applies exclusively to type of tasks, which show and test exhaustion such as time to exhaustion tests. Therefore, a factor to be limiting must cause exhaustion.

A determinant, on the other hand, is “a factor, circumstance, that influences or determines a given variable”. This may be established with several types of experiments not necessary conducted at exhaustion. By assuming the a variable is not a limiting factor of a variable, it cannot be excluded its influence on such a variable as determinant.

As explained in the introduction, the muscle fatigue model assumes that, in well-motivated subjects, exercise terminates when the neuromuscular system is no longer able to produce the force/power required, a point known as exhaustion or task failure. Failure can consist in maintaining the minimum cadence (when on cycle ergometer) or speed or when there is the inability to produce the minimum force required by the task (Allen et al., 2008, Jones et al., 2008). However, in the first study it has been demonstrated that force never decreases to the point in which it cannot match the minimum force required by the task. Actually, the loss of locomotor muscle force was never greater than 30-35% of the maximal voluntary cycling power after the high intensity aerobic exercise as we reported. This study are in line with previous results showing that locomotor muscle force after an high intensity aerobic cycling exercise at exhaustion (Marcora et al., 2008) and sub maximal isometric contraction (Taylor and Gandevia, 2008) is still far above the minimum force require d to continue the task, even at exhaustion.

According to Lollgen et al. (1980) the MVC required to cycle at $\dot{V}$ O2 max in just 20% and so this may justify in the first study the massive power output generated after exhaustion. Furthermore, evidences from studies measuring high intensity aerobic exercise with pre-fatigued muscle protocol (Marcora et al., 2008) showed that no further decrease of MVC has been found in subjects performing a TTE test after a pre-fatiguing protocol.

The protocol presented two potential limitations, which have been already discussed in details in letters, and comments to the editor on the paper by Marcora and Staiano (2010). The difference in pedal frequency between the TTE test (40 rpm) and the maximal voluntary cycling power (MVCP) test (above 100 rpm) and the latency time of 2-3 seconds recovery time between the TTE test and the MVCP test (Burnley, 2010).

Although there is no need to discuss these issues in this thesis, it may be of support of the first study to mention that Bosio and Marcora (unpublished data, see Appendix IIII) recently conducted a study using a similar protocol as the one in the first study. In this study, the two main issues described above have been solved by having the MVCP test at the same pedal frequency of the TTE test and with no latent (recovery) period between the two tests. Results were still consistent with the one of the first study (chapter 2) although the magnitude of the difference in power between TTE and MCVP was different (3 times higher in the study in chapter one and 2 times higher in the unpublished data by Bosio and Marcora).

The traditional peripheral fatigue model states that performance during high-intensity exercise until exhaustion is directly limited by the development of muscle fatigue. This is because the involvement of the anaerobic energy system is required to sustain the high-energy demands with consequent accumulation of fatiguing metabolites (Fitts, 2006). The important role of calcium and potassium changes in causing muscle fatigue has been demonstrated (Fitts, 2008, Fitts, 2006, Allen et al., 2008). The assumption of this model is that these peripheral changes would result in a progressive reduction in muscle contractility until the required force or power cannot be longer produced. At this point, the exercise is terminated (Allen et al., 2008, Sejersted and Sjogaard, 2000, Jones et al., 2008). According to the traditional peripheral fatigue model, subjects with fatigued muscles should have attained more rapidly the point at which they were no longer able to produce the workload required by the exercise task. However, the findings in the first study are in contrast with the fundamental assumptions underpinning the traditional model.

It is known that about 20% of the MVC is required to cycle at VO2max (Lollgen et al., 1980; Marcora et al., 2008). Therefore, despite significant muscle fatigue, the locomotor muscle power found after exhaustion in the first study is more than sufficient to cycle at the workload at which exhaustion occurred. This evidence does not support the direct role of muscle fatigue in determining the limit to endurance performance. It can be argued that we measured MVCP 2-3 sec after after exhaustion, and this may represents one of the limits of our research program. However, it is unlikely that profound losses of strength, such those hypothetically necessary to prove the validity of the peripheral fatigue model, might recover so quickly after exhaustion. Moreover, experimental data show that the MVC measured immediately after an isometric submaximal exercise to exhaustion is much higher than that required by the task (Fulco et al., 1996, Gondin et al., 2006).

Moreover, Marcora et al. (2008) found that high-intensity cycling exercise does not further reduce force of pre-fatigued locomotor muscles. This interesting finding has been confirmed by (Amann and Dempsey, 2008b), and suggests that once the fatigue-sensitive type II fibres are impaired, no further strength losses can occur because the remaining fibre types (fastoxidative and slow-oxidative) are fatigue-resistant (Sargeant, 2007). Therefore, it is unlikely that fatigue of human muscles with mixed fibre type composition can reduce force to the low level necessary to cause exhaustion during even very high-intensity cycling exercise tests.

Results in the first study cannot take into account central fatigue, defined as progressive exercise reduction in voluntary activation of a muscle during exercise (Gandevia, 2001), as possible explanation for the task failure occurred at exhaustion. It is not intentions of the author to minimize or exclude important changes at spinal and supraspinal levels (refers to Figure 1), however they cannot be relevant in this context in which participants clearly were able to expressed, during the MVCP test, more than the power required in the TTE test.

The model proposed by Amann and Dempsey (Amann and Dempsey, 2008b, Amann and Dempsey, 2008a) explain exercise termination during constant-power tests and the regulation of exercise intensity during time trials by an inhibitory afferent feedback system aimed at preventing peripheral muscle fatigue to develop beyond a critical threshold.

Noakes and colleagues (St Clair Gibson and Noakes, 2004, Noakes et al., 2004) have proposed instead a more complex central governor model in which afferent sensory feedback coming from many different organs (e.g., skeletal muscles, heart, lungs, skin, and the brain itself) is processed at subconscious level by an intelligent system located in a not yet identified part of the brain.

Like Noakes and Marino (2007) and Marcora (2008a) have done previously, we argue that the significant increase in running velocity measured at the end of the 30-min time trial (the so-called “end-spurt”) is not compatible with the inhibitory afferent feedback model proposed by Amann and Dempsey. Indeed, metabolic stress (and related afferent feedback) should be higher at the end rather than at the start or middle part of an intense time trial.

Thus, it should not be possible to significantly increase central motor drive when the "finishing line" is in sight. Results in the first study (chapter 2) support this theory as the inhibitory afferent feedback should not allow participants to generate such a power, which was higher compared to the one required by the task, even if for just one more pedalling.

In addition, the central governor model cannot explain these findings. Afferent feedback related to inflammation may inform this intelligent system to reduce central motor drive to the locomotor muscles, however how could it be possible to pedalling at such high intensity during the MVCP, straight after exhaustion?

Furthermore, neither the inhibitory afferent feedback model nor the central governor model can explain the significant reduction in performance measured during intense constant-power cycling in the study by Marcora et al. (2008) where participants were pre-fatigued before complete a time to exhaustion test. This suggestion is based on two main facts. First of all, the body does not have receptors capable of detecting changes in MVC. Secondly, afferent feedback related to fatiguing metabolites and muscle injury was controlled by using a non metabolically stressful 100 drop jumps protocol, and by testing subjects 30 min after eccentric exercise when exaggerated afferent sensory feedback (as indicated by DOMS) has yet to develop. Finally, it is known that eccentric exercise does not affect the function of muscle spindles and Golgi tendon organs (Gregory et al., 2002, Gregory et al., 2004). Therefore, afferent sensory inputs directly inhibiting supraspinal centres or feeding information to the central governor were similar in the fatigue and control condition.

A possible explanation it is that participants stopped exercise not when their muscle reached its critical limit but when their RPE was too high to be tolerable and thus they would voluntarily disengage from the cycling task. Moreover, a phenomenon such as the end spurt cannot be explained with the muscle fatigue model while it is perfectly in line with the

Psychobiological model of exercise performance, as the competitor near the finish line would feel that the end of the race is close and it can decide to accelerate despite any muscle fatigue or central impairment. Results in the first study support the psychobiological model of exercise tolerance by moving the focus of research on the only parameter not yet widely explored in the chain of motor command:

Central mechanisms

- Excitatory input to higher motor centres
- ~~Excitatory drive to lower motor neurons~~
- ~~Motor neuron excitability~~
- ~~Neuromuscular transmission~~

Excitatory input to higher motor centres refers to all those effort-based decision making processes, which are considered relevant in any motivated behaviour including exercise. Those processes along with all the mechanisms that can affect or alter them, above all motivational aspects, constitute a crucial aspects to be considered when we study exercise tolerance and human performance. The psychobiological model of exercise tolerance stresses the importance of motivational factors and the critical role of perception of effort in exercise performance.

In the introduction, we delineate the importance of understand the origin research perception of effort: centrally generated or afferent feedback dependent? The debate on the origin of perception of effort is firstly raised because of a problem of definition. As we stressed in our second study (chapter three) there has always been a problem of definition, use and interpretation of perceptual measures, in particular perception of effort. Several authors (Marcora, 2008; Noble and Robertson, 1996) pointed out the importance of properly instructing subjects on what exactly to rate and to use a proper anchoring to have reliable and precise data. Defined as conscious sensation of the difficulty of a physical task, perception of effort cannot be expressed as leg discomfort, pain or general discomfort.

In the second study, perceptual measures were used by applying validated definitions and taking into account their psychological constructs. Our results were in line with several studies conducted before by O`Connor et al.(1999); Cook et al.(1997); Hollander et al.(2003) showing how the impact of perception of pain (naturally occurring muscle pain) is significant lower compared to the predominant aspect of rating of perceived exertion. From a psychological perspective, we can suggest that pain unpleasantness measured in our study never reached such a level of intolerability to actually constitute a major issue for performance. Furthermore, several studies on pain modulation and attention (Bantick et al., 2002) may suggest that driven the attention away from a pain stimulus can actually decrease the perception of it.

If we consider the RPE in our second study as an intolerable stimulus, it is plausible to think that in presence of two unpleasant stimuli participant`s attention will be driven on the one which is stronger. In our case the perception of pain which was already low, it has an even less influence performance because attention may be driven on the RPE which reached the highest rating by the end of the TTE test. Although there is still scarce research on neural mechanisms of perception of effort, it can be suggested that, while perception of pain is directly generated from the afferent feedback from the peripheral muscle, perception of effort is, instead centrally originated, and it may not be directly affected by sensory input from muscle, lungs and heart (Marcora, 2008).

As stated earlier in this section, it may become of crucial interest for the understanding of exercise performance to point the attention on the "excitatory input to higher motor centres" mechanisms referring to all those effort-based decision making processes, which are considered relevant in any motivated behaviour including exercise. Findings from the third study (Chapter 4), although just preliminary and not completed, are in line with several along neurophysiological studies conduit or electroencephalography (de Moree et al. 2012; Fontes et al. 2013; Williamson et al. 2006; 2002; 2001). An increase in the central motor command generated by the primary motor cortex is a common result across all those studies, which may link an increase of RPE with an increase of activation of such Areas. Although the protocol used in the third study may have potential limitation in terms of controlling for any sign of muscle pain due to the eccentric protocol, a significant activation of the sensory cortex area in the contrast analysis of fatigued leg (FL) vs. non-fatigued leg (NFL) has been found. This may support the theory of the corollary discharge which postulates that an efferent copy is sent from the motor cortex area directly to the sensory cortex along with the signal generates to the muscle (McCloskey, 1981).

One of the major interesting result in the third study has been a significant activation of the Anterior Cingular Cortex (ACC) when comparing the last 4 runs of FL vs. NFL ones. This result is definitively in line with previous results suggested by Fontes et al. (2013) and Williamson, and colleagues. Activation of the ACC towards the end of the task, when the RPE is reaching consistently high values, (around 7 on the CR 10 Borg`s scale in the third study and above 15 in the study proposed by Fontes and collegues) suggests the implication of this area in the developing of RPE. As stated by Williamson et al. (2006, 2002, 2001), this particular area along with the insular cortex is, not only in charge of the higher regulation of decision processes related to the effort/reword relationship, but it is also implicated in the emotion modulation and in response to an increase of perceived exertion during active exercise when heart rate and blood pressure are elevated. The results in study three are in line with the psychobiological theory proposing that when effort increases up to the point to become intolerable it will trigger that process of decision making about disengage vs. carry on, according to the effort perceived. Moreover, the psychobiological model may interpret such results defining task disengagement as a conscious decision rather than a series of catastrophic physiological events.

It is of particular relevance a series of studies, published on animals showing the involvement of the ACC as major area of effort-related motivated behaviours (Walton et al. 2006). In such studies has been possible to collect data on particular neurotransmitters in different area of mice`s brain. It has been revealed how levels of dopamine in the cingulate cortex and nucleus accumbens, are important for commencing a behaviour, effort-related choices and exertion (Salamone et al. 2003, 2007; Correa and Salamone, 2002). In particular the level of dopamine in those areas will determine a behavioural changes in rats engaging in rewarded task (Schweimer and Huber, 2006). As proposed by Salamone and Collegues (2002, 2003, 2007), rats will disengage in a simple task to run for food by choosing the shortest way with less food (reward) compared to the longest run with an higher reward when level of dopamine in the cingulate cortex and nuclei accumbens are low. Although the limitation of the research purely on rats, those results are quite consistent and in support of the theory that low level of neurotransmitters such as dopamine in determined area of the brain may alter the conscious decision to engage in specific tasks. If translated in the human world and, more in particular, in exercise performance, this may reflect the decision to slow down by changing pace or gear if on a bicycle. Therefore, more research is needed that account for more neurophysiological measures to enlighten this area which may help the general understanding of fatigue phenomena.

CONCLUSION

In conclusion, this research programme has provided the first experimental evidence that locomotor muscle fatigue, although it reduces high-intensity exercise performance, does not directly limit performance as it was commonly thought by traditional physiology. The effects of locomotor muscle fatigue on exercise performance seem to be mediated by their effects on perception of effort as predicted by the psychobiological model. Furthermore, these results support the main idea that the impact of muscle pain on exercise performance is minimal compared to the high impact and correlation to exhaustion produced by the rating of perceived exertion. Moreover, neurophysiological findings presented suggest the implication of several areas of the brain (independently from the motor cortex areas) in the process of developing rating of perceived exertion. Such areas are of great interest for any effort-based decision-making behaviour and support the psychobiological model of exercise tolerance on the nature and causes of exhaustion, observed as a conscious disengagement due to balance between reward obtained and effort spent to reach such reward.

Finally, this thesis demonstrated that the psychobiological models proposed in the recent years by Marcora and Collegues is, indeed, a valid model to explain all the multifaceted phenomena of fatigue, human performance and exercise tolerance, along with the other existing models of exercise tolerance.

Future research is necessary to better understand the neurocognitive and physiological factors determining perceived exertion in different conditions such as muscle fatigue, mental fatigue, sleep deprivation and to explore their effects on endurance performance of longer duration. In addition, more research is needed to better clarify the role of several neurotransmitters in determining changes in RPE and their link with brain activations and physical performance.

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APPENDIX I

This appendix contains an example of the scales for rating of perceived exertion (used in all studies). An example of the instruction used for rating perceived exertion during resistance exercise (used in chapter 4) and an examples of instruction used for rating of perceived exertion during whole-body exercise (used in chapter 2 and 3).

Rating of Perceived Effort

0	No effort at all
0.5	Very, very light
1	Very light
2	Light
3	Moderate
4	Somewhat hard
5	Hard (heavy)
6	
7	Very hard
8	
9	Very very hard
10	"Maximal" Effort
*	

Instructions for rating of perceived effort (RPE) scale

You are about to undergo weight lifting exercise. The scale before you contains numbers from 0 to 10. You will use this scale to assess the perceptions of effort while lifting weights. The perception of effort is defined as the subjective intensity of effort, strain and heaviness that you feel during exercise. We use this scale so that you might translate into numbers your feeling of effort while exercising

The numbers on this scale represent a range of feelings from "no effort at all" to "maximal effort". To help you select a number that corresponds to your subjective feelings within this range, consider the following. When the effort during weight lifting feels "very light", respond with a number 1. As an example, you should respond with a number 1 when you are performing your repetition with a very light weight. When the effort during weight lifting feels "very very hard", respond with a number 9. As an example, a response of 9 would be appropriate when you are feeling of effort is the same as when you are lifting your maximum weight.

10, "Maximal effort", is the main anchor. It is the highest effort you have ever experienced. It may be possible, however, to experience an even higher effort. Therefore, the symbol * is placed somewhat further down the scale without a fixed number. If you perceive an effort higher than 10, you may use a higher number that better reflects your feelings your feelings, for example 11 or 12.

In summary

Give each rating as accurately as possible. Do not underestimate or overestimate the effort; simply rate your feelings of effort caused by the weightlifting exercise at the moment. Try to appraise your feelings of exertion as honestly as possible, without thinking about what actual physical load is (weight, heart rate, speed, power output, intensity level on the exercise machine). It is your own feeling of effort that's important, not how it compares to other people's. What other people think is not important either.

Use the attached verbal expressions to help you rate your feeling. Give any number you feel is appropriate to describe your perception of effort in the muscles that you are using during the lift and also in your total body. It does NOT depend on muscle pain, i.e. the aching and burning sensation in your leg or arm muscles.

You are welcome to use half values such as 1.5 or 3.5.

6	**No exertion at all**
7	**Extremely light**
8	
9	**Very Light**
10	
11	**Light**
12	
13	**Somewhat hard**
14	
15	**Hard (heavy)**
16	
17	**Very hard**
18	
19	**Extremely hard**
20	**Maximal exertion**

Borg's RPE Scale Instructions

While exercising we want you to rate your perception of effort, i.e. how hard, heavy and strenuous exercise feels to you. The perception of exertion depends on how hard driving your legs or arms, how heavy is your breathing, and the overall sensation of how strenuous exercise is. It does NOT depend on muscle pain, i.e. the aching and burning sensation in your leg or arm muscles.

Look at this rating scale; we want you to use this scale from 6 to 20, where 6 means "not exertion at all" and 20 means "maximal exertion".

9 corresponds to "very light" exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes.

13 on the scale is "somewhat hard" exercise, but it still feels OK to continue.

17 "very hard" is very strenuous exercise. A healthy person can still go on, but he or she really has to push him- or herself. It feels very heavy, and the person is very tired.

19 on the scale is "extremely hard" exercise. For most people this is the most strenuous exercise they have ever experienced.

Try to appraise your feelings of exertion as honestly as possible, without thinking about what actual physical load is (heart rate, speed, power output, intensity level on the exercise machine). Don't underestimate your perception of exertion, but don't overestimate it either. It is your own feeling of effort that's important, not how it compares to other people's. What other people think is not important either. Look carefully at scale and expressions, and then give a number.

Any questions?

APPENDIX II

This appendix contains an example of the Cook`s scale and instructions for the rating of pain intensity and unpleasantness (used in chapter 3). An example of the instruction used for rating perceived exertion during resistance exercise (used in chapter 4) and an examples of instruction used for rating of perceived exertion during whole-body exercise (used in chapter 2 and 3).

Pain Intensity Scale

0	No pain at all
½	Very faint pain (just noticeable)
1	Weak pain
2	Mild pain
3	Moderate pain
4	Somewhat strong pain
5	Strong pain
6	
7	Very strong pain
8	
9	
10	Extremely intense pain (almost unbearable)
•	Unbearable pain

Category Scale Instructions

You are about to undergo a maximal exercise test. The scale before you contains the numbers 0 to 10. You will use this scale to assess the perceptions of pain in your legs during and after the exercise test. In this context, pain is defined as *the intensity of hurt that you feel.* Don't underestimate or overestimate the degree of hurt you feel, just try to estimate it as honestly and objectively as possible.

The numbers on scale represent a range of pain intensity from "very faint pain" (number ½) to "extremely intense pain-almost unbearable" (number 10). When you feel no pain in your legs, you should respond with the number zero. When the pain in your legs becomes just noticeable, you should respond with the number ½. If your legs feel extremely strong pain is that is almost unbearable, you should respond with the number 10. If the pain is greater than 10 respond with the number that represents the pain intensity you feel in relation to 10. In other words, if the pain is twice as great then respond with the number 20.

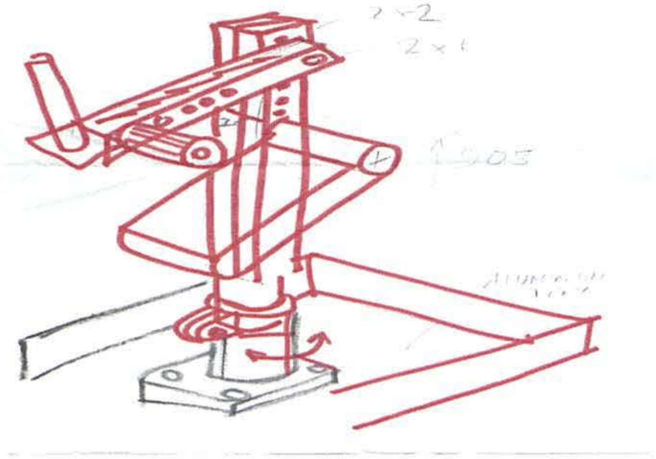
Repeatedly during the test you will asked to rate the feelings of pain in your legs. When rating these pain sensations, be sure to attend only to the specific sensations in your legs and not report other pains you may be feeling (*e.g.* seat discomfort).

It is very important that your ratings of pain intensity reflect only the degree of hurt you are feeling in your legs both during and after exercise. Do not use your ratings as an expression of fatigue (i.e. inability of the muscle to produce force) or belief that the exercise task is completed.

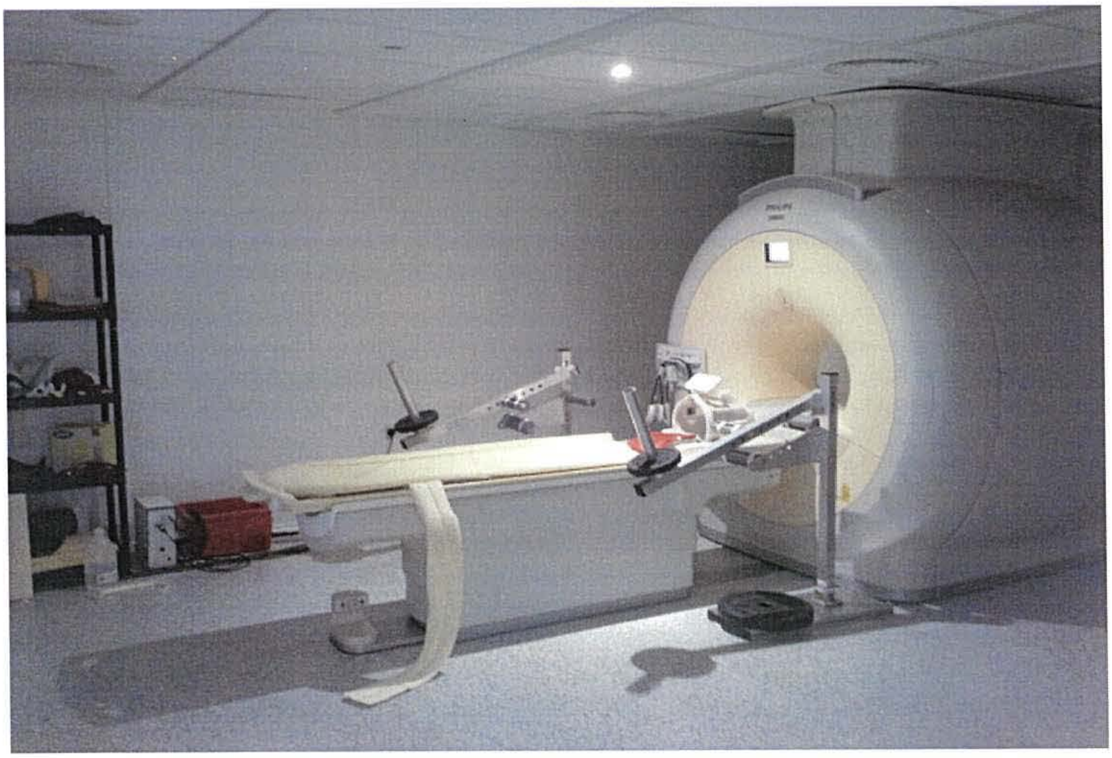
In summary you'll be asked to: (a) provide pain intensity ratings in your legs only; (b) give ratings as accurately as possible; and (c) not under-or-over-estimate the pain, but simply rate your pain honestly. You should use the verbal expressions to help rate your sensations.

APPENDIX III

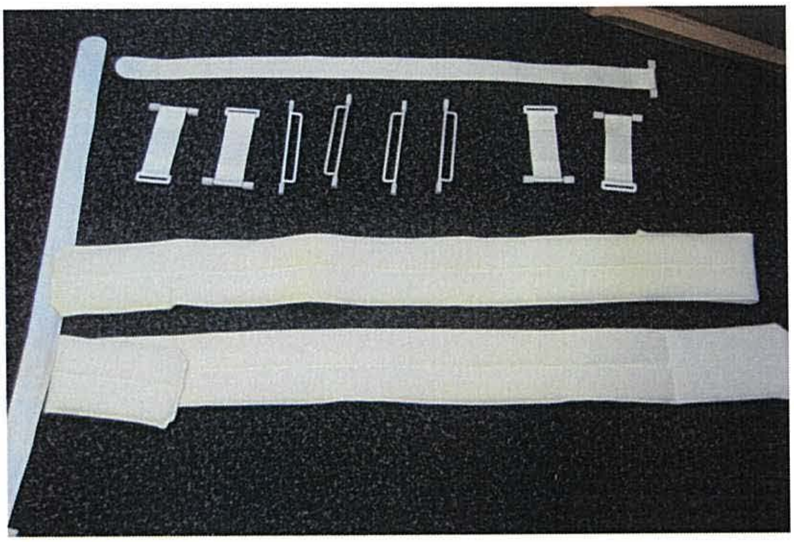
This appendix contains some images of the fMRI compatible scaffolds used in chapter 4 from its first conception (draft of the idea, image 1) to the actually realization and implementation in the scanner room (Image 2). The third picture shows a series of straps used to immobilize hips, chest and shoulders of the participant during the data recording. Unfortunately, no pictures of the final set up including a subject while performing a leg extension on the scaffold, has been taken.



1



2

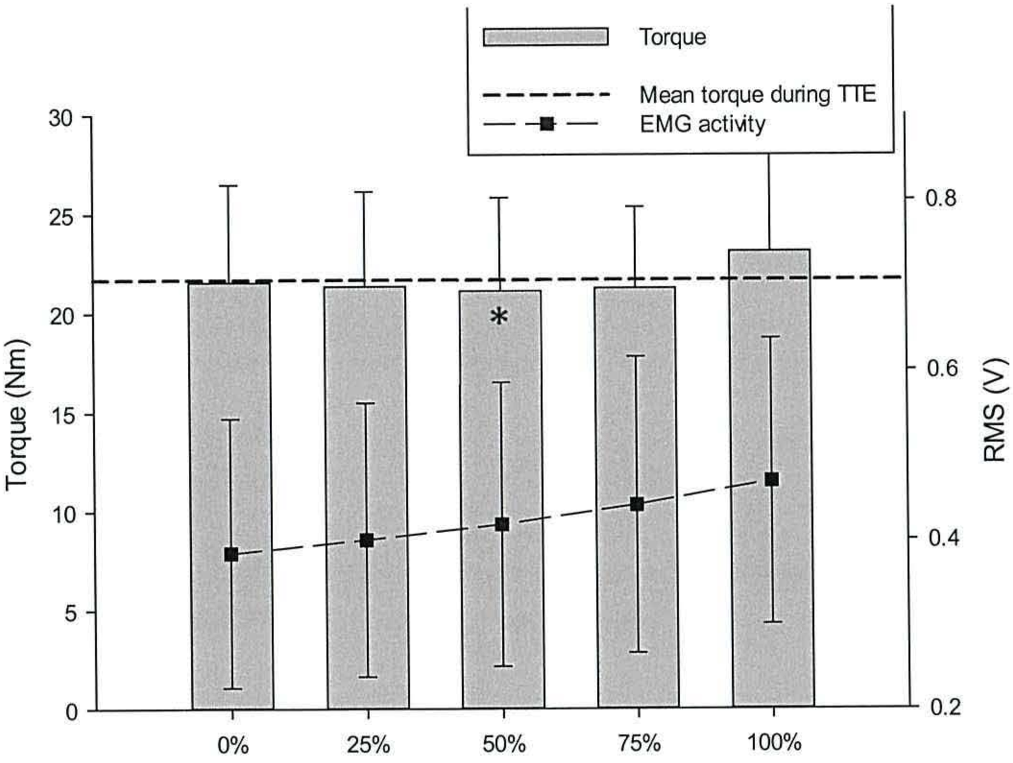


3

APPENDIX IV

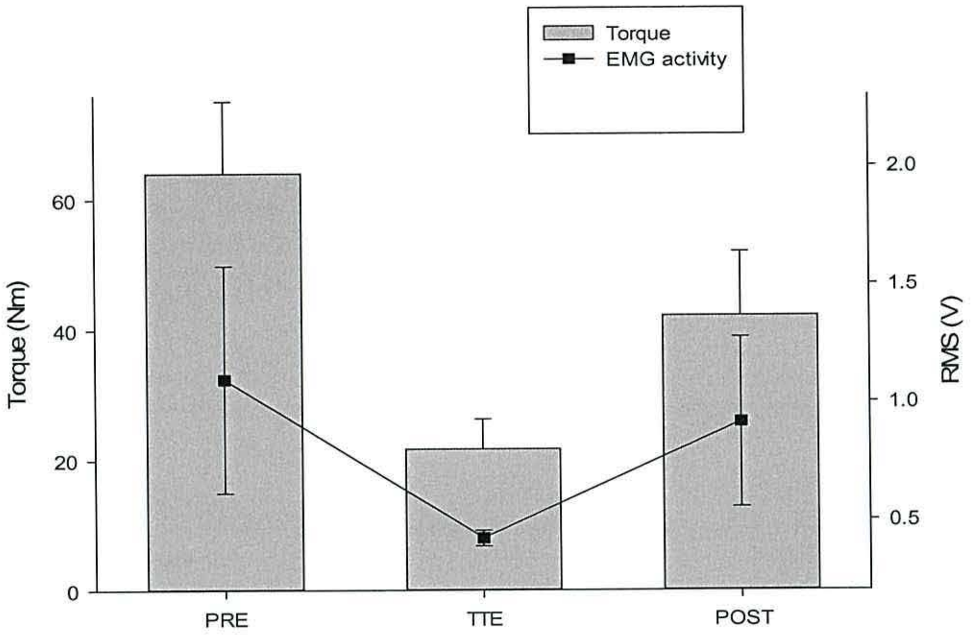
This appendix contains some unpublished data from a study conducted by Bosio A. and Marcora SM, which reproduces the study in chapter 2 but at constant RPM and with no time break between the TTE cycling test and the power cycling test Wingate. The number of subjects tested was 11. As follow are some graphs derived from those data.

1) Torque e EMG activity of Vastus Lateralis during TTE.



* Significant "main effect of time" (p<0.001) for EMG.

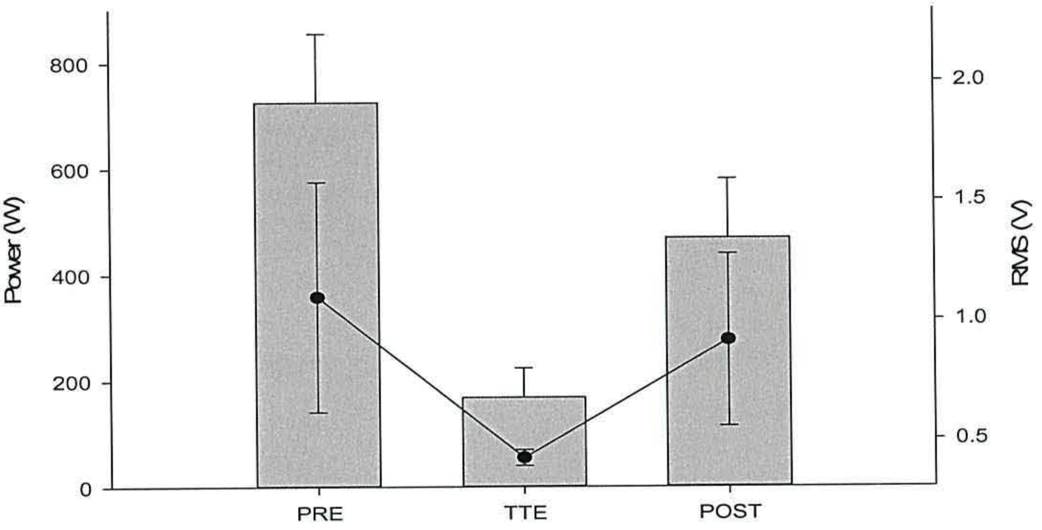
2) Capacity to produce power (Nm) and EMG before and after TTE



-Peak Torque: decrease of 34% ($p<0.001$) in maximal isokinetic power test after TTE, but it is still about the double of power compared to the power at which subjects were pedalling during exhaustion.

EMG activity of Vastus lateralis during the test of maximal isokinetic power PRE and POST the TTE cycling test did not show any significant difference ($p=0.127$).

3) Capacity to produce (W) power and EMG before and after TTE



Peak Power: decrease of 34% (p<0.001) in maximal isokinetic power test after TTE, but it is still about the double of power compared to the power at which subjects were pedalling during exhaustion.

EMG activity of Vastus lateralis during the test of maximal isokinetic power PRE and POST the TTE cycling test did not show any significant difference (p=0.127).