

**CENTRAL AND PERIPHERAL MANIPULATIONS OF  
PERCEIVED EXERTION AND ENDURANCE  
PERFORMANCE**

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54 539 words

PhD Sport and Exercise Science and Sports Therapy  
School of Sport and Exercise Sciences

2014

# *UN GRAND MERCI À ...*

Three years... Three years on this thesis project with a mood like a roller coaster going through all kind of emotions. This thesis would simply not exist without the precious help of so many people who were constantly present to support me, help me, advise me and make me move forward. So all of you mentioned below, simply UN GRAND MERCI!! And also many thanks for those who are not apparent in this document but who contributed to the completion of the thesis (undergraduate and postgraduate students who helped with subjects recruitment and data collection, all subjects, the research lab in Dijon University etc...)

Sam, you trusted me following the PhD interview, you challenged me during three years and provided feedback to make me understand how important and complicated research is. You made me understand that research takes time and quality matters more than quantity. Thank you for your patience and passion, the numerous unexpected meetings when I knocked on your door and welcomed me even though you were busy. I know how emotional I can be, and I am really grateful that you helped me and gave me responsibilities. Grazie mille !!

Romu, que dire... tu m'as fait confiance depuis ma 4<sup>ème</sup> année, malgré le fait que je travaillais à côté. Tu m'as appris avec passion ce qu'était la recherche dans le domaine de la fatigue. Tu m'as transmis ta passion, ton expertise dans ce domaine. Tu as su me pousser à partir à l'étranger, et tu m'as tellement donné de feedback et de conseils durant la thèse... Si j'en suis là aujourd'hui c'est le fruit de ton travail ! Merci de m'avoir confirmé dans mon désir de faire de la recherche mon métier. Tu es et restera pour moi un exemple de réussite sur le plan professionnel, sportif et personnel.

Sam and Romu, simply, working with you was the best thing that could happen to me. I hope our collaboration will keep going and grow.

Luca and Tutti ! Thanks for your help and support. You were my best guinea pig in the lab, always available and lot of advice. Our numerous exchanges and discussions were awesome and so helpful. And Luca let's be honest, go Juventus!

James, Lex and Mark. Our (never-ending) discussions, pilot work, laughs your advise were crucial during these three years!! I know and I am sure we will stay in touch. Oh importantly... Senior Vader, sorry that you did not convert me to the dark side of the central governor model... but many thanks for the 2 weeks of your summer spent on proof reading!!

Kat and Sarah, we started all together. I remember the first week when I was barely able to speak and you helped me. My frenglish is understandable now mainly because of you, many thanks. Mini and Leprechaun don't forget if you need anything anytime don't hesitate. Of course also many thanks to all PhD students and staff of the department that help me continuously these years. Special thanks for James Hogg. Mate let's be honest... how could you be so patient with me in the lab? Many many thanks for all you did there.

Louise, you played a really important role in the hardest time of my PhD. Un grand merci pour tout ce que tu as fait pour moi, sans ta présence et ton soutien cette thèse ne se serait certainement pas terminé en temps et en heure. Tu peux compter sur moi pour te soutenir durant ta thèse et la suite...

Papa, maman... Je n'ai pas toujours été un fils facile à vivre, mais j'espère que vous êtes fiers de moi. Sans vous deux il n'y aurait ni études, ni thèse, ni basket. Merci, je vous aime. Betty, ma sœur, ces mots te concernent aussi, car tu as toujours été là pour moi.

Caro... comme on dit le meilleur pour la fin ;-) Sans toi, ma meilleure amie, cette aventure n'existerait simplement pas. Tu as été là avant la thèse, pendant la thèse, et je sais que tu seras toujours là. Merci n'est pas suffisant pour ce que tu as fait pour moi, alors disons un grand merci ! Notre bout de chemin continue et j'espère que je pourrais te rendre tout ce que tu m'as apporté.

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# ***SUMMARY OF THE THESIS***

*This thesis was supervised by Prof. Samuele M. Marcora (University of Kent, UK) and co-supervised by Prof. Romuald Lepers (University of Burgundy, France)*

Perception of effort, defined as “the conscious sensation of hard, heavy and strenuous exercise”, is known to regulate endurance performance and human behaviour. Perception of effort has recently been shown to be exacerbated by mental exertion and is also known to be a main feature of fatigue. However, to date, not only its neurophysiology but also how manipulations of perceived exertion might impact endurance performance remain poorly understood. The main aim of this thesis was to investigate how manipulations of perceived exertion might impact endurance performance.

This thesis is divided in two parts: central and peripheral manipulations of perceived exertion. In each part, three experimental chapters aimed to get a better insight in the neurophysiology of perceived exertion and its impact on endurance performance.

In the first part (central manipulations), we firstly investigated the impact of exacerbating perceived exertion via mental exertion involving the response inhibition process on self-paced running endurance performance. This study demonstrated that as with time to exhaustion tests, time trial performance is impaired following mental exertion leading to mental fatigue. Secondly, we investigated whether mental exertion leading to mental fatigue could alter the rate of central fatigue development during constant load whole-body exercise. This study demonstrated that the exacerbated perception of effort in presence of mental fatigue does not reflect an altered rate of central fatigue development, but is likely to be due to i) an impaired central motor command and/or ii) an alteration of the central processing of the corollary discharge. Thirdly, we investigated whether mental exertion could impact the repeatability of maximal voluntary contraction of the knee extensors. We found that contrary to submaximal exercise, force production capacity is not altered by mental exertion. Finally, these three studies demonstrated that i) mental exertion negatively impacts submaximal exercise but not maximal exercise and that ii) mental fatigue differs from central fatigue.

In the second part (peripheral manipulation), we firstly developed and tested the reliability of a new endurance exercise model non-limited by the cardiorespiratory system

(one leg dynamic exercise), which will be of benefits for future researches aiming to manipulate feedback from group III-IV muscle afferents. Secondly, we described neuromuscular alterations induced by this exercise and tested a new methodology to indirectly measure feedback from group III-IV muscle afferents. This study demonstrated that one leg dynamic exercise induced central and peripheral fatigue and also a decrease in spinal excitability associated with an increase in cortical excitability. Furthermore, this study also suggests that monitoring cardiovascular responses during muscle occlusion might be a suitable tool to indirectly measure feedback from group III-IV muscle afferents. Thirdly, we tested the corollary discharge and afferent feedback model of perceived exertion with electromyostimulation. This study demonstrated for the first time that for the same force output, perception of effort generation is independent of muscle afferents and reflects the magnitude of the central motor command (manipulated by electromyostimulation). All together, these findings provide further evidence in support of the corollary discharge model of perceived exertion, and provide a new exercise model to investigate and manipulate perception of effort.

This thesis, when integrating both experimental parts, provides new insight on how perception of effort regulates endurance performance. Specifically, it demonstrates how muscle fatigue is a contributor of the continuous increase in perception of effort during endurance exercise, but also that other contributors play a role in this increase in perception of effort. Indeed, we demonstrated for the first time that i) perception of effort alterations in the presence of mental fatigue is independent of any alterations of the neuromuscular system, and ii) muscle afferents does not directly impact perception of effort, but may influence it indirectly via their role in motor control.

# ***GLOSSARY***

<b>ACC</b>	anterior cingulate cortex
<b>ANOVA</b>	analysis of variance
<b>BRUMS</b>	Brunel mood scale
<b>CGM</b>	central governor model
<b>CMEP</b>	cervicomedullary motor evoked potentials
<b>CNS</b>	central nervous system
<b>Ct</b>	contraction time
<b>EMG</b>	electromyography
<b>HR</b>	heart rate
<b>HRT</b>	half relaxation time
<b>KE</b>	knee extensors
<b>M-wave</b>	muscular wave
<b>M1</b>	motor cortex
<b>MEP</b>	motor evoked potential
<b>MVC</b>	maximal voluntary contraction
<b>NASA-TLX</b>	National Aeronautics and Space Administration task load index
<b>RF</b>	rectus femoris
<b>RFD</b>	rate of force development
<b>RMS</b>	root mean square
<b>RPE</b>	rating of perceived exertion
<b>TMS</b>	transcranial magnetic stimulation
<b>Tw</b>	twitch
<b>VAL</b>	voluntary activation level
<b>VL</b>	vastus lateralis

# ***GENERAL INTRODUCTION***

## **I. Perception of effort**

### **1. Definition and applications**

#### **DEFINITION**

Perception could be defined as “the conscious experience of sensation” and is known to be the result of central processing (brain’s interpretation) of sensory input (Gardner and Martin, 2000). As perception results from central processing of sensory signals, perception might vary between individuals and is consequently highly subjective (Weiten, 2010).

Effort, defined as “strenuous physical or mental exertion” (Oxford Dictionary), is known to provide information about task difficulty and significantly contributes to the feeling of conscious will (Preston and Wegner, 2009). As stated in the previously mentioned definition, effort can be perceived during both physical and mental tasks. It is well known that humans are using this feeling of effort to judge the difficulty of a task. Therefore, both feeling of effort and task difficulty are strongly linked.

Originally, perception of effort, also called perceived exertion or sense of effort, was defined by Gunnar Borg as “*the feeling of how heavy, strenuous and laborious exercise is*” (Borg, 1962). In the description provided by the author, perceived exertion is presented as “*the sensation from the organs of circulation and respiration, from the muscles, the skin, the joints and force*” (Borg, 1962). Later, linked to the original definition previously mentioned, the notion of discomfort and/or fatigue was added in the definition of perceived exertion as follow: “*the subjective intensity of effort, strain, discomfort, and/or fatigue that is experienced during physical exercise*” (Noble and Robertson, 1996; Utter et al., 2007). However, it has been shown by numerous studies that humans are able to dissociate their perception of effort from other exercise-related sensations, such as pain (O’ Connor and Cook, 2001), discomfort (Christian et al., 2014), force (Jones, 1995) or fatigue (i.e. effort can be perceived in absence of fatigue; de Morree and Marcora, 2010; de Morree et al., 2012). Therefore, as i) effort can be rated and perceived separately from other exercise-related sensations and ii) these exercise-related sensations have their own neurophysiological mechanisms (Marcora, 2009), the definition including discomfort (Noble and Robertson, 1996; Utter et al., 2007) should not be used to investigate

underlying neurophysiological mechanisms of perceived exertion. Indeed, if discomfort is included, any changes in unpleasant exercise-related sensations might alter effort rating, thus independently of an actual alteration of the perceived exertion (Marcora, 2009). Consequently, in the present thesis, perception of effort is defined as the conscious sensation of “*how hard, heavy and strenuous exercise is*” (Marcora, 2009; Marcora, 2010b). This definition is in line with the verbal descriptors originally chosen by Borg for his RPE scale (Borg, 1998) and does not refer to other exercise-related sensations.

## APPLICATIONS

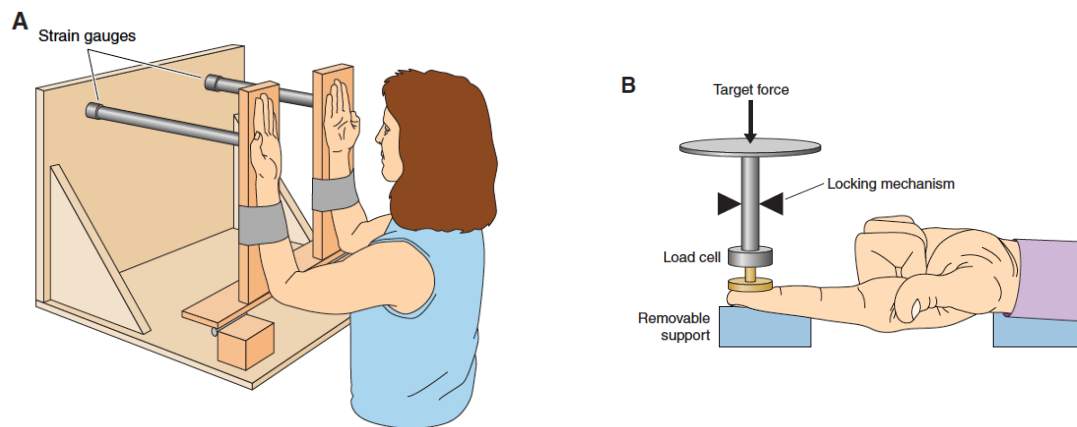
Perception of effort is a common phenomenon in daily life that play an important role in regulating our physical activity behaviours, from choosing a sedentary life to engaging in various sport activities (Marcora, 2010b). Clinically, because perception of effort is related to exercise intensity (de Morree et al., 2012; de Morree and Marcora, 2012), it is a useful tool to prescribe and monitor exercise during a rehabilitation programme (Noble and Robertson, 1996). Furthermore, numerous studies have demonstrated the crucial role of perception of effort in endurance performance during constant load (Marcora et al., 2008; Marcora et al., 2009; Pageaux et al., 2013) and self-paced (de Morree and Marcora, 2013; Pageaux, 2014; Pageaux et al., 2014) endurance exercise. Finally, an increase in perception of effort is also known to be a main feature of fatigue (Enoka and Stuart, 1992), but it has to be noticed that effort can be experienced in absence of any exercise-induced fatigue (de Morree and Marcora, 2010; de Morree et al., 2012).

### **2. How to measure perception of effort?**

#### **FORCE MATCHING TASKS**

Underlying neurophysiological mechanisms of perceived exertion were, and still are extensively investigated via contralateral force matching tasks (e.g. McCloskey et al., 1974; Scotland et al., 2014). Briefly, during force matching tasks, subjects are instructed to match a reference force with their contralateral limb (figure 1). These tasks provided support to the role of the corollary discharge associated with the central motor command in

perception of effort generation (see I.3.b of the General Introduction). Interestingly, studies using force matching tasks also demonstrated that experienced subjects are able to differentiate between perception of effort and perception of force (Jones, 1995). Therefore, it seems crucial to separate rating of effort and force. Furthermore, another limitation of force matching task is that rating of perceived exertion (RPE) is not the dependent variable, and any conclusion is based on a force produced by the subject not his own rating of effort.



**Figure 1 - Example of force matching tasks.**

Panel A represents a force matching task involving the elbow flexors and panel B the index. Briefly subjects have to produce a force with one limb and to match this force with the controlateral limb. From Proske and Gandevia (2012)

## PSYCHOPHYSICAL SCALES

To investigate perception of effort, researchers also use psychophysical scales consisting in rating the magnitude of the sensation perceived. The most common scales used to measure perception of effort are the 6-20 Borg scale (Borg, 1970) and the category ratio (CR10; Borg, 1982) scale (figure 2). The 6-20 Borg scale was designed in a way that rating grows linearly in parallel to changes in heart rate (heart rate divided by 10) during endurance exercise (Borg, 1998). The CR10 can be used for rating effort, but also for rating other sensation such as pain. At the bottom of the scale a black dot is placed to allow the subjects to rate any sensation above 10 and consequently avoiding a 'ceiling effect'. Both scales (6-20 Borg scale and CR10 scale) are known to be a valid and reliable measurement of effort (Borg, 1998) as far as standardised instructions are provided to the



subjects, and provide the advantage to investigate perception of effort as a dependent variable.

Other alternative scales have been used in an attempt to measure effort (e.g. Williams et al., 1994; Robertson et al., 2000). All of these scales have been shown to be highly correlated with the 6-20 Borg scale but their diversity has been described as unnecessary, especially when pictorial scales are used with adults (Faulkner et al., 2008). Therefore, in the present thesis, all experiments will use the 6-20 Borg scale to measure effort during physical exercise.

rating	description	rating	description
0	NOTHING AT ALL	6	NO EXERTION AT ALL
0.5	VERY, VERY LIGHT	7	EXTREMELY LIGHT
1	VERY LIGHT	8	
2	FAIRLY LIGHT	9	VERY LIGHT
3	MODERATE	10	
4	SOMEWHAT HARD	11	LIGHT
5	HARD	12	
6		13	SOMEWHAT HARD
7	VERY HARD	14	
8		15	HARD (HEAVY)
9		16	
10	VERY VERY HARD (MAXIMAL)	17	VERY HARD
		18	
		19	EXTREMELY HARD
		20	MAXIMAL EXERTION

**Figure 2 - CR10 and 6-20 Borg scales.**

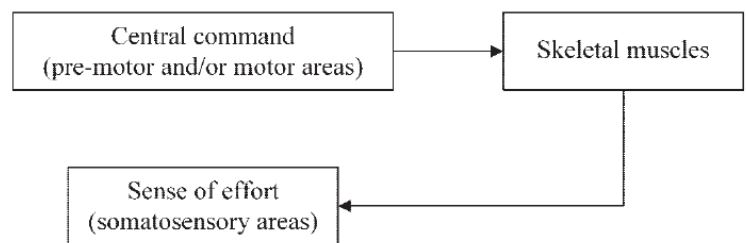
From Borg (1998)

### **3. Neurophysiology of perceived exertion**

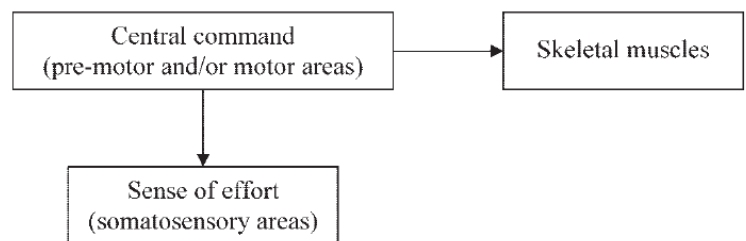
All human perceptions are known to share three common steps: i) a stimulus, ii) the central processing of this stimulus, leading to iii) the perception or conscious experience of the sensation (Gardner and Martin, 2000). Based on these three common steps, two models

emerged in the literature aiming to explain underlying mechanisms of perceived exertion: the corollary discharge model (McCloskey et al., 1974; Marcora, 2009) and the afferent feedback model (Noble and Robertson, 1996; Amann et al., 2013; Amann and Light, 2014). Independently of the model of perceived exertion, numerous studies suggest that brain areas involved in perception of effort might be the anterior cingulate cortex, insular cortex, pre-supplementary motor areas, supplementary motor areas, and possibly the thalamus (Williamson et al., 2001; 2002; de Morree et al., 2012).

**A Afferent feedback model of perceived exertion**



**B Corollary discharge model of perceived exertion**



**Figure 3 - Simplified afferent feedback (A) and corollary discharge (B) models of perceived exertion.**

From (Marcora, 2009)

***a. Corollary discharge model***

The corollary discharge model (figure 3B) states that perception of effort is generated by central integration of the corollary discharge (i.e. internal signal that arise from centrifugal motor commands and that influence perception; McCloskey, 1981) associated with the central motor command (i.e. activity of premotor and motor areas of the brain related to voluntary muscle contractions; de Morree et al., 2012). Corollary discharges are thought to have perceptual consequences in two different ways (McCloskey, 1981). Firstly, they are thought to modify the processing of incoming sensory information.

For example, for motor control, the corollary discharge is compared to external stimuli in order to plan the outcome of the movement (Bays and Wolpert, 2007). Secondly, corollary discharge might be used as the only stimulus to generate some specific sensation (McCloskey, 1981). The second type of corollary discharge is the one involved in the corollary discharge model of perceived exertion.

Most of the support for this model comes from experiments using force-matching tasks. These experiments demonstrate that any changes in the central motor command required to perform a task were associated with concomitant changes in perception of effort (McCloskey et al., 1983). For example, in presence of muscle fatigue, perception of effort is known to increase despite absence of any exercise-induced metabolites in the muscle milieu (i.e. known to stimulate group III-IV muscle afferents), thus in correlation with an increase in motor related cortical potential, known to be an indirect index of central motor command (de Morree et al., 2012). Alternatively, by stimulating muscle spindles by tendon vibration, it is possible to induce spinal reflexes inducing inhibition of the antagonist and excitation of the agonist muscles (Gandevia, 2001), consequently altering the central motor command when a force has to be held constant. Indeed, when a force has to be held constant, tendon vibration applied on the antagonist (inhibition of the muscle used to held the force) should lead to an increase in central motor command, and tendon vibration applied on the agonist (excitation of the muscle used to held the force) should decrease the central motor command. These results have been shown to occur when agonist and antagonist muscle tendons are vibrated during biceps force matching tasks (McCloskey et al., 1974).

### ***b. Afferent feedback model***

Despite evidence in favour of the corollary discharge model the experiments previously presented do not completely disprove a hypothetical role of afferent feedback (figure 3A) in perception of effort. Since the growing interest of physiologists' in the 'muscle sense' (for review see Proske and Gandevia, 2012), a continual debate exists between peripheralists (supporting the afferent feedback model; e.g. Amann et al., 2013) and centralists (supporting the corollary discharge model; e.g. Lafargue and Sirigu, 2006; Marcora, 2009). Peripheralists base their arguments on correlative data between increase in perceived exertion and increase in blood lactate concentration and metabolites

concentration in the muscle milieu (Noble and Robertson, 1996). As muscle afferents are composed of type III-IV muscle fibres (i.e. free nerve endings activated by contraction-induced mechanical and chemical stimuli; Rowell and O'Leary, 1990), these free nerve endings might be a plausible candidate being involved in perceived exertion generation. This hypothesis finds anatomical support as group III-IV muscle afferents are known to have central projections to various spinal and supraspinal sites including the sensory cortex (Craig, 2002).

To investigate whether muscle afferents might have a direct role in perception of effort generation, dissociation between changes in afferent feedback and central motor command has to be made. This dissociation was made by experiments using epidural anaesthesia. Interestingly, these studies provide evidence against the afferent feedback model and in favour of the corollary discharge model. Indeed, despite a significant reduction in muscle afferent feedback from the working muscles, RPE was unchanged or higher with spinal blockade during cycling (Kjaer et al., 1999; Smith et al., 2003) or isometric contractions (Mitchell et al., 1989). Taken all together, these results provide strong evidence that muscle afferents are not the sensory signals generating perception of effort.

## II. Endurance performance

### 1. Definition

Endurance performance can be defined as the prolonged maintenance of submaximal power or velocity (Coyle, 1999). We consider prolonged exercise as all physical exercise performed for more than one minute and consequently involving mainly the aerobic system of energy production. Endurance performance corresponds to the completion of whole-body (e.g. Place et al., 2004; Hettinga et al., 2006; Hettinga et al., 2011) or single joint exercise (e.g. Place et al., 2005; Rossman et al., 2012; Pageaux et al., 2013) and can be performed at various intensities (from low to high; e.g. Marcora et al., 2009; Amann et al., 2011a) using different modes of muscle contraction (isometric and dynamic; e.g. Rossman et al., 2012; Pageaux et al., 2013). Description of how exercise intensity is characterised can be found in table 1.

<b>Intensity</b>	<b>% HR<sub>max</sub></b>	<b>% VO<sub>2max</sub></b>	<b>% 1RM or PPO</b>	<b>RPE</b>
<b>Low</b>	≤ 65	≤ 45	≤ 50	≤ 11
<b>Moderate</b>	≤ 75	≤ 65	≤ 70	≤ 13
<b>High</b>	≤ 95	≤ 90	≤ 85	≤ 17
<b>Maximal</b>	> 95	> 90	> 95	> 17

**Table 1 – Description of exercise intensity.**

Table modified from (Deschenes, 2013). HR = heart rate, VO<sub>2max</sub> = maximum oxygen consumption, RM = one maximum repetition, RPE= rating of perceived exertion.

### **HOW TO MEASURE ENDURANCE PERFORMANCE?**

Endurance performance is well known to be altered by physical (e.g. Marcora et al., 2008; de Morree and Marcora, 2013) and mental fatigue (e.g. Marcora et al., 2009; Pageaux et al., 2013) and can be measured during time to exhaustion tests and time trials.

Time to exhaustion can be defined as the maintenance of a fixed power output, torque or velocity until exhaustion (i.e. disengagement from the exercise). On the other hand, a time trial is not performed at a fixed power, velocity or torque, but instead consists of the completion of a set amount of work as quickly as possible or as much work as possible in a set time. Despite the fact that both methods were shown to be valid and reliable (Amann et al., 2008a), time to exhaustion tests do not allow the investigation of the self-regulation of speed/power output during the exercise (i.e. pacing).

## **PACING**

Pacing can be defined as the self-regulation of speed/power during exercise (Smits et al., 2014). As pacing is involved in all competition events, it is important for athletes and coaches to understand its regulation. Depending on the endurance performance model aiming to explain its regulation (models are presented later in the manuscript), pacing is thought to be regulated either consciously (Marcora, 2010a; Pageaux, 2014) or unconsciously (Amann, 2011) by the central nervous system. Recently, a lot of evidence has been provided in the literature to support its conscious regulation, and pacing is now investigated as a behavioural response based on decision-making process that can be influenced by both internal (e.g. perception of effort, physiological responses) and external factors (e.g. tactical decisions, presence of competitors) (Pageaux, 2014; Renfree et al., 2014).

To date, numerous models aim to explain the regulation of endurance performance (e.g. Millet, 2011). This thesis will focus on introducing the three main models used in the exercise sciences: the inhibitory feedback model (Amann, 2011) the central governor model (Noakes et al., 2001), and the psychobiological model (Marcora, 2010a).

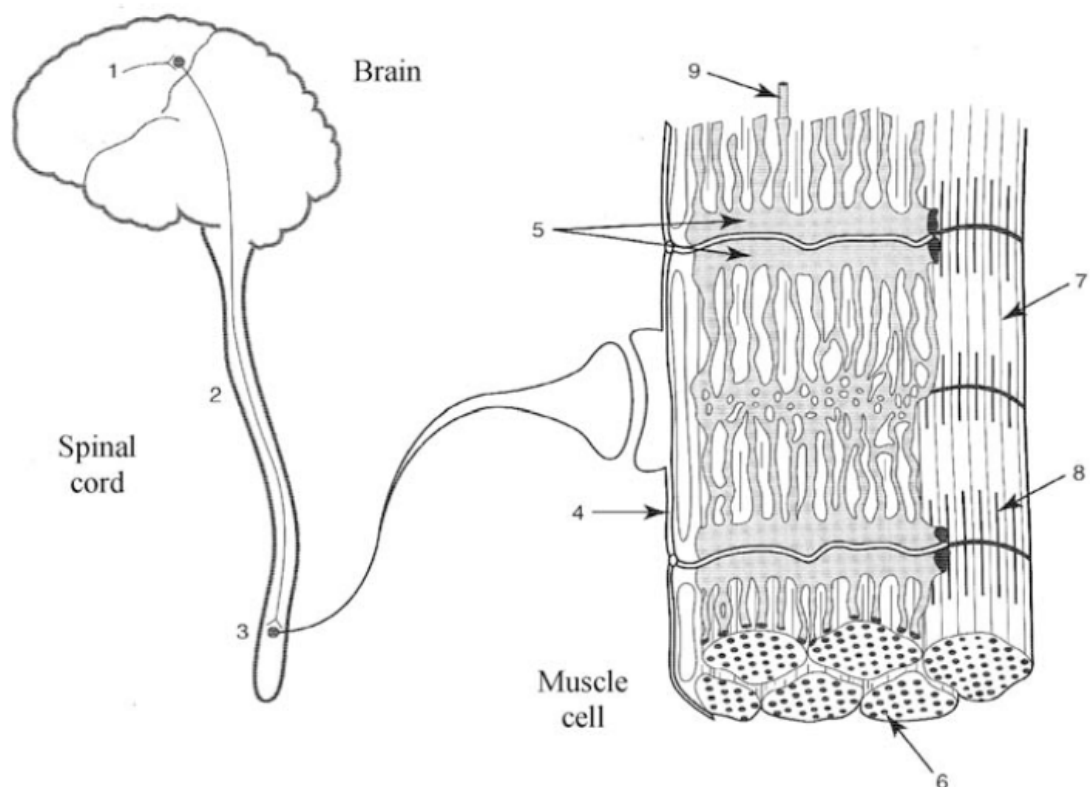
## **2. The inhibitory feedback model**

### ***a. Muscle fatigue***

The inhibitory feedback model is based on the interaction between peripheral and central fatigue phenomena (Amann, 2011). Therefore, before introducing this model, it is

important to present what muscle fatigue is and its peripheral and central fatigue components.

Muscle fatigue can be defined as “*any exercise-induced reduction in the ability of a muscle to generate force or power*” (Gandevia, 2001). Muscle fatigue can be investigated via measurement of maximal voluntary contractions (MVC) of the muscle group involved in the exercise. This technique allows for example quantification of muscle fatigue pre vs post exercise (e.g. Amann et al., 2011a), or during the exercise (e.g. Place et al., 2004) to describe the time course of exercise-induced muscle fatigue. Muscle fatigue is composed of central and peripheral phenomena (figure 4).



**Figure 4 – Sites contributing to muscle fatigue.**

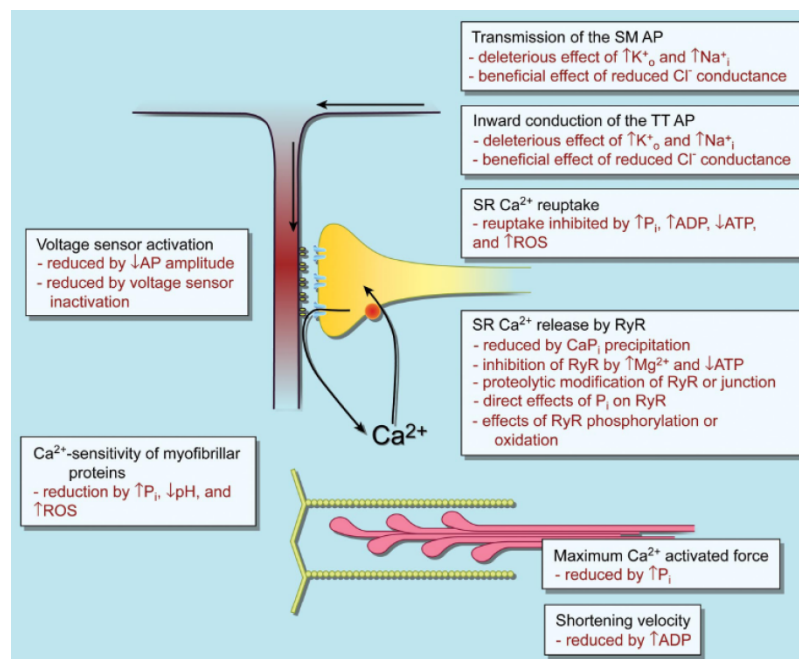
Modified from Bigland-Ritchie (1981) and published in Boyas and Guevel (2011). Fatigue may be due to alterations in: 1) activation of the primary motor cortex (supraspinal fatigue); 2) propagation of the command from the central nervous system to the motoneurons (spinal fatigue); 3) activation of the motor units and muscles; 4) neuromuscular propagation (including propagation at the neuromuscular junction); 5) excitation-contraction coupling; 6) availability of metabolic substrates; 7) state of the intracellular medium; 8) performance of the contractile apparatus; 9) blood flow.

## PERIPHERAL FATIGUE

Peripheral fatigue could be defined as fatigue produced by changes at or distal to the neuromuscular junction (Gandevia, 2001). Peripheral fatigue involves alteration in various processes such as propagation of the muscular wave (M-wave) or excitation-contraction coupling (figure 5). Peripheral fatigue can be investigated via peripheral nerve or myo-stimulation.

The decrease in neuromuscular excitability in humans can be investigated via the M-wave. The M-wave corresponds to the muscular wave evoked by nerve or myostimulation at supramaximal intensity. An alteration of the M-wave (changes in amplitude, duration or root mean square (RMS)/area) is considered to represent an alteration of the neuromuscular propagation. Changes in neurotransmitter concentration or increase in extracellular  $K^+$  concentration are some of the mechanisms contributing to alterations in M-wave parameters.

Peripheral fatigue might also reflect an alteration in the excitation-contraction coupling. The excitation-contraction coupling corresponds to all phenomena allowing transformation of the electrical stimulus (M-wave) to the mechanical response (muscular contraction). Changes in the excitation-contraction coupling can be demonstrated through analysis of the evoked contraction, induced by a supramaximal nerve or myostimulation



**Figure 5 – Various mechanisms contributing to peripheral fatigue.**

From (Allen et al., 2008)



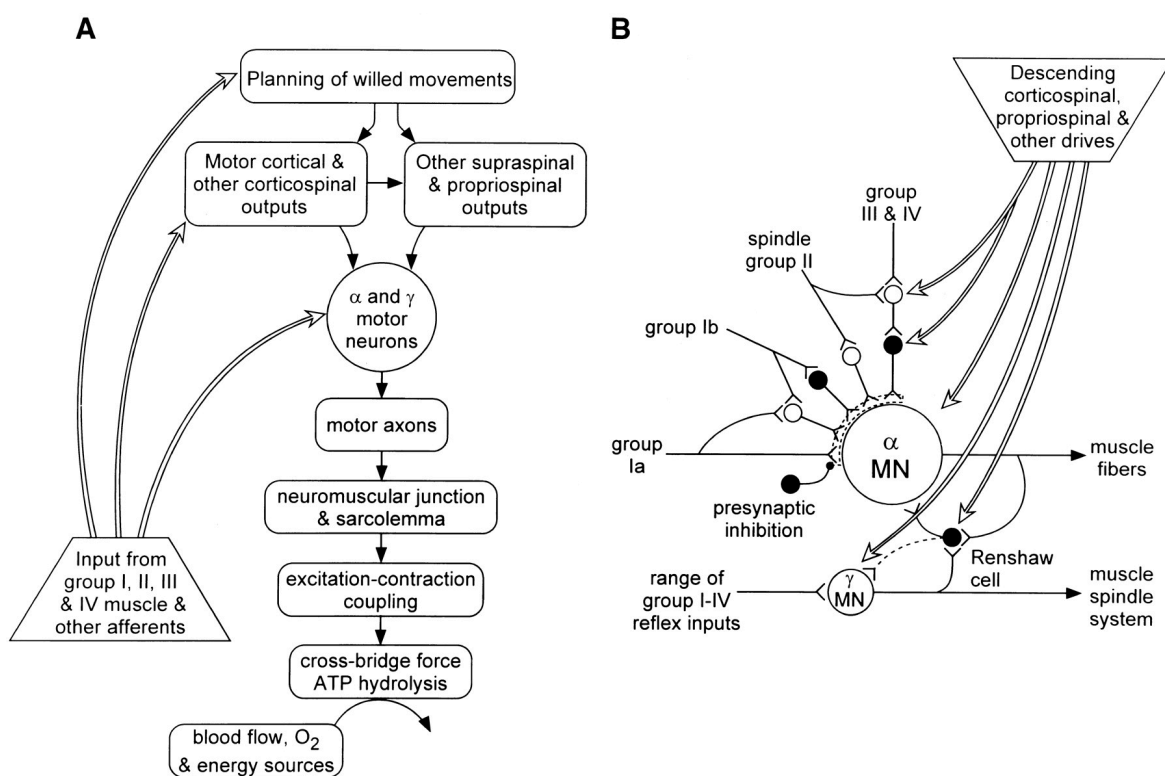
## CENTRAL FATIGUE

Central fatigue, i.e. decrease in maximal voluntary activation level (VAL; Gandevia, 2001), represents an inability of the central nervous system to fully recruit the active muscles. Central fatigue can be investigated via the twitch-interpolated technique (Gandevia et al., 2013) during an MVC. Briefly, this technique consists of the comparison of a superimposed evoked contraction (stimulation occurring during the MVC) with a resting evoked contraction. The stimulation, by being supramaximal, allows recruitment of the whole motoneuronal pool. Therefore, during an MVC, any superimposed force induced by the stimulation reflects a muscular inactivation (the subject is not able to fully recruit the active muscle). As the resting evoked contraction represents recruitment of the whole motoneuronal pool, normalisation of the superimposed evoked contraction by the resting evoked contraction provides an estimation of the percentage of muscle fibres voluntarily recruited by the subject. In the presence of central fatigue, this percentage, also named VAL, will decrease. From a methodological point of view, it is crucial to use paired stimulation at high frequency (doublet) rather than single stimulation (twitch), in order to appreciate the full extent of central fatigue. Indeed, contrary to high frequency paired stimulation, single stimulation is likely to be altered by changes in the excitation-contraction coupling (low frequency fatigue; Shield and Zhou, 2004).

Central fatigue is known to occur at a spinal and/or supraspinal level (for review see Gandevia, 2001). At a spinal level, the inhibition of the central motor drive (i.e. output from motor cortex, M1) is well understood and known to be caused by changes in excitability of the motoneuronal pool due to spinal projection of various muscle afferents (figure 6). At a supraspinal level, central fatigue corresponds to a submaximal output from the M1 due to inhibition occurring upstream to the motor cortex (Gandevia et al., 1996). The causes of supraspinal fatigue are poorly understood and the physiological processes causing a decrease in VAL remain unclear. Group III-IV muscle afferents are likely to cause an inhibition of the central motor drive (Gandevia, 2001). However, to date, the cause and effect relationship between discharge of group III-IV muscle afferents and central fatigue during locomotor exercise still needs to be established. Indeed, all studies manipulating group III-IV muscle afferents via epidural anaesthesia failed to demonstrate a difference in central fatigue between presence and absence of feedback from group III-IV muscle afferents (Amann et al., 2008b; Amann et al., 2009; Amann et al., 2011a; Amann et al., 2013). However, group III-IV muscle afferents are not the only contributors proposed to cause supraspinal fatigue. Impaired brain oxygenation (Goodall et al., 2012), alterations

in brain dopamine (Meeusen et al., 2006) or brain glycogen concentration (Matsui et al., 2011) might contribute to the decrease in VAL observed following endurance exercise.

Central fatigue is also associated with changes in corticospinal excitability (Gandevia, 2001). Corticospinal excitability can be investigated by the use of transcranial magnetic stimulation (Goodall et al., 2014a), cervicomedullary stimulation (Taylor and Gandevia, 2004), and other techniques measuring reflexes activity (e.g. Grospretre and Martin, 2012). Despite the fact that corticospinal excitability, as force production capacity, is known to be altered by exercise, the functional consequence of altered corticospinal excitability remains unclear. Indeed, changes in corticospinal excitability are not consistently associated with changes in force production capacity (Kalmar and Cafarelli, 2006).



**Figure 6 – Steps involved in voluntary force production and factors acting at motoneuronal level.**

From (Gandevia, 2001). A: diagrammatic representation of the “chain” involved in voluntary contractions. A major source of feedback, which from the muscle, is shown acting at three levels in the central nervous system. Other sources of feedback that also act at these levels are not shown. B: summary of inputs to  $\alpha$ - and  $\gamma$ -motoneurons for an agonist muscle. Cells with solid circles are inhibitory. Dotted curved region at pre motoneuronal terminals denotes presynaptic inhibition acting selectively on the afferent paths to motoneurons.

### ***b. The model***

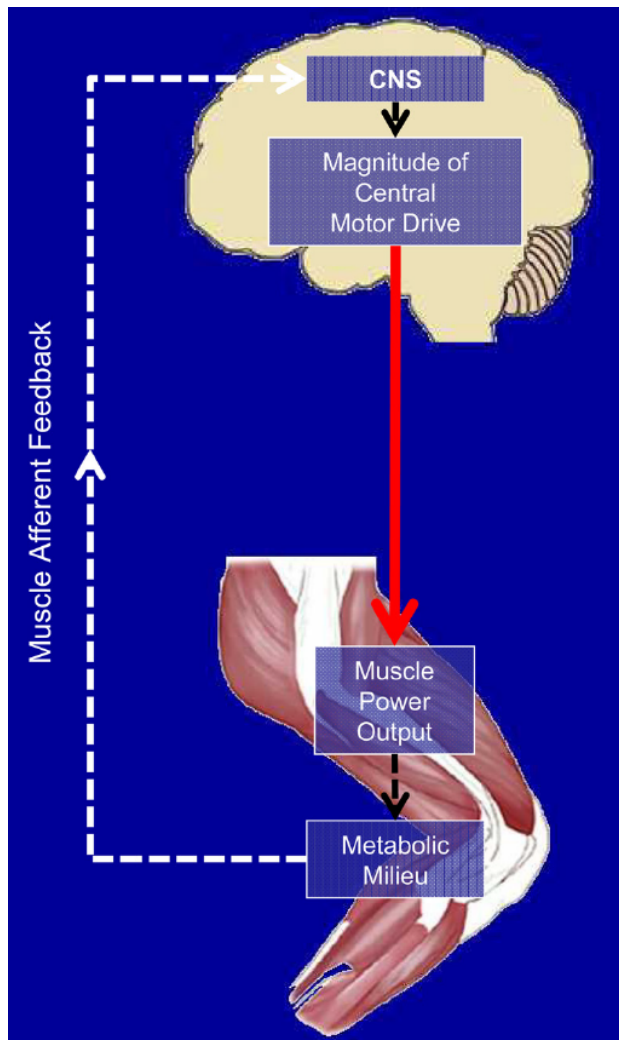
The inhibitory feedback model (figure 7) is based on the hypothesis that exhaustion during a time to exhaustion test occurs when the subject is unable to produce the required force/power (Edwards, 1981). Therefore, exhaustion should occur due to a failure of the neuromuscular system to produce the force/power.

Interestingly, some researches demonstrated that a certain level of peripheral fatigue is never exceeded despite numerous experimental manipulations aiming to increase the extent of peripheral fatigue at exhaustion (for review see Amann, 2011). The authors explained that once this peripheral fatigue threshold is reached, central fatigue induces the inability of the subject to produce the required force/power, causing exhaustion (for review see Amann, 2011).

During muscle contractions, degradation of adenosine triphosphate causes production of metabolites ( $H^+$ , bradykinin) in the muscle milieu, stimulating group III-IV muscle afferents. This discharge activity of group III-IV muscle afferents is proposed to provide somatosensory feedback inhibiting the central motor drive to the working muscles at a spinal (Gandevia, 2001) and/or supraspinal level (Amann, 2011), inducing a decrease in VAL. Interestingly, several studies involving cycling exercise found an effect of spinal blockade of somatosensory feedback on endurance performance and the EMG signal during the exercise (Amann et al., 2008b; Amann et al., 2009; Amann et al., 2011a). However, these studies failed to demonstrate a cause and effect relationship between discharge activity of III-IV muscle afferents and decrease in VAL, likely due to the time delay for neuromuscular testing. Therefore, to date, the link between both phenomena remains unclear.

Furthermore, the idea that exhaustion is caused by the inability of the neuromuscular system to produce the required force/power was recently disproved. Marcora and Staiano (2010) demonstrated that at exhaustion of high intensity cycling exercise, the subjects were still able to produce up to three times the required power output. Therefore, despite a plausible small recovery between exhaustion and production of maximal voluntary cycling power (time delay < 5 s), it is clear that at exhaustion, the neuromuscular system is still able to produce the required power.

The limit of the model presented above is not the only one. Firstly, during endurance exercise, the intensity is submaximal and the concept of central fatigue is not relevant (Gandevia, 2001). Secondly, even if the present model might explain exhaustion,



the inhibitory feedback model cannot explain pacing strategies during time trials (tactical decisions).

Finally, the inhibitory feedback model is linked to the afferent feedback model of perceived exertion. This model considers muscle afferent feedback as the sensory signal generating perception of effort (Noble and Robertson, 1996; Amann et al., 2006; Amann et al., 2007; Romer et al., 2007; Amann and Dempsey, 2008; Amann et al., 2008b; Amann et al., 2013).

**Figure 7 – The inhibitory feedback model.**

From (Amann, 2011). Schematic illustration of the inhibitory feedback model The continuous red line indicates efferent nerve activity (central motor drive), the dashed white line indicates afferent nerve activity. This regulatory mechanism shows that the cortical projection of muscle afferents (inhibitory feedback) affects the determination of the magnitude of central motor drive, which in turn determines power output of the locomotor muscles. The magnitude of power output determines the metabolic milieu within the working muscles, which in turn determines the magnitude of the inhibitory afferent feedback

### **3. Central Governor model**

The central governor model (CGM, figure 8) proposed by Noakes et al. (2001) is historically the first model bringing forward the role of the brain in endurance performance regulation. This model is a development of the ‘teleoanticipation’ theory proposed by

(Ulmer, 1996). The teleoanticipation theory states that to avoid important homeostatic disturbance, a feedback control system must exist, thus including the consideration of a finishing point. The model explains that the brain constantly relies on signals from the body to subconsciously make adjustments to the pacing strategy (Tucker, 2008).

Building upon this, the CGM suggests that the central nervous system regulates exercise in order to prevent any catastrophic physiological failure (i.e. heart ischemia) and to maintain body homeostasis (Noakes 2011). This implies that maximal fatigue is never reached, and a physiological reserve exists and cannot be used by the athletes. As proposed by the inhibitory afferent feedback model (Amann, 2011), the CGM also supports the theory that muscle fibres recruitment is regulated by afferent feedback from the working muscles, but also from other organs such as the heart and lungs. This regulation of muscle fibres recruitment is thought to avoid reaching a critical level of fatigue causing catastrophic physiological failure (Noakes, 2011). During time trials, the CGM suggests that pacing strategy is adjusted through sensory afferent feedback, which is interpreted consciously as the sensation of fatigue (Noakes et al., 2004; St Clair Gibson et al., 2006). Pacing strategy is therefore continually altered through this sensory afferent feedback, which acts as a feed forward control of skeletal muscle fibres recruitment (Noakes, 2012).

The CGM also considers feedback from muscle afferents as the sensory signal generating perceived exertion. It considers both conscious and unconscious decisions (related to this perceived exertion) made by each individual as the ultimate determinant of fatigue and performance (Noakes, 2012).

However, the CGM faces several criticisms. Firstly, the location of this central governor remains unknown. Secondly, the end-spurt phenomenon cannot be explained by a teleoanticipation theory and an unconscious regulation of pacing (Marcora, 2008). Finally, the unconscious regulation of pacing cannot explain tactical decisions taken by the athletes during an event (e.g. overtaking an opponent).

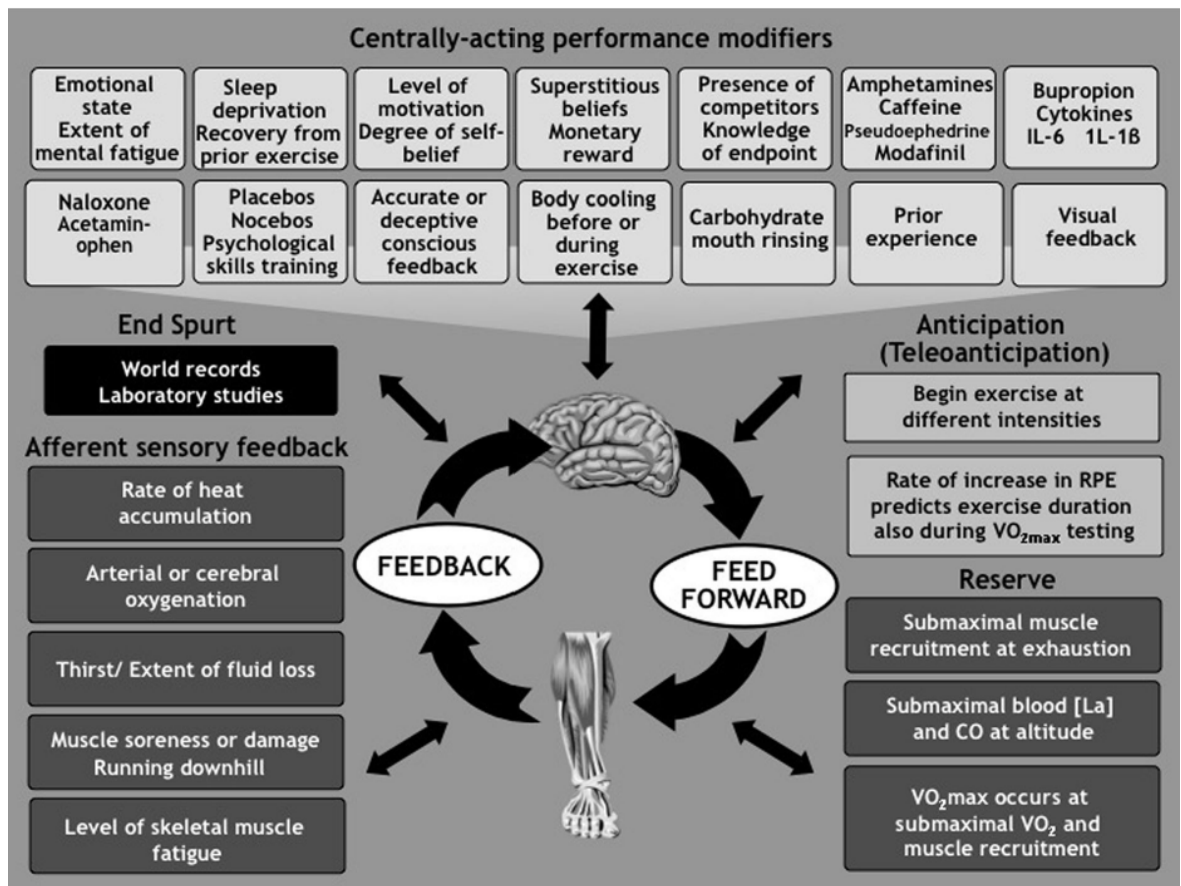


Figure 8 – Best representation of the central governor model

From (Noakes, 2012)

#### 4. Psychobiological model

This part is partially published in (Pageaux, 2014)

The psychobiological model has been shown to provide a valid explanation of the effects of both psychological (Marcora et al., 2009; Pageaux et al., 2013) and physiological (Marcora et al., 2008) manipulations on endurance performance during time to exhaustion tests. Recently, its explanatory validity was extended to time trials where endurance performance was altered by psychological (mental fatigue; Pageaux et al., 2014) and physiological (muscle fatigue; de Morree and Marcora, 2013) manipulations.

The psychobiological model (Marcora, 2010a) is an effort-based decision-making model based on motivational intensity theory (Brehm and Self, 1989), and postulates that the conscious regulation of pace is determined primarily by five different cognitive/motivational factors:

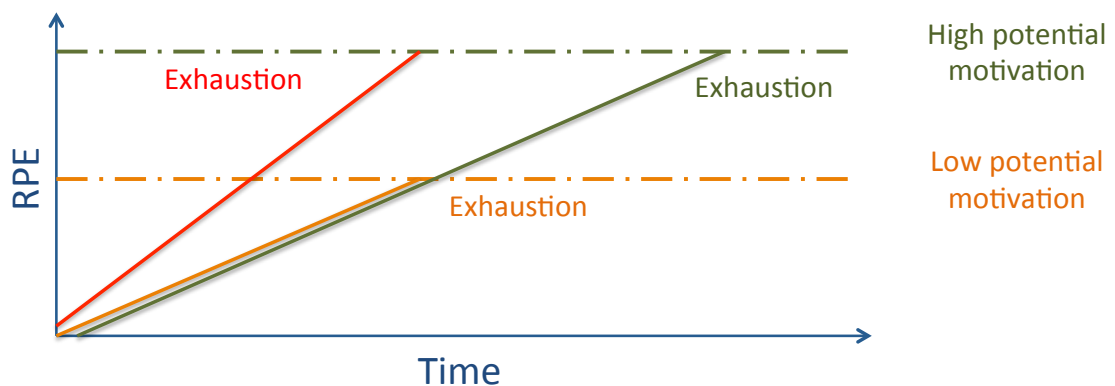
- 1) Perception of effort
- 2) Potential motivation

- 3) Knowledge of the distance/time to cover
- 4) Knowledge of the distance/time remaining
- 5) Previous experience/memory of perception of effort during exercise of varying intensity and duration

Factor 2 (potential motivation) refers to the maximum effort an individual is willing to exert to satisfy a motive, and could be easily influenced by external factors (e.g. higher motivation during an event with competitors than during laboratory testing). Factors 3 to 5 are self-explanatory and can explain the end-spurt phenomenon (Marcora, 2008) or why athletes start different races at different paces (Joseph et al., 2008). Perception of effort (factor 1) is the key determinant of this model. Indeed, according to this model, the conscious regulation of pace is primarily determined by the effort perceived by the athlete. Therefore, when perception of effort is increased by muscle (de Morree and Marcora, 2013) or mental (Pageaux et al., 2014) fatigue, or reduced (same perception of effort for a higher power output) by pharmacological manipulation (Watson et al., 2005), the athlete will consciously change its pace to compensate for the negative/positive effect of the experimental manipulation on perception of effort, thus leading to an improvement (if decreased perception of effort) or impairment (if increased perception of effort) in self-paced endurance performance. Because the five factors mentioned above are sensitive to external and/or physiological factors known to impact endurance performance, the psychobiological model could be considered as a tool to explain regulation of self-paced endurance performance. For time to exhaustion tests, the psychobiological model states that exhaustion is not caused by muscle fatigue, but is caused by the conscious decision to disengage from the endurance task. In highly motivated subjects, this effort-based decision is taken when they perceive their effort as maximal and continuation of the endurance task seems impossible (figure 9).

Contrary to the models previously presented, the psychobiological model of endurance performance postulates that the sensory signal processed by the brain to generate perception of effort is not the afferent feedback from skeletal muscles and other interoceptors (Marcora, 2009). Perception of effort is thought to result from the central processing of the corollary discharge associated with the central motor command (Marcora, 2009; de Morree et al., 2012), thus explaining the alteration of perception of effort and performance when central motor command is increased to compensate for muscle fatigue (de Morree and Marcora, 2013) or central processing of the corollary discharge is altered by mental fatigue (Pageaux et al., 2013; Pageaux et al., 2014).

So far, no study disproving the validity of the psychobiological model of endurance performance exists. Indeed, all studies on endurance performance reported maximal or near maximal effort exerted by the subjects at exhaustion. Furthermore, all studies inducing alterations in perception of effort through various experimental manipulations (psychological or physiological) demonstrated an alteration in endurance performance (e.g. Watson et al., 2005). Consequently, in order to test the validity of this model, further studies should aim to manipulate perception of effort and/or motivation to investigate whether endurance performance could be altered in absence of alteration of perception of effort and/or motivation. Further studies, should also determine i) the maximal exercise intensity that can be explained by this model and ii) the maximal duration of exercise that can be sustained in absence of pacing inducing submaximal power output.



**Figure 9 – Exhaustion during time to exhaustion tests explained by the psychobiological model.**

The plain lines represent the time course of RPE during exercise. The dotted lines represent the potential motivation. When potential motivation is high, exhaustion occurs later compared to an exercise performed with a low potential motivation (green vs orange line). When potential motivation is the same, a change in time course of RPE induces an earlier disengagement from the task (red vs green line).



### **III. Mental fatigue and performance**

#### **1. Effects of mental fatigue on physical performance**

These two following parts are partially published in (Pageaux et al., 2013)

Prolonged mental exertion is well known to induce mental fatigue, a psychobiological state characterised by subjective feelings of “tiredness” and “lack of energy” (Boksem and Tops, 2008). The negative effects of mental fatigue on cognitive performance are well established and include impairments in attention, action monitoring, and cognitive control (e.g. van der Linden et al., 2003; Boksem and Tops, 2008). On the contrary, the effects of mental fatigue on physical performance have been scarcely investigated. In 1906, Mosso reported that two of his colleagues did poorly in a muscle fatigue test performed after delivering long physiology lectures and viva examinations. More recently, Bray et al. (2008, 2012) showed that performing a demanding cognitive task before or between isometric contractions significantly reduces the endurance and MVC repeatability of isolated upper limb muscles. However, neuromuscular function was assessed with EMG, a method that does not provide a valid measure of maximal voluntary activation of muscle (Gandevia, 2001).

Marcora et al. (2009) conducted the first experimental study on the effect of prolonged mental exertion on endurance performance during dynamic whole-body exercise. These investigators induced mental fatigue in a group of healthy and fit subjects using a prolonged demanding cognitive task performed for 90 min, and found a significant reduction in time to exhaustion during subsequent high-intensity cycling exercise. However, the physiological mechanisms underlying the negative effect of prolonged mental exertion on endurance performance are currently unknown. Marcora et al. (2009) did not find any effect of mental fatigue on the cardiovascular, respiratory and metabolic responses to high-intensity cycling exercise. Motivation related to the time to exhaustion test was also unaffected by mental fatigue. In this study, the only factor that could explain a premature exhaustion was the higher perception of effort experienced by mentally fatigued subjects during high-intensity cycling exercise. According to the psychobiological model of endurance performance, mentally fatigued subjects disengaged earlier from the task as perception of effort was maximal and continuation of the endurance task seemed impossible.

Although this explanation is plausible, all studies previously mentioned did not measure neuromuscular function. Therefore, a reduction in maximal muscle activation or an increase in the extent of central fatigue induced by endurance exercise may also explain the negative effect of mental fatigue on endurance performance. Central fatigue is thought to negatively affect endurance performance (Amann, 2011) and several authors have proposed a strong link between mental and central fatigue (e.g. Newsholme et al., 1992; Di Giulio et al., 2006; Bray et al., 2012). Because supraspinal fatigue seems to occur in brain areas upstream of the primary motor cortex (Taylor et al., 2000), it is plausible that prolonged mental exertion can alter maximal muscle activation and, thus, impair endurance performance.

Pageaux et al. (2013) conducted the first experimental study assessing neuromuscular function of the knee extensors before and after a prolonged and demanding cognitive task leading to mental fatigue, and after a subsequent endurance task (submaximal isometric knee extensors time to exhaustion). The authors found that mental fatigue did not decrease VAL during MVC of the knee extensors before exercise, and that mental fatigue did not exacerbate central fatigue when measured at exhaustion. These findings suggest that mental fatigue and central fatigue (i.e. muscle activation) are two separate phenomena. However, as the extent of central fatigue was not assessed for the same duration of exercise between conditions, it remains unknown whether mental fatigue could increase the rate of central fatigue development. Furthermore, as Bray et al. (2012), found a decrease in MVC repeatability capacity, it remains unclear whether i) mental fatigue could impact differently the upper and lower limbs, and ii) if mental exertion could negatively impact repeated MVC.

To date, only one study (Brownsberger et al., 2013) investigated the effect of mental fatigue on self-paced exercise. These authors demonstrated that following completion of mental exertion leading to mental fatigue, mentally fatigued subjects produced a lower power output at a fixed perception of effort. However, as this study is the only one investigating the effect of mental fatigue on self-paced exercise, the effect of mental fatigue on time trials (self-paced performance) remains unknown.

## **2. Mental fatigue versus central fatigue**

Bray et al. (2008) and Pageaux et al. (2013) demonstrated that completion of mental exertion leading or not to mental fatigue does not impair force production capacity, despite a reduction in endurance performance. These results suggest that contrary to physical fatigue, mental fatigue does not limit the ability of the central nervous system to maximally recruit the active muscles.

The different effects of mental exertion leading to mental fatigue and endurance exercise on maximal muscle activation suggest that different mechanisms are involved. One possibility is that mental exertion and endurance exercise are associated with different neurochemical changes in the brain. However, both prolonged mental exertion (Lorist and Tops, 2003; Gailliot, 2008) and endurance exercise (Davis et al., 2003; Matsui et al., 2011) have been associated with an increase in brain adenosine and a reduction in brain glycogen. Therefore, at present, the most likely explanation for the different effects of prolonged mental exertion and endurance exercise on maximal muscle activation is that the neurochemical changes associated with both phenomena occur in different areas of the CNS.

The cognitive tasks used by Bray et al. (2008) and Pageaux et al. (2013) are known to strongly activate the anterior cingulate cortex (ACC; Carter et al., 1998), an area of the brain associated with task difficulty and sustained attention in a variety of cognitive tasks (Paus, 2001). Importantly, the ACC has also been linked with perception of effort during endurance exercise (Williamson et al., 2001). It is, therefore, biologically plausible that prolonged mental exertion induces changes in the ACC, which in turn, increase perception of effort and reduce endurance performance. However, the results from Bray et al. (2008) and Pageaux et al. (2013) suggest that continuous activation of the ACC does not reduce the capacity of the CNS to maximally recruit the active muscles.

Endurance exercise involving isometric exercise has been shown to induce a progressive increase in activity in several brain areas such as the sensorimotor cortex, supplementary motor areas, frontal cortex, and the insular cortex during submaximal fatiguing exercise (Liu et al., 2003; van Duinen et al., 2007; van Duinen et al., 2008; Post et al., 2009). However, it is not clear whether the concept of central fatigue is meaningful during submaximal muscle contractions (Taylor and Gandevia, 2008). In fact, these changes in cerebral activity during submaximal fatiguing exercise are likely to reflect brain adaptations to compensate for spinal and/or peripheral muscle fatigue rather than

mechanisms of supraspinal fatigue. To date, only van Duinen et al. (2007) have investigated the brain areas associated with supraspinal fatigue by measuring their activity during MVCs performed before and after fatiguing exercise. These authors showed a significant decrease in activity of the supplementary motor areas and, to a lesser extent, in parts of the paracentralgyrus, right putamen, and in a small cluster of the left parietal operculum. The fact that central fatigue was not associated with changes in ACC activity suggests that the brain areas affected by prolonged mental exertion and endurance exercise are different.

Furthermore, we have to consider that the neurochemical changes induced by mental exertion are likely to be confined to the brain, whilst some of the neurochemical changes leading to central fatigue may also occur at spinal level (Gandevia, 2001). Therefore, the different effects of mental exertion leading to mental fatigue and endurance exercise on maximal muscle activation could be explained by i) the different brain areas affected by prolonged mental exertion and endurance exercise, and ii) the spinal alterations likely to occur during endurance exercise but not during prolonged mental exertion.

#### **IV. Aims and outline of the thesis**

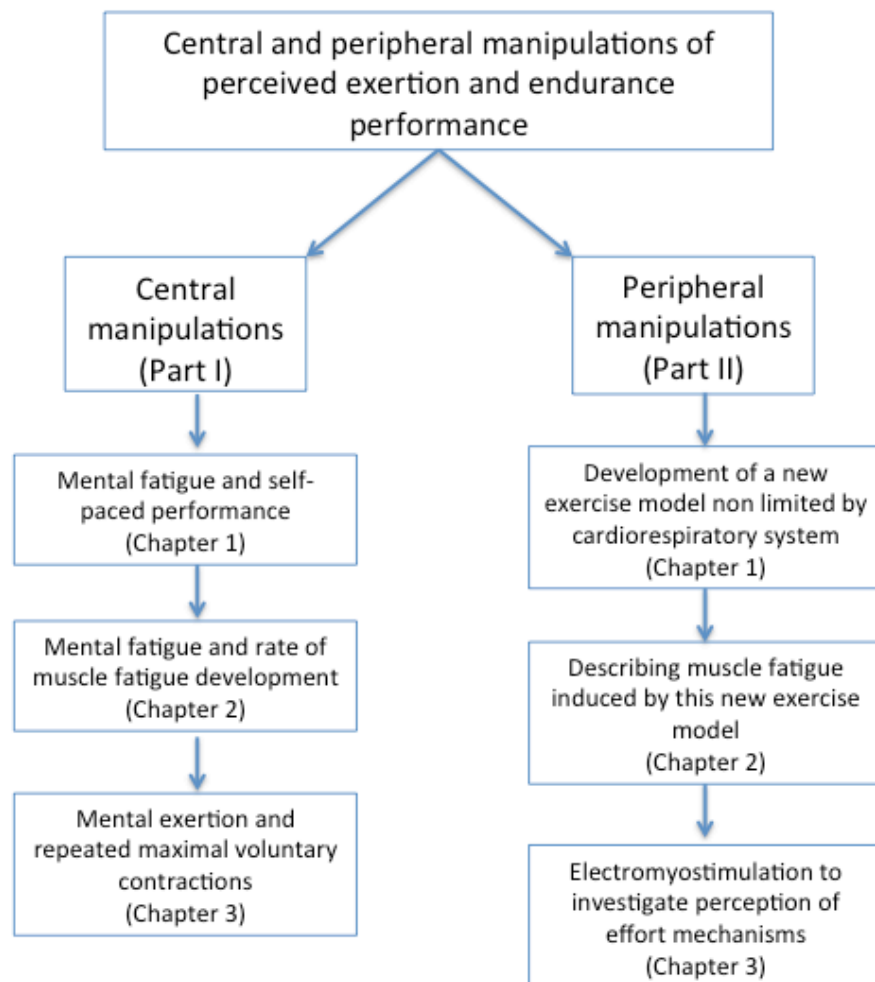
The aim of the present thesis is to investigate the effects of various central and peripheral manipulations on perception of effort and/or endurance performance. As previously presented in the general introduction, perception of effort is a key component of endurance performance. However, as only few studies investigated the impact of mental fatigue on endurance performance, it is important to explore whether mental fatigue and central fatigue could be linked. Furthermore, as both theories (corollary discharge and afferent feedback model) of generation of perception of effort should be considered until one is disproved, the link between increase in perception of effort and muscle fatigue remains unclear. Thus, to explore these gaps in the literature, the present thesis will present six experimental studies divided in two parts: central (part I) and peripheral (part II) manipulations of perceived exertion (figure 10). Central manipulations are considered as changes in perception of effort induced by completion of cognitive tasks. Peripheral manipulations are considered as any manipulations of neuromuscular function that can either impact muscle force production or muscle afferents.

All experimental chapters are either published or submitted in peer review journals, or are written for future submission. Therefore, it exists a necessary overlap in the contents of these manuscripts. Furthermore, all publications resulting from this PhD can be found in the Appendices.

In the first part (central manipulations), three studies were conducted to investigate whether i) mental fatigue could impair self-paced endurance performance, ii) mental fatigue could increase the rate of central fatigue development and iii) completion of mental exertion could impair MVC repeatability. Taken all together, the results of these three studies will provide a better insight on the relation between mental and muscle fatigue, with particular interest on the central component of muscle fatigue. We hypothesised that i) mental fatigue would impair self-paced endurance performance, ii) mental fatigue would differ from central fatigue and iii) mental exertion would not impair MVC repeatability.

In the second part (peripheral manipulations), three studies were conducted to i) develop a new endurance exercise model not limited by the cardiorespiratory system (for future manipulations of group III-IV muscle afferents), ii) describe muscle fatigue and changes in corticospinal excitability induced by this new exercise model and iii) testing the validity of the two models of perceived exertion via the use of electromyostimulation. Taken all together, the results of these three studies will provide a better insight on how to manipulate muscle afferent feedback to investigate their role in endurance performance. This part will also investigate the role of central motor command (and indirectly its corollary discharge) and muscle afferents in perception of effort generation. We hypothesised that i) the endurance exercise model developed would be valid and reliable, ii) this exercise model would induce central and peripheral alterations of neuromuscular system and iii) electrical stimulation of muscle afferents would not alter perception of effort.

Figure 10 – Summary of the thesis.



***PART I: CENTRAL  
MANIPULATIONS OF  
PERCEIVED EXERTION***

## **CHAPTER 1: RESPONSE INHIBITION IMPAIRS SUBSEQUENT SELF-PACED ENDURANCE PERFORMANCE**

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**Published in** the European Journal of Applied Physiology (2014)

Pageaux, B., Lepers, R., Dietz, K. C. & Marcora, S. M. 2014. Response inhibition impairs subsequent self-paced endurance performance. *European journal of applied physiology*, 114, 1095-105.



## **Abstract**

The aim of this study was to test the effects of mental exertion involving response inhibition on pacing and endurance performance during a subsequent 5 km running time trial. After familiarisation, 12 physically active subjects performed the time trial on a treadmill after two different cognitive tasks: i) an incongruent Stroop task involving response inhibition (inhibition task), and ii) a congruent Stroop task not involving response inhibition (control task). Both cognitive tasks were performed for 30 min. **Results:** Neither the inhibition nor the control task induced subjective feelings of mental fatigue. Nevertheless, time trial performance was impaired following the inhibition task ( $24.4 \pm 4.9$  min) compared to the control task ( $23.1 \pm 3.8$  min) because of a significant reduction in average running speed chosen by the subject. The response inhibition task did not affect pacing strategy, which was negative in both conditions. Heart rate and blood lactate responses to the time trial were not affected by the inhibition task, but subjects rated perceived exertion higher compared to the control condition ( $13.5 \pm 1.3$  vs  $12.4 \pm 1.3$ ). These findings show for the first time that 30 min of mental exertion involving response inhibition reduces subsequent self-paced endurance performance despite no overt mental fatigue. The impairment in endurance performance observed after the incongruent Stroop task seems to be mediated by the higher perception of effort as predicted by the psychobiological model of endurance performance.

## **I. Introduction**

Mental exertion refers to the engagement with a demanding cognitive task. When prolonged, it can induce a psychobiological state of mental fatigue characterised by subjective feelings of “tiredness” and “lack of energy” (Boksem and Tops, 2008). Recent studies have demonstrated the negative impact of mental fatigue induced by prolonged mental exertion (90 minutes) on subsequent endurance performance during whole-body (Marcora et al., 2009) and single joint exercise (Pageaux et al., 2013). These studies demonstrate a higher perception of effort independently of any alteration of the cardiorespiratory, metabolic and neuromuscular responses to exercise. These results

support the psychobiological model of endurance performance in which perception of effort plays a major role in limiting endurance performance (Marcora and Staiano, 2010).

In these studies, the negative effects of prior mental exertion on endurance performance were demonstrated with time to exhaustion tests. These tests are sensitive to changes in endurance performance (Amann et al., 2008a) but they do not allow for the self-regulation of speed/power output during endurance exercise (pacing). Therefore, the effect of prior mental exertion on pacing is not known at present. As pacing is involved in all competitive endurance events, it is important for coaches and athletes to know whether prior mental exertion can affect the pacing strategy, i.e. self-selected strategy or tactic adopted by an athlete (Abbiss and Laursen, 2008).

From a more basic perspective, it is important to understand the contribution of specific cognitive process to the reduction in endurance performance observed after mental exertion. Of particular interest is response inhibition. This cognitive process refers to the inhibition of inappropriate/unwanted motor or emotional responses (Mostofsky and Simmonds, 2008) and it is a main component of decision making in human volition (Haggard, 2008). Cognitive tasks involving response inhibition are known to activate the pre-supplementary motor area and the anterior cingulate cortex (ACC) during Stroop tasks (Mostofsky and Simmonds, 2008). Activity in these cortical areas has been linked with perception of effort (Williamson et al., 2001; 2002; de Morree et al., 2012), and damage to the ACC is known to affect effort-based decision making in animals (Walton et al., 2003; Rudebeck et al., 2006; Walton et al., 2006). Therefore, it is biologically plausible that prior mental exertion involving response inhibition would affect the effort-based decision making process, thought to regulate self-paced endurance performance (Marcora, 2010a).

The aim of our study was to investigate the effects of response inhibition on pacing, perception of effort and performance during subsequent self-paced endurance exercise. Specifically, we hypothesised that prior mental exertion involving response inhibition would increase perception of effort and impair endurance performance to a larger extent than prior mental exertion without response inhibition. To test these hypotheses, we compared an inhibition condition (incongruent Stroop task) with a cognitive task that does not involve response inhibition (congruent Stroop task; Stroop, 1992; Bray et al., 2008). As the negative effects of prior mental exertion on perception of effort and endurance performance are well known (Marcora et al., 2009; Pageaux et al., 2013), we did not include a pure control condition with no prior mental exertion. In order to investigate the

effect of response inhibition on pacing, we measured endurance performance with a 5 km running time trial in which subjects were free to self-regulate their speed on the treadmill.

## II. Methods

### SUBJECTS AND ETHICAL APPROVAL

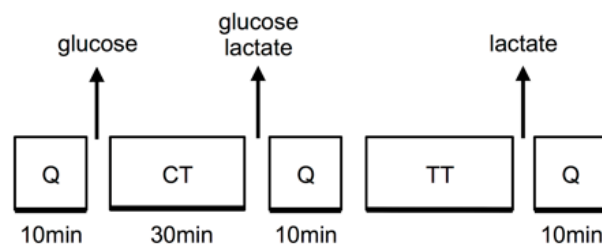
Twelve adults (eight males and four females; mean  $\pm$  SD; age:  $21 \pm 1$  yrs, height:  $174 \pm 12$  cm, weight:  $69 \pm 11$  kg) volunteered to participate in this study. None of the subjects had any known mental or somatic disorder. All subjects were involved in aerobic activities for at least two times a week in the previous six months. This level of training corresponds to the performance level 2 in the classification of subject groups in Sport Science Research (De Pauw et al., 2013). Each subject gave written informed consent prior to the study. The experimental protocol and procedures were approved by the local Ethics Committee of the School of Sport and Exercise Sciences, University of Kent, UK. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008). All subjects were given written instructions describing the experimental protocol and procedures but were naive of its aims and hypotheses. To ensure high motivation during the cognitive tasks and the time trials, a reward (£10 Amazon voucher) was given to the best overall performance in all the cognitive tasks and time trials. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants.

### EXPERIMENTAL PROTOCOL

Subjects visited the laboratory on three different occasions. During the first visit, subjects were familiarised with the experimental procedures. During the second and third visit, subjects performed either a cognitive task involving the response inhibition process (inhibition condition) or a cognitive task that did not involve response inhibition (control condition, see *Cognitive Tasks* for more details) in a randomised and counterbalanced order (randomised cross over design). After the cognitive task, subjects performed a 5 km running time trial on a treadmill (see *Time Trial* for more details). An overview of the experimental protocol is provided in figure 11. Mood was assessed before and after the

cognitive task, subjective workload was assessed after the cognitive task and after the time trial, whilst motivation was only measured before the time trial. Heart rate (HR) was recorded continuously throughout the experiment. Capillary blood samples were taken before and after the cognitive task, and after the time trial. For more details see *Physiological Measurements* and *Psychological Measurements*.

Each participant completed all three visits over a period of 2 weeks with a minimum of 48 hours recovery period between visits. All participants were given instructions to sleep for at least 7 hours, refrain from the consumption of alcohol, and not to practice vigorous physical activity the day before each visit. Participants were also instructed to avoid caffeine and nicotine for at least 3 hours before visiting the laboratory, and were asked to declare if they had taken any medication or had any acute illness, injury or infection.



**Figure 11 - Graphical overview of the experimental protocol**

Order and timing was the same for each subject and each session. CT = cognitive tasks Q = Psychological Questionnaires, TT = 5km running time trial.

## COGNITIVE TASKS

**Inhibition task.** The inhibition condition consisted of 30 min engagement with a modified incongruent version of the Stroop colour-word task. This 30 min task is known to reduce persistence in a figure-tracing task (Wallace and Baumeister, 2002). Participants performed this inhibition task on a computer whilst sitting comfortably in a quiet and dim lit room. Four words (YELLOW, BLUE, GREEN, RED) were serially presented on the screen until the participant gave a valid answer and were followed by a 1500 ms interval. Subjects were instructed to press one of four coloured buttons on the keyboard (yellow, blue, green, red) with the correct response being the button corresponding to the ink colour (either yellow, blue, green, red) of the word presented on the screen. For example, if the word BLUE appeared in yellow ink, the yellow button had to be pressed. If however the ink colour was red, the button to be pressed was the button linked to the real meaning of

the word, not the ink colour (e.g. if the word blue appears in red, the button blue has to be pressed). If the ink colour was blue, green or yellow, then the button pressed matched the ink colour. The word presented and its ink colour were randomly selected by the computer (100% incongruent). Twenty practice attempts were allowed before the inhibition task to ensure the participant understood the concept fully. The inhibition task was also performed for five minutes during the familiarisation visit. Subjects were instructed to respond as quickly and accurately as possible. Visual feedback was given after each word in form of correct or incorrect answer, response speed and accuracy. Participants were also informed that points would be awarded for speed and accuracy of their responses, and the score for both cognitive tasks would be added to the score for each time trial, in order to reward the overall highest score with a £10 Amazon voucher to increase motivation.

**Control Task.** The control condition consisted of 30 min engagement with a congruent version of the Stroop colour-word task. This control task was similar to the modified incongruent version of the Stroop colour-word task. However, the response inhibition process was not involved in this congruent version. Indeed, all words presented and their ink colour were matched (e.g., the word GREEN was presented with a green ink colour).

Cognitive performance during the congruent and incongruent Stroop colour-word tasks was measured in term of response accuracy (percentage of correct responses) and reaction time. Performance data were analysed offline using the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) and averaged in a non-cumulative way for each of six 5-min periods during both cognitive tasks.

## **TIME TRIAL**

Ten minutes after completion of the allocated cognitive task, subjects performed a time trial on a treadmill to evaluate pacing and endurance performance. The treadmill (PowerJog, Expert Fitness UK Ltd, Glamorgan, Wales) was set at a one per cent gradient (Jones and Doust, 1996). Subjects were asked to run five kilometres in the quickest time possible. Each participant performed a standardised warm up running on the treadmill at 8 km/h for five minutes. Feedback on the distance covered was available throughout the time trial. On the contrary, information about running speed, HR and time elapsed was not provided to the subject. The time trial started with subjects standing on the treadmill belt while running speed was increased up to 9 km/h. After this running speed was reached,

subjects were free to choose their running speed using the + and – button on the right side of the treadmill. Throughout the time trial, participants were reminded at the end of each kilometre that they were able to increase or decrease their running speed at any time; however the experimenters provided no encouragement during the time trial. Once the 5 kilometres were completed, subjects stopped running immediately and placed their feet on the platform at the sides of the belt while time elapsed was recorded. The time elapsed was used as a measure of endurance performance. A fan was placed in a standardised position in front of the subject during the entire duration of the time trial, and subjects were allowed to drink water. At the end of the first minute, and at the end of each kilometre, rating of perceived exertion (RPE), HR and running speed were recorded. In order to reduce the learning effect, subjects performed a familiarisation time trial during the first visit to the laboratory.

## PHYSIOLOGICAL MEASUREMENTS

**Heart Rate.** HR was recorded continuously during both cognitive tasks and the time trial using a HR monitor (Polar RS400, Polar Electro Oy, Kempele, Finland) with an acquisition frequency of 1 sample/s. Data were analysed offline and averaged for the whole duration of both cognitive tasks. During the time trial, HR values were collected the last 15 s of the warm-up, the first minute, and for each kilometre completed.

**Blood lactate and glucose concentrations.** 10 µl samples of capillary blood were taken from the thumb of the non-dominant hand of the subjects for measurement of blood lactate and blood glucose concentrations (Biosen, EFK Diagnostics, London, England). Blood glucose concentration was measured pre and post cognitive task, and blood lactate concentration was measured pre and post time trial.

## PSYCHOLOGICAL MEASUREMENTS

**Perception of effort.** Perception of effort, defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (Marcora, 2010b), was measured at the end of the first minute and at the end of each kilometre of the time trial using the 15 points RPE scale (Borg, 1998). Standardised instructions for the scale were given to each subject before the warm-up. Briefly subjects were asked to rate how hard they were driving their legs, how heavily they were breathing, and the overall sensation of how strenuous exercise

was. For example, 9 corresponds to a “very light” exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes. 17 corresponds to a “very hard” and 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.

**Mood.** The Brunel Mood Scale (BRUMS) developed by Terry et al. (2003) was used to quantify current mood (“How do you feel right now?”) before and after the cognitive task. This questionnaire contains 24 items (e.g., “angry, uncertain, miserable, tired, nervous, energetic”) divided into six subscales: anger, confusion, depression, fatigue, tension, and vigor. The items are answered on a 5 point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscales, with four relevant items, can achieve a raw score in the range of 0 to 16. Only scores for the Fatigue and Vigour subscales were considered in this study as subjective markers of mental fatigue.

**Motivation.** Motivation related to the time trial was measured using the success motivation and intrinsic motivation scales developed and validated by (Matthews et al., 2001). Each scale consists of 7 items (e.g., “I want to succeed on the task” and “I am concerned about not doing as well as I can”) scored on a 5-point scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely). Therefore, total scores for these motivation scales range between 0 and 28.

**Subjective workload.** The National Aeronautics and Space Administration Task Load Index (NASA-TLX) rating scale (Hart and Staveland, 1988) was used to assess subjective workload. The NASA-TLX is composed of six subscales: Mental Demand (How much mental and perceptual activity was required?), Physical Demand (How much physical activity was required?), Temporal Demand (How much time pressure did you feel due to the rate or pace at which the task occurred?), Performance (How much successful do you think you were in accomplishing the goals of the task set by the experimenter?), Effort (How hard did you have to work to accomplish your level of performance?) and Frustration (How much irritating, annoying did you perceive the task?). The participants had to score each of the items on a scale divided into 20 equal intervals anchored by a bipolar descriptor (e.g. High/Low). This score was multiplied by 5, resulting in a final score between 0 and 100 for each of the subscales. Participants completed the NASA-TLX after the cognitive task and after the time trial. All participants were familiarised with all psychological measurements during their first visit to the laboratory.

## STATISTICS

All data are presented as means  $\pm$  standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. Paired t-tests were used to assess the effect of condition (inhibition vs control) on endurance performance, motivation scores, NASA-TLX scores after the cognitive tasks and after the time trial, HR during both cognitive tasks, and HR during the warm-up before the time trial. Fully repeated measure 2 x 6 ANOVAs was used to test the effect of time (5-min blocks) and condition on response accuracy and reaction time during cognitive tasks. Fully repeated measure 2 x 2 ANOVAs were used to test the effect of condition and time on mood before and after the cognitive tasks, and the effect of condition and time on blood glucose and lactate concentrations. Fully repeated measure 2 x 6 ANOVAs were used to test the effect of condition and distance on HR, RPE and running speed during the time trial. Significant main effects of time with more than two levels, and significant interactions were followed-up with simple main effects of time or condition using a Bonferroni correction as appropriate. Significance was set at 0.05 (two-tailed) for all analyses. Effect size for each statistical test was also calculated as partial eta squared ( $\eta_p^2$ ). All analyses were conducted using the Statistical Package for the Social Sciences, version 19 for Mac OS X (SPSS Inc., Chicago, IL, USA). As interactions were not significant, only main effects are reported.

## III. Results

### EFFECTS OF RESPONSE INHIBITION ON HR, BLOOD GLUCOSE CONCENTRATION AND COGNITIVE PERFORMANCE DURING THE COGNITIVE TASKS

Heart rate (figure 12A) was significantly higher during the inhibition task compared to the control task ( $P=0.003$ ,  $\eta_p^2=0.120$ ). Response inhibition did not affect ( $F_{(1, 11)}=0.059$ ;  $P=0.812$ ,  $\eta_p^2=0.005$ ) the significant decrease in blood glucose concentration observed after the cognitive tasks ( $F_{(1, 11)}=7.209$ ;  $P=0.021$ ,  $\eta_p^2=0.396$ ) (figure 12B).

Accuracy of responses during the cognitive tasks (figure 12C) was not affected by response inhibition ( $F_{(1, 11)}=2.561$ ;  $P=0.138$ ,  $\eta_p^2=0.189$ ) and did not change significantly

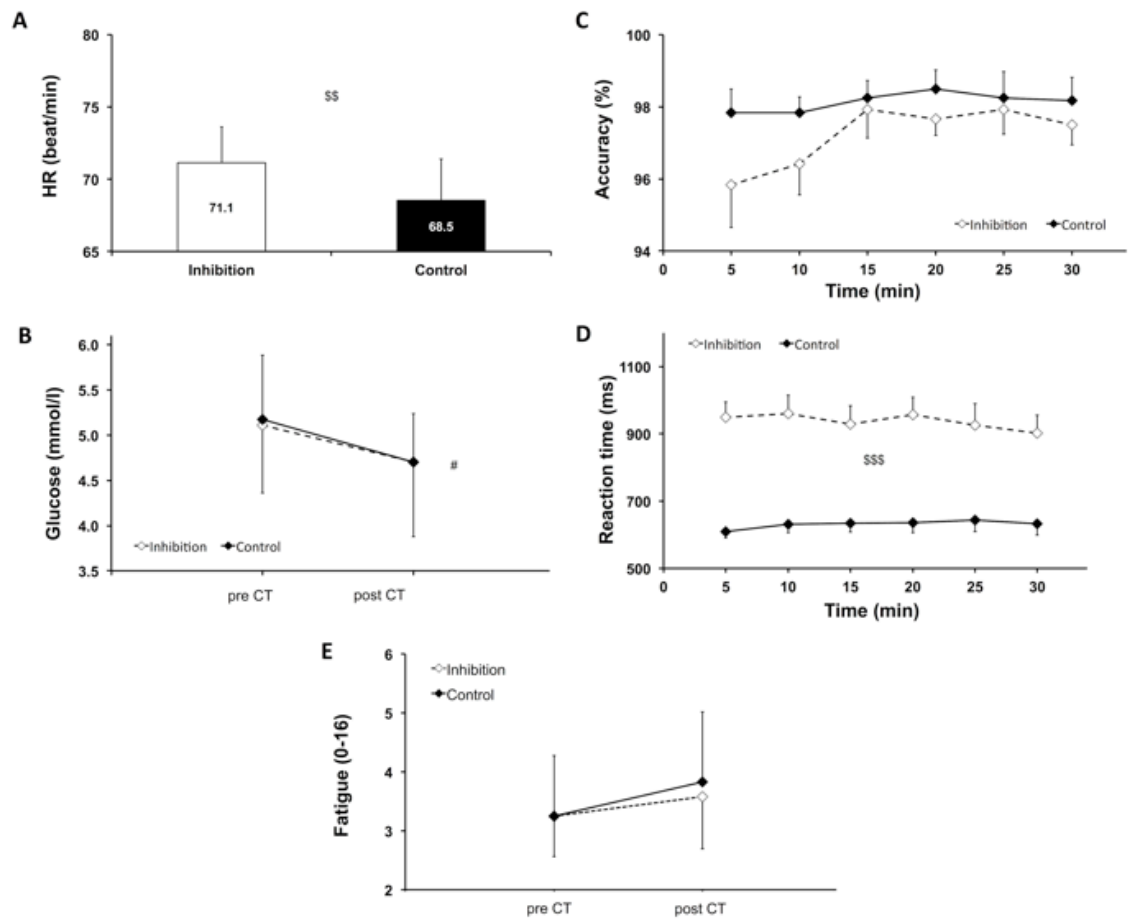


over time ( $F_{(2.214, 24.353)}$ ;  $P=0.058$ ,  $\eta_p^2=0.221$ ). Similarly, reaction time (figure 12D) did not change significantly over time ( $F_{(1.948, 21.425)}=0.585$ ;  $P=0.562$ ,  $\eta_p^2=0.0050$ ), but it was significantly longer during the inhibition task compared to the control task ( $F_{(1, 11)}=68.474$ ;  $P<0.001$ ,  $\eta_p^2=0.862$ ) (Figure 2D).

## **EFFECTS OF RESPONSE INHIBITION ON MOOD AND MOTIVATION**

The mood questionnaire did not show any significant main effect of time ( $F_{(1, 11)}=1.194$ ;  $P=0.298$ ,  $\eta_p^2=0.098$ ), condition ( $F_{(1, 11)}=0.021$ ;  $P=0.888$ ,  $\eta_p^2=0.002$ ) or interaction ( $F_{(1, 11)}=0.096$ ;  $P=0.763$ ,  $\eta_p^2=0.009$ ) in the Fatigue scores (figure 12E). The vigour scores decreased over time (inhibition condition  $5.9 \pm 1.1$  to  $4.2 \pm 1.0$ , control condition  $6.1 \pm 1.4$  to  $4.6 \pm 1.5$ ;  $F_{(1, 11)}=6.396$ ;  $P=0.028$ ,  $\eta_p^2=0.368$ ) independently of the response inhibition process ( $F_{(1, 11)}=0.074$ ;  $P=0.791$ ,  $\eta_p^2=0.057$ ).

There were no significant differences between conditions in intrinsic motivation (inhibition condition  $18.5 \pm 3.2$ , control condition  $18.9 \pm 4.5$ ;  $P=0.622$ ,  $\eta_p^2=0.023$ ) and success motivation (inhibition condition  $17.5 \pm 5.6$ , control condition  $16.4 \pm 6.0$ ;  $P=0.151$ ,  $\eta_p^2=1.78$ ) related to the subsequent time trial.



**Figure 12 - Effects of cognitive tasks (CT) on heart rate (HR, panel A), blood glucose concentration (panel B), response accuracy (panel C), reaction time (panel D) and self-reported fatigue (panel E)**

<sup>SS</sup> Significant main effect of condition ( $P < 0.01$ ). <sup>SSS</sup> Significant main effect of condition ( $P < 0.001$ ). # Significant main effect of time ( $P < 0.05$ ). Data are presented as means  $\pm$  SEM.

## EFFECTS OF RESPONSE INHIBITION ON PACING AND PERFORMANCE DURING THE TIME TRIAL

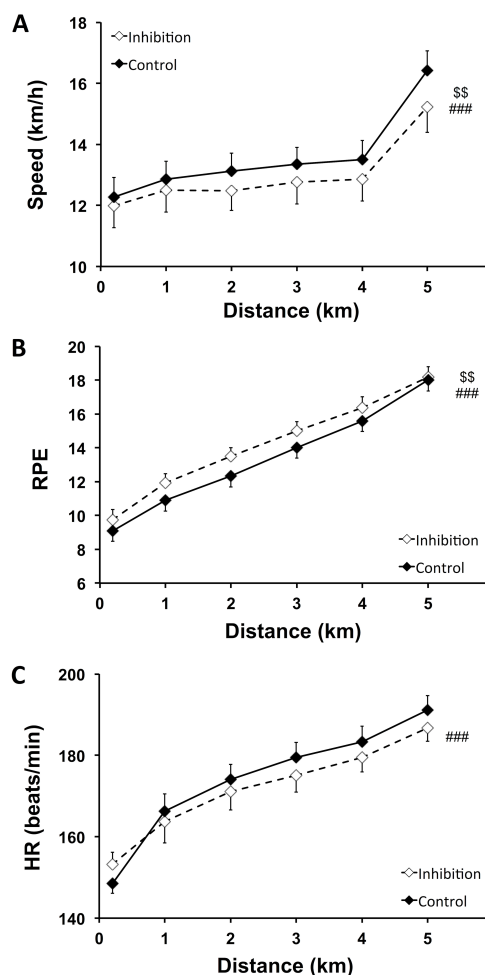
Time to perform the time trial was significantly longer following the inhibition task ( $24.4 \pm 4.9$  min) compared to the control task ( $23.1 \pm 3.8$  min;  $P = 0.008$ ,  $\eta_p^2 = 0.489$ ), with no significant learning effect ( $P = 0.571$ ,  $\eta_p^2 = 0.026$ ). Time trial performance decreased following the inhibition task in 10 out of 12 subjects.

Impaired time trial performance was caused by a significant reduction in running speed in the inhibition condition compared to the control condition ( $F_{(1, 11)}=14.117$ ;  $P=0.003$ ,  $\eta_p^2=0.562$ ) (figure 13A). However, response inhibition did not affect pacing strategy as demonstrated by the lack of significant interaction between condition and distance ( $F_{(1.724, 18.964)}=0.832$ ;  $P=0.434$ ,  $\eta_p^2=0.070$ ). In both conditions, subjects chose a negative pacing strategy which consists of a significant increase in speed over distance ( $F_{(2.165, 23.817)}=21.568$ ;  $P<0.001$ ,  $\eta_p^2=0.662$ ).

### **EFFECTS OF RESPONSE INHIBITION ON PERCEPTION OF EFFORT, HR AND BLOOD LACTATE CONCENTRATION DURING THE TIME TRIAL**

RPE during the time trial (figure 13B) increased similarly over distance in both conditions ( $F_{(1.560, 17.158)}=102.289$ ;  $P<0.001$ ,  $\eta_p^2=0.903$ ). However, subjects rated a higher perception of effort in the inhibition condition compare to the control condition ( $F_{(1, 11)}=12.156$ ,  $P=0.005$ ,  $\eta_p^2=0.525$ ).

Heart rate during the warm-up did not differ significantly between conditions ( $P=0.742$ ,  $\eta_p^2=0.199$ ). As expected, HR during the time trial (figure 13C) increased significantly over distance ( $F_{(1.795, 19.744)}=58.650$ ;  $P<0.001$ ,  $\eta_p^2=0.842$ ) with no significant difference between the inhibition and the control task ( $F_{(1, 11)}=1.286$ ;  $P=0.281$ ,  $\eta_p^2=0.105$ ). Similarly, response inhibition did not affect ( $F_{(1, 11)}=0.236$ ;  $P=0.637$ ,  $\eta_p^2=0.021$ ) the significant increase ( $F_{(1, 11)}=48.825$ ;  $P<0.001$ ,  $\eta_p^2=0.816$ ) in blood lactate concentration observed after the time trial (inhibition condition  $1.6 \pm 0.4$  to  $9.4 \pm 4.8$ , control condition  $1.4 \pm 0.5$  to  $9.0 \pm 3.2$ ).



**Figure 13 - Effects of cognitive tasks on speed (panel A), rating of perceived exertion (RPE, panel B) and heart rate (HR) during the 5 km running time trial**

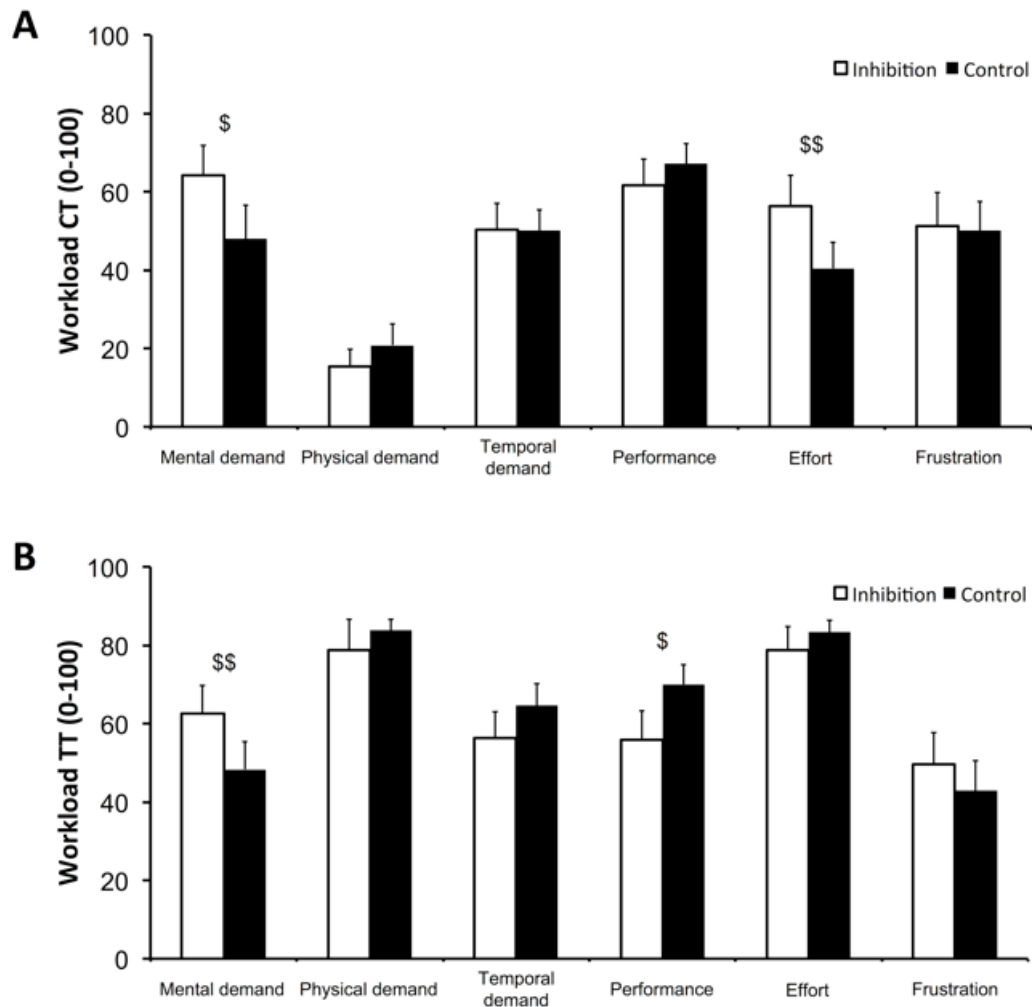
\$\$ Significant main effect of condition ( $P < 0.01$ ). ### Significant main effect of time ( $P < 0.001$ ). Data are

presented as means  $\pm$  SEM.

## EFFECTS OF RESPONSE INHIBITION ON SUBJECTIVE WORKLOAD SUBSCALES

**Cognitive tasks.** Subjective workload data related to the cognitive tasks are presented in figure 14A. Subjects rated the Mental Demand ( $P=0.042$ ,  $\eta_p^2=0.324$ ) and Effort ( $P=0.009$ ,  $\eta_p^2=0.481$ ) subscales higher during the response inhibition condition. Response inhibition did not have significant effects on the Performance, Temporal Demand, and Frustration subscales of the NASA-TLX questionnaire.

**Time trial.** Subjective workload data related to the time trial are presented in figure 14B. Subjects rated the time trial as more mentally demanding during the response inhibition condition ( $P=0.005$ ,  $\eta_p^2=0.524$ ) and perceived their performance lower during the response inhibition condition ( $P=0.044$ ,  $\eta_p^2=0.319$ ). Response inhibition did not have significant effects on the Effort, Temporal Demand, and Frustration subscales of the NASA-TLX questionnaire.



**Figure 14 - Effects of cognitive tasks (CT, panel A) and 5km running time trial (TT, panel B) on subjective workload (NASA-TLX scale)**

<sup>\$</sup> Significant effect of response inhibition ( $P < 0.05$ ). <sup>\$\$</sup> Significant effect of response inhibition ( $P < 0.01$ ). Data are presented as means  $\pm$  SEM.

## V. Discussion

The aim of our study was to investigate the effects of response inhibition on pacing, perception of effort and endurance performance. In accordance with our hypotheses, results suggest that response inhibition increases perception of effort and impairs endurance performance via a reduction in average speed during the 5km running time trial.

However, response inhibition does not seem to affect the pacing strategy chosen by the subject.

### **RESPONSE INHIBITION, MENTAL FATIGUE AND ENDURANCE PERFORMANCE**

The higher HR observed during the inhibition task compared with the control task attests its more demanding nature (Richter et al., 2008). Moreover, the higher demanding nature of the inhibition task was confirmed by the higher mental demand and effort rated by the subjects using the subjective workload questionnaire. However, similar to a previous study (Marcora et al., 2009), blood glucose concentration decrease independently of the nature of the cognitive task. This finding argues against the idea that glucose depletion is one of the physiological mechanisms underlying the negative effects of mental exertion on subsequent physical or cognitive tasks (Gailliot, 2008). The longer reaction time observed during the inhibition task confirms the presence of an additional cognitive process compared to the control task. Because both cognitive tasks included decision-making process (selecting an answer) and sustained attention, the longer reaction time during the inhibition task is likely to be related to the response inhibition process (Stroop, 1992; Sugg and McDonald, 1994). Indeed, contrary to the control task, subjects did not only have to select an answer, but also to inhibit the wrong motor response (e.g. pressing the yellow button if the word blue appears in yellow) in order to select the appropriate one (press the blue button). Taken altogether, these manipulation checks suggest that we were successful in inducing different levels of mental exertion and response inhibition between the two conditions.

Previous studies using more prolonged mental exertion induced significant mental fatigue defined as an increase in subjective feelings of fatigue and/or a decrease in cognitive performance (Marcora, 2010b; Pageaux et al., 2013). Interestingly, in the present study, mental exertion neither induces alterations in cognitive performance (i.e., changes in reaction time and/or accuracy) nor significant changes in subjective fatigue. Also as shown in previous studies, the cognitive tasks induced a significant decrease in vigour (Marcora et al., 2009; Pageaux et al., 2013). The lack of changes in these markers of mental fatigue could be due to the shorter duration of mental exertion in the present study (30 min) compared to previous studies (90 min).

Despite no clear evidence of mental fatigue in the present study, 30 minutes of mental exertion involving response inhibition had a negative effect on subsequent

endurance performance. Indeed, the time to perform the time trial was 6% longer following the inhibition task compared to the control task. These findings are in agreement with the results of the study by (Bray et al., 2008) in which as little as 220 seconds of mental exertion involving response inhibition were capable of reducing endurance of the handgrip muscles despite no subjective feelings of mental fatigue. From an applied perspective, it is therefore important to warn coaches and athletes that mental exertion involving response inhibition may have a detrimental effect on subsequent endurance performance even if the athlete does not feel mentally fatigued.

### **RESPONSE INHIBITION AND PACING**

The only significant effect of response inhibition on pacing was a reduction in the average running speed chosen by the subject during the time trial. On the other hand, pacing strategy was not significantly affected by prior mental exertion. In fact, in both the inhibition and control condition, a negative pacing strategy was observed. A negative pacing strategy, defined as an increase in speed over time, is commonly observed during middle distance events when speed is increased towards the end of both simulated and actual time trial events (for review see Abbiss and Laursen, 2008). In fact, the negative pacing strategy observed in our study has been previously observed during 5km running time trial in both elite (Tucker et al., 2006) and well-trained athletes (Nummela et al., 2006). As these time trials were conducted on a track, we are confident that the pacing strategy observed in our study is not specific to time trials performed on a treadmill, where speed is changed manually by pressing a button and RPE asked at the end of each kilometre.

This is the first report on the effect of mental exertion involving response inhibition on pacing. However, because of the low performance level of the subjects included in the present study, it is difficult to generalise our findings to competitive endurance athletes. More studies on the effects of mental exertion on pacing are required to investigate whether response inhibition may affect pacing strategy in subjects of higher performance level.

## **RESPONSE INHIBITION AND PERCEPTION OF EFFORT**

Previous studies have shown that mentally fatigued subjects perceived endurance exercise as more effortful (Marcora et al., 2009; Pageaux et al., 2013). We have extended these findings by showing that response inhibition is capable of inducing higher perception of effort during subsequent endurance exercise even in the absence of overt mental fatigue.

As no neurophysiological measurements at brain level were taken in the present study, we can only speculate about the neurobiological mechanisms underlying the negative effect of response inhibition on perception of effort during subsequent endurance exercise. A possible explanation is that 30 min of engagement with the incongruent Stroop colour-word task induced adenosine accumulation in the ACC leading to higher perception of effort during subsequent endurance exercise. This speculation is based on previous human studies showing that the ACC is strongly activated during Stroop tasks involving response inhibition (Bush et al., 1998; Swick and Jovanovic, 2002), and that this cortical area is associated with perception of effort (Williamson et al., 2001; 2002). Furthermore, there is experimental evidence from *in vitro* and animal studies that neural activity increases extracellular concentrations of adenosine (Lovatt et al., 2012), and that brain adenosine induces a reduction in endurance performance (Davis et al., 2003). Finally, there is strong evidence that caffeine (an antagonist of adenosine) reduces perception of effort during endurance exercise in humans (Doherty and Smith, 2005). Further research in humans and animals is needed to confirm the role of the ACC and brain adenosine in mediating the negative effect of mental exertion on perception of effort and performance during subsequent endurance exercise.

## **PSYCHOBIOLOGICAL MODEL OF SELF-PACED ENDURANCE PERFORMANCE**

The present findings demonstrate that mental exertion involving response inhibition does not reduce blood glucose concentration before the time trial, and it does not alter HR immediately before and during the time trial. The blood lactate response to the time trial was also not significantly affected by response inhibition. Therefore, it is unlikely that cardiovascular and metabolic factors can explain the negative effect of response inhibition on endurance performance. Our findings are in accordance with previous observations during time to exhaustion tests. Indeed, it has already been demonstrated the impairment in endurance performance following prolonged mental exertion occurs without any



alterations of the cardiorespiratory, metabolic and neuromuscular responses to the exercise (Marcora et al., 2009; Pageaux et al., 2013). Therefore, the negative effect of response inhibition on subsequent self-paced endurance performance is likely to be mediated by other factors.

The psychobiological model of endurance performance (Marcora, 2010a) provides a plausible explanation for the negative effect of prior response inhibition on the average running speed chosen by the subject during the time trial. According to this model of endurance performance, the self-regulation of speed/power output during endurance exercise (pacing) is determined primarily by five different cognitive/motivational factors: 1) perception of effort; 2) potential motivation; 3) knowledge of the distance/time to cover; 4) knowledge of the distance/time remaining and 5) previous experience/memory of perceived exertion during exercise of varying intensity and duration. The effect of previous experience (Factor 5) was controlled in the present study by using a randomised crossover design and a familiarisation session. Furthermore, in both the inhibition and control conditions, subjects had the same knowledge of the distance to cover (Factor 3) and of the distance remaining (Factor 4). According to the motivation questionnaire, response inhibition did not affect potential motivation (Factor 2). This finding is an agreement with the results of previous studies also showing no significant effect of mental exertion on questionnaires related to potential motivation (Marcora et al., 2009; Pageaux et al., 2013). However, the significantly higher RPE observed after the response inhibition task suggests that response inhibition may affect the willingness to exert effort during subsequent endurance exercise. Furthermore, the psychophysical relationship between RPE and running speed suggests an even greater effect of response inhibition on perception of effort (Factor 1). Indeed, the effort was perceived higher during the inhibition condition compared to the control condition despite a lower running speed. According to the psychobiological model of endurance performance, the reduction in the average running speed during the time trial is a conscious decision to compensate for the negative effect of response inhibition on perception of effort. Indeed, if the subjects did not choose a lower running speed, the progressive increase in perception of effort over time would have caused premature exhaustion as observed during tests in which the subject could not choose a lower power/torque (Marcora et al., 2009; Pageaux et al., 2013). As not finishing the time trial is a more negative outcome than completing the time trial in a longer time, reducing the average running speed was the most appropriate behavioural response.

## **CONCLUSIONS AND PRACTICAL PERSPECTIVES**

The present study provides the first experimental evidence that self-paced endurance performance can be altered by prior mental exertion involving response inhibition. This negative effect was associated with a reduction in average running speed chosen by the subject during the time trial. However, pacing strategy was not affected by prior mental exertion involving response inhibition. Importantly, this study suggests that performing only 30 minutes of mental exertion can reduce endurance performance without any subjective feeling of mental fatigue at rest. Therefore, athletes and coaches should avoid any cognitive tasks involving response inhibition process before competition, such as controlling emotion (e.g. anger) during pre-event interviews. Furthermore, the results of the present study suggest that monitoring of RPE during endurance training sessions may be a more sensitive measure to identify fatigue states than administering generic mood questionnaires. Since monitoring fatigues states is important to prevent non-functional overreaching and overtraining in endurance athletes (Nederhof et al., 2008), more applied research in this area is warranted.

## **CHAPTER 2: MENTAL FATIGUE DOES NOT EXACERBATE CENTRAL FATIGUE DURING SUBSEQUENT WHOLE-BODY ENDURANCE EXERCISE**

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**Submitted in** Frontiers in Human Neuroscience

## **I. Abstract**

Prolonged self-regulation (SR) leading to mental fatigue is known to increase perception of effort and impair endurance performance. It has been shown that mental fatigue does not induce a decrease in maximal muscle activation. However, to date, an interaction between mental fatigue and central fatigue phenomena cannot be excluded. The aim of this study was to examine whether mental fatigue could exacerbate the extent of muscle fatigue induced by whole-body exercise, with particular interest on its central component. Twelve subjects randomly performed 30 min of cognitive tasks involving either SR (incongruent Stroop task, leading to mental fatigue) or non-involving SR (congruent Stroop task). Both cognitive tasks were followed by 6 min of submaximal cycling at 80% of peak power output. Neuromuscular function of the knee extensors was assessed before and after the cognitive task, and after the cycling task. Rating of perceived exertion (RPE) was measured during cycling. Both cognitive tasks did not induce any decrease (time effect:  $P > 0.05$ ) in maximal voluntary contraction (MVC) torque. During cycling, mentally fatigued subjects rated a higher RPE (SR  $13.9 \pm 3.0$ , control  $13.3 \pm 3.2$ , condition effect:  $P = 0.044$ ). Cycling induced a similar decrease in MVC torque (SR  $-17 \pm 15\%$ , control condition  $-15 \pm 11\%$ , time effect:  $P = 0.001$ ), voluntary activation level (SR  $-6 \pm 9\%$ , control  $-6 \pm 7\%$ , time effect:  $P = 0.013$ ) and resting twitch (SR  $-30 \pm 14\%$ , control  $-32 \pm 10\%$ , time effect:  $P < 0.001$ ) in both conditions. This study confirms that prolonged SR leading to mental fatigue does not induce a decrease in the ability of the central nervous system to fully recruit the active muscles. Our results suggest that the higher-than normal RPE in presence of mental fatigue might be due to i) an alteration of the central processing of the corollary discharge associated with the central motor command, ii) an alteration of the central motor command itself, or iii) an alteration of both phenomena previously mentioned.

## **II. Introduction**

Prolonged bouts of cognitive tasks requiring self-regulation are known to induce a psychobiological state of mental fatigue. Subjectively, mental fatigue is characterised by feelings of “tiredness” and “lack of energy” and/or a higher-than-normal perception of effort during submaximal physical tasks (Marcora et al., 2009; Brownsberger et al., 2013; Pageaux et al., 2013; Pageaux et al., 2014). Objectively, mental fatigue is well known to impair attention, action monitoring and self-regulation (e.g. van der Linden et al., 2003; van der Linden and Eling, 2006; Boksem and Tops, 2008) although the relationship

between subjective mental fatigue and impaired cognitive performance is not a straightforward one. In fact, because of compensatory effort or alternative cognitive strategies, cognitive performance can often be maintained for some periods of time in conditions of mental fatigue (Ackerman, 2011).

Recent studies have consistently demonstrated a negative effect of mental fatigue on performance during physical tasks requiring endurance. These physical tasks range from single-joint exercise lasting ~4 min to whole-body exercise lasting ~25 min (Marcora et al., 2009; Pageaux et al., 2013; Pageaux et al., 2014). In these studies, the authors did not find any effect of mental fatigue on the cardiorespiratory and metabolic responses to exercise. As motivation related to the endurance tasks was also unaffected, the authors ascribed the decrease in endurance performance to the higher-than-normal perception of effort associated with mental fatigue. Indeed, as stated by the psychobiological model of endurance performance (Marcora et al., 2008; Marcora and Staiano, 2010), exhaustion is not caused by muscle fatigue (i.e., by the inability to produce the force/power required by the endurance task despite a maximal voluntary effort), but is caused by the conscious decision to disengage from the endurance task. In highly motivated subjects, this effort-based decision is taken when they perceive their effort as maximal and continuation of the endurance task seems impossible. During time to exhaustion tests with a fixed workload, higher-than-normal perception of effort means that mentally fatigued subjects reach their maximal perceived effort and disengage from the endurance task prematurely. During self-paced time trials, the psychobiological model correctly predicts that subjects consciously reduce their workload in order to compensate for the higher-than-normal perception of effort and, thus, avoid premature exhaustion (Marcora, 2010a; Pageaux, 2014).

Although the psychobiological model seems to provide a valid explanation for the negative effects of mental fatigue on endurance performance, at present we cannot totally exclude the possibility that the negative effects of mental fatigue on endurance performance may be mediated, at least in part, by the central component of muscle fatigue: central fatigue (i.e. decrease in maximal voluntary activation level, VAL; Gandevia, 2001). This is relevant because, similarly to mental fatigue, muscle fatigue can also increase perception of effort and reduce performance during endurance tasks (Marcora et al., 2008; de Morree and Marcora, 2013). Pageaux et al. (2013) recently assessed neuromuscular function of the knee extensors before and after a prolonged and demanding cognitive task leading to mental fatigue, and after a subsequent endurance task (submaximal isometric knee extensor exercise until exhaustion). The authors found that mental fatigue did not

decrease VAL during maximal voluntary contraction (MVC) of the knee extensors before exercise, and that mental fatigue did not exacerbate central fatigue, i.e. the reduction in VAL induced by subsequent exercise. Although these findings suggest that mental fatigue does not increase the extent of central fatigue induced by single-joint exercise, it has to be noticed that neuromuscular function was not assessed for the same duration of exercise between conditions. As mental fatigue reduced exercise duration, it is possible that mental fatigue increased the rate of central fatigue development compared to the control condition. Furthermore, it is well known that muscle fatigue is task specific (Bigland-Ritchie et al., 1995) and that both neural control of movement and systemic stress differ between single-joint and whole-body exercise (Sidhu et al., 2013). Of particular interest is the fact that prolonged whole-body exercise is known to induce homeostatic disturbances within the central nervous system (CNS) that subsequently induces central fatigue (for review see Nybo and Secher, 2004). It is therefore possible that mental fatigue can interact with these processes leading to a greater rate of central fatigue development (i.e. greater extent of central fatigue when measured after same duration of exercise).

The aim of this study was to test the hypothesis that mental fatigue induced by prolonged self-regulation (incongruent Stroop task) exacerbates central fatigue induced by whole-body exercise. We examined both central and peripheral (i.e. fatigue produced by changes at or distal to the neuromuscular junction; Gandevia, 2001) components of muscle fatigue before and after prolonged self-regulation leading to mental fatigue. Neuromuscular function was also examined after six minutes of submaximal constant load cycling exercise (whole-body endurance task) in order to control for the confounding effect of exercise duration.

### **III. Methods**

#### **SUBJECTS AND ETHICAL APPROVAL**

Twelve physically active male adults (mean  $\pm$  SD; age:  $25 \pm 4$  yrs, height:  $182 \pm 5$  cm, weight:  $77 \pm 11$  kg) volunteered to participate in this study. None of the subjects had any known mental or somatic disorder. “Active” was defined as taking part in a moderate to high level of physical activity at least twice a week for a minimum of six months. Each subject gave written informed consent prior to the study. Experimental protocol and

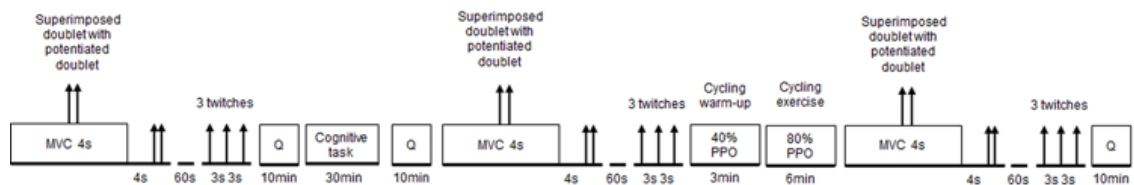
procedures were approved by the local Ethics Committee of the Faculty of Sport Sciences, University of Burgundy in Dijon. All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008).

## EXPERIMENTAL PROTOCOL

Subjects visited the laboratory on three different occasions. During the first visit, a preliminary cycling incremental exercise test (2 min at 50 W + 50 W increments every 2 min) was performed until exhaustion (defined as a cadence below 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 peak power output ( $303 \pm 30$  W). The cycle ergometer was set in hyperbolic mode, which allows the power output to be regulated independently of pedal frequency over the range of 30–120 RPM. Before the incremental exercise test the position on the cycle ergometer was adjusted for each subject, and settings were recorded and reproduced at each subsequent visit. Thirty minutes after the incremental test, subjects were familiarised with all experimental procedures.

During the second and third visit, subjects performed a 30-min cognitive task either involving the self-regulation process (self-regulation task) or a control task (see *Cognitive tasks* for more details) in a randomised and counterbalanced order. After the cognitive tasks, subjects performed a constant load cycling exercise for six minutes at high intensity (see *Whole-body endurance task* for more details). Neuromuscular function of the knee extensor muscles was tested before and after the cognitive tasks, and after the endurance task (see *Neuromuscular function tests* for more details). Mood was assessed before and after the cognitive tasks, subjective workload was assessed after the cognitive tasks and the endurance task. For more details see *Physiological and psychological measurements*. An overall view of the protocol can be found in figure 15. Heart rate (HR) was recorded continuously through the experiment. Each participant completed all three visits over a period of 2 weeks with a minimum of 48 hours recovery period between visits. All participants were given instructions to sleep for at least 7 hours, refrain from the

consumption of alcohol, and not to practise vigorous physical activity the day before each visit. Participants were also instructed not to consume caffeine and nicotine at least 3 hours before testing, and were asked to declare if they had taken any medication or had any acute illness, injury or infection.



**Figure 15 - Graphical overview of the protocol for one session.**

Order and timing was the same for each subject and each session. Q = psychological questionnaires, PPO = peak power output, MVC = maximal voluntary contraction

## COGNITIVE TASKS

Both cognitive tasks performed during thirty minutes in the present study are identical as those performed in Pageaux et al. (2014). An incongruent modified Stroop task and a congruent Stroop task were used respectively for the *Self-regulation task* and the *Control task* (Stroop, 1992). A brief recap of these cognitive tasks can be found below.

***Self-regulation task.*** Mental exertion (30 min) involving specifically self-regulation was induced by the modified incongruent Stroop task. Colour words (yellow, blue, green, red) printed in a different ink color (either yellow, blue, green, red) were presented on a screen. Subjects were instructed to press one of four coloured buttons on the keyboard (yellow, blue, green, red) with the correct response being the button corresponding to the ink colour (either yellow, blue, green, red) of the word presented on the screen. If however the ink colour was red, the button to be pressed was the button linked to the real meaning of the word, not the ink colour (e.g. if the word blue appears in red, the button blue has to be pressed). If the ink colour was blue, green or yellow, then the button pressed matched the ink colour. The word presented and its ink colour were randomly selected by the computer (100% incongruent). Subjects were instructed to respond as quickly and accurately as possible. Visual feedback was given after each word in form of correct or incorrect answer, response speed and accuracy. Participants were also informed that points would be awarded for speed and accuracy of their responses, and the score for both cognitive tasks would be added to the score for each time trial.



**Control Task.** The control condition consisted of 30 min engagement with a congruent version of the Stroop colour-word task. This control task was similar to the modified incongruent version of the Stroop colour-word task. However, the response self-regulation process was not involved in this congruent version (all words and their ink colour presented were matched).

Subjects were familiarised with all the procedures described above during the first visit in the laboratory. The specificity of the self-regulation task is the existence of the response inhibition process. Response accuracy (percentage of correct responses) and reaction time were measured to monitor cognitive performance. Data were analysed offline using the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) and for each five minutes of elapsed time during both cognitive tasks.

## **WHOLE-BODY ENDURANCE TASK**

The whole-body endurance task consisted of a constant load cycling exercise. Fifteen minutes after completion of the cognitive task, subjects performed the whole-body endurance task during six minutes on an electromagnetically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands). The cycle ergometer was set in hyperbolic mode. The constant load consisted of a 3-min warm-up at 40% of peak power output ( $121 \pm 12$  W) followed by a rectangular workload corresponding to 80% of peak power output ( $242 \pm 23$  W) for duration of six minutes. Pedal frequency was freely chosen between 60 and 100 RPM, and a fan was placed in a standardised position in front of the subject during the entire duration of the constant load exercise. Feedback on elapsed time, cadence, workload and HR were not available for the subject. Once the six minutes were elapsed (isotime), subjects stopped cycling immediately and were transferred to the ergometer for neuromuscular function tests (see *Neuromuscular Function Tests* for more details). At the end of the warm-up, and at the end of each minute, rating of perceived exertion (RPE) and cadence was recorded. Subjects were familiarised with all the procedures described above during the first visit in the laboratory.

## NEUROMUSCULAR FUNCTION TESTS

All participants were familiarised with all neuromuscular function tests during their first visit to the laboratory. The neuromuscular function tests performed in this study are identical as those performed in Pageaux et al. (2013).

**Electrical stimulation.** Both single and double (100 Hz frequency) stimulation were used for assessment of neuromuscular function. All central fatigue parameters were obtained within 45 s after completion of the whole-body endurance task. Transcutaneous electrically-evoked contractions of the knee extensor muscles were induced by using a high-voltage (maximal voltage 400 V) constant-current stimulator (model DS7 modified, Digitimer, Hertfordshire, UK). A monopolar cathode ball electrode (0.5 cm diameter) pressed into the femoral triangle by the same experimenter during all tests was used to stimulate the femoral nerve. To ensure reliability of measurement, the site of stimulation producing the largest resting twitch amplitude and compound muscle action potential (M-wave) was marked on the skin with permanent marker. The anode was a 50 cm<sup>2</sup> (10 × 5 cm) rectangular electrode (Compex SA, Ecublens, Switzerland) located on the gluteus maximus opposite to the cathode. The stimulus intensity required to evoke a maximal compound muscle action potential ( $M_{\max}$ ) was determined at rest and during submaximal isometric knee contractions (50% MVC) before the experiment on each day. The stimulus duration was 1 ms and the interval of the stimuli in the doublet was 10 ms. Supramaximal intensities ranged from 74 to 140 mA. Timing of stimulation was as follows (figure 15): i) MVC (duration of ~4 s) with superimposed supramaximal paired stimuli (doublet) at 100 Hz and followed (4 s intervals) by paired stimuli at 100 Hz, ii) 60 s rest and iii) three single supramaximal stimulations at rest (interspaced by 3 s). Methodology and supramaximal intensities are according to previous studies (e.g. Place et al., 2005; Pageaux et al., 2013).

**Mechanical recordings.** A Biodex isokinetic dynamometer (Biodex Medical Systems Inc., New York, USA) was used to record the torque signal. The axis of the dynamometer was aligned with the knee axis, and the lever arm was attached to the shank with a strap. Two crossover shoulder harnesses and a belt limited extraneous movement of the upper body. Neuromuscular function tests were performed with a knee angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The following parameters were analysed from the twitch response (average of 3 single stimulation interspaced by 3 s): peak twitch (Tw), time to peak twitch (contraction time, Ct), average rate of force development (RFD = Tw/Ct) and half-relaxation time. The peak torque of the doublet (potentiated doublet, 5 s after the MVC) was also analysed. MVC torque was considered as

the peak torque attained during the MVC, and guidelines to perform MVCs were respected (Gandevia, 2001). Voluntary activation level (VAL) during the MVC was estimated according to the following formula:

$$\text{VAL} = \left( 1 - \frac{\text{superimposed doublet amplitude}}{\text{potentiated doublet amplitude}} \right) \times 100$$

Due to technical issue (no potentiated doublet for one subject as the stimulator wire was damaged), VAL and doublets were analysed for only 11 of 12 subjects. Mechanical signals were digitised on-line at a sampling frequency of 1 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.1 for MP Systems, Biopac Systems Inc., Goleta, USA).

***Electromyographic recordings.*** EMG of the vastus lateralis (VL) and rectus femoris (RF) muscles was recorded with pairs of silver chloride circular (recording diameter of 10 mm) surface electrodes (Swaromed, Nessler Medizintechnik, ref 1066, Innsbruck, Austria) with an interelectrode (center-to-center) distance of 20 mm. Low resistance between the two electrodes (< 5k $\Omega$ ) was obtained by shaving the skin and removing any dirt from the skin using alcohol swabs. The reference electrode was attached to the patella of the right knee. Myoelectrical signals were amplified with a bandwidth frequency ranging from 10 Hz to 500 Hz (gain = 1000 for RF and 500 for VL), digitised on-line at a sampling frequency of 2 kHz using a computer, and stored for analysis with a commercially available software (AcqKnowledge 4.1 for MP Systems, Biopac Systems Inc., Goleta, USA). The root mean square (RMS), a measure of EMG amplitude, was automatically calculated with the software.

Peak-to-peak amplitude of the M-waves was analysed for VL and RF muscles with the average of the three trials used for analysis. EMG amplitude of VL and RF muscles during the knee extensors MVC was quantified as the RMS for a 0.5 s interval at peak torque (250 ms interval either side of the peak torque). Maximal EMG RMS values for VL and RF muscles were then normalised by the M-wave peak-to-peak amplitude for the respective muscles, in order to obtain the RMS/M-wave ratio. This normalisation procedure accounted for peripheral influences such as neuromuscular propagation failure. EMG RMS was calculated for the last 30 s of each minute during the whole-body endurance task for both VL and RF. The EMG RMS during the whole-body endurance

task was normalised to the EMG RMS of the last 30 s of the first minute of the constant load exercise.

## PHYSIOLOGICAL AND PSYCHOLOGICAL MEASUREMENTS

All participants were familiarised with all psychological measurements during their first visit to the laboratory. The psychological measurements performed in this study are identical as those performed in (Pageaux et al., 2014).

**Heart rate.** Heart rate was recorded continuously during both cognitive tasks and the whole-body endurance task using a heart rate monitor (Polar RS400, Polar Electro Oy, Kempele, Finland) with an acquisition frequency of a sample every 5 s. Data were analysed offline and averaged for both cognitive tasks. During the whole-body endurance task HR values were averaged for each minute completed.

**Perception of effort.** Perception of effort defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (Marcora, 2010b) was measured at the end of the warm-up and at the end of each minute of the constant load exercise using the 15 points RPE scale (Borg, 1998). Standardised explanations of the scale were given to each subject before the warm-up. Briefly subjects were asked to rate how much effort they were exerting based on how hard they were driving their legs, how heavy their breathing was and the overall sensation of how strenuous exercise is. For example 9 corresponds to a “very light” exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes. 17 corresponds to a “very hard” and 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.

**Mood.** The Brunel Mood Scale (BRUMS) developed by (Terry et al., 2003) was used to quantify current mood (“How do you feel right now?”) before and after the cognitive tasks. This questionnaire contains 24 items (e.g., “angry, uncertain, miserable, tired, nervous, energetic”) divided into six respective subscales: anger, confusion, depression, fatigue, tension, and vigour. The items are answered on a 5 points scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscales, with four relevant items, can achieve a raw score in the range of 0 to 16. Only scores for the fatigue and vigour subscales were considered in this study as subjective markers of mental fatigue.

**Subjective workload.** The National Aeronautics and Space Administration Task Load Index (NASA-TLX) rating scale (Hart and Staveland, 1988) was used to assess subjective workload. The NASA-TLX is composed of six subscales: Mental Demand (How much mental and perceptual activity was required?), Physical Demand (How much physical activity was required?), Temporal Demand (How much time pressure did you feel due to the rate or pace at which the task occurred?), Performance (How much successful do you think you were in accomplishing the goals of the task set by the experimenter?), Effort (How hard did you have to work to accomplish your level of performance?) and Frustration (How irritating, annoying did you perceive the task?). The participants had to score each of the items on a scale divided into 20 equal intervals anchored by a bipolar descriptor (e.g. High/Low). This score was multiplied by 5, resulting in a final score between 0 and 100 for each of the subscales. Participants completed the NASA-TLX after the cognitive task and after the whole-body endurance task.

## STATISTICS

All data are presented as means  $\pm$  standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Lower-Bound correction to the degrees of freedom was applied when violations to sphericity were present. Paired t-tests were used to assess the effect of condition (self-regulation vs control) on HR during both cognitive tasks and on NASA-TLX scores after the cognitive tasks and after the whole-body endurance task. Fully repeated measure 2 x 6 ANOVAs were used to test the effect of time (5-min blocks) and condition on response accuracy and reaction time during the cognitive tasks. Fully repeated measure 2 x 2 ANOVAs were used to test the effect of condition and time on mood before and after the cognitive tasks. Fully repeated measure 2 x 3 ANOVAs were used to test the effect of condition and time on MVC torque, VAL, M-wave parameters for each muscle, RMS/M-wave ratio, twitch properties, and peak doublet torque before and after the cognitive tasks, and after the whole-body endurance task. Fully repeated measure 2 x 6 ANOVAs were used to test the effect of condition and time on HR, and EMG RMS during the whole-body endurance task. Fully repeated measure 2 x 7 ANOVA was used to test the effect of condition and time on RPE and cadence during the whole-body endurance task. When interactions are not significant, only main effects are reported. Significant main effects of time and significant interactions were followed up with Bonferonni tests as

appropriate. Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 20 for Mac OS X (SPSS Inc., Chicago, IL, USA). Cohen's effects size  $d_z$  and  $f(V)$  were calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany) and reported.

## IV. Results

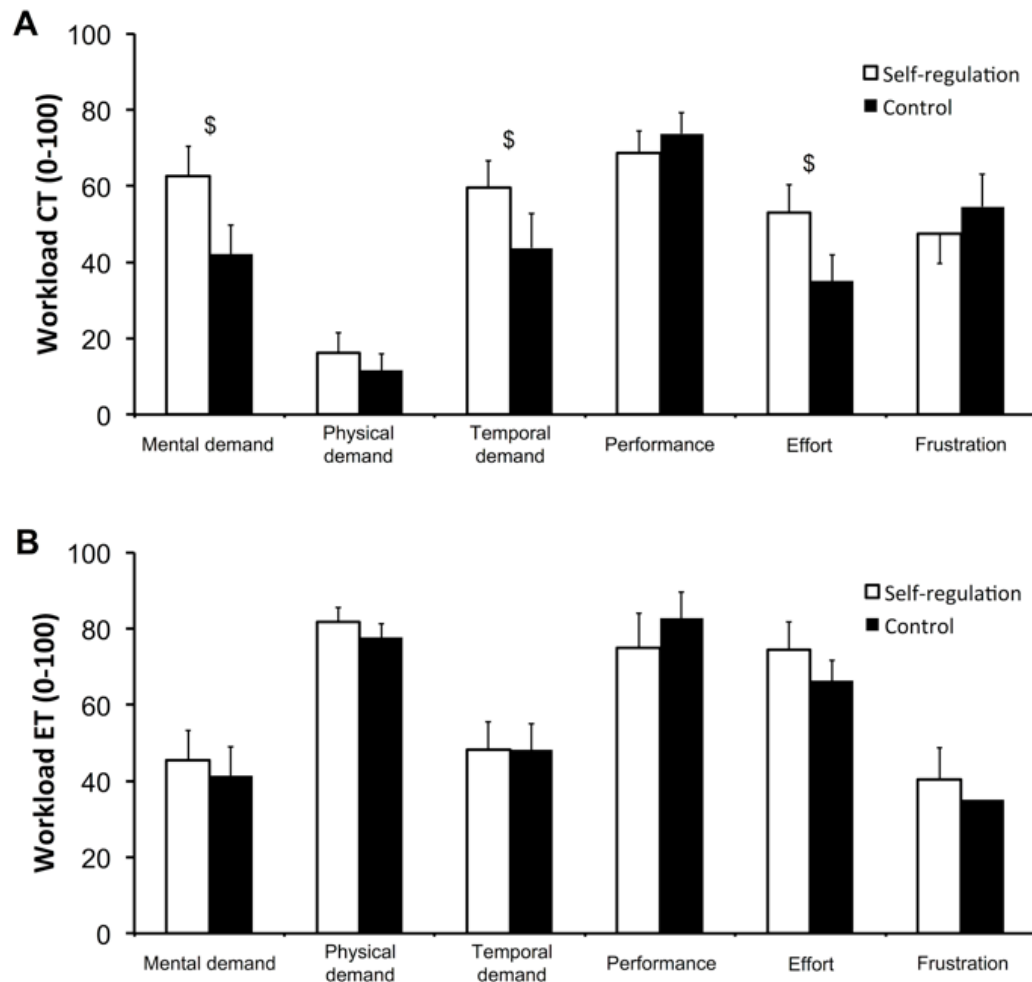
### COGNITIVE TASKS

**Mood.** Self-reported fatigue was significantly higher ( $P=0.009$ ,  $f(V)=0.957$ ) post-cognitive tasks (self-regulation condition  $3.7 \pm 3.4$ , control condition  $4.5 \pm 3.6$ ) compared to pre-cognitive tasks (self-regulation condition  $1.5 \pm 2.0$ , control condition  $1.8 \pm 1.5$ ). However neither condition ( $P=0.369$ ,  $f(V)=0.951$ ) nor interaction effect ( $P=0.401$ ,  $f(V)=0.264$ ) were significant. Vigour decreased ( $P=0.009$ ,  $f(V)=0.283$ ) significantly after the self-regulation task ( $10.2 \pm 3.0$  to  $8.3 \pm 3.9$ ) and the control task ( $10.6 \pm 4.0$  to  $7.8 \pm 4.7$ ) with no significant difference between conditions ( $P=1.000$ ,  $f(V)=0.032$ ).

**Cognitive Performance.** Accuracy during cognitive tasks did not present any effect of condition ( $P=0.070$ ,  $f(V)=0.605$ ) or time ( $P=0.236$ ,  $f(V)=0.378$ ). Reaction time during both conditions did not change over time ( $P=0.507$ ,  $f(V)=0.207$ ) but was significantly longer during the self-regulation task compared to the control task ( $834 \pm 109$  ms vs  $597 \pm 80$  ms,  $P<0.001$ ,  $f(V)=2.500$ ). Reaction time during the self-regulation task was significantly higher for all subjects.

**Heart Rate.** HR was significantly higher ( $P<0.001$ ,  $d_z=0.577$ ) during the self-regulation task ( $65.8 \pm 9.3$  beats/min) compared to the control task ( $62.0 \pm 4.5$  beats/min).

**Subjective Workload.** Subjective workload data are presented in figure 16. Following the cognitive tasks (figure 16A), subjects rated higher the items Mental demand ( $P=0.012$ ,  $d_z=0.861$ ), Temporal demand ( $P=0.050$ ,  $d_z=0.626$ ) and Effort ( $P=0.022$ ,  $d_z=0.772$ ) during the self-regulation condition compared to the control condition. Physical demand, performance and frustration did not differ significantly between conditions.



**Figure 16 - Effects of cognitive tasks (CT, panel A) and whole-body endurance task (ET, panel B) on subjective workload (NASA-TLX scale).**

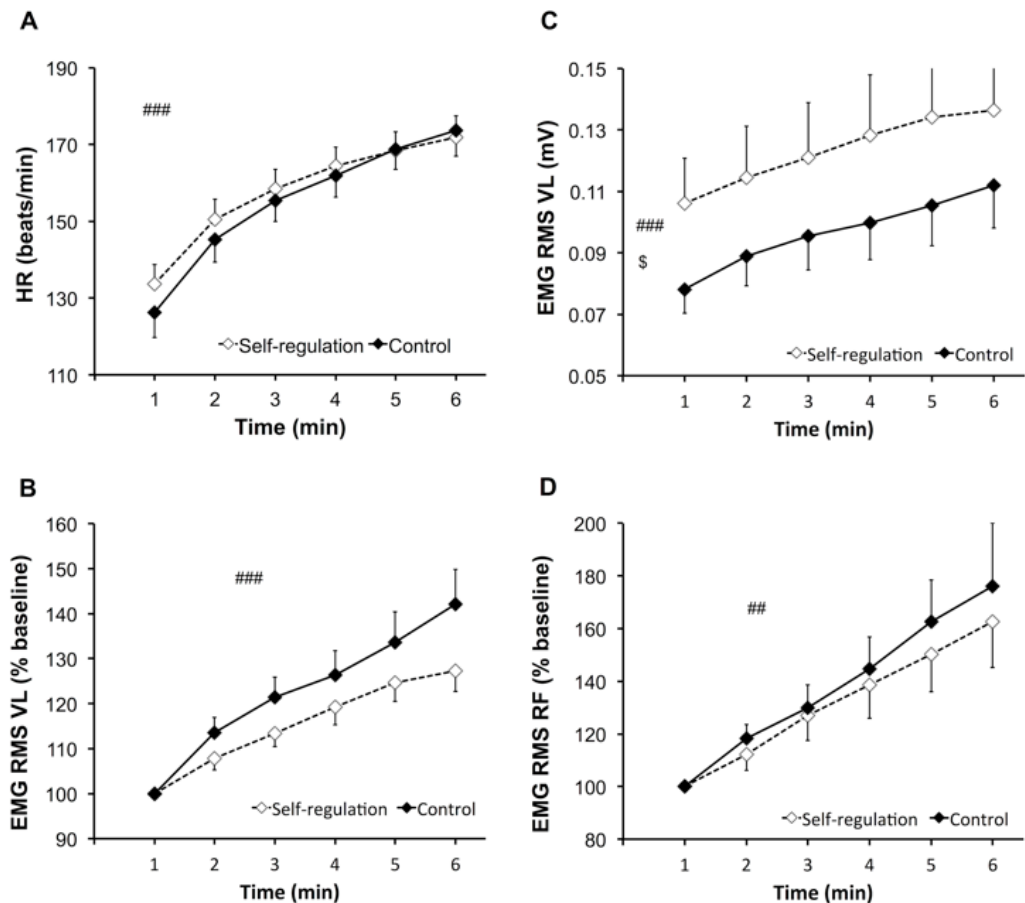
\$ Significant main effect of condition ( $P < 0.05$ ). Data are presented as means  $\pm$  SEM.

## PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF MENTAL FATIGUE ON THE WHOLE-BODY ENDURANCE TASK

**Heart Rate.** Heart rate (figure 17A) increased significantly over time ( $P < 0.001$ ,  $f(V) = 4.776$ ) but did not differ between conditions ( $P = 0.381$ ,  $f(V) = 0.274$ ).

**EMG RMS.** Cadence during the whole-body endurance task did not present any effect of condition ( $P = 0.919$ ,  $f(V) = 0.031$ ), time ( $P = 0.175$ ,  $f(V) = 0.418$ ) or interaction ( $P = 0.101$ ,  $f(V) = 0.412$ ). EMG RMS of the VL muscle (figure 17C) increased significantly during the whole-body endurance task ( $P = 0.002$ ,  $f(V) = 1.25$ ). EMG RMS of the VL muscle was significantly higher during the self-regulation condition compared to the control

condition ( $P=0.046$ ,  $f(V)=0.678$ ). EMG RMS of the RF muscle increased significantly during the whole-body endurance task ( $P=0.002$ ,  $f(V)=1.305$ ) without any condition ( $P=0.610$ ,  $f(V)=0.167$ ) or interaction ( $P=0.626$ ,  $f(V)=0.160$ ) effects. Time course of EMG RMS for the VL (figure 17B) and RF (figure 17D) did not differ between conditions (VL,  $P=0.111$ ,  $f(V)=0.523$ ; RF,  $P=0.410$ ,  $f(V)=0.272$ ) and did not present a significant interaction effect (VL,  $P=0.091$ ,  $f(V)=0.557$ ; RF,  $P=0.384$ ,  $f(V)=0.289$ ).



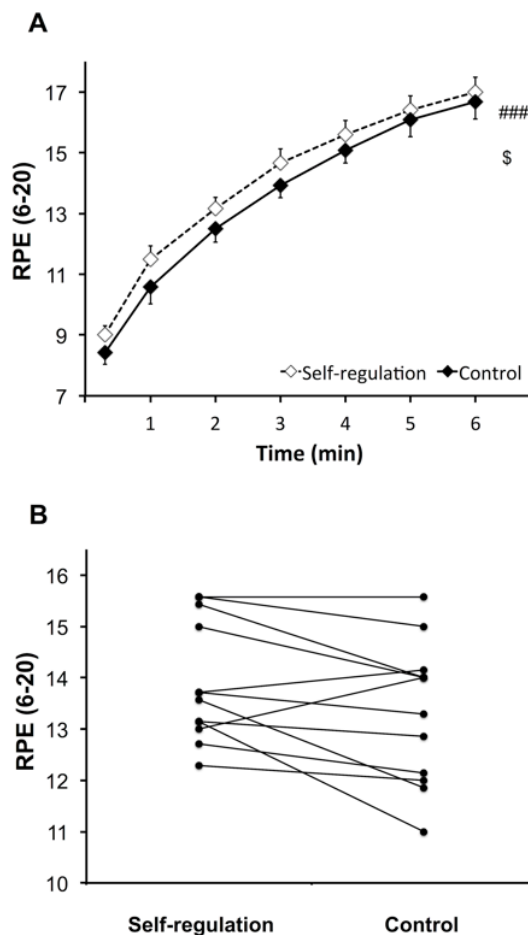
**Figure 17 - Effects of cognitive tasks on heart rate and EMG root mean square during the whole-body endurance task.**

Heart rate (HR) during constant load exercise (panel A). EMG root mean square (RMS) normalized by the first minute of the constant load exercise for the vastus lateralis (VL) muscle (panel B). EMG root mean square (RMS) of the vastus lateralis (VL) muscle during the constant load exercise (panel C). EMG root mean square (RMS) normalised by the first minute of the constant load exercise for the rectus femoris (RF) muscle (panel D). \$ Significant main effect of condition ( $P < 0.05$ ). ## Significant main effect of time ( $P < 0.01$ ). ### Significant main effect of time ( $P < 0.001$ ). Data are presented as means  $\pm$  SEM.



**Perception of Effort.** Perception of effort was measured during the whole-body endurance task. RPE (figure 18A) increased over time ( $P < 0.001$ ,  $f(V) = 3.590$ ) following both cognitive tasks. However, subjects rated a higher perceived exertion during the self-regulation condition compared to the control condition ( $P = 0.044$ ,  $f(V) = 0.680$ ). No interaction effect ( $P = 0.630$ ,  $f(V) = 0.217$ ) was demonstrated. Perception of effort was significantly higher during the self-regulation condition compared to the control condition for 9 out of all subjects (figure 18B).

**Subjective Workload.** Following the whole-body endurance task (figure 18B), none of the items presented any significant difference between conditions (all  $P > 0.05$ ).



**Figure 18 - Effect of cognitive tasks on perception of effort during the whole-body endurance task.**

Overall rating of perceived exertion (RPE) during the constant load exercise (panel A). Individual effect of cognitive tasks on the mean RPE (panel B). ### Significant main effect of time ( $P < 0.001$ ). \$ Significant main effect of condition ( $P < 0.05$ ). Data are presented as means  $\pm$  SEM

## EFFECTS OF COGNITIVE TASKS AND WHOLE-BODY ENDURANCE TASK ON NEUROMUSCULAR FUNCTION

**MVC.** There was no significant main effect of condition ( $P=0.920$ ,  $f(V)=0.032$ ) or interaction ( $P=0.515$ ,  $f(V)=0.204$ ) on knee extensors MVC torque (figure 19A). Follow-up tests on the significant main effect of time ( $P=0.001$ ,  $f(V)=1.319$ ) revealed that the cognitive tasks did not affect MVC torque ( $P=0.194$ ,  $d_z=0.580$ ). The whole-body endurance task caused a significant reduction in MVC torque in both self-regulation and control conditions (self-regulation condition  $-17 \pm 15$  %, control condition  $-15 \pm 11$  %,  $P=0.001$ ,  $d_z=1.890$ ).

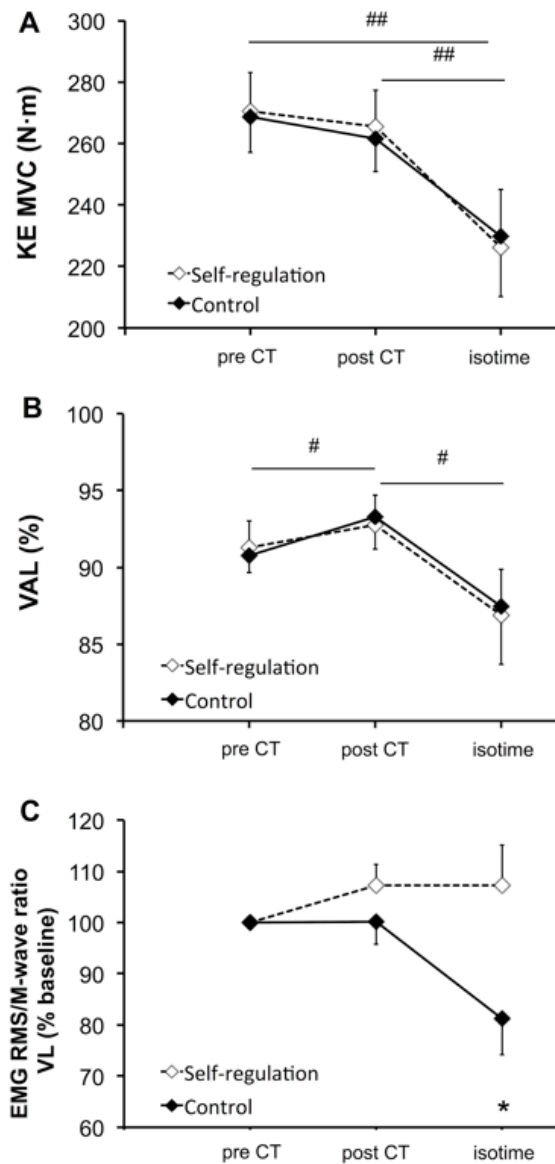
**Peripheral Fatigue.** Peripheral parameters of neuromuscular functions are presented in table 2. There were no significant main effects of condition or interactions on all twitch parameters (all  $P>0.05$ ). Tw ( $P<0.001$ ,  $f(V)=2.610$ ), doublet ( $P<0.001$ ,  $f(V)=1.636$ ), Ct ( $P=0.010$ ,  $f(V)=0.936$ ) and RFD ( $P=0.003$ ,  $f(V)=0.938$ ) decreased over time. Follow-up tests results on the significant main effect of time are presented in table 2. M-wave amplitude of VL ( $P=0.338$ ,  $f(V)=0.303$ ) and RF ( $P=0.079$ ,  $f(V)=0.584$ ) muscles were not significantly affected by the cognitive tasks and the whole-body endurance task. M-wave amplitude of VL and RF muscles did not change between conditions ( $P=0.958$ ,  $f(V)=0.032$  and  $P=0.367$ ,  $f(V)=0.283$ ) and did not show any interaction effect ( $P=0.620$ ,  $f(V)=0.153$  and  $P=0.771$ ,  $f(V)=0.090$ ).

**Central Fatigue.** There was no significant main effect of condition ( $P=0.869$ ,  $f(V)=0.054$ ) or interaction ( $P=0.672$ ,  $f(V)=0.201$ ) on VAL (figure 19B). Follow-up tests of the significant main effect of time ( $P = 0.011$ ,  $f(V)=0.990$ ) revealed an increase in VAL post cognitive tasks ( $P=0.024$ ,  $d_z=0.438$ ). Moreover, the whole-body endurance task significantly reduced VAL ( $P=0.013$ ,  $d_z=0.880$ ). RMS/M-wave ratio of the VL muscle (figure 19C) did not present any significant effect of time ( $P=0.313$ ,  $f(V)=0.318$ ) or condition ( $P=0.279$ ,  $f(V)=0.343$ ). Follow-up tests of the main effects of interaction ( $P=0.021$ ,  $f(V)=0.810$ ) revealed that the RMS/M-wave ratio of the VL muscle decreased only during the control condition following the whole-body endurance task ( $P=0.038$ ,  $d_z=0.305$ ). RMS/M-wave ratio of the RF muscle did not change overtime ( $P=0.063$ ,  $f(V)=0.280$ ) and did not present any effect of condition ( $P=0.915$ ,  $f(V)=0.032$ ) or interaction ( $P=0.335$ ,  $f(V)=0.335$ ).

**Table 2 - Changes in peripheral parameters of muscle fatigue**

Ct = Contraction time of the twitch, Tw =Peak twitch, RFD = Average rate of force development the twitch, HRT = Half relaxation time of the twitch. CT = Cognitive task, ET = Whole-body endurance task, VL = vastus lateralis muscle, RF = rectus femoris muscle. <sup>£</sup> Main effect of time, significantly different from pre cognitive task; <sup>§</sup> Main effect of time, significantly different from post cognitive task. One item corresponds to P<0.05, two items correspond to P<0.01 and three items corresponds to P<0.001. Data are presented as means ± SD.

	Self-regulation			Control		
	pre CT	post CT	post ET	pre CT	post CT	post ET
Amplitude VL (mV)	17.77 ± 4.06	17.41 ± 3.99	18.35 ± 5.28	17.85 ± 3.85	17.69 ± 3.24	17.83 ± 3.97
Amplitude RF (mV)	9.61 ± 2.59	9.17 ± 2.32	8.67 ± 2.49	9.13 ± 2.41	8.59 ± 2.10	8.37 ± 2.36
Tw (N.m)	60 ± 14	58 ± 15 <sup>££</sup>	40 ± 12 <sup>£££§§§</sup>	56 ± 15	54 ± 12 <sup>££</sup>	36 ± 11 <sup>£££§§§</sup>
Ct (ms)	76 ± 14	76 ± 10	67 ± 10 <sup>§</sup>	79 ± 10	80 ± 1.09	69 ± 11 <sup>§</sup>
RFD (N.m/s)	817 ± 243	780 ± 244	610 ± 219 <sup>££§</sup>	727 ± 244	686 ± 192	526 ± 143 <sup>££§</sup>
HRT (ms)	79 ± 27	83 ± 26	75 ± 27	78 ± 27	77 ± 29	72 ± 27
Doublet (N.m)	108 ± 16	105 ± 17 <sup>£</sup>	87 ± 18 <sup>£££§§</sup>	104 ± 19	95 ± 19 <sup>£</sup>	83 ± 15 <sup>£££§§</sup>



**Figure 19 - Effects of cognitive tasks on isometric maximal voluntary contraction and central parameters of neuromuscular function.**

Isometric maximal voluntary contraction (MVC) torque of the knee extensor muscles (KE, panel A). Maximal voluntary activation level (VAL, panel B). Root mean square (RMS)/Mmax (M-wave) ratio of the vastus lateralis (VL) muscle (panel C). # Significant main effect of time ( $P < 0.05$ ). ## Significant main effect of time ( $P < 0.01$ ). \* Significant difference between condition for the same time ( $P < 0.05$ ). Data are presented as means  $\pm$  SEM.

## **V. Discussion**

The aim of this study was to test the hypothesis that mental fatigue exacerbates central fatigue induced by whole-body exercise. The results of the present study do not support this hypothesis. Furthermore, mental fatigue did not exacerbate peripheral fatigue induced by whole-body exercise. Therefore, the increase in perception of effort experienced by mentally fatigued subjects is independent of any central or peripheral alteration of neuromuscular function.

### **SELF-REGULATION, MENTAL FATIGUE AND PERCEPTION OF EFFORT**

We used a congruent (control task) and incongruent (self-regulation task) Stroop task to induce mental fatigue. The higher heart rate experienced during the incongruent Stroop task confirms that self-regulation is cognitively demanding and requires higher effort mobilisation compared to the control task (Richter et al., 2008). The higher demanding nature of the self-regulation task is also supported by higher ratings of Mental Demand, Temporal Demand and Effort compared to the control task. Moreover, the subjects presented a longer reaction time during the self-regulation task compared to the control task, confirming the presence of an additional cognitive process during the self-regulation task. As both control and self-regulation tasks involved sustained attention, the longer reaction time is likely to be due to the presence of the response inhibition process during the self-regulation task (Stroop, 1992; Sugg and McDonald, 1994).

Interestingly, both self-regulation and control tasks induced an increase in subjective feeling of fatigue, suggesting presence of mental fatigue (i.e. subjective feeling of tiredness and lack of energy) following both cognitive tasks. As in a previous study (Pageaux et al., 2014) a subjective state of mental fatigue was more clearly identified by a higher perception of effort during the subsequent whole-body endurance task. In fact, during the six minutes of constant load cycling, RPE was significantly higher during the self-regulation condition compared to the control condition.

### **MENTAL FATIGUE DOES NOT IMPAIR NEUROMUSCULAR FUNCTION**

To ensure that mental fatigue did not alter the neuromuscular function at the onset of the whole-body endurance task, we performed neuromuscular function tests pre and post

mental exertion. According to previous studies, completion of short (Bray et al., 2008) or prolonged (Pageaux et al., 2013) mental exertion involving self-regulation did not alter force production capacity. Our results are also supported by a previous study (Rozand et al., 2014) where mental exertion involving 80 intermittent maximal imagined contractions of the elbow flexors did not alter force production capacity despite presence of mental fatigue. Indeed, in our study, none of the cognitive tasks induced a significant decrease in knee extensors MVC. Furthermore, as Bray et al. (2008) failed to demonstrate an impaired MVC of the upper limb following mental exertion involving self-regulation, it is unlikely that self-regulation and mental fatigue impact differently upper and lower limbs.

Interestingly, as previously observed, the absence of warm-up post mental exertion altered only muscle contractile properties and not MVC production (Bishop, 2003). The absence of MVC reduction despite impaired-muscle contractile properties can be explained by the slight increase in maximal muscle activation measured post cognitive tasks in both conditions. Indeed, an increase in maximal muscle activation measured by the twitch-interpolated technique is likely to reflect an increase in muscle fibre recruitment (Gandevia et al., 2013).

It has been suggested that completion of mental exertion involving self-regulation may cause the expenditure of CNS resources, leading to an inability of the CNS to drive the working muscles (Bray et al., 2008; Bray et al., 2012). As both cognitive tasks did not induce a decrease in maximal muscle activation, our results and those of previous studies (Bray et al., 2008; Pageaux et al., 2013) do not support this hypothesis. However, because our study did not involve repeated MVCs, further studies are required to investigate the effect of mental exertion on the ability to repeat maximal effort and contraction over time.

## **MENTAL FATIGUE AND PHYSIOLOGICAL RESPONSES TO THE WHOLE-BODY ENDURANCE TASK**

It has been shown that completion of mental exertion involving self-regulation leading to mental fatigue does not alter physiological responses during a subsequent whole-body endurance task (Marcora et al., 2009; Pageaux et al., 2014). The lack of difference in heart rate between conditions in our study confirms these findings. Therefore, according to previous studies, the significantly higher perception of effort during the self-regulation condition is unlikely to be explained by a higher solicitation of the cardiorespiratory and metabolic systems (Marcora et al., 2009; Pageaux et al., 2014).

Muscle activation measured by EMG during the whole-body endurance task increased during the six minutes of exercise. Despite the fact that EMG during dynamic exercise is not a good measure of central motor drive (Farina, 2006), the concomitant increase in perception of effort and EMG during the exercise is likely to reflect a compensatory mechanism to overcome the progressive increase in peripheral fatigue induced by the whole-body endurance task. Indeed, due to exercise-induced peripheral fatigue, the subjects had to increase the central motor command to increase muscle fibre recruitment and ensure continuation of the whole-body endurance task. As the time course of EMG for the vastus lateralis and rectus femoris muscles did not differ between conditions, our results suggest that mental exertion involving self-regulation does not alter the progressive increase in muscle activation during whole-body exercise.

Interestingly, the EMG RMS of the vastus lateralis muscle during the whole-body endurance task was significantly higher following the self-regulation task compared to the control task. As cadence did not differ between conditions, this result suggests an alteration of muscle recruitment at the onset of the exercise induced by the self-regulation task. This is not the first report of an increase in EMG activity during a physical task following completion of mental exertion involving response self-regulation. In accordance with our results, Bray et al. (2008) found a higher EMG activity during a submaximal handgrip isometric contraction following short (3 min 40 s) mental exertion involving self-regulation. Therefore, our results, combined with those of Bray et al. (2008), suggest a plausible alteration in muscle activation pattern during a physical task performed subsequently to mental exertion involving self-regulation. This alteration in muscle activation pattern, and consequently in motor control, is supported by a recent study demonstrating a decrease in mechanically induced tremor following mental exertion leading to mental fatigue (Budini et al., 2014). Another alternative explanation for the higher EMG RMS during the self-regulation condition would be an increase in skin conductance due to self-regulation task-induced mental stress. Indeed, mental exertion-induced mental stress is known to increase whole-body perspiration (Machado-Moreira and Taylor, 2012), and this plausible increase in perspiration during the self-regulation condition might lead to an increase in skin conductance, consequently impairing the EMG signal (Abdoli-Eramaki et al., 2012). However, as our study did not aim to measure mental stress and alteration in motor control induced by the response self-regulation task, further studies should investigate whether mental exertion impairs motor control or not. As injury in sport is more likely to occur in the later stage of an event or a season (e.g. Ekstrand et

al., 2011), it is therefore important for athletes that further studies investigate the relation between mental fatigue and motor control in humans.

### **MENTAL FATIGUE DOES NOT EXACERBATE CENTRAL FATIGUE INDUCED BY WHOLE-BODY EXERCISE**

The main aim of this study was to investigate whether mental fatigue exacerbates central fatigue induced by whole-body exercise. Muscle fatigue could be caused by peripheral and/or central alterations (for review see Gandevia, 2001). Contrary to our hypothesis, the extent of peripheral and central fatigue at isotime did not differ between conditions. These results demonstrate for the first time that mental exertion leading to mental fatigue does not alter the rate of central fatigue development during whole-body exercise. The present findings are similar to those of our previous study showing that mental fatigue does not exacerbate central fatigue induced by single-joint exercise when measured at exhaustion.

Therefore the present study provides further evidence supporting the hypothesis that the negative effect of mental fatigue on whole-body endurance performance cannot be explained by an exacerbated central and peripheral fatigue. Consequently, the reduction in performance in presence of mental fatigue observed in previous studies (Marcora et al., 2009; Pageaux et al., 2013; Pageaux et al., 2014) can be explained by an alteration in perception of effort independent of any physiological alterations.

As mental fatigue does not affect the ability of the CNS to recruit the active muscles (i.e. central fatigue), it is now clear that mental fatigue and central fatigue are two distinct phenomena. The most plausible explanation for the lack of interaction between mental fatigue and central fatigue is that these CNS functions involve different brain areas (Pageaux et al., 2013). Indeed, functional magnetic resonance imaging studies showed that central fatigue during index finger abduction exercise is associated with decrease in activation of the supplementary motor area and to a lesser extent, in parts of the paracentral gyrus, right putamen and in a small cluster of the left parietal operculum (van Duinen et al., 2007). Interestingly, none of these brain areas are significantly associated with mental exertion involving response inhibition. This cognitive process is significantly associated with activity of the pre-supplementary motor area and the anterior cingulate cortex (Mostofsky and Simmonds, 2008).



## **MENTAL FATIGUE AND PERCEPTION OF EFFORT**

The higher-than normal perception of effort experienced by mentally fatigued subjects in the present experiment is supported by previous studies involving constant load single-leg (Pageaux et al., 2013) and whole body (Marcora et al., 2009) exercise, and also self-paced exercise (Brownsberger et al., 2013; Pageaux et al., 2014). However, despite evidence that mental fatigue increases perception of effort during submaximal exercise, the underlying mechanisms of this alteration in perceived exertion remain unclear.

It is well accepted that perception of effort generation results from the central processing of sensory signals. However, the nature of the sensory signals involved in perception of effort generation remains debated. Briefly, two different theories suggest that perception of effort reflects the central processing of i) the corollary discharge associated with the central motor command (corollary discharge model; Marcora, 2009); or ii) afferent feedback (afferent feedback model; Amann et al., 2013). Despite much recent evidence that perception of effort is generated from the corollary discharge associated with the central motor command (e.g. Marcora, 2011; de Morree et al., 2012), to date, a role of these muscle afferents III-IV in its generation cannot be excluded (Amann et al., 2013). Interestingly, in our study, mentally fatigued subjects experienced a higher than normal perception of effort independently of higher-than normal heart rate responses and peripheral fatigue (i.e. known to induce discharge activity of III-IV muscle afferents in presence of exercise-induced metabolites; Dempsey, 2012) induced by the exercise. According to these results, it is unlikely that the increase in RPE observed in our study reflects an alteration of afferent feedback. Therefore, the higher than-normal perception of effort observed in our study can be explained by the corollary discharge model. As previously suggested (Marcora et al., 2009; Pageaux et al., 2013; Pageaux et al., 2014), the increase in perception of effort following mental exertion involving response self-regulation might be caused by an alteration of the central processing of the corollary discharge associated with the central motor command. However, as our study revealed an altered EMG response to the exercise (i.e. alteration in muscle activation), it cannot be excluded that mental fatigue could impair the central motor command leading to a higher than normal perception of effort in presence of mental fatigue. Further studies are required to investigate whether mental fatigue i) alters the central processing of the corollary discharge associated with the central motor command, ii) alters the central motor command itself, or iii) alters both phenomena previously mentioned.

Despite the fact that we did not measure intrinsic changes in the brain induced by prolonged self-regulation leading to mental fatigue, it is possible to speculate on the mechanisms involved based on previous studies. The anterior cingulate cortex (ACC) is strongly activated during Stroop tasks involving self-regulation (Bush et al., 1998; Swick and Jovanovic, 2002) and is also known to be linked with perception of effort (Williamson et al., 2001; 2002). Furthermore, mental exertion has been associated with an increase in brain adenosine (Lorist and Tops, 2003). As previously suggested (Pageaux et al., 2014), it is therefore plausible that the higher perception of effort caused by continuous engagement in mental exertion involving self-regulation might be caused by an accumulation of adenosine in the ACC. Indeed, experimental evidence that neural activity increases extracellular concentration of adenosine (Lovatt et al., 2012) and that adenosine accumulation reduces endurance performance (Davis et al., 2003) support this hypothesis. Caffeine is known to block brain adenosine receptors, increasing cognitive performance in time-reaction task, arousal and attention (Lorist and Tops, 2003), and improving endurance performance in humans (Cole et al., 1996; Plaskett and Cafarelli, 2001). As caffeine has an antagonist effect of mental exertion, it could be interesting to investigate the interaction between ACC and perception of effort with/without caffeine intake.

## **LIMITATIONS, CONCLUSIONS AND PERSPECTIVES**

Our results present the first evidence that mental fatigue does not induce a greater rate of central fatigue development during whole-body exercise. However, we must acknowledge some limitations in the present study. Firstly, whole-body endurance exercise has to be performed on an ergometer, inducing a time delay to start neuromuscular testing due to the need to transfer the participant from the ergometer to the dynamometer. Therefore, the extent of muscle fatigue at isotime is likely to be underestimated in both experimental conditions. Secondly, brain activation during exercise was not measured in the present study and we can only speculate, based on previous imaging studies, on the mechanisms causing the increased perception of effort.

Despite these limitations, this study provides further evidence that mental fatigue does not induce a reduction in the ability of the CNS to fully recruit the active muscles. Our results also support the hypothesis that mental exertion involving self-regulation induces either i) an alteration of the central processing of the corollary discharge associated with the central motor command, or ii) an alteration of the central motor command itself.

Therefore, further studies should investigate brain alterations underlying the negative effect of mental fatigue on perception of effort. A better understanding of these brain alterations could lead to development of novel targeted interventions to decrease perception of effort and improve endurance performance in athletes, and reduced exertional fatigue in patients (Macdonald et al., 2012).

## **CHAPTER 3: DOES MENTAL EXERTION ALTER MAXIMAL MUSCLE ACTIVATION?**

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**Published in** *Frontiers in Human Neuroscience* (2014)

Rozand, V., Pageaux, B., Marcora, S. M., Papaxanthis, C. & Lepers, R. 2014. Does mental exertion alter maximal muscle activation? *Frontiers in human neuroscience*, 8, 755.

## Abstract

Mental exertion is known to impair endurance performance, but its effects on neuromuscular function remain unclear. The purpose of this study was to test the hypothesis that mental exertion reduces torque and muscle activation during intermittent maximal voluntary contractions of the knee extensors. Ten subjects performed in a randomised order three separate mental exertion conditions lasting 27 minutes each: i) high mental exertion (incongruent Stroop task), ii) moderate mental exertion (congruent Stroop task), iii) low mental exertion (watching a movie). In each condition, mental exertion was combined with ten intermittent maximal voluntary contractions of the knee extensor muscles (one maximal voluntary contraction every 3 minutes). Neuromuscular function was assessed using electrical nerve stimulation. Maximal voluntary torque, maximal muscle activation and other neuromuscular parameters were similar across mental exertion conditions and did not change over time. These findings suggest that mental exertion does not affect neuromuscular function during intermittent maximal voluntary contractions of the knee extensors.

## **II. Introduction**

Mental exertion refers to the engagement with a demanding cognitive task. When performed simultaneously to physical exertion, mental exertion is known to impair endurance performance (Yoon et al., 2009; Mehta and Agnew, 2012). Interestingly, mental exertion also has a negative impact on endurance performance when performed prior to physical exertion (Bray et al., 2008; Marcora et al., 2009; Pageaux et al., 2013). Therefore, there seems to be a clear link between mental exertion and endurance performance in humans.

Contrary to studies on endurance performance, few studies investigated the effect of mental exertion on neuromuscular function. Bray et al. (2008) using a handgrip squeezing task, did not find any decrease in maximal voluntary contraction (MVC) force of the handgrip muscles following 3 min 40 s of mental exertion (incongruent Stroop task). Furthermore, mental exertion induced by 20 min of motor imagery did not alter maximal force production capacity of the elbow flexors (Rozand et al., 2014). Even with 90 min of prior mental exertion induced by the AX-CP test, Pageaux et al. (2013) demonstrated that prolonged mental exertion does not induce a decrease in MVC torque of the knee extensor

muscles. Together, these results suggest that mental exertion does not alter maximal force production. However, in 2012, Bray and colleagues measured a significant decrease in force during intermittent handgrip MVCs interspaced with 3-min bouts of high mental exertion (incongruent Stroop task) for a total of 22 min (Bray et al., 2012). In fact, the authors found a significant reduction in maximal force production during the last MVC of this experimental protocol. These results suggest a possible interaction between intermittent MVCs and high mental exertion on maximal force production.

Bray et al. (2012) suggested that the decrease in maximal force production observed during repeated MVCs in the high mental exertion condition (incongruent Stroop task) was caused by a central mechanism, specifically the expenditure of central nervous system (CNS) resources. Indeed, cognitive, emotional, and behavioural effort control draw upon a common pool of resources, and a self-regulation effort inducing resource depletion could deteriorate a subsequent performance task (Hagger et al., 2010). According to Bray et al. (2012), this expenditure of CNS resources might cause central fatigue, i.e. a decrease in maximal muscle activation during intermittent MVCs, leading to a decrease in handgrip force. However, the late decrease in handgrip force observed in this study occurred without changes in EMG amplitude during the intermittent MVCs. This finding suggests that central fatigue was not induced by this combination of intermittent MVCs and high mental exertion. Unfortunately, EMG amplitude during MVCs is not the most accurate measure of maximal muscle activation (Millet and Lepers, 2004). Therefore, further investigations are necessary to understand the central mechanisms underlying the decrease in maximal force production observed during intermittent MVCs performed in conditions of high mental exertion.

In the present study, we measured the capacity of the CNS to maximally drive the working muscles using the twitch interpolation technique following the guidelines provided by Gandevia in 2001 (Gandevia, 2001). This technique is considered as the gold-standard to assess maximal muscle activation in humans (Gandevia et al., 2013), and consists of delivering a superimposed stimulation (electrical or magnetic) during a MVC to recruit the motor units not voluntarily recruited. If the subject is not able to fully recruit the working muscles, then an additional force will be produced by the stimulation.

In his review on central fatigue, Gandevia (2001) provided guidelines to ensure that subjects exert a true maximal effort during MVCs. As submaximal effort due to poor motivation can negatively affect measures of maximal muscle activation (Enoka, 1995),

these methodological considerations are crucial to ensure the validity of studies investigating the effects of mental exertion on neuromuscular function. Among these methodological considerations, of particular interest is the use of visual feedback performance to maximise voluntary effort (Gandevia, 2001). Unfortunately, in Bray et al. study (2012), performance feedback was not available to participants during MVCs. Therefore, it cannot be excluded that the late decrease in handgrip force observed in this study was due to a decrease in motivation to exert a true maximal effort rather than central fatigue. In the present study, visual feedback was provided to the participants for each MVC.

Furthermore, there is evidence that performing the Stroop task involves activation of the trapezius muscle (MacDonell and Keir, 2005; Waersted and Westgaard, 1996) and the forearm muscles (Laursen et al., 2002) also used in handgrip squeezing. This muscle activity during the Stroop task could be due to holding the sheets (paper-based Stroop task), or selecting the correct responses with a keyboard or a mouse (computer-based Stroop task, Laursen et al., 2002). The continuous use of the upper limb muscles during mental exertion could impact performance during a subsequent physical effort involving the same muscle group. Therefore, it cannot be excluded that fatigue within the handgrip muscles (peripheral fatigue) contributed to the late decrease in maximal force production observed by Bray et al. (2012). To avoid the potential confounding effect of peripheral fatigue induced by the Stroop task on maximal force production, assessment of a muscle group not involved in the Stroop task (e.g. knee extensor muscles) would be more appropriate.

In this context, the aim of the present study was to analyse the effects of mental exertion on neuromuscular function of the knee extensor muscles. As both mental (Gailliot, 2008; Lorist and Tops, 2003) and physical (Davis et al., 2003; Matsui et al., 2011) exertion have been associated with an increase in brain adenosine and a reduction in brain glycogen, we hypothesised that mental exertion would reduce maximal force production during intermittent MVCs. Specifically, we expected that this reduction would be associated with a decrease in maximal muscle activation. To test this hypothesis, we used the twitch interpolation technique to assess maximal muscle activation during intermittent MVCs of the knee extensors following the guidelines of Gandevia (2001) to ensure a true maximal effort

### III. Methods

#### SUBJECTS

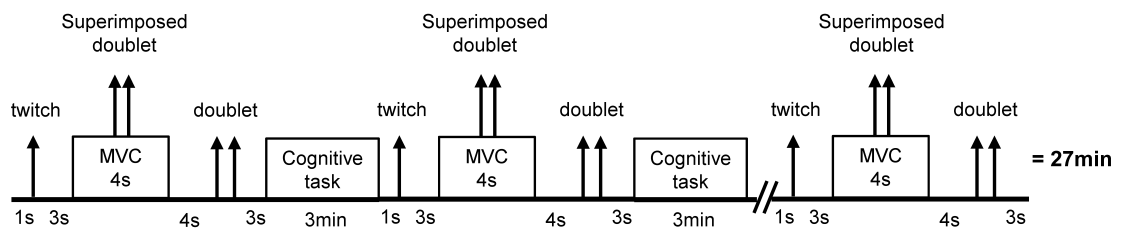
Ten healthy active male subjects (age =  $24.5 \pm 1.4$  yrs, weight =  $73.4 \pm 1.8$  kg, height:  $178.1 \pm 1.6$  cm), volunteered to participate in this study. None of the subjects had any known mental or somatic disorder and written consent was obtained from each subject prior to the study. Experimental protocol and procedures were approved by the local Ethics Committee of the Faculty of Sport Sciences, University of Burgundy in Dijon. All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants. All procedures were conducted according to the Declaration of Helsinki.

#### PROCEDURES

Subjects visited the laboratory on four different occasions. During the first visit, subjects were familiarised with the laboratory and the experimental procedures. During the next three visits, subjects randomly performed a mental exertion during 27 minutes: an incongruent Stroop task, a congruent Stroop task or watching a movie (see *Cognitive Tasks* for more details). Every 3 minutes, subjects stopped the mental exertion for 15 seconds to perform neuromuscular tests on the knee extensor muscles. Ten neuromuscular tests were performed for each condition (T0, 3, 6, 9, 12, 15, 18, 21, 24, and 27 minutes). Motivation was measured before the first neuromuscular test and mood was measured before the first and after the last neuromuscular test. Subjective workload was measured after the final neuromuscular test. For more details see *Psychological Measurements*. An overall view of the protocol can be found in figure 20.

Each subject completed all four visits over a period of 4 weeks with a minimum of 48 hours recovery period between visits. All subjects were given instructions to sleep for at least 7 hours, refrain from the consumption of alcohol, and not to practice vigorous physical activity the day before each visit. Subjects were also instructed not to consume caffeine and nicotine at least 3 hours before testing, and were asked to declare if they had taken any medication or had any acute illness, injury or infection.





**Figure 20 - Overview of the experimental protocol.**

The cognitive task was either an incongruent Stroop task (high mental exertion task), a congruent Stroop task (moderate mental exertion task), or watching a movie (low mental exertion, control task). Arrows represent transcutaneous electrical stimuli on the femoral nerve. Single stimuli are represented by one arrow. Paired stimuli (10Hz) are represented by two arrows. Timing was similar between conditions.

## COGNITIVE TASKS

Subjects had to perform a high mental exertion task (incongruent Stroop task involving sustained attention and response inhibition), a moderate mental exertion task (congruent Stroop task not involving the response inhibition process), and a low mental exertion task (watching a movie) for a prolonged period of time (27 minutes).

**High mental exertion task.** A modified incongruent version of the Stroop-word task (100% incongruent) was used for the high mental exertion condition. Subjects read aloud, as fast as possible, a list of printed words selected in a randomised way (Wallace and Baumeister, 2002). The ink colour in which the words were printed was mismatched (e.g. the word "green" printed in blue ink). Participants had to say aloud the colour of the ink in which the word was printed (e.g. for the word "green" printed in blue ink, they had to say "blue"). Moreover, for words appearing in red ink, participants were asked to ignore the previous instructions, and say the name of the printed word (e.g. for the word "yellow" printed in red ink, they should say "yellow"). An experimenter recorded the number of incorrect answer with a control sheet, and asked to restart the current line when the answer was incorrect. The modified incongruent Stroop task has been used in several studies on the effects of mental exertion on subsequent physical or mental tasks (Bray et al., 2008; Martin Ginis and Bray, 2010; Wallace and Baumeister, 2002).

**Moderate mental exertion task.** A congruent version of the Stroop-word task was used for the moderate mental exertion condition. Subjects were asked to read aloud,

without constraint of speed, a list of printed words. The words and the ink in which they were printed were identical (e.g. the word "green" printed in green ink).

*Low mental exertion task.* The low mental exertion condition (control task) consisted in watching a wildlife documentary ("Earth", A. Fothergill and M. Linfield, 2007). This movie was previously shown to be emotionally neutral (Pageaux et al., 2013).

During all three tasks, subjects were sitting on the ergometer chair used for the intermittent MVCs of the knee extensors. During both incongruent and congruent Stroop tasks, word-sheets were held by the subjects on their lap, whilst the movie was shown on a computer screen placed on a table in front of them. During the tasks, heart rate was recorded every 5 s during the entire protocol (MVCs and cognitive task) via a heart rate monitor chest strap (Polar RS400, Polar Electro Oy, Kempele, Finland) affixed to the skin near the midpoint of the participant's sternum. Average heart rate was calculated as a psychophysiological index of mental workload (Yoon et al., 2009; Richter et al., 2008).

## NEUROMUSCULAR FUNCTION TESTS

*Mechanical recordings.* Subjects were seated upright and performed isometric contractions of the right knee extensor muscles. Isometric torque was recorded using a Biodex dynamometer (Biodex Medical System Inc., New York, USA). Two crossover shoulder harnesses and a belt cross above the abdomen limited extraneous movements of the upper body. Neuromuscular tests were performed with the right leg at a knee joint angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The dynamometer axis was aligned with the knee joint axis. Torque signal was digitised on-line at a sampling frequency of 1 kHz using a computer, and stored for analysis with commercially available software (Acqnowledge 4.1.0, Biopac Systems Inc, Goleta, USA). At the beginning of each experiment, subjects performed a standardised warm-up, executing 10 brief submaximal contractions (~ 50 % MVC) of the knee extensor muscles, followed by a 3 minutes rest (Place et al., 2007). Then participants performed two isometric MVCs to determine their maximal force production. Subjects were motivated to exert maximal effort during MVCs via verbal encouragements provided by an experimenter, and visual feedback corresponding to the torque produced during the previous MVC.

**Electrical recordings.** EMG activity of the vastus lateralis (VL) muscle was recorded with pairs of bipolar silver chloride circular (recording diameter of 10 mm) surface electrodes (Controle Graphique Medical, Brie-Comte-Robert, France) positioned lengthwise over the middle of the muscle belly with an interelectrode (centre to centre) distance of 20 mm. The reference electrode was placed on the opposite patella. Low resistance between the two electrodes ( $< 5 \text{ k}\Omega$ ) was obtained by shaving the skin and dirt were removed from the skin using alcohol. EMG signals were amplified with a bandwidth frequency ranging from 10 Hz to 500 Hz (gain = 500), digitised on-line at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge, Biopac Systems Inc, Goleta, USA).

**Evoked contractions.** Both single and double (100 Hz frequency) stimulations were used for assessment of neuromuscular function. Transcutaneous electrically-evoked contractions of the knee extensors muscles were induced using a high-voltage (maximal voltage 400 V) constant-current stimulator (model DS7 modified, Digitimer, Hertfordshire, UK). The femoral nerve was stimulated using a monopolar cathode ball electrode (0.5 cm diameter), pressed into the femoral triangle by the same experimenter during all tests. The site of stimulation producing the largest resting twitch and M-wave amplitudes was located and marked on the skin so that it could be repeated reliably through all the protocol. The anode was a large (10 x 5 cm) rectangular electrode (Compex SA, Ecublens, Switzerland) located in the gluteal fold opposite the cathode. The optimal intensity of stimulation (i.e., that which recruited all knee extensor motor units) was considered to be reached when an increase in the stimulation intensity did not induce a further increase in the amplitude of the twitch force and the peak-to-peak amplitude of the VL M-wave (Place et al., 2005). Once the optimal intensity was found, 130% of this intensity was used and kept constant throughout the session for each subject. The supramaximal intensities ranged from 70 to 140 mA. The stimulus duration was 1 ms and the interval of the stimuli in the doublet was 10 ms. Single stimulus was evoked at rest 3 s before the MVCs to investigate the M-wave of the VL muscle associated with the evoked twitch. Paired stimuli were evoked during (superimposed doublet) and 4 s after the MVC (potentiated doublet) to investigate knee extensors muscle contractile properties and to estimate the VAL using the twitch interpolation technique (Merton, 1954). Methodology and supramaximal intensities are according to previous studies (e.g. (Place et al., 2007)).

**Data analysis.** M-wave peak-to-peak amplitude of the VL muscle was measured during the single stimuli at rest before each MVC. Maximal EMG for the MVC of the VL

muscle was quantified as the root mean square (RMS) value over a 0.5 s interval about the same interval of the MVC torque measurement. Maximal EMG RMS values were then normalised to the M-wave amplitude for the respective muscles to obtain the EMG RMS/M-wave ratio. This normalisation procedure takes into account the changes in the peripheral parameters (neuromuscular transmission-propagation failure and/or changes in impedance) from the EMG recordings (Place et al., 2007). Potentiated doublet peak (Dt) was measured from the peak torque associated with electrical paired stimuli at rest, 4 s after the end of the MVC. MVC was considered as the peak torque attained during the contraction, and maximal voluntary activation level was quantified by measurement of the superimposed torque response to nerve stimulation during the MVC (Allen et al., 1995; Gandevia, 2001). The voluntary activation level (VAL) was estimated according to the formula:

$$\text{VAL} = (1 - \text{superimposed doublet} / \text{potentiated doublet}) \times 100$$

(MVC<sub>at stimulation</sub> / MVC) corresponding to Strojnik and Komi (1998) correction was used if stimulation was not delivered at the MVC torque value. All VAL calculations were performed for a MVC<sub>at stimulation</sub> between 95 and 100% MVC in order to ensure reliability of measurement.

## PSYCHOLOGICAL MEASUREMENTS

**Motivation.** Motivation related to the entire protocol was measured using the success motivation and intrinsic motivation scales developed and validated by (Matthews et al., 2001)[22]. Each scale consists of 7 items (e.g., “I want to succeed on the task” and “I am concerned about not doing as well as I can”) scored on a 5-point scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely). Therefore, total scores for these motivation scales range between 0 and 28.

**Mood.** The Brunel Mood Scale (BRUMS) developed by Terry et al. (2003) was used to quantify current mood (“How do you feel right now?”) before the first and after the final neuromuscular test. This questionnaire contains 24 items (e.g., “angry, uncertain, miserable, tired, nervous, energetic”) divided into six respective subscales: anger, confusion, depression, fatigue, tension, and vigour. The items are answered on a 5-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscale, with four relevant items, can achieve a raw score in the range of 0 to 16. Only scores for the Fatigue and Vigour subscales were considered in this study.

**Subjective workload.** The National Aeronautics and Space Administration Task Load Index (NASA-TLX) rating scale (Hart and Staveland, 1988) was used to assess subjective workload. The NASA-TLX is composed of six subscales: Mental Demand (How much mental and perceptual activity was required?), Physical Demand (How much physical activity was required?), Temporal Demand (How much time pressure did you feel due to the rate or pace at which the task occurred?), Performance (How much successful do you think you were in accomplishing the goals of the task set by the experimenter?), Effort (How hard did you have to work to accomplish your level of performance?) and Frustration (How much irritating, annoying did you perceive the task?). The participants had to score each of the items on a scale divided into 20 equal intervals anchored by a bipolar descriptor (e.g. High/Low). This score was multiplied by 5, resulting in a final score between 0 and 100 for each of the subscales. Participants completed the NASA-TLX after the entire protocol.

## STATISTICAL ANALYSIS

Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. One-way repeated ANOVAs were used to compare subjective workload, motivation and average heart rate across the three conditions. A fully repeated 3 x 2 (condition x time) ANOVA was used to test the effects of the entire protocol on mood. Fully repeated 3 x 10 ANOVAs were used to test the effects of condition and time on MVC torque, VAL, EMG RMS/M-wave ratio (VL muscles), peak torque of the doublet and amplitude of the M-wave (VL muscles). Percentage of errors during both Stroop tasks was analysed with a fully repeated 2 x 9 (condition x time) ANOVA. Significant main effects of time or session, or interactions were followed up with Bonferonni tests as appropriate.

By using predicted effect size provided by Bray et al. (2012) for changes in MVC torque, an a priori power analysis revealed that nine participants would provide 83 % power to detect differences at an  $\alpha$ -level of 0.05. Statistical analyses were conducted using the Statistical Package for the Social Sciences, version 19 for Mac OS X (SPSS Inc., Chicago, IL, USA). A significance level of  $p < 0.05$  was used for all analyses. Cohen's effects size  $f(V)$  and a priori power analysis were calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany). Thresholds for small, moderate and

large effects were set at 0.2, 0.5 and 0.8, respectively. Data are presented as Mean  $\pm$  SD in the text and tables, and Mean  $\pm$  SEM in the figures.

## IV. Results

### MOTIVATION AND MOOD

Intrinsic ( $F_{(1.1, 11.1)} = 1.360$ ,  $p = 0.273$ ,  $f(V) = 0.369$ ) and success ( $F_{(1.1, 11.1)} = 1.360$ ,  $p = 0.168$ ,  $f(V) = 0.465$ ) motivation related to the entire protocol were similar in all conditions (table 3). The mood questionnaire revealed a significant decrease in vigour over time in both conditions ( $F_{(1,9)} = 7.204$ ,  $p < 0.05$ ,  $f(V) = 0.895$ ) with no main effect of condition ( $F_{(2, 18)} = 0.171$ ,  $p = 0.845$ ,  $f(V) = 0.139$ ) or condition x time interaction ( $F_{(1.276, 11.483)} = 0.212$ ,  $p = 0.811$ ,  $f(V) = 0.153$ ) effect. The fatigue subscale of the mood questionnaire presented a condition effect ( $F_{(2, 18)} = 5.580$ ,  $p < 0.05$ ,  $f(V) = 0.787$ ). Follow-up tests revealed that subjects rated fatigue lower in the control condition compared to the moderate mental exertion condition ( $p < 0.05$ ). Neither a main effect of time ( $F_{(1, 9)} = 2.748$ ,  $p = 0.132$ ,  $f(V) = 0.552$ ) nor a condition x time interaction ( $F_{(2, 18)} = 0.212$ ,  $p = 0.132$ ,  $f(V) = 0.503$ ) were found for self-reported fatigue (table 3).

	Motivation		Mood			
	<i>Intrinsic</i>	<i>Success</i>	<i>Fatigue</i>		<i>Vigor</i>	
			Pre	Post	Pre	Post
High mental exertion task	18.7 (4.9)	18.9 (5.0)	1.1 (1.3)	2.9 (4.01)	10.6 (1.7)	8.4 (3.0)
Moderate mental exertion task	18.4 (5.0)	18.9 (3.4)	1.1 (1.2)	3.7 (3.4)	10.7 (1.2)	10.1 (1.6)
Control task	17.7 (6.4)	16.3 (4.3)	0.7 (0.9)	1.5 (2.4)	8.6 (2.1)	8.5 (2.8)

**Table 3 – Motivation and mood for the three experimental conditions.**

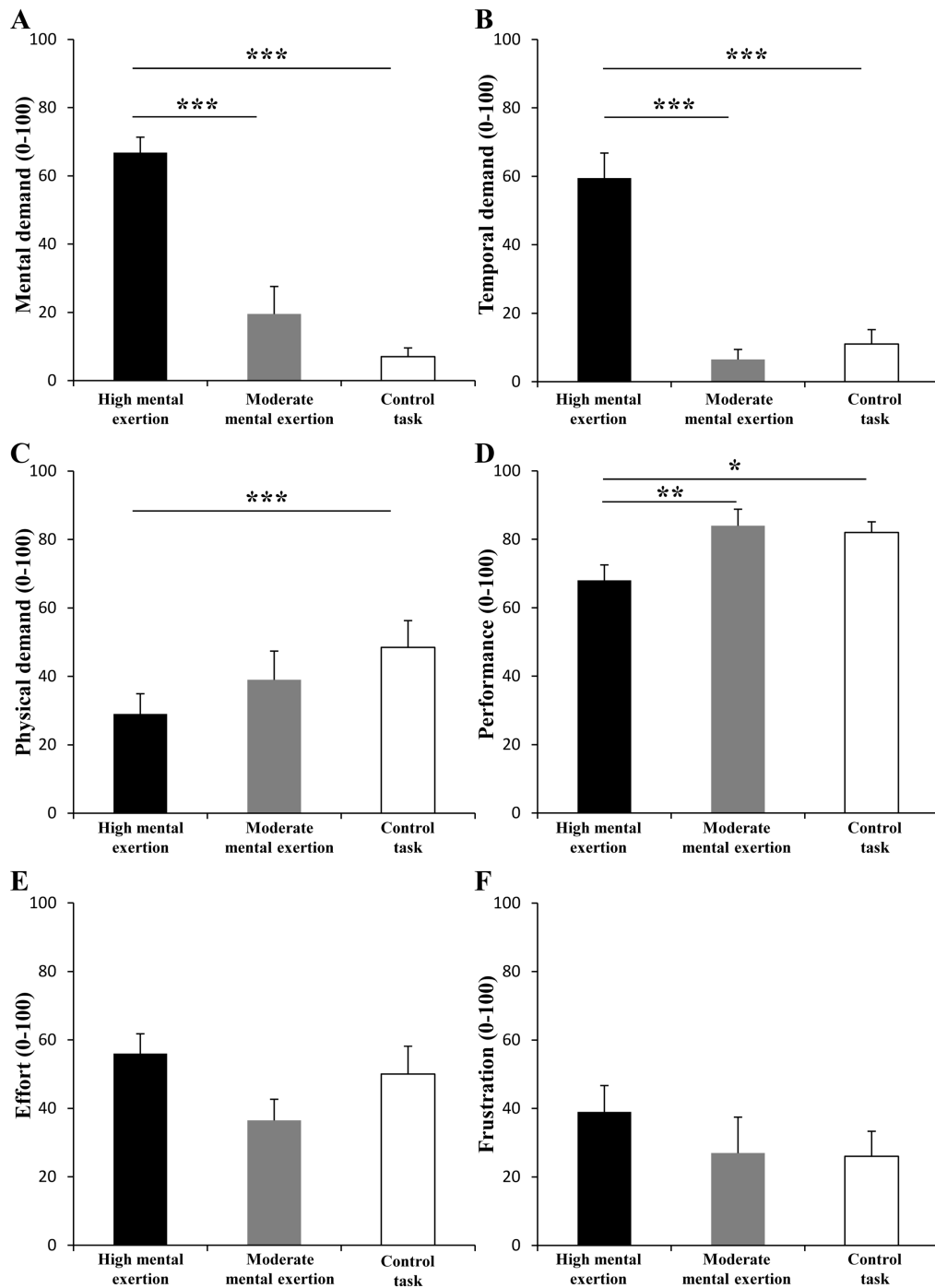
Data are presented as means (SD).

## HEART RATE, SUBJECTIVE WORKLOAD AND COGNITIVE PERFORMANCE

There was a significant main effect of condition on average heart rate ( $F_{(2, 18)} = 9.396$ ,  $p < 0.01$ ,  $f(V) = 1.022$ ). Follow-up tests showed a significantly lower heart rate during the control task ( $69.5 \pm 5.9$  beats/min) compared to during the high mental exertion task ( $81.7 \pm 9.7$  beats/min;  $p < 0.05$ ) and the moderate mental exertion task ( $80.3 \pm 8.7$  beats/min;  $p < 0.05$ ).

The NASA-TLX scale revealed significant main effects of condition for mental demand (figure 21A,  $F_{(2, 18)} = 33.061$ ,  $p < 0.001$ ,  $f(V) = 1.916$ ), temporal demand (figure 21B,  $F_{(1.2, 11.4)} = 43.441$ ,  $p < 0.001$ ,  $f(V) = 2.194$ ), physical demand (figure 21C,  $F_{(2, 18)} = 4.801$ ,  $p < 0.05$ ,  $f(V) = 0.348$ ), performance (figure 21D,  $F_{(2, 18)} = 6.909$ ,  $p < 0.01$ ,  $f(V) = 0.876$ ) and effort (figure 21E,  $F_{(2, 18)} = 4.428$ ,  $p < 0.05$ ,  $f(V) = 0.876$ ). Follow-up tests showed greater scores for mental and temporal demand after the high mental exertion task than after the moderate mental exertion task ( $p < 0.001$ ) and the control task ( $p < 0.001$ ). In addition, participants rated a higher performance during the moderate mental exertion task ( $p < 0.01$ ) and the control task ( $p < 0.05$ ) compared to during the high mental exertion task. Furthermore, participants perceived higher physical demand during the control task than during the high mental exertion task ( $p < 0.05$ ). Finally, subjects tended to rate a higher effort after the high mental exertion task and the control task than after the moderate exertion task ( $p = 0.064$ ,  $p = 0.088$ ). Frustration (figure 21F) was not significantly different between the three conditions ( $F_{(2, 18)} = 1.184$ ,  $p = 0.329$ ,  $f(V) = 0.362$ ).

Percentage of errors was significantly greater during the high mental exertion task ( $9.3 \pm 4.4$  %) than during the moderate mental exertion task ( $0.5 \pm 0.6$  %) (main effect of condition  $F_{(1, 9)} = 42.495$ ,  $p < 0.001$ ,  $f(V) = 2.171$ ). However, there was no main effect of time ( $F_{(8, 72)} = 2.570$ ,  $p = 0.093$ ,  $f(V) = 0.446$ ) nor a condition x time interaction ( $F_{(8, 72)} = 1.778$ ,  $p = 0.096$ ,  $f(V) = 0.444$ ).



**Figure 21 - Effect of mental exertion on subjective workload.**

A: Mental demand. B: Temporal demand. C: Physical demand. D: Performance. E: Effort. F: Frustration. \* and \*\*\*: Significantly different ( $p < 0.05$  and  $p < 0.001$  respectively).

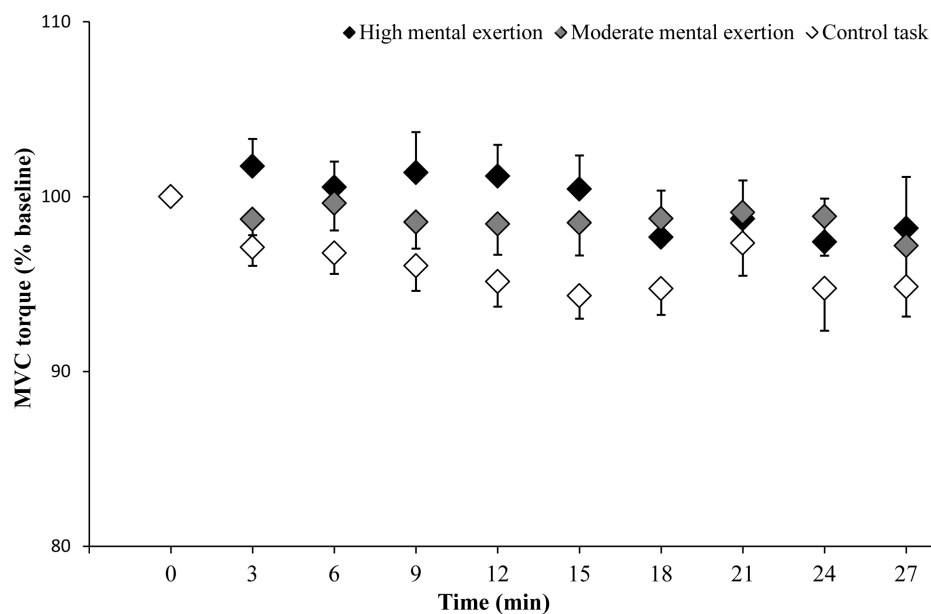
Data are represented as means  $\pm$  SEM.



## NEUROMUSCULAR FUNCTION

MVC torque of the knee extensor muscles (figure 22) showed neither a condition x time interaction ( $F_{(18, 162)} = 1.226$ ,  $p = 0.246$ ,  $f(V) = 0.369$ , observed power of 0.803) nor main effects of time ( $F_{(2.7, 23.9)} = 2.088$ ,  $p = 0.13$ ,  $f(V) = 0.481$ ) and condition ( $F_{(2, 18)} = 0.293$ ,  $p = 0.749$ ,  $f(V) = 0.182$ ).

Maximal muscle activation parameters are shown in table 4. VAL tended to decrease over time in all three conditions ( $F_{(3.7, 42.1)} = 2.570$ ,  $p = 0.061$ ,  $f(V) = 0.534$ ). However, there was neither a main effect of condition ( $F_{(2, 18)} = 0.121$ ,  $p = 0.887$ ,  $f(V) = 0.115$ ) nor a condition x time interaction ( $F_{(18, 162)} = 1.159$ ,  $p = 0.345$ ,  $f(V) = 0.359$ , observed power of 0.773). Similarly, EMG RMS/M-wave ratio for the VL muscle during the MVCs showed no main effect of condition ( $F_{(1.2, 11.2)} = 1.790$ ,  $p = 0.211$ ,  $f(V) = 0.446$ ), no main effect of time ( $F_{(3.2, 28.8)} = 1.728$ ,  $p = 0.181$ ,  $f(V) = 0.438$ ), no condition x time interaction ( $F_{(18, 162)} = 1.314$ ,  $p = 0.267$ ,  $f(V) = 0.381$ ).



**Figure 22 - Maximal voluntary contraction (MVC) torque of the knee extensor muscles during the high mental exertion task (black), the moderate mental exertion task (grey) and the control task (white).**

Data are normalised by the first MVC torque and are represented as means  $\pm$  SEM.

	<b>Time (min)</b>									
	T0	3	6	9	12	15	18	21	24	27
<b>MVC (N.m)</b>										
High mental exertion task	237 (42)	240 (41)	238 (43)	240 (43)	239 (41)	237 (40)	231 (41)	233 (40)	231 (44)	232 (43)
Moderate mental exertion task	239 (33)	236 (35)	237 (30)	235 (33)	235 (33)	234 (31)	235 (33)	237 (37)	236 (38)	232 (37)
Control task	240 (34)	233 (34)	232 (31)	230 (32)	228 (33)	227 (32)	228 (36)	235 (42)	228 (41)	229 (39)
<b>VAL (%)</b>										
High mental exertion task	91.2 (5.6)	91.3 (5.6)	89.9 (6.4)	90.6 (7.4)	90.0 (8.8)	88.3 (8.9)	86.4 (9.7)	87.9 (7.9)	88.2 (8.8)	88.3 (8.4)
Moderate mental exertion task	90.9 (6.6)	88.7 (8.7)	90.0 (5.4)	87.4 (6.2)	90.6 (6.6)	88.9 (6.6)	89.3 (7.2)	88.6 (8.0)	87.8 (6.9)	86.9 (6.9)
Control task	90.8 (5.9)	90.1 (6.1)	89.8 (7.3)	88.9 (6.9)	89.7 (6.6)	89.9 (7.0)	89.1 (6.2)	89.3 (4.6)	88.5 (6.0)	89.2 (4.9)
<b>RMS/M</b>										
High mental exertion task	0.053 (0.011)	0.056 (0.009)	0.051 (0.012)	0.052 (0.014)	0.051 (0.011)	0.050 (0.013)	0.045 (0.010)	0.050 (0.012)	0.050 (0.011)	0.051 (0.010)
Moderate mental exertion task	0.055 (0.012)	0.054 (0.017)	0.055 (0.016)	0.054 (0.020)	0.049 (0.014)	0.051 (0.011)	0.052 (0.013)	0.051 (0.011)	0.047 (0.010)	0.051 (0.011)
Control task	0.058 (0.008)	0.055 (0.011)	0.054 (0.012)	0.053 (0.013)	0.053 (0.010)	0.055 (0.012)	0.055 (0.010)	0.056 (0.011)	0.053 (0.012)	0.058 (0.015)

**Table 4 – Evolution of maximal voluntary contraction (MVC) torque and maximal muscle activation parameters.**

Data are presented as means (SD) for MVC torque, voluntary activation level (VAL) and EMG RMS/M-wave ratio of the vastus lateralis muscle

Peripheral parameters of neuromuscular function are presented table 5. The amplitude of the potentiated doublet remained constant over time in all three conditions ( $F_{(2.5, 22.4)} = 2.427$ ,  $p = 0.101$ ,  $f(V) = 0.519$ ). There was neither a significant main effect of condition ( $F_{(2, 18)} = 0.306$ ,  $p = 0.740$ ,  $f(V) = 0.185$ ) nor a condition x time interaction ( $F_{(18, 162)} = 0.714$ ,  $p = 0.794$ ,  $f(V) = 0.280$ ). Furthermore, M-wave amplitude data for the VL muscle showed no significant main effect of time ( $F_{(1.9, 17.1)} = 2.645$ ,  $p = 0.102$ ,  $f(V) = 0.542$ ), no significant main effect of condition ( $F_{(1.2, 10.4)} = 0.991$ ,  $p = 0.356$ ,  $f(V) = 0.331$ ) and no condition x time interaction ( $F_{(18, 162)} = 0.706$ ,  $p = 0.802$ ,  $f(V) = 0.281$ ).

	<b>Time (min)</b>									
	T0	3	6	9	12	15	18	21	24	27
<b>Potentiated doublet (Nm)</b>										
High mental exertion task	99.8 (17.6)	97.4 (17.9)	96.0 (20.8)	96.1 (19.3)	90.5 (16.4)	93.5 (17.3)	86.6 (18.3)	89.0 (18.1)	91.0 (16.9)	90.2 (15.0)
Moderate mental exertion task	94.7 (21.8)	92.1 (27.6)	93.0 (24.3)	89.7 (25.3)	94.6 (19.2)	91.6 (16.6)	88.5 (15.2)	88.6 (20.1)	89.3 (19.0)	90.6 (17.8)
Control task	95.5 (19.4)	94.2 (20.1)	93.1 (18.8)	93.6 (19.8)	90.9 (21.2)	91.8 (19.5)	90.2 (19.9)	90.9 (19.2)	89.6 (20.0)	89.1 (19.0)
<b>M-wave amplitude (mV)</b>										
High mental exertion task	17.9 (1.3)	18.1 (1.4)	18.0 (1.4)	17.9 (1.3)	17.8 (1.5)	17.8 (1.2)	17.7 (1.3)	17.6 (1.1)	17.6 (1.2)	17.6 (1.3)
Moderate mental exertion task	18.8 (2.2)	18.7 (2.8)	18.8 (2.5)	18.7 (2.6)	18.8 (2.6)	18.7 (2.4)	18.7 (2.4)	18.5 (2.5)	18.5 (2.2)	18.4 (2.5)
Control task	18.1 (1.6)	18.3 (1.7)	18.4 (1.6)	18.3 (1.5)	18.2 (1.6)	17.8 (1.5)	17.7 (1.5)	17.5 (1.5)	17.4 (1.6)	17.5 (1.6)

**Table 5 – Evolution of peripheral parameters of neuromuscular function.**

Data are presented as means (SD) for potentiated doublet and M-wave amplitude of the vastus lateralis muscle.

## V. Discussion

The aim of this study was to test the hypothesis that mental exertion would reduce maximal force production during intermittent MVCs by decreasing maximal muscle activation. Contrary to our hypothesis, neither high mental exertion nor moderate mental exertion altered maximal force production and maximal muscle activation during intermittent MVCs of the knee extensors. These findings demonstrate that the combination of intermittent MVCs and high mental exertion does not reduce the capacity of the CNS to drive to the working muscles.

### MANIPULATION CHECKS AND MOTIVATION

Similarly to Bray et al. (2012), the subjects of the present study rated higher mental and temporal demand after the high mental exertion task compared to the moderate mental exertion and the control tasks. Additionally, we found a higher average heart rate during both high and moderate mental exertion tasks compared to the control task. These

subjective and psychophysiological checks suggest that we were successful in inducing different levels of mental exertion across conditions.

As submaximal effort due to poor motivation can negatively affect measures of maximal force production and maximal muscle activation (Enoka, 1995), we followed Gandevia (2001) six-point guideline to maximise motivation during MVCs: 1) maximal efforts should be accompanied by some instruction and practice, 2) feedback of performance should be given during the MVCs, 3) verbal encouragements should be given, 4) subjects must be allowed to reject efforts that they do not regard as maximal, 5) feedback for repeated MVCs should be updated, and 6) rewards for repeated testing should be considered to ensure consistent motivation between sessions. In our study, points 1 to 5 were respected, and the point 6 was controlled by completion of a motivation questionnaire at the beginning of each session. All subjects presented similar intrinsic and success motivation to perform the entire protocol across all three conditions. Therefore, we are confident that poor motivation did not negatively affect measures of maximal force production and maximal muscle activation in our study.

## **EFFECTS OF MENTAL EXERTION ON MAXIMAL FORCE PRODUCTION AND MAXIMAL MUSCLE ACTIVATION**

It is well known that both mental (Gailliot, 2008; Lorist and Tops, 2003) and physical (Davis et al., 2003; Matsui et al., 2011) exertion have been associated with an increase in brain adenosine and a reduction in brain glycogen. Therefore, our hypothesis was that high mental exertion would induce a significant decrease in maximal force production during intermittent MVCs by reducing the capacity of the CNS to drive the working muscles. Contrary to our hypothesis, we found that high mental exertion did not induce a further decrease in torque and maximal muscle activation during intermittent MVCs of the knee extensors. The present findings support those of Pageaux et al. (2013) and Bray et al. (2008) who showed that short (3 min 40 s of incongruent Stroop task) or prolonged (90 min of the AX-Continuous Performance Task) mental exertion did not alter MVC torque and maximal muscle activation of both upper and lower limbs muscles. Indeed, torque, VAL and EMG RMS/M-wave ratio during MVCs remained constant over time even in the high mental exertion condition. Taken all together, these results suggest that mental exertion does not reduce the capacity of the CNS to drive the working muscles.

The most plausible explanation for the lack of interaction between mental exertion involving response inhibition and maximal muscle activation is that these CNS functions involve different brain areas (Pageaux et al., 2013). Indeed, functional magnetic resonance imaging studies showed that central fatigue during index finger abduction exercise is associated with decrease in activation of the supplementary motor area and to a lesser extent, in parts of the paracentral gyrus, right putamen and in a small cluster of the left parietal operculum (van Duinen et al., 2007). Interestingly, none of these brain areas are significantly associated with mental exertion involving response inhibition. This cognitive process is significantly associated with activity of the pre-supplementary motor area and the anterior cingulate cortex (Mostofsky and Simmonds, 2008). Therefore, it is neurobiologically plausible that the differentiation in brain areas involved in response inhibition and maximal muscle activation could explain why mental exertion does not reduce the capacity of the CNS to drive the working muscles. However, other neurophysiological techniques have to be used to assess brain activation during both mental and physical exertion (Mauger, 2013). Thus, prefrontal cortex activity could be assessed by near infra-red spectroscopy (Derosière et al., 2013), as its activity increases along with the perception of effort (Berchicci et al., 2013) and the level of physical performance (Mandrick et al., 2013).

## **MENTAL EXERTION AND PERIPHERAL FATIGUE**

Contrary to the present study, Bray et al. (2012) observed a significant decrease in maximal force production during intermittent MVCs. In addition to poor motivation exacerbated by high mental exertion, another possible explanation for the results of Bray et al. (2012) is the presence of peripheral fatigue induced by the incongruent Stroop task. Recent studies on the upper limb suggest that mental exertion could induce an earlier onset of peripheral fatigue on shoulder muscles (Mehta and Agnew, 2012). This is supported by an activation of the trapezius muscle when handgrip squeeze is performed in the same time of a shoulder abduction in interaction with mental exertion (MacDonell and Keir, 2005). This activation of the trapezius muscle or forearm muscles (Waersted and Westgaard, 1996; Laursen et al., 2002) could be due to holding the sheets (paper-based Stroop task), or selecting the correct responses with a keyboard or a mouse (computer-based Stroop task).

We avoided these confounding effects of the Stroop task by testing maximal muscle activation of the knee extensor muscles, not functionally connected with muscle

affected by combined mental and physical exertion (e.g. shoulder muscles). Indeed, in the present study, both resting evoked contraction and M-wave amplitude remained constant during the 27 minutes of combined mental exertion and intermittent MVCs of the knee extensors. These results demonstrate that the three minutes intervals between MVCs were sufficient to avoid any exercise-induced peripheral fatigue, and that the Stroop task did not significantly affect the knee extensors neuromuscular function.

Although the results of Bray et al. (2012) may be explained by poor motivation of their subjects and the peripheral fatigue induced by the Stroop task, it has to be acknowledged that the effects of mental exertion on intermittent MVCs could differ between upper and lower limbs. However, this differentiation between upper and lower limbs is unlikely. Indeed, previous studies demonstrated that upper limb (Bray et al., 2008), lower limb (Pageaux et al., 2013) and whole-body endurance performance (Marcora et al., 2009; Pageaux et al., 2014) are impaired by mental exertion.

## LIMITS AND CONCLUSION

Despite a small sample size, the statistical power in this study for the interaction effect (the investigated effect) reached an acceptable level of 0.8 (Cohen, 2013). Furthermore, it has to be noticed that all large effects sizes (calculated with  $f(V)$ ) successfully reached significance. Finally, the control condition presented the greater decrease in MVC torque (high mental exertion: -2.1 %; moderate mental exertion: -2.9 %; control condition: -4.6 %), suggesting that, if a Type II error were present, the negative effect on force production capacity occurred during the control condition and not during the high mental exertion condition. Therefore, it is unlikely that mental exertion reduces the ability of the CNS to recruit the active muscles.

From a psychobiological point of view, the present study suggests that mental exertion does not alter maximal muscle activation. From an applied point of view, these findings combined with previous observations on upper and lower limbs (Bray et al., 2008; Pageaux et al., 2013) indicate that mental exertion does not reduce maximal force production. Therefore, unlike endurance tasks (Marcora et al., 2009; Pageaux et al., 2013), physical tasks requiring high level of force should not be negatively affected by mental exertion.

***PART II: PERIPHERAL  
MANIPULATIONS OF  
PERCEIVED EXERTION***

**CHAPTER 1: HIGH-INTENSITY ONE-LEG DYNAMIC EXERCISE: A  
RELIABILITY STUDY TO ASSESS ENDURANCE PERFORMANCE AND  
DESCRIBE ISOKINETIC FATIGUE**

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**To be submitted in** European Journal of Applied Physiology



## **I. Abstract**

Recently, high intensity one leg dynamic exercise (OLDE) has been used to investigate central nervous system processes involved in regulation of muscle fatigue and exercise performance. However, the reliability of OLDE time to exhaustion tests and the isokinetic fatigue induced by high intensity OLDE and its recovery still need to be determined. Eight subjects performed three time to exhaustion tests (right leg) at 85% of peak power output with isokinetic maximal voluntary contraction (MVC) at 60, 100 and 140 °/s measured pre-exercise, shortly after exhaustion (13±4s), 20s (+20) and 40s post exhaustion (+40) test. Electromyographic (EMG) signal was analysed via the root mean square (RMS) for all three superficial knee extensors. Mean time to exhaustion was 5.96±1.40 min, coefficient of variation was 8.42±6.24% and intraclass correlation was 0.795. MVC decreased after exhaustion for all contraction speeds (all  $P < 0.001$ ). MVC at 60 and 100 °/s recovered between +20 ( $P < 0.05$ ) and exhaustion and then plateaued. MVC at 140 °/s recovered only at +40 ( $P < 0.05$ ). High intensity OLDE did not alter EMG RMS of the three superficial knee extensors during MVC. The results of this study demonstrate that high intensity OLDE could be used as a reliable new model to measure endurance performance. Furthermore, our data suggest that to appreciate its full extent, muscle fatigue induced by high intensity OLDE should be measured within ~30s post exhaustion, and that EMG RMS remains stable despite presence of exercise induced-muscle fatigue.

## **II. Introduction**

Endurance performance (i.e. exercise duration  $> 1$ min) is generally studied in Exercise Sciences using cycling and/or running exercise (e.g. Millet and Lepers, 2004; Marcora et al., 2008; Amann, 2011; Pageaux et al., 2014). Despite being close to real competition events by involving the whole-body, the use of cycling and/or running exercise present some important limitations in understanding the role of the central nervous system (CNS) in regulation of muscle fatigue and endurance performance. Indeed, as whole-body exercise involves greater systemic responses to the exercise than isolated exercise (Sidhu et al., 2013) , it is difficult to perform some specific experimental

manipulations which aim to understand CNS processes regulating muscle fatigue and endurance performance (e.g. manipulation of III-IV muscle afferents; Amann et al., 2011b; Dempsey et al., 2013). Furthermore, due to the need to transfer the participant from the treadmill/bicycle to the dynamometer, the true extent of muscle fatigue (i.e. determinant of endurance performance; Marcora et al., 2008) at exhaustion is underestimated (Pageaux et al., submitted), leading to inconclusive results on how peripheral (i.e. fatigue produced by changes at or distal to the neuromuscular junction; Gandevia, 2001) and central (i.e. decrease in maximal voluntary activation level, VAL; Gandevia, 2001) components of muscle fatigue might interact between each other (for review see Gandevia, 2001; Amann, 2011). Therefore, due to the aforementioned limitations, it is crucial to develop an exercise model allowing investigation of the CNS processes regulating endurance performance.

Around thirty years ago, Andersen et al. (1985) developed a novel exercise model (i.e. one leg dynamic exercise, OLDE) allowing dynamic isotonic contractions of the knee extensor muscles. This exercise model isolates the knee extensor muscles via an active knee extension and passive knee flexion, and due to the reduced muscle mass involved, this exercise is not limited by cardiorespiratory function (Rossman et al., 2014). Therefore, this model was extensively used to investigate the effect of OLDE on the cardiorespiratory system (e.g. Strange, 1999), skeletal muscle physiology (e.g. Bangsbo et al., 1993) but also with patients suffering from cardiorespiratory limitations (Rossman et al., 2013a; Rossman et al., 2013b) or for studying mechanisms regulating circulatory response to rhythmic dynamic exercise (Amann et al., 2011b; Garten et al., 2014). More recently, high intensity OLDE has been used to investigate CNS processes involved in regulation of muscle fatigue and exercise performance (Rossman et al., 2012; Amann et al., 2013; Rossman et al., 2014). Thus, as OLDE seems to be an adequate model to investigate endurance performance without being limited by cardiorespiratory function, its use might be of particular interest for researchers aiming to understand how the CNS regulates the development of muscle fatigue and endurance performance.

When performed at high intensity until exhaustion, OLDE has been shown to induce both peripheral and central fatigue (Rossman et al., 2012; Amann et al., 2013; Rossman et al., 2014). However, as the exercise performed in these studies did not take place on the same ergometer where neuromuscular function was tested, the extent of peripheral and central fatigue immediately after exhaustion remained unclear. To avoid the need to transfer the participant from the exercising ergometer to the dynamometer (to assess muscle fatigue), we recently developed in our laboratory an OLDE exercise on a

dynamometer, reducing the time delay between cessation of the exercise and start of neuromuscular testing (Pageaux et al., submitted). In this study, we demonstrated that both peripheral and central fatigue significantly recovered between exhaustion and after three minutes, but also that high intensity exhaustive OLDE alters cortical and spinal excitability. Nevertheless, even though muscle fatigue induced by OLDE being fully described, to date, the reliability of this new protocol to measure endurance performance remains unknown. Furthermore, previous studies describing muscle fatigue induced by high intensity exhaustive OLDE focused only on isometric fatigue (i.e. measured during isometric contractions) and did not describe the extent of isokinetic fatigue (i.e. measured during isokinetic contractions) and its recovery.

The aims of the present study were to assess the reliability of exhaustive high intensity OLDE to measure endurance performance, and to describe the isokinetic fatigue and its recovery induced by exhaustive high intensity OLDE. We firstly hypothesised that exhaustive high intensity OLDE would present a sufficient reliability to investigate endurance performance. Secondly, we hypothesised that isokinetic fatigue would quickly recover, emphasising the need to use an exercise model allowing a short time delay to assess neuromuscular function.

### **III. Methods**

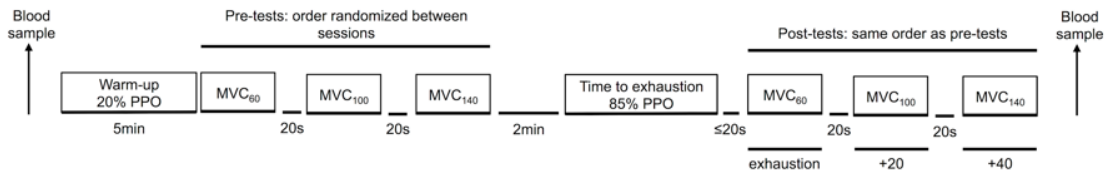
#### **SUBJECTS AND ETHICAL APPROVAL**

Eight healthy and moderately active adults (mean  $\pm$  SD; age:  $22 \pm 2$  yrs, height:  $171 \pm 8$  cm, weight:  $69 \pm 8$  kg, 5 males and 3 females) volunteered to participate in this study. None of the subjects had any known mental or somatic disorder. Each subject gave written informed consent prior to the study. Experimental protocol and procedures were approved by the local Ethics Committee of the School of Sport and Exercise Sciences, University of Kent at Medway. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008). All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants.

## EXPERIMENTAL PROTOCOL

The main aim of this study was to test the reliability of a one-leg dynamic exercise (OLDE) time to exhaustion test performed at high intensity (workload fixed at 85% peak power output, Deschenes, 2013). Neuromuscular isokinetic fatigue and its recovery up to 40 s post exhaustion test was also measured. Subjects visited the laboratory on four different days. During the first visit, subjects were familiarised with the OLDE (see *One Leg Dynamic Exercise* for more details), and performed after 30 min recovery an incremental test to measure peak power output. After 30 min recovery following the incremental test, subjects were familiarised with MVC testing (see *Neuromuscular Function Tests* for more details) and the time to exhaustion test. As suggested by Andersen et al. (1985), torque and electromyographic (EMG) feedback were used during the familiarisation exercise to ensure a quick and reliable familiarisation to the OLDE. The three following visits (experimental sessions) consisted of completing the time to exhaustion test with neuromuscular testing pre- and post-exercise. An overview of the three experimental sessions can be seen in figure 23.

Each experimental session took place on a Monday, Wednesday and Friday morning at the same time. All subjects 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. Finally, subjects were instructed to consume a set breakfast (2 slices of toast spread with margarine or butter, 250 ml of orange juice, and a banana) 1 h before all testing sessions. 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.



**Figure 23 – An overview of the experimental protocol**

Pre and post isokinetic maximal voluntary contraction (MVC) of the knee extensors (KE) tests were randomised between sessions (60-100-140 °/s, 100-140-40 °/s or 140-60-100 °/s). Please note that one isometric MVC of the knee flexors was also performed pre and post exercise, 20 s following completion of the last KE MVC. Post-tests were performed either shortly after exhaustion (13±4 s), 20 s following exhaustion (+20) or 40 s following exhaustion (+40).

## ONE LEG DYNAMIC EXERCISE

**Model Development.** OLDE and neuromuscular function tests were performed on a Cybex NORM isokinetic dynamometer (CMSi, Computer Sports Medicine Inc., Stoughton, USA). The axis of the dynamometer was aligned with the knee axis, and the lever arm was attached to the shank with a strap. Two shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. Full description of the OLDE model can be found in (Pageaux et al., submitted). Briefly, this exercise model allows isolating the knee extensor muscles during a dynamic exercise involving an active isotonic knee extension (from 90 ° to 10 °, 0 ° = knee fully extended) and a passive knee flexion. The passive flexion speed was set up at 300 °/s automatically cushioned by the dynamometer for safety purposes. Due to this cushion, the passive knee flexion speed was ~180°/s. According to a previous study (Pageaux et al., submitted), a cadence of 50 contractions per minute (cpm) was chosen (knee extension speed ~106 °/s). Power output produced by the subject was controlled according to the formula:

$$P = T \times \theta$$

$P$  corresponds to the power expressed in watts (W),  $T$  the torque in newton meters (N·m) and  $\theta$  the angular speed in rad/s.

**Incremental test.** After familiarisation, a preliminary OLDE incremental test was performed until exhaustion to measure peak power output. For males, the incremental test started with the isotonic resistance set at 4 N·m (~7.4 W) for 1 min, and increased each minute by 3 N·m (~4.5 W) to exhaustion. For females, the isotonic resistance was set up at 4 N·m (~7.4 W) for 1 min and increased each minute by 2 N·m (~3.7 W). Exhaustion was

defined as either volitional disengagement from the exercise, or a decrease in cadence below 40 cpm for a duration  $\geq 10$  s.

**Time to exhaustion test.** After 5 min warm up at 20% of peak power output, subjects performed a time to exhaustion at 85% of peak power output. Exhaustion was defined as either volitional disengagement from the exercise or a decrease in cadence below 40 cpm for a duration  $\geq 10$  s.

## PHYSIOLOGICAL AND PERCEPTUAL MEASUREMENTS

**Heart rate.** Heart rate was monitored at the end of each minute during the incremental test and every 30 s during all time to exhaustion tests using a heart rate monitor (Polar RS400, Polar Electro Oy, Kempele, Finland). Heart rate was also monitored immediately at exhaustion of the incremental and time to exhaustion tests.

**Blood lactate and glucose concentrations.** A 10  $\mu$ l sample of capillary blood was taken from the left thumb pre-exercise (before the warm-up) and after the last MVC (post-exercise) to measure blood lactate and glucose concentrations (Biosen, EFK Diagnostics, London, England).

**Effort.** Perception of effort, defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (Marcora 2010b), was measured during the incremental test (at the end of each minute) and during the time to exhaustion tests (at the end of the warm-up and every 30 s) using the 15 points RPE scale (Borg 1998). Standardised instructions for the scale were given to each subject before the warm-up. Briefly, subjects were asked to rate how hard they were driving their leg during the exercise (leg RPE, Pageaux et al., 2013). Subjects were also asked to not use this rating as an expression of leg muscle pain (i.e., the intensity of hurt that a subject feels in his quadriceps muscles only).

**Leg muscle pain.** Leg muscle pain, defined as “the intensity of hurt that a subject feels in his quadriceps muscles only” (O' Connor and Cook, 2001), was measured during the incremental test (at the end of each minute) and during the time to exhaustion tests (at the end of the warm-up and every 30 s) using the Cook scale (O' Connor and Cook, 2001). Standardised instructions for the scale were given to each subject before the warm-up. Briefly, subjects asked to rate the feelings of pain specifically in their quadriceps and not to report other pains they may have experienced (e.g., seat discomfort). Subjects were also

asked to not use this rating as an expression of exertion (i.e., how hard they were driving their leg).

**EMG.** EMG of the vastus lateralis (VL), rectus femoris (RF), vastus medialis (VM) and biceps femoris was recorded with pairs of silver chloride circular (recording diameter of 10 mm) surface electrodes (Swaromed, Nessler Medizintechnik, ref 1066, Innsbruck, Austria) with an interelectrode (center-to-center) distance of 20 mm. Recording sites (belly of each muscle, as distal as possible from the hips when the subject was asked to contract his quadriceps at a knee angle of 10 °) were then carefully adjusted at the beginning of each testing session (electrode placement was drawn on the skin with permanent marker to ensure reproducibility of the recording site). Low resistance between the two electrodes (< 5 k $\Omega$ ) was obtained by shaving the skin, and any dirt was removed from the skin using alcohol swabs. The reference electrode was attached to the patella of the right knee. Myoelectrical signals were amplified with a bandwidth frequency ranging from 10 Hz to 500 Hz (gain: VL=500; RF and VM=1000), digitised on-line at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems, Biopac Systems Inc., Goleta, USA). Due to the pressure of the thigh on the dynamometer chair, the biceps femoris EMG signal quality was impaired (e.g. numerous artefacts, problems with electrodes) and therefore not analysed.

The EMG signals were filtered with a Butterworth band pass filter (cutoff frequencies 20 and 400 Hz). Then, the root mean square (RMS), a measure of EMG amplitude, was automatically calculated with the software. During the incremental test, the EMG RMS was averaged for the last 5 EMG bursts of each step (at the end of each minute) and at exhaustion. During the time to exhaustion tests, the EMG RMS was averaged for the last 5 EMG bursts prior each time point measurement (10, 20, 30, 40, 50, 60, 70, 80, 90 and 100% of the time to exhaustion). EMG RMS of each muscle during the time to exhaustion tests was normalised by the maximal EMG RMS of the respective muscle obtained during the pre-exercise MVC performed at 100 %/s. During the MVCs, maximal EMG RMS was averaged over a range of 20 ° extension ( $\pm 10$  °) around the peak torque.

## NEUROMUSCULAR FUNCTION TESTS

Neuromuscular function tests were performed pre and post-exercise to quantify neuromuscular fatigue. As previous studies (Rossman et al., 2012; Amann et al., 2013; Rossman et al., 2014; Pageaux et al., submitted) documented the extent of isometric neuromuscular fatigue induced by OLDE, we chose to focus only on isokinetic neuromuscular fatigue. Therefore, KE MVCs were performed at 60 (MVC<sub>60</sub>), 100 (MVC<sub>100</sub>, OLDE performed  $\sim 106$  °/s) and 140 (MVC<sub>140</sub>) °/s pre (after the warm-up) and post-exercise ( $13 \pm 4$ s after exhaustion). Subjects were asked to perform two maximal isokinetic knee extensions at each speed (starting position corresponded to knee angle at 90 °; range of motion was the same as the OLDE). The highest peak torque values of the two trials were considered, and a 20 s recovery was set between each set of KE MVCs. The order of contractions was randomised between sessions (as follows: 60-100-140 °/s, 100-140-60 °/s or 140-60-100 °/s) and identical for testing pre and post-exercise of the same session. Randomisation was performed with the three contractions order previously mentioned in order to obtain MVC measurement at exhaustion, +20 and +40 for each contraction speed. Therefore we obtained a time course of KE MVC recovery following the time to exhaustion: shortly after exhaustion ( $13 \pm 4$ s after exhaustion), 20s following exhaustion test (+20) and 40s following exhaustion test (+40). An overview of timing can be found in figure 23. Twenty seconds after completion of the last KE MVC, a maximal MVC of the knee flexors was performed (KF MVC). Visual feedback and strong encouragement were provided for each MVC.

***Mechanical recordings.*** The torque signal was recorded using the same dynamometer as for the OLDE (Cybex NORM isokinetic dynamometer, CMSi, Computer Sports Medicine Inc., Stoughton, USA). During the tests a two shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. Torque signal was digitized on-line at a sampling frequency of 1 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems, Biopac Systems Inc., Goleta, USA). The torque signal was filtered prior to data analysis (Butterworth low-pass filter at 100 Hz).



## STATISTICAL ANALYSIS

All data are presented as means  $\pm$  standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. For reliability statistics, assumptions of homoscedasticity and heteroscedasticity were checked as appropriate. Reliability analysis was conducted following the guidelines provided by Atkinson and Nevill (1998):

**Incremental test.** One way repeated ANOVAs (time: isotime from first to seventh minute and exhaustion) were used to test the time course of EMG RMS of all muscles, leg RPE, leg muscle pain and HR. Significant effect of time was explored with planned comparison (1<sup>st</sup> minute vs other time points, exhaustion vs other time points) and adjusted with a Holm-Bonferonni correction.

**Time to exhaustion.** One way repeated ANOVA was used to compare time to exhaustion between sessions (S1, S2 and S3). Reliability was calculated with the intraclass correlation (ICC) model (3,1). Time to exhaustion data were heteroscedastic, therefore we also calculated the coefficient of variation (CV) for each subject as follow:  $CV=100 \times (SD \text{ of the three measurements}) / (\text{mean of the three measurements})$ . Mean CV for all subjects was also calculated. Bland and Altman's 95% limits of agreement were also used (calculated for S1 vs S2, S1 vs S3 and S2 vs S3). As data were heteroscedastic, both raw data and log transformed Bland and Altman's plots are presented. Limit of agreement ratio (LOA) was also calculated from the log transformed data as follows:  $LOA=(1.96 \times SD_{diff} / \text{grand mean}) \times 100$ ; where "SD<sub>diff</sub>" represents the SD of the differences between tests (S1 vs S2, S1 vs S3, S2 vs S3) and "grand mean" represents  $(\text{mean S1} + \text{mean S2} + \text{mean S3}) / 3$ .

Time course of normalised EMG RMS for all muscles was analysed with fully repeated measures 3 (session) x 10 (time: from 10 to 100% of time to exhaustion) ANOVA. Fully repeated measures 3 (session) x 11 (time: warm-up and from 10 to 100% of time to exhaustion) ANOVAs were used to analyse the time course of leg RPE, leg muscle pain, HR and cadence. Significant effect of time was explored with planned comparison (10% vs other time points, 100% vs other time points) and adjusted with a Holm-Bonferonni correction.

Changes in blood lactate and glucose concentration was analysed with fully repeated measures 3 (session) x 2 (time: pre and post exercise) ANOVA.

As the time to exhaustion did not differ between sessions, only main effects of time are reported for each analysis.

**Neuromuscular tests.** One way repeated ANOVA was used to compare pre-exercise neuromuscular values between sessions (S1, S2 and S3). Reliability data was calculated for pre-exercise neuromuscular parameters only. Indeed, due to randomisation of KE MVCs speed order, the difference in recovery between sessions for each parameter does not allow to assess reliability of these parameters on fatigued muscles. Reliability was calculated with the intraclass correlation (ICC) model (3,1). Standard error of measurement (SEm) was calculated as follows for homoscedastic data:  $SEm = SD \times \sqrt{1 - ICC}$ . For heteroscedastic data mean CV is presented.

As no pre-exercise (pre) neuromuscular parameters differed between sessions (except EMG RMS RF at 60 °/s), all pre-exercise parameters (except EMG RMS RF at 60 °/s) were averaged. Neuromuscular parameters were then analysed with a one-way repeated measures ANOVA (time: pre, exhaustion, +20 and +40). Significant effect of time was explored with planned comparison (pre vs exhaustion, exhaustion vs +20, +20 vs +40) adjusted with Holm-Bonferonni correction. Cohen's effect size  $f(V)$  was also calculated.

Changes in KF MVC was analysed with fully repeated measures 3 (session) x 2 (time: pre and post exercise) ANOVA. As the time to exhaustion did not differ between sessions, only main effect of time is reported.

Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 20 for Mac OS X (SPSS Inc., Chicago, IL, USA). Cohen's effects size  $f(V)$  was calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany).

## **IV. Results**

### **INCREMENTAL TEST**

Incremental test duration ranged from 7.0 to 11.3 min ( $9.8 \pm 1.6$  min). Peak power output ranged from 30 to 56 W ( $42 \pm 11$  W). Physiological, psychological and EMG responses to the incremental test are presented table 6. All parameters increased over time (all  $P < 0.009$ ) and planned comparison are presented table 6.

	Isotime (min)							Exhaustion
	1	2	3	4	5	6	7	
<b>Perceptual responses</b>								
Leg RPE (Borg scale)	8.5 <sup>SSS</sup> (1.9)	10.2 <sup>SSS**</sup> (2.3)	11.4 <sup>SS**</sup> (2.8)	12.4 <sup>SS**</sup> (3.0)	13.4 <sup>SS**</sup> (3.4)	14.3 <sup>SS**</sup> (3.2)	15.1 <sup>SS**</sup> (3.5)	19.8 <sup>***</sup> (0.5)
Leg muscle pain (Cook scale)	0.4 <sup>SSS</sup> (0.6)	1.4 <sup>SSS*</sup> (1.2)	2.0 <sup>SSS**</sup> (1.3)	2.6 <sup>SS**</sup> (1.7)	3.0 <sup>SS*</sup> (1.8)	3.7 <sup>S*</sup> (2.3)	4.6 <sup>S**</sup> (2.7)	8.2 <sup>***</sup> (2.0)
HR (beats/min)	93.9 <sup>SSS</sup> (14.2)	98.5 <sup>SSS</sup> (15.0)	105.3 <sup>SSS*</sup> (18.4)	110.8 <sup>SSS*</sup> (24.5)	117.4 <sup>SS*</sup> (27.6)	122.1 <sup>S*</sup> (34.4)	128.8 <sup>S**</sup> (34.6)	146.4 <sup>***</sup> (26.7)
<b>EMG RMS</b>								
VL (mV)	0.096 <sup>SS</sup> (0.030)	0.109 <sup>S</sup> (0.012)	0.123 <sup>S</sup> (0.050)	0.127 <sup>S</sup> (0.055)	0.052 <sup>SS</sup> (0.093)	0.175 (0.136)	0.175 (0.088)	0.231 <sup>**</sup> (0.090)
RF (mV)	0.073 <sup>S</sup> (0.026)	0.089 <sup>S</sup> (0.028)	0.096 (0.033)	0.096 (0.031)	0.109 (0.037)	0.128 (0.040)	0.128 (0.041)	0.165 <sup>*</sup> (0.051)
VM (mV)	0.085 <sup>S</sup> (0.014)	0.099 <sup>S*</sup> (0.013)	0.110 (0.016)	0.113 (0.019)	0.126 (0.026)	0.141 (0.037)	0.144 (0.032)	0.196 <sup>*</sup> (0.041)
KE (mV)	0.255 <sup>SS</sup> (0.048)	0.297 <sup>S*</sup> (0.055)	0.328 <sup>S</sup> (0.103)	0.336 <sup>S</sup> (0.115)	0.387 <sup>S</sup> (0.174)	0.437 (0.244)	0.448 <sup>*</sup> (0.175)	0.593 <sup>**</sup> (0.194)

**Table 6 - Time course of perceptual responses and EMG root mean square (EMG RMS) during the incremental test.**

EMG RMS was measured for the following muscles: vastus lateralis (VL), rectus femoris (RF), vastus medialis (VM) and the overall knee extensors (KE; sum VL, RF and VM). Data are presented as mean (SD). HR = heart rate. Isotime corresponds to the time completed by all subjects prior to exhaustion. \* significantly different from first minute, <sup>S</sup> significantly different from exhaustion, 1 item for P<0.05, 2 items for P<0.01 and 3 items for P<0.001.

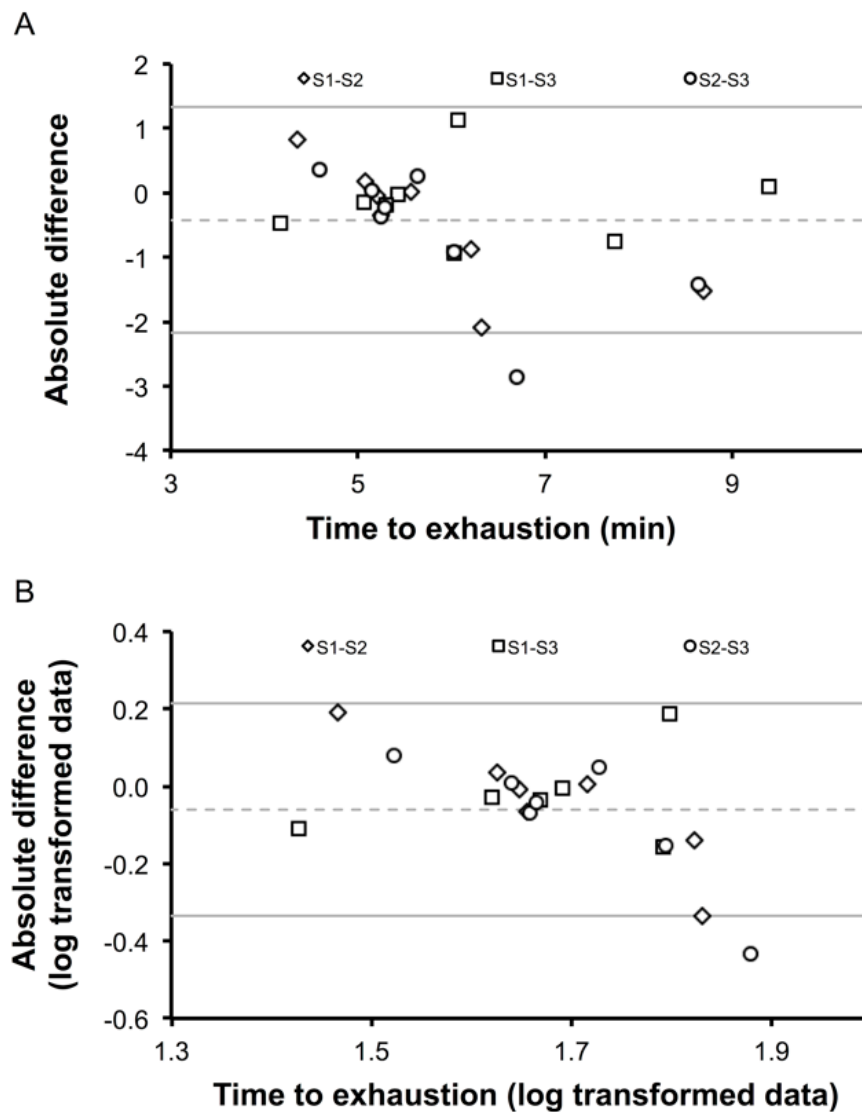
## TIME TO EXHAUSTION TESTS

**Reliability analysis.** Individual and group time to exhaustion duration are presented in table 7. Time to exhaustion duration ranged from 3.94 to 9.44 min (S1: 6.07 ± 1.71 min, S2: 5.59 ± 0.99 min, S3: 6.23 ± 1.68 min) and did not differ between sessions (P=0.156). Individual and group CV are presented in table 7 and ICC=0.795 (0.493,0.950). Bland-Altman plots for raw and log transformed data are presented in figure 24. LOA ratio was also calculated and LOA=15.59.

**Table 7 - High-intensity one-leg dynamic exercise (85% peak power output) time to exhaustion and coefficient of variation (CV).**

One-way repeated ANOVA revealed no difference between sessions ( $p=0.156$ ). Intraclass correlation coefficient (95% confidence interval) model (3,1) = 0.795 (0.493,0.950). Mean (SD) and individual data are presented.

Subjects	Time to exhaustion (min)			Mean	CV (%)
	Session 1	Session 2	Session 3		
<b>1</b>	5.41	5.07	5.44	5.31	3.90
<b>2</b>	5.22	5.18	5.40	5.26	2.22
<b>3</b>	4.99	5.17	5.13	5.10	1.94
<b>4</b>	6.64	5.77	5.50	5.97	9.98
<b>5</b>	9.44	7.93	9.34	8.91	9.49
<b>6</b>	3.94	4.77	4.41	4.37	9.43
<b>7</b>	7.37	5.28	8.13	6.92	21.33
<b>8</b>	5.55	5.57	6.49	5.87	9.08
<b>Mean</b>	<b>6.07 (1.71)</b>	<b>5.59 (0.99)</b>	<b>6.23 (1.68)</b>	<b>5.96 (1.40)</b>	<b>8.42 (6.24)</b>

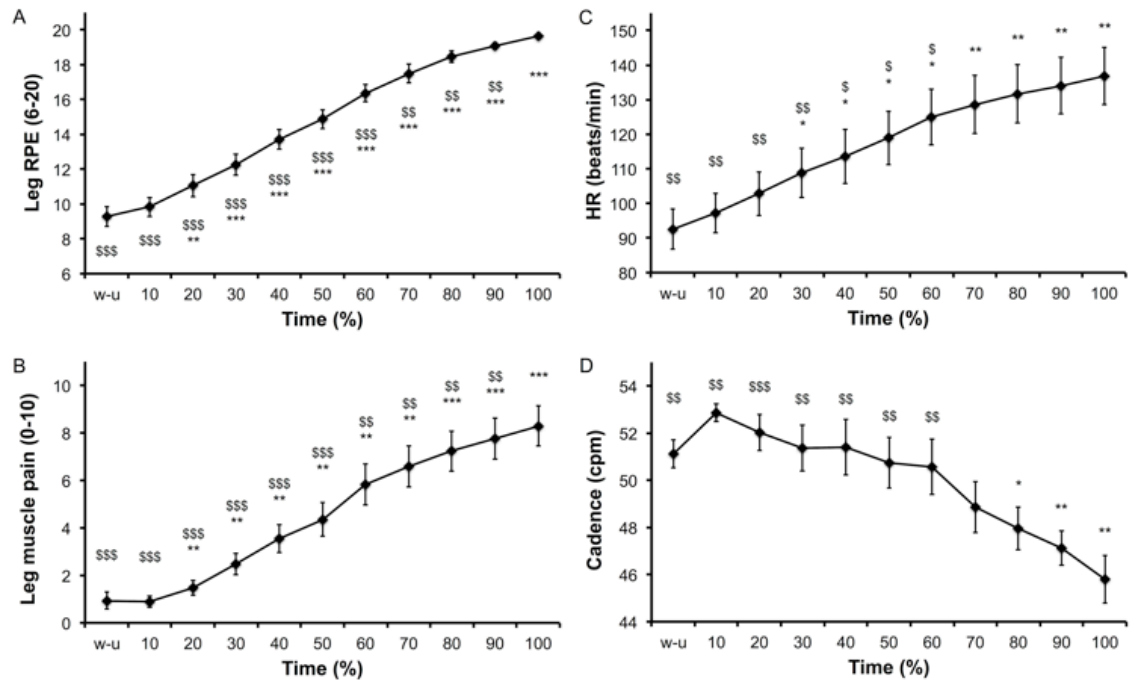


**Figure 24 - Bland Altman plots (raw data, panel A; log transformed data, panel B) for the time to exhaustion tests.**

The differences between sessions (S; S1-S2, S1-S3, S2-S3) are plotted against each individual's mean of the respective two tests. As data were heteroscedastic, limits of agreement ratio (LOA) was also calculated from the log transformed data (LOA=15.59).

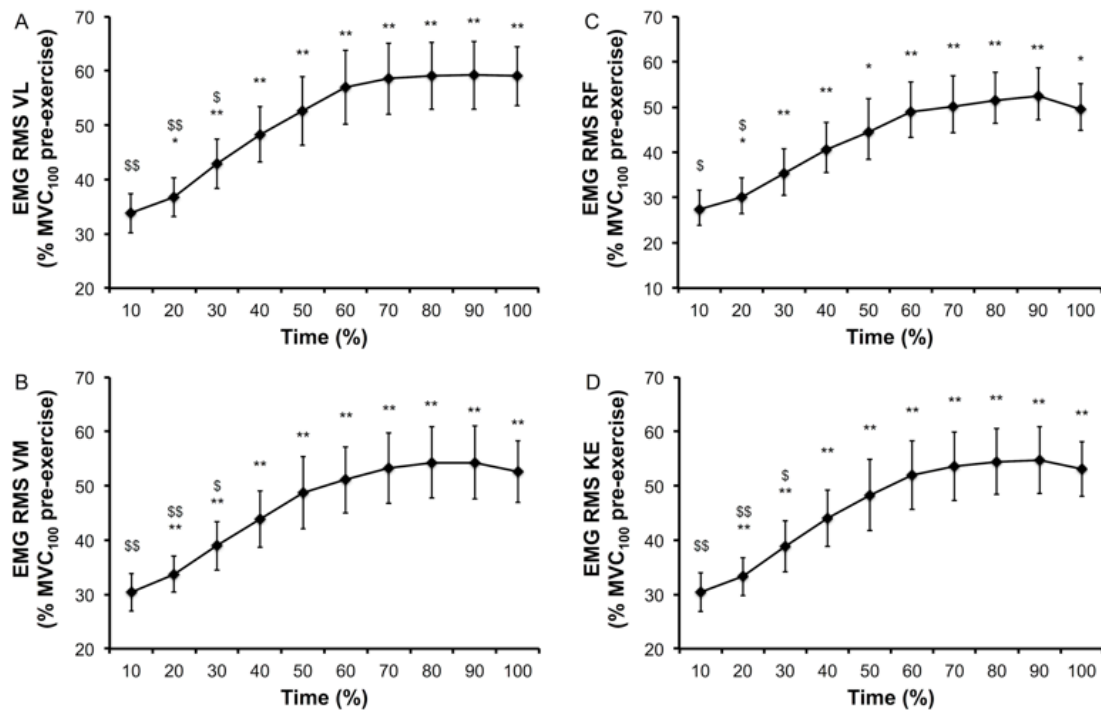
**Physiological and perceptual measurements.** Physiological, psychological and EMG responses to the time to exhaustion tests are presented in figures 25 and 26. Leg RPE (figure 25A), leg muscle pain (figure 25B) and HR (figure 25C) increased over time (all  $P < 0.001$ ). Cadence during the time to exhaustion decreased over time ( $P < 0.001$ ). Planned comparisons for these aforementioned parameters are presented in figure 25. EMG RMS of the VL (figure 26A), VM (figure 26B), RF (figure 26C) and the sum of these muscles

(figure 4D) increased over time (all  $P < 0.001$ ). Planned comparisons for EMG parameters are presented figure 4. Blood lactate concentration increased ( $1.3 \pm 0.5$  to  $6.0 \pm 1.1$  mmol/L,  $P < 0.001$ ) and blood glucose concentration decreased ( $5.3 \pm 0.5$  to  $4.4 \pm 0.3$  mmol/L,  $P = 0.001$ ) over time.



**Figure 25 - Time course of perceptual responses (panel A and B), heart rate (panel C) and cadence (panel D) during the time to exhaustion tests.**

Data are presented as main effect of time and mean (SE). \* significantly different from 10% and <sup>S</sup> significantly different from 100%, 1 item for  $P < 0.05$ , 2 items for  $P < 0.01$  and 3 items for  $P < 0.001$ .



**Figure 26 - Time course of EMG root mean square (EMG RMS) normalised by the maximum EMG RMS pre-exercise at 100 °/s ( $MVC_{100}$ ) responses during the time to exhaustion tests (85% peak power output).**

EMG RMS was measured for the following muscles: vastus lateralis (VL, panel A), vastus medialis (VM, panel B), rectus femoris (RF, panel C) and the overall knee extensors (KE; sum VL, RF and VM, panel D). Data are presented as main effect of time and mean (SE). \*

significantly different from 10% and § significantly different from 100%, 1 item for

$P < 0.05$ , 2 items for  $P < 0.01$  and 3 items for  $P < 0.001$ .

## ISOKINETIC FATIGUE INDUCED BY HIGH INTENSITY OLDE AND ITS RECOVERY

**Reliability pre-exercise values.** Due to randomisation of KE MVCs speed order, reliability data was calculated for pre-exercise neuromuscular parameters only. Reliability of pre-exercise values is presented table 8.

	Session			P-value	Inter-day reliability			
	1	2	3		Heteroscedasticity (R <sup>2</sup> )	ICC (95% CI)	CV (%)	SEm
<b>60 deg/s</b>								
MVC (N·m)	189.8 (53.5)	187.5 (60.7)	185.6 (59.3)	0.643	No (0.002)	0.932 (0.799-0.985)	-	14.6
EMG RMS VL (mV)	0.374 (0.139)	0.346 (0.109)	0.346 (0.124)	0.689	No (0.010)	0.684 (0.290-0.918)	-	0.067
EMG RMS RF (mV)	0.424 (0.124)	0.347 (0.111)	0.331 (0.123)	0.038	No (0.009)	0.595 (0.185-0.884)	-	0.077
EMG RMS VM (mV)	0.318 (0.120)	0.301 (0.100)	0.326 (0.145)	0.558	Yes (0.210)	0.864 (0.632-0.968)	13.19 (6.29)	-
EMG RMS KE (mV)	1.115 (0.317)	0.995 (0.283)	1.004 (0.347)	0.135	No (0.044)	0.823 (0.544-0.957)	-	0.129
<b>100 deg/s</b>								
MVC (N·m)	165.6 (52.5)	160.6 (48.2)	162.5 (60.0)	0.756	Yes (0.174)	0.943 (0.828-0.987)	7.37 (4.54)	-
EMG RMS VL (mV)	0.418 (0.162)	0.403 (0.175)	0.354 (0.154)	0.273	No (0.010)	0.759 (0.431-0.939)	-	0.078
EMG RMS RF (mV)	0.404 (0.150)	0.354 (0.125)	0.348 (0.170)	0.237	No (0.090)	0.782 (0.472-0.946)	-	0.068
EMG RMS VM (mV)	0.338 (0.131)	0.340 (0.150)	0.333 (0.188)	0.966	Yes (0.122)	0.882 (0.663-0.973)	13.57 (11.32)	-
EMG RMS KE (mV)	1.159 (0.376)	1.097 (0.408)	1.035 (0.474)	0.321	No (0.045)	0.850 (0.606-0.964)	-	0.157
<b>140 deg/s</b>								
MVC (N·m)	147.3 (44.1)	155.5 (41.1)	149.8 (48.2)	0.269	No (0.097)	0.950 (0.844-0.989)	-	9.6
EMG RMS VL (mV)	0.425 (0.191)	0.427 (0.191)	0.392 (0.137)	0.559	Yes (0.116)	0.844 (0.588-0.963)	14.24 (4.52)	-
EMG RMS RF (mV)	0.428 (0.133)	0.391 (0.122)	0.384 (0.133)	0.257	No (0.009)	0.812 (0.527-0.954)	-	0.054
EMG RMS VM (mV)	0.347 (0.151)	0.367 (0.148)	0.387 (0.141)	0.284	No (0.002)	0.887 (0.688-0.973)	-	0.047
EMG RMS KE (mV)	1.200 (0.415)	1.184 (0.401)	1.163 (0.368)	0.706	No (0.028)	0.955 (0.863-0.990)	-	0.080

**Table 8 - Between sessions comparison of pre-exercise isokinetic maximal voluntary contraction (MVC).**

MVCs were performed at 60, 100 and 140 °/s. Intraclass correlation coefficient (ICC) model (3,1), coefficient of variation (CV, for heteroscedastic data) and standard error of measurement (SEm, for homoscedastic data) were calculated. CI, confidence interval; VL, vastus lateralis muscle; RF, rectus femoris muscle; VM, vastus medialis muscle, KE, knee extensor muscles (sum VL, RF and VM). One-way repeated ANOVA revealed no difference (see P-value) between sessions except for EMG RMS RF at 60 °/s. Data are presented as mean (SD).



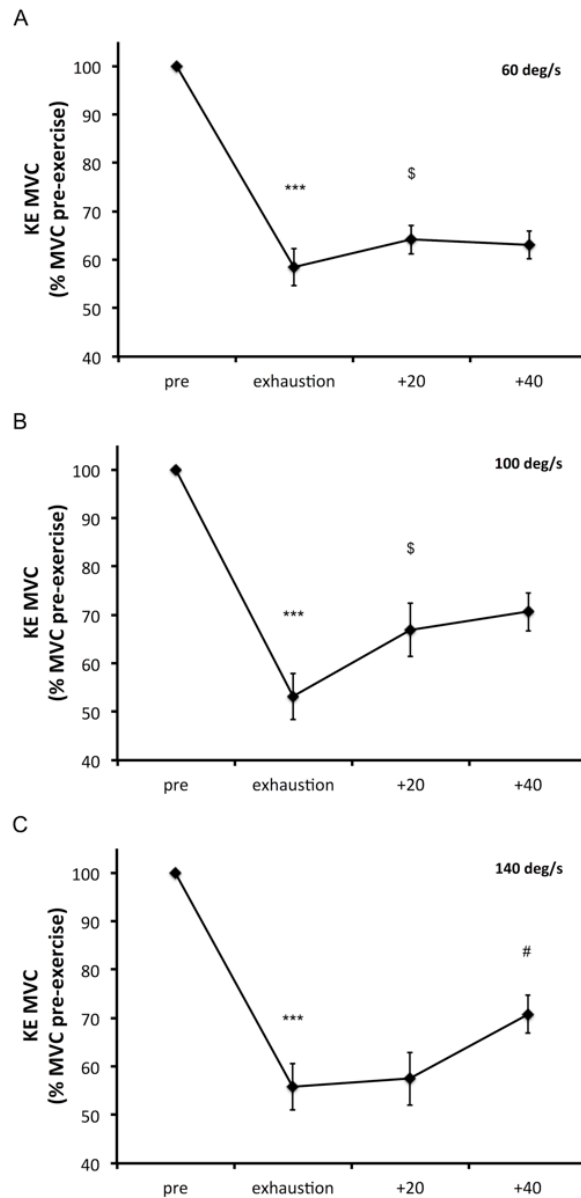
	Time				ANOVA	
	Pre	Exhaustion	+20	+40	P-value	Cohen's effect size f(V)
<b>60 deg/s</b>						
MVC (N·m)	188.7 (57.2)	112.0 <sup>***</sup> (41.4)	121.3 <sup>S</sup> (41.3)	117.4 (33.0)	<0.001	3.161
EMG RMS VL (mV)	0.355 (0.110)	0.402 (0.171)	0.392 (0.153)	0.390 (0.170)	0.341	0.410
EMG RMS RF (mV)	-	-	-	-	-	-
EMG RMS VM (mV)	0.315 (0.117)	0.301 (0.182)	0.346 (0.134)	0.354 (0.163)	0.686	0.179
EMG RMS KE (mV)	1.038 (0.300)	1.069 (0.294)	1.104 (0.336)	1.087 (0.440)	0.931	0.146
<b>100 deg/s</b>						
MVC (N·m)	162.9 (52.7)	86.5 <sup>***</sup> (34.2)	107.6 <sup>S</sup> (32.8)	111.4 (28.6)	<0.001	1.648
EMG RMS VL (mV)	0.392 (0.151)	0.381 (0.144)	0.425 (0.194)	0.361 (0.151)	0.150	0.530
EMG RMS RF (mV)	0.369 (0.139)	0.359 (0.170)	0.364 (0.145)	0.351 (0.093)	0.978	0.095
EMG RMS VM (mV)	0.337 (0.151)	0.339 (0.132)	0.335 (0.150)	0.364 (0.179)	0.600	0.301
EMG RMS KE (mV)	1.038 (0.300)	1.069 (0.294)	1.104 (0.336)	1.087 (0.440)	0.868	0.185
<b>140 deg/s</b>						
MVC (N·m)	150.8 (43.8)	84.0 <sup>**</sup> (28.9)	87.8 (32.7)	106.8 <sup>#</sup> (37.1)	<0.001	2.092
EMG RMS VL (mV)	0.414 (0.165)	0.386 (0.156)	0.403 (0.161)	0.428 (0.139)	0.641	0.285
EMG RMS RF (mV)	0.401 (0.122)	0.327 (0.125)	0.336 (0.189)	0.428 (0.139)	0.031	0.594
EMG RMS VM (mV)	0.367 (0.141)	0.346 (0.165)	0.351 (0.157)	0.344 (0.117)	0.873	0.182
EMG RMS KE (mV)	1.182 (0.389)	1.059 (0.368)	1.090 (0.454)	1.200 (0.372)	0.090	0.594

**Table 9 - Time course of maximal voluntary contraction (MVC) and EMG root mean square (EMG RMS) during the time to exhaustion (85% peak power output).**

MVCs were performed at 60, 100 and 140 °/s. Testing was performed pre-exercise (pre, average of all three sessions pre-exercise values), shortly after exhaustion (13±4s after exhaustion), 20s following exhaustion test (+20) and 40s following exhaustion test (+40). As pre-exercise values for

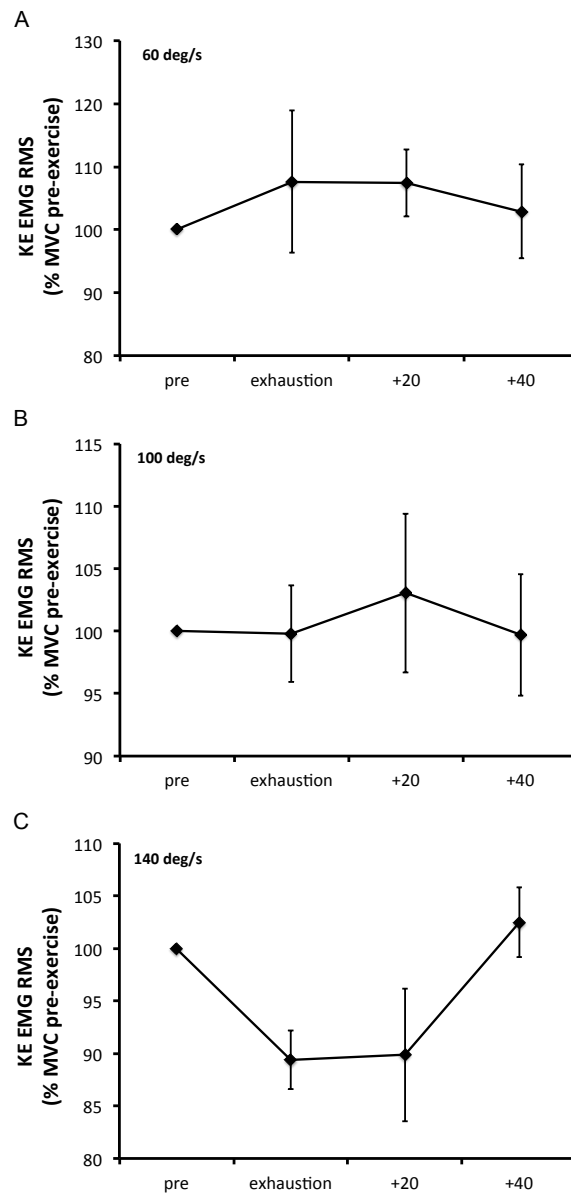
the EMG RMS RF at 60 °/s differ between sessions ( $P=0.038$ ), its time course was not analysed. Planned comparisons failed to demonstrate significant difference between means for EMG RMS RF at 140 °/s. VL, vastus lateralis muscle; RF, rectus femoris muscle; VM, vastus medialis muscle, KE, knee extensor muscles (sum VL, RF and VM). Data are presented as mean (SD). \* significantly different from pre, \$ significantly different from exhaustion and # significantly different from +20, 1 item for  $P<0.05$ , 2 items for  $P<0.01$  and 3 items for  $P<0.001$ .

***Torque and EMG.*** Absolute values for KE MVC peak torques and maximal EMG RMS are presented in table 9. As EMG RMS of the RF at 60 °/s pre-exercise values significantly differ between sessions, these data were not analysed. Planned comparisons to explore main effect of time are presented in table 9. Despite a significant main effect of time for the EMG RMS of the RF at 140 °/s, planned comparison failed to demonstrate a significant difference between times. Changes in KE MVC and KE EMG RMS related to baseline are presented figures 27 and 28. KF MVC peak torque did not change over time ( $75 \pm 31$  to  $73 \pm 27$  Nm,  $P=0.368$ )



**Figure 27 - Changes in isokinetic knee extensors maximal voluntary contraction (KE MVC) following the time to exhaustion tests (85% peak power output) and their recovery.**

MVCs were performed at 60 (panel, A), 100 (panel B) and 140 (panel C) °/s. Isokinetic KE MVCs were measured pre-exercise (pre, average of all three sessions pre-exercise values), shortly after exhaustion (13 ± 4s after exhaustion), 20s following exhaustion test (+20) and 40s following exhaustion test (+40). Data are presented as mean (SE). \* significantly different from pre, <sup>\$</sup> significantly different from exhaustion and <sup>#</sup> significantly different from +20, 1 item for P<0.05 and 3 items for P<0.001.



**Figure 28 - Changes in electromyography root mean square (EMG RMS) during isokinetic knee extensors maximal voluntary contraction (KE MVC) following the time to exhaustion tests (85% peak power output) and their recovery.**

KE EMG RMS corresponds to the sum of EMG RMS of the following muscles: vastus lateralis, rectus femoris and vastus medialis. Isokinetic KE MVCs were performed at 60 °/s (panel, A), 100 °/s (panel B) and 140 °/s (panel C). Isokinetic KE MVCs were measured pre-exercise (pre, average of all three sessions pre-exercise values), shortly after exhaustion (13±4s after exhaustion), 20s following exhaustion test (+20) and 40s following exhaustion test (+40). Data are presented as mean (SE).

## V. Discussion

The aim of the present study was twofold: i) to assess the reliability of exhaustive high intensity OLDE to measure endurance performance, and ii) to describe the isokinetic fatigue induced by exhaustive high intensity OLDE and its recovery. The results showed that exhaustive high intensity OLDE could be used as a reliable model to measure endurance performance, and that isokinetic fatigue recovered and plateaued within ~30 s post exhaustion. Therefore, the new exercise model presented in this study might provide the ideal tool to investigate CNS processes involved in muscle fatigue and endurance performance regulation.

### **RELIABILITY OF EXHAUSTIVE HIGH INTENSITY OLDE**

During the time to exhaustion tests, all perceptual and physiological measurements increased over time. The increase in HR is similar to a previous study using the same protocol on a different ergometer (Rossman et al., 2012). Furthermore, these authors demonstrated that the solicitation of the respiratory system is not a limiting factor for this exercise. Despite the fact that we did not measure the maximum HR of our subjects via a typical whole-body incremental test (e.g. cycling), it is clear that a HR of ~130 beats/min is far off the maximum heart rate of our subjects. Therefore, taken all together, these results confirm that exhaustive high intensity OLDE is not limited by the cardiorespiratory system.

We measured endurance performance in the present study by completion of time to exhaustion tests (i.e. subject has to maintain a fix workload until disengagement from the task). All time to exhaustion tests lasted less than 10 minutes, confirming that the exercise was performed at high intensity. The duration of the time to exhaustion tests in the present study corroborates results of previous studies using the same exercise on a different ergometer (Rossman et al., 2012; Amann et al., 2013; Rossman et al., 2014). Traditionally, time to exhaustion tests are known to present a greater CV ( $CV > 10\%$ ) than time trials (i.e. subjects has to perform the maximum amount of work possible in a fixed time/distance;  $CV < 5\%$ ) (Currell and Jeukendrup, 2008). Interestingly, in our study, CV is below 10%, confirming the reliability of exhaustive high intensity OLDE to measure endurance performance. This low CV in the present study is of particular interest to detect small, but

important, changes in performance (Currell and Jeukendrup, 2008). The high ICC (0.795) also confirms the reliability of the present protocol. However, as no consensus really exists on threshold to interpret ICC results (Morrow and Jackson, 1993), the practical significance of its value has to be determined with caution by the readers according to their future use of the present protocol.

Interestingly, one of our subjects presented both a CV and a time to exhaustion much greater than the other subjects. As both CV and time to exhaustion are known to increase when the intensity of the exercise decreases (Currell and Jeukendrup, 2008), it is likely that this subject did not reach his true peak power output during the incremental test, and then performed the three time to exhaustion tests at an intensity below 85%. This result is of particular importance for future research aiming to manipulate endurance performance using this protocol. Indeed, when the true peak power output is not reached during the incremental test, it might be harder to detect significant changes in endurance performance due to an increase in variability (when exercise intensity is reduced). Therefore, in order to better understand the variability in reaching the true peak power output of subjects, further studies should investigate the reliability of the incremental test used in the present study.

## **RELIABILITY OF NEUROMUSCULAR PARAMETERS ON FRESH MUSCLES DURING ISOKINETIC CONTRACTIONS**

We did not only measure the reliability of the time to exhaustion tests, but also the reliability of neuromuscular parameters on fresh muscles (KE MVC and EMG RMS of the knee extensor muscles). Knowing the variability of these parameters can help the reader in order to choose which parameters to use to investigate the effects of various experimental manipulations (e.g. training intervention) on fresh muscle force production capacity during isokinetic contraction at different speeds. According to a previous study investigating the reliability of neuromuscular parameters during isometric contractions (Place et al., 2007), our results suggest that only KE MVC presents a reliable independently of the contraction speed. Indeed, KE MVC is the only parameter presenting a low SEM/CV independently of the contraction speed performed.

Contrary to the KE MVC, the EMG RMS reliability varied considerably between muscles and also with the contraction speed performed. Interestingly, when the EMG RMS is summed over the three superficial knee extensor muscles, the reliability significantly

increases and the ICC is above 0.8 for all three contraction speeds. Therefore, our results suggest that all three superficial knee extensor muscles should be taken into account when investigating the effect of an experimental manipulation on fresh muscle force production capacity during isokinetic contraction at different speed.

Furthermore, it has to be noticed that our study design did not allow assessing the reliability of these parameters on fatigued muscle, thus due to the randomisation of contraction speed order. Future studies should investigate the reliability of these parameters on fatigued muscles.

### **ISOKINETIC FATIGUE INDUCED BY OLDE**

The second aim of this study was to describe the isokinetic fatigue induced by exhaustive high intensity OLDE and its recovery. Firstly, the absence of KF MVC decrease confirms that our exercise only solicits the knee extensors and does not fatigue the knee flexors. Secondly, according to our hypothesis, isokinetic MVC quickly recovered and plateaued after exhaustion (within ~30 s at 60 and 100 °/s, and within ~50 s at 140 °/s). This quick recovery in torque production capacity is likely to be associated with recovery in both central and peripheral fatigue. This assumption is supported by one previous study in our laboratory demonstrating that not only peripheral and central fatigue, but also cortical and spinal excitability, recovered shortly after exhaustion (Pageaux et al., submitted). Froyd et al. (2013) also demonstrated a significant recovery in skeletal muscle function within 1-2 minutes after completion of a one-leg isokinetic time trial performed at high intensity. Taken all together, these results demonstrate that to fully appreciate the extent of neuromuscular alterations induced by high intensity dynamic exercise, assessment of muscle fatigue must be performed within 30 s of cessation of the exercise.

Despite EMG being known to not be a reliable measure of muscle fatigue during dynamic exercise (Farina, 2006; de Morree et al., 2012), numerous studies are using the EMG signal as an index of muscle fatigue during dynamic exercise (e.g. Amann et al., 2011a; Amann et al., 2013). In the present study, when measured shortly after exhaustion and even during the recovery period, none of the EMG RMS values were significantly altered by the exercise. These physiological responses contrast with those of the KE MVC, known to be the gold standard for muscle fatigue measurement. Therefore, as KE MVC can be altered independently of any alterations in the EMG signal, our results suggest that EMG signal cannot be used to quantify exercise induced muscle fatigue. The lack of

changes in EMG signal is likely to be caused by a potentiation of the maximal evoked muscular wave (M-wave) induced by exhaustive high intensity OLDE (Pageaux et al., submitted). Other studies using the EMG signal as an index of muscle fatigue normalised this signal by the M-wave (for review see Millet and Lepers, 2004). This normalisation procedure aims to account for peripheral influences including neuromuscular propagation failure and changes in impedance from the EMG recordings (Millet and Lepers, 2004). However, a recent study demonstrated that even when normalised by the M-wave, the ratio EMG/M-wave is not a reliable index of muscle fatigue induced by dynamic exercise (Pageaux et al., submitted). Consequently, caution has to be taken in EMG changes interpretation during dynamic exercise, and thus with or without normalisation of the EMG signal by the M-wave.

## **CONCLUSION AND PERSPECTIVES**

The results of this study present evidence in favour of the use of exhaustive high intensity OLDE to investigate CNS processes regulating muscle fatigue development and endurance performance. Indeed, the new protocol developed in our laboratory i) presents a lower variability than other high intensity time to exhaustion tests (Currell and Jeukendrup, 2008), ii) is not limited by the cardiorespiratory system and iii) allows neuromuscular testing quickly after exhaustion to fully appreciate the extent of muscle fatigue induced by the exercise. Additionally, the results of the present study confirm that EMG signal is not a good index of muscle fatigue induced by dynamic exercise. Therefore, the exercise model used in the present study provides the ideal tool to manipulate various physiological processes known to regulate cardiorespiratory system and supposed to play a role in muscle fatigue development (e.g. spinal blockade of afferent feedback from the working muscles) during high intensity dynamic endurance exercise.



**CHAPTER 2: CENTRAL ALTERATIONS OF NEUROMUSCULAR  
FUNCTION AND FEEDBACK FROM GROUP III-IV MUSCLE  
AFFERENTS FOLLOWING EXHAUSTIVE HIGH INTENSITY ONE LEG  
DYNAMIC EXERCISE**

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**Submitted in** American Journal of Physiology, Regulatory, Integrative and Comparative Physiology

## **I. Abstract**

High intensity one leg dynamic exercise (OLDE) has recently been used to investigate the role of feedback from group III-IV muscle afferents (MA) in regulation of muscle fatigue and exercise performance. The aim of this investigation was i) to describe central alterations of neuromuscular function following exhaustive OLDE (study 1), and ii) to non-invasively quantify MA via muscle occlusion (MO, study 2). Both studies consisted of two time to exhaustion tests (85% peak power output). In study 1, voluntary activation level (VAL), M-wave (M), cervicomedullary motor evoked potential (CMEP), motor evoked potential (MEP) and MEP cortical silent period (CSP) were measured on the knee extensors. In study 2, mean arterial pressure (MAP) and leg muscle pain were measured during MO. Measurements were performed pre-exercise, at exhaustion and after three minutes recovery. Compared to pre-exercise values, VAL was lower at exhaustion ( $-13\pm 13\%$ ,  $P<0.05$ ) and after three minutes recovery ( $-6\pm 6\%$ ,  $P=0.05$ ).  $CMEP_{area}/M_{area}$  was lower at exhaustion ( $-38\pm 13\%$ ,  $P<0.01$ ) and recovered after three minutes.  $MEP_{area}/M_{area}$  was higher at exhaustion ( $+25\pm 27\%$ ,  $P<0.01$ ) and after three minutes recovery ( $+17\pm 20\%$ ,  $P<0.01$ ). CSP was higher ( $+19\pm 9\%$ ,  $P<0.01$ ) only at exhaustion and recovered after three minutes. MAP and leg muscle pain were higher only at exhaustion ( $+20\pm 15\%$ ,  $P<0.05$ ). Study 1 demonstrated that exhaustive OLDE alters spinal excitability and increases CSP. Study 2 confirmed the possibility to assess MA non-invasively in humans and demonstrated significant MA activity only at exhaustion. These results suggest an association between decrease in spinal excitability, increase in CSP and MA activity following exhaustive OLDE.

## **II. Introduction**

One leg dynamic exercise (OLDE) is characterised by rhythmic voluntary isotonic contractions of the knee extensors interspaced by passive knee flexion (Andersen et al., 1985). Contrary to whole-body exercise (e.g. cycling), due to the reduced muscle mass involved, OLDE is not limited by cardiorespiratory function (Rossman et al., 2014). Therefore, it has been used with patients suffering from cardiorespiratory limitations

(Rossman et al., 2013a; Rossman et al., 2013b) or for studying mechanisms regulating circulatory response to rhythmic dynamic exercise (Amann et al., 2011b; Garten et al., 2014). From a training perspective, OLDE has been shown to induce greater adaptations in the metabolic and oxidative mechanisms in skeletal muscle compared to double leg exercise (Abbiss et al., 2011), consequently providing a new innovative training method for endurance athletes and clinical populations. Furthermore, high intensity OLDE has recently been used to investigate the role of the central nervous system in regulation of muscle fatigue and exercise performance (Rossman et al., 2012; Amann et al., 2013; Rossman et al., 2014). Thus, the use of OLDE is of particular interest for researchers, clinicians and athletes.

Contrary to one leg isometric exercise (e.g. Place et al., 2005; Goodall et al., 2010; Gruet et al., 2014) and isokinetic eccentric and concentric exercise (e.g. Babault et al., 2001), neuromuscular alterations induced by OLDE have been scarcely investigated. In 1995, Fulco et al. (Fulco et al., 1995) developed an OLDE exercise on a customised ergometer to assess isometric maximal voluntary contraction (MVC) almost instantaneously at cessation of the exercise. These authors demonstrated a progressive decrease in MVC up to ~50% of pre-exercise values following exhaustive OLDE (Fulco et al., 1995). Unfortunately, these authors did not assess peripheral (i.e. fatigue produced by changes at or distal to the neuromuscular junction; Gandevia, 2001) and central (i.e. decrease in maximal voluntary activation level, VAL; Gandevia, 2001) components of muscle fatigue during their work. More recently, Rossman et al. (Rossman et al., 2012; Rossman et al., 2014) demonstrated that within 2.5 minutes after cessation of exhaustive high intensity OLDE the extent of peripheral alterations is greater than that induced by double leg exercise (Rossman et al., 2012; Rossman et al., 2014). These authors have also demonstrated that exhaustive high intensity OLDE also induces central fatigue (decrease in VAL; Rossman et al., 2014). Despite the fact that engagement in a fatiguing physical task is known to induce not only a decrease in VAL, but also alterations in cortical and spinal excitability (for review see Gandevia, 2001), no study to date has investigated whether high intensity OLDE could alter cortical and spinal excitability. Therefore, in the present investigation, we assessed the extent of central alterations of neuromuscular function (i.e. decrease in VAL and changes in corticospinal excitability) and their recovery following exhaustive high intensity OLDE.

Group III-IV muscle afferents are free nerve endings activated by contraction-induced mechanical and chemical stimuli (Rowell and O'Leary, 1990). It is well known

that activation of group III-IV muscle afferents by fatigue-related metabolites increases their discharge activity (Kaufman et al., 2002). It has been proposed that this afferent feedback from fatigued locomotor muscles might be one of several contributors of central fatigue by spinal (for review see Gandevia, 2001) and supraspinal reflexes (for review see Gandevia, 2001; Amann, 2011), but could also alter corticospinal excitability (for review see Gandevia, 2001). However, in these studies, feedback from group III-IV muscle afferents was never quantified. Indeed, to date there is no non-invasive methodology to quantify feedback from group III-IV muscle afferents in humans. Interestingly, feedback from group III-IV muscle afferents is known to increase mean arterial pressure (MAP; Kaufman et al., 1984; Crisafulli et al., 2006). This response is called metaboreflex and is independent of central motor command (McCloskey and Mitchell, 1972; Kaufman et al., 1984). Furthermore, in the absence of central motor command, which is known to alter pain perception (Degtyarenko and Kaufman, 2003), rating of muscle pain reflects feedback from group III-IV muscle afferents (O'Connor and Cook, 1999). Therefore, when measurement is performed in absence of central motor command, i.e. during muscle occlusion, MAP and leg muscle pain could be considered as markers to indirectly quantify feedback from group III-IV muscle afferents. In the present investigation, we used these two markers to indirectly measure feedback from group III-IV afferents in locomotor muscles following exhaustive high intensity OLDE and after recovery.

The aims of the present studies were: i) to describe central alterations of neuromuscular function (i.e. changes in VAL and corticospinal excitability) induced by exhaustive high intensity OLDE and their recovery, ii) to quantify non-invasively feedback from group III-IV muscle afferents in humans, and iii) to integrate the results of both studies to get a better insight in the association between central alterations of neuromuscular function and feedback from group III-IV muscle afferents. Firstly, we hypothesised (study 1) that central alterations of neuromuscular function measured shortly after exhaustion would be greater than those measured after three minutes recovery, including changes in corticospinal parameters. Secondly, we hypothesised (study 2) that both MAP and leg muscle pain (i.e. markers of feedback from group III-IV muscle afferents) would recover after three minutes. Finally, we hypothesised that central fatigue and changes in corticospinal parameters following exhaustive OLDE would be associated with feedback from group III-IV muscle afferents. As neuromuscular fatigue might be underestimated by a recovery between cessation of the exercise and start of neuromuscular

testing (Cairns et al., 2005), we used an OLDE model developed in our laboratory to perform both high intensity OLDE and neuromuscular testing on the same dynamometer.

### **III. Methods**

#### **SUBJECTS AND ETHICAL APPROVAL**

Two studies were conducted on healthy active adults. Ten subjects (mean  $\pm$  SD; age:  $27 \pm 3$  yrs, height:  $180 \pm 7$  cm, weight:  $80 \pm 12$  kg, 8 males and 2 females) volunteered to participate in study 1 and eight male subjects (age:  $25 \pm 3$  yrs, height:  $180 \pm 6$  cm, weight:  $78 \pm 15$  kg) volunteered to participate in study 2. Five subjects participated in both studies. None of the subjects had any known mental or somatic disorder. Each subject gave written informed consent prior to the study. Experimental protocol and procedures were approved by the local Ethics Committee of the School of Sport and Exercise Sciences, University of Kent at Medway. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008). All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants.

#### **EXPERIMENTAL PROTOCOL**

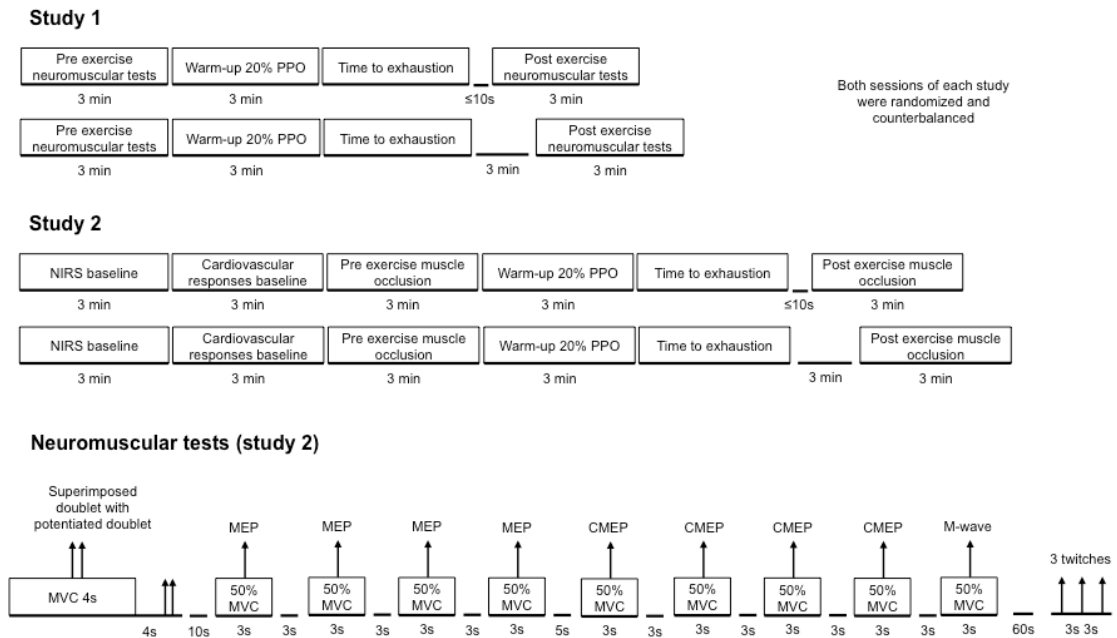
Both studies described below included two experimental sessions to avoid the confounding effects of testing shortly after exhaustion on subsequent recovery of neuromuscular parameters (study 1) and markers from group III-IV muscle afferents (study 2). Furthermore, as MAP and leg muscle pain can be considered as markers of feedback from group III-IV muscle afferents only in absence of central motor command (Kaufman et al., 1984; O'Connor and Cook, 1999), assessment of feedback from group III-IV was performed in a second study.

**Study 1.** The main aim of this study was to assess central fatigue and changes in corticospinal parameters shortly after exhaustion ( $OLDE_{exh}$ ) and after three minutes recovery ( $OLDE_{3min}$ ) following exhaustive high intensity (intensity fixed at 85% peak

power output and average RPE > 14; Deschenes, 2013) OLDE. Subjects visited the laboratory on four different occasions. During the first visit, subjects were familiarised with all experimental procedures, including the OLDE (see *One Leg Dynamic Exercise* for more details) and neuromuscular testing (see *Neuromuscular Function Tests* for more details). As suggested by Andersen et al. (1985), torque and electromyographic (EMG) feedback were used during the first visit to ensure a quick and reliable familiarisation to the OLDE. During the second visit, a preliminary OLDE incremental test was performed until exhaustion (see *One Leg Dynamic Exercise* for more details) to determine peak power output. After thirty minutes recovery, subjects were familiarised with neuromuscular testing and performed a time to exhaustion test at 85% of peak power output. During the third and fourth visits, subjects performed a time to exhaustion test at 85% of peak power output, with neuromuscular testing being performed either shortly after exhaustion, or after three minutes of inactive recovery (no leg movement with knee angle fixed at 90°) in a randomised and counterbalanced order.

**Study 2.** The main aim of study 2 was to assess feedback from group III-IV muscle afferents via measurement of MAP and leg muscle pain during muscle occlusion shortly after exhaustion (OLDE<sub>exh</sub>) and after three minutes recovery (OLDE<sub>3min</sub>) following exhaustive high intensity OLDE. Muscle oxygenation was also recorded via near-infrared spectroscopy during the exercise and the subsequent recovery. Experimental procedures are similar as those performed in Study 1 with muscle occlusion (see *Markers of Feedback from Group III-IV Muscle Afferents* for more details) performed instead of neuromuscular testing. An overview of visits three and four can be seen in figure 29.

Each visit was interspaced by a minimum of 48 hours recovery. All participants were given instructions to sleep for at least 7 hours, refrain from the consumption of alcohol, and not to undertake vigorous physical activity the day before each visit. Participants were also instructed not to consume caffeine and nicotine at least 3 hours before testing, and were asked to declare if they were ill and/or were taking any medication.



**Figure 29 - Overall view of the protocol for both studies and timing of neuromuscular tests performed in study 1.**

CMEP, cervicomedullary motor evoked potential; M-wave, maximal muscular wave; MEP, motor evoked potential; MVC, maximal voluntary contraction; NIRS, near-infrared spectroscopy; PPO, peak power output.

## ONE LEG DYNAMIC EXERCISE

**Model Development.** The OLDE model we used for the present study was developed to reproduce the exercise model of Andersen et al. (Andersen et al., 1985) on a dynamometer to remove the time delay involved in transferring the participant from the exercising ergometer to the dynamometer. This exercise model allows isolating the knee extensor muscles during a dynamic exercise involving an active isotonic knee extension and a passive knee flexion. We carefully controlled the power output produced by the subject according to the formula:

$$P = T \times \theta$$

P corresponds to the power expressed in watt (W),  $T$  the torque in newton meters (N·m) and  $\theta$  the angular speed in rad/s.

OLDE was performed on a Cybex NORM isokinetic dynamometer (CMSi, Computer Sports Medicine Inc., Stoughton, USA) with customised software specially

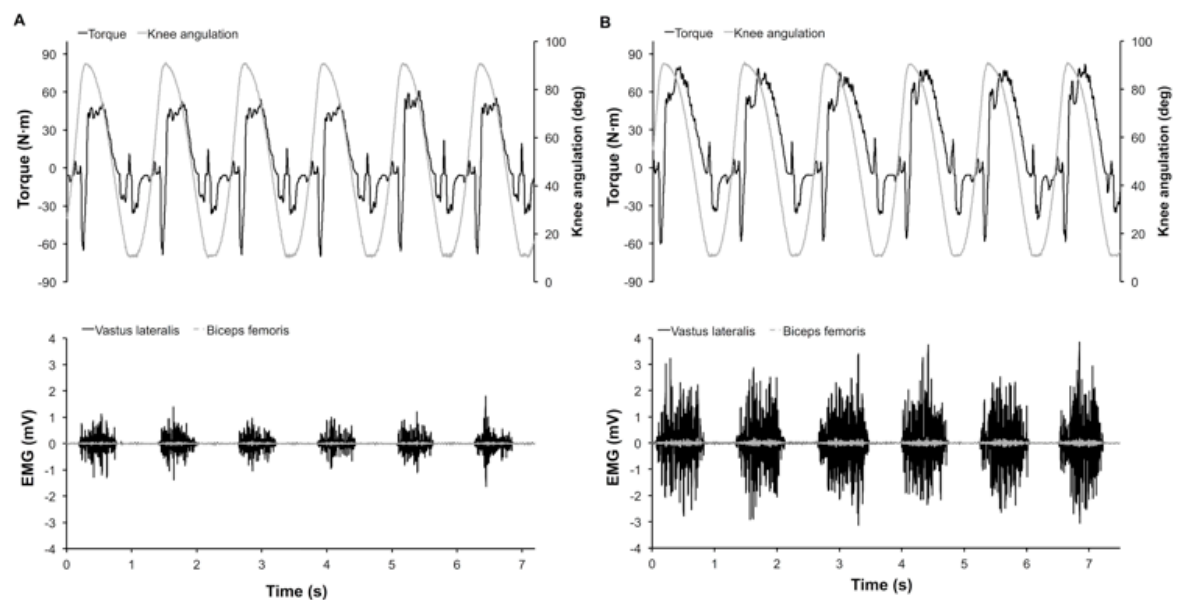
designed by the company for our experiment. This dynamometer was also used for the neuromuscular function tests. The axis of the dynamometer was aligned with the knee axis, and the lever arm was attached to the shank with a strap. Two shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. As used in previous studies assessing endurance performance with the original exercise model of Andersen et al. (Andersen et al., 1985), a range of motion from  $10^\circ$  to  $90^\circ$  ( $0^\circ$  = knee fully extended) was chosen (Rossman et al., 2012; Amann et al., 2013). The active knee extension was performed using the isotonic mode of the dynamometer, with the knee flexion phase of the movement being performed by the passive mode (CPM mode) of the dynamometer. The software was configured for a passive flexion speed of  $300^\circ/\text{s}$  automatically cushioned by the dynamometer for safety purposes (speed of the arm movement decreasing when close to the range of motion to protect the subject). Due to this cushion, the passive knee flexion speed was  $\sim 180^\circ/\text{s}$ . After pilot testing in our laboratory, a cadence of 50 contractions per minute (cpm) was chosen, thus allowing an active knee extension of  $\sim 106^\circ/\text{s}$ . Therefore, during the incremental test performed on the dynamometer, each isotonic increment of  $1 \text{ N}\cdot\text{m}$  corresponded to an increment of  $\sim 1.85 \text{ W}$ . Subjects maintained a cadence of 50 cpm at all visits via the use of a metronome.

Typical recordings of torque, position and EMG signals from the vastus lateralis (knee extensor) and biceps femoris (knee flexor) could be found in figure 30. This figure presents all signals previously mentioned for an isotonic resistance of  $9 \text{ N}\cdot\text{m}$  ( $\sim 16.7 \text{ W}$ , panel A) and  $37 \text{ N}\cdot\text{m}$  ( $\sim 68.5 \text{ W}$ , panel B). The inactivity of the biceps femoris during the flexion phase confirms that we were successful in creating a protocol on the dynamometer that isolates the knee extensor muscles during dynamic exercise, as in the exercise model originally proposed by Andersen et al. (Andersen et al., 1985). Reproduction of this exercise model on the dynamometer allowed us to start neuromuscular testing within 10 s of exhaustion at the end of OLDE.

***Incremental test.*** During the second visit, a preliminary OLDE incremental test was performed until exhaustion to measure peak power output (Study 1:  $72.6 \pm 37.4 \text{ W}$ , Study 2:  $65.3 \pm 28.1 \text{ W}$ ). For males, the incremental test started with the isotonic resistance set at  $4 \text{ N}\cdot\text{m}$  ( $\sim 7.4 \text{ W}$ ) for 1 min, and increased each minute by  $3 \text{ N}\cdot\text{m}$  ( $\sim 4.5 \text{ W}$ ) to exhaustion. For females, the isotonic resistance was set up at  $4 \text{ N}\cdot\text{m}$  ( $\sim 7.4 \text{ W}$ ) for 1 min and increased each minute by  $2 \text{ N}\cdot\text{m}$  ( $\sim 3.7 \text{ W}$ ). Exhaustion was defined as either volitional disengagement from the exercise, or a decrease in cadence below 40 cpm for a duration  $\geq 10 \text{ s}$ .



**Time to exhaustion test.** After three minutes warm up at 20% of peak power output, subjects performed a time to exhaustion at 85% of peak power output (Study 1:  $61.7 \pm 31.6$  W, Study 2:  $55.5 \pm 23.9$  W). Exhaustion was defined as either volitional disengagement from the exercise or a decrease in cadence below 40 cpm for a duration  $\geq 10$  s. Rating of perceived exertion related to the exercising leg (leg RPE) and leg muscle pain were recorded during the last 15 s of the warm up (baseline) and at exhaustion (during Study 1) using the Borg scale (Borg, 1998) and Cook scale (O' Connor and Cook, 2001) respectively.



**Figure 30 - A typical recording of torque, knee angle, vastus lateralis electromyography (EMG) and biceps femoris EMG during one leg dynamic exercise with isotonic resistance at 9 N·m (~16.7 W, panel A) and 37 N·m (~68.5 W, panel B).**

## PHYSIOLOGICAL MEASUREMENTS

**Cardiovascular measurements.** In study 2, heart rate and arterial blood pressure were recorded via an automatic blood pressure device (Tango<sup>+</sup>, SunTech Medical, Morrisville, USA). Cardiovascular responses were recorded during the three minutes rest (baseline), pre-exercise muscle occlusion and post-exercise muscle occlusion (see *Markers of Feedback from Group III-IV Muscle Afferents* for more details). Cardiovascular responses were averaged from the values collected at the end of each minute of the three minutes rest, pre-exercise muscle occlusion and post-exercise muscle occlusion. Cardiovascular responses were also measured at exhaustion. MAP was calculated as:

$$MAP = \text{diastolic pressure} + \frac{1}{3} \times (\text{systolic pressure} - \text{diastolic pressure})$$

**Muscle oxygenation.** In study 2, muscle oxygenation was assessed via near infrared spectroscopy using an Oxymon Mk III device (Artinis, Zetten, The Netherlands) emitting continuous wavelengths of 780 and 850 nm light. Muscle oxygenation was assessed via probes (transmitters-receptor interspaced by 4.0 cm) placed on the exercising vastus lateralis (~15 cm proximal and 5 cm lateral to the midline of the superior border of the patella). Probe position was marked on the skin with indelible ink to ensure reliability of re-positioning between sessions. Muscle near infrared spectroscopy data were collected with a sampling frequency of 10 Hz. Data were averaged for the 5 s prior each time point measurement. The Beer-Lambert Law was used to calculate changes in tissue oxygenation. Relative concentration changes ( $\Delta\mu\text{Mol}$ ) were measured from resting baseline (figure 29) for oxyhaemoglobin ( $\Delta\text{O}_2\text{Hb}$ ), deoxyhaemoglobin ( $\Delta\text{HHb}$ ), total haemoglobin ( $\Delta\text{tHb} = \text{O}_2\text{Hb} + \text{HHb}$ ) and haemoglobin difference ( $\Delta\text{Hb diff} = \text{O}_2\text{Hb} - \text{HHb}$ ).  $\Delta\text{tHb}$  was calculated to give an index of change in regional blood volume (Van Beekvelt et al., 2001).

**Blood lactate.** In study 2, blood lactate concentration was collected at rest prior to pre-exercise muscle occlusion, at exhaustion and after two minutes recovery. We did not collect blood lactate after three minutes recovery to not influence measurement of MAP and leg muscle pain during muscle occlusion. 10  $\mu\text{l}$  samples of capillary blood were taken from the thumb of the right hand of the subjects and measured pre warm up and at exhaustion of each session by a lactate analyser (Biosen, EFK Diagnostics, London, England).

## NEUROMUSCULAR FUNCTION TESTS

In Study 1, neuromuscular function tests were performed pre OLDE and either shortly after exhaustion or after three minutes recovery. Each session began with a warm-up of 10 brief (4 s) submaximal voluntary isometric contractions at 50% of the estimated MVC force, followed by a 1 min rest before starting the protocol. A 4 s MVC with superimposed doublet was performed followed by a resting potentiated doublet (4 s post MVC). After the MVC, subjects performed four brief (3 s) submaximal contractions at 50% MVC with superimposed transcranial magnetic stimulation and one submaximal contraction at 50% MVC with superimposed femoral nerve stimulation. Six subjects tolerated electrical cervicomedullary stimulation, and so also performed four brief (3 s) submaximal contractions at 50% MVC with superimposed cervicomedullary stimulation,

interspaced between the transcranial magnetic stimulations and femoral nerve stimulation. The target contraction of 50% MVC corresponds to the MVC previously performed (i.e. non-fatigued MVC pre OLDE and fatigued MVC post OLDE). Each contraction was interspaced by 3 s. Once TMS and cervicomedullary stimulation were performed, three single resting femoral nerve stimulations (interspaced by 3 s) were performed. An overview of stimulation timing can be found in figure 29. Visual feedback and strong encouragements were provided during MVCs.

***Femoral nerve stimulation.*** A high-voltage constant-current stimulator (maximal voltage 400 V, model DS7 modified, Digitimer, Hertfordshire, UK) was used to perform transcutaneous electrically-evoked contractions of the knee extensor muscles. The femoral nerve was stimulated using a surface electrode (Swaromed, Nessler Medizintechnik, ref 1066, Innsbruck, Austria) positioned over the nerve, high in the femoral triangle. The anode was a rectangular electrode (10 × 5 cm, Phoenix Healthcare Products Ltd., Nottingham, UK) located in the gluteal fold opposite to the cathode. The optimal intensity of stimulation required to evoke a maximal compound muscle action potential ( $M_{\max}$ ) was determined at rest and during brief submaximal isometric knee contractions (~50% MVC). The optimal intensity of stimulation was set to 130% of that required to elicit  $M_{\max}$  during the submaximal isometric contraction (current higher during submaximal contractions compared to rest). Stimulation intensity was determined before each session and kept constant throughout the protocol (mean current,  $364 \pm 57$  mA). The stimulus duration was 200  $\mu$ s and the interval of the stimuli in the doublet was 10 ms (100 Hz frequency).

***Transcranial magnetic stimulation.*** Corticospinal excitability was assessed via TMS. Briefly, TMS consists of delivering a magnetic stimulation over the motor cortex to induce depolarisation of a specific population of neurons. This depolarisation induces an electrical potential named motor evoked potential (MEP) that can be recorded from a muscle via EMG surface electrodes (Goodall et al., 2014a). A magnetic stimulator (Magstim 200<sup>2</sup>, The Magstim Company Ltd, Whitland, UK) was used to deliver TMS. A concave double cone coil (110 mm diameter) was held over the vertex (postero-anterior intracranial current flow) to elicit motor evoked potentials (MEP) in the right knee extensor muscles. The optimal coil position (marked on the scalp with permanent marker) was determined in order to elicit a large MEP in the vastus lateralis, and a small MEP in the biceps femoris (<10% of the raw quadriceps MEP amplitude). The stimulator output intensity (mean:  $56 \pm 9\%$  of maximum stimulator output) was set to produce the largest possible MEP in the vastus lateralis, while causing a small MEP in the biceps femoris

during brief (3 s) submaximal isometric contractions at 50% MVC (Sidhu et al., 2009). MEPs were elicited during submaximal isometric contraction at 50% MVC as this intensity of contraction is known to provide the most stable and informative cortical silent period (CSP, Saisanen et al., 2008). Because CSP is known to be influenced by instructions provided to the subjects, subjects were instructed “to contract as fast as possible after the stimulation” (Mathis et al., 1998; Gandevia, 2001). This instruction is known to provide the most reliable CSP (Mathis et al., 1998). The stimulator output was determined before the experiment on each day and was kept constant throughout the protocol. All MEP parameters at exhaustion were obtained within ~50 s.

***Cervicomedullary stimulation.*** Spinal excitability was assessed via electrical cervicomedullary stimulation. Briefly, this method consists in delivering an electrical stimulation over the back of the head to induce depolarisation of axons in the corticospinal tracts. This depolarisation induces an electrical potential named cervicomedullary motor evoked potential (CMEP) that can be recorded from a muscle via EMG surface electrodes. CMEP is known to be the most appropriate comparison to allow interpretation of changes in MEP (Taylor and Gandevia, 2004). The corticospinal tract was stimulated via a high-voltage constant-voltage stimulator (maximal voltage 1000 V, model D185, Digitimer, Hertfordshire, UK). Surface electrodes (Ambu Neuroline 720, Ambu, Ballerup, Denmark) were positioned 1-2 cm posterior and superior to the tip of the mastoid process (cathode on the left side). The stimulus intensity required to evoke a maximal cervicomedullary motor evoked potential (CMEP) was determined during brief (3 s) submaximal isometric contractions at 50% MVC before the experiment on each day. Submaximal contraction intensity at 50% MVC was chosen to elicit CMEP at the same submaximal contraction intensity used to elicit MEP. All CMEP parameters at exhaustion were obtained within ~81 s. The stimulator output (mean current:  $375 \pm 54$  V) was determined before the experiment on each day and was kept constant throughout the protocol.

***Mechanical recordings.*** Mechanical parameters were recorded using the same dynamometer as for the OLDE (Cybex NORM isokinetic dynamometer, CMSi, Computer Sports Medicine Inc., Stoughton, USA). During the tests a two shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. Neuromuscular function tests were performed with the right leg at a knee joint angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The following parameters were analysed from the twitch response (average of 3 single stimulations interspaced by 3 s): peak twitch (Tw), time to peak twitch (contraction time, Ct) and average rate of force development (RFD =

Tw/Ct). The peak torque of the doublet (potentiated doublet, 4 s after the MVC) was also analysed. MVC torque was considered as the peak torque attained during the MVC. Voluntary activation level (VAL) during the MVC was estimated according to the following formula:

$$VAL = 100 \times \left(1 - \frac{\text{superimposed doublet amplitude}}{\text{potentiated doublet amplitude}}\right)$$

We ensured that all superimposed stimulation occurred as close as possible to the MVC peak torque to ensure reliability of VAL measurement. We used high frequency paired stimulations to elicit the superimposed and potentiated doublet to overcome low frequency fatigue induced by prolonged dynamic exercise of the knee extensor muscles (Froyd et al., 2013). Indeed, single stimuli in presence of low frequency fatigue is known to dictate a decline in evoked torque more important than the decline induced by paired stimulation (Shield and Zhou, 2004). All VAL values at exhaustion were obtained within ~15 s. Mechanical signals were digitised on-line at a sampling frequency of 1 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems, Biopac Systems Inc., Goleta, USA).

***Electromyographic recordings.*** EMG of the vastus lateralis and biceps femoris was recorded with pairs of silver chloride circular (recording diameter of 10 mm) surface electrodes (Swaromed, Nessler Medizintechnik, ref 1066, Innsbruck, Austria) with an interelectrode (center-to-center) distance of 20 mm. Recording sites (belly of the vastus lateralis muscle proximal to the knee axis and belly of the biceps femoris) were then carefully adjusted by eliciting the greatest M-wave amplitude for each muscle at a given intensity via femoral nerve stimulation at the beginning of each testing session. Low resistance between the two electrodes (< 5 k $\Omega$ ) was obtained by shaving the skin, and dirt was removed from the skin using alcohol swabs. The reference electrode was attached to the patella of the right knee. Myoelectrical signals were amplified with a bandwidth frequency ranging from 10 Hz to 500 Hz (gain = 500), digitised on-line at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems, Biopac Systems Inc., Goleta, USA). The root mean square (RMS), a measure of EMG amplitude, was automatically calculated with the software.

Peak-to-peak amplitude and EMG RMS (including positive and negative phase of the EMG signal) of the resting M-waves were calculated and averaged for the three stimulations. For MEP, CMEP and M-waves obtained during brief submaximal contractions at 50% MVC, the area (including positive and negative phase of the EMG

signal) was calculated and averaged for the four stimulations (MEP and CMEP). CSP duration of the MEP was determined by the same experimenter from the point of stimulation to the return of continuous EMG signal (Goodall et al., 2014a). EMG amplitude during the knee extensors MVC was quantified as the RMS for a 0.5 s interval at peak torque (250 ms interval either side of the peak torque). Maximal RMS EMG values were then normalised by the resting M-wave RMS EMG, in order to obtain  $RMS_{MVC}/RMS_M$  ratio. This normalisation procedure accounted for peripheral influences including neuromuscular propagation failure and changes in impedance from the EMG recordings. RMS EMG during OLDE was calculated for the last 30 s of the first minute (baseline) and the last 30 s prior to exhaustion.

### **MARKERS OF FEEDBACK FROM GROUP III-IV MUSCLE AFFERENTS.**

In Study 2, muscle occlusion was used at exhaustion or after three minutes recovery to trap in the knee extensor muscles the metabolites known to stimulate group III-IV muscle afferents. To date, no non-invasive method exists which allows assessment of feedback from group III-IV muscle afferents in humans. However, in absence of central motor command, these muscle afferents are known to induce an increase in MAP during muscle occlusion (Kaufman, 2012) and are also the sensory signal generating muscle pain (O'Connor and Cook, 1999). Therefore, when measured during muscle occlusion at rest (in absence of central motor command), MAP and leg muscle pain can be used as indirect markers of feedback from group III-IV muscle afferents in humans. Furthermore, as muscle occlusion is known to induce degradation of adenosine triphosphate, increase in bradykinin and reactive oxygen species in the muscle milieu and consequently activating group III-IV muscle afferents (Crisafulli, 2006; Crisafulli et al., 2011), we compared MAP and leg muscle pain values during pre and post-exercise muscle occlusion.

**Mean arterial pressure.** Subjects sat on the same ergometer where the OLDE was performed. After three minutes at rest, a pneumatic cuff previously placed as high as possible on the exercising thigh was rapidly inflated (< 2 s) to 300 mmHg by an automatic inflator device (Hokanson E20 Rapid Cuff Inflator and AG101 Air Source, Bellevue, WA). The pre-exercise occlusion was maintained for three minutes to identify if the muscle occlusion (in absence of metabolites produced by exercise) could elicit an increase in arterial blood pressure. Subjects then performed the OLDE warm-up and the time to

exhaustion. Immediately at exhaustion, or after three minutes of passive recovery, the pneumatic cuff was then re-inflated to 300 mmHg for three minutes.

**Leg muscle pain.** Leg muscle pain was also recorded during muscle occlusion pre and post OLDE. Values were collected at the end of each minute of the occlusion and then averaged. Subjects were also asked to report any muscle pain prior starting each session.

## STATISTICAL ANALYSIS

All data are presented as means  $\pm$  standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. Paired t-tests were used to compare time to exhaustion between sessions in each study, and MAP at rest and during pre-exercise muscle occlusion. Fully repeated measures 2 x 2 ANOVAs were used to test the effects of session (OLDE<sub>exh</sub> vs OLDE<sub>3min</sub>) and time (baseline and exhaustion) on leg RPE, leg muscle pain, cardiovascular parameters and EMG RMS. Fully repeated measures 2 x 11 ANOVAs were used to test the effects of session (OLDE<sub>exh</sub> vs OLDE<sub>3min</sub>) and time on muscle oxygenation during exhaustive OLDE. One-way repeated measures ANOVAs were used to test the effects of time (pre, exhaustion and three minutes recovery) on muscle oxygenation, blood lactate, cardiovascular responses during muscle occlusion and neuromuscular function parameters. Significant effect was followed up with Holm-Bonferonni tests as appropriate. As no cardiovascular and neuromuscular function parameter differed between sessions pre-exercise, pre-exercise values of each session were averaged. Assumption of normality for leg muscle pain during muscle occlusion after three minutes recovery was violated. Therefore, a Friedman ANOVA was performed. Significant effect was followed-up by Wilcoxon signed ranked tests with Holm-Bonferonni correction. When interactions were not significant, only main effects are reported. When interactions were significant, relevant simple main effects are reported. Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 20 for Mac OS X (SPSS Inc., Chicago, IL, USA). Cohen's effects size ( $d_z$ ) were calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany) and reported for follow up tests on cardiovascular responses and leg muscle pain during muscle occlusion and neuromuscular function parameters.

## IV. Results

OLDE<sub>exh</sub> and OLDE<sub>3min</sub> refer to the session with either muscle occlusion or neuromuscular tests performed respectively shortly after exhaustion and after three minutes recovery. Time to exhaustion was similar between sessions in Study 1 (OLDE<sub>exh</sub>:  $9.0 \pm 2.9$  min, OLDE<sub>3min</sub>:  $10.3 \pm 4.3$  min,  $P=0.164$ ) and Study 2 (OLDE<sub>exh</sub>:  $10.7 \pm 5.4$  min, OLDE<sub>3min</sub>:  $11.1 \pm 5.4$  min,  $P=0.555$ ).

### PHYSIOLOGICAL RESPONSES TO EXHAUSTIVE OLDE

*Cardiovascular responses.* Except systolic arterial pressure that presented a significant interaction effect ( $P=0.002$ ), all parameters did not present any main effect of session (all  $P>0.05$ ) or interaction (all  $P>0.05$ ), and significantly increased at exhaustion compared to baseline (all  $P<0.01$ ). Follow up tests on the interaction effect ( $P=0.007$ ) for the systolic arterial pressure revealed that exhaustion values were significantly higher than baseline in both sessions ( $P<0.001$ ). However, baseline values ( $P=0.817$ ) and exhaustion values ( $P=0.066$ ) did not significantly differ between sessions. Blood lactate concentration was greater at exhaustion ( $5.27 \pm 1.69$  mmol/L,  $P<0.001$ ) and after two minutes recovery  $4.57 \pm 1.48$  mmol/L,  $P<0.001$ ) than at baseline ( $1.13 \pm 0.27$  mmol/L). Blood lactate concentration did not recover after two minutes ( $P=0.174$ ). Main effect of time for cardiovascular and perceptual responses to exhaustive OLDE are presented table 10.

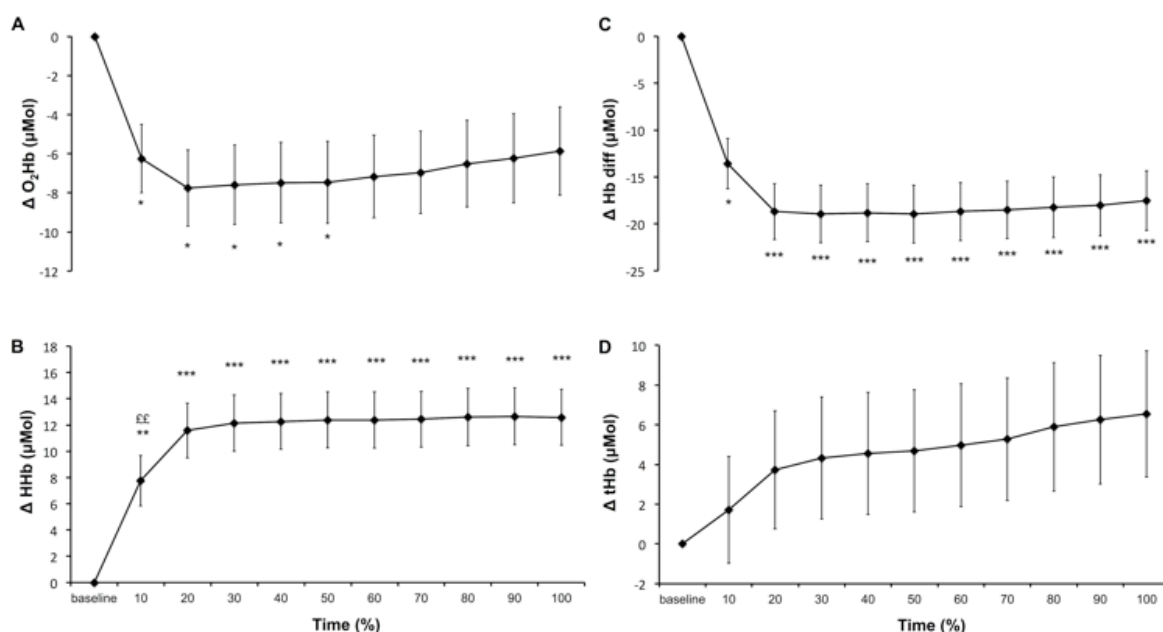


	Baseline	Exhaustion
Leg RPE	7.6 ± 0.9	19.7 ± 0.4 <sup>***</sup>
Leg muscle pain	0.3 ± 0.5	6.8 ± 2.8 <sup>***</sup>
Lactate (mmol/L)	1.13 ± 0.27	5.27 ± 1.69 <sup>***</sup>
Heart Rate (beats/min)	64.3 ± 10.9	129 ± 10.8 <sup>***</sup>
Systolic arterial pressure (mmHg)	113.7 ± 8.6	185.5 ± 26.8 <sup>***</sup>
Diastolic arterial pressure (mmHg)	71.9 ± 7.5	94.9 ± 17.0 <sup>**</sup>
Mean arterial pressure (mmHg)	85.8 ± 6.5	125.1 ± 17.4 <sup>***</sup>

**Table 10 - Cardiovascular and perceptual responses to exhaustive high intensity one leg dynamic exercise.**

Baseline values were measured at rest prior to pre-exercise muscle occlusion. Leg RPE (rating of perceived exertion) and leg muscle pain baseline values were measured during the last 15 s of the warm-up. Values are presented as mean ± SD for the main effect of time. <sup>\*\*\*</sup> significant difference from baseline P<0.001, <sup>\*\*</sup> significant difference from baseline P<0.01.

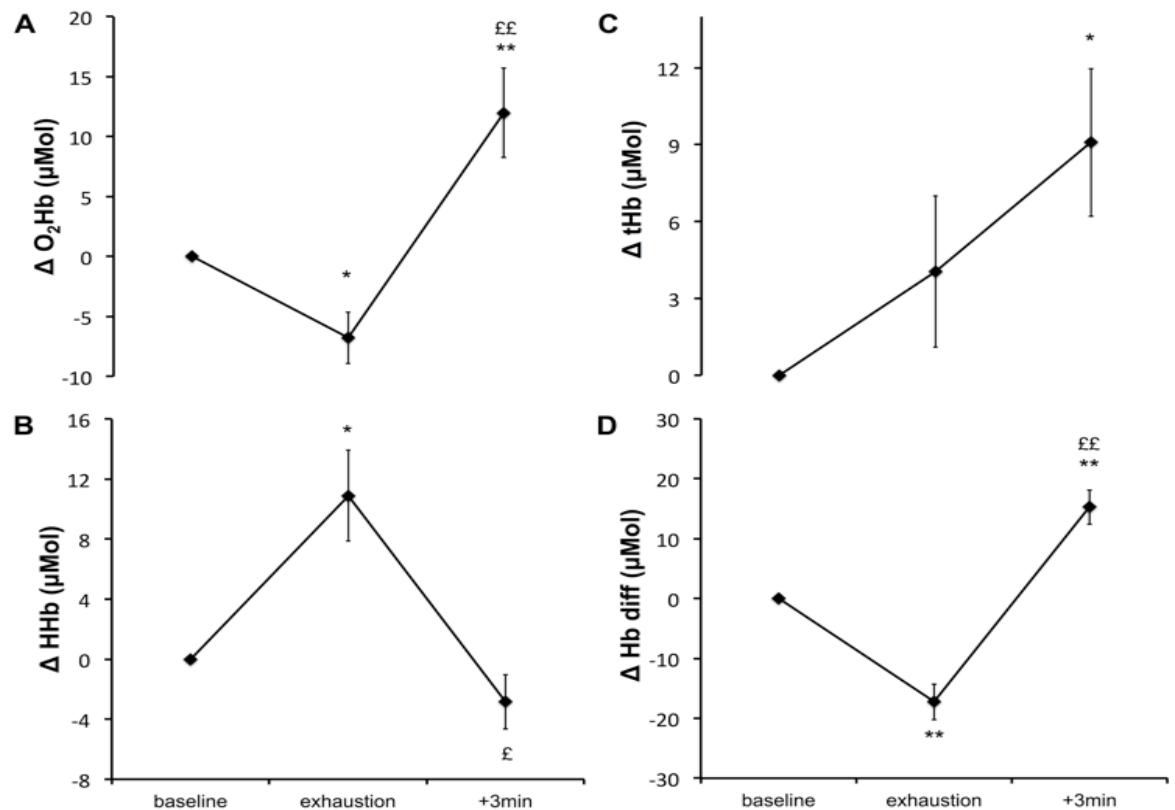
**Muscle oxygenation during OLDE.** None of the parameters presented any main effects of session (all P>0.05) or interaction (all P>0.05). Main effect of time for muscle oxygenation parameters is presented in figure 31.  $\Delta O_2Hb$  was lower than baseline (P<0.001) only from 10% to 50% of the time to exhaustion.  $\Delta HHb$  progressively increased until 20% of the time to exhaustion had been completed, and then plateaued (P<0.001).  $\Delta Hb$  diff decreased and then plateaued after 10% of the time to exhaustion (P<0.001). Despite  $\Delta tHb$  increasing over time (P=0.001), follow up tests failed to reveal any significant difference between different times compared to baseline and exhaustion values.



**Figure 31 - Changes from resting values (baseline) in vastus lateralis muscle oxyhaemoglobin ( $O_2Hb$ , panel A), deoxyhaemoglobin (HHb, panel B), haemoglobin difference (Hb diff, panel C) and total haemoglobin (tHb, panel D) during exhaustive high intensity one leg dynamic exercise expressed in percentage of time to exhaustion.**

Data are presented as mean  $\pm$  SEM for the main effect of time. Despite  $\Delta tHb$  increasing over time ( $P=0.001$ ), follow up tests failed to reveal any significant difference between different times compared to baseline and exhaustion values. \* significant difference from baseline  $P<0.05$ , \*\* significant difference from baseline  $P<0.01$ , \*\*\* significant difference from baseline  $P<0.001$ . ££ significant difference from 100% (exhaustion)  $P<0.01$ .

**Muscle oxygenation following OLDE.** Muscle oxygenation at exhaustion and after three minutes recovery are presented figure 32. At exhaustion,  $\Delta O_2Hb$  was lower than baseline ( $P=0.013$ ). After three minutes recovery,  $\Delta O_2Hb$  was higher than baseline ( $P=0.006$ ) and than exhaustion ( $P=0.002$ ).  $\Delta HHb$  was higher than baseline ( $P=0.014$ ). After three minutes of recovery,  $\Delta HHb$  was lower than exhaustion ( $P=0.006$ ) but did not differ from baseline ( $P=0.101$ ). At exhaustion,  $\Delta tHb$  did not differ from baseline ( $P=0.208$ ) but was higher after three minutes recovery compared to baseline ( $P=0.036$ ). At exhaustion,  $\Delta Hb$  diff was lower than baseline ( $P=0.006$ ), but after three minutes recovery muscle  $\Delta Hb$  diff was higher than baseline ( $P=0.006$ ) and higher than exhaustion ( $P=0.002$ ).



**Figure 32 - Changes in muscle oxygenation following exhaustive high intensity one leg dynamic exercise. Panel A,B,C and D present changes from resting values in vastus lateralis muscle oxyhaemoglobin ( $O_2Hb$ ), deoxyhaemoglobin ( $HHb$ ), haemoglobin difference ( $Hb$  diff) and total haemoglobin ( $tHb$ ) following exhaustive one leg dynamic exercise.**

Data were recorded at exhaustion and after three minutes of passive recovery (+3min). Data are presented as mean  $\pm$  SEM. \* significant difference from baseline  $P<0.05$ , \*\* significant difference from baseline  $P<0.01$ . <sup>£</sup> significant difference from exhaustion  $P<0.05$ , <sup>££</sup> significant difference from exhaustion  $P<0.01$ .

## CHANGES IN NEUROMUSCULAR FUNCTION INDUCED BY EXHAUSTIVE OLDE AND RECOVERY

There were no significant differences in pre-exercise neuromuscular function parameters between sessions (table 11). Therefore, pre-exercise values of each session were averaged (table 12). Changes in neuromuscular parameters induced by exhaustive OLDE are presented table 12. MVC decreased significantly at exhaustion ( $-41 \pm 17$  %,  $P<0.001$ ,  $d_z=2.897$ ). MVC recovered between exhaustion and after three minutes recovery ( $P=0.005$ ,  $d_z=1.401$ ), but was still significantly lower than pre-exercise values ( $-25 \pm 15$  %,  $P=0.002$ ,  $d_z=2.073$ ).

	<b>OLDE<sub>exh</sub></b>	<b>OLDE<sub>3min</sub></b>	<b>P value</b>
MVC (N·m)	235 ± 53	237 ± 44	0.928
<b><i>Peripheral parameters</i></b>			
Doublet (N·m)	92 ± 20	89 ± 10	0.538
Tw (N·m)	41 ± 13	42 ± 6	0.900
Tw <sub>RFD</sub> (N·m/ms)	0.51 ± 0.12	0.50 ± 0.06	0.836
M <sub>amplitude</sub> (VL) at rest (mV)	15.1 ± 0.5	14.9 ± 0.6	0.487
M <sub>amplitude</sub> (VL) at 50% MVC (mV)	13.8 ± 0.7	14.0 ± 1.0	0.490
M <sub>area</sub> (VL) at 50% MVC (mV/s)	0.092 ± 0.011	0.095 ± 0.013	0.391
<b><i>Central parameters</i></b>			
RMS <sub>MVC</sub> /RMS <sub>M</sub> (VL) EMG (%)	36.6 ± 10.4	36.1 ± 12.6	0.717
VAL (%)	92.8 ± 7.1	93.7 ± 6.8	0.502
<b><i>Cortical and spinal excitability</i></b>			
MEP <sub>area</sub> (mV/s)	0.056 ± 0.007	0.060 ± 0.014	0.201
MEP <sub>area</sub> /M <sub>area</sub> (%)	61.5 ± 12.1	63.9 ± 17.5	0.090
CSP (ms)	102.3 ± 16.8	109.0 ± 14.3	0.297
CMEP <sub>area</sub> (mV/s)	0.033 ± 0.011	0.033 ± 0.012	0.835
CMEP <sub>area</sub> /M <sub>area</sub> (%)	36.7 ± 16.3	35.1 ± 11.8	0.620
CMEP <sub>area</sub> /MEP <sub>area</sub> (%)	59.5 ± 17.8	57.3 ± 19.4	0.444

**Table 11 - Between sessions comparison of pre-exercise neuromuscular function parameters.**

Paired t-tests revealed no difference between sessions. CMEP, cervicomedullary evoked motor potential; CSP, cortical silent period; M, OLDE, one leg dynamic exercise: OLDE<sub>exh</sub>, session with testing shortly after exhaustion; OLDE<sub>3min</sub>, session with testing after three minutes recovery; maximal M-wave; MEP, motor evoked potential; MVC, maximal voluntary contraction; RMS, root mean square; VAL, voluntary activation level; VL, vastus lateralis; RFD, rate of force development; Tw, peak twitch. n=8 for MEP parameters, n=6 for CMEP parameters and n=6 for

$$\text{CMEP}_{\text{area}}/\text{MEP}_{\text{area}}$$

	pre	exhaustion	+3min
MVC (N·m)	236 ± 46	141 ± 50 <sup>***</sup>	180 ± 62 <sup>**££</sup>
<b>Peripheral parameters</b>			
Doublet (N·m)	91 ± 14	55 ± 21 <sup>***</sup>	66 ± 13 <sup>***£</sup>
Tw (N·m)	41 ± 8	25 ± 12 <sup>***</sup>	26 ± 10 <sup>***</sup>
Tw <sub>RFD</sub> (N·m/ms)	0.50 ± 0.07	0.32 ± 0.12 <sup>***</sup>	0.33 ± 0.09 <sup>***</sup>
M <sub>amplitude</sub> (VL) at rest (mV)	15.0 ± 0.5	15.5 ± 1.1	15.2 ± 0.8
M <sub>amplitude</sub> (VL) at 50% MVC (mV)	13.9 ± 0.8	14.8 ± 0.6 <sup>*</sup>	14.2 ± 1.2
M <sub>area</sub> (VL) at 50% MVC (mV/s)	0.094 ± 0.011	0.111 ± 0.008 <sup>**</sup>	0.105 ± 0.017
<b>Central parameters</b>			
RMS <sub>MVC</sub> /RMS <sub>M</sub> (VL) EMG (%)	36.3 ± 11.4	43.0 ± 19.7	40.9 ± 19.2
VAL (%)	93.2 ± 6.7	81.4 ± 15.2 <sup>*</sup>	88.2 ± 9.7 <sup>*£</sup>
<b>Cortical and spinal excitability</b>			
MEP <sub>area</sub> (mV/s)	0.058 ± 0.010	0.085 ± 0.015 <sup>***</sup>	0.074 ± 0.013 <sup>***££</sup>
MEP <sub>area</sub> /M <sub>area</sub> (%)	63.3 ± 13.9	76.7 ± 11.8 <sup>***</sup>	72.8 ± 16.6 <sup>***££</sup>
CSP (ms)	105.6 ± 13.2	126.3 ± 20.0 <sup>**</sup>	110.5 ± 19.7
CMEP <sub>area</sub> (mV/s)	0.033 ± 0.011	0.026 ± 0.015	0.034 ± 0.010
CMEP <sub>area</sub> /M <sub>area</sub> (%)	35.9 ± 13.7	23.2 ± 12.7 <sup>***</sup>	32.4 ± 10.0 <sup>£</sup>
CMEP <sub>area</sub> /MEP <sub>area</sub> (%)	57.3 ± 16.1	31.4 ± 16.3 <sup>**</sup>	47.2 ± 11.8 <sup>**££</sup>

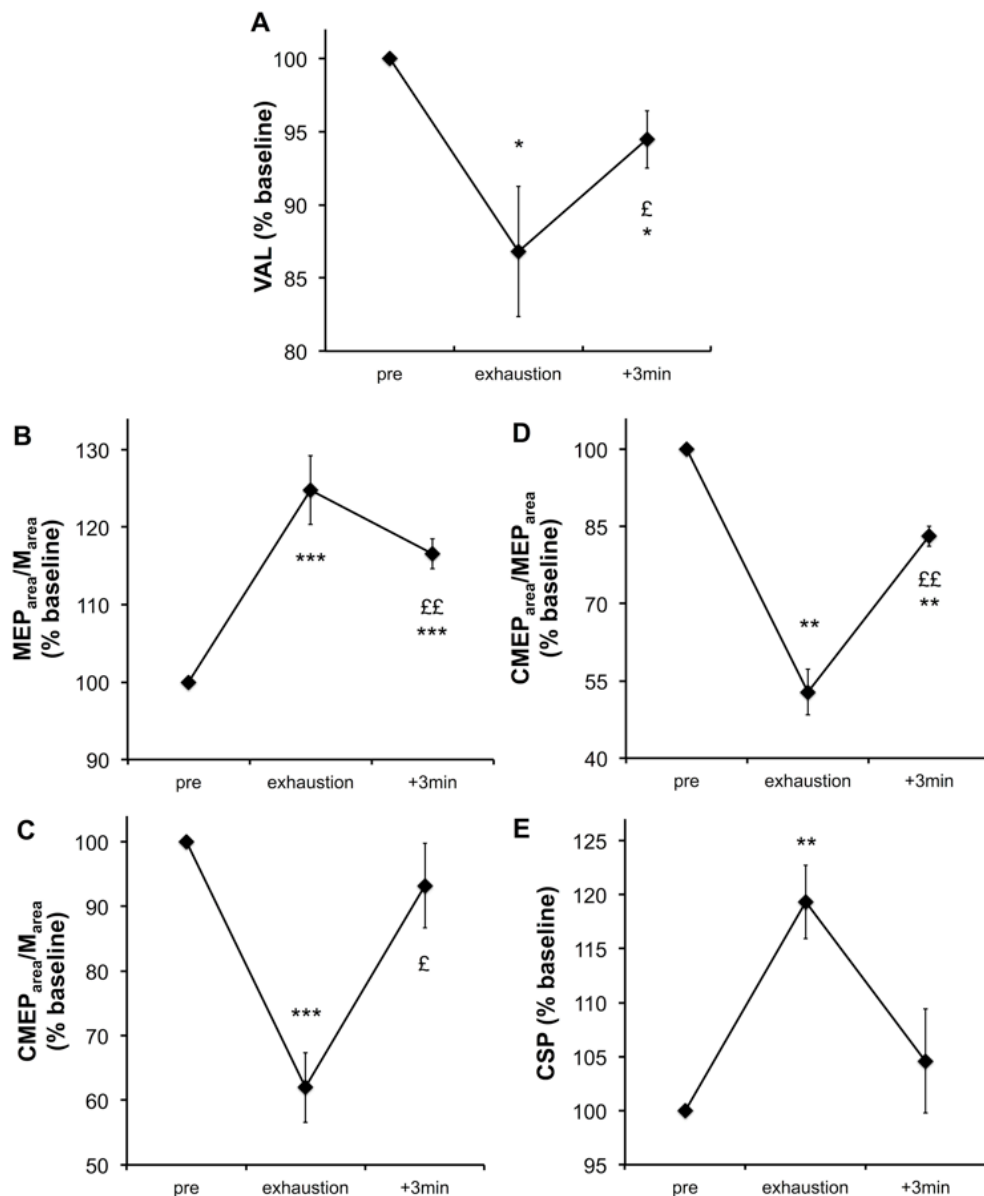
**Table 12 - Changes in neuromuscular parameters following exhaustive high intensity one leg dynamic exercise.**

Neuromuscular tests were performed pre and post time to exhaustion, either shortly after exhaustion or after three minutes recovery (+3min). CMEP, cervicomedullary evoked motor potential; CSP, cortical silent period; M, maximal M-wave; MEP, motor evoked potential; MVC, maximal voluntary contraction; RMS, root mean square; VAL, voluntary activation level; VL, vastus lateralis; RFD, rate of force development; Tw, peak twitch. n=8 for MEP parameters, n=6 for CMEP parameters and n=6 for CMEP<sub>area</sub>/MEP<sub>area</sub>. <sup>\*</sup> significant difference from pre P<0.05, <sup>\*\*</sup> significant difference from pre P<0.01, <sup>\*\*\*</sup> significant difference from pre P<0.001, <sup>£</sup> significant difference from exhaustion P<0.05, <sup>££</sup> significant difference from exhaustion P<0.01.

**Peripheral fatigue.** Doublet amplitude decreased significantly at exhaustion ( $-40 \pm 15 \%$ ,  $P < 0.001$ ,  $d_z = 2.735$ ) and remained lower than pre-exercise values after three minutes recovery ( $-28 \pm 9 \%$ ,  $P < 0.001$ ,  $d_z = 5.128$ ). However, doublet amplitude partially recovered after three minutes ( $P = 0.023$ ,  $d_z = 0.722$ ).  $T_w$  and  $T_{w_{RFD}}$  decreased at exhaustion and remained lower than pre-exercise values after three minutes recovery (all  $P < 0.001$ ).  $T_w$  and  $T_{w_{RFD}}$  did not recover after three minutes ( $P = 0.740$ ,  $d_z = 0.122$  and  $P = 0.814$ ,  $d_z = 0.086$ ).  $M_{\text{amplitude}}$  at rest did not change over time ( $P = 0.373$ ).  $M_{\text{amplitude}}$  at 50% MVC was significantly higher than pre-exercise only at exhaustion ( $+7 \pm 6 \%$ ,  $P = 0.036$ ,  $d_z = 1.198$ ).  $M_{\text{area}}$  at 50 % MVC was significantly higher than pre-exercise at exhaustion ( $+20 \pm 12 \%$ ,  $P = 0.006$ ,  $d_z = 1.727$ ) and tended to be higher than pre-exercise after three minutes recovery ( $+12 \pm 12 \%$ ,  $P = 0.060$ ,  $d_z = 0.958$ ).

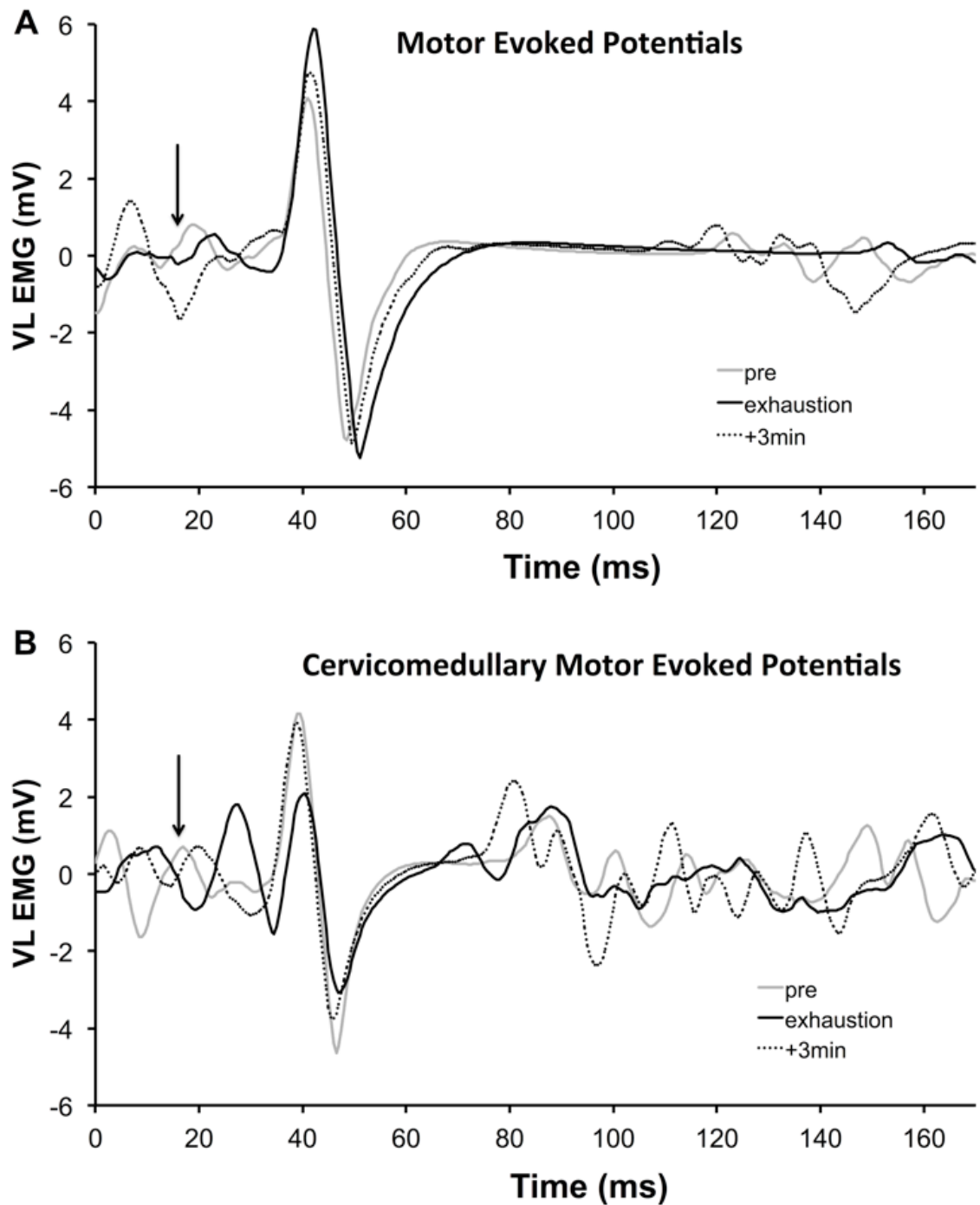
**Central fatigue.** VAL (figure 33A) decreased significantly at exhaustion ( $-13 \pm 13 \%$ ,  $P = 0.039$ ,  $d_z = 1.160$ ) and remained lower than pre-exercise values after three minutes recovery ( $-6 \pm 6 \%$ ,  $P = 0.036$ ,  $d_z = 1.087$ ). However, VAL partially recovered after three minutes ( $P = 0.050$ ,  $d_z = 0.835$ ).  $RMS_{MVC}/RMS_M$  of the vastus lateralis did not change over time ( $P = 0.272$ ).

**Cortical and spinal excitability.** A typical recording of MEP and CMEP changes can be found in figure 34.  $MEP_{\text{area}}/M_{\text{area}}$  ratio (figure 33B) increased at exhaustion ( $+25 \pm 27 \%$ ,  $P < 0.001$ ,  $d_z = 1.005$ ) and remained higher than pre-exercise values after three minutes recovery ( $+17 \pm 20 \%$ ,  $P < 0.001$ ,  $d_z = 0.902$ ). However,  $MEP_{\text{area}}/M_{\text{area}}$  ratio partially recovered after three minutes ( $P = 0.003$ ,  $d_z = 0.249$ ).  $CMEP_{\text{area}}/M_{\text{area}}$  ratio (figure 33C) was significantly lower than pre-exercise only at exhaustion ( $-38 \pm 13 \%$ ,  $P < 0.001$ ,  $d_z = 4.245$ ).  $CMEP_{\text{area}}/M_{\text{area}}$  ratio fully recovered after three minutes ( $P = 0.032$ ,  $d_z = 1.450$ ).  $CMEP_{\text{area}}/MEP_{\text{area}}$  (figure 33D) decreased at exhaustion ( $-48 \pm 17 \%$ ,  $P = 0.003$ ,  $d_z = 2.891$ ) and remained lower than pre-exercise values after three minutes recovery ( $-17 \pm 14 \%$ ,  $P = 0.033$ ,  $d_z = 1.192$ ).  $CMEP_{\text{area}}/MEP_{\text{area}}$  ratio partially recovered after three minutes ( $P = 0.010$ ,  $d_z = 1.975$ ). Finally, CSP (figure 33E) was significantly higher than pre-exercise only at exhaustion ( $+19 \pm 9 \%$ ,  $P = 0.003$ ,  $d_z = 1.946$ ) and not after three minutes recovery ( $+5 \pm 13 \%$ ,  $P = 0.345$ ,  $d_z = 0.358$ ).



**Figure 33 - Changes in central fatigue and corticospinal parameters relative to baseline (i.e. pre-exercise values) following exhaustive high intensity one leg dynamic exercise.**

Data were recorded shortly after exhaustion and after three minutes recovery (+3min). Decrease in voluntary activation level (VAL) is presented panel A. Changes in motor evoked potential (MEP, n=8) area normalised by maximal M-wave (M) area (panel B). Changes in cervicomedullary motor evoked potential (CMEP, n=6) area normalised by maximal M-wave area (panel C). Changes in the ratio CMEP<sub>area</sub>/MEP<sub>area</sub> (panel D, n=6) and the MEP cortical silent period (CSP, panel E). Data are presented as mean  $\pm$  SEM. Baseline corresponds to values pre-exercise. \* significant difference from baseline value for the same session ( $P < 0.05$ ), \*\* significant difference from baseline value for the same session ( $P < 0.01$ ), \*\*\* significant difference from baseline value for the same session ( $P < 0.001$ ), £ significant difference from exhaustion value ( $P < 0.05$ ), ££ significant difference from exhaustion value ( $P < 0.01$ ).



**Figure 34 - A typical recording of changes in motor evoked potentials (panel A) and cervicomedullary motor evoked potentials (panel B) recorded on the vastus lateralis muscle (VL).**

The arrow represents the point of stimulation. Measurements were performed pre exhaustive high intensity one leg dynamic exercise (grey line), at exhaustion (black line) and after three minutes recovery (+3min, dotted line).



## CHANGES IN MARKERS OF FEEDBACK FROM GROUP III-IV MUSCLE AFFERENTS INDUCED BY EXHAUSTIVE OLDE AND RECOVERY

**Cardiovascular responses.** MAP during muscle occlusion pre-exercise was significantly higher compared to resting values ( $90.0 \pm 7.9$  mmHg vs  $85.9 \pm 5.9$  mmHg,  $p=0.025$ ), despite absence of exercise-induced metabolites. Therefore, elevation of cardiovascular responses in response to muscle metabolites elicited during post-exercise muscle occlusion was compared to cardiovascular responses during pre-exercise muscle occlusion. There were no significant differences in pre-exercise cardiovascular responses during muscle occlusion (table 13). Therefore, pre-exercise values of each session were averaged. Cardiovascular responses during muscle occlusion pre- and post-exercise are presented in figure 35. Heart rate was higher during muscle occlusion at exhaustion ( $P=0.009$ ,  $d_z=1.294$ ) and remained higher than pre-exercise values after three minutes recovery ( $P=0.006$ ,  $d_z=1.264$ ). Systolic arterial pressure was higher during muscle occlusion at exhaustion ( $P=0.006$ ,  $d_z=1.388$ ) and remained higher than pre-exercise values after three minutes recovery ( $P=0.014$ ,  $d_z=0.940$ ). After three minutes recovery, systolic arterial pressure during muscle occlusion was lower compared to values at exhaustion ( $P=0.026$ ,  $d_z=1.439$ ). Diastolic arterial pressure during muscle occlusion was higher than pre-exercise values only at exhaustion ( $P=0.006$ ,  $d_z=0.971$ ). MAP was higher during muscle occlusion at exhaustion ( $P=0.006$ ,  $d_z=1.339$ ) compared to pre-exercise values, but recovered after three minutes ( $P=0.172$ ,  $d_z=0.470$ ). MAP during muscle occlusion after three minutes recovery was lower than MAP at exhaustion ( $P=0.006$ ,  $d_z=1.241$ ).

**Table 13 - Between sessions comparison of cardiovascular parameters during pre-exercise muscle occlusion**

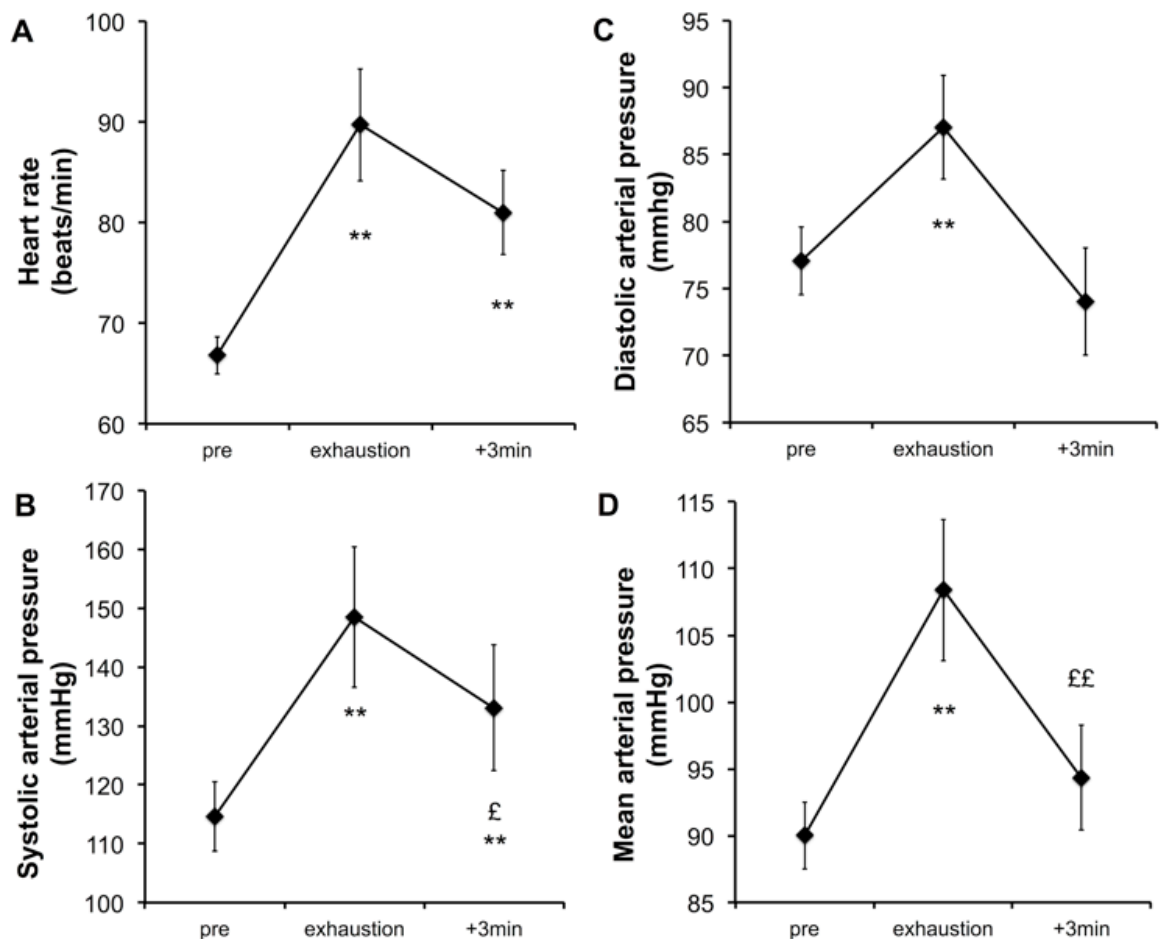
Paired t-tests revealed no difference between sessions. OLDE, one leg dynamic exercise; OLDE<sub>exh</sub>, session with testing shortly after exhaustion; OLDE<sub>3min</sub>, session with testing after three minutes recovery.

	OLDE <sub>exh</sub>	OLDE <sub>3min</sub>	P value
Heart Rate (beats/min)	$65.5 \pm 6.7$	$68.1 \pm 10.0$	0.491
Systolic arterial pressure (mmHg)	$116.2 \pm 16.6$	$113.0 \pm 21.4$	0.286
Diastolic arterial pressure (mmHg)	$78.3 \pm 10.4$	$75.8 \pm 8.5$	0.465
Mean arterial pressure (mmHg)	$91.4 \pm 8.0$	$88.7 \pm 9.8$	0.335

**Leg muscle pain.** None of the subjects reported leg muscle pain at the start of each session. Leg muscle pain pre-exercise was higher during the OLDE<sub>exh</sub> session compared to the OLDE<sub>3min</sub> session ( $2.48 \pm 1.55$  vs  $1.74 \pm 1.27$ ,  $P=0.047$ ,  $d_z = 0.728$ ). At exhaustion during the OLDE<sub>exh</sub> session, pain was higher than pre-exercise values ( $6.24 \pm 2.83$  vs  $2.48 \pm 1.55$ ,  $P=0.044$ ,  $d_z = 1.286$ ). After three minutes recovery during the OLDE<sub>3min</sub> session, pain was similar as pre-exercise values ( $2.93 \pm 2.11$  vs  $1.74 \pm 1.27$ ,  $P=0.514$ ,  $d_z = 0.392$ ). After three minutes recovery during the OLDE<sub>3min</sub> session pain was perceived lower than at exhaustion during the OLDE<sub>exh</sub> session ( $6.24 \pm 2.83$  vs  $2.93 \pm 2.11$ ,  $P=0.036$ ,  $d_z = 1.189$ ).

**Figure 35 - Cardiovascular responses during muscle occlusion pre and post exhaustive high intensity one leg dynamic exercise.**

Occlusion post-exercise occurred either at exhaustion or after three minutes of passive recovery (+3min). Values are presented as mean  $\pm$  SEM. \*\* significant difference from pre  $P<0.01$ , <sup>£</sup> significant difference from exhaustion  $P<0.05$ , <sup>££</sup> significant difference from exhaustion  $P<0.01$ .



## V. Discussion

The aim of study 1 was to describe central alterations of neuromuscular function (i.e. central fatigue and changes in corticospinal parameters) and their recovery following exhaustive high intensity OLDE. According to our hypothesis, central fatigue and changes in corticospinal parameters induced by exhaustive high intensity OLDE were greater shortly after exhaustion than after three minutes recovery. This is the first study reporting an increase in cortical excitability and CSP, and a decrease in spinal excitability at exhaustion following exhaustive high intensity OLDE. The aim of study 2 was to use MAP and leg muscle pain during muscle occlusion as markers of feedback from group III-IV muscle afferents. These markers demonstrate that high intensity OLDE significantly increase afferent feedback from group III-IV muscle afferents. Furthermore, our results suggest that after three minutes of recovery, feedback from group III-IV muscle afferent is no longer significant. Also, when integrating the results of both studies, the present investigation suggests that the observed increase in CSP and decrease in spinal excitability could be associated with feedback from group III-IV muscle afferents. However, contrary to our initial hypothesis, central fatigue (i.e. decrease in VAL) was not strongly associated with feedback from group III-IV muscle afferents as demonstrated by the persistence of central fatigue in absence of increased-leg muscle pain and MAP during muscle occlusion after three minutes recovery.

### **PHYSIOLOGICAL RESPONSES DURING HIGH INTENSITY OLDE**

As observed in previous studies, exhaustive high intensity OLDE performed to exhaustion induced significant increases in blood lactate, perception of effort and pain, and EMG activity of the vastus lateralis muscle (Rossman et al., 2012; Amann et al., 2013). Additionally, MAP and heart rate also increased during exhaustive OLDE.

We monitored changes in oxygenation of the vastus lateralis muscle via near infrared spectroscopy. Interestingly, the vastus lateralis muscle  $\Delta$ HHb signal continued to increase until 20% of the time to exhaustion test, and then plateaued, with no change in tHb. This early increase and plateau suggests an increase in oxygen extraction that is then held constant until exhaustion. This early alteration in vastus lateralis muscle oxygenation is likely to reflect important changes within the muscle, such as accumulation of exercise-induced metabolites. Indeed, Froyd et al. (2013) highlighted that major changes in skeletal

muscle function occurred within the first 40% of high intensity self-paced isokinetic exercise.

## **MVC AND PERIPHERAL FATIGUE FOLLOWING EXHAUSTIVE HIGH INTENSITY OLDE AND RECOVERY**

Exhaustive high intensity OLDE induced significant muscle fatigue, as demonstrated by the decrease in MVC torque shortly after exhaustion and after three minutes recovery. The decrease shortly after exhaustion in MVC torque in the present study (~40%) is greater than that demonstrated by Cheng and Rice (~25%; Cheng and Rice, 2005) following OLDE performed at maximal velocity. The difference between both studies is likely due to the fact that their subjects did not reach volitional exhaustion but were stopped once the contraction velocity was reduced by 35%. Contrary to Cheng and Rice (2005), the isometric torque production capacity in our study partially recovered after three minutes. This recovery process was associated with a recovery in peripheral fatigue (e.g. doublet amplitude evoked at rest), confirming a recovery in skeletal muscle function (Froyd et al., 2013). Our findings also support the existence of low frequency fatigue following exhaustive dynamic exercise (Decorte et al., 2010; Froyd et al., 2013). Indeed, only torque amplitude evoked by high frequency stimulation (doublet at 100 Hz), and not by single stimulation, recovered after three minutes. Furthermore, it has to be noticed that the significant potentiation in  $M_{\max}$  shortly after exhaustion suggests that exhaustive OLDE impairs membrane excitability (Millet and Lepers, 2004).

## **CENTRAL FATIGUE FOLLOWING EXHAUSTIVE HIGH INTENSITY OLDE AND RECOVERY**

The aim of the first study was to investigate the extent of central alterations of neuromuscular function following exhaustive high intensity OLDE and their recovery. Of particular interest is central fatigue. Central fatigue is an exercise-induced reduction in the capacity of the central nervous system to fully recruit the active muscles during an MVC, and can occur at both spinal and/or supraspinal level (for review see Gandevia, 2001). In the present study, the decrease in VAL was significantly greater shortly after exhaustion (~13%) than after three minutes recovery (~6%). The extent of central fatigue shortly after exhaustion in our study is similar to those measured following exhaustive submaximal

(Place et al., 2005) or intermittent (Goodall et al., 2010; Gruet et al., 2014) isometric contraction of the knee extensor muscles.

To the best of our knowledge, only one study (Rossman et al., 2014) demonstrated a significant decrease in VAL measured within 2.5 min after cessation of exhaustive high intensity OLDE. Our results suggest that the typical time delay between cessation of the exercise and the start of neuromuscular testing following exhaustive high intensity OLDE may lead to an underestimation of the extent of central fatigue. Interestingly, contrary to previous studies on exhaustive high intensity OLDE (Rossman et al., 2012; Amann et al., 2013) and cycling exercise (e.g. Amann et al., 2006), we found a significant decrease in VAL after three minutes recovery. This persistent decrease in VAL three minutes after exhaustion in the present study is likely to be explained by i) the use of high frequency paired stimulation (100 Hz) to overcome the negative effect of low frequency fatigue on force production; and ii) the fact that we used electrical stimulation and not magnetic stimulation to induce the superimposed and potentiated doublet. Despite the fact that magnetic and electrical stimulation are known to be both valid for neuromuscular function testing (Verges et al., 2009), some studies assessing neuromuscular function following exhaustive dynamic exercise with magnetic stimulation were unable to stimulate at supramaximal intensity (stimulation performed at a near-plateau of resting twitch and M-wave; e.g. Amann et al., 2006; Amann et al., 2008b). Therefore, as the excitation threshold of nerve fibres increases with fatigue (Burke, 2002), these studies may have underestimated the magnitude of knee extensor muscle fatigue.

Several studies used the  $\text{RMS}_{\text{MVC}}/\text{RMS}_{\text{M}}$  EMG ratio to quantify the amount of central fatigue following prolonged exercise (for review see Millet and Lepers, 2004) or isometric contraction (e.g. Pageaux et al., 2013). In contrast to previous studies showing similar changes in VAL and  $\text{RMS}_{\text{MVC}}/\text{RMS}_{\text{M}}$  EMG ratio following isometric contraction of the knee extensor muscles (e.g. Pageaux et al., 2013), our study failed to provide evidence for a decrease in the  $\text{RMS}_{\text{MVC}}/\text{RMS}_{\text{M}}$  EMG ratio either shortly after exhaustion or after three minutes recovery. This result confirms that EMG signal is not a reliable index of central motor drive during high intensity dynamic exercise (Farina, 2006). Therefore, as recently reminded, assessment of the inhibition of the central motor drive in humans, i.e. central fatigue, should be performed via the twitch interpolation technique (Gandevia et al., 2013).

## CORTICAL AND SPINAL EXCITABILITY FOLLOWING EXHAUSTIVE HIGH INTENSITY OLDE AND RECOVERY

We also investigated changes in corticospinal parameters induced by exhaustive OLDE. Isometric exercise is well known to induce alterations of both spinal and supraspinal excitability (for review see Gandevia, 2001), but to date, no study has investigated changes in corticospinal parameters induced by exhaustive OLDE. Furthermore, cervicomedullary stimulation (known to be the most appropriate comparison to allow interpretation of changes in MEP; Taylor and Gandevia, 2004) has been used only during submaximal cycling exercise (Sidhu et al., 2012a; Sidhu et al., 2012b), and not following exhaustive dynamic exercise. Therefore, it is unknown whether dynamic exercise could impair motoneuron responsiveness.

Our findings provide the first evidence that high intensity OLDE performed to exhaustion significantly decreases spinal excitability, whilst increasing supraspinal excitability. Shortly after exhaustion,  $MEP_{area}/M_{area}$  ratio presented an increase of ~30%, while  $CMEP_{area}/M_{area}$  ratio decreased by ~40% compared to pre-exercise levels. Contrary to  $MEP_{area}/M_{area}$  ratio,  $CMEP_{area}/M_{area}$  ratio fully recovered after three minutes. The MEP results differ from those obtained following intermittent submaximal isometric contractions performed until exhaustion (Goodall et al., 2010; Gruet et al., 2014) or task failure (defined as a decrease in MVC of 35%; Kalmar and Cafarelli, 2006). In the studies previously mentioned, the authors found both an unchanged MEP (Goodall et al., 2010; Gruet et al., 2014) and a decrease in corticospinal excitability (Kalmar and Cafarelli, 2006). Interestingly, Jubeau et al. (2014) and Temesi et al. (2013) found an increase in MEP following prolonged cycling and running exercise. Therefore, taking the findings of these studies together, there is the suggestion that changes in corticospinal excitability of the knee extensor muscles might be specific to the muscle contraction performed. Moreover, the 50% decrease in  $CMEP_{area}/MEP_{area}$  ratio shortly after exhaustion also suggests that increases in cortical excitability are likely to be underestimated. Indeed, MEP may be influenced by fatigue related changes in responsiveness of the motoneuron pool, as is the case in the present study (i.e. decrease in CMEP). The relatively short time course of recovery in cortical and spinal excitability could be a factor in the previously reported lack of significant changes in corticospinal excitability following exhaustive cycling exercise (e.g. Goodall et al., 2012).

During muscle contraction, TMS applied over the motor cortex is known to cause a short latency silent period in the EMG signal, named CSP (Inghilleri et al., 1993). An

increase in CSP has been suggested to reflect an increase in excitability of inhibitory gamma-aminobutyric acid (GABA)<sub>B</sub> interneurons. To the best of our knowledge, only one study (Temesi et al., 2013) has demonstrated an increase in CSP (at sub-optimal and not optimal TMS intensity) following prolonged running exercise, and only one study following intermittent isometric exercise performed until exhaustion (Gruet et al., 2014). Our findings present the first experimental evidence that exhaustive OLDE induces an increase in CSP. However, caution has to be taken in CSP interpretation, as CSP may reflect impaired motoneurons responsiveness rather than intracortical inhibition (McNeil et al., 2011). Therefore, as the increase in CSP and its recovery were associated with impaired motoneuron responsiveness and its recovery, the present study limits the conclusions on whether the observed increase in CSP reflects solely an increase in cortical inhibition, a decrease in motoneurons responsiveness, or a combination of both phenomena.

### **FEEDBACK FROM GROUP III-IV MUSCLE AFFERENTS FOLLOWING EXHAUSTIVE HIGH INTENSITY OLDE AND RECOVERY**

The aim of study 2 was to use a novel method to non-invasively quantify feedback from group III-IV muscle afferents in humans. We monitored MAP and leg muscle pain during post-exercise muscle occlusions shortly after exhaustion and after three minutes recovery. As previously demonstrated (Kaufman et al., 1984), in absence of central motor command, an increase in MAP during post-exercise muscle occlusion (i.e. metaboreflex) is known to be elicited by feedback from group III-IV muscle afferents. Therefore, quantification of MAP during muscle occlusion shortly after exhaustion and after three minutes recovery provides an indirect marker of feedback from group III-IV muscle afferents in humans (Crisafulli et al., 2006).

As expected, muscle occlusion pre-exercise (in absence of exercise-induced metabolites) induced an increase in MAP and leg muscle pain compared to resting values (with no muscle occlusion). This increase in MAP and leg muscle pain during pre-exercise muscle occlusion is likely to be caused by degradation of adenosine triphosphate, increase in bradykinin and reactive oxygen species in the muscle milieu during the muscle occlusion, inducing feedback from group III-IV muscle afferents (Crisafulli, 2006; Crisafulli et al., 2011). Therefore, indirect assessment of exercise-induced feedback from group III-IV muscle afferents must be compared between pre- and post-exercise muscle

occlusion and not between resting (no muscle occlusion) and post-exercise muscle occlusion.

Both MAP and leg muscle pain during post-exercise muscle occlusion increased shortly after exhaustion and returned to pre-exercise values after three minutes recovery. Moreover, MAP and leg muscle pain significantly decreased during the three minutes recovery. Therefore, our results suggest a strong feedback from group III-IV muscle afferents only shortly after exhaustion and not after three minutes recovery. The decrease in feedback from group III-IV muscle afferents is likely to be explained by a decrease in metabolites in the muscle milieu during the recovery period. This hypothesis is supported by our near infrared spectroscopy data. Indeed, near infrared spectroscopy can be used as an indirect index of oxidative metabolism (Hamaoka et al., 1996). The higher O<sub>2</sub>Hb and Hb diff after three minutes recovery compared to exhaustion is suggestive of a decrease in accumulated metabolites in the muscle. Indeed O<sub>2</sub>Hb is known to be correlated with regulatory metabolites (ADP and PCr) of oxidative phosphorylation (Hamaoka et al., 1996). However, interpretation of the O<sub>2</sub>Hb signal is complicated by contaminant increases in tHb following the exhaustive exercise.

Previous studies have demonstrated that metabolites concentration in the muscle milieu following dynamic exercise is known to quickly decrease (Sahlin et al., 1976; Lott et al., 2001), providing further support to the decrease in feedback from group III-IV muscle afferents observed in the present study. Our results on the recovery of feedback from group III-IV muscle afferents support previous studies hypothesising a quick recovery of these muscle afferents after cessation of exercise in humans (e.g. Amann et al., 2013).

## **FEEDBACK FROM GROUP III-IV MUSCLE AFFERENTS AND CENTRAL ALTERATIONS OF NEUROMUSCULAR FUNCTION**

By integrating the results of study 1 and 2 we also investigated the association between central alterations of neuromuscular function and feedback from group III-IV muscle afferents. The concomitant increased-leg muscle pain and MAP during muscle occlusion and decrease in VAL shortly after exhaustion is consistent with the hypothesis that feedback from group III-IV muscle afferents might induce a reduction in the capacity of the central nervous system to fully recruit the active muscles during an MVC (for review see Gandevia, 2001). Our findings on the recovery time course of central fatigue



are of particular importance in the interpretation of previous studies, which proposed feedback from group III-IV muscle afferents as a contributor to the inhibition of the central motor drive (e.g. Amann et al., 2011a). Indeed, the persistent decrease in VAL after three minutes recovery occurred in absence of increased-leg muscle pain and MAP during muscle occlusion, two markers of feedback from III-IV muscle afferents (Freund et al., 1978; Cairns et al., 2005; Crisafulli et al., 2006). The persistence of central fatigue after three minutes recovery confirms that mechanisms other than feedback from group III-IV muscle afferents significantly contribute to central fatigue (for review see Gandevia, 2001). Therefore, alterations in brain dopamine (Meeusen et al., 2006) or brain glycogen concentration (Matsui et al., 2011) might contribute to the decrease in VAL observed following exhaustive rhythmic dynamic exercise.

Our results on central fatigue suggest that the cause and effect relationship between feedback from group III-IV muscle afferents and inhibition of the central motor drive still needs to be determined. Indeed, in one of the few experimental studies on the knee extensor muscles to date, Graven-Nielsen et al. (Graven-Nielsen et al., 2002) found a decrease of 20% in MVC of the knee extensor muscles following injection of hypertonic saline solution (known to induce afferent feedback from the injected muscles) in the rectus femoris muscle. This decrease in MVC occurred in absence of peripheral alteration, suggesting a causal link between feedback from group III-IV muscle afferents and central fatigue. However, because the authors did not measure VAL, this causal link remains unclear. Furthermore, Hilty et al. (Hilty et al., 2011) failed to demonstrate an effect of intrathecal fentanyl (known to block afferent feedback from the working muscles) on knee extensors MVC after a fatiguing isometric exercise. At first glance, the results of Hilty et al. (Hilty et al., 2011) seem to argue against the causal association between feedback from group III-IV muscle afferents and neuromuscular fatigue (i.e. exercise-induced decline in MVC). However, the authors measured MVC seven minutes after cessation of exercise (Hilty et al., 2011). Our results clearly suggest that after such a long time delay feedback from group III-IV muscle afferents is not significant. Therefore, further investigations are required to establish the cause and effect relationship between discharge activity of III-IV muscle afferents and decrease in VAL.

The present study demonstrates complete recovery of the  $CMEP_{area}/M_{area}$  ratio after three minutes (as leg muscle pain and cardiorespiratory responses during muscle occlusion) suggesting that feedback from group III-IV muscle afferents is likely to decrease the responsiveness of the motoneuron pool innervating the knee extensor

muscles. Similar to MAP and leg muscle pain during muscle occlusion (i.e. both markers of feedback from group III-IV muscle afferents), the CSP increased only shortly after exhaustion and was fully recovered after three minutes. These parallel changes in metaboreflex and CSP suggest that feedback from group III-IV muscle afferents might cause the lengthening of the CSP. This hypothesis has received experimental support from a spinal blockade study by Hilty et al. (Hilty et al., 2011). These authors found a lack of increase in CSP following isometric knee extension exercise, only when subjects received injection of intrathecal fentanyl that is known to block feedback from group III-IV muscle afferents from the working muscles.

## LIMITATIONS, CONCLUSIONS AND PERSPECTIVES

The results of the first study demonstrate the extent of central fatigue and changes in corticospinal excitability following exhaustive high intensity OLDE. However, as CMEP in the lower limbs can only be elicited during submaximal contraction for most subjects (Taylor and Gandevia, 2004), our data does not provide any information on the resting corticospinal excitability. Furthermore, as  $MEP_{amplitude}$  and  $CMEP_{amplitude}$  ratio were not matched and consequently activated a different proportion of the motoneuron pool, further studies matching MEP and CMEP amplitude are required. However, because MEP increased and CMEP decreased (antagonistic responses), we are confident that future studies matching MEP and CMEP amplitude will strengthen the results of the present study.

The second study demonstrated a recovery in MAP and leg muscle pain during muscle occlusion after three minutes post-exercise. As both MAP and leg muscle pain in absence of central motor command are known to reflect central integration of feedback from group III-IV muscle afferents, our results suggest the possibility to indirectly assess via muscle occlusion feedback from group III-IV muscle afferents in humans.

Finally, by integrating both studies, our results suggest a significant association between spinal excitability, CSP and feedback from group III-IV muscle afferents following exhaustive OLDE. Nevertheless, the cause and effect relationship between feedback from group III-IV muscle afferents and inhibition of the central motor drive (central fatigue) still needs to be established. Therefore, the exercise model and new integrative methodology used in the present studies provide the ideal tools to assess the effects of various experimental manipulations (e.g. spinal blockade of afferent feedback

from the working muscles) on the cause and effect relationship between feedback from group III-IV muscle afferents, central fatigue and corticospinal excitability in humans.

## **CHAPTER 3: PERCEPTION OF EFFORT GENERATION IS INDEPENDENT OF MUSCLE AFFERENTS FEEDBACK**

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**To be submitted in** Plos One, Medicine and Science in Sports and Exercise or Sports Medicine

## **Abstract**

Two models explain the mechanisms underlying perception of effort generation: i) the corollary discharge (CD) model and ii) the afferent feedback (AF) model. In order to investigate the validity of these models, we used electromyostimulation (EMS) to manipulate the magnitude of central motor command during voluntarily (VOL), evoked (EMS) and combined (EMS+VOL) contractions at same level of force. As EMS is known to send sensory volley to the central nervous system, EMS was used to stimulate AF. We hypothesised that perception of effort would reflect the magnitude of the central motor command, supporting the CD model. Ten subjects experienced with EMS took part in this study. VOL, EMS and EMS+VOL contractions were performed during isotonic (5% and 20% MVC) and isometric contractions (10 and 20% MVC). Subjects were asked to report effort for each contraction. For the same level of force, subjects did not report any effort during evoked contractions (no central motor command), but all reported effort during voluntarily contractions. Furthermore, subjects rated the effort lower (isometric:  $P=0.036$ ,  $d_z=1.062$ ; isotonic:  $P<0.001$ ,  $d_z=1.725$ ) during combined contractions (low central motor command) than during voluntarily contractions (full central motor command). Our results suggest that muscle afferent feedback is not the sensory signal generating perception of effort. This study provides further support in favour of the CD model, and future-imaging studies should investigate the brain areas associated with the generation of the CD responsible of perceived exertion generation.

## **I. Introduction**

Perception of effort, also called perceived exertion or sense of effort, is the conscious sensation of how hard, heavy and strenuous exercise is (Marcora, 2010b; de Morree et al., 2012). Perception of effort is a common phenomenon in daily life that plays an important role in regulating our physical activity behaviours, from choosing a sedentary life to engaging in various sport activities (Marcora, 2010b). Clinically, because perception of effort is related to exercise intensity (de Morree et al., 2012; de Morree and Marcora, 2012), it is a useful tool to prescribe and monitor exercise during a rehabilitation program

(Noble and Robertson, 1996). From a sport performance point of view, numerous studies demonstrated the crucial role of perception of effort in endurance performance during constant load (Marcora et al., 2008; Marcora et al., 2009; Pageaux et al., 2013) and self-paced (de Morree and Marcora, 2013; Pageaux, 2014; Pageaux et al., 2014) endurance exercise.

Interestingly, despite its role in human behaviour regulation, the neurophysiology of perception of effort has been scarcely investigated, and its mechanisms are still being debated (e.g. Marcora, 2011; Amann et al., 2013). It is well accepted that perception of effort generation results from the central processing of sensory signals. This central processing is likely to involve the pre supplementary motor area and also the anterior cingulate cortex (Williamson et al., 2001; 2002; de Morree et al., 2012). However, the nature of the sensory signals involved in perception of effort generation remains debated. Two different theories suggest that perception of effort reflects the central processing of i) the corollary discharge associated with the central motor command (corollary discharge model; Marcora, 2009); or ii) muscle afferents III-IV and muscle spindles (afferent feedback model, Luu et al., 2011; Amann et al., 2013).

Group III-IV muscle afferents are free nerve endings activated by contraction-induced mechanical and chemical stimuli (Rowell and O'Leary, 1990). Feedback from group III-IV muscle afferents is known to significantly contribute to cardiorespiratory regulation during exercise (metaboreflex, Kaufman, 2012), and also to be the sensory signal responsible for muscle pain (O'Connor and Cook, 1999). Their central projections to various spinal and supraspinal sites including the sensory cortex (Craig, 2002), present a logical pathway to hypothesise that perception of effort might be based on these afferent stimuli (see figure 1A in Marcora, 2009). However, as numerous studies manipulating group III-IV muscle afferents included limb discomfort in the instructions to rate perception of effort (e.g. Amann et al., 2009; Amann et al., 2011a), the rating of perceived exertion (RPE) values reported by the subjects cannot be interpreted. Indeed, as limb discomfort might be caused by muscle pain (i.e. group III-IV muscle afferents), any change in RPE in the aforementioned studies cannot be interpreted in favour or against the afferent feedback model. Furthermore, discomfort and pain cannot be part of the rating of effort as these sensations have been shown to be dissociated from each other (O'Connor and Cook, 2001; Marcora, 2009; Christian et al., 2014). Despite much recent evidence that perception of effort is generated from the corollary discharge associated with the motor command (e.g. Marcora, 2011; de Morree et al., 2012), to date, a role of muscle afferents

in its generation cannot be excluded (Amann et al., 2013) and further investigations are required (Amann and Light, 2014).

Traditionally, neurophysiology of perceived exertion is investigated via controlateral force matching tasks (e.g. McCloskey et al., 1974; Scotland et al., 2014). This approach clearly supported the role of the corollary discharge associated with the central motor command in perception of effort generation, but also demonstrated that with experience subjects are able to differentiate between sense of effort and sense of force (Jones, 1995). Therefore, as humans have the possibility to dissociate these two perceptions (effort vs force), it seems crucial to separate rating of effort and force. An alternative method to measure perception of effort and/or force is to use psychophysical scales (e.g. Borg, 1998) to measure the magnitude of the perception for different contraction intensities. This approach presents two advantages: i) perception of effort becomes the dependent variable and ii) subjects can rate their effort independently of their perception of force (i.e. perception that human can dissociate from effort).

Muscle force can be produced either by voluntary contraction (i.e. presence of central motor command) or by electromyostimulation (EMS, i.e. in absence of central motor command). EMS induces production of muscle force by depolarising motor axons beneath the stimulating electrodes (motor volley; Bergquist et al., 2011). Interestingly, EMS also induces depolarisation of sensory axons that will send a large sensory volley (antidromic transmission) into the CNS (at a spinal and supraspinal level), involving consequently the overall muscle afferents neuronal pool (from type I to IV muscle afferents; Bergquist et al., 2011). Therefore, EMS can simultaneously produce muscle force and stimulating group III-IV muscle afferents and muscle spindles (Bergquist et al., 2011). Furthermore, EMS can be used during both isometric (e.g. Zory et al., 2005) and dynamic (e.g. Kim et al., 1995) contractions, and volitional contraction can also be superimposed to the evoked contraction (combined contractions; Wahl et al., 2012). Consequently, the use of EMS to investigate the neurophysiology of perceived exertion is of particular interest as it allows the experimenter, for the same level of force produced, to i) manipulate the presence or absence of central motor command (voluntary vs evoked contractions), ii) manipulate the magnitude of the central motor command (voluntary contractions only vs combined contractions), and iii) involve both isometric and dynamic contractions.

The aim of this study was to test the validity of the afferent feedback model of perceived exertion. We used EMS to manipulate the magnitude of the central motor

command and the sensory volley associated with the stimulation during contractions (isometric and dynamic) at a same force output (voluntarily, evoked or combined contraction), and asked our subjects to rate distinctively for each contraction effort, pain and force. We hypothesised that perception of effort would reflect the magnitude of the central motor command and would be independent of stimulation of muscle afferents via the sensory volley.

## **II. Methods**

### **SUBJECTS AND ETHICAL APPROVAL**

Ten healthy and moderately active adults (mean  $\pm$  SD; age:  $26 \pm 4$  yrs, height:  $177 \pm 7$  cm, weight:  $75 \pm 10$  kg, 9 males and 1 female) volunteered to participate in this study. Each subject gave written informed consent prior to the study. All subjects were experienced with protocols involving evoked contractions. An experienced subject was defined as a subject that i) participated in at least two studies involving electrical stimulation or ii) participated in training/rehabilitation (prior to the current experiment) involving electromyostimulation. Experimental protocol and procedures were approved by the local Ethics Committee of the School of Sport and Exercise Sciences, University of Kent at Medway. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008). All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants.

### **EXPERIMENTAL PROTOCOL**

Subjects visited the laboratory on two different occasions. During the first visit (familiarisation session), subjects were familiarised with all experimental procedures. During the second visit, subjects performed various contractions (isometric and isotonic at different torque level) in a randomised and counterbalanced order. An overview of each experimental session can be found in figure 36. Each session started with a standardised



warm-up, consisting of 10 brief submaximal contractions ( $\sim 50\%$  MVC) of the knee extensor muscles (Place et al., 2007). Then participants performed two isometric MVCs (3s duration) to determine their maximal force production (a third MVC was performed if the increase in MVC was above 5%). Subjects were motivated to exert maximal effort during MVCs via verbal encouragement provided by an experimenter, and visual feedback corresponding to the torque produced during the previous MVC. Following determination of the MVC peak torque, the intensity of stimulation required to elicit 10% of the MVC peak torque previously obtained was determined (see *Electromyostimulation* for more details). Then, the following contractions were performed in a randomised and counterbalanced order:

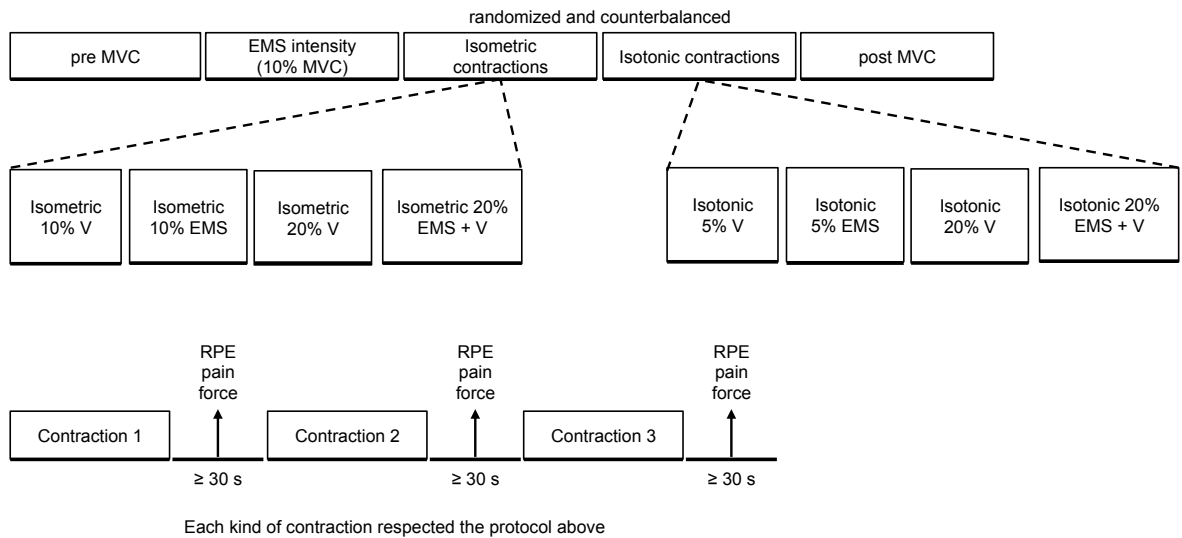
- Isometric contractions of 5 s (knee angle at  $90^\circ$ ): i) 10% MVC by voluntary contraction only (10% VOL, presence of central motor command), ii) 10% MVC by EMS only (10% EMS, no central motor command, iii) 20% MVC by voluntary contraction only (20% VOL, full central motor command), and iv) 20% MVC by 10% produced by EMS (1s before the onset of the voluntary contraction) and 10% produced via voluntary contraction (20% EMS+VOL, contraction with low motor command for same torque output of contraction iii). Subjects were asked to match a line on a computer screen ( $\sim 1.5$ m front of the subject) corresponding to the required target torque. To avoid any bias, subjects were blind of the x and y axis that were updated by an experimenter between each contraction.

- Isotonic contractions from  $90^\circ$  to  $40^\circ$  ( $0^\circ$ =knee fully extended, torque target is related to the isometric MVC previously determined): i) 5% MVC by voluntary contraction only (5% VOL, presence of central motor command), ii) 5% MVC by EMS only (5% EMS, no central motor command, iii) 20% MVC by voluntary contraction only (20% VOL, full central motor command), and iv) 20% MVC by 10% produced by EMS (1s before the onset of the voluntary contraction, producing half of the torque required to move the dynamometer arm) and 10% produced via voluntary contraction (20% EMS+VOL, contraction with low motor command for same torque output of contraction iii). Subjects were asked to move the dynamometer arm smoothly for the whole range of motion (from  $90^\circ$  to  $40^\circ$ ) by producing only the torque required to move the arm. To avoid any bias no visual feedback of the torque produced was provided. During pilot testing subjects reported intense leg muscle pain during evoked isotonic contraction when the range of motion was above  $40^\circ$ . Therefore, to increase subject comfort, we chose a range of motion from  $90^\circ$  to  $40^\circ$ .

Each contraction was interspaced by a minimum of 30 s to avoid any exercise-induced metabolite accumulation in the muscle milieu (Marcora et al., 2008; de Morree et al., 2012). Before each contraction, an experimenter provided a countdown ('3, 2, 1, GO') to the subject. For voluntary contractions only (isometric 10% and 20% VOL, isotonic 5% and 20% VOL) subjects were asked to produce the required torque at 'GO'. For evoked contractions only (isometric 10% EMS, isotonic 5% EMS) subjects were asked to fully relax during the stimulation that occurred at 'GO'. During combined contractions (isometric and isotonic 20% EMS+VOL) the evoked contraction started at '1' and subjects were asked to superimpose the required torque at 'GO'. The contraction stopped either when the experimenter said 'STOP' (after 5 s during isometric contractions) or when the subject reached the end of the range of motion (during isotonic contractions).

Leg RPE, leg muscle pain and perceived force (see *Perceptual measurements* for more details) were asked during the resting period between each contraction. Each contraction was repeated three times and each three perceptual measurements was averaged to obtain one rating of leg RPE, leg muscle pain and force perceived for each type of contraction.

All subjects were given pre-test instructions they were required to follow prior the experimental session. The instructions included the following: refrain from drinking alcohol 24 hours prior to testing and consuming caffeine 3 hours before testing, sleep for a minimum of 7 hours before testing, no vigorous activity within the 24 hours before testing.



**Figure 36 - An overview of the experimental protocol.**

The order of isometric and isotonic (dynamic) contractions was randomised and counterbalanced between subjects. The target torque was reached and maintained either by voluntary contractions only (VOL, presence of central motor command), by electromyostimulation only (EMS, evoked contraction, absence of central motor command) or by combination of both EMS and V (EMS + VOL, lower motor command than the V contraction for the same torque). The target force for both isometric and isotonic contraction is related to the pre MVC value obtained during an isometric contraction.

## ELECTROMYOSTIMULATION AND MECHANICAL RECORDING

**Electromyostimulation.** A high-voltage constant-current stimulator (maximal voltage 400 V, model DS7 modified, Digitimer, Hertfordshire, UK) was used to perform EMS on the knee extensor muscles. The knee extensor muscles were stimulated using a pair of surface electrodes (10 × 5 cm, Phoenix Healthcare Products Ltd., Nottingham, UK) positioned perpendicular to the long axis of the femur. Proximal and distal electrodes were respectively positioned ~5 cm below the inguinal ligament and ~10 cm above the patella. After pilot testing, a stimulation frequency of 30Hz was chosen to obtain a torque plateau during the stimulation; thus allowing the subject to easily superimpose a voluntary contraction in addition of the evoked contraction. The intensity producing 10% of the pre MVC was kept constant through the protocol ( $72.7 \pm 12.5$  mA).

**Mechanical recordings.** Torque was recorded using a dynamometer (Cybex NORM isokinetic dynamometer, CMSi, Computer Sports Medicine Inc., Stoughton, USA).

During the tests a two shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. MVCs and isometric contractions were performed with the right leg at a knee joint angle of 90 ° of flexion (0 ° = knee fully extended) and a hip angle of 90 °.

## PERCEPTUAL MEASUREMENTS

**Effort.** Perception of effort (leg RPE), defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (Marcora, 2010b), was measured during the resting period between each contraction using the 15 points RPE scale (Borg 1998). Standardised instructions for the scale were given to each subject before the warm-up: *“During this experiment we want you to rate your perception of effort defined as the sensation of how hard you are driving your leg. Look at the scale before you; we want you to use this scale from 6 to 20, where 6 means “no exertion at all” and 20 means “maximal exertion”. To help you choose a number that corresponds to how you feel within this range, consider the following. When you do not have the sensation to drive your leg, choose number 6 (“no exertion at all”). When you have the sensation to drive your leg “hard”, choose number 15. Number 20 (“Maximal exertion”) corresponds to the feeling of effort you have experienced during the preliminary maximal voluntary contraction (MVC) test. Try to appraise your perception of effort as honestly as possible, without thinking what the actual physical load is. Don’t underestimate your perception of effort but do not overestimate it either. It’s your own feeling of effort that’s important, not how it compares to other people. What other people think is not important either. Look at the scale and the expressions and then give a number. Any questions?”*

**Leg muscle pain.** Leg muscle pain, defined as “the intensity of hurt that a subject feels in his quadriceps muscles only” (O’ Connor and Cook, 2001), was measured during the resting period between each contraction using the Cook scale (O’ Connor and Cook, 2001). Standardised instructions for the scale were given to each subject before the warm-up: *“You are about to undergo a resistance exercise with your knee extensor muscles (quadriceps). The scale before you contains the numbers 0 to 10. You will use this scale to assess the perceptions of pain in your quadriceps during the exercise test. For this task, pain is defined as the intensity of hurt that you feel in your quadriceps muscles only. 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 the scale represent a range of pain intensity*

*from "very faint pain" (number 0.5) to "extremely intense pain—almost unbearable" (number 10). When you feel no pain in your quadriceps, you should respond with the number zero. When the pain in your quadriceps becomes just noticeable, you should respond with the number 0.5. If your quadriceps feels extremely strong pain that is almost unbearable, you should respond with the number 10. You can also respond with numbers greater than 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 be asked to rate the feelings of pain in your quadriceps. When rating these pain sensations, be sure to attend only to the specific sensations in your quadriceps 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 quadriceps. Do not use your ratings as an expression of fatigue (i.e., inability of the muscle to produce force) or exertion (i.e., how hard is it for you to drive your leg)."*

**Force.** Subjects were also asked to rate the force perceived during the contraction using a visual analogic scale ranging from 0 ("no force at all") to 100 ("maximal force"). Subjects were instructed that the MVC performed at the beginning of the experimental session corresponded to a force of 100.

## STATISTICAL ANALYSIS

All data are presented as means  $\pm$  standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present.

One way repeated ANOVAs (4 contractions) were used to test the effect of contraction type on leg RPE and force perceived. As we were interested in comparing the perceptual measurements for the same torque output, significant effect of contraction was explored with planned comparison (isometric: 10% VOL vs 10% EMS and 20% VOL vs 20% EMS+VOL; isotonic 5% V vs 5% EMS and 20% VOL vs 20% EMS) adjusted with a Holm-Bonferonni correction. Assumption of normality for leg muscle pain was violated. Therefore, a Friedman ANOVA was performed. Significant effect of contraction was explored with planned comparisons (isometric: 10% VOL vs 10% EMS and 20% VOL vs

20% EMS+VOL; isotonic 5% VOL vs 5% EMS and 20% VOL vs 20% EMS) adjusted with a Holm-Bonferonni correction.

Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 20 for Mac OS X (SPSS Inc., Chicago, IL, USA). Cohen's effects size  $f(V)$  and  $d_z$  were calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany).

### **III. Results**

The experimental manipulation of this study consisted of manipulating the magnitude of the central motor command for the same torque output via EMS. In the following results, 10% VOL and 5% VOL correspond to contraction in the presence of central motor command (isometric and isotonic contractions). Ten per cent EMS and 5% EMS correspond to contraction in the absence of central motor command (isometric and isotonic contractions). 20% V corresponds to the contraction with full motor command (isometric and isotonic contractions) and 20% EMS+VOL (combined contraction) corresponds to the contraction with low motor command (isometric and isotonic contractions).

During isometric contractions, leg RPE ( $P<0.001$ ,  $f(V)=1.718$ ) and leg muscle pain ( $P<0.001$ ) presented a significant main effect of contraction. However, main effect of contraction for perceived force only tended to reach significance ( $P=0.059$ ,  $f(V)=0.630$ ). During isotonic contractions, leg RPE ( $P<0.001$ ,  $f(V)=2.058$ ), leg muscle pain ( $P<0.001$ ) and perceived force ( $P<0.001$ ,  $f(V)=1.636$ ) presented a significant main effect of contraction. Planned comparisons (comparison of perceptual measurements at same torque output within the same contraction mode) are presented below.

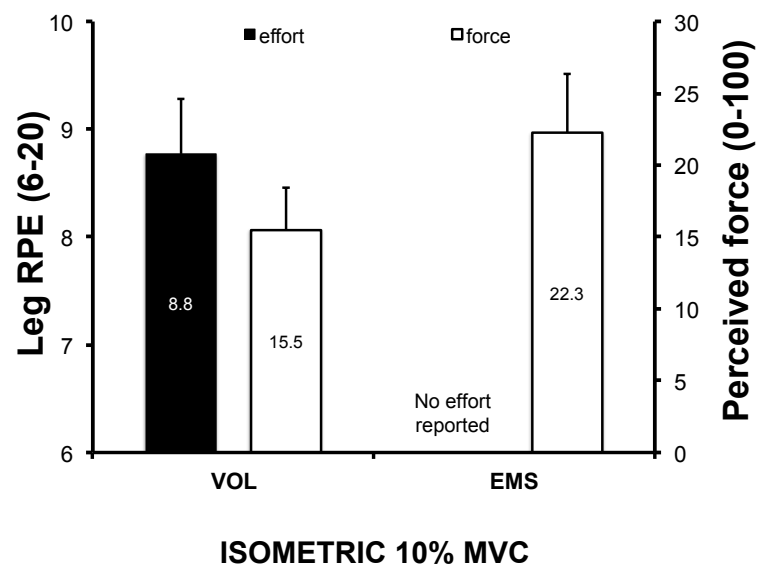
#### **CENTRAL MOTOR COMMAND VS NO CENTRAL MOTOR COMMAND**

*Isometric.* During isometric contractions, the force target corresponded to 10% MVC ( $22 \pm 4$  Nm). None of the subjects reported any physical effort in absence of central motor command (EMS), but all subjects reported physical effort in presence of central motor command (VOL). Subjects rated the pain higher during EMS compared to VOL ( $1.5 \pm 1.3$  vs  $0.1 \pm 0.3$ ,  $P=0.023$ ). RPE and perceived force data are presented figure 37.

**Isotonic.** During isotonic contractions, the force target corresponded to 5% MVC ( $11 \pm 2$  Nm). None of the subjects reported any physical effort in absence of central motor command (EMS), but all subjects reported physical effort in presence of central motor command (VOL). The perceived force by the subjects was significantly lower in presence of central motor command (VOL) than in absence of central motor command (EMS,  $P=0.015$ ,  $d_z=1.086$ ). Subjects rated the pain higher during EMS compared to VOL ( $1.4 \pm 1.4$  vs  $0.2 \pm 0.6$ ,  $P=0.016$ ). RPE and force perceived data are presented in figure 38.

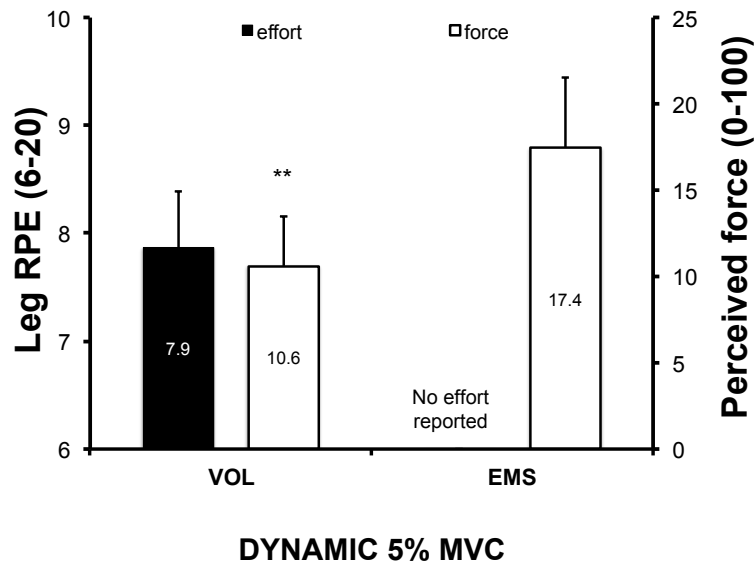
**Figure 37 - Leg rating of perceived exertion (RPE) and perceived force during isometric contraction (5s, knee angle fixed at 90 °, 0 °=knee fully extended) at 10% of maximal voluntary contraction (MVC, target determined following pre MVC).**

The target torque was reached and maintained either by voluntary contraction only (VOL) or by electromyostimulation only (EMS). Data are presented as means  $\pm$  SEM.



**Figure 38 - Leg rating of perceived exertion (RPE) and perceived force during isotonic contraction (from 90 ° to 40 °, 0 °=knee fully extended) at 5% of maximal voluntary contraction (MVC, target determined following pre MVC).**

The contraction was performed either by voluntary contraction only (VOL) or by electromyostimulation only (intensity eliciting 10% of the pre MVC, EMS). Data are presented as means  $\pm$  SEM. \*\* significant difference between contractions,  $P < 0.05$ .



### FULL CENTRAL MOTOR COMMAND VS LOW CENTRAL MOTOR COMMAND

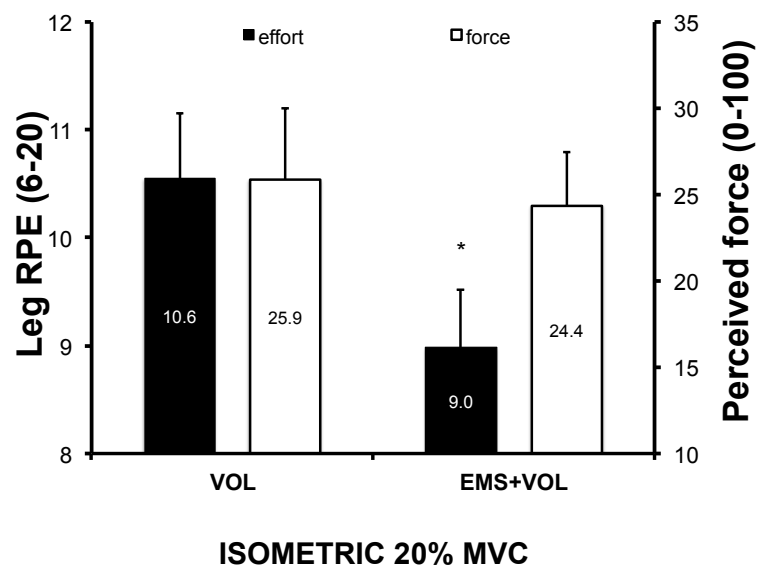
**Isometric.** During isometric contractions, the force target corresponded to 20% MVC ( $44 \pm 7$  Nm). RPE was rated lower with a low central motor command (20% EMS+VOL) than with a full central motor command (20% VOL,  $P=0.036$ ,  $d_z=1.062$ ). Subjects rated the pain higher during the combined contraction (20% EMS+VOL) compared to the voluntary contraction (20% VOL,  $1.1 \pm 1.2$  vs  $0.2 \pm 0.3$ ,  $P=0.011$ ). RPE and perceived force data are presented in figure 39.

**Isotonic.** During isotonic contractions, the force target corresponded to 20% MVC ( $44 \pm 7$  Nm). RPE was rated lower with a low central motor command (20% EMS+VOL) than with a full central motor command (20% VOL,  $P < 0.001$ ,  $d_z=1.725$ ). The perceived force did not differ between contractions ( $P=0.068$ ,  $d_z=0.655$ ). Subjects rated the pain higher during the evoked contraction compared to the voluntary contraction ( $1.4 \pm 1.4$  vs  $0.2 \pm 0.6$ ,  $P < 0.001$ ). RPE and force perceived data are presented in figure 40.



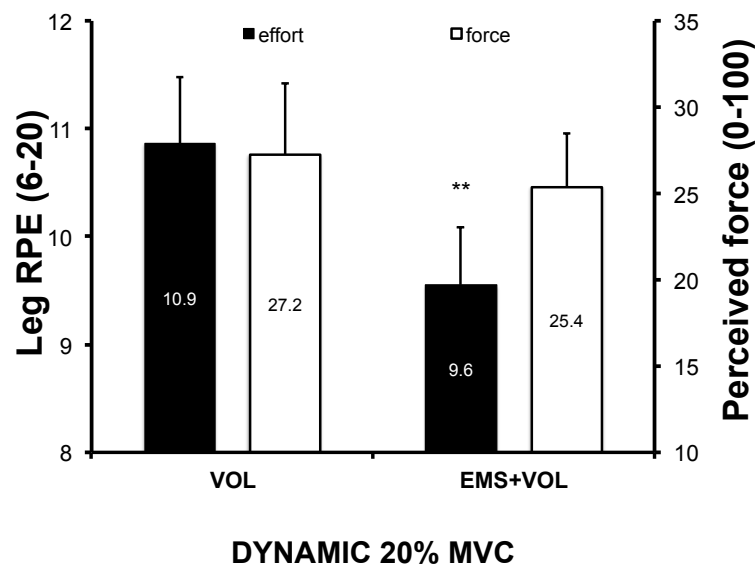
**MVC.** The experimental protocol induced a significant decrease in MVC (from  $222 \pm 37$  to  $209 \pm 39$  Nm,  $P=0.005$ ).

**Figure 39 - Leg rating of perceived exertion (RPE) and perceived force during isometric contraction (5s, knee angle fixed at  $90^\circ$ ,  $0^\circ$ =knee fully extended) at 20% of maximal voluntary contraction (MVC, target determined following pre MVC).**



The target torque was reached and maintained either by voluntarily contraction only (VOL) or by a combination of electromyostimulation and voluntary contraction (EMS+VOL). For the low central motor command, 10% MVC was evoked by electromyostimulation only 1 s prior the subject was asked to superimposed the other 10% MVC on the top of the evoked contraction (torque target corresponding to 20% MVC during both contractions type). Data are presented as means  $\pm$  SEM. \* significant difference between contractions,  $P<0.05$ .

**Figure 40 - Leg rating of perceived exertion (RPE) and perceived force during isotonic contraction (from 90 ° to 40 °, 0°=knee fully extended) at 20% of maximal voluntary contraction (MVC, target determined following pre MVC).**



The contraction was performed either by voluntary contraction only (VOL) or by a combination of electromyostimulation and voluntary contraction (EMS+VOL). For the low central motor command, 10% MVC was evoked by electromyostimulation only 1 s prior the subject was asked to superimposed the other 10% MVC on the top of the evoked contraction (torque target corresponding to 20% MVC during both contractions type). Data are presented as means  $\pm$  SEM.

\*\* significant difference between contractions,  $P < 0.01$ .

## V. Discussion

The aim of this study was to test the validity of the afferent feedback model in perception of effort generation. To the best of our knowledge, this study is the first to use EMS to produce the same level of force between contractions with different magnitude of central motor command, thus to compare rating of effort, force and pain. Our data does not support the validity of the afferent feedback model of perceived exertion. Indeed, despite the presence of the sensory volley known to send sensory signal at a spinal and supraspinal

level, the rating of effort seems independent of muscle afferent feedback and seems to reflect the magnitude of the central motor command.

### **CENTRAL MOTOR COMMAND IS COMPULSORY TO PERCEIVE PHYSICAL EFFORT**

In this study, we firstly compared for the same force output (10% MVC during isometric contractions and 5% MVC during isotonic contractions) perceptual responses associated with the contraction in presence (voluntary contractions) or absence (evoked contractions) of central motor command. The presence of leg muscle pain and the ability of the subjects to rate perceived force during the evoked contractions (no central motor command) confirm that we were successful in stimulating muscle afferents. Indeed, it is well known that both perception of pain (for review see O'Connor and Cook, 1999) and perception of force (for review see Proske and Gandevia, 2012) result from the central processing of the corollary discharge associated with the motor command and sensory feedback associated with the contraction. Interestingly, during isotonic contractions at same force output, the perceived force was lower in presence of central motor command than in absence (evoked contraction). This result is not surprising, as it has been previously shown (for review see Proske and Gandevia, 2012) that perception of force is based on a feedforward mechanism (Bays and Wolpert, 2007). The lack of significant update of the perceived force in presence of central motor command during isometric contractions (contrary to isotonic contraction) is likely to be due to i) a small sample size as a medium effect size was detected and ii) a different contribution of muscle spindles during dynamic and isometric contractions (Kakuda and Nagaoka, 1998).

Interestingly, none of our subjects reported effort during contraction in absence of central motor command (evoked contraction). This result is supported by a recent study of Pollak et al. (2014) where injection of different concentrations of metabolites (in absence of any contraction) induced sensation of muscle pain/discomfort and not of effort. Taken all together, these results clearly confirm the need of volition in order to perceive an effort and question the results of studies measuring resting RPE in various environmental conditions (e.g. Goodall et al., 2014b). In these studies, subjects rated presence of physical effort in resting conditions, likely due to the inclusion of discomfort in RPE instructions.

The absence of physical effort in resting conditions is supported by a recent study of Pollak et al. (2014) and our study. Therefore, rating an effort other than “no exertion” at

rest revealed that either the subjects did not understand what RPE is or that discomfort was included in the RPE instructions. Asking RPE in resting condition might present an interesting manipulation check to ensure that subjects understood the instructions to report effort.

### **MUSCLE AFFERENTS FEEDBACK DURING VOLUNTARY CONTRACTIONS DOES NOT IMPACT PERCEPTION OF EFFORT**

We also used combined contractions (voluntary contractions and evoked contractions) and voluntary contractions at same level of force to manipulate the magnitude of central motor command. On one hand, when subjects had to produce 20% MVC (during both isometric or isotonic contractions) by voluntary contractions, the central motor command was “full”. On the other hand, when subjects had to produce the same level of force (20% MVC) by combined contractions, the level of force that had to be produced voluntarily was only 10% MVC and the central motor command was “low”. Indeed, the other 10% MVC was produced by EMS. Therefore, even though that we did not directly measure the magnitude of the central motor command, it is obvious that the central motor command was lower during combined contraction than during voluntarily contraction.

Interestingly, despite the presence of the sensory volley during combined contractions known to stimulate both group III-IV muscle afferents and muscle spindles (Bergquist et al., 2011), subjects reported lower RPE values during combined contractions (low central motor command) compared to voluntary contraction (full central motor command). This result supports the corollary discharge model of perceived exertion stating that perception of effort is the conscious awareness of the corollary discharge associated with the central motor command. This model is also supported by another study (de Morree et al., 2012) demonstrating a correlation between movement-related cortical potential and perception of effort during unilateral dynamic elbow flexion. Convincing evidence in favour of the corollary discharge model are also provided by experiments using epidural anaesthesia. Indeed, despite a significant reduction in muscle afferent feedback from the working muscles, RPE was unchanged or higher with spinal blockade during cycling (Kjaer et al., 1999; Smith et al., 2003) or isometric contractions (Mitchell et al., 1989). Taken all together, these results provide strong evidence that muscle afferents are not the sensory signals generating perception of effort.

Only RPE was rated lower during the combined contractions as perceived force was similar between the two types of contractions. This result provides additional support in favour of the possibility that humans can dissociate between perception of effort and force (Jones, 1995). Our results also confirm the ability of humans to dissociate perception of effort from discomfort (Christian et al., 2014) and pain (O' Connor and Cook, 2001). Therefore, as subjects are able to dissociate between perception of effort, force and pain, studies aiming to investigate the neurophysiology of perceived exertion should provide clear instructions to ensure that subjects does not include in their rating of effort other perceptions such as pain, discomfort and force.

## **APPLICATIONS, CONCLUSION AND PERSPECTIVES**

Our results combined with those of O' Connor and Cook (2001) and Christian et al. (2014) strongly question the validity of the definition of perceived exertion provided by the ACSM guidelines, where discomfort is included (Utter et al., 2007). Indeed, if subjects are instructed that RPE refers to the discomfort experienced during exercise, then muscle pain and other unpleasant sensations (e.g. heat or thirst) will be included in this rating (Marcora, 2009). Therefore, any experimental manipulation leading to a change in RPE cannot be directly attributed to a change in perception of effort, but can also be due to an increase or decrease in discomfort perceived by the subject. For the reasons previously mentioned, we believe that in order to get a better insight in the underlying mechanism of perceived exertion, a narrower definition of perceived exertion should be adopted for future research: i) “how hard is it for the subject to drive his leg/arm” (isolated exercise; de Morree and Marcora, 2010; de Morree et al., 2012; Pageaux et al., 2013; Pageaux et al., submitted) and ii) “how hard, heavy and strenuous exercise is” (whole-body exercise; de Morree and Marcora, 2013; Pageaux et al., 2014; Pageaux et al., In Press)

Finally our study provides strong evidence that perception of effort is independent from muscle afferents and is generated by the central processing of the corollary discharge associated with the central motor command. However, it has to be noticed that precise mechanisms explaining how perception arises from the central motor command still need to be determined, and future research should aim to investigate whether this corollary discharge responsible of the perceived exertion is originated from the motor areas or the pre motor areas (de Morree et al., 2012).

# ***GENERAL DISCUSSION***

## **I. Part I: central manipulations of perceived exertion**

Perception of effort (measured during physical tasks) was well known to be increased by prolonged mental exertion leading to a psychobiological state called mental fatigue. Its increase, caused by mental fatigue, led to an impairment in endurance performance during whole-body (Marcora et al., 2009) and single-joint (Pageaux et al., 2013) time to exhaustion tests. However, before completion of the present thesis, it remained unknown whether time trials and pacing could also be impaired by mental fatigue. As time to exhaustion and time trials are both sensitive to changes in endurance performance (Amann et al., 2008a), it was expected and confirmed by the first study that mental fatigue impairs self-paced endurance performance. However, it has to be noticed that despite choosing a lower running speed, the subjects did not change their pacing strategy.

Interestingly, this increase in perceived exertion (observed also during the chapter II of this part) and decrease in endurance performance occurred with no overt mental fatigue. This result is of particular importance, as it extends our knowledge on the impact of mental exertion and fatigue on human performance. Indeed, even completion of short mental exertion (30 min) involving response inhibition is sufficient to increase perception of effort and impair endurance performance, without the subject being aware of being mentally fatigued. Therefore, it seems important to monitor perception of effort (during physical tasks) before and after completion of mental exertion to detect the presence or not of mental fatigue induced by the cognitive task previously performed. Furthermore, when presenting the effects of mental fatigue on human behaviour (e.g. decrease in attention), an increase in perception of effort should be stated.

Before completion of this thesis, the hypothetical link between mental and central fatigue remained unclear. None of the studies in the literature attempting to measure central fatigue (Gandevia, 2001) was successful in demonstrating an impaired-force production capacity following mental exertion. The three studies of this thesis confirm and extend these results. Indeed, MVC production on fresh and fatigued muscle (measured at isotime), and also repeated MVC production were not affected by completion of mental exertion. Therefore, it is clear that following mental exertion involving response inhibition, subjects are still able to maximally recruit the active muscles, but will experience a higher than normal perception of effort during submaximal exercise. Consequently, future studies

should not use the terminology mental fatigue and central fatigue as synonymous, as both neurophysiological processes do not share the same mechanisms and have a different impact on human performance. Indeed, one is impacting submaximal exercise (mental fatigue), and the other maximal exercise (central fatigue). Indeed, despite the fact that central fatigue is well known to occur during endurance exercise (e.g. Decorte et al., 2010) it has been recently shown that at exhaustion subjects keep the ability to produce up to three times the required power/force (Marcora and Staiano, 2010).

Interestingly, our central manipulations induced an alteration in endurance performance independently of any alteration of neuromuscular function at the onset of the exercise and during exercise. Therefore, it is clear that the increase in perception of effort observed during endurance exercise is not solely caused by the progressive increase in muscle fatigue. The altered endurance performance observed in absence of mental fatigue induced muscle fatigue clearly demonstrates that perception of effort has a direct role in limiting endurance performance. Furthermore, it has to be noted that these central manipulations were an ideal test for the psychobiological model of endurance performance, stating that perception of effort is the ultimate regulator of endurance performance. Indeed, if endurance performance would have been dissociated from any change in perception of effort, the psychobiological model of endurance performance would have been refuted. Therefore, as chapter II and I failed to dissociate changes in perception of effort and endurance performance, the present results strengthen the psychobiological model of endurance performance.

The present thesis focused on the relationship between perception of effort and endurance performance. Therefore, the negative impact of mental fatigue was investigated in relation to endurance performance. However, to date, only one study investigated the impact of mental fatigue on motor control, and demonstrated an increase in tremor (Budini et al., 2014). This result, associated with the impaired EMG signal during cycling under mental fatigue, suggests that mental fatigue could also negatively impact motor control. Future studies should investigate the impact of mental fatigue on motor control, and if its negative effects has a different impact for example with gender and age.



## **II. Part II: peripheral manipulations of perceived exertion**

Perception of effort was thought to arise either from the corollary discharge associated with the motor command (Marcora, 2009; de Morree et al., 2012), or from muscle afferents (Amann et al., 2013). Chapter III, by using EMS to test the validity of the two models previously mentioned, provides a unique insight in the mechanisms underlying perception of effort generation. To date, this study is the only one investigating neurophysiology of perceived exertion i) as a dependant variable during force matching tasks and ii) for same torque output with a different magnitude of central motor command. The results of this study exclude a role of muscle afferents in perception of effort generation. Indeed, contrary to perception of force (i.e. known to arise from both corollary discharge of the central motor command and muscle afferents; Proske and Gandevia, 2012), perception of effort was non-existent in absence of central motor command (evoked contraction), and lower than normal for the same force output with a lower central motor command (combined contraction). Therefore, it can be concluded that perception of effort generation results from the central integration of the corollary discharge associated with the central motor command, and is independent from muscle afferents.

There is a lot of support in the literature in favour of the corollary discharge model of perceived exertion (e.g. McCloskey and Mitchell, 1972; McCloskey et al., 1974; McCloskey, 1981; McCloskey et al., 1983; de Morree et al., 2012). Strongest evidence supporting this model is provided by experiments using epidural anaesthesia. Indeed, despite a significant reduction in muscle afferent feedback from the working muscles, RPE was unchanged or higher with spinal blockade during cycling (Kjaer et al., 1999; Smith et al., 2003) or isometric contractions (Mitchell et al., 1989). Therefore, it is clear that perception of effort generation should be considered as independent of muscles afferents. However, as it will be detailed in the following paragraph, these muscle afferents are likely to play an indirect role in perception of effort.

The confirmation that perception of effort generation is independent from muscle afferents is of particular importance regarding to the definition used. Indeed, the ACSM definition (the one commonly used in Exercise Sciences) includes discomfort (Utter et al., 2007). However, as perception of effort generation is independent from muscle afferents, discomfort should be excluded. Indeed, for example, stimulation of group III-IV muscle afferents is known to generate pain and consequently increase discomfort during exercise. Therefore, if discomfort is included in the instructions provided to the subject to rate their

effort, any change in effort rating might be attributed to either a change in effort itself or a change in discomfort (Marcora, 2009).

Unfortunately, all recent studies manipulating muscle afferents feedback via epidural anaesthesia included discomfort in the RPE instruction or did not report the instructions provided to the subjects (Amann et al., 2008b; Amann et al., 2009; Amann et al., 2011a; Amann et al., 2013). Consequently it is not possible to use the results of these studies to get a better insight into the underlying mechanisms of perceived exertion. Therefore, it is crucial that i) future studies aim to manipulate muscle afferents in order to see their effect on perception of effort and endurance performance, ii) these studies provide clear instructions to the subject to dissociate effort from discomfort and other perceptions such as pain or force. The instructions provided to the subjects have been reported in the methods of the chapter III.

The conclusion that perception of effort is independent of afferent feedback from the working muscles is of particular importance in the interpretation of the increase in perception of effort observed during high intensity one leg dynamic exercise (chapter II and I). Indeed, this increase in perception of effort is likely to reflect the progressive increase in central motor command (and its corollary discharge), thus to increase muscle fibers recruitment to compensate the progressive development of exercise-induced peripheral fatigue.

### **III. Integration of peripheral and central manipulations**

Part II and I aimed to investigate central and peripheral manipulations of perceived exertion. By integrating the results of both parts, it is possible to get a new insight in the neurophysiology of perceived exertion. This thesis demonstrated that i) perception of effort can be altered independently of central fatigue, and that ii) perception of effort generation is independent of muscle afferents. Explanation on how muscle fatigue indirectly impacts perception of effort is presented in figure 41.

The intention to move is created in the pre-frontal cortex and neural signal are transferred to the pre-motor areas where the central motor command will be generated. Then, this central motor command will be transmitted to the primary motor cortex, consequently generating the central motor drive that will be forwarded to the active muscles in order to create movements. Internal models use i) a corollary discharge associated with the central

motor command, and ii) internal and external feedback provided by the body and the environment (mechanisms of motor control) to adjust the central motor command and ensure efficient movement. At the same time, when the central motor command is created or adjusted, another corollary discharge is generated and centrally processed (neuronal process) to generate perception of effort.

Part I demonstrated an exacerbated perception of effort independently of an inhibition of the central motor drive (i.e. central fatigue). This result suggests that alteration in perceived exertion, and consequently the brain area impacted by mental fatigue, are likely to be upstream of those impacted by central fatigue. Therefore, it is likely that mental fatigue might impact either the generation of the central motor command and/or its central processing (red stars in figure 41). Several studies proposed the anterior cingulate cortex, pre supplementary and supplementary motor areas as brain areas linked with generation of perceived exertion (Williamson et al., 2001; 2002; de Morree et al., 2012).

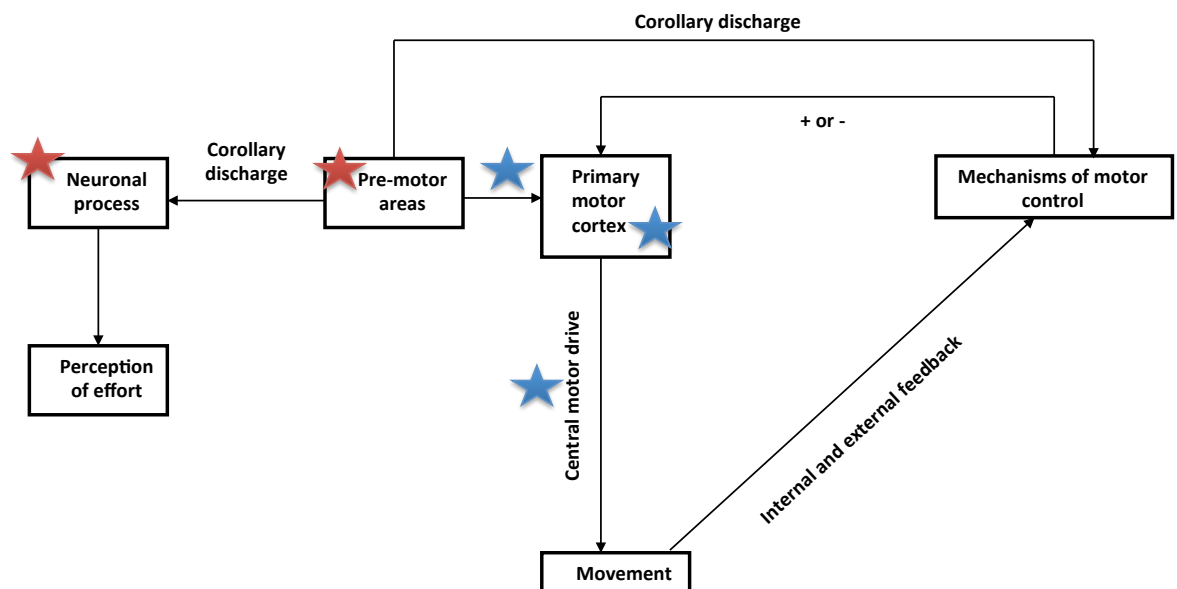
Part II demonstrated that despite the presence of a sensory volley, for the same torque output, perception of effort reflect the magnitude of the central motor command when this one is manipulated with EMS. This excludes a possible role of muscle afferents in perception of effort generation. Therefore, as muscle afferents are known to be involved i) in mechanisms of motor control and ii) in central fatigue (blue stars in figure 41), any muscle afferents feedback may have an indirect role in perception of effort changes. Indeed, any change in motor control will update the central motor command, which will update in turn the corollary discharges associated with this the central motor command and consequently indirectly update perception of effort. For example, in presence of central fatigue, in order to produce the same force as before the central motor drive becomes inhibited; the central motor command will be increase to overcome the inhibition, which in turn will lead to an increase in perception of effort. This is also the case in presence of peripheral fatigue. Indeed, when the muscle loses its ability to generate force, central motor command has to be increased to generate a greater central motor drive and recruit additional muscle fibres. This increase in central motor command will then impact the corollary discharge involved in perception of effort and consequently increase perceived exertion.

As a conclusion, it is possible to state that YES perception of effort generation is independent of muscle afferents and muscle fatigue, and that YES muscle fatigue and

muscle afferents, through their role in motor control, indirectly play a role in perception of effort changes.

**Figure 41 – Model synthesising the neurophysiology of perceived exertion**

Red stars represent potential sites where mental fatigue can alter perception of effort (generation of the central motor command and/or central processing of the corollary discharge associated with the central motor command.) Blue stars represent potential sites where central fatigue can alter force production capacity. Central fatigue can i) inhibit the central motor drive upstream the motor cortex (inhibition of the transmission of the central motor command to the primary motor cortex), ii) decrease the excitability of the primary motor cortex, or iii) inhibit the central motor drive at a spinal level.



#### **IV. Perception of effort and endurance performance**

Perception of effort is known to be a key determinant of endurance performance. To date there is no study demonstrating changes in endurance performance without a decrease or increase in perceived exertion. Indeed, when effort is perceived as the same during a time trial between two experimental conditions, the decrease (or increase) in

performance is always associated with a decrease (or increase) in power output (e.g. Watson et al., 2005; Mauger et al., 2010). Therefore, as the stimulus generating perception of effort in these studies was either lower (reduction in performance) or higher (increase in performance), any change in performance was associated with a change in perception of effort.

The fact that perception of effort is the ultimate regulator of endurance performance is also supported by its rating at exhaustion. Indeed, for highly motivated subjects/athletes, perception of effort is always perceived as maximal when volitional disengagement from the task occurs. Interestingly, despite the fact that muscle fatigue plays an indirect role in the increase in perception of effort (see previous part of the general discussion), a mismatch was demonstrated between the increase in muscle fatigue and perception of effort (Marcora et al., 2008; Marcora and Staiano, 2010; McNeil et al., 2011). This mismatch confirms that muscle fatigue is not a limiting but determinant factor of endurance performance (Marcora et al., 2008), and that other contributors than muscle fatigue are involved in the increase in perception of effort during endurance exercise.

Future experiments should aim to identify other contributors to this increase in perception of effort during exercise. Indeed, if it is possible to manipulate these additional contributors, it could be therefore possible to change the time course of increase in perception of effort during exercise, consequently improving endurance performance. Acute mental exertion, as physical exertion is now known to impair endurance performance. For this reason, the use of mental exertion as endurance training purposes should be considered for future research. Indeed, as both mental and physical fatigues are known to negatively impact perception of effort, it is likely that mental exertion associated with completion of physical exertion could be one additional contributor of the increase in perceived exertion during endurance exercise.

## **V. Using high intensity one leg dynamic exercise to understand regulation of endurance performance**

This thesis provides new insight into how mental fatigue can impact endurance performance, and also into the neurophysiology of perceived exertion. An additional aim of part II of this thesis was to develop a new endurance exercise model i) not limited by the

cardiorespiratory system and ii) allowing a short time delay to assess neuromuscular fatigue. Why develop this model? Group III-IV muscle afferents feedback are involved in both muscle fatigue regulation and also cardiorespiratory response to the exercise (metaboreflex). Therefore, their role is crucial in increasing cardiorespiratory response to the exercise in order to ensure adequate input of oxygen in the muscle milieu. However, their role in endurance performance remains unclear (Marcora et al., 2008; Marcora, 2009; Marcora and Staiano, 2010; Marcora, 2011).

Previous studies (Amann et al., 2009; Amann et al., 2011a) investigated the role of group III-IV muscle afferents in endurance performance regulation via epidural anaesthesia (blocking sensory feedback from the working muscles). In these studies, subjects had to perform high intensity cycling exercise either during a time trial or a time to exhaustion tests. However, as group III-IV muscle afferents are involved in the stimulation of cardiorespiratory response, epidural anaesthesia compromised this response. This altered cardiorespiratory response to the exercise lead to impairment in oxygen supply to the working muscle, inducing an exacerbated peripheral fatigue leading to premature exhaustion (Amann et al., 2011a). Therefore, as whole body exercise involves an important solicitation of the cardiorespiratory system, blocking feedback from group III-IV muscle afferents during whole-body exercise does not allow investigation of the role of these muscle afferents in muscle fatigue and endurance performance regulation (due to lack of O<sub>2</sub> supply to the working muscles).

For the reasons previously mentioned, it was crucial to develop a new exercise model not limited by the cardiovascular system in order to investigate the role of group III-IV muscle afferents in endurance performance and muscle fatigue regulation. The model developed in this thesis, originally based on Andersen et al. (1985) model, was previously demonstrated not to be limited by cardiorespiratory function. Furthermore, by developing this model on a dynamometer, we demonstrated its reliability and also the possibility to quickly assess neuromuscular function at cessation of the exercise. Additionally, chapter 2 described the extent of neuromuscular alterations induced by the one leg dynamic exercise. Interestingly, one leg dynamic exercise induced peripheral and central fatigue, but also changes in cortical and spinal excitability. Consequently, this new exercise model can provide the ideal tool to manipulate group III-IV muscle afferents (e.g. epidural anaesthesia) and investigate the role of these muscle afferents in endurance performance and muscle fatigue regulation.

## **VI. Conclusion and perspectives**

The aim of the present thesis was to investigate the effects of various central and peripheral manipulations on perception of effort and/or endurance performance. By integrating both experimental parts, this thesis provides new insights on how perception of effort regulates endurance performance. Specifically, it demonstrates how muscle fatigue is a contributor of the continuous increase in perception of effort during endurance exercise (through the progressive increase in central motor command), but also that other contributors play a role in this increase in perception of effort. Indeed, we demonstrated for the first time that i) perception of effort alterations in presence of mental fatigue is independent of any alterations of the neuromuscular system, and ii) muscle afferents do not directly impact perception of effort, but may influence it indirectly via their role in motor control.

Future studies should investigate the underlying mechanisms causing the increase in perceived exertion following mental exertion leading to mental fatigue. Specifically, the impact of mental fatigue on motor control requires extensive investigation as it can have direct implication for elderly and also clinical patients. Additionally, the new exercise model developed in the present thesis could be used to manipulate afferent feedback and then investigate its precise role in regulating endurance performance. As three years was not sufficient to use the new one leg dynamic exercise model to manipulate feedback from group III-IV muscle afferents, further studies should use this model to increase or decrease feedback from group III-IV muscle afferents. Among plausible experimental manipulations, spinal blockade of these muscle afferents would be an interesting way of decreasing feedback from these afferents. Indeed, as cycling exercise is too demanding for the cardiorespiratory system (causing an exacerbated peripheral fatigue and premature exhaustion), results of previous studies (Amann et al., 2009; Amann et al., 2011a; Hilty et al., 2011) cannot determine the role of feedback from group III-IV muscle afferents in endurance performance regulation and central fatigue.

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# *APPENDICES*

## *Ethical clearance*

Below are ethical clearance references for each study. Please note that both studies performed in the Faculty of Sport Sciences in Dijon were included in the same project.

<b>Chapter</b>	<b>Ethics number</b>	<b>University</b>
1	Prop08_2011_12	Kent
2	AEC/B90097-40	Dijon
3	AEC/B90097-40	Dijon
4	Prop68_2013_14	Kent
5	016S12/13	Kent
6	Prop97_2013_14	Kent

# Prolonged Mental Exertion Does Not Alter Neuromuscular Function of the Knee Extensors

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## ABSTRACT

PAGEAUX, B., S. M. MARCORA, and R. LEPERS. Prolonged Mental Exertion Does Not Alter Neuromuscular Function of the Knee Extensors. *Med. Sci. Sports Exerc.*, Vol. 45, No. 12, pp. 2254–2264, 2013. **Purpose:** The aim of this study was to test the hypotheses that prolonged mental exertion (i) reduces maximal muscle activation and (ii) increases the extent of central fatigue induced by subsequent endurance exercise. **Methods:** The neuromuscular function of the knee extensor muscles was assessed in 10 male subjects in two different conditions: (i) before and after prolonged mental exertion leading to mental fatigue and (ii) before and after an easy cognitive task (control). Both cognitive tasks lasted 90 min and were followed by submaximal isometric knee extensor exercise until exhaustion (endurance task), and a third assessment of neuromuscular function. **Results:** Time to exhaustion was  $13\% \pm 4\%$  shorter in the mental fatigue condition ( $230 \pm 22$  s) compared with the control condition ( $266 \pm 26$  s) ( $P < 0.01$ ). Prolonged mental exertion did not have any significant effect on maximal voluntary contraction torque, voluntary activation level, and peripheral parameters of neuromuscular function. A similar significant decrease in maximal voluntary contraction torque (mental fatigue condition:  $-26.7\% \pm 5.7\%$ ; control condition:  $-27.6\% \pm 3.3\%$ ,  $P < 0.001$ ), voluntary activation level (mental fatigue:  $-10.6\% \pm 4.3\%$ ; control condition:  $-11.2\% \pm 5.2\%$ ,  $P < 0.05$ ), and peripheral parameters of neuromuscular function occurred in both conditions after the endurance task. However, mentally fatigued subjects rated perceived exertion significantly higher during the endurance task compared with the control condition ( $P < 0.05$ ). **Conclusions:** These findings provide the first experimental evidence that prolonged mental exertion (i) does not reduce maximal muscle activation and (ii) does not increase the extent of central fatigue induced by subsequent endurance exercise. The negative effect of mental fatigue on endurance performance seems to be mediated by the higher perception of effort rather than impaired neuromuscular function. **Key Words:** PERCEPTION OF EFFORT, MUSCLE ACTIVATION, MENTAL FATIGUE, PERIPHERAL FATIGUE, CENTRAL FATIGUE, ENDURANCE PERFORMANCE

Prolonged mental exertion is well known to induce mental fatigue, a psychobiological state characterized by subjective feelings of “tiredness” and “lack of energy” (3). The negative effects of mental fatigue on cognitive performance are well established and include impairments in attention, action monitoring, and cognitive control (e.g., 3, 37). On the contrary, the effects of mental fatigue on physical performance have been scarcely investigated. In 1906, Mosso (25) reported that two of his colleagues did poorly in a muscle fatigue test performed after delivering long physiology lectures and viva examinations. More re-

cently, Bray et al. (5,6) showed that performing a demanding cognitive task before or between isometric contractions significantly reduces the endurance and strength of isolated upper limb muscles. However, in these studies, mental exertion was not prolonged enough to induce subjective feelings of mental fatigue. Furthermore, neuromuscular function was assessed with EMG, a method that does not provide a valid measure of maximal voluntary activation of muscle (15). Therefore, the link between the prolonged mental exertion and the central component of muscle fatigue is still unclear. Marcora et al. (21) conducted the first experimental study on the effect of prolonged mental exertion on endurance performance during dynamic whole-body exercise. These investigators induced mental fatigue in a group of healthy and fit subjects using a prolonged demanding cognitive task performed for 90 min and found a significant reduction in time to exhaustion during subsequent high-intensity cycling exercise. However, the physiological mechanisms underlying the negative effect of prolonged mental exertion on endurance performance are currently unknown. Marcora et al. (21) did not find any effect of mental fatigue on the cardiovascular, respiratory, and metabolic responses to

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Submitted for publication February 2013.

Accepted for publication May 2013.

0195-9131/13/4512-2254/0

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DOI: 10.1249/MSS.0b013e31829b504a

high-intensity cycling exercise. Motivation related to the time to exhaustion test was also unaffected by mental fatigue. In this study, the only factor that could explain a premature exhaustion was the higher perception of effort experienced by mentally fatigued subjects during high-intensity cycling exercise. According to the psychobiological model of endurance performance, exhaustion is not caused by muscle fatigue (20), that is, by the failure of the fatigued neuromuscular system to produce the force/power required by the endurance task despite a maximal voluntary effort. On the contrary, it is proposed that exhaustion results from a conscious decision to disengage from the endurance task. In highly motivated subjects, this effort-based decision is taken when the perception of effort is maximal and continuation of the endurance task seems impossible.

Although this explanation is plausible, Marcora et al. (21) did not measure neuromuscular function. Therefore, a reduction in maximal muscle activation or an increase in the extent of central fatigue induced by endurance exercise may also explain the negative effect of mental fatigue on endurance performance. Central fatigue is an exercise-induced reduction in the capacity of the central nervous system (CNS) to fully recruit the active muscles (muscle activation) during a maximal voluntary contraction (MVC) and occurs at both spinal and/or supraspinal level (15). Central fatigue is thought to negatively affect endurance performance (1), and several authors have proposed a strong link between mental and central fatigue (e.g., 5,11,26). Because supraspinal fatigue seems to occur in brain areas upstream of the primary motor cortex (34), it is plausible that prolonged mental exertion can alter maximal muscle activation and, thus, impair endurance performance.

The main aim of the present study was to test experimentally this hypothetical link between mental fatigue, maximal muscle activation, and central fatigue. Specifically, we hypothesized that prolonged mental exertion leading to mental fatigue (i) would reduce maximal muscle activation and (ii) would increase the extent of central fatigue induced by subsequent endurance exercise. We tested these two main hypotheses by measuring maximal muscle activation of the knee extensor muscles before and after prolonged mental exertion and immediately after subsequent submaximal isometric contraction of the knee extensor muscles until exhaustion (endurance task). In addition, we hypothesized that prolonged mental exertion would reduce endurance performance via a higher perception of effort during the endurance task.

## METHODS

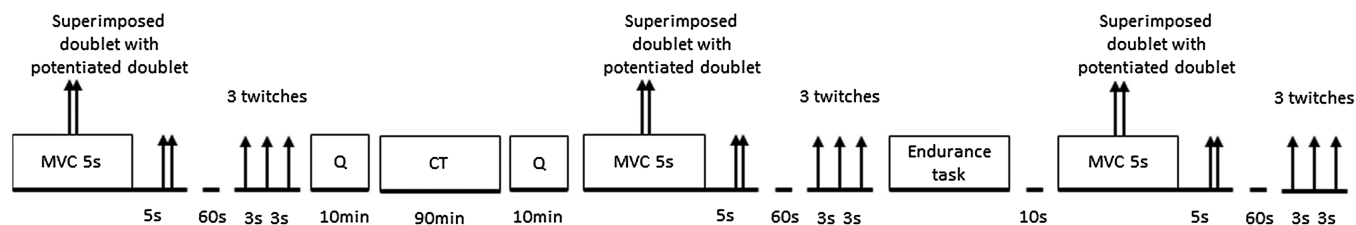
### Subjects and Ethical Approval

Ten physically active male adults (mean  $\pm$  SD; age =  $22 \pm 2$  yr, height =  $177 \pm 6$  cm, weight =  $70 \pm 8$  kg) volunteered to participate in this study. None of the subjects had any known mental or somatic disorder. Each subject gave written informed consent before the study. Experimental protocol and procedures were approved by the local ethics committee of the Faculty of Sport Sciences, University of Burgundy in Dijon. All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. Participants believed that the study was on the effects of two different cognitive activities (a computerized task and watching a movie) on the neuromuscular responses to an endurance task. To ensure high motivation during the cognitive and endurance tasks, a reward (ticket to a professional sport event) was given to the best performances in both the cognitive and endurance tasks. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants. The study conformed to the standards set by the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (2008).

### Experimental Protocol

Subjects visited the laboratory on three different occasions. During the first visit, subjects were familiarized with the laboratory and the experimental procedures. During the second and third visit, subjects performed either a mental fatigue task or a control task (for more details, see Cognitive Tasks section) in a randomized and counterbalanced order. After the cognitive task, subjects performed submaximal isometric knee extensor exercise until exhaustion (for more details, see Endurance Task section). The neuromuscular function of the knee extensor muscles was tested before and after the cognitive task and after the subsequent endurance task. Mood was assessed before and after the cognitive task, whereas motivation was measured before the subsequent endurance task (Fig. 1). For more details, see Neuromuscular Function Tests and Psychological Questionnaires sections.

Each participant completed all three visits for a period of 3 wk, with a minimum of 72 h of recovery period between



**FIGURE 1**—Graphical overview of the protocol for one session. Order and timing was the same for each subject and each session. Q, psychological questionnaires; CT, cognitive task; MVC, maximal voluntary contraction.



visits. All participants were given instructions to sleep for at least 7 h, refrain from the consumption of alcohol, and not to practice vigorous physical activity the day before each visit. Participants were also instructed not to consume caffeine and nicotine at least 3 h before testing and were asked to declare if they had taken any medication or had any acute illness, injury, or infection.

## Cognitive Tasks

**Mental fatigue task.** Mental fatigue was induced by asking the subject to perform the AX-Continuous Performance Test (AX-CPT) (8) for 90 min on a personal computer. In this cognitive task, sequences of letters were visually presented one at a time in a continuous fashion on a computer screen with black background. All letters were presented centrally, for a duration of 300 ms in 24-point uppercase Helvetica font. Each letter was followed by a 1200-ms interval, for a total of a 4500-ms delay between the presentation of cue and probe stimuli. Participants sat in front of the computer screen and were instructed to press the keyboard space bar on target trials and the control button otherwise. Any missed or incorrect response activated a beep sound from two speakers as a prompt to increase speed and accuracy. To further increase engagement in the mental fatigue task, a ticket for a professional sporting event was given as a prize for the best performance. Feedback on performance was presented on the computer screen every 30 min as a percentage of the maximum possible score. Performance was scored automatically by the computer on the basis of correct responses and response time. Target trials were defined as a cue-probe sequence in which the letter A (in red) appeared as a cue and the letter X (in red) as the probe. To increase task difficulty, two white distractor letters (except A, K, X, or Y) were presented between the cue and the probe (in white). All other cue-probe sequences served as invalid cues and nontarget probes. Letter sequences were presented in pseudorandom order, such that target (AX) trials occurred with 70% and nontarget trials occurred with 30% frequency.

**Control task.** The nonfatiguing cognitive task consisted of watching *Earth*, a documentary following the migration paths of four animal families (Alastair Fothergill and Mark Linfield, 2007), for 90 min on the same computer. During both cognitive tasks, HR was recorded continuously using an HR monitor (Polar RS400; Polar Electro Oy, Kempele, Finland).

**Endurance task.** To evaluate endurance performance, subjects performed one prolonged submaximal isometric contraction of the knee extensor muscles until exhaustion. Equipment and subject position was similar to that used for mechanical recordings during the neuromuscular function tests. A target value of 20% MVC torque was chosen. The MVC before the cognitive task was used to calculate the target torque. Visual feedback of the torque exerted during the endurance task was clearly displayed on a computer

screen located 1 m in front of the subject. Torque feedback was represented as a horizontal line, and subjects were required to reach an upper target line fixed at the target level. The endurance task terminated when torque fell below the required target value for more than 3 s despite strong verbal encouragement (exhaustion) given by a research assistant blind to the nature of the cognitive task previously performed by the subject. Endurance performance was measured as time to exhaustion. Subjects were not aware of time during the endurance task, and they were made aware of their times to exhaustion after the study was completed. The perception of effort defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (18) was measured using the 15-point RPE scale (4). Standardized explanations of the scale were given to each subject before the warm-up. Briefly, subjects were asked to rate how hard they were driving their leg during the endurance task. Leg RPE was assessed every 20 s. HR and electromyographic (EMG) signal (see Electromyographic recordings section) for the knee extensor muscles were continuously recorded during the endurance task. HR was calculated for consecutive sampling intervals of 20 s.

## Neuromuscular Function Tests

**Electrical stimulation.** Both single and double (100 Hz frequency) stimulation were used for assessment of neuromuscular function. Transcutaneous electrically evoked contractions of the knee extensor muscles were induced by using a high-voltage (maximal voltage, 400 V) constant-current stimulator (model DS7 modified; Digitimer, Hertfordshire, UK). The femoral nerve was stimulated using a monopolar cathode ball electrode (0.5-cm diameter) pressed into the femoral triangle by the same experimenter during all tests. The site of stimulation producing the largest resting twitch amplitude and compound muscle action potential (M-wave) was located and was marked on the skin so that it could be repeated reliably before and after the cognitive task and after the endurance task. The anode was a 50-cm<sup>2</sup> (10 × 5 cm) rectangular electrode (Compex SA, Ecublens, Switzerland) located in the gluteal fold opposite the cathode. The optimal intensity of stimulation (i.e., that which recruited all knee extensors motor unit) was considered to be reached when an increase in the stimulation intensity did not induce a further increase in the amplitude of the twitch torque and of the peak-to-peak amplitude of the knee extensors compound muscle action potentials (M-waves). The stimulus duration was 1 ms, and the interval of the stimuli in the doublet was 10 ms. Once the optimal intensity was found, 130% of this intensity was used and kept constant throughout the session for each subject. The supramaximal intensities ranged from 60 to 140 mA. Methodology and supramaximal intensities are according to previous studies (e.g., 29,30).

**Mechanical recordings.** Mechanical parameters were recorded using a Biodex isokinetic dynamometer (Biodex Medical Systems Inc., Shirley, NY). The axis of the dynamometer was aligned with the knee axis, and the lever arm

was attached to the shank with a strap. The extraneous movement of the upper body was limited by two crossover shoulder harnesses and a belt across the abdomen. Neuromuscular function tests were performed with the right leg at a knee joint angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The following parameters were analyzed from the twitch response (average of three single stimulation interspaced by 3 s): peak twitch (Tw), time to peak twitch (contraction time, Ct), and half-relaxation time. The peak torque of the doublet (potentiated doublet, 5 s after the MVC) was also analyzed. MVC torque was considered as the peak torque attained during the MVC. Voluntary activation level (VAL) during the MVC was estimated according to the following formula:

$$\text{VAL} = 100 \left( 1 - \frac{\text{superimposed doublet amplitude}}{\text{potential doublet amplitude}} \right)$$

(MVC at stimulation/MVC) corresponding to the Strojnik and Komi correction (4) was used if the stimulation appears not at the MVC torque value. All VAL calculations were performed for an MVC<sub>at stimulation</sub> between 95% and 100% MVC to ensure reliability of measurement. Mechanical signals were digitized online at a sampling frequency of 1 kHz using a computer and stored for analysis with commercially available software (Acqnowledge 4.1 for MP Systems; Biopac Systems Inc., Goleta, CA). The timing of stimulation could be found in Figure 1.

**Electromyographic recordings.** The EMG of the vastus lateralis (VL) and rectus femoris (RF) muscles was recorded with pairs of silver chloride circular (recording diameter of 10 mm) surface electrodes (ref 1066, Swaromed; Nessler Medizintechnik, Innsbruck, Austria) with an inter-electrode (center-to-center) distance of 20 mm. Recording sites were then carefully adjusted by eliciting the greatest M-wave amplitude for each muscle at a given intensity via femoral nerve stimulation at the beginning of each testing session. The low resistance between the two electrodes (<5 kΩ) was obtained by shaving the skin, and dirt were removed from the skin using alcohol swabs. The reference electrode was attached to the patella of the left knee. Myoelectrical signals were amplified with a bandwidth frequency ranging from 1 Hz to 5 kHz (common mode rejection ratio = 110 dB, impedance input = 1000 MΩ, gain = 1000 for RF and 500 for VL), digitized online at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (Acqnowledge 4.1 for MP Systems; Biopac Systems Inc.). The root mean square (RMS), a measure of EMG amplitude, was automatically calculated with the software.

Peak-to-peak amplitude and duration of the M-waves were analyzed for VL and RF muscles, with the average of the three trials used for analysis. The EMG amplitude of VL and RF muscles during the knee extensors MVC was quantified as the RMS for a 0.5-s interval at peak torque (250-ms interval either side of the peak torque). The maxi-

mal RMS values for VL and RF muscles were then normalized by the M-wave peak-to-peak amplitude for the respective muscles to obtain the RMS/M-wave ratio. This normalization procedure accounted for peripheral influences including neuromuscular propagation failure and changes in impedance from the EMG recordings. RMS EMG was calculated for consecutive sampling intervals of 20 s during the endurance task for both VL and RF. The RMS EMG during endurance task was normalized to the RMS EMG determined during the MVC precognitive task.

## Psychological Questionnaires

**Mood.** The Brunel Mood Scale developed by Terry et al. (36) was used to quantify current mood (“How do you feel right now?”) before and after the cognitive tasks. This questionnaire contains 24 items (e.g., “angry, uncertain, miserable, tired, nervous, and energetic”) divided into six respective subscales: anger, confusion, depression, fatigue, tension, and vigor. The items are answered on a 5-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely), and each subscales, with four relevant items, can achieve a raw score in the range of 0 to 16. Only the scores for the fatigue and vigor subscales were considered in this study as subjective markers of mental fatigue.

**Motivation.** Motivation related to the endurance task was measured using the success motivation and intrinsic motivation scales developed and validated by Matthews et al. (23). Each scale consists of 7 items (e.g., “I want to succeed on the task” and “I am concerned about not doing as well as I can”) scored on a 5-point scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, and 4 = extremely). Therefore, total scores for these motivation scales ranged between 0 and 28.

**Statistics.** All data are presented as means ± SEM. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. The Greenhouse–Geisser correction to the degrees of freedom was applied when violations to sphericity were present. Paired *t*-tests were used to assess the effect of condition (mental fatigue vs control) on time to exhaustion, motivation scores, HR at exhaustion, leg RPE at exhaustion, and RMS at exhaustion. One-way repeated-measures ANOVA was used to test the effect of time (15-min blocks) on the number of incorrect answers, reaction time, and HR during the AX-CPT task. Fully repeated-measure 2 × 2 ANOVAs were used to test the effect of condition and time on mood before and after the cognitive tasks. Fully repeated-measure 2 × 3 ANOVAs were used to test the effect of condition and time on MVC torque, VAL, M-wave parameters for each muscle, RMS/M-wave ratio, twitch properties, and peak doublet torque before and after the cognitive tasks and after the endurance task. Fully repeated-measure 2 × 7 ANOVAs were used to test the effect of condition and time on HR, leg RPE, and RMS at isotime (time elapsed from the beginning of the

endurance task to the last measurement before exhaustion of the shortest performance). Significant main effects of time and significant interactions were followed up with Bonferonni tests as appropriate. Significance was set at 0.05 (two-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 19 for Mac OS X (SPSS Inc., Chicago, IL).

## RESULTS

### Manipulation Checks

HR decreased over time in both conditions ( $P < 0.001$ ), but it was significantly higher in the mental fatigue condition ( $73 \pm 1$  beat per minute) compared with the control condition ( $69 \pm 1$  beat per minute) ( $P = 0.004$ ) (Fig. 2B). The number of incorrect responses (Fig. 2C) and reaction time (Fig. 2D) did not change significantly over time during the AX-CPT task.

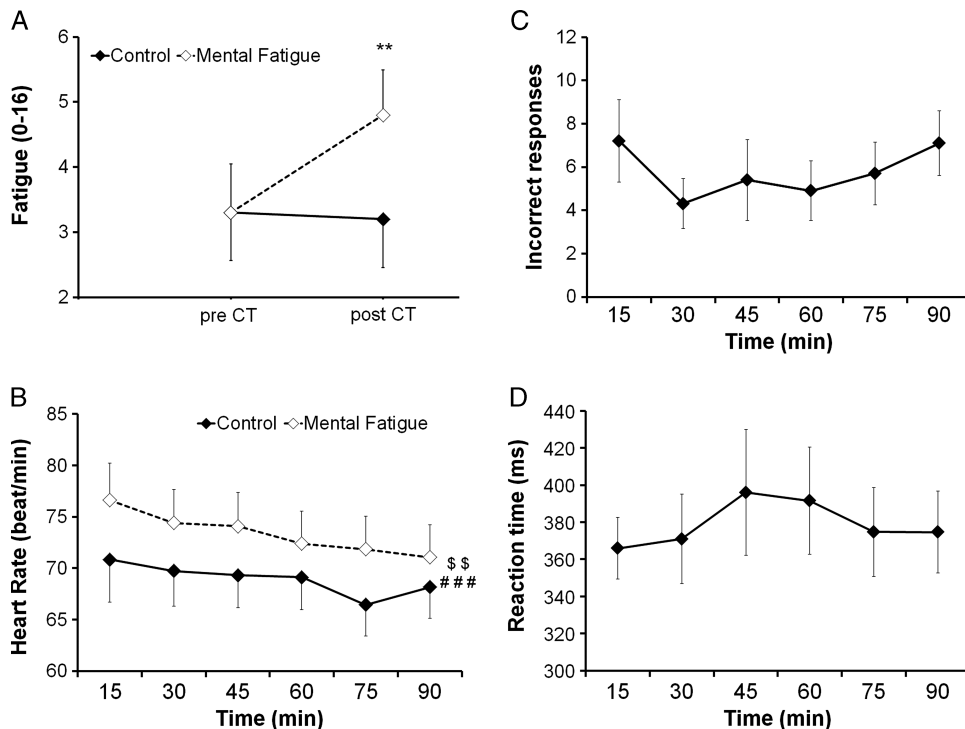
The mood questionnaire revealed a significant decrease in vigor after both the AX-CPT task ( $9.0 \pm 0.9$  to  $6.5 \pm 0.9$ ) and the control task ( $9.7 \pm 0.6$  to  $7.1 \pm 0.7$ ) ( $P = 0.003$ ) with no significant difference between conditions. However, there was a significant interaction for the subjective fatigue ( $P = 0.033$ ). Follow-up tests demonstrated that fatigue increased significantly only after the AX-CPT task ( $P = 0.007$ ) with no significant change after the control task (Fig. 2A).

### Effects of Mental Fatigue on Intrinsic and Success Motivation

There were no significant differences between conditions in intrinsic motivation (mental fatigue condition  $16.5 \pm 1.3$ , control condition  $16.5 \pm 1.1$ ,  $P = 1.000$ ) and success motivation (mental fatigue condition  $18.8 \pm 1.6$ , control condition  $15.8 \pm 1.8$ ,  $P = 0.111$ ).

### Effects of Mental Fatigue on Time to Exhaustion, HR, EMG Amplitude, and Perception of Effort during the Endurance Task

Time to exhaustion (Fig. 3A) was  $13\% \pm 4\%$  shorter in the mental fatigue condition compared with the control condition ( $P = 0.008$ ). Individual times to exhaustion were shorter in the mental fatigue condition compared with the control condition in 8 of 10 subjects (Fig. 3B). HR (Fig. 3D) increased significantly during the endurance task ( $P < 0.001$ ), with no significant differences between conditions at both isotime and exhaustion. EMG amplitude (RMS/RMS pre-cognitive task MVC) of the VL muscle (Fig 3C) increased significantly during the endurance task ( $P = 0.003$ ) with no significant difference between conditions at isotime. At exhaustion, however, VL EMG amplitude tended to be higher in the control condition ( $52.8\% \pm 6.8\%$ ) compared with the mental fatigue condition ( $41.5\% \pm 5.9\%$ ) ( $P = 0.095$ ). Leg



**FIGURE 2**—Markers of mental fatigue. **A.** Effect of cognitive tasks on self-reported fatigue. **B.** HR during both cognitive tasks. **C.** Number of incorrect responses during the mental fatigue task. **D.** Reaction time during the mental fatigue tasks. CT, cognitive task.  $^{SS}$ Significant main effect of condition ( $P < 0.01$ ).  $^{**}$ Significant condition–time interaction ( $P < 0.01$ ).  $^{###}$ Significant main effect of time ( $P < 0.001$ ). Data are presented as means  $\pm$  SEM.

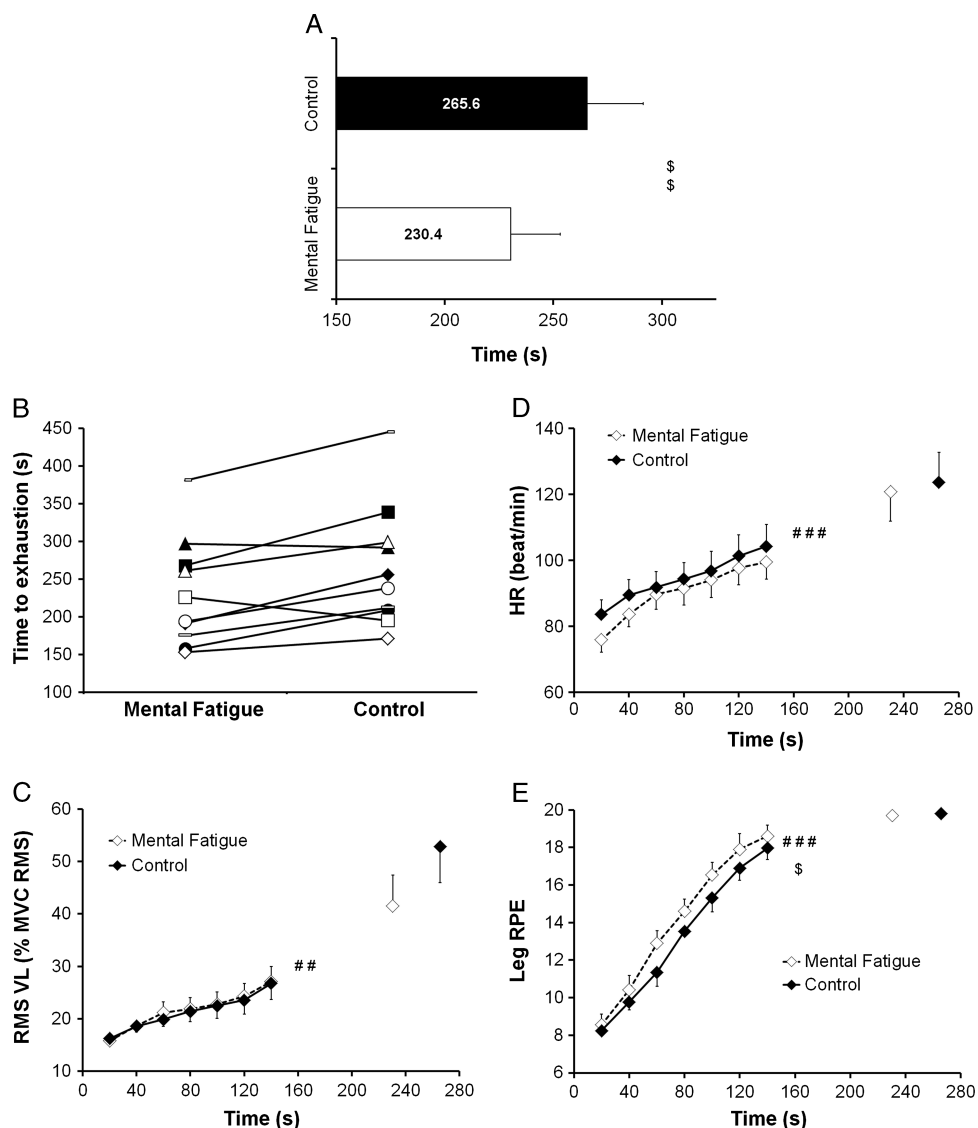


FIGURE 3—Effects of cognitive tasks on time to exhaustion and physiological and perceptual responses during the endurance task. A. Mean effect of mental fatigue on time to exhaustion. B. Individual effect of mental fatigue on time to exhaustion. C. Root mean square (RMS) EMG of the vastus lateralis (VL) muscle during the endurance task. Values are expressed as a percentage of the maximal value before the cognitive task. D. HR during the endurance task. E. Leg RPE during the endurance task. <sup>s</sup>Significant main effect of condition ( $P < 0.05$ ). <sup>ss</sup>Significant main effect of condition ( $P < 0.01$ ). <sup>###</sup>Significant main effect of time ( $P < 0.001$ ). <sup>\$\$\$</sup>Significant main effect of time ( $P < 0.001$ ). Data are presented as means  $\pm$  SEM.

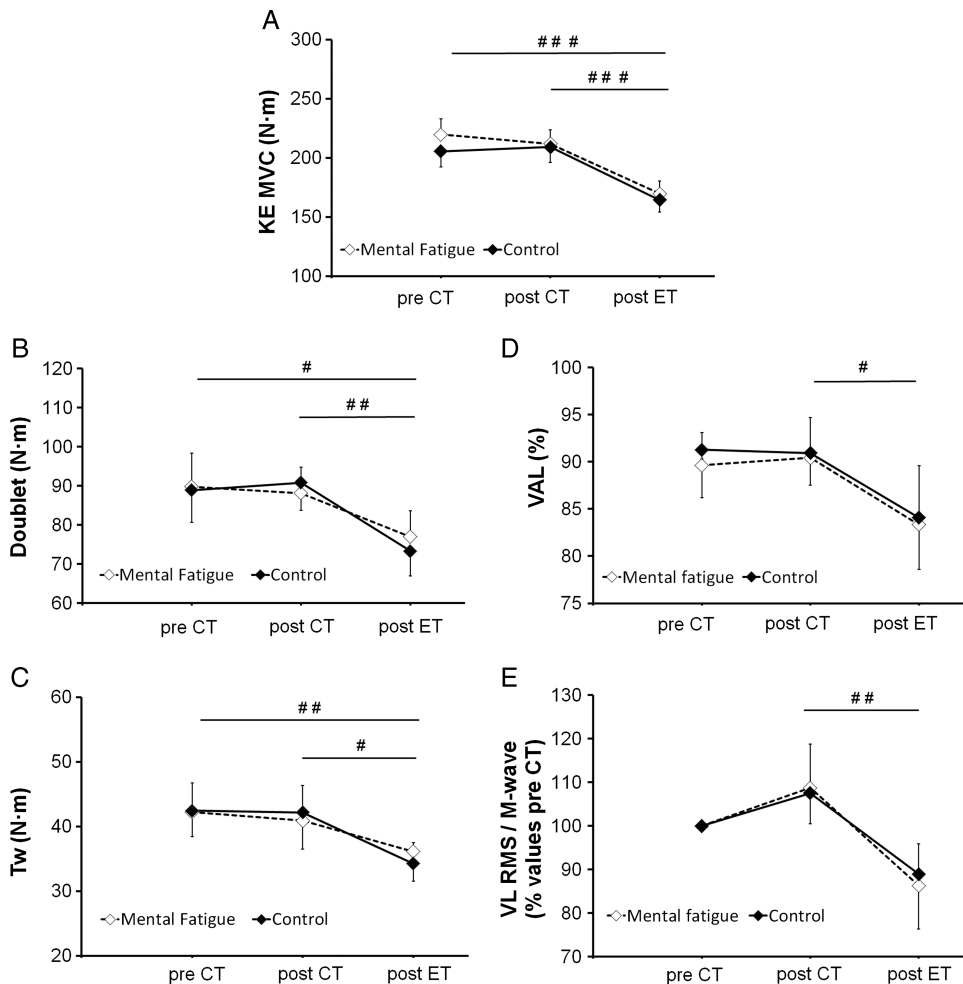
RPE (Fig. 3E) increased significantly during the endurance task ( $P < 0.001$ ), and it was significantly higher in the mental fatigue condition compared with the control condition ( $P = 0.045$ ), without interaction effect ( $P = 0.353$ ). Leg RPE at exhaustion was not significantly different between conditions.

### Effects of Mental Fatigue and the Endurance Task on Neuromuscular Function

**MVC.** There was no significant main effect of condition or interaction on knee extensors MVC (Fig. 4A). Follow-up tests of the significant main effect of time ( $P < 0.001$ ) revealed that the cognitive tasks did not affect MVC torque.

The endurance task caused a significant reduction in MVC torque in both the mental fatigue and control condition (mental fatigue condition  $-26.7\% \pm 5.7\%$ , control condition  $-27.6\% \pm 3.3\%$ ) ( $P < 0.001$ ). The MVC torque of the knee flexors was not significantly affected by the cognitive tasks and the endurance task (precognitive task: mental fatigue condition  $94 \pm 5$  N·m, control condition  $91 \pm 6$  N·m; postcognitive task: mental fatigue condition  $86 \pm 5$  N·m, control condition  $93 \pm 6$  N·m; postendurance task: mental fatigue condition  $89 \pm 6$  N·m, control condition  $93 \pm 7$  N·m).

**Peripheral fatigue.** There were no significant main effects of condition or interactions on all twitch parameters. Follow-up tests of the significant main effects of time (all  $P < \text{or} = 0.010$ ) revealed that the cognitive tasks did not affect Tw (Fig. 4C), Ct, and doublets (Fig. 4B). Half



**FIGURE 4—Effects of cognitive tasks and endurance task on central and peripheral parameters of neuromuscular function. A. Maximal voluntary contraction (MVC) torque of the knee extensors (KE). B. Peak torque of the doublet. C. Peak twitch (Tw). D. Voluntary activation level (VAL). E. Root mean square (RMS)/M<sub>max</sub> (M-wave) ratio of the vastus lateralis (VL) muscle. Values are expressed as a percentage of baseline values (precognitive task values). CT, cognitive task; ET, endurance task. #Significant main effect of time ( $P < 0.05$ ). ##Significant main effect of time ( $P < 0.01$ ). ###Significant main effect of time ( $P < 0.001$ ). Data are presented as means  $\pm$  SEM.**

relaxation time of the twitch peak force was significantly higher after the cognitive tasks ( $P = 0.047$ ). The endurance task significantly affected Tw ( $P = 0.021$ ) (Fig. 4C), Ct ( $P = 0.021$ ), half relaxation time of the twitch peak force ( $P = 0.034$ ), and doublet ( $P = 0.035$ ) (Fig. 4B). M-wave amplitude and duration for VL and RF (Table 1) muscles were not significantly affected by the cognitive tasks and the endurance task (amplitude:  $P = 0.352$  and  $P = 0.444$ ; duration:  $P = 0.488$  and  $P = 0.792$ ). M-wave amplitude and

duration for VL and RF muscles did not change between condition (amplitude:  $P = 0.177$  and  $P = 0.740$ , duration:  $P = 0.088$  and  $P = 0.177$ ) and did not show any interaction effect (amplitude:  $P = 0.804$  and  $P = 0.972$ , duration:  $P = 0.804$  and  $P = 0.360$ ).

**Central fatigue.** There was no significant main effect of condition or interaction on VAL (Fig. 4D). Follow-up tests of the significant main effect of time ( $P = 0.027$ ) revealed that the cognitive tasks did not significantly affect VAL.

**TABLE 1. Peak-to-peak amplitude and duration of the maximal M-wave associated with the single twitch.**

	Mental Fatigue			Control		
	Pre-CT	Post-CT	Post-ET	Pre-CT	Post-CT	Post-ET
Amplitude VL (mV)	12.19 $\pm$ 2.52	11.81 $\pm$ 2.37	12.5 $\pm$ 2.47	13.30 $\pm$ 2.13	13.38 $\pm$ 1.95	13.89 $\pm$ 2.07
Duration VL (ms)	8.85 $\pm$ 0.48	9.08 $\pm$ 0.47	9.22 $\pm$ 0.47	10.63 $\pm$ 0.67	11.11 $\pm$ 0.66	10.78 $\pm$ 0.73
Amplitude RF (mV)	7.70 $\pm$ 1.35	7.46 $\pm$ 1.22	7.79 $\pm$ 1.24	7.44 $\pm$ 1.04	7.11 $\pm$ 1.09	7.43 $\pm$ 1.00
Duration RF (ms)	8.03 $\pm$ 0.57	8.68 $\pm$ 0.86	8.53 $\pm$ 1.07	9.88 $\pm$ 0.85	9.67 $\pm$ 0.89	9.70 $\pm$ 0.98

CT, cognitive task; ET, endurance task; VL, vastus lateralis; RF, rectus femoris.

However, the endurance task significantly reduced VAL ( $P = 0.024$ ). Similarly, there was no significant main effect of condition or interaction on RMS/M-wave ratio of the RF and VL (Fig. 4E) muscles. Follow-up tests of the significant main effects of time (all  $P < 0.009$ ) revealed that the cognitive tasks did not affect RMS/M of the RF and VL muscles. However, RMS/M decreased significantly after the endurance task for both the RF ( $P < 0.001$ ) and VL ( $P = 0.010$ ) muscles.

## DISCUSSION

The main aim of the present study was to test the hypotheses that prolonged mental exertion leading to mental fatigue (i) would reduce maximal muscle activation and (ii) would increase the extent of central fatigue induced by subsequent endurance exercise. Contrary to our hypotheses, this study demonstrates that prolonged mental exertion does not lead to any impairment in neuromuscular function. In accordance with previous findings (21), the negative effect of prolonged mental exertion on endurance performance seems to be mediated by the higher perception of effort experienced by mentally fatigued subjects during the endurance task.

**Prolonged mental exertion and mental fatigue.** The higher HR observed during the AX-CPT task compared with watching a movie confirms the demanding nature of this cognitive task. In fact, an increase in HR and other cardiovascular changes are associated with exertion of effort during cognitive tasks (32). Given its demanding nature, it is not surprising that 90 min of the AX-CPT task induced a significant increase in subjective feelings of fatigue. This effect is in accordance with previous studies (21,38) and demonstrates we were successful in experimentally inducing a state of mental fatigue in our subjects. However, we did not observe any significant decrease in cognitive performance during the AX-CPT task. It is possible that the reward we gave for best performance in the AX-CPT task made our subjects able to overcome the negative effects of mental fatigue on cognitive performance (2).

**Prolonged mental exertion does not reduce maximal muscle activation.** Our first hypothesis was that prolonged mental exertion would reduce maximal muscle activation. It is well known that endurance exercise can reduce maximal muscle activation (15); but until now, it was not known whether prolonged mental exertion could also reduce the capacity of the CNS to maximally recruit the active muscles. We tested this hypothesis by examining neuromuscular function before and after the two cognitive tasks. Because small changes in maximal muscle activation may be hard to detect using the twitch interpolation technique (33), careful consideration of numerous experimental details was taken (e.g., use of pair stimuli or high resolution measurement of torque). Contrary to our hypothesis, the present study failed to show a decrease in knee extensors muscles MVC

torque following the fatiguing cognitive task (90-min AX-CPT). Furthermore, VAL and RMS/M-wave ratio during MVC were not affected by mental fatigue. These novel results suggest that, unlike endurance exercise, prolonged mental exertion does not reduce maximal muscle activation. However, in the present study, the 90-min AX-CPT induced a relatively moderate level of mental fatigue. Therefore, we cannot exclude that cognitive tasks leading to higher levels of mental fatigue may reduce maximal muscle activation.

Interestingly, some literature suggests that mental fatigue can have systemic effects such as alterations of amino acids concentration in the blood (24,27). These and other unknown systemic effects of mental fatigue could theoretically cause some peripheral fatigue. Our experimental study, however, failed to find any significant effect of prolonged mental exertion on twitches and M-waves properties.

Our findings are in contrast with those of Bray et al. (5), who found a negative effect of a demanding cognitive task on MVC of the hand flexor muscles. These authors suggested an interaction between the demanding cognitive task and an alteration of the ability of the CNS to maximally recruit the active muscles. However, no valid measure of maximal muscle activation was included in their study. The discrepancy between our results and those of Bray et al. (5) may also be explained by the difference in muscle group tested to measure neuromuscular function (hand flexor muscles vs knee extensor muscles). Furthermore, the increase in MVC observed by Bray et al. (5) in the control condition suggests that their subject did not exert a maximal voluntary effort during all tests of neuromuscular function. Lack of maximal voluntary effort is well known to negatively affect measures of neuromuscular function (12). Further research is required to get better insights on the possible effect of prolonged mental exertion on maximal muscle activation in different muscle groups.

**Prolonged mental exertion does not increase the extent of central fatigue induced by subsequent endurance exercise.** Although prolonged mental exertion did not reduce maximal muscle activation, it may be possible that exercising in a mental fatigue state would increase the extent of central fatigue measured at exhaustion. To investigate the hypothetical interaction between mental and central fatigue, we chose a submaximal isometric knee extensor exercise protocol known to induce a reduction in VAL, that is, to induce central fatigue (e.g., 30). Moreover because timing for neuromuscular assessment is crucial (13), submaximal isometric exercise immediately followed by an MVC of the same muscle group provides us with the fastest way to accurately quantify the extent of central fatigue at exhaustion. As expected, the endurance task induced significant central and peripheral fatigue in both the mental fatigue and control conditions. However, the similar reduction in VAL at exhaustion in both conditions is against our hypothesis that prolonged mental exertion would increase the extent of central fatigue induced by subsequent endurance exercise. Because time to exhaustion was significantly different

between the mental fatigue and control conditions, further investigations on the effect of prolonged mental exertion on the time course of central fatigue during endurance exercise are required. However, it should be pointed that any small difference in voluntary activation between mental fatigue and control conditions may be hard to detect. Further research is also needed to investigate whether higher levels of mental fatigue or different endurance tasks (e.g., dynamic whole-body exercise) are associated with an increase in the extent of central fatigue induced by subsequent endurance exercise.

**Prolonged mental exertion versus endurance exercise.** Our findings demonstrate for the first time that prolonged mental exertion and endurance exercise have different effects on neuromuscular function. The fact that prolonged mental exertion, unlike endurance exercise, does not alter peripheral muscle function is not surprising because the fatiguing cognitive task (90-min AX-CPT) does not involve the knee extensor muscles. However, we expected that prolonged mental exertion would reduce maximal muscle activation of the knee extensors. As in previous studies (30), our submaximal isometric knee extensor exercise protocol induced a significant reduction in maximal muscle activation, a phenomenon called central fatigue (15). However, the 90-min AX-CPT did not reduce maximal muscle activation of the knee extensors despite leading to a significant level of mental fatigue. The different effects of prolonged mental exertion and endurance exercise on maximal muscle activation suggest that different mechanisms are involved. One possibility is that prolonged mental exertion and endurance exercise are associated with different neurochemical changes in the brain. However, both prolonged mental exertion (14,17) and endurance exercise (9,22) have been associated with an increase in brain adenosine and a reduction in brain glycogen. Therefore, at present, the most likely explanation for the different effects of prolonged mental exertion and endurance exercise on maximal muscle activation is that the neurochemical changes associated with both phenomena occur in different areas of the CNS.

The AX-CPT task we used to experimentally induce mental fatigue in our subjects is known to strongly activate the anterior cingulate cortex (ACC) (8), an area of the brain associated with task difficulty and sustained attention in a variety of cognitive tasks (28). Importantly, the ACC has also been linked with the perception of effort during endurance exercise (41). It is, therefore, biologically plausible that prolonged mental exertion induces changes in the ACC, which in turn, increase the perception of effort and reduce endurance performance. However, our results suggest that prolonged activation of the ACC does not reduce the capacity of the CNS to maximally recruit the active muscles.

The reduction in maximal muscle activation induced by exercise (central fatigue) can occur at both spinal and supraspinal level (15). Although it has been proposed that supraspinal fatigue during maximal and submaximal

isometric contractions is localized in brain areas upstream of the primary motor cortex (34), there are few neuroimaging studies investigating the brain areas associated with supraspinal fatigue. Some studies have shown progressive increase in activity in several brain areas such as the sensorimotor cortex, supplementary motor areas, frontal cortex, and the insular cortex during submaximal fatiguing exercise (16,31,39,40). However, it is not clear whether the concept of central fatigue is meaningful during submaximal muscle contractions (35). In fact, these changes in cerebral activity during submaximal fatiguing exercise are likely to reflect brain adaptations to compensate for spinal and/or peripheral muscle fatigue rather than mechanisms of supraspinal fatigue. To the best of our knowledge, only van Duinen et al. (39) have investigated the brain areas associated with supraspinal fatigue by measuring their activity during MVCs performed before and after fatiguing exercise. These authors showed a significant decrease in activity of the supplementary motor areas and, to a lesser extent, in parts of the paracentralgyrus, right putamen, and in a small cluster of the left parietal operculum. The fact that central fatigue was not associated with changes in ACC activity suggests that the brain areas affected by prolonged mental exertion and endurance exercise are different.

Furthermore, we have to consider that the neurochemical changes induced by prolonged mental exertion are likely to be confined to the brain, and some of the neurochemical changes leading to central fatigue may also occur at spinal level (15). Therefore, the different effects of prolonged mental exertion and endurance exercise on maximal muscle activation could be explained by (i) the different brain areas affected by prolonged mental exertion and endurance exercise and (ii) the spinal alterations likely to occur during endurance exercise but not during prolonged mental exertion.

**Mental fatigue, perceived exertion, and the psychobiological model of endurance performance.** Finally, the present results provide experimental evidence that the higher perception of effort induced by prolonged mental exertion is not associated with lower muscle activation before exercise. In fact, the higher perception of effort experienced by mentally fatigued subjects occurs despite no reduction of maximal muscle activation before the endurance task, and similar extent of central fatigue at exhaustion in the mental fatigue and control conditions. However, the increase in the perception of effort occurring over time during the endurance task in both conditions may be caused, at least in part, by the central and peripheral fatigue induced by endurance exercise. In fact, in the presence of significant muscle fatigue, an increase in central motor command is required to maintain the same submaximal force. Because the sensory signal for the perception of effort is the corollary discharge of the central motor command, the increase in central motor command required to overcome muscle fatigue is reflected in a significant increase in the perception of effort (10,19). A previous study (21) suggests that the higher perception of effort experienced by mentally fatigued subjects during the endurance

task may be due to altered central processing of sensory signals. However, further research is required to understand the neurophysiological mechanisms underlying the negative effect of mental fatigue on the perception of effort during endurance exercise.

Similar to previous findings on the effect of mental fatigue on endurance performance during dynamic whole-body exercise (21), we found that mental fatigue significantly reduces time to exhaustion during submaximal isometric knee extensor exercise. These results suggest that mental fatigue has a negative effect on endurance performance regardless of the type of contraction and muscle mass active during endurance exercise.

A plausible explanation for the negative effect of mental fatigue on endurance performance is provided by the psychobiological model of endurance performance (20) based on Motivational Intensity Theory (7). This model postulates that exhaustion is a form of task disengagement that occurs when subjects perceive the task as being impossible to complete despite their maximal effort, or when the effort required by the task exceeds the upper limit of what people are willing to do (potential motivation). Accordingly, a reduction in time to exhaustion can occur either because of an increase in the perception of effort or a reduction in potential motivation. In accordance to a previous study (21), we did not measure any negative effect of mental fatigue on intrinsic and success motivation related to the endurance task. Therefore, the only mechanism that can explain the negative effect of prolonged mental exertion on time to exhaustion is the higher perception of effort experienced by mentally fatigued subjects during the endurance task. As leg RPE increased similarly over time

in both conditions, mentally fatigued subjects reached their maximal level of perceived exertion and disengaged from the endurance task earlier than that in the control condition.

## CONCLUSIONS AND PERSPECTIVES

The present study provides the first experimental evidence that prolonged mental exertion does not alter neuromuscular function measured as maximal muscle activation and central fatigue induced by subsequent endurance exercise. These findings suggest that prolonged mental exertion and endurance exercise affect different areas of the CNS. Future studies on brain and endurance performance should investigate the specific mechanisms of mental fatigue and central fatigue without making the wrong assumption that these two phenomena are two different aspects of the same central alterations. Because the perception of effort is the most likely mediator of the negative effect of mental fatigue on endurance performance, further studies are required to investigate the neurophysiological alterations associated with the higher perception of effort experienced by mentally fatigued subjects during endurance exercise. On a more practical perspective, the present study suggests that the negative impact of mental fatigue on physical performance is limited to endurance and may not have a negative impact on performance of short maximal voluntary efforts such as sprint or jump.

The authors thank Cyril Sirandre and Yves Ballay for their technical advice and support.

The results of the present study do not constitute endorsement by the American College of Sports Medicine. No conflict of interest, financial or otherwise, is declared by the authors. No funding was received for this study.

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# Response inhibition impairs subsequent self-paced endurance performance

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Received: 2 December 2013 / Accepted: 27 January 2014 / Published online: 15 February 2014  
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## Abstract

**Purpose** The aim of this study was to test the effects of mental exertion involving response inhibition on pacing and endurance performance during a subsequent 5-km running time trial.

**Methods** After familiarization, 12 physically active subjects performed the time trial on a treadmill after two different cognitive tasks: (i) an incongruent Stroop task involving response inhibition (inhibition task) and (ii) a congruent Stroop task not involving response inhibition (control task). Both cognitive tasks were performed for 30 min.

**Results** Neither the inhibition nor the control task induced subjective feelings of mental fatigue. Nevertheless, time trial performance was impaired following the inhibition task ( $24.4 \pm 4.9$  min) compared to the control task ( $23.1 \pm 3.8$  min) because of a significant reduction in average running speed chosen by the subject. The response inhibition task did not affect pacing strategy, which was negative in both conditions. Heart rate and blood lactate responses to the time trial were not affected by the inhibition task, but subjects rated perceived exertion higher compared to the control condition ( $13.5 \pm 1.3$  vs  $12.4 \pm 1.3$ ).

**Conclusion** These findings show for the first time that 30 min of mental exertion involving response inhibition

reduces subsequent self-paced endurance performance despite no overt mental fatigue. The impairment in endurance performance observed after the incongruent Stroop task seems to be mediated by the higher perception of effort as predicted by the psychobiological model of endurance performance.

**Keywords** Perception of effort · Time trial · Mental fatigue · Running · Cognitive task · Stroop task

## Abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
HR	Heart rate
RPE	Rating of perceived exertion

## Introduction

Mental exertion refers to the engagement with a demanding cognitive task. When prolonged, it can induce a psychobiological state of mental fatigue characterized by subjective feelings of “tiredness” and “lack of energy” (Boksem and Tops 2008). Recent studies have demonstrated the negative impact of mental fatigue induced by prolonged mental exertion (90 min) on subsequent endurance performance during whole-body (Marcora et al. 2009) and single-joint exercise (Pageaux et al. 2013). These studies demonstrated a higher perception of effort independently of any alteration of the cardiorespiratory, metabolic and neuromuscular responses to exercise. These results support the psychobiological model of endurance performance in which perception of effort plays a major role in limiting endurance performance (Marcora and Staiano 2010).

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Communicated by Guido Ferretti.

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In these studies, the negative effects of prior mental exertion on endurance performance were demonstrated with time to exhaustion tests. These tests are sensitive to changes in endurance performance (Amann et al. 2008), but do not allow for the self-regulation of speed/power output during endurance exercise (pacing). Therefore, the effect of prior mental exertion on pacing is not known at present. Because pacing is involved in all competitive endurance events, it is important for coaches and athletes to know whether prior mental exertion can affect the pacing strategy, i.e. the self-selected strategy or tactic adopted by an athlete (Abbiss and Laursen 2008).

From a more basic perspective, it is important to understand the contribution of specific cognitive process to the reduction in endurance performance observed after mental exertion. Of particular interest is response inhibition. This cognitive process refers to the inhibition of inappropriate/unwanted motor or emotional responses (Mostofsky and Simmonds 2008) and it is a main component of decision-making in human volition (Haggard 2008). Cognitive tasks involving response inhibition are known to activate the pre-supplementary motor area and the anterior cingulate cortex (ACC) during Stroop tasks (Mostofsky and Simmonds 2008). Activity in these cortical areas has been linked with perception of effort (de Morree et al. 2012; Williamson et al. 2001, 2002), and damage to the ACC is known to affect effort-based decision-making in animals (Rudebeck et al. 2006; Walton et al. 2003, 2006). Therefore, it is biologically plausible that prior mental exertion involving response inhibition would affect the effort-based decision-making process thought to regulate self-paced endurance performance (Marcora 2010a).

The aim of our study was to investigate the effects of response inhibition on pacing, perception of effort and performance during subsequent self-paced endurance exercise. Specifically, we hypothesized that prior mental exertion involving response inhibition would increase perception of effort and impair endurance performance to a larger extent than prior mental exertion without response inhibition. To test these hypotheses, we compared an inhibition condition (incongruent Stroop task) with a cognitive task that does not involve response inhibition (congruent Stroop task; Bray et al. 2008; Stroop 1992). Because the negative effects of prior mental exertion on perception of effort and endurance performance are well known (Marcora et al. 2009; Pageaux et al. 2013), we did not include a pure control condition with no prior mental exertion. To investigate the effect of response inhibition on pacing, we measured endurance performance with a 5-km running time trial in which subjects were free to self-regulate their speed on the treadmill.

## Methods

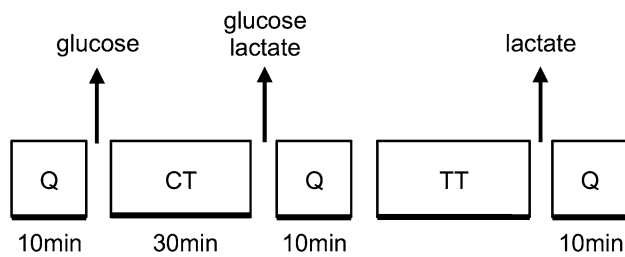
### Subjects and ethical approval

Twelve adults (eight males and four females; mean  $\pm$  standard deviation (SD); age:  $21 \pm 1$  year, height:  $174 \pm 12$  cm, weight:  $69 \pm 11$  kg) volunteered to participate in this study. None of the subjects had any known mental or somatic disorder. All subjects were involved in aerobic activities for at least two times a week in the previous 6 months. This level of training corresponds to the performance level 2 in the classification of subject groups in sport science research (De Pauw et al. 2013). Each subject gave written informed consent prior to the study. The experimental protocol and procedures were approved by the Ethics Committee of the School of Sport and Exercise Sciences, University of Kent, UK. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008) All subjects were given written instructions describing the experimental protocol and procedures, but were naive to its aims and hypotheses. To ensure high motivation during the cognitive tasks and the time trials, a reward (£10 Amazon voucher) was given to the best overall performance in all the cognitive tasks and time trials. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants.

### Experimental protocol

Subjects visited the laboratory on three different occasions. During the first visit, subjects were familiarized with the experimental procedures. During the second and third visit, subjects performed either a cognitive task involving the response inhibition process (inhibition condition) or a cognitive task that did not involve response inhibition (control condition, see “Cognitive tasks” for more details) in a randomized and counterbalanced order (randomized cross-over design). After the cognitive task, subjects performed a 5-km running time trial on a treadmill (see “Time trial” for more details). An overview of the experimental protocol is provided in Fig. 1. Mood was assessed before and after the cognitive task, and subjective workload was assessed after the cognitive task and after the time trial, whilst motivation was only measured before the time trial. Heart rate (HR) was recorded continuously throughout the experiment. Capillary blood samples were taken before and after the cognitive task, and after the time trial. For more details see “Physiological measurements” and “Psychological measurements”.

Each participant completed all three visits over a period of 2 weeks with a minimum of 48 h recovery period



**Fig. 1** Graphical overview of the experimental protocol. Order and timing were the same for each subject and each session. *CT* cognitive tasks, *Q* psychological questionnaires, *TT* 5-km running time trial

between visits. All participants were given instructions to sleep for at least 7 h, refrain from the consumption of alcohol and not to practice vigorous physical activity the day before each visit. Participants were also instructed to avoid caffeine and nicotine for at least 3 h before visiting the laboratory and were asked to declare if they had taken any medication or had any acute illness, injury or infection.

#### Cognitive tasks

##### *Inhibition task*

The inhibition condition consisted of 30 min of engagement with a modified incongruent version of the Stroop colour-word task. This 30-min task is known to reduce persistence in a figure-tracing task (Wallace and Baumeister 2002). Participants performed this inhibition task on a computer whilst sitting comfortably in a quiet and dim lit room. Four words (yellow, blue, green, red) were serially presented on the screen until the participant validated an answer and were followed by a 1,500 ms interval. Subjects were instructed to press one of four coloured buttons on the keyboard (yellow, blue, green, red) with the correct response being the button corresponding to the ink colour (either yellow, blue, green, red) of the word presented on the screen. For example, if the word blue appeared in yellow ink, the yellow button had to be pressed. If however the ink colour was red, the button to be pressed was the button linked to the real meaning of the word, not the ink colour (e.g. if the word blue appears in red, the button blue has to be pressed). If the ink colour was blue, green or yellow, then the button pressed matched the ink colour. The word presented and its ink colour were randomly selected by the computer (100 % incongruent). Twenty practice attempts were allowed before the inhibition task to ensure the participant understood the concept fully. The inhibition task was also performed for 5 min during the familiarization visit. Subjects were instructed to respond as quickly and accurately as possible. Visual feedback was given after each word in the form of correct or incorrect answer, response

speed and accuracy. Participants were also informed that points would be awarded for speed and accuracy of their responses, and the score for both cognitive tasks would be added to the score for each time trial, to reward the overall highest score with a £10 Amazon voucher to increase motivation.

##### *Control task*

The control condition consisted of 30 min of engagement with a congruent version of the Stroop colour-word task. This control task was similar to the modified incongruent version of the Stroop colour-word task. However, the response inhibition process was not involved in this congruent version. Indeed, all words presented and their ink colour were matched (e.g. the word green was presented with a green ink colour).

Subjects were familiarized with all the procedures described above during the first visit to the laboratory. Cognitive performance during the congruent and incongruent Stroop colour-word tasks was measured in term of response accuracy (percentage of correct responses) and reaction time. Performance data were analysed off-line using the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) and averaged in a non-cumulative way for each of six 5-min periods during both cognitive tasks.

##### *Time trial*

Ten minutes after completion of the allocated cognitive task, subjects performed a time trial on a treadmill to evaluate pacing and endurance performance. The treadmill (PowerJog, Expert Fitness UK Ltd, Glamorgan, Wales) was set at a 1 % gradient (Jones and Doust 1996). Subjects were asked to run 5 km in the quickest time possible. Each participant performed a standardized warm-up running on the treadmill at 8 km/h for 5 min. Feedback on the distance covered was available throughout the time trial. On the contrary, information about running speed, HR and time elapsed was not provided to the subject. The time trial started with subjects standing on the treadmill belt while running speed was increased up to 9 km/h. After this running speed was reached, subjects were free to choose their running speed using the + and – button on the right side of the treadmill. Throughout the time trial, participants were reminded at the end of each kilometre that they were able to increase or decrease their running speed at any time; however, the experimenters provided no encouragement during the time trial. Once the 5 km were completed, subjects stopped running immediately and placed their feet on the platform at the sides of the belt while time elapsed was recorded. The time elapsed was used as a measure of endurance performance. A fan was placed in a standardized

position in front of the subject during the entire duration of the time trial and subjects were allowed to drink water. At the end of the first minute, and at the end of each kilometre, rating of perceived exertion (RPE), HR and running speed were recorded. To reduce the learning effect, subjects performed a familiarization time trial during the first visit to the laboratory.

#### Physiological measurements

##### *Heart rate*

HR was recorded continuously during both cognitive tasks and the time trial using an HR monitor (Polar RS400, Polar Electro Oy, Kempele, Finland) with an acquisition frequency of 1 sample/s. Data were analysed off-line and averaged for the whole duration of both cognitive tasks. During the time trial, HR values were collected the last 15 s of the warm-up, the first minute and for each kilometre completed.

##### *Blood lactate and glucose concentrations*

10  $\mu$ l samples of capillary blood were taken from the thumb of the non-dominant hand of the subjects for measurement of blood lactate and blood glucose concentrations (Biosen, EFK Diagnostics, London, England). Blood glucose concentration was measured pre- and post-cognitive task, and blood lactate concentration was measured pre- and post-time trial.

#### Psychological measurements

##### *Perception of effort*

Perception of effort, defined as “the conscious sensation of how hard, heavy, and strenuous exercise is” (Marcora 2010b), was measured at the end of the first minute and at the end of each kilometre of the time trial using the 15 points RPE scale (Borg 1998). Standardized instructions for the scale were given to each subject before the warm-up. Briefly, subjects were asked to rate how hard they were driving their legs, how heavily they were breathing and the overall sensation of how strenuous exercise was. For example, nine corresponds to a “very light” exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes. Seventeen corresponds to a “very hard” and 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.

##### *Mood*

The Brunel Mood Scale developed by Terry et al. (2003) was used to quantify current mood (“How do you feel

right now?”) before and after the cognitive task. This questionnaire contains 24 items (e.g. “angry, uncertain, miserable, tired, nervous, energetic”) divided into six subscales: Anger, Confusion, Depression, Fatigue, Tension and Vigour. The items are answered on a five-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscale, with four relevant items, can achieve a raw score in the range of 0–16. Only scores for the Fatigue and Vigour subscales were considered in this study as subjective markers of mental fatigue.

##### *Motivation*

Motivation related to the time trial was measured using the success motivation and intrinsic motivation scales developed and validated by Matthews et al. (2001). Each scale consists of seven items (e.g. “I want to succeed on the task” and “I am concerned about not doing as well as I can”) scored on a five-point scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely). Therefore, total scores for these motivation scales range between 0 and 28.

##### *Subjective workload*

The National Aeronautics and Space Administration Task Load Index (NASA-TLX) rating scale (Hart and Staveland 1988) was used to assess subjective workload. The NASA-TLX is composed of six subscales: mental demand (How much mental and perceptual activity was required?), physical demand (How much physical activity was required?), temporal demand (How much time pressure did you feel due to the rate or pace at which the task occurred?), performance (How much successful do you think you were in accomplishing the goals of the task set by the experimenter?), effort (How hard did you have to work to accomplish your level of performance?) and frustration (How much irritating or annoying did you perceive the task?). The participants had to score each of the items on a scale divided into 20 equal intervals anchored by a bipolar descriptor (e.g. high/low). This score was multiplied by 5, resulting in a final score between 0 and 100 for each of the subscales. Participants completed the NASA-TLX after the cognitive task and after the time trial. All participants were familiarized with all psychological measurements during their first visit to the laboratory.

#### Statistics

All data are presented as mean  $\pm$  SD unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate.

Greenhouse–Geisser correction to the degrees of freedom was applied when violations to sphericity were present. Paired *t* tests were used to assess the effect of condition (inhibition vs control) on endurance performance, motivation scores, NASA-TLX scores after the cognitive tasks and after the time trial, HR during both cognitive tasks and HR during the warm-up before the time trial. Fully repeated measure  $2 \times 6$  ANOVAs were used to test the effect of time (5-min blocks) and condition on response accuracy and reaction time during cognitive tasks. Fully repeated measure  $2 \times 2$  ANOVAs were used to test the effect of condition and time on mood before and after the cognitive tasks, and the effect of condition and time on blood glucose and lactate concentrations. Fully repeated measure  $2 \times 6$  ANOVAs were used to test the effect of condition and distance on HR, RPE and running speed during the time trial. Significant main effects of time with more than two levels and significant interactions were followed up with simple main effects of time or condition using Bonferroni correction as appropriate. The significance was set at 0.05 (two-tailed) for all analyses. Effect size for each statistical test was also calculated as partial eta squared ( $\eta_p^2$ ). All analyses were conducted using the Statistical Package for the Social Sciences, version 19 for Mac OS X (SPSS Inc., Chicago, IL, USA).

## Results

### Effects of response inhibition on HR, blood glucose concentration and cognitive performance during the cognitive tasks

Heart rate (Fig. 2a) was significantly higher during the inhibition task compared to the control task ( $P = 0.003$ ,  $\eta_p^2 = 0.120$ ). Response inhibition did not affect ( $F_{(1, 11)} = 0.059$ ;  $P = 0.812$ ,  $\eta_p^2 = 0.005$ ) the significant decrease in blood glucose concentration observed after the cognitive tasks ( $F_{(1, 11)} = 7.209$ ;  $P = 0.021$ ,  $\eta_p^2 = 0.396$ ) (Fig. 2b).

Accuracy of responses during the cognitive tasks (Fig. 2c) was not affected by response inhibition ( $F_{(1, 11)} = 2.561$ ;  $P = 0.138$ ,  $\eta_p^2 = 0.189$ ) and did not change significantly over time ( $F_{(2, 214, 24, 353)} = 0.058$ ,  $\eta_p^2 = 0.221$ ). Similarly, reaction time (Fig. 2d) did not change significantly over time ( $F_{(1, 948, 21, 425)} = 0.585$ ;  $P = 0.562$ ,  $\eta_p^2 = 0.050$ ), but it was significantly longer during the inhibition task compared to the control task ( $F_{(1, 11)} = 68.474$ ;  $P < 0.001$ ,  $\eta_p^2 = 0.862$ ) (Fig. 2d).

### Effects of response inhibition on mood and motivation

The mood questionnaire did not show any significant main effect of time ( $F_{(1, 11)} = 1.194$ ;  $P = 0.298$ ,  $\eta_p^2 = 0.098$ ),

condition ( $F_{(1, 11)} = 0.021$ ;  $P = 0.888$ ,  $\eta_p^2 = 0.002$ ) or interaction ( $F_{(1, 11)} = 0.096$ ;  $P = 0.763$ ,  $\eta_p^2 = 0.009$ ) in the Fatigue scores (Fig. 2e). The Vigour scores decreased over time (inhibition condition  $5.9 \pm 1.1$ – $4.2 \pm 1.0$ , control condition  $6.1 \pm 1.4$ – $4.6 \pm 1.5$ ;  $F_{(1, 11)} = 6.396$ ;  $P = 0.028$ ,  $\eta_p^2 = 0.368$ ) independently of the response inhibition process ( $F_{(1, 11)} = 0.074$ ;  $P = 0.791$ ,  $\eta_p^2 = 0.057$ ).

There were no significant differences between conditions in intrinsic motivation (inhibition condition  $18.5 \pm 3.2$ , control condition  $18.9 \pm 4.5$ ;  $P = 0.622$ ,  $\eta_p^2 = 0.023$ ) and success motivation (inhibition condition  $17.5 \pm 5.6$ , control condition  $16.4 \pm 6.0$ ;  $P = 0.151$ ,  $\eta_p^2 = 1.78$ ) related to the subsequent time trial.

### Effects of response inhibition on pacing and performance during the time trial

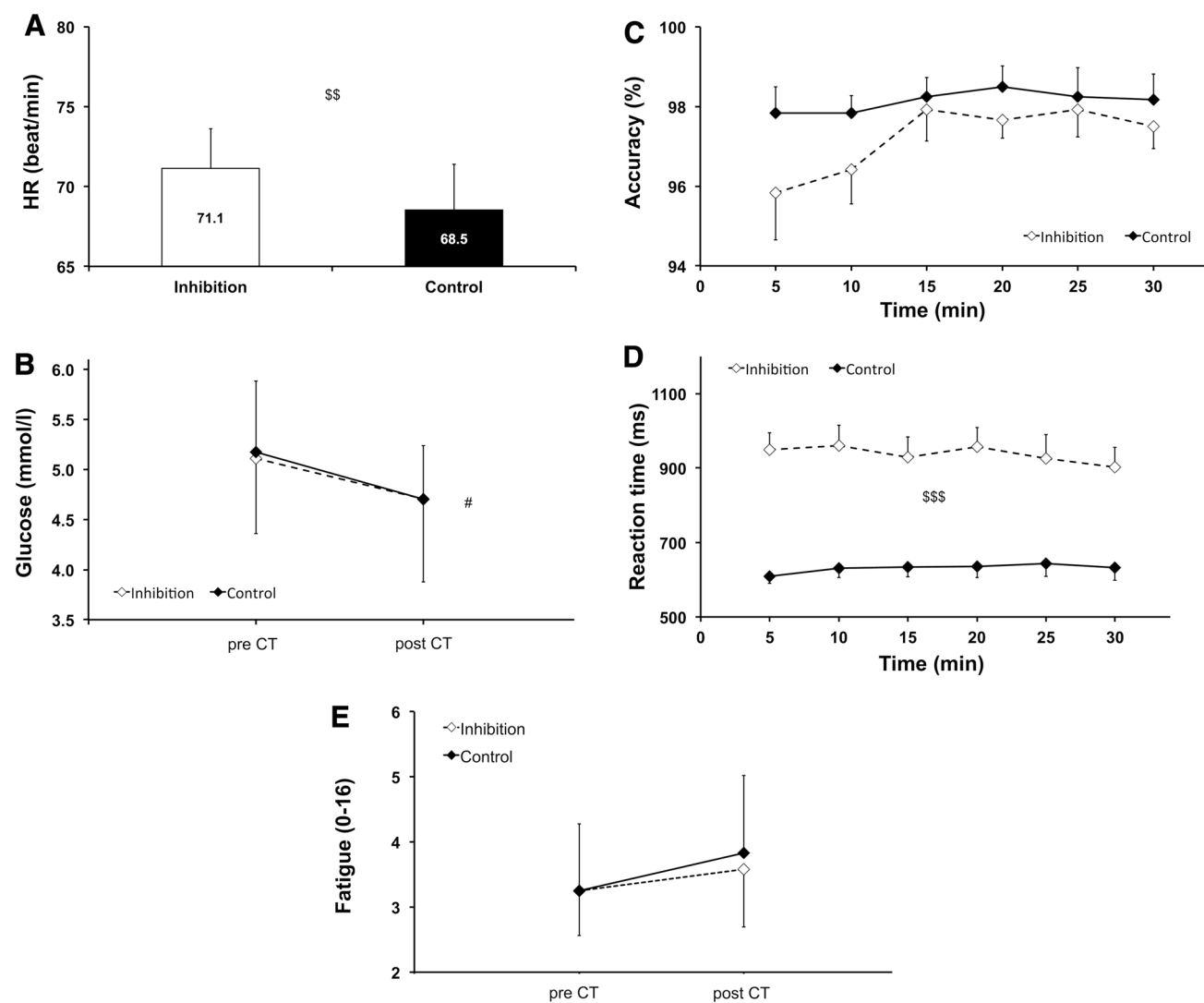
Time to perform the time trial was significantly longer following the inhibition task ( $24.4 \pm 4.9$  min) compared to the control task ( $23.1 \pm 3.8$  min;  $P = 0.008$ ,  $\eta_p^2 = 0.489$ ), with no significant learning effect ( $P = 0.571$ ,  $\eta_p^2 = 0.026$ ). Time trial performance decreased following the inhibition task in 10 out of 12 subjects.

Impaired time trial performance was caused by a significant reduction in running speed in the inhibition condition compared to the control condition ( $F_{(1, 11)} = 14.117$ ;  $P = 0.003$ ,  $\eta_p^2 = 0.562$ ) (Fig. 3a). However, response inhibition did not affect pacing strategy as demonstrated by the lack of significant interaction between condition and distance ( $F_{(1, 724, 18, 964)} = 0.832$ ;  $P = 0.434$ ,  $\eta_p^2 = 0.070$ ). In both conditions, subjects chose a negative pacing strategy which consists of a significant increase in speed over distance ( $F_{(2, 165, 23, 817)} = 21.568$ ;  $P < 0.001$ ,  $\eta_p^2 = 0.662$ ).

### Effects of response inhibition on perception of effort, HR and blood lactate concentration during the time trial

RPE during the time trial (Fig. 3b) increased similarly over distance in both conditions ( $F_{(1, 560, 17, 158)} = 102.289$ ;  $P < 0.001$ ,  $\eta_p^2 = 0.903$ ). However, subjects rated a higher perception of effort in the inhibition condition compared to the control condition ( $F_{(1, 11)} = 12.156$ ,  $P = 0.005$ ,  $\eta_p^2 = 0.525$ ).

Heart rate during the warm-up did not differ significantly between conditions ( $P = 0.742$ ,  $\eta_p^2 = 0.199$ ). As expected, HR during the time trial (Fig. 3c) increased significantly over distance ( $F_{(1, 795, 19, 744)} = 58.650$ ;  $P < 0.001$ ,  $\eta_p^2 = 0.842$ ) with no significant difference between the inhibition and the control task ( $F_{(1, 11)} = 1.286$ ;  $P = 0.281$ ,  $\eta_p^2 = 0.105$ ). Similarly, response inhibition did not affect ( $F_{(1, 11)} = 0.236$ ;  $P = 0.637$ ,  $\eta_p^2 = 0.021$ ) the significant increase ( $F_{(1, 11)} = 48.825$ ;  $P < 0.001$ ,  $\eta_p^2 = 0.816$ ) in blood



**Fig. 2** Effects of cognitive tasks (CT) on heart rate (HR, **a**), blood glucose concentration (**b**), response accuracy (**c**), reaction time (**d**) and self-reported fatigue (**e**). <sup>\$\$</sup>Significant main effect of condi-

tion ( $P < 0.01$ ). <sup>\$\$\$</sup>Significant main effect of condition ( $P < 0.001$ ). <sup>#</sup>Significant main effect of time ( $P < 0.05$ ). Data are presented as mean  $\pm$  SEM

lactate concentration observed after the time trial (inhibition condition  $1.6 \pm 0.4$ – $9.4 \pm 4.8$ , control condition  $1.4 \pm 0.5$ – $9.0 \pm 3.2$ ).

Effects of response inhibition on subjective workload subscales

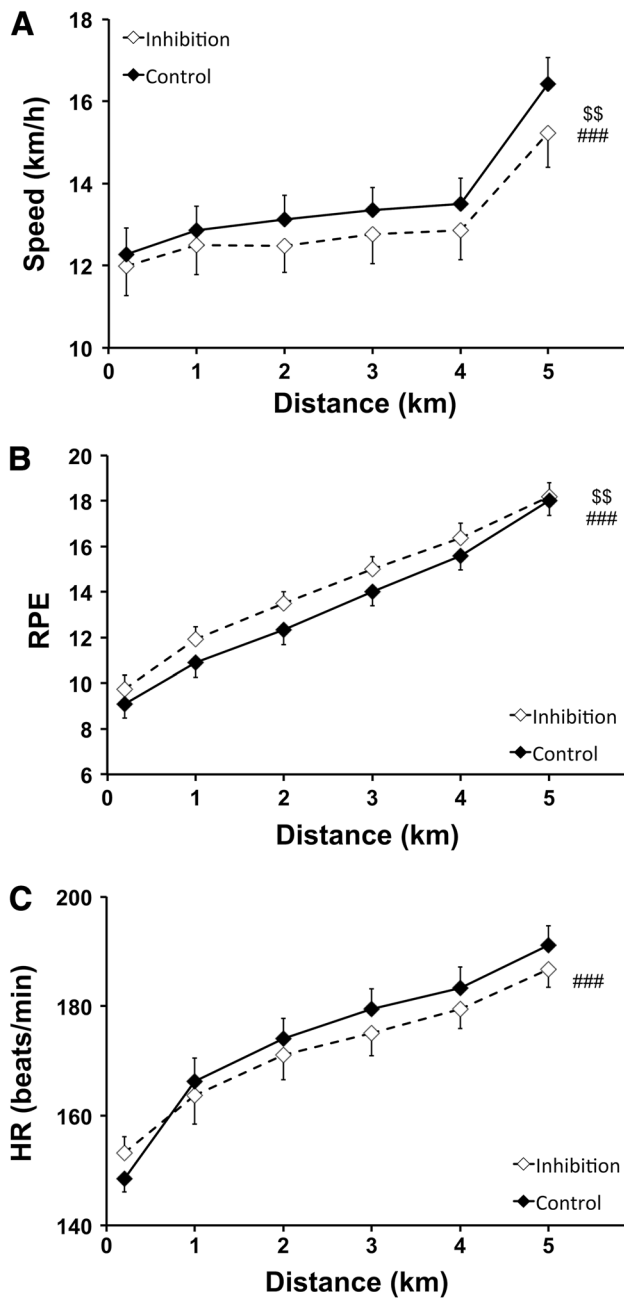
#### Cognitive tasks

Subjective workload data related to the cognitive tasks are presented in Fig. 4a. Subjects rated the mental demand ( $P = 0.042$ ,  $\eta_p^2 = 0.324$ ) and effort ( $P = 0.009$ ,  $\eta_p^2 = 0.481$ ) subscales higher in the response inhibition condition. Response inhibition did not have significant effects on the

performance, temporal demand and frustration subscales of the NASA-TLX questionnaire.

#### Time trial

Subjective workload data related to the time trial are presented in Fig. 4b. Subjects rated the time trial as more mentally demanding in the response inhibition condition ( $P = 0.005$ ,  $\eta_p^2 = 0.524$ ) and perceived their performance to be lower in the response inhibition condition ( $P = 0.044$ ,  $\eta_p^2 = 0.319$ ). Response inhibition did not have significant effects on the effort, temporal demand and frustration subscales of the NASA-TLX questionnaire.



**Fig. 3** Effects of cognitive tasks on speed (**a**), rate of perceived exertion (**RPE**, **b**) and heart rate (**HR**, **c**) during the 5-km running time trial. \$\$Significant main effect of condition ( $P < 0.01$ ). ###Significant main effect of time ( $P < 0.001$ ). Data are presented as mean  $\pm$  SEM

## Discussion

The aim of our study was to investigate the effects of response inhibition on pacing, perception of effort and endurance performance. In accordance with our hypotheses, results suggest that response inhibition increases perception of effort and impairs endurance performance via a reduction in average speed during the 5-km running time

trial. However, response inhibition does not seem to affect the pacing strategy chosen by the subject.

## Response inhibition, mental fatigue and endurance performance

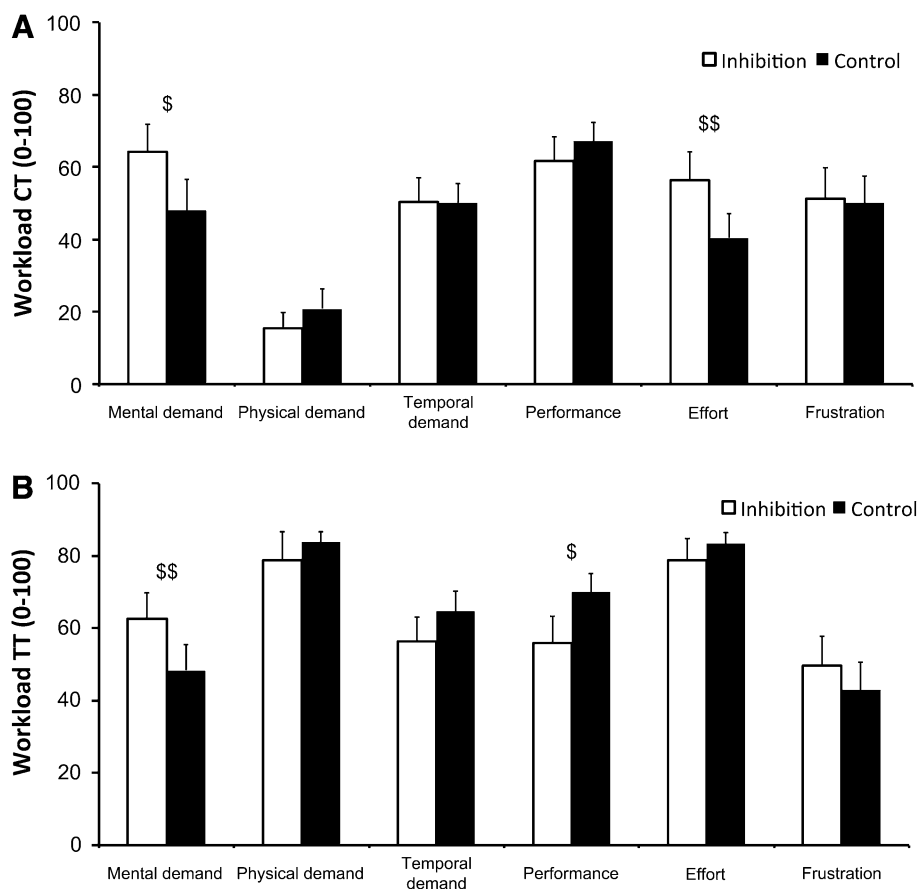
The higher HR observed during the inhibition task compared with the control task attests to its more demanding nature (Richter et al. 2008). Moreover, the more demanding nature of the inhibition task was confirmed by the higher mental demand and effort rated by the subjects. However, similar to a previous study (Marcora et al. 2009), blood glucose concentration decreased independently of the nature of the cognitive task. This finding argues against the idea that glucose depletion is the physiological mechanisms underlying the negative effects of mental exertion on subsequent physical or cognitive tasks (Gailliot 2008). The longer reaction time observed during the inhibition task confirms the presence of an additional cognitive process compared to the control task. Because both cognitive tasks included decision-making (selecting an answer) and sustained attention, the longer reaction time during the inhibition task is likely to be related to the response inhibition process (Sugg and McDonald 1994; Stroop 1992). Indeed, contrary to the control task, subjects did not have only to select an answer, but also to inhibit the wrong motor response (e.g. pressing the blue button if the word blue appears in yellow) to select the appropriate one (press the yellow button). Taken altogether, these manipulation checks suggest that we were successful in inducing different levels of mental exertion and response inhibition between the two conditions.

Previous studies using more prolonged mental exertion induced significant mental fatigue defined as an increase in subjective feelings of fatigue and/or a decrease in cognitive performance (Marcora 2010b; Pageaux et al. 2013). Interestingly, in the present study, mental exertion neither induces alterations in cognitive performance (i.e. changes in reaction time and/or accuracy) nor significant changes in subjective fatigue. Also as shown in previous studies, the cognitive tasks induced a significant decrease in vigour (Marcora et al. 2009; Pageaux et al. 2013). The lack of changes in these markers of mental fatigue could be due to the shorter duration of mental exertion in the present study (30 min) compared to previous studies (90 min).

Despite no clear evidence of mental fatigue in the present study, 30 min of mental exertion involving response inhibition had a negative effect on subsequent endurance performance. Indeed, the time to perform the time trial was 6 % longer following the inhibition task compared to the control task. These findings are in agreement with the results of the study by Bray et al. (2008) in which as little as 220 s of mental exertion involving response inhibition was capable of reducing endurance of the handgrip



**Fig. 4** Effects of cognitive tasks (CT, **a**) and 5-km running time trial (TT, **b**) on subjective workload (NASA-TLX scale). <sup>\$</sup>Significant effect of response inhibition ( $P < 0.05$ ). <sup>\$\$</sup>Significant effect of response inhibition ( $P < 0.01$ ). Data are presented as mean  $\pm$  SEM



muscles despite no subjective feelings of mental fatigue. From an applied perspective, it is therefore important to warn coaches and athletes that mental exertion involving response inhibition may have a detrimental effect on subsequent endurance performance even if the athlete does not feel mentally fatigued.

#### Response inhibition and pacing

The only significant effect of response inhibition on pacing was a reduction in the average running speed chosen by the subject during the time trial. On the other hand, the pacing strategy was not significantly affected by prior mental exertion. In fact, in both the inhibition and control condition, a negative pacing strategy was observed. A negative pacing strategy, defined as an increase in speed over distance, is commonly observed during middle distance events when speed is increased towards the end of both simulated and actual events (for review see Abbiss and Laursen 2008). In fact, the negative pacing strategy observed in our study has been previously observed during 5-km running time trial in both elite (Tucker et al. 2006) and well-trained athletes (Nummela et al. 2006). Because these time trials were conducted on a track, we are confident that the pacing strategy observed in our study is not specific to time trials

performed on a treadmill, where speed is changed manually by pressing a button and RPE asked at the end of each kilometre.

This is the first report on the effect of mental exertion involving response inhibition on pacing. However, because of the low performance level of the subjects included in the present study, it is difficult to generalize our findings to competitive endurance athletes. More studies on the effects of mental exertion on pacing are required to investigate whether response inhibition may affect pacing strategy in subjects of higher performance level.

#### Response inhibition and perception of effort

Previous studies have shown that mentally fatigued subjects perceived endurance exercise as more effortful (Marcora et al. 2009; Pageaux et al. 2013). We have extended these findings by showing that response inhibition is capable of inducing higher perception of effort during subsequent endurance exercise even in the absence of overt mental fatigue.

Because no measurements at brain level were taken in the present study, we can only speculate about the neurobiological mechanisms underlying the negative effect of response inhibition on perception of effort during

subsequent endurance exercise. A possible explanation is that 30 min of engagement with the incongruent Stroop colour-word task induced adenosine accumulation in the ACC leading to higher perception of effort during subsequent endurance exercise. This speculation is based on previous human studies showing that the ACC is strongly activated during Stroop tasks involving response inhibition (Bush et al. 1998; Swick and Jovanovic 2002), and that this cortical area is associated with perception of effort (Williamson et al. 2001, 2002). Furthermore, there is experimental evidence from *in vitro* and animal studies that neural activity increases extracellular concentrations of adenosine (Lovatt et al. 2012) and that brain adenosine induces a reduction in endurance performance (Davis et al. 2003). Finally, there is strong evidence that caffeine (an antagonist of adenosine) reduces perception of effort during endurance exercise in humans (Doherty and Smith 2005). Further research in humans and animals is needed to confirm the role of the ACC and brain adenosine in mediating the negative effect of mental exertion on perception of effort and performance during subsequent endurance exercise.

#### Psychobiological model of self-paced endurance performance

The present findings demonstrate that mental exertion involving response inhibition does not further reduce blood glucose concentration before the time trial, and it does not alter HR immediately before and during the time trial. The blood lactate response to the time trial was also not significantly affected by response inhibition. Therefore, it is unlikely that cardiovascular and metabolic factors can explain the negative effect of response inhibition on endurance performance. Our findings are in accordance with previous observations during time to exhaustion tests. Indeed, it has already been demonstrated the impairment in endurance performance following prolonged mental exertion occurs without any alterations of the cardiorespiratory, metabolic and neuromuscular responses to the exercise (Marcora et al. 2009; Pageaux et al. 2013). Therefore, the negative effect of response inhibition on subsequent self-paced endurance performance is likely to be mediated by other factors.

The psychobiological model of endurance performance (Marcora 2010a) provides a plausible explanation for the negative effect of prior response inhibition on the average running speed chosen by the subject during the time trial. According to this model of endurance performance, the self-regulation of speed/power output during endurance exercise (pacing) is determined primarily by five different cognitive/motivational factors: (1) perception of effort; (2) potential motivation; (3) knowledge of the distance/time to cover; (4) knowledge of the distance/time remaining; and

(5) previous experience/memory of perceived exertion during exercise of varying intensity and duration. The effect of previous experience (Factor 5) was controlled in the present study using a randomized crossover design and a familiarization session. Furthermore, in both the inhibition and control conditions, subjects had the same knowledge of the distance to cover (Factor 3) and of the distance remaining (Factor 4). According to the motivation questionnaire, response inhibition did not affect potential motivation (Factor 2). This finding is an agreement with the results of previous studies also showing no significant effect of mental exertion on questionnaires related to potential motivation (Marcora et al. 2009; Pageaux et al. 2013). However, the significantly higher RPE observed after the response inhibition task suggests that response inhibition may affect the willingness to exert effort during subsequent endurance exercise. Furthermore, the psychophysical relationship between RPE and running speed suggests an even greater effect of response inhibition on the perception of effort (Factor 1). Indeed, the effort was perceived higher during the inhibition condition compared to the control condition despite a lower running speed. According to the psychobiological model of endurance performance, the reduction in the average running speed during the time trial is a conscious decision to compensate for the negative effect of response inhibition on perception of effort. Indeed, if the subjects did not choose a lower running speed, the progressive increase in perception of effort over time would have caused premature exhaustion as observed during tests in which the subject could not choose a lower power/torque (Marcora et al. 2009; Pageaux et al. 2013). Because not finishing the time trial is a more negative outcome than completing the time trial in a longer time, reducing the average running speed was the most appropriate behavioural response.

#### Conclusions and practical perspectives

The present study provides the first experimental evidence that self-paced endurance performance can be altered by prior mental exertion involving response inhibition. This negative effect was associated with a reduction in average running speed chosen by the subject during the time trial. However, pacing strategy was not affected by prior mental exertion involving response inhibition. Importantly, this study suggests that performing only 30 min of mental exertion can reduce endurance performance without any subjective feeling of mental fatigue at rest. Therefore, athletes and coaches should avoid any cognitive tasks involving response inhibition process before competition, such as controlling anger during pre-event interviews with nosy journalists. Furthermore, the results of the present study suggest that monitoring of RPE during endurance training

sessions may be a more sensitive measure to identify mental fatigue than administering generic mood questionnaires. Because monitoring fatigue states is important to prevent non-functional overreaching and overtraining in endurance athletes (Nederhof et al. 2008), more applied research in this area is warranted.

**Acknowledgments** The authors thank Tiffany Weedon for her help with participant recruitment and data collection.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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# The Psychobiological Model of Endurance Performance: An Effort-Based Decision-Making Theory to Explain Self-Paced Endurance Performance

Benjamin Pageaux

Published online: 9 May 2014  
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To the Editor,

In a recent review published in this journal [1], Renfree and colleagues demonstrated the importance of considering decision-making theories to understand self-paced endurance performance. The authors aimed to examine current models/theories of decision-making in an attempt to explain the manner in which regulation of muscular work (pacing) is achieved during self-paced endurance performance. As explained by the authors, it is crucial that models explaining self-paced endurance performance take into account both internal (e.g. perception of effort, physiological responses) and external (e.g. tactical decisions, presence of competitors) factors. Interestingly, among all models presented in their review, the authors omitted to present an effort-based decision-making model recently proposed to explain self-paced endurance performance: the psychobiological model (of endurance performance) [2]. The psychobiological model has been shown to provide a valid explanation of the effects of both psychological [3, 4] and physiological [5] manipulations on endurance performance during constant-load exercise (time to exhaustion). Recently, its explanatory validity was extended to self-paced exercise where endurance performance was altered by psychological (mental fatigue) [6] and physiological (muscle fatigue) [7] manipulations. Consequently, it seems important to mention its existence in a review on decision-making theories relevant to self-regulation of pacing. Therefore, the main aim of this letter is to briefly present

the psychobiological model and its sensitivity to internal and external factors known to alter self-paced endurance performance. This letter will also attempt to provide to the reader a brief alternative interpretation of the role of perception of effort in endurance performance.

The psychobiological model is an effort-based decision-making model [2] based on motivational intensity theory [8], and postulates that the conscious regulation of pace is determined primarily by five different cognitive/motivational factors:

1. Perception of effort
2. Potential motivation
3. Knowledge of the distance/time to cover
4. Knowledge of the distance/time remaining
5. Previous experience/memory of perception of effort during exercise of varying intensity and duration

Factor 2 (potential motivation) refers to the maximum effort an individual is willing to exert to satisfy a motive, and could be easily influenced by external factors (e.g. higher motivation during an event with competitors than during laboratory testing). Factors 3 to 5 are self-explanatory and can explain the end-spurt phenomenon [9] or why athletes start different races at different paces [10]. Perception of effort (factor 1) could be defined as “the conscious sensation of how hard, heavy and strenuous a physical task is” [2], and is the key determinant of this model. Indeed, according to this model, the conscious regulation of pace is primarily determined by the effort perceived by the athlete. Therefore, when perception of effort is increased by muscle [7] or mental [6] fatigue, or reduced (same perception of effort for a higher power output) by pharmacological manipulation [11], the athlete will consciously change its pace to compensate for the negative/positive effect of the experimental manipulation

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on perception of effort, thus leading to an improvement (if decreased perception of effort [11]) or impairment (if increased perception of effort [6, 7]) in self-paced endurance performance. Because the five factors mentioned above are sensitive to external and/or physiological factors known to impact endurance performance, the psychobiological model could be considered as a tool to explain regulation of self-paced endurance performance.

Contrary to the models presented by Renfree and colleagues, the psychobiological model of endurance performance postulates that the sensory signal processed by the brain to generate perception of effort is not the afferent feedback from skeletal muscles and other interoceptors [12]. Perception of effort is thought to result from the central processing of the corollary discharge associated with the central motor command [12, 13], thus explaining the alteration of perception of effort and performance when central motor command is increased to compensate for muscle fatigue [7] or central processing of the corollary discharge is altered by mental fatigue [3, 6]. Despite this theoretical difference in the underlying sensory signals thought to generate perception of effort, the models presented by Renfree and colleagues and the psychobiological model agree on the crucial role of perception of effort in the self-regulation of pacing. Therefore, it is important to understand the neurocognitive link between perception of effort and the regulation of endurance performance during self-paced exercise. Recently, a strong link between the response inhibition process (a main component of decision-making in human volition [14]) and perception of effort was suggested [6]. In this study, subjects performed 30 min of either incongruent (involving response inhibition) or congruent (non involving response inhibition) Stroop task followed by a five kilometres running time trial. Interestingly, endurance performance following completion of the incongruent Stroop task was decreased in association with an increased perception of effort. One plausible explanation provided by the authors is the similarity in brain areas involved in both mechanisms. Indeed, perception of effort, response inhibition and consequently decision-making process are known to be associated with activity in the anterior cingulate cortex and the pre supplementary motor areas [3, 4, 6]. Therefore, independently of the model/theory used to explain endurance performance, further researches on the neurophysiology of perception of effort are required to provide a better understanding of the regulation of endurance performance during self-paced exercise.

**Acknowledgments** I would like to thank Romuald Lepers and Samuele Marcora for our numerous discussions on this topic and their feedback on this manuscript.

**Conflict of interest** The author has no potential conflicts of interest that are directly relevant to the content of this letter.

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# Does mental exertion alter maximal muscle activation?

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Mental exertion is known to impair endurance performance, but its effects on neuromuscular function remain unclear. The purpose of this study was to test the hypothesis that mental exertion reduces torque and muscle activation during intermittent maximal voluntary contractions of the knee extensors. Ten subjects performed in a randomized order three separate mental exertion conditions lasting 27 min each: (i) high mental exertion (incongruent Stroop task), (ii) moderate mental exertion (congruent Stroop task), (iii) low mental exertion (watching a movie). In each condition, mental exertion was combined with 10 intermittent maximal voluntary contractions of the knee extensor muscles (one maximal voluntary contraction every 3 min). Neuromuscular function was assessed using electrical nerve stimulation. Maximal voluntary torque, maximal muscle activation and other neuromuscular parameters were similar across mental exertion conditions and did not change over time. These findings suggest that mental exertion does not affect neuromuscular function during intermittent maximal voluntary contractions of the knee extensors.

**Keywords: Stroop task, mental fatigue, neuromuscular fatigue, knee extensors, motivation, central fatigue**

## INTRODUCTION

Mental exertion refers to the engagement with a demanding cognitive task. When performed simultaneously to physical exertion, mental exertion is known to impair endurance performance (Yoon et al., 2009; Mehta and Agnew, 2012). Interestingly, mental exertion also has a negative impact on endurance performance when performed prior to physical exertion (Bray et al., 2008; Marcora et al., 2009; Pageaux et al., 2013). Therefore, there seems to be a clear link between mental exertion and endurance performance in humans.

Contrary to studies on endurance performance, few studies investigated the effect of mental exertion on neuromuscular function. Bray et al. (2008), using a handgrip squeezing task, did not find any decrease in maximal voluntary contraction (MVC) force of the handgrip muscles following 3 min 40 s of mental exertion (incongruent Stroop task). Furthermore, mental exertion induced by 20-min of motor imagery did not alter maximal force production capacity of the elbow flexors (Rozand et al., 2014). Even with 90 min of prior mental exertion induced by the AX-CP test, Pageaux et al. (2013) demonstrated that prolonged mental exertion does not induce a decrease in MVC torque of the knee extensor muscles. Together, these results suggest that mental exertion does not alter maximal force production. However, Bray et al. (2012) measured a significant decrease in force during intermittent handgrip MVCs interspaced with 3-min bouts of high mental exertion (incongruent Stroop task) for a total of 22 min (Bray et al., 2012). In fact, the authors found a significant reduction in maximal force production during the last MVC of this experimental protocol. These results suggest a possible interaction between

intermittent MVCs and high mental exertion on maximal force production.

Bray et al. (2012) suggested that the decrease in maximal force production observed during repeated MVCs in the high mental exertion condition (incongruent Stroop task) was caused by a central mechanism, specifically the expenditure of central nervous system (CNS) resources. These authors considered that there is a brain-based energy resource that governs performance of tasks requiring cognitive, emotional, and physical effort regulation (Baumeister et al., 1994; Gailliot et al., 2007). Indeed, it has been proposed that self-regulatory tasks draw upon a common pool of resources that, when depleted, could impair performance during a subsequent physical or mental task requiring self-regulation (Hagger et al., 2010). According to Bray et al. (2012), this expenditure of CNS resources might cause central fatigue, i.e., a decrease in maximal muscle activation during intermittent MVCs, leading to a decrease in handgrip force. However, the late decrease in handgrip force observed in this study occurred without changes in EMG amplitude during the intermittent MVCs. This finding suggests that central fatigue was not induced by this combination of intermittent MVCs and high mental exertion. Unfortunately, EMG amplitude during MVCs is not the most accurate measure of maximal muscle activation (Millet and Lepers, 2004). Therefore, further investigations are necessary to understand the central mechanisms underlying the decrease in maximal force production observed during intermittent MVCs performed in conditions of high mental exertion.

In the present study, we measured the capacity of the CNS to maximally drive the working muscles using the twitch

interpolation technique following the guidelines provided by Gandevia (2001). This technique is considered as the gold-standard to assess maximal muscle activation in humans (Gandevia et al., 2013), and consists of delivering a superimposed stimulation (electrical or magnetic) during a MVC to recruit the motor units not voluntarily recruited. If the subject is not able to fully recruit the working muscles, then an additional force will be produced by the stimulation.

In his review on central fatigue, Gandevia (2001) provided guidelines to ensure that subjects exert a true maximal effort during MVCs. Because submaximal effort due to poor motivation can negatively affect measures of maximal muscle activation (Enoka, 1995), these methodological considerations are crucial to ensure the validity of studies investigating the effects of mental exertion on neuromuscular function. Among these methodological considerations, of particular interest is the use of visual feedback performance to maximize voluntary effort (Gandevia, 2001). Unfortunately, in Bray et al. (2012), performance feedback was not available to participants during MVCs. Therefore, it cannot be excluded that the late decrease in handgrip force observed in this study was due to a decrease in motivation to exert a true maximal effort rather than central fatigue. In the present study, visual feedback was provided to the participants for each MVC.

Furthermore, there is evidence that performing the Stroop task involves activation of the trapezius muscle (Waersted and Westgaard, 1996; MacDonell and Keir, 2005) and the forearm muscles (Laursen et al., 2002) are also used in handgrip squeezing. This muscle activity during the Stroop task could be due to holding the sheets (paper-based Stroop task), or selecting the correct responses with a keyboard or a mouse (computer-based Stroop task, Laursen et al., 2002). The continuous use of the upper limb muscles during mental exertion could impact performance during a subsequent physical task involving the same muscle group. Therefore, it cannot be excluded that fatigue within the handgrip muscles (peripheral fatigue, i.e., fatigue produced by changes at or distal to the neuromuscular junction; Gandevia, 2001) contributed to the late decrease in maximal force production observed by Bray et al. (2012). To avoid the potential confounding effect of peripheral fatigue induced by the Stroop task on maximal force production, assessment of a muscle group not involved in the Stroop task (e.g., knee extensor muscles) would be more appropriate.

In this context, the aim of the present study was to analyze the effects of mental exertion on neuromuscular function of the knee extensor muscles. As both mental (Lorist and Tops, 2003; Gailliot, 2008) and physical (Davis et al., 2003; Matsui et al., 2011) exertion has been associated with a reduction in brain glycogen and an increase in brain adenosine which inhibits excitatory activity (Lovatt et al., 2012), we hypothesized that mental exertion would reduce maximal force production during intermittent MVCs. Specifically, we expected that this reduction would be associated with a decrease in maximal muscle activation. To test this hypothesis, we used the twitch interpolation technique to assess maximal muscle activation during intermittent MVCs of the knee extensors following the guidelines of Gandevia (2001) to ensure a true maximal effort.

## METHODS

### SUBJECTS

Ten healthy active male subjects (age =  $24.5 \pm 1.4$  yrs, weight =  $73.4 \pm 1.8$  kg, height:  $178.1 \pm 1.6$  cm), volunteered to participate in this study. None of the subjects had any known mental or somatic disorder and written consent was obtained from each subject prior to the study. Experimental protocol and procedures were approved by the local Ethics Committee of the Faculty of Sport Sciences, University of Burgundy in Dijon. All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the real aims of the study with other participants. All procedures were conducted according to the Declaration of Helsinki.

### PROCEDURES

Subjects visited the laboratory on four different occasions. During the first visit, subjects were familiarized with the laboratory and the experimental procedures. During the next three visits, subjects randomly performed a mental exertion task lasting 27 min: an incongruent Stroop task, a congruent Stroop task or watching a movie (see *Cognitive Tasks* for more details). Every 3 min, subjects stopped the mental exertion for 15 s to perform neuromuscular tests on the knee extensor muscles. Ten neuromuscular tests were performed for each condition (T0, 3, 6, 9, 12, 15, 18, 21, 24, and 27 min). Motivation was measured before the first neuromuscular test and mood was measured before the first and after the last neuromuscular test. Subjective workload was measured after the final neuromuscular test. For more details see *Psychological Measurements*. An overall view of the protocol can be found **Figure 1**.

Each subject completed all four visits over a period of 4 weeks with a minimum of 48 h recovery period between visits. All subjects were given instructions to sleep for at least 7 h, refrain from the consumption of alcohol, and not to practice vigorous physical activity the day before each visit. Subjects were also instructed not to consume caffeine and nicotine at least 3 h before testing, and were asked to declare if they had taken any medication or had any acute illness, injury or infection.

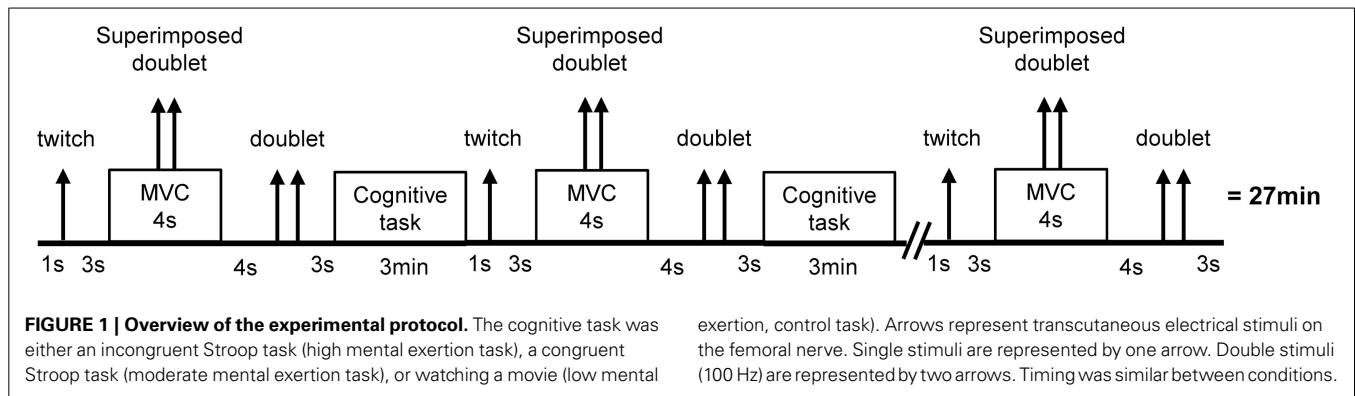
### COGNITIVE TASKS

Subjects had to perform a high mental exertion task (incongruent Stroop task involving sustained attention and response inhibition), a moderate mental exertion task (congruent Stroop task not involving the response inhibition process), and a low mental exertion task (watching a movie) for a prolonged period of time (27 min).

#### *High mental exertion task*

A modified incongruent version of the Stroop-word task (100% incongruent) was used for the high mental exertion condition. Subjects read aloud, as fast as possible, a list of printed words selected in a randomized way (Wallace and Baumeister, 2002). The ink color in which the words were printed was mismatched (e.g., the word “green” printed in blue ink). Participants had to say aloud the color of the ink in which the word was printed





(e.g., for the word “green” printed in blue ink, they had to say “blue”). Moreover, for words appearing in red ink, participants were asked to ignore the previous instructions, and say the name of the printed word (e.g., for the word “yellow” printed in red ink, they should say “yellow”). An experimenter recorded the number of incorrect answer with a control sheet, and asked to restart the current line when the answer was incorrect. The modified incongruent Stroop task has been used in several studies on the effects of mental exertion on subsequent physical or mental tasks (Wallace and Baumeister, 2002; Bray et al., 2008; Martin Ginis and Bray, 2010).

#### **Moderate mental exertion task**

A congruent version of the Stroop-word task was used for the moderate mental exertion condition. Subjects were asked to read aloud, without constraint of speed, a list of printed words. The words and the ink in which they were printed were identical (e.g., the word “green” printed in green ink).

#### **Low mental exertion task**

The low mental exertion task (control task) consisted in watching a wildlife documentary (“Earth”, directed by A. Fothergill and A. Linfield, 2007). This movie was previously shown to be emotionally neutral (Pageaux et al., 2013).

During all three tasks, subjects were sitting on the ergometer chair used for the intermittent MVCs of the knee extensors. During both incongruent and congruent Stroop tasks, word-sheets were held by the subjects on their lap, whilst the movie was shown on a computer screen placed on a table in front of them. During the tasks, heart rate was recorded every 5 s during the entire protocol (MVCs and cognitive task) via a heart rate monitor chest strap (Polar RS400, Polar Electro Oy, Kempele, Finland) affixed to the skin near the midpoint of the participant’s sternum. Average heart rate was calculated as a psychophysiological index of mental workload (Richter et al., 2008; Yoon et al., 2009).

### **NEUROMUSCULAR FUNCTION TESTS**

#### **Mechanical recordings**

Subjects were seated upright and performed isometric contractions of the right knee extensor muscles. Isometric torque was recorded using a Biodex dynamometer (Biodex Medical System Inc., New York, USA). Two crossover shoulder harnesses and a belt cross above the abdomen limited extraneous movements

of the upper body. Neuromuscular tests were performed with the right leg at a knee joint angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The dynamometer axis was aligned with the knee joint axis. Torque signal was digitized on-line at a sampling frequency of 1 kHz using a computer, and stored for analysis with a commercially available software (Acknowledge 4.1.0, Biopac Systems Inc, Goleta, USA). At the beginning of each experiment, subjects performed a standardized warm-up, executing 10 brief submaximal contractions (~50% MVC) of the knee extensor muscles, followed by a 3 min rest (Place et al., 2007). Then participants performed two isometric MVCs to determine their maximal force production. Subjects were motivated to exert maximal effort during MVCs via verbal encouragements provided by an experimenter, and visual feedback corresponding to the torque produced during the previous MVC.

#### **Electrical recordings**

EMG activity of the vastus lateralis (VL) muscle was recorded with pairs of bipolar silver chloride circular (recording diameter of 10 mm) surface electrodes (Control Graphique Medical, Briec-Comte-Robert, France) positioned lengthwise over the middle of the muscle belly with an interelectrode (center to center) distance of 20 mm. The reference electrode was placed on the opposite patella. Low resistance between the two electrodes (<5 kΩ) was obtained by shaving the skin and dirt were removed from the skin using alcohol. EMG signals were amplified with a bandwidth frequency ranging from 10 to 500 Hz (gain = 500), digitized on-line at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (Acknowledge, Biopac Systems Inc, Goleta, USA).

#### **Evoked contractions**

Both single and double (100 Hz frequency) stimulations were used for assessment of neuromuscular function. Transcutaneous electrically-evoked contractions of the knee extensors muscles were induced using a high-voltage (maximal voltage 400 V) constant-current stimulator (model DS7 modified, Digitimer, Hertfordshire, UK). The femoral nerve was stimulated using a monopolar cathode ball electrode (0.5 cm diameter), pressed into the femoral triangle by the same experimenter during all tests. The site of stimulation producing the largest resting twitch and M-wave amplitudes was located and marked on the skin so that it

could be repeated reliably through all the protocol. The anode was a large (10 × 5 cm) rectangular electrode (Compex SA, Ecublens, Switzerland) located in the gluteal fold opposite the cathode. The optimal intensity of stimulation (i.e., that which recruited all knee extensor motor units) was considered to be reached when an increase in the stimulation intensity did not induce a further increase in the amplitude of the twitch force and the peak-to-peak amplitude of the VL M-wave (Place et al., 2005). Once the optimal intensity was found, 130% of this intensity was used and kept constant throughout the session for each subject. The supramaximal intensities ranged from 70 to 140 mA. The stimulus duration was 1 ms and the interval of the stimuli in the doublet was 10 ms. Single stimulus was evoked at rest 3 s before the MVCs to investigate the M-wave of the VL muscle associated with the evoked twitch. Paired stimuli were evoked during (superimposed doublet) and 4 s after the MVC (potentiated doublet) to investigate knee extensors muscle contractile properties and to estimate the VAL using the twitch interpolation technique (Merton, 1954). Methodology and supramaximal intensities are according to previous studies (e.g., Place et al., 2007).

### Data analysis

M-wave peak-to-peak amplitude of the VL muscle was measured during the single stimuli at rest before each MVC. Maximal EMG for the MVC of the VL muscle was quantified as the root mean square (RMS) value over a 0.5 s interval about the same interval of the MVC torque measurement. Maximal EMG RMS values were then normalized to the M-wave amplitude for the respective muscles to obtain the EMG RMS/M-wave ratio. This normalization procedure allows to take into account of the changes in the peripheral parameters (neuromuscular transmission-propagation failure and/or changes in impedance) from the EMG recordings (Place et al., 2007). Potentiated doublet peak (Dt) was measured from the peak torque associated with electrical paired stimuli at rest, 4 s after the end of the MVC. MVC was considered as the peak torque attained during the contraction, and maximal voluntary activation level was quantified by measurement of the superimposed torque response to nerve stimulation during the MVC (Allen et al., 1995; Gandevia, 2001). The voluntary activation level (VAL) was estimated according to the formula:

$$\text{VAL} = (1 - \text{superimposed doublet/potentiated doublet}) \times 100$$

(MVC<sub>at stimulation</sub>/MVC) corresponding to Strojnik and Komi (1998) correction was used if stimulation was not delivered at the MVC torque value. All VAL calculations were performed for a MVC<sub>at stimulation</sub> between 95 and 100% MVC in order to ensure reliability of measurement.

## PSYCHOLOGICAL MEASUREMENTS

### Motivation

Motivation related to the entire protocol was measured using the success motivation and intrinsic motivation scales developed and validated by (Matthews et al., 2001)[22]. Each scale consists of 7 items (e.g., “I want to succeed on the task” and “I am concerned about not doing as well as I can”) scored on a 5-point scale

(0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely). Therefore, total scores for these motivation scales range between 0 and 28.

### Mood

The Brunel Mood Scale (BRUMS) developed by Terry et al. (2003) was used to quantify current mood (“How do you feel right now?”) before the first and after the final neuromuscular test. This questionnaire contains 24 items (e.g., “angry, uncertain, miserable, tired, nervous, energetic”) divided into six respective subscales: anger, confusion, depression, fatigue, tension, and vigor. The items are answered on a 5-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscale, with four relevant items, can achieve a raw score in the range of 0 to 16. Only scores for the Fatigue and Vigor subscales were considered in this study.

### Subjective workload

The National Aeronautics and Space Administration Task Load Index (NASA-TLX) rating scale (Hart and Staveland, 1988) was used to assess subjective workload. The NASA-TLX is composed of six subscales: Mental Demand (How much mental and perceptual activity was required?), Physical Demand (How much physical activity was required?), Temporal Demand (How much time pressure did you feel due to the rate or pace at which the task occurred?), Performance (How much successful do you think you were in accomplishing the goals of the task set by the experimenter?), Effort (How hard did you have to work to accomplish your level of performance?) and Frustration (How much irritating, annoying did you perceive the task?). The participants had to score each of the items on a scale divided into 20 equal intervals anchored by a bipolar descriptor (e.g., High/Low). This score was multiplied by 5, resulting in a final score between 0 and 100 for each of the subscales. Participants completed the NASA-TLX after the entire protocol.

## STATISTICAL ANALYSIS

Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. One-Way repeated ANOVAs were used to compare subjective workload, motivation and average heart rate across the three conditions. A fully repeated 3 × 2 (condition × time) ANOVA was used to test the effects of the entire protocol on mood. Fully repeated 3 × 10 ANOVAs were used to test the effects of condition and time on MVC torque, VAL, EMG RMS/M-wave ratio (VL muscles), peak torque of the doublet and amplitude of the M-wave (VL muscles). Percentage of errors during both Stroop tasks was analyzed with a fully repeated 2 × 9 (condition × time) ANOVA. Significant main effects of time or condition, or interactions were followed up with Bonferonni tests as appropriate.

By using predicted effect size provided by Bray et al. (2012) for changes in MVC torque, an a priori power analysis revealed that nine participants would provide 83 % power to detect differences at an  $\alpha$ -level of 0.05. Statistical analyses were conducted using the Statistical Package for the Social Sciences, version 19 for Mac OS

X (SPSS Inc., Chicago, IL, USA). A significance level of  $p < 0.05$  was used for all analyses. Cohen's effects size  $f(V)$  and a priori power analysis were calculated with G\*Power software (version 3.1.6, Universität Düsseldorf, Germany). Thresholds for small, moderate and large effects were set at 0.2, 0.5, and 0.8, respectively. Data are presented as Mean  $\pm$  SD in the text and tables, and Mean  $\pm$  s.e.m. in the figures.

## RESULTS

### MOTIVATION AND MOOD

Intrinsic [ $F_{(1.1, 11.1)} = 1.360, p = 0.273, f_{(V)} = 0.369$ ] and success [ $F_{(1.1, 11.1)} = 1.360, p = 0.168, f_{(V)} = 0.465$ ] motivation related to the entire protocol were similar in all conditions (See **Table 1**). The mood questionnaire revealed a significant decrease in vigor over time in both conditions [ $F_{(1, 9)} = 7.204, p < 0.05, f_{(V)} = 0.895$ ] with no main effect of condition [ $F_{(2, 18)} = 0.171, p = 0.845, f_{(V)} = 0.139$ ] or condition  $\times$  time interaction [ $F_{(1.276, 11.483)} = 0.212, p = 0.811, f_{(V)} = 0.153$ ]. The fatigue subscale of the mood questionnaire presented a condition effect [ $F_{(2, 18)} = 5.580, p < 0.05, f_{(V)} = 0.787$ ]. Follow-up tests revealed that subjects rated fatigue lower in the control condition compared to the moderate mental exertion condition ( $p < 0.05$ ). Neither a main effect of time [ $F_{(1, 9)} = 2.748, p = 0.132, f_{(V)} = 0.552$ ] nor a condition  $\times$  time interaction [ $F_{(2, 18)} = 0.212, p = 0.132, f_{(V)} = 0.503$ ] were found for self-reported fatigue (See **Table 1**).

### HEART RATE, SUBJECTIVE WORKLOAD AND COGNITIVE PERFORMANCE

There was a significant main effect of condition on average heart rate [ $F_{(2, 18)} = 9.396, p < 0.01, f_{(V)} = 1.022$ ]. Follow-up tests showed a significantly lower heart rate during the control task ( $69.5 \pm 5.9$  beats/min) compared to during the high mental exertion task ( $81.7 \pm 9.7$  beats/min;  $p < 0.05$ ) and the moderate mental exertion task ( $80.3 \pm 8.7$  beats/min;  $p < 0.05$ ).

The NASA-TLX scale revealed significant main effects of condition for mental demand [**Figure 2A**,  $F_{(2, 18)} = 33.061, p < 0.001, f_{(V)} = 1.916$ ], temporal demand [**Figure 2B**,  $F_{(1.2, 11.4)} = 43.441, p < 0.001, f_{(V)} = 2.194$ ], physical demand [**Figure 2C**,  $F_{(2, 18)} = 4.801, p < 0.05, f_{(V)} = 0.348$ ], performance [**Figure 2D**,  $F_{(2, 18)} = 6.909, p < 0.01, f_{(V)} = 0.876$ ] and effort [**Figure 2E**,  $F_{(2, 18)} = 4.428, p < 0.05, f_{(V)} = 0.876$ ]. Follow-up tests showed greater scores for mental and temporal demand after the high mental exertion task than after the

moderate mental exertion task ( $p < 0.001$ ) and the control task ( $p < 0.001$ ). In addition, participants rated a higher performance during the moderate mental exertion task ( $p < 0.01$ ) and the control task ( $p < 0.05$ ) compared to during the high mental exertion task. Furthermore, participants perceived higher physical demand during the control task than during the high mental exertion task ( $p < 0.05$ ). Finally, subjects tended to rate a higher effort after the high mental exertion task and the control task than after the moderate exertion task ( $p = 0.064, p = 0.088$ ). Frustration (**Figure 2F**) was not significantly different between the three conditions [ $F_{(2, 18)} = 1.184, p = 0.329, f_{(V)} = 0.362$ ].

Percentage of errors was significantly greater during the high mental exertion task ( $9.3 \pm 4.4$  %) than during the moderate mental exertion task ( $0.5 \pm 0.6$  %) [main effect of condition  $F_{(1, 9)} = 42.495, p < 0.001, f_{(V)} = 2.171$ ]. However, there was no main effect of time [ $F_{(8, 72)} = 2.570, p = 0.093, f_{(V)} = 0.446$ ] nor a condition  $\times$  time interaction [ $F_{(8, 72)} = 1.778, p = 0.096, f_{(V)} = 0.444$ ].

### NEUROMUSCULAR FUNCTION

MVC torque of the knee extensor muscles (**Figure 3**) showed neither a condition  $\times$  time interaction [ $F_{(18, 162)} = 1.226, p = 0.246, f_{(V)} = 0.369$ ] nor main effects of time [ $F_{(2.7, 23.9)} = 2.088, p = 0.13, f_{(V)} = 0.481$ ] and condition [ $F_{(2, 18)} = 0.293, p = 0.749, f_{(V)} = 0.182$ ].

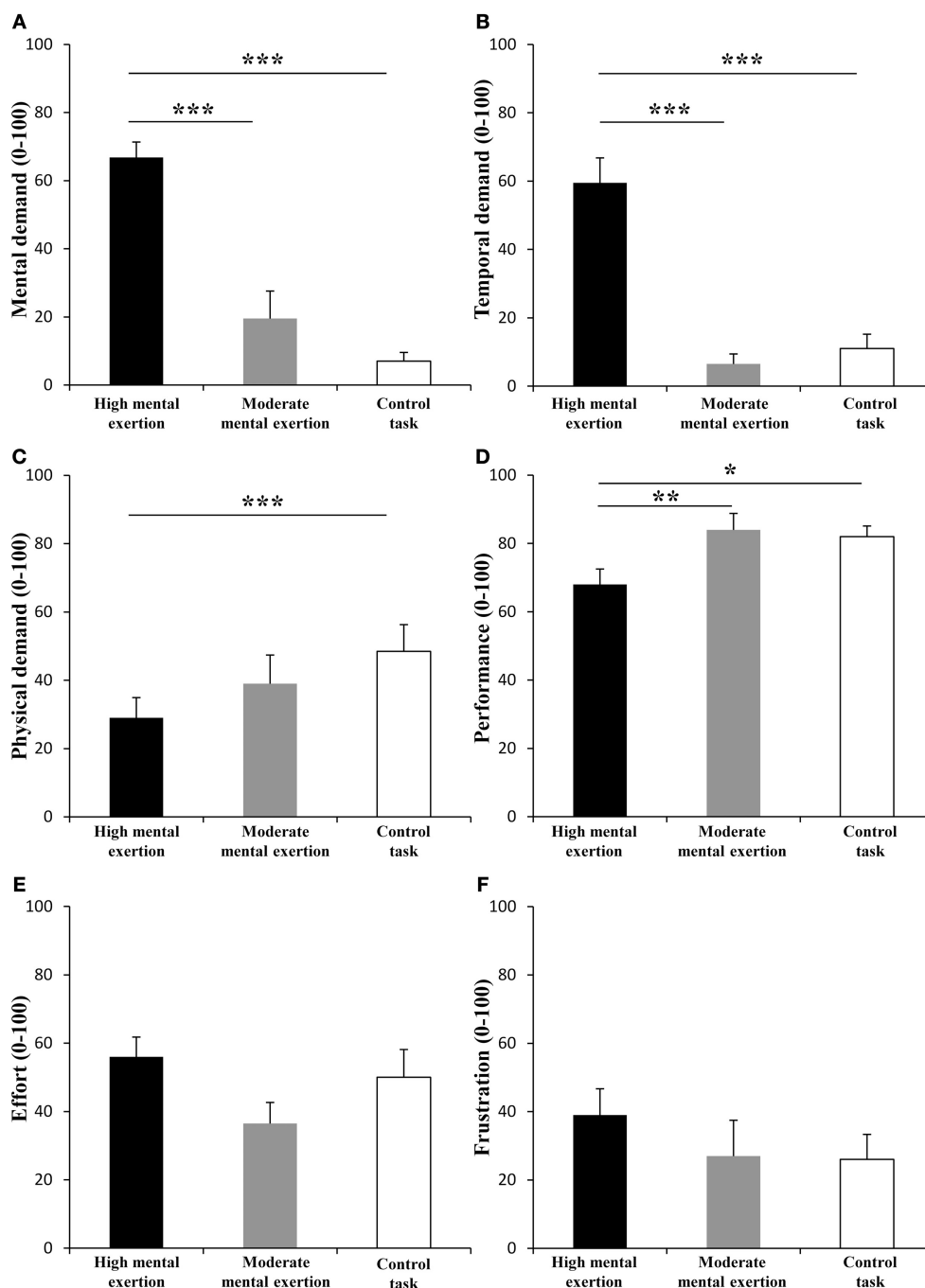
Maximal muscle activation parameters are shown in **Table 2**. VAL tended to decrease over time in all three conditions [ $F_{(3.7, 42.1)} = 2.570, p = 0.061, f_{(V)} = 0.534$ ]. However, there was neither a main effect of condition [ $F_{(2, 18)} = 0.121, p = 0.887, f_{(V)} = 0.115$ ] nor a condition  $\times$  time interaction [ $F_{(18, 162)} = 1.159, p = 0.345, f_{(V)} = 0.359$ ]. Similarly, EMG RMS/M-wave ratio for the VL muscle during the MVCs showed no main effect of condition [ $F_{(1.2, 11.2)} = 1.790, p = 0.211, f_{(V)} = 0.446$ ], no main effect of time [ $F_{(3.2, 28.8)} = 1.728, p = 0.181, f_{(V)} = 0.438$ ], no condition  $\times$  time interaction [ $F_{(18, 162)} = 1.314, p = 0.267, f_{(V)} = 0.381$ ].

Peripheral parameters of neuromuscular function are presented **Table 3**. The amplitude of the potentiated doublet remained constant over time in all three conditions [ $F_{(2.5, 22.4)} = 2.427, p = 0.101, f_{(V)} = 0.519$ ]. There was neither a significant main effect of condition [ $F_{(2, 18)} = 0.306, p = 0.740, f_{(V)} = 0.185$ ] nor a condition  $\times$  time interaction [ $F_{(18, 162)} = 0.714, p = 0.794, f_{(V)} = 0.280$ ]. Furthermore, M-wave amplitude data for the VL muscle showed no significant main effect of

**Table 1 | Motivation and Mood for the three experimental conditions.**

	Motivation		Mood			
	Intrinsic	Success	Fatigue		Vigor	
			Pre	Post	Pre	Post
High mental exertion task	18.7 (4.9)	18.9 (5.0)	1.1 (1.3)	2.9 (4.01)	10.6 (1.7)	8.4 (3.0)
Moderate mental exertion task	18.4 (5.0)	18.9 (3.4)	1.1 (1.2)	3.7 (3.4)	10.7 (1.2)	10.1 (1.6)
Control task	17.7 (6.4)	16.3 (4.3)	0.7 (0.9)	1.5 (2.4)	8.6 (2.1)	8.5 (2.8)

Data are presented as means (SD).



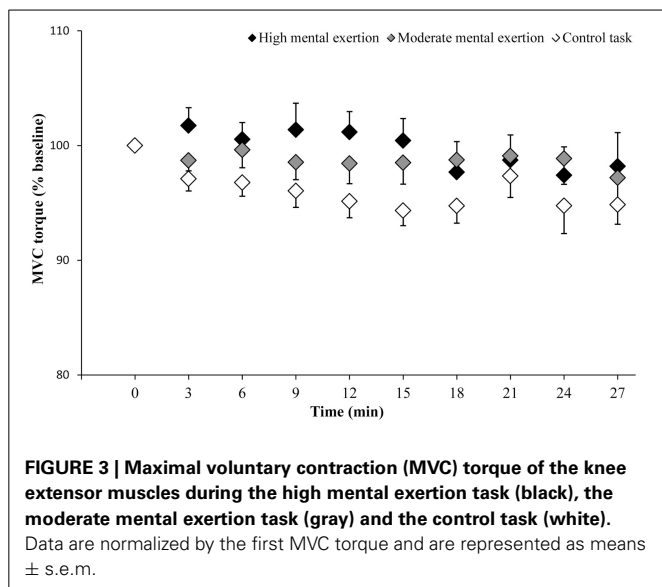
**FIGURE 2 | Effect of mental exertion on subjective workload. (A)** Mental demand. **(B)** Temporal demand. **(C)** Physical demand. **(D)** Performance. **(E)** Effort. **(F)** Frustration. \*, \*\* and \*\*\*: Significantly different ( $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ , respectively). Data are represented as means  $\pm$  s.e.m.

time [ $F_{(1,9, 17.1)} = 2.645$ ,  $p = 0.102$ ,  $f_{(V)} = 0.542$ ], no significant main effect of condition [ $F_{(1,2, 10.4)} = 0.991$ ,  $p = 0.356$ ,  $f_{(V)} = 0.331$ ] and no condition x time interaction [ $F_{(18, 162)} = 0.706$ ,  $p = 0.802$ ,  $f_{(V)} = 0.281$ ].

**DISCUSSION**

The aim of this study was to test the hypothesis that mental exertion would reduce maximal force production during

intermittent MVCs by decreasing maximal muscle activation. Contrary to our hypothesis, neither high mental exertion nor moderate mental exertion altered maximal force production and maximal muscle activation during intermittent MVCs of the knee extensors. These findings demonstrate that the combination of intermittent MVCs and high mental exertion does not reduce the capacity of the CNS to drive to the working muscles.



**MANIPULATION CHECKS AND MOTIVATION**

Similarly to Bray et al. (2012), the subjects of the present study rated higher mental and temporal demand after the high mental exertion task compared to the moderate mental exertion and the control tasks. Additionally, we found a higher average heart rate during both high and moderate mental exertion tasks compared to the control task. These subjective and psychophysiological manipulation checks suggest that we were successful in inducing different levels of mental exertion across conditions.

Because submaximal effort due to poor motivation can negatively affect measures of maximal force production and maximal muscle activation (Enoka, 1995), we followed Gandevia (2001) six-point guideline to maximize motivation during MVCs: (1) maximal efforts should be accompanied by some instruction and practice, (2) feedback of performance should be given during the MVCs, (3) verbal encouragements should be given, (4) subjects must be allowed to reject efforts that they do not regard as maximal, (5) feedback for repeated MVCs should be updated, and (6) rewards for repeated testing should be considered to ensure consistent motivation between sessions. In our study, points 1–5 were respected, and the point 6 was controlled by completion of a motivation questionnaire at the beginning of each session. All subjects presented similar intrinsic and success motivation to perform the entire protocol across all three conditions. Therefore, we are confident that poor motivation did not negatively affect measures of maximal force production and maximal muscle activation in our study.

**EFFECTS OF MENTAL EXERTION ON MAXIMAL FORCE PRODUCTION AND MAXIMAL MUSCLE ACTIVATION**

It is well known that both mental (Lorist and Tops, 2003; Gailliot, 2008) and physical (Davis et al., 2003; Matsui et al., 2011) exertions reduces brain glycogen and increases brain adenosine, a metabolite known to inhibit excitatory activity at neural level (Lovatt et al., 2012). Therefore, our hypothesis was that high mental exertion would induce a significant decrease in maximal force

**Table 2 | Evolution of maximal voluntary contraction (MVC) torque and maximal muscle activation parameters.**

	T0	3	6	9	12	15	18	21	24	27
<b>MVC (N.m)</b>										
High mental exertion task	237 (42)	240 (41)	238 (43)	240 (43)	239 (41)	237 (40)	231 (41)	233 (40)	231 (44)	232 (43)
Moderate mental exertion task	239 (33)	236 (35)	237 (30)	235 (33)	235 (33)	234 (31)	235 (33)	237 (37)	236 (38)	232 (37)
Control task	240 (34)	233 (34)	232 (31)	230 (32)	228 (33)	227 (32)	228 (36)	235 (42)	228 (41)	229 (39)
<b>VAL (%)</b>										
High mental exertion task	91.2 (5.6)	91.3 (5.6)	89.9 (6.4)	90.6 (7.4)	90.0 (8.8)	88.3 (8.9)	86.4 (9.7)	87.9 (7.9)	88.2 (8.8)	88.3 (8.4)
Moderate mental exertion task	90.9 (6.6)	88.7 (8.7)	90.0 (5.4)	87.4 (6.2)	90.6 (6.6)	88.9 (6.6)	89.3 (7.2)	88.6 (8.0)	87.8 (6.9)	86.9 (6.9)
Control task	90.8 (5.9)	90.1 (6.1)	89.8 (7.3)	88.9 (6.9)	89.7 (6.6)	89.9 (7.0)	89.1 (6.2)	89.3 (4.6)	88.5 (6.0)	89.2 (4.9)
<b>RMS/M</b>										
High mental exertion task	0.053 (0.011)	0.056 (0.009)	0.051 (0.012)	0.052 (0.014)	0.051 (0.011)	0.050 (0.013)	0.045 (0.010)	0.050 (0.012)	0.050 (0.011)	0.051 (0.010)
Moderate mental exertion task	0.055 (0.012)	0.054 (0.017)	0.055 (0.016)	0.054 (0.020)	0.049 (0.014)	0.051 (0.011)	0.052 (0.013)	0.051 (0.011)	0.047 (0.010)	0.051 (0.011)
Control task	0.058 (0.008)	0.055 (0.011)	0.054 (0.012)	0.053 (0.013)	0.053 (0.010)	0.055 (0.012)	0.055 (0.010)	0.056 (0.011)	0.053 (0.012)	0.058 (0.015)

Data are presented as means (SD) for MVC torque, voluntary activation level (VAL) and EMG RMS/M-wave ratio of the vastus lateralis muscle.

**Table 3 | Evolution of peripheral parameters of neuromuscular function.**

	Time (min)									
	T0	3	6	9	12	15	18	21	24	27
<b>POTENTIATED DOUBLET (Nm)</b>										
High mental exertion task	99.8 (17.6)	97.4 (17.9)	96.0 (20.8)	96.1 (19.3)	90.5 (16.4)	93.5 (17.3)	86.6 (18.3)	89.0 (18.1)	91.0 (16.9)	90.2 (15.0)
Moderate mental exertion task	94.7 (21.8)	92.1 (27.6)	93.0 (24.3)	89.7 (25.3)	94.6 (19.2)	91.6 (16.6)	88.5 (15.2)	88.6 (20.1)	89.3 (19.0)	90.6 (17.8)
Control task	95.5 (19.4)	94.2 (20.1)	93.1 (18.8)	93.6 (19.8)	90.9 (21.2)	91.8 (19.5)	90.2 (19.9)	90.9 (19.2)	89.6 (20.0)	89.1 (19.0)
<b>M-WAVE AMPLITUDE (mV)</b>										
High mental exertion task	17.9 (1.3)	18.1 (1.4)	18.0 (1.4)	17.9 (1.3)	17.8 (1.5)	17.8 (1.2)	17.7 (1.3)	17.6 (1.1)	17.6 (1.2)	17.6 (1.3)
Moderate mental exertion task	18.8 (2.2)	18.7 (2.8)	18.8 (2.5)	18.7 (2.6)	18.8 (2.6)	18.7 (2.4)	18.7 (2.4)	18.5 (2.5)	18.5 (2.2)	18.4 (2.5)
Control task	18.1 (1.6)	18.3 (1.7)	18.4 (1.6)	18.3 (1.5)	18.2 (1.6)	17.8 (1.5)	17.7 (1.5)	17.5 (1.5)	17.4 (1.6)	17.5 (1.6)

Data are presented as means (SD) for potentiated doublet and M-wave amplitude of the vastus lateralis muscle.

production during intermittent MVCs by reducing the capacity of the CNS to drive the working muscles. Contrary to our hypothesis, we found that high mental exertion did not induce a further decrease in torque and maximal muscle activation during intermittent MVCs of the knee extensors. The present findings support those of Pageaux et al. (2013) and Bray et al. (2008) who showed that short (3 min 40 s of incongruent Stroop task) or prolonged (90 min of the AX-Continuous Performance Task) mental exertion did not alter MVC torque and maximal muscle activation of both upper and lower limbs muscles. Indeed, torque, VAL and EMG RMS/M-wave ratio during MVCs remained constant over time even in the high mental exertion condition. Taking all together, these results suggest that mental exertion does not reduce the capacity of the CNS to drive the working muscles.

The most plausible explanation for the lack of interaction between mental exertion involving response inhibition and maximal muscle activation is that these CNS functions involve different brain areas (Pageaux et al., 2013). Indeed, functional magnetic resonance imaging studies showed that central fatigue during index finger abduction exercise is associated with decrease in activation of the supplementary motor area and to a lesser extent, in parts of the paracentral gyrus, right putamen and in a small cluster of the left parietal operculum (Van Duinen et al., 2007). Interestingly, none of these brain areas is significantly associated with mental exertion involving response inhibition. This cognitive process is significantly associated with activity of the pre-supplementary motor area and the anterior cingulate cortex (Mostofsky and Simmonds, 2008). Therefore, it is neurobiologically plausible that the differentiation in brain areas involved in response inhibition and maximal muscle activation could explain why mental exertion does not reduce the capacity of the CNS to drive the working muscles. However, other neurophysiological techniques have to be used to assess brain activation during both mental and physical exertion (Mauger, 2013). Thus, prefrontal cortex activity could be assessed by near infra-red spectroscopy (Derosière et al., 2013), as its activity increases along with the perception of effort (Berchicci et al., 2013) and the level of physical performance (Mandrick et al., 2013).

**MENTAL EXERTION AND PERIPHERAL FATIGUE**

Contrary to the present study, Bray et al. (2012) observed a significant decrease in maximal force production during intermittent MVCs. In addition to poor motivation exacerbated by high mental exertion, another possible explanation for the results of Bray et al. (2012) is the presence of peripheral fatigue induced by the incongruent Stroop task. Recent studies on the upper limb suggested that mental exertion could induce an earlier onset of peripheral fatigue on shoulder muscles (Mehta and Agnew, 2012). This is supported by an activation of the trapezius muscle when handgrip squeeze is performed in the same time of a shoulder abduction in interaction with mental exertion (MacDonell and Keir, 2005). This activation of the trapezius muscle or forearm muscles (Waersted and Westgaard, 1996; Laursen et al., 2002) could be due to holding the sheets (paper-based Stroop task), or selecting the correct responses with a keyboard or a mouse (computer-based Stroop task).

We avoided these confounding effects of the Stroop task by testing maximal muscle activation of the knee extensor muscles, not functionally connected with muscle affected by combined mental and physical exertion (e.g., shoulder muscles). Indeed, in the present study, both resting evoked contraction and M-wave amplitude remained constant during the 27 min of combined mental exertion and intermittent MVCs of the knee extensors. These results demonstrate that the 3 min intervals between MVCs were sufficient to avoid any exercise-induced peripheral fatigue, and that the Stroop task did not significantly affect the knee extensors neuromuscular function.

Although the results of Bray et al. (2012) may be explained by poor motivation of their subjects and the peripheral fatigue induced by the Stroop task, it has to be acknowledged that the effects of mental exertion on intermittent MVCs could differ between upper and lower limbs. However, this differentiation between upper and lower limbs is unlikely. Indeed, previous studies demonstrated that upper limb (Bray et al., 2008), lower limb (Pageaux et al., 2013) and whole-body endurance performance (Marcora et al., 2009; Pageaux et al., 2014) are impaired by mental exertion.

## LIMITS AND CONCLUSION

Despite a small sample size, the statistical power to test our two main hypotheses (condition  $\times$  time interactions on MVC torque and VAL) reached an acceptable level of 0.8 (Cohen, 2013). Furthermore, it has to be noticed that the control condition presented the greater decrease in MVC torque (high mental exertion:  $-2.1\%$ ; moderate mental exertion:  $-2.9\%$ ; control condition:  $-4.6\%$ ), suggesting that, if a Type II error was present, the negative effect on neuromuscular function would occur during the control condition and not during the high mental exertion condition. Therefore, it is highly unlikely that we failed to detect a significant effect of mental exertion on the capacity of the CNS to drive the working muscles.

From a psychobiological point of view, the present study suggests that mental exertion does not alter maximal muscle activation. From an applied point of view, these findings combined with previous observations on upper and lower limbs (Bray et al., 2008; Pageaux et al., 2013) indicate that mental exertion does not reduce maximal force production. Therefore, unlike endurance tasks (Marcora et al., 2009; Pageaux et al., 2013), short duration physical tasks requiring high level of force should not be negatively affected by mental exertion.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 10 June 2014; accepted: 08 September 2014; published online: 26 September 2014.

Citation: Rozand V, Pageaux B, Marcora SM, Papaxanthis C and Lepers R (2014) Does mental exertion alter maximal muscle activation? *Front. Hum. Neurosci.* 8:755. doi: 10.3389/fnhum.2014.00755

This article was submitted to the journal *Frontiers in Human Neuroscience*.

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