Mental Fatigue and Sleep Deprivation: Effects, Mechanisms and Countermeasures in Endurance Exercise Performance

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MENTAL FATIGUE AND SLEEP DEPRIVATION: EFFECTS, MECHANISMS AND COUNTERMEASURES IN ENDURANCE EXERCISE PERFORMANCE

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Thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy

School of Sport and Exercise Sciences
Faculty of Science
University of Kent
2019

Keywords

Mental fatigue, cognitive fatigue, sleep deprivation, recovery sleep, endurance exercise, ultra-endurance exercise, endurance performance, cognitive performance, exertion, effort, perception of effort, motivation, tolerance, time trial, cycling, running, training, brain endurance training, sleep deprivation training, cognition, acute adaptations, chronic adaptations, EEG, brain, anterior cingulate cortex, psychobiological model.

Abstract

Mental fatigue and sleep deprivation are two common conditions in our modern societies, affecting millions of healthy people. Whereas mental fatigue is considered a psychobiological state caused by prolonged and demanding cognitive activities, sleep deprivation can be defined as a brain state caused by at least 24 hours of wakefulness.

The first aim of this thesis was to investigate the acute effects of mental fatigue, sleep deprivation and subsequent recovery sleep on endurance exercise performance. The second aim was to evaluate the effects of two innovative training interventions, Brain Endurance Training (BET) and Sleep Deprivation Training (SDT) on endurance performance. It was hypothesized that: 1) 50-min of mentally-demanding cognitive task and 25-h of sleep deprivation would impair endurance performance and that the following night of recovery sleep would be enough to restore rested endurance performance; 2) six weeks of BET (alone) and six weeks of SDT (combined with physical training) would improve endurance performance.

The first and second study do not provide reliable evidence that mental fatigue and sleep deprivation reduce endurance performance during a half-marathon and a 20-min cycling time trial, respectively. However, an alternative statistical analysis used in study one, suggests that the hypothesis that mental fatigue is harmful cannot be rejected. The third study shows that BET is not effective in physically-inactive males. The fourth study reveals that SDT in combination with physical training might be beneficial to counteract the effects of sleep deprivation on endurance performance.

In conclusion, the findings do not provide statistical evidence of a negative effect of mental fatigue and sleep deprivation on endurance performance. However, it might be prudent to avoid them prior to races. The use of BET alone does not enhance endurance performance. Nonetheless, the combination of SDT with a physical training program might be beneficial in preparation for an endurance/ultra-endurance event.

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List of Abbreviations

AAT	Alpha attenuation test
ACC	Anterior cingulate cortex
Ag/AgCl	Silver/silver chloride
AM	Ante meridiem
ANOVA	Analysis of variance
AX-CPT	AX-continuous performance task
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BRUMS	Brunel mood scale
CI	Confidence interval
CO_2	Carbon dioxide
CON	Control group
BET	Brain endurance training
EEG	Electroencephalography
EMG	Electromyography
ERN	Event related negativity
ERP	Event related potential
FIB	Fatigue item bank
FIDAL	Italian athletics federation
fMRI	Functional magnetic resonance imaging
FAS	Fatigue assessment scale
FS	Fatigue scale
FSS	Fatigue severity scale
GPS	Global positioning system
HR	Heart rate
HSD	Honest significant difference
LA	Lactate
LT	Lactate threshold
MDN	Median
MEQ	Morningness-eveningness questionnaire
MVC	Maximal voluntary contraction
N	Number
NASA	National aeronautics and space administration
O_2	Oxygen
PA-R	Physical activity rating
PAR-Q	Physical activity readiness questionnaire
$PETCO_2$	End-tidal carbon dioxide partial pressure
$PETO_2$	End-tidal oxygen partial pressure
PM	Post meridiem

POMS	Profile of mood states
PROMIS	Patient reported outcome measurement information system
PSQI	Pittsburgh sleep quality index
PVT	Psychomotor vigilance task
Q-Q	Quantile-quantile
RCI	Reliable change index
RH	Relative Humidity
RPE	Rating of perceived exertion
RT	Reaction time
SD	Standard deviation or sleep deprivation when appropriate
SDT	Sleep deprivation training
SESOI	Smallest effect size of interest
SPM	Statistical parametric mapping
SPSS	Statistical package for social sciences
SR	Sleep restriction
SWAT	Subjective workload assessment technique
TLX	Task load index
TOST	Two one-sided tests
TT	Time trial
TTE	Time to exhaustion
VAS	Visual analogue scale
$\dot{V}CO_2$	Rate of carbon dioxide production
$\dot{V}E$	Minute ventilation
$\dot{V}E/\dot{V}O_2$	Ventilatory equivalents for oxygen
$\dot{V}E/\dot{V}CO_2$	Ventilatory equivalents for carbon dioxide
$\dot{V}O_2$	Rate of oxygen uptake
$\dot{V}O_{2max}$	Maximum oxygen uptake
$\dot{V}O_{2peak}$	Peak oxygen uptake
VT	Ventilatory threshold
VT1	First ventilatory threshold
VT2	Second ventilatory threshold
WHOQOL	World health organisation quality of life
WP	Workload profile
yr	Years
α	Alpha
β	Beta
γ	Gamma
δ	Delta
θ	Theta

Units of Measure

>	Greater than
<	Less than
≥	Equal to or greater than
≤	Equal to or less than
=	Equals
−	Minus
+	Plus
±	Plus or minus
~	Tilde
%	Percent
bpm	Beats per minute
°C	Degree Celsius
cm	Centimetres
GHZ	Gigahertz
h	Hours
hPA	Hectopascal
Hz	Hertz
kcal	Kilocalories
kg	Kilograms
kg/m^2	Kilogram per square metre
kJ	Kilojoules
km	Kilometres
km/h	Kilometres per hour
kΩ	Kiloohm
m	Metres
mg	Milligrams
min	Minutes
ml	Millilitres
ml/kg	Millilitres per kilogram
ml/kg/min	Millilitres per kilogram per minute
mmol/l	Millimole per litre
ms	Milliseconds
rpm	Revolutions per minute
s	Seconds
W	Watts
W/min	Watts per minute
µl	Microlitres
Δ_L	Lower equivalence bound
Δ_U	Upper equivalence bound

Statement of Original Authorship

No part of this thesis has been submitted in support of an application for any degree or other qualification of the University of Kent, or any other University or Institution of learning.

Acknowledgments

The first and most important thanks goes to my main supervisor Professor Samuele Marcora. Thank you Sam for everything you have done for me. I feel so grateful I have had the chance to work with you. Your guidance, support and advice have been so precious to me. Your passion for research so inspiring. Thank you for the time you have dedicated to me and for the skills I have gained during my PhD journey. Finally, thank you for being so human and for the many laughs. I had never thought that doing a PhD would have been so much fun too.

I would also like to thank my second supervisors, Dr Barry O'Neill for his support, particularly during the early phases of the PhD, Dr Glen Davison, during the late phases of the PhD, and Dr Amir-Homayoun Javadi for his help with the EEG analysis, which will never be forgotten.

A special thanks goes to my friends and colleagues Borja Martinez Gonzalez and Dr Luca Angius, for their help and support in the lab, and Davide Lombardi, for his precious contribution in the data collection.

To Michele, for his patience to introduce me to the unknown world of Matlab and for his help with Matlab data analysis.

To my big fantastic italian family, for all their love and positivity.

And finally to Mamma, Papà, Giada and Tommaso. Thank you for all the love and support you have given me in these years. This PhD would not have been possible without you! Thank you for always believing in me!

Chapter 1

General Introduction

1.1 Background

What is mental fatigue? Defining mental fatigue has always been difficult and controversial. Many researchers have tried to give their own interpretation over the past 100 years or so, however, a universal definition has not been found yet. The most recent and utilized definition of mental fatigue will be used throughout this thesis. From an operational point of view, mental fatigue can be defined as a psychobiological state caused by prolonged and demanding cognitive activities (i.e. boring and complex cognitive tasks which require high levels of effort despite low rewards perceived) (Matthews & Hancock, 2017; Boksem & Tops, 2008). It is an extremely complex phenomenon characterized by tiredness (even exhaustion), changes in mood and reluctance to carry on a task (Matthews & Hancock, 2017). Mental fatigue can also be a symptom in patients affected by several chronic diseases, such as cancer, Parkinson's disease and chronic fatigue syndrome (Matthews & Hancock, 2017). However, it is crucial to make a distinction between pathological mental fatigue and mental fatigue experienced by the majority of the healthy population during their everyday life (i.e. non-pathological). Pathological mental fatigue is chronic, might involve different biological substrates (Boksem & Tops, 2008) and its exact cause is still unclear (most probably multifactorial) (Jason et al., 2010); non-pathological mental fatigue is acutely manifested and mainly task-induced (Ackerman, 2011). In this thesis, mental fatigue will refer to the operational definition of the term itself (mentioned above).

Fatigue has always been one of the main research cornerstones since the beginning of modern psychology. The first studies ever conducted date back to the

1890s in Germany by Ebbinghaus, Kraepelin and others, and focused their attention on fatigue-related impairments in learning and performance in schools (cited in (Ackerman, 2011). Since then, research on mental fatigue reached its first and highest peak in the 1940s, during which fatigue became extremely relevant in both military and industrial contexts (Ackerman, 2011). Although research conducted in those years contains valuable historical resources, all the experiments were carried out much earlier than the beginning of the modern experimental psychology and cognitive neuroscience. It is only in the 1980s that mental fatigue takes a new theoretical interest, with the development of new models and theories and the use of new behavioural, physiological and neuropsychological approaches and methods (Ackerman, 2011).

Nowadays mental fatigue is an extensive problem which negatively affects the entire population (Boksem & Tops, 2008; Craig et al., 2006; Ricci et al., 2007). As a consequence, in the last five decades the literature on mental fatigue has considerably increased. Many studies have focused their attention on mental fatigue in the work, military, educational and healthcare environments. In particular, researchers have used, both in laboratory and field settings, the above mentioned new techniques to investigate fatigue-associated task characteristics and human attributes, operator's behaviour over prolonged tasks or during sleep deprivation, the effects of drugs on mental fatigue, the effects of potential pharmaceutical or natural remedies, such as modafinil and caffeine, to overcome mental fatigue, neural activity associated with mental fatigue, and so on.

Numerous research has also been conducted on sleep deprivation and other forms of sleep debt (Matthews & Hancock, 2017). From an operational perspective, sleep deprivation can be defined as a psychobiological state induced by at least 24 hours of continuous wakefulness, of which, sleepiness is the main manifestation (Wesensten et al., 2012) (for other types of sleep debt, see Chapter 3). Sleep deprivation (as well as other forms of sleep debt) is considered one of the main associated determinants of mental fatigue (Owens, 2007) and for this reason these two terms are often used interchangeably. Even though mental fatigue and sleep deprivation are closely interconnected and may often have a cyclical relationship (i.e. cause-effect relationship), it is important to underline that they are two distinct phenomena. Indeed, although they can both induce performance decrements, tiredness and changes in mood, mental

fatigue is generally associated with demanding cognitive activity, whereas sleep deprivation is related to lack of sleep (Ackerman, 2011).

Whilst a considerable number of studies have investigated both mental fatigue and sleep deprivation in relation to cognitive performance, less attention has been given on physical performance. Surprisingly, the effects of mental fatigue on physical performance and more specifically on endurance exercise performance, have started being investigated only in the past decade (Van Cutsem et al., 2017b), and many of the studies conducted on sleep deprivation and exercise performance present evident limitations (Fullagar et al., 2015).

In this thesis, mental fatigue and sleep deprivation have both been investigated, as considered two essential and highly linked phenomena in the field of fatigue. Their cyclical cause-effect relationship as well as their similar effects on subjective and behavioural human responses, would not have allowed the inclusion of mental fatigue without taking sleep deprivation into consideration, and vice versa.

1.2 General aims and outline of the thesis

Although there is growing research on the effects of mental fatigue and sleep deprivation on endurance exercise performance, there is very little knowledge on the neurobiological mechanisms involved and even less on the possible countermeasures athletes and trainers can use to overcome negative effects of mental fatigue and sleep deprivation on endurance exercise performance. Therefore, the main purpose of this thesis was to investigate the effects of mental fatigue and sleep deprivation and to look into new training strategies aimed at counteracting potential negative effects on endurance exercise performance.

This thesis is divided into seven content sections. The literature on mental fatigue (Chapter 2) and sleep deprivation (Chapter 3) in both cognitive and physical performance, in particular on endurance exercise performance, is firstly reviewed, focusing the attention on effects, neurobiological mechanisms involved and countermeasures to adopt. Moreover, Chapter 2 includes an overview on current training strategies aimed at counteracting and increasing resilience to mental fatigue.

Chapter 3 focuses on the other countermeasures available to minimise the negative effects of sleepiness and mental fatigue. The four experiments conducted during my doctoral research program are then presented. The experimental trials consist of two acute studies (Chapter 4 and 5) and two chronic studies (Chapter 6 and 7) respectively. In Chapter 4 my first experiment, a field study aimed at investigating the effects of mental fatigue during a half-marathon race in amateur runners, is presented. In Chapter 5 the second experiment on the acute effects of sleep deprivation and sleep recovery on endurance cycling performance is described. The results of a new training methodology, called Brain Endurance Training (BET), as a potential new strategy to increase resilience to mental fatigue and enhance endurance exercise performance in physically-inactive people are then presented (Chapter 6). Finally, in Chapter 7 a case study conducted on an ultra-endurance runner, with the purpose of investigating another new training strategy, called sleep deprivation training (SDT), aimed at increasing resilience to sleep deprivation and enhancing endurance exercise performance is described. The thesis ends with a general discussion of the experimental findings (Chapter 8).

The four studies conducted during my doctoral research program should provide new knowledge on the topic and from a practical perspective should help athletes and trainers to better overcome potential negative effects of mental fatigue and sleep deprivation on endurance exercise performance.

1.3 Thesis format

This thesis contains two literature reviews and four experimental studies. All the above mentioned experiments are treated individually, in singular chapters and written in a conventional paper format. All the manuscript is written in the formatting style adopted by the School of Sports and Exercise Sciences at the University of Kent. All cited references are included at the end of the thesis in a single list. Figures and tables are numbered chronologically, but separately within each chapter.

Finally, it is important to underline again that mental fatigue and sleep deprivation are two important and distinctly studied phenomena, and for this reason the

literature has been reviewed separately. Nevertheless, as they are strongly interconnected, the presence of overlap has been inevitable, in particular in the sections related to the measures used to assess them and the countermeasures aimed at overcoming their effects. Moreover, since all the experimental studies have been written as independent papers, there might also be some overlaps in the central chapters occasionally.

Chapter 2

Mental Fatigue:
Effects, Mechanisms and Countermeasures

2.1 Introduction

Even though mental fatigue (and more generally all types of fatigue) has always received a lot of interest among researchers and has always been one of the main core constructs in psychology and neuroscience research, after more than 100 years of research this phenomenon is still poorly comprehended. At present, its origins and function are not clearly explained, and for now, scientists can mainly rely on a very broad and old hypothesis that mental fatigue is related to energy deficiency due to mental (or physical, in case of physical fatigue) work (Hockey, 2017).

Mental fatigue, as already mentioned previously, has been widely investigated in certain contexts and populations. Work, military, educational and healthcare environments are the most popular ones in this field (Ackerman, 2011). However, the effects of mental fatigue on exercise performance have started being investigated only in the last decade, when Professor Samuele Marcora decided to explore at that time a largely unknown field (Marcora et al., 2009). Indeed, to the best of our knowledge, the only findings available in the literature prior to Marcora's study date back to 1891, when Professor Angelo Mosso observed that long lectures and oral examinations had a negative impact on muscle endurance of two fellow physiology professors (Mosso, 1891).

The aim of the present review is to give an overview of the current knowledge about mental fatigue in healthy populations, emphasizing its role on endurance exercise performance. Given the complexity of this phenomenon, attention has been focused

only on some aspects rather than others. In particular, in the first part of this chapter the term mental fatigue has been introduced and defined, the research tools currently available for its assessment identified and the literature on the effects caused by mental fatigue, on both cognitive performance (only a short literature review, as it is not the main variable of interest in this Thesis) and endurance exercise performance reviewed. A short overview of the role played by mental fatigue on other types of physical performance has also been included. Finally, in the last section, the main neurobiological mechanisms underlying mental fatigue and the current training strategies developed to increase resilience to mental fatigue and improve cognitive and endurance exercise performance have been described.

2.2 What is mental fatigue?

Fatigue is a controversial field of investigation. Despite a universal definition of fatigue remaining elusive (Broughton & Hasan, 1995; Bültmann et al., 2002; Craig et al., 2006; Desmond et al., 2012), the specific term mental fatigue has been mainly described as a change in the psychophysiological state induced by prolonged and demanding cognitive activities (i.e. boring and complex cognitive tasks during which high levels of effort are required and low rewards perceived) (Boksem & Tops, 2008; Hancock et al., 2017).

It has been demonstrated that mental fatigue is a common symptom in people affected by some chronic diseases, such as chronic fatigue syndrome, cancer, Parkinson's disease, multiple sclerosis and depressive and anxiety-based disorders (Chaudhuri & Behan, 2000, 2004; Siegert & Abernethy, 2005). Mental fatigue, however, does not affect only specific patients. Acute manifestation of mental fatigue, indeed, is a considerable problem in all healthy populations (Boksem & Tops, 2008; Craig et al., 2006; Ricci et al., 2007).

Mental fatigue is a very common phenomenon in our everyday modern life, which involves different kinds of subjective and objective aspects, such as tiredness (Hockey, 1983), changes in mood (Desmond et al., 2001), reluctance to carry on a task

(Drenth, 1998) and cognitive functions impairment (Lorist et al., 2005). In addition to that, mental fatigue has been associated with behavioural cognitive (e.g. (Boksem et al., 2005; Lorist et al., 2005; van der Linden & Eling, 2006) and physical impairments (e.g. (MacMahon et al., 2014; Marcora et al., 2009; Smith et al., 2016; Smith et al., 2015).

Research on mental fatigue includes several areas of interest. Sources of fatigue, types of fatigue-induced responses and underlying processes are the main ones (Desmond et al., 2012). The determinants of mental fatigue can be classified as environmental, physiological and psychological factors (Matthews & Desmond, 1998). In particular, the main adverse factors investigated in the literature are lack of sleep (or poor quality of sleep) (Owens, 2007), 'time of day' effects (i.e. circadian rhythms) (Matthews et al., 2012) and task workload (Friswell & Williamson, 2008; Knauth, 2007). Other secondary elements such as the use of some drugs (Smith, 2011) or the exposure to several environmental stressors including noise, high temperatures and computer screens (Hancock, 2000) may induce mental fatigue. Mental fatigue can be subjective, behavioural and (neuro)physiological (Desmond et al., 2012). Whereas subjective responses includes greater tiredness (Boksem & Tops, 2008), lower motivation (Boksem et al., 2006) and decreased vigilance (van der Linden et al., 2006), behavioral responses refer to declines in performance (e.g. impaired accuracy and/or reaction time during a cognitive task) (Möckel et al., 2015; Wascher et al., 2014) and physiological responses to brain activity alterations (Brownsberger et al., 2013; Cook et al., 2007; Hopstaken et al., 2015; Wascher et al., 2014).

Although these manifestations reflect the presence of a mental fatigue state, they are not essential for mental fatigue to be present. Indeed, it has been found that mentally-exhausted individuals have a recovered effective behavior when they are externally motivated, for example by a monetary reward (Boksem et al., 2006; Hockey, 2013; Hopstaken et al., 2015). This suggests that mental fatigue can be considered as an adaptive state (Hockey, 2013) which can be counteracted by high levels of self-control and motivation and that individuals can be mentally fatigued without any evident decline in cognitive performance.

2.3 Assessing mental fatigue

Mental fatigue is a condition difficult to assess. In particular, there is no general agreement on how this condition should be measured (DeLuca, 2005). Even though research in this field has made important progress no universal acceptable biological markers have been found. Mental fatigue can be mostly assessed in terms of performance decrement and subjective feeling (Wessely et al., 1998). The selection between one of these two approaches depends mainly on the researcher's interest. In particular, the investigation of performance decrements over time during a specific task (Noll, 1932) is mostly used in business and military fields for assessing loss of productivity and potential increased accidents (Caldwell & Caldwell, 2005; Folkard & Lombardi, 2006). On the other hand, clinicians tend to assess mental fatigue by asking the subjects to report their subjective feelings of fatigue more often at rest (Hockey et al., 2000; Michielsen et al., 2004).

Given the complexity and multitude of the neural mechanisms underlying mental fatigue, it is very difficult to deduce the specific processes involved in the control of a certain task through questionnaires/scales and performance data alone (Desmond et al., 2012). Cognitive psychology and neuroscience research has made great improvement in this sense and a variety of different tools are now used to study neural processes involved with psychobiological state, such as electroencephalography (EEG) and neuroimaging (Desmond et al., 2012).

Questionnaires

Self-reported feelings of fatigue in the general population are mostly evaluated using questionnaires and they are used in different contexts like health assessment (Lai et al., 2011) and worker traits (Åhsberg, 2000; Michielsen et al., 2004). Mental fatigue sometimes is also measured through general quality of life instruments, such as the Vitality subscale of the Medical Outcomes Study Short-Form (SF-36) (Ware & Sherbourne, 1992) and the WHOQOL-100 of the World Health Organization (Power et

al., 1999), or by taking general measurements of mood (e.g. Profile of Mood States (POMS) (McNair et al., 1992) or Brunel Mood Scale (BRUMS) (Terry et al., 2003). Moreover, fatigue is frequently measured using specific fatigue-related scales such as the Chalder's Fatigue Scale (FS) (Chalder et al., 1993), the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the Fatigue Assessment Scale (FAS) (Michielsen et al. 2003) and the Patient-Reported Outcome Measurement Information System Fatigue Item Bank (PROMIS-FIB) (Lai et al., 2011).

Fatigue questionnaires can be grouped into three main categories. The most common one assesses the level of fatigue using a single item (Krupp et al., 1989). This kind of scales is generally given prior to, during and following a task and can assess the feeling of fatigue (e.g. specific feeling-of-fatigue scales (Lai et al., 2011), which go from 'not exhausted at all' to 'highly exhausted', such as visual analogue scales (McCormack et al., 1988; Price et al., 1983) or indirect mental-fatigue-related feelings like those associated with motivation (e.g. feeling unmotivated or indifferent) (Watt et al., 2000) and perceived exertion (e.g. Borg Scale of perceived exertion (Borg, 1982)). Other questionnaires consist of multidimensional scales (Smets et al., 1995), such as in the case of the Activation-Deactivation Adjective Check List, in which each scale is related to a specific fatigue-related factor (e.g. wakeful, drowsy, calm and energetic) (Lorist et al., 2009; Thayer, 1989). This type of questionnaire is given to measure subjective feelings at the exact moment of the assessment. In addition to feelings, they can also include items that assess the perceived impact of fatigue on everyday life (Lai et al., 2011) and this is often differentiated between fatigue perceived on cognitive and physical activities (Chalder et al., 1993; DeLuca, 2005; Smets et al., 1995). The third type of questionnaires are those multidimensional scales which assess subjective workload and perceived tasks demand. NASA Task Load indeX (NASA-TLX) (Hart & Staveland, 1988), Subjective Workload Assessment Technique (SWAT) and Workload Profile (WP) (Rubio et al., 2004) are among the most used ones.

It is still not clear whether subjective feelings of fatigue should be measured multidimensionally (Lai et al., 2011; Michielsen et al., 2004; Smets et al., 1995). There is evidence that some aspects of fatigue increase more than others and this seems to be job/task-related (Åhsberg & Gamberale, 1998; Ahsberg et al., 2000; Åhsberg et al.,

1997). For example, physical dimensions of fatigue, such as physical discomfort and perceived exertion, are generally rated higher than mental dimensions of fatigue and sleepiness during endurance exercise (Ashberg et al., 2000). However, a considerable number of studies have demonstrated that a single general dimension can explain much of the variation in several fatigue scales (Åhsberg, 2000; De Vries et al., 2003; Lai et al., 2011; Swaen et al., 2003).

Cognitive performance tests

To assess mental fatigue in the form of performance decrement, scientists generally collect different behavioural cognitive measures during real life, simulations of real life or laboratory tasks. The main metrics used to assess cognitive behavioural performance usually comprise reaction time and error rates (i.e. accuracy), which have been shown to impair significantly with mental fatigue (Liu et al., 2010; Sun et al., 2014). The primary procedures used to evaluate cognitive performance based on these metrics are to either measure them before and after a specific mentally-fatiguing task using pre- and post-cognitive tests or to assess them over time, during the mentally-fatiguing task itself (i.e time on task).

Psychomotor Vigilance Task (PVT) (Dorrian et al., 2005), N-back task (Jaeggi et al., 2010), Go/NoGo Tasks and Stroop Tasks (Peterson et al., 2002), and AX-CPT (Barch et al., 1997) are among the most used tasks to measure changes in cognitive performance and assess mental fatigue. Nevertheless, it is important to underline that the above mentioned cognitive tasks show some limitations as they do not always reveal the presence of mental fatigue (i.e. performance impairment) (see Section 2.4 for further details). Therefore, it is highly recommended to use more than one method (e.g. questionnaires, cognitive performance tasks and neurophysiological measurements together) to properly evaluate a mental fatigue state.

Cognitive tasks characteristics to induce mental fatigue

The cognitive tasks mentioned above possess specific characteristics, which are generally combined and contribute together to the development of mental fatigue itself. Not being intrinsically interested in a task is one of the main elements necessary to decrease performance (first noted by (Dodge, 1913). Intrinsic interest seems to be dependent on some general characteristics of the task, individuals motivation, individuals interest in certain aspects of the task and the extent to which the individual attempts to make the task engaging (Cooper, 1973; Dickey, 2005; Malone, 1981). High task demands on intellectual functioning, such as serial mental addition tasks (Baranski, 2007; Baranski et al., 2002), is another relevant aspect which helps to accelerate the onset of mental fatigue compared to lower task demands, like simple memorization tasks (Nolte et al., 2008). The same faster performance decrement is found in tasks that require continuous and prolonged in time effort (Matthews & Desmond, 1998) compared to those that require discrete effort (Åhsberg, 2000). In general, when more attention is required by a task or when there are no breaks, available attentional resources in individuals are faster reduced.

Other two relevant task characteristics are high rewards situations and high rates of failure (Bonner & Sprinkle, 2002). It has been shown that individuals are likely to allocate higher effort in high reward-tasks and lower effort when time on-task increases as a result of high rates of failure perception (Ackerman, 2011; Kurzban et al., 2013). Moreover individuals may also encounter off-task distractions during a task, which might compromise task performance (Ackerman, 2011). General stressors, like noise or temperature, are generally associated with mental fatigue (Laird, 1933; Persinger et al., 1999; Thorndike et al., 1916) and individuals are likely to draw their attention away from the task to concern about these off-task distractions (Desmond et al., 2012). Finally, it has been shown that characteristics like high levels of time pressure, high demands on visual attention or verbal content in a task generate more effort compared to low levels of time pressure, auditory attention and math content respectively (Ackerman, 2011).

EEG, brain wave activity and electrocardiography

EEG is considered one of the most promising tools to measure mental fatigue (Wijesuriya et al., 2007). It generally shows the total sum of the inhibitory and excitatory postsynaptic potentials of neurons and measures the synchronous activity of cortical neurons that have a similar spatial direction (Santamaria & Chiappa, 1987). EEG is described in terms of rhythmic activity, which is divided into bands by frequency, which in turn allow accurate frequency and time-frequency analyses. These bands comprise: delta (δ) (0.5-4 Hz) and theta (θ) slow waves (4-7.5 Hz), the former associated with transition to drowsiness and sleep, the latter linked to psychological conditions associated with decreased information processing such as meditation and low levels of alertness (i.e. drowsiness and sleep, but not deep sleep) (Lal & Craig, 2001); alpha waves (α) (8-13 Hz) associated with wakefulness, relaxed states and negatively related to attention (Tran et al., 2001), the fast beta waves (β) (13.5-30 Hz) associated with increased alertness, arousal and excitement and the gamma waves (γ) (30-80 Hz) related to higher level of cognitive processing (Lal & Craig, 2001).

Another very well known and used measurement in cognitive psychology and neuroscience to assess mental fatigue is the Event Related Potentials (ERP) (Boksem et al., 2005). ERPs are defined as voltage deflections in the natural EEG activity of the brain that are time locked to specific events of interest, such as the onset of a stimulus during a task (Dien et al., 2003). This measure allows to detect brain temporal processing within the first seconds or milliseconds after a stimulus. The so called P300 component (i.e. the positive peak around 300 ms following a given stimulus) (Zhao et al., 2012) and the N1 and N2 components (i.e. Event Related Negativity (ERN), defined as ERPs occurring subsequently following an error or in case of high levels of response conflicts) (Boksem et al., 2005) seem to be affected in amplitude and latency by mental fatigue.

Other studies have shown that electrocardiography might also be another important instrument to assess mental fatigue, as it allows to identify changes in the autonomic nervous system activity (increments in the sympathetic activity and decrements in the parasympathetic activity), which in turn seems to be associated with

manifestations of acute mental fatigue (Tanaka et al., 2009; Tanaka et al., 2011). However, future research needs to be conducted.

2.4 Effects of mental fatigue on cognitive performance

Although past studies have demonstrated that subjective manifestations of mental fatigue do not always corresponds to objective decrements of performance during a cognitive task, and people who appear highly mentally fatigued may continue to show normal levels of functioning (Hockey, 1983; Thorndike, 1914), the majority of the experiments present in literature have found that mental fatigue have a detrimental effect on cognitive performance (Boksem et al., 2005; Faber et al., 2012; Langner et al., 2010; Lorist et al., 2000; Lorist et al., 2005; van der Linden & Eling, 2006; van der Linden et al., 2003a). Mental fatigue involves higher levels of distraction (Boksem et al., 2005) and significant difficulties in adequately preparing responses (Boksem et al., 2006), which result in cognitive performance decrements (e.g increments in error rates and/or slower responses) and behavioral adjustments impairments (Boksem et al., 2006; Lorist et al., 2005).

More specifically, mental fatigue impairs both attention/vigilance (Ackerman, 2011; Reteig et al., 2019; Warm et al., 2008) and the so called executive functions (also known as executive control or cognitive control) (van der Linden et al., 2003a; van der Linden et al., 2003b; van der Linden & Eling, 2006). Executive functions are complex higher-order cognitive functions that play a primary role when automatic processes cannot be used because considered inappropriate or insufficient or even impossible (Burgess & Simons, 2005; Diamond, 2013; Espy, 2004; Miller & Cohen, 2001). There are three main kinds of executive functions (e.g., (Lehto et al., 2003; Miyake et al., 2000): inhibition (i.e. inhibitory control, defined as the ability to suppress occurring or predetermined motor or cognitive actions allowing response adaptations to sudden situations changes (Aron, 2007)), which includes self-control (behavioral inhibition) and interference control (selective attention and cognitive inhibition), working memory, and cognitive flexibility, also called mental flexibility (which is directly involved with

creativity) (Diamond, 2013). From these, even higher order executive functions are developed, such as reasoning, problem solving, and planning (Collins & Koechlin, 2012; Lunt et al., 2012).

It has been shown that mentally fatigued subjects have decreased levels of selective attention (Holtzer et al., 2011; van der Linden et al., 2003a), sustained attention (Dorrian et al., 2007; Langner et al., 2010; Lim et al., 2010), goal-directed attention (Boksem et al., 2005), alternating attention (van der Linden et al., 2003b), divided attention (van der Linden & Eling, 2006), response inhibition (Kato et al., 2009), planning (Lorist et al., 2000; Lorist, 2008), and novelty processing (Massar et al., 2010). Inhibitory control seems to be more susceptible to mental fatigue than other executive functions (Tanaka et al., 2012). Indeed, even though sustained attention and working memory have not been altered following a prolonged demanding cognitive task, response inhibition assessed during a Stroop task have been significantly impaired (Tanaka et al., 2012).

Many studies have also shown that a variety of real life situations are associated with cognitive performance impairments due to mental fatigue, such as work and school (Ackerman, 2011). It has been demonstrated that college students can make more errors during a memory recognition task after a day of mentally fatiguing activities (Schellekens et al., 2000). Moreover, there is evidence that performance decrements during work can be due to overtime work hours in different occupations (Baker et al., 1994; Landrigan et al., 2004; Lockley et al., 2007). Specifically, it has been found that medical interns who work greater than 24 hours are more involved in motor vehicle accidents (Lockley et al., 2007) and they are five times more likely to make serious diagnostic errors compared with their colleagues whose shifts lasted approximately 16 hours (Landrigan et al., 2004).

These results would lead to think that mental fatigue is the direct product of a continuous, prolonged period of demanding tasks, and that the longer the tasks, the more the performance would decrease (Borragán et al., 2017). However, there is evidence that mental fatigue does not always impair performance. The explanation to this might be associated with the rewards individuals would expect from a specific task. It has been demonstrated that when rewards related to a specific task are perceived as

high (e.g. high salary, appreciation by peers), working for protracted time does not induce fatigue (Siegrist, 1996; Van Der Hulst & Geurts, 2001). On the contrary, short duration tasks, which require high levels of effort and attention can cause very quick significant performance decrement (Ackerman, 2011). Boksem and Tops in their review have explained mental fatigue as the consequence of a cost and benefits subconscious analysis on whether to spend or preserve energy (Boksem & Tops, 2008). If costs are relatively low and benefits relatively high, such as in the case of long-/short-term rewards, intrinsic motivating tasks (e.g. when the task is fun) or avoidance of negative consequences, then individuals would spend more effort on a specific task (Boksem & Tops, 2008). However, when the effort is perceived too high and outweigh these potential benefits, as often happens during prolonged tasks, the result is a decrement in motivation and a consequent drive to abandon behaviour (Boksem & Tops, 2008).

Nonetheless it is well established that people adopt different individual strategies during mental fatigue-related tasks (Ackerman et al., 2010). Individual differences would result in overall increased, decreased or no altered levels of performance over time across the entire task depending on the proportion of subjects who have adopted the same strategies (Ackerman et al., 2010; Desmond et al., 2012). Future studies need to be conducted in order to better understand both general and individual strategies implicated in mental fatigue and cognitive behavioural performance.

2.5 Effects of mental fatigue on physical performance

It has been demonstrated that mental fatigue does not seem to have negative effects on high-intensity anaerobic exercise (Budini et al., 2014; Duncan et al., 2015; Martin et al., 2015; Pageaux et al., 2013; Pageaux et al., 2015). In particular, the majority of the studies have found no impairments in maximal voluntary contraction (MVC) of the knee extensor muscles (Budini et al., 2014; Martin et al., 2015; Pageaux et al., 2013; Pageaux et al., 2015) and in MVC torque (Martin et al., 2015; Pageaux et al., 2013; Pageaux et al., 2015) following a mentally-fatiguing task. Moreover, mean torque, peak torque, time to half peak torque, time to peak torque and peak torque slope during the

MVC did not reveal any significant change (Martin et al., 2015). However, a significantly reduced MVC during a leg extension has been found following a 100-min mentally-demanding task (Budini et al., 2014). From a sport-specific anaerobic performance perspective, three studies have suggested no effects of mental fatigue on countermovement jump (Martin et al., 2015), on mean cycling power during Wingate tests (Duncan et al., 2015) and on high intensity running performance (Smith et al., 2015), respectively.

In addition to that, no physiological and perceptual changes have also been found. Heart rate, lactate, peripheral variables correlated to the neuromuscular function, such as peak twitch and time to peak twitch, and central parameters, such as the voluntary activation level, have not been affected by mental fatigue (Duncan et al., 2015; Pageaux et al., 2013; Pageaux et al., 2015). Changes in RPE, motivation and subjective workload have not been reported either (Duncan et al., 2015; Martin et al., 2015; Pageaux et al., 2013; Pageaux et al., 2015).

2.6 Effects of mental fatigue on endurance performance

Endurance performance has been defined as any whole-body, dynamic exercise performance lasting for 75 s or longer that requires continuous effort (McCormick et al., 2015). As mentioned previously in this Chapter, Professor Mosso was the first one who reported in his seminal book that mental fatigue had a negative impact on muscle endurance (Mosso, 1891). Nevertheless, his observation has not been resumed by any researcher for more than a century. It is only with Marcora and colleagues that mental fatigue takes on importance in the field of sport, in particular in endurance exercise performance. For the first time ever, the effect of mental fatigue on endurance exercise performance in humans has been investigated using a proper experimentally controlled approach (Marcora et al., 2009). The findings have provided evidence that 90 min of mentally demanding tasks impairs subsequent endurance exercise tolerance by 15% during a time to exhaustion cycling test at 80% of the peak power output and that this

impairment seems to be caused by higher perception of effort rather than by any cardiorespiratory and muscular-energetic mechanisms (Marcora et al., 2009).

Though still limited, there is a growing number of studies in the literature investigating mental fatigue in endurance exercise performance (Van Cutsem et al., 2017b). Even though the protocols used and the outcome measures of performance vary, the experiments conducted so far confirm a moderate negative effect of mental fatigue on endurance exercise performance in trained, physically active, healthy populations and in normal ambient conditions (Brownsberger et al., 2013; MacMahon et al., 2014; Marcora et al., 2009; Martin et al., 2015; Pageaux et al., 2014; Pageaux et al., 2013; Smith et al., 2016, 2015). Specifically, these studies have shown that the use of prolonged cognitively demanding tasks (i.e. between 30 and 90-min duration), such as the AX-CPT and the Stroop colour-word task, prior to endurance exercise is detrimental to its performance.

The most popular protocols used to measure endurance exercise performance in mental fatigue research are mainly time to exhaustion or time trial tests (Pageaux & Lepers, 2016) during cycling (Brownsberger et al., 2013; Marcora et al., 2009; Martin et al., 2015; Smith et al., 2016; Van Cutsem et al., 2017a), running (MacMahon et al., 2014; Pageaux et al., 2014; Smith et al., 2016) and swimming (Penna et al., 2018). Most of these experiments have been conducted in standardised laboratories (Brownsberger et al., 2013; Marcora et al., 2009; Martin et al., 2016, 2015; Pageaux et al., 2014; Pageaux, et al., 2013; Smith et al., 2015; Van Cutsem et al., 2017a) and only a few of them have been field-based (MacMahon et al., 2014; Penna et al., 2018; Smith et al., 2016; Veness et al., 2017).

It has been demonstrated that mental fatigue impairs endurance running performance by 2-5% in self-paced running distance time-trials (MacMahon et al., 2014; Pageaux et al., 2014). Moreover, mental fatigue seems to have a detrimental effect on intermittent running performance with a 2% decrease in overall distance covered and a 3% decrease in distance covered at low intensity (Smith et al., 2015). The effect of mental fatigue has also been investigated on a Yo-Yo intermittent recovery test (level 1) both in football (Smith et al., 2016; Veness et al., 2017) and cricket players

(Veness et al., 2017), where significant decrements in the distance covered have been found.

The effects of mental fatigue on endurance cycling performance have more conflicting results. Indeed, whereas (Brownsberger et al., 2013) have shown that subjects in the mental fatigue condition have had greater self-reported feelings of fatigue immediately before two different RPE-based 10-min time trials and produced less work (16% and 8%) than in the control condition, (Pageaux et al., 2015) have not found any performance decrement due to mental fatigue on a 6-min fixed-resistance cycling protocol. Moreover, similar results have been found among professional cyclists, who possibly have greater resistance to the negative effects of mental fatigue compared to recreational cyclists (Martin et al., 2016) and in the heat, where the brain is perhaps already under stress due to the extreme environmental conditions (Van Cutsem et al., 2017a). Further studies need to be conducted in order to confirm these first findings.

Most of the experimental trials conducted on endurance exercise performance so far have mainly assessed subjective and behavioural aspects, with a consequent limitation in the quantification of mental fatigue. Marcora and colleagues have speculated that greater subjective fatigue and/or declines in cognitive performance would show the presence of mental fatigue (Marcora et al., 2009). However, the presence of these two markers has been found only in few studies (Brownsberger et al., 2013; MacMahon et al., 2014; Marcora et al., 2009; Pageaux et al., 2013; Smith et al., 2016, 2015), suggesting that they might not be enough to identify whether or not mental fatigue has been induced. The addition of neurophysiological measurements might be essential, however clear markers of fatigue need to be established first.

Another important aspect that requires further investigation is the length of the tasks used to induce mental fatigue. It has been shown that vigilance impairments (Nuechterlein et al., 1983) as well as increments in subjective fatigue (Smith et al., 2016) seem to occur after 20-30 minutes of uninterrupted mentally-fatiguing task and that this seems to be task-difficulty independent (Hagger et al., 2016). However, future research is essential to better understand the role of task duration on mental fatigue and

to identify the potential neurobiological changes occurring at this cut-off time. Moreover, potential variability between individuals should also be considered.

To the best of my knowledge only two mental fatigue studies on endurance exercise performance have measured brain activity through the use of EEG to assess electrocortical activity in the prefrontal cortex (Brownsberger et al., 2013; Van Cutsem et al., 2017a). In particular, Brownsberger and his research group have demonstrated an associated increase in beta-band activity (dominant EEG band during a normal wakefulness state) in the prefrontal lobe during and after a mentally-fatiguing task compared with a control task (Brownsberger et al., 2013). Since increments in beta-band activity are correlated with higher alertness and arousal these results might be explained in terms of greater attention, information processing and cognitive engagement, indicating the presence of potential compensatory mechanisms to sustain performance in mental fatigue conditions (Wang et al., 2016), although these findings do not guarantee the presence of mental fatigue. No increments in the alpha-band activity (EEG band mainly associated with relaxation and when eyes are closed) has been observed by the same authors (Brownsberger et al., 2013).

On the other hand a significant increase in the alpha-band activity has been found in the other study conducted by Van Cutsem and colleagues (Van Cutsem et al., 2017a), which would confirm a potential EEG power shift towards lower-frequency bands during a mental fatigue state (Wascher et al., 2014). Further studies on electrocortical activity associated with mental fatigue and endurance exercise performance are crucial in order to have a better understanding of the neurophysiological mechanisms underneath mental fatigue and give a further contribution to what has already been found from a subjective and behavioral perspective.

2.7 Neurobiological mechanisms of mental fatigue

Whereas behavioral and subjective elements of mental fatigue have been widely investigated, less is known regarding neurobiological mechanisms underpinning this state (Wang et al., 2016). Modern cognitive neuroscience has established that brain

activity is a sensitive measure of mental fatigue (Ackerman, 2011). However, evaluating time-changing neurophysiological signals is one of the main issues when mental fatigue is involved. These time-associated variations may explain functional impairments of those systems involved with task performance, engagement of effort-/fatigue-based monitoring systems and engagement of compensatory systems aimed at preserving performance during mentally-fatiguing tasks (Wang et al., 2016).

Many studies have investigated the effects of mental fatigue on brain activity throughout an examination of the changes in the EEG from a vigilant status to a fatigued status, showing general greater power in alpha and theta bands in fatigued states compared to vigilant states (Campagne et al., 2004; Eoh et al., 2005; Pal et al., 2008; Papadelis et al., 2006; Trejo et al., 2015). In particular, most of the research has focused the attention on theta and alpha amplitude and power variations related to mental fatigue (Akerstedt et al., 1991; Caldwell et al., 2002; Eoh et al., 2005; Strijkstra et al., 2003). Although some studies have demonstrated contrasting findings in the activity of theta (Akerstedt et al., 1991; Eoh et al., 2005) and alpha waves (Caldwell et al., 2002; Strijkstra et al., 2003), most of the investigations have shown that increasing in alpha and theta wave activity are positively associated with mental fatigue (Cajochen et al., 1995; Campagne et al., 2004; Craig et al., 2012; Lal & Craig, 2002; Macchi et al., 2002; Pal et al., 2008; Umemoto et al., 2019). In particular, it has been found that decreased levels of vigilance and performance assessed in 46 males during a simulated driving task were associated with higher theta and alpha wave activity (Campagne et al., 2004) and that this increased brain wave activity may occur over the entire cortex (Craig et al., 2012). Interestingly, there is evidence that fatigue-related changes in theta and alpha activity might occur before any fatigue-related performance decline (Gevins et al., 1990), suggesting that increases in these specific band waves may be a sensitive indicator of fatigue and that changes in EEG might accurately predict performance decrements prior the occurrence of potential errors or accidents. Less is known about delta and beta waves. In their study, Craig and colleagues have found no significant changes in delta activity, but a considerable increase in beta waves (Craig et al., 2012). Interestingly, increments in fast waves have been translated as the brain attempting to avoid fatigue. However, as suggested by the heterogeneous findings, the status of delta

and beta wave activity associated with fatigue is still unclear (Akerstedt et al., 1991; Caldwell et al., 2002; Eoh et al., 2005; Lal & Craig, 2002; Papadelis et al., 2006; Tanaka et al., 1997) and further studies need to be conducted in order to better understand the brain activity associated with fatigue.

Several studies have investigated neurophysiological mechanisms associated with mentally-demanding task performance, such as lapse of attention (Hanslmayr et al., 2007; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Mathewson et al., 2009; Padilla et al., 2006) and decreased cognitive control neural patterns (Kok et al., 2004; O'Connell et al., 2009; Ridderinkhof et al., 2003; Schmajuk et al., 2006) by assessing ERPs (Bode & Stahl, 2014; Hajcak et al., 2005; Masaki et al., 2012; Ora et al., 2015; Padilla et al., 2006; Ridderinkhof et al., 2003). Decrements in sustained attention, have been associated with decrements in the P3 amplitude, which is considered a physiological indicator of task engagement (Hopstaken et al., 2015; Murphy et al., 2011; Nieuwenhuis et al., 2011), in the centro-parietal region (Hanslmayr et al., 2007; Jensen & Mazaheri, 2010; Mathewson et al., 2009; Padilla et al., 2006), whereas reductions in N2 amplitude have been linked to impaired cognitive control (Falkenstein, 2006; Kok et al., 2004; O'Connell et al., 2009) and with time on task (Boksem et al., 2006; Lorist et al., 2005). However, contrasting data have been found, showing also an association between N2 amplitude increments and cognitive control impairments (Kok, 1990; Pinal et al., 2015).

It has been demonstrated that mental fatigue is associated with compromised error monitoring (Boksem et al., 2006; Lorist et al., 2005). Decrements in ERNs, which are mainly distributed in the fronto-central region, have been shown to explain function attenuations in the anterior cingulate cortex (ACC) (Carter et al., 1998; Kiehl et al., 2000; Mathalon et al., 2003; Miltner et al., 2003), a fundamental area for task performance monitoring (Gehring & Knight, 2000; Lorist et al., 2005; Luu et al., 2000; Ullsperger & von Cramon, 2003). ACC indeed, is believed to identify error-related/conflicting responses and to warn the need of a compensatory systems activation, aimed at minimising performance impairments (Botvinick & Braver, 2015; Botvinick et al., 2001; Cohen et al., 2000; Holroyd & Umemoto, 2016; Kerns et al., 2004; Shenhav et al., 2017; Vassena et al., 2017). This monitoring function by ACC in

turn seems to depend on the mesencephalic dopamine system (de Bruijn et al., 2004; Holroyd & Coles, 2002), which extends to the cortex and the striatum (Holroyd & Coles, 2002). Therefore, reductions in the mesencephalic dopaminergic projections to ACC due to prolonged demanding cognitive activity might result in performance monitoring impairments and, as a consequence, in performance adjustment deficiencies (Lorist et al., 2005).

Despite a growing number of studies, the neurophysiological mechanisms involved in sustaining cognitive effort are not well-understood yet (Shenhav et al., 2017). Prolonged cognitive effort generally causes mental fatigue. However, it has been demonstrated that cognitive performance impairments can be counterbalanced when motivational incentives are given (Boksem et al., 2006; Boksem & Tops, 2008; Hockey, 2011; Hopstaken et al., 2015). It has been proposed that mental fatigue may derive from the analyses of cost and benefits (incentives/rewards) to expend or to conserve energy during a certain task and this would happen subconsciously (Boksem et al., 2006; Botvinick & Braver, 2015; Umemoto et al., 2019; Westbrook & Braver, 2015). Such cost-reward processes seem to be regulated by the brain through an elaborate system that warns about the rewarding value of events and actions (Gendolla et al., 2012; Schultz, 2002). It has been established that midbrain dopamine neurons (Schultz, 2009) and the prefrontal cortex (Kringelbach, 2005; Walter et al., 2005) play an important role in the estimation of the stimuli reward value. In particular, the prefrontal cortex would be involved in the generation and regulation of cognitive control processes, which are needed for complex goal-directed and optimal-choice behaviour (Walton et al., 2007). Projections of brain dopamine and acetylcholine neurons, which are connected with brain structures involved in reward processing, are capable of sustaining and activating the prefrontal cortex systems involved in attention and cognitive control (Christakou et al., 2004; Sarter et al., 2006; Sarter & Parikh, 2005) when motivation to maintain performance is high. It has been suggested that changes in brain dopamine neurons activity in reward processing-related structures due to detrimental challenges (e.g. prolonged task performance), may weaken the acetylcholine projections activity to the cortex and lead to reduced attentional performance and cognitive control (Sarter et al., 2006). Since impairment in attention and cognitive control processes have been

observed in fatigued subjects, dopamine and acetylcholine neurons projections to prefrontal cortex may be fundamental to the changes in performance due to mental fatigue.

Mental fatigue and exercise-mediated mechanisms

The mechanisms that influence the capacity to sustain endurance exercise have been studied for over a century (McKenna & Hargreaves, 2008). Research has always focused its interest on the physiological aspects related to physical fatigue such as the cardiovascular, respiratory, metabolic and neuromuscular responses (Allen et al., 2008; Amann & Calbet, 2008; McKenna & Hargreaves, 2008; Secher et al., 2008). However, the effects and the associated mechanisms underlying mental fatigue on endurance exercise performance have only recently been investigated.

It has been demonstrated that mental fatigue does not alter cardiorespiratory responses during subsequent endurance exercise performance. In particular, no changes in oxygen uptake, stroke volume, cardiac output, blood pressure and heart rate have been found (Marcora et al., 2009). Moreover, a study conducted on the neuromuscular function of the knee extensors have also indicated no changes induced by mental fatigue in maximal voluntary activation level, twitch and doublet parameters and electromyography (EMG) measurements, concluding that mental fatigue seems not to affect exercise-associated peripheral and central fatigue during a six-min fixed-intensity cycling task (Pageaux et al., 2015). Conversely, the same experiment has found an association between mental fatigue and higher EMG root mean square of the vastus lateralis (Pageaux et al., 2015). These findings might indirectly suggest that changes in motor control due to mental fatigue may increase the activity of the central command in order to maintain the same power output. However, further studies are needed to confirm this assumption.

Other studies have also reported no effects of mental fatigue on central fatigue (Martin et al., 2015; Pageaux et al., 2013; Rozand et al., 2014). However, in contrast with these results, decrements in MVC have been found following a prolonged mentally-fatiguing task, suggesting that mental fatigue might have reduced the

synchronized activity of the motor cortex and the spinal motoneuron pool (i.e. cortico-muscular coupling) (Budini et al., 2014). Therefore, although the overall findings indicate that mental fatigue does not seem to affect any cardiorespiratory and peripheral and central neuromuscular parameters, future investigations on muscle fiber recruitment are crucial.

Mental fatigue and perception of effort

Several studies have found an association between endurance exercise performance decrements due to mental fatigue and higher perception of effort (Brownsberger et al., 2013; MacMahon et al., 2014; Marcora et al., 2009; Pageaux et al., 2014; Pageaux et al. 2013; Pageaux et al., 2015; Smith et al., 2016, 2015). These findings have suggested that mental-fatigue-induced impairments in endurance exercise performance might be directly mediated by higher perception of effort during exercise.

Perception of effort can be defined as the 'conscious sensation of how hard, heavy, and strenuous, a physical task is' (Van Cutsem et al., 2017b). Two different theories are currently available in the literature, aiming at explaining the generation of perception of effort: the afferent feedback model, based on feedback coming from the muscles and other peripheral systems (Noble, 1996) and the corollary discharge model, based on neural signals coming from the premotor/motor cortical areas (i.e. corollary discharges) to sensory areas of the brain and linked to the central motor command (i.e. motor-related cortical activity) (Jürgens, 1984; Marcora, 2009; Zenon et al., 2015).

Whereas afferent feedback seems not to be altered by mental fatigue, as no changes in physiological responses to exercise (which in turn are supposed to provide afferent feedback to the brain) have been found, recent studies have provided evidence in support of the corollary discharge model (de Morree et al., 2014; Pageaux & Gaveau, 2016; Sharples et al., 2016; Zenon et al., 2015). From this perspective, increments in perception of effort during exercise might be explained through an increased activity of the central motor command and consequently its corollary discharges (i.e. sensory signals for perception of effort) and/or by possible neural processing changes in the sensory areas (Goldstein & Learning, 2007). However, these potential variations have

not directly been measured yet and can only be supported by indirect findings (Balagué et al., 2015; Lohse & Sherwood, 2011). Future studies on the cortical substrates of perception of effort are necessarily required.

2.8 Cognitive training to counteract mental fatigue

In psychology and neuroscience, different cognitive training strategies have been widely studied to improve several executive functions, such as inhibitory control (Spierer et al., 2013), working memory (Melby-Lervåg & Hulme, 2013) and attention (Tang & Posner, 2009). Cognitive training consists in the repetition of prolonged demanding cognitive tasks (e.g. Flanker, Stroop and Go-No-Go tasks), during which several cognitive components are involved (Aron, 2011). It has been demonstrated that this type of training can induce both behavioural and neurobiological changes of different executive functions. In particular, training interventions on working memory or planning skills have been evidenced to improve performance (Dahlin et al., 2008; Jaeggi et al., 2008; Li et al., 2008; von Bastian et al., 2013) and to induce brain activity changes in the front-parietal or medial-frontal areas (Beauchamp et al., 2003; Dahlin et al., 2008; Klingberg, 2010; Olesen et al., 2004). However, whether or not this type of cognitive training can have prolonged effects and counteract behavioural and neurobiological impairments induced by mental fatigue (in other words, increase resilience to mental fatigue), still remains unknown.

To the best of my knowledge, the only experimental evidence currently present in the literature testing the effects of brain training interventions to increase resistance to mental fatigue, comes from the field of sports and exercise sciences. Marcora and colleagues have tested for the first time the efficacy of a new training method, called Brain Endurance Training (BET), aimed at inducing chronic reductions in fatigue during endurance exercise by using acute mental fatigue as a training stimulus (Marcora et al., 2015). BET consists in systematic repetitions of prolonged and demanding cognitive tasks used to increase resistance to fatigue and improve endurance performance. Participants in this study were randomly assigned into two groups (BET

and control group). Both groups were trained on a cycle ergometer for 60 min at 65% of their $\dot{V}O_{2max}$ (three times per week for twelve weeks). Whilst cycling, the BET group was required to perform a cognitive task (AX-CPT task) on a computer screen. The results have revealed that the inclusion of BET into a 12-week typical aerobic training program significantly reduces RPE and increases endurance exercise performance (BET group +126% vs control group +42%) during a cycling TTE in healthy male adults.

The rationale behind this result possibly relies on the crucial role that perception of effort seems to play as one of the main limiting factors of endurance exercise performance (Marcora & Staiano, 2010; Marcora et al., 2008). It has been demonstrated that perception of effort is strongly associated with the activity of certain areas of the brain, such as the ACC (Williamson et al., 2001, 2002) and the supplementary motor area (e.g. a physical task is perceived less effortful if such areas are disrupted) (Zenon et al., 2015). These cortical areas are also known to be highly activated during prolonged and demanding cognitive tasks (Boksem & Tops, 2008). Therefore, performing this kind of cognitive tasks in combination with endurance physical tasks for several weeks, might increase the workload of each training session at the brain level, and induce structural and functional adaptations (i.e. brain plasticity (Kolb & Whishaw, 1998)) in the above mentioned cortical areas (and most probably in other relevant cortical areas). BET might have induced chronic reductions in the activity of these areas, with consequent decrements in perception of effort and improvements in endurance exercise performance during a cycling TTE (Marcora et al., 2015). However, further research needs to be conducted in order to better understand the neurobiological mechanisms underlying BET and the role played by perception of effort in this context, as well as its efficacy in other populations, such as females, elite endurance athletes and sedentary individuals.

2.9 Summary and conclusions

Mental fatigue is a very common phenomenon in our everyday modern life which is defined as a psychobiological state caused by sustained cognitive activity. Mental fatigue can be mostly assessed in terms of subjective feelings, performance decrement

and physiological manifestations. Whereas the effects of mental fatigue on cognitive performance have been widely studied and actual findings suggest behavioural performance impairments associated with specific neurophysiological mechanisms, the effects of mental fatigue on endurance exercise performance have only recently been investigated. The main results indicate a decrease in endurance exercise performance caused by mental fatigue, which seems to be associated with higher ratings of perceived exertion rather than with any endurance-performance-related physiological parameters alterations. A new training strategy (BET) has been recently introduced with the purpose of increasing resistance to the negative effects of mental fatigue on perception of effort and endurance exercise performance.

The current literature presents some gaps and further studies are required to better understand the effects of mental fatigue on endurance exercise performance as well as to explore in more depth the role of BET and the neurobiological mechanisms underneath it. In the next chapters I try to cover some of the gaps, by testing the effects of mental fatigue in a more ecologically valid context and during a longer-term endurance exercise task, and by verifying whether the use of BET alone has positive implications on endurance exercise performance.

Chapter 3

Sleep Deprivation:
Effects, Mechanisms and Countermeasures

3.1 Introduction

Mental fatigue can be significantly influenced by several state variables and sleep deprivation (or lack of sleep) is certainly one of them (Ackerman, 2011). As in the case of mental fatigue, sleep deprivation is a very complex and multifaceted topic still not adequately understood.

In this chapter the up-to-date literature of sleep deprivation in healthy population has been reviewed. In the first section, after having defined what sleep deprivation is, the literature on the effects of sleep deprivation on both cognitive (only a short literature review though, as it is not the main variable of interest in this thesis) and endurance exercise performance has been reviewed. A short literature on the effects of sleep deprivation on other types of physical performance has also been included. The main neurobiological mechanisms underlying sleep deprivation have then been identified and the countermeasures available to minimise its negative effects described. Finally, in the last section, the attention has been focused on the role that recovery sleep plays in overcoming potential negative effects induced by sleep deprivation on both cognitive and endurance exercise performance.

3.2 What is sleep deprivation?

The terms mental fatigue and sleepiness are often interchangeable and used as synonyms in the scientific community. However, these are two different factors that can

be distinguished both conceptually and experimentally (Ackerman, 2011). The official definitions of mental fatigue and sleepiness are discrete and they do not overlap. Indeed, although they both contribute to performance impairments, sleepiness entails sleep deprivation/lack of sleep, whereas mental fatigue implies effort (Ackerman, 2011).

Sleep deprivation can be defined as a continuous and prolonged period of lack of sleep (i.e. at least 24 hours) and it is generally differentiated from sleep restriction, defined as a partial lack of sleep (i.e. sleeping less hours per night) and sleep fragmentation, which in turn is described as an interval sleep (Boonstra et al., 2007; Jones & Harrison, 2001). Although different, these forms of sleep debt seem to have similar effects on sleepiness and cognitive performance (Bonnet & Arand, 2003).

It has been shown that sleep deprivation is associated with several pathologies, which can be grouped into direct sleep disorders, such as primary insomnia (Baglioni et al., 2010) and obstructive sleep apnoea (Lévy et al., 2015) and indirect sleep disorders, which implied lack of sleep, such as depression (Murphy & Peterson, 2015), chronic pain (Nijs et al., 2018) and restless-legs syndrome (Wetter et al., 1998). However, sleep deprivation can also be induced voluntarily, 'fighting' against the urge to sleep, for instance during long travelling across time zones (Sack et al., 2007) and night work shifts (Kecklund & Axelsson, 2016).

3.3 Assessing sleep deprivation

Sleepiness is a complex condition difficult to measure (Cluydts et al., 2002). As a result of its multidimensionality, many tools have been developed to assess it. The instruments used to measure sleepiness can be grouped into three main categories: 1) subjective measures of sleepiness through the use of rating scales; 2) objective measures of sleepiness through the use of cognitive tests (i.e. behavioural assessment); 3) electrophysiological measures.

Subjective ratings of sleepiness

Subjective sleepiness is mainly assessed by using rating scales (Cluydts et al., 2002). Sleepiness scales themselves can be divided into two different groups. The first group includes those scales which assess an acute sleepiness state, such as the Stanford Sleepiness Scale (Hoddes et al., 1973), the Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) and Visual Analogue Scales (Wewers & Lowe, 1990). The second group comprises trait scales, which assess a more general level of sleepiness. The Epworth Sleepiness Scale (Johns, 1991) and the Sleep Wake Activity Inventory (Rosenthal et al., 1993) are the most used ones, measuring subjective sleep propensity and multidimensional aspects of sleepiness, respectively.

Finally, sleepiness can also be assessed through general measurements of mood (e.g. POMS (McNair et al., 1992) or BRUMS (Terry et al., 2003)) and quality of life instruments, such as the Vitality subscale of the Medical Outcomes Study Short-Form (SF-36) (Ware & Sherbourne, 1992).

Sleepiness and cognitive performance

The main measures used to assess sleepiness from an objective behavioural perspective are the ones used for evaluating mental fatigue (see Chapter 2). In particular, it has been shown that the PVT (Dorrian et al., 2005) is the most sensitive cognitive test to monitor sleepiness related-performance decrements (Balkin et al., 2004). 10-Choice Reaction Time (Thorne et al., 1985), Serial Addition/Subtraction Task (Thorne et al., 1985) and Wilkinson 4-Choice Reaction Time (Wilkinson & Houghton, 1975) are also other sensitive tasks used to detect sleepiness-induced performance impairments (Balkin et al., 2004).

Electrophysiological Measures

Multiple sleep latency test and Maintenance of wakefulness test

The Multiple Sleep Latency Test is currently the gold standard measure for sleepiness and one of the first and most commonly used tools (Carskadon et al., 1986). This test is sensitive to sleep restriction, sleep deprivation and sleep extension (Janjua et al., 2003; Punjabi et al., 2003). It is a scientific test performed the day after an overnight polysomnogram and it consists of 4–5 nap sessions (every 2 hours across the entire day) during which individuals are required to sleep in a quiet darkened room for 20-30 minutes and electrophysiological and electrooculogram measurements are recorded (Carskadon et al., 1986). This test allows to assess levels of sleep latency and sleep propensity (Thorpy et al., 1992) with high reliability in both healthy (Zwyghuizen-Doorenbos et al., 1988) and clinical populations (Drake et al., 2000).

The Maintenance of Wakefulness Test is another polysomnographic validated test (Mitler et al., 1982) assessing the ability to maintain wakefulness and providing an objective measure of sleep propensity. Individuals, in this case, are required to attend the same 4-5 sessions, but not to fall asleep for a specific period of time (generally 20-40 minutes).

Pupillometry

Pupillometry consists in measuring pupil diameter by using an infrared pupillometer while the individual is seated in a dark room and asked to stay awake while fixating on a red target for a period of 15 min. Several variables related to this measurement are valid indicators of sleepiness (McLaren et al., 2002).

Alpha Attenuation Test (AAT)

The AAT is a validated test used to assess objective decrements in alertness due to sleep deprivation (Stampi et al., 1995). Individuals are generally asked to sit down in a quiet and illuminated room, to remain relaxed but awake (Stampi et al., 1995) and to look at a fixation point on a computer screen in front of them (Zunini et al., 2013). The test lasts a total of twelve minutes, and consists to alternate two-minutes eyes closed with two-minutes eyes opened. The AAT measures EEG power alterations in the alpha-band frequency, which are expected to decrease when eyes are closed and increase when eyes are open in sleepiness conditions.

3.4 Effects of sleep deprivation on cognitive performance

The amount of experimental literature on sleep deprivation is extensive and can be generally grouped into three levels, based on how sleep deprivation has been observed: macro-level, meso-level and micro-level. Conducting research at a macro-level refers to study sleep deprivation from a behavioural perspective, at a meso-level to investigate the neural activity underlying sleep deprivation and at a micro-level to study all those molecular and cellular processes occurring due to sleep deprivation (Boonstra et al., 2007).

From a behavioural perspective, it has been widely recognised that sleep loss has numerous negative consequences. It is very difficult, indeed, to determine what is not affected by sleep deprivation (Dinges et al., 1997; Krueger, 1989; Pilcher & Huffcutt, 1996). Sleep deprivation results in overall mood and emotional functioning changes, such as increased levels of subjective fatigue, sleepiness, confusion, stress and depression (Dinges et al., 1997) which are associated with decreased levels of vigour (Martin et al., 1986; Meney et al., 1998) and liveliness (Scott et al., 2006; Skein et al., 2011). Sleep deprivation can even cause hallucinations (Kahn-Greene et al., 2007) and in extreme cases, such as during prolonged sleep deprivation experimental trials on animals, has also led to death (Everson et al., 1989).

Among all the cognitive capabilities vigilance and sustained attention seem to be the most consistently influenced ones (Doran et al., 2001; Dorrian et al., 2005; Goel et al., 2013; Lim & Dinges, 2008, 2010; Lowe et al., 2017). Testing sustained attention, indeed, has become one of the most useful ways for assessing behaviour during sleep deprivation, which is translated into significant impairments in reaction time, response accuracy and increments in performance variability (Belenky et al., 2003; Dinges et al., 1997; Goel et al., 2009; Jewett et al., 1999; Karakorpi et al., 2006; Samkoff & Jacques, 1991). In general, it has been shown that several nights of sleep restriction induce the same level of impairment in vigilance performance as after one or more consecutive nights of sleep deprivation (Van Dongen et al., 2003a). Significant increments in simple reaction time have also been found following 1 h of sleep restriction for 2 nights (Bonnet, 1985) and 4 h of sleep restriction for 5 nights (Axelsson et al., 2008), suggesting that cognitive performance can be compromised by even a few hours of sleep restriction.

Sleep deprivation have also detrimental effects on several cognitive functions (Axelsson et al., 2008; Belenky et al., 2003; Dinges & Kribbs, 1991; Dorrian & Dinges, 2005; Durmer & Dinges, 2005), such as working memory (Chee et al., 2006; Karakorpi et al., 2006), logical reasoning, coding and decision making (Harrison & Horne, 2000) and filtering efficiency (Drummond et al., 2012). Decrements in performance have also been found on measures of verbal fluency, creativity and planning skills (Jones & Harrison, 2001; Nilsson et al., 2005) as well as learning and developing new skills (Gosselin et al., 2005; Wimmer et al., 1992). However, contrasting findings have been reported in relation to sleep restriction and decision making and short term memory performance. Indeed, no changes in decision making skills have been shown after 5 nights of sleep restriction (Khazaie et al., 2010) and in short term working memory following only 4 h of sleep (Drummond et al., 2012). These findings indicate that decision making and short term working memory might not always be influenced by acute sleep restriction.

The effects of sleep deprivation on cognitive performance have also been investigated among athletes and during exercise (Fullagar et al., 2015). In particular, increments in simple reaction time and reductions in attention have been found in

handball goalkeepers after 4-5 hours of sleep restriction (Jarraya et al., 2014). However, memory of how a motor skill is executed seems not to be affected following sleep restriction (Drummond et al., 2012). Although sleep deprivation unequivocally impairs cognitive performance and mood responses in relation to exercise (Angus et al., 1985; Martin et al., 1986; Meney et al., 1998; Scott et al., 2006; Skein et al., 2011), a limited number of studies are available in the literature regarding the effects of sleep deprivation on cognitive functions during sport events (Fullagar et al., 2015). It has been found that prolonged sleep deprivation has detrimental effects on cognitive performance during long-haul yacht racing (Hurdiel et al., 2014), whereas no effects have been shown on modified decision making Stroop task performance during 96-125 h of adventure racing following 100 hours of sleep deprivation (Lucas et al., 2009). Further investigation is crucial to better understand the role played by sleep deprivation and sleep restriction on cognitive functions and mood responses in athletes.

Whereas rewards and high levels of motivation (i.e. the will to spend effort in order to achieve a certain goal (Chong et al., 2016)) in general can enhance a task performance (Esterman et al., 2014; Massar et al., 2016, 2019), it has been suggested that lack of sleep may reduce the motivation to perform a certain task, with the consequence of investing less effort and disengaging from that task (Lim & Dinges, 2008; Massar et al., 2019). In the context of sleep deprivation, it has been shown a preference to perform less effortful tasks and a higher devaluation of monetary rewards when sleep-deprived (Engle-Friedman et al., 2003). Moreover, a sleep deprivation state might also lead to withdraw processing resources in case of task-performance rewards not reasonably high (Massar et al., 2019), something very similar to what has been proposed in several theoretical models of performance with mental fatigue (Boksem & Tops, 2008; Hockey, 1997; Kanfer & Ackerman, 1989).

Finally, despite the general negative effects of sleep deprivation on cognitive performance have been well identified, significant variability among individuals has been frequently found. Indeed, several studies have shown individual differences, with some subjects particularly vulnerable and others resilient to the negative effects of sleep deprivation on behavioural cognitive performance (Lim et al., 2007; Rupp et al., 2012; Van Dongen et al., 2004a; Van Dongen et al., 2004b). Although these individual traits

are remarkably stable and it has been demonstrated that they might be genetically determined (Kuna et al., 2012), the reasons behind these behavioural differences among individuals are still unclear and further research needs to be conducted.

3.5 Effects of sleep deprivation on physical performance

In the context of physical performance the results on the effects of sleep restriction and sleep deprivation are still controversial. It has been demonstrated that sleep restriction seems not to effect anaerobic exercise performance, with no changes in mean and peak power output during a Wingate cycling test (Mougin et al., 1996). On the contrary, significant changes in the same performance variables have been found after 4 h of SR (Abedelmalek et al., 2013; Souissi et al., 2013, 2008). The same controversial results have also been observed in studies testing muscle strength and power (Reilly & Hales, 1988; Reilly & Piercy, 1994).

More clear results have been found during the execution of sport-specific skills following SR, with impairments in serving accuracy in tennis players (Reyner & Horne, 2013), decrements in mean score in dart players (Edwards & Waterhouse, 2009), and increased reaction time in handball goalkeepers (Jarraya et al., 2014) suggesting that SR might affect more fine-motor activities than gross-motor ones (Sinnerton & Reilly, 1992).

Similar to SR, the effects of SD on physical performance are heterogeneous and still poorly understood. It has been shown that 30 h of SD have caused slower mean sprint time and voluntary force in team sport athletes (Skein et al., 2011). Likewise, detrimental effects have been found on muscle strength (Bulbulian et al., 1996; Meney et al., 1998; Takeuchi et al., 1985), power (Souissi et al., 2003) and speed (How et al., 1994). However, contrasting results have shown no alterations in both isometric and isokinetic strength exercises (Symons et al., 1988), shuttle run scores (Racinais et al., 2004) and grip strength tests (Reilly & George, 1983; Reilly & Walsh, 1981).

From a physiological perspective, no alterations in cardiorespiratory parameters have been observed during anaerobic and muscular strength tests following SR (Mougin et al., 1996; Sinnerton & Reilly, 1992), as well as no difference in blood lactate

concentrations after SD (Souissi et al., 2003). In summary, the effects of SR and SD on anaerobic performance remains unclear, and further research is certainly required.

3.6 Effects of sleep deprivation on endurance performance

While a considerable amount of research has been conducted on the effects of sleep deprivation and sleep restriction on cognitive performance, the number of studies investigating their impact on endurance exercise performance are still limited and the findings controversial (Fullagar et al., 2015; Thun et al., 2015).

Regarding sleep restriction, it has been found that one partially disrupted night of sleep (i.e. 3 h of sleep restriction) does not affect the performance of 7 cyclists during an incremental cycling test to exhaustion (Mougin et al., 1991). The same results have been shown by (Reilly & Deykin, 1983), who have seen no impairments in 8 trained subjects during an incremental running test until exhaustion following three nights of sleep restriction, and by (Mejri et al., 2014), who have found no differences in the total distance covered during a Yo-Yo intermittent recovery test (level one) in 10 Taekwondo players following partial sleep recovery. By contrast, it has been demonstrated that two nights of sleep restriction significantly impair the maximal work rate during a similar incremental cycling test protocol until exhaustion as the one used by Mougin and colleagues (Mougin et al., 2001). In general, sleep restriction seems not to be detrimental for endurance exercise performance. However, these results might be due to the relatively small sample sizes used, which might have contributed to reach not enough statistical power, and/or to a substantial variability on the effects of lack of sleep among the subjects tested. Furthermore, the typology of tests used for these experiments (i.e. incremental test protocols and Yo-Yo intermittent recovery test) is mainly developed to measure cardiorespiratory parameters and maximal aerobic power (directly and indirectly). Consequently, these tests might not be the best for assessing performance.

The effects of sleep deprivation on endurance exercise performance are also controversial (Fullagar et al., 2015). Prolonged sleep deprivation (i.e. 25-50 h of continuous wakefulness) has been shown to induce decrements in endurance exercise

tolerance during both running/walking time to exhaustion tests at fixed intensities (Martin, 1981; Martin & Chen, 1984; Temesi et al., 2013) and during an incremental cycling test (Azboy & Kaygisiz, 2009), although no changes in total work have been found using the same incremental test (Hill et al., 1994). Specifically, it has been found that 36 h and 50 h of sleep deprivation impairs endurance exercise tolerance by 11% (Martin, 1981) and 20% respectively (Martin & Chen, 1984). Moreover, 30 h and 29 h of sleep deprivation has also been found to have detrimental effects on the total distance run during a 30-min self-paced running time-trial (i.e. 2.9% distance decrement) (Oliver et al., 2009), and on the final time of a 5-km self-paced running time-trial (i.e. 4.4% time increment) (Oliver et al., 2015), respectively. Conversely, no performance decrements have been seen during a shuttle run test after 38 h of continuous sleep deprivation (Racinais et al., 2004). There is enough evidence which suggests sleep-deprivation-induced detrimental effects on endurance exercise tolerance, in particular in those activities lasting longer than 30 min. Further research, however, is required in order to better understand the effects of sleep deprivation in other types of endurance exercise activities.

The reasons why sleep deprivation might negatively affect endurance exercise performance are still unclear. Several studies have found limited changes in cardio-respiratory parameters (with longer periods of sleep deprivation more detrimental than acute sleep deprivation (i.e. 24-36 h of sleep loss)), such as heart rate, oxygen uptake, ventilation and respiratory exchange ratio (Azboy & Kaygisiz, 2009; Martin & Haney, 1982; Martin, 1981; Mougin et al., 1989, 1991; Oliver et al., 2009; Plyley et al., 1987) and in thermoregulatory function (Dewasmes et al., 1993; Oliver et al., 2009; Sawka et al., 1984). Different experiments have also shown that decrements in endurance exercise performance might be associated with increments in ratings of perceived exertion during time to exhaustion tests at constant intensities and steady state exercises (Bond et al., 1986; Martin, 1981; Martin & Gaddis, 1981; Symons et al., 1988; Temesi et al., 2013), more specifically at high intensities rather than low intensities (Martin & Gaddis, 1981). Moreover, despite significant decrements in the distance covered during a 30-min self-paced run following 30 h of sleep deprivation, no differences in ratings of perceived exertion have been found (Oliver et al., 2009),

indicating that perception of effort would have been higher if running speeds were equal. In support of these findings (Temesi et al., 2013) have proposed that increased peripheral and central fatigue unlikely explain impairments in endurance exercise performance after sleep deprivation, supporting once again perception of effort as the limiting factor of endurance exercise performance. However, contrasting results have been found (Mejri et al., 2014) and future research is certainly required to better understand what causes decrements in endurance exercise performance following sleep deprivation.

3.7 Neurobiological mechanisms of sleep deprivation

The neurobiological processes underlying sleep are still largely unclear. The balance between wakefulness and sleep, which implies the propensity to fall asleep and to stay awake, is defined as the sleep homeostatic process (Achermann & Borbély, 2017). The sleep homeostatic process is related to the hours of sleep and wake and to potential accumulated lack of sleep (McCauley et al., 2009). This homeostatic system seems to be correlated with higher levels of adenosine in the extracellular space of the forebrain and areas of the cortex during extended wakefulness and with lower levels of adenosine following recovery sleep (Basheer et al., 2000; Murillo-Rodriguez, Blanco-Centurion et al., 2004; Porkka-Heiskanen et al., 2000; Porkka-Heiskanen et al., 1997).

Adenosine is a neuromodulator which has been demonstrated to be involved with several sleep-related mechanisms (Dunwiddie & Masino, 2001). In particular, systemic and intracerebroventricular injections of adenosine have been found to stimulate sleep and decrease wakefulness (Radulovacki et al., 1984) by binding their own receptors (Basheer et al., 2004). Moreover, additional evidence has been given by pharmacological studies on adenosine receptors, showing sleep promotion by agonists (Portas et al., 1997) and wakefulness promotion by antagonists, such as caffeine (Lin et al., 1997).

Wakefulness has been attributed to the activity of different wake-promoting brain areas which in turn use monoaminergic and cholinergic neurotransmitters to do so (Saper et al., 2001). Contrary, the ventrolateral preoptic nucleus brain area seems to be

involved with sleep willingness, by inhibiting certain areas of the brain involved with wake-promotion (e.g. reticular activating system and locus coeruleus) (Fuller et al., 2006). These subcortical brain systems work all together in order to provide a wake state stability and a certain coordination between sleep and alertness. In case of prolonged wakefulness, however, an uncoordinated brain state (i.e. wake state instability) may potentially occur (Van Dongen et al., 2011). This possible but not certain phenomenon might be one of the possible explanations for the sleep-deprivation-induced decrements in cognitive performance (Doran et al., 2001).

Findings from neuroimaging studies have shown that prefrontal and parietal cortex and subcortical regions are subjected to a reduction in activity during sleep deprivation, which further declines during prolonged cognitive tasks (Asplund & Chee, 2013; Drummond et al., 2005; Thomas et al., 2000; Zhu et al., 2018) and partially comes back to wake resting activity following sleep recovery (Wu et al., 2006). Moreover, sleep deprivation seems to negatively interfere with memory consolidation via significantly decreasing the activity of the hippocampus, an essential region implicated in learning (Yoo et al., 2007). EEG experiments have also found a general decline in the alpha-band activity following sleep deprivation and progressive increments in the theta-band activity (Boonstra et al., 2007; Cajochen et al., 1995; Finelli et al., 2000). The combination of these activities have been translated into a prevalence of slow-wave activity, which might offer an index of cortical deactivation and therefore, of sleep willingness (Borbély, 1982; Borbély et al., 1981; Brunner et al., 1993; Cajochen et al., 1995). Furthermore, several studies have also reported the same changes in the EEG activity along the anterior-posterior axis, which might suggest a main local effect of sleep deprivation in the prefrontal areas (Boonstra et al., 2005; Horne, 1993).

Several studies have also investigated neurophysiological mechanisms associated with sleep deprivation by assessing ERPs. Two components, N1 and P3, seems to be mainly associated with sleep deprivation. In particular, reductions in N1 amplitude have been found following sleep fragmentation (Cote et al., 2003) and total sleep deprivation (Corsi-Cabrera et al., 1999) and in relation to auditory (Ferrara et al., 2002), visual (Corsi-Cabrera et al., 1999) and motor responses (Boonstra et al., 2005).

An onset delay and a decreased amplitude of P3 have also been associated with sleep deprivation (Jones & Harrison, 2001) and subsequent cognitive performance impairments during attention-related demanding tasks (Gosselin et al., 2005), suggesting alterations of the entire attentional network.

3.8 Countermeasures

As mentioned previously, sleep deprivation can significantly impair productivity and compromise individuals' safety. In order to overcome daytime sleepiness and fatigue-induced performance decrements, several effective countermeasures for sleep deprivation, and for mental fatigue in general, have been investigated. These countermeasures can be grouped into pharmacological and non-pharmacological countermeasures.

Non-pharmacological countermeasures

Sleep

Regarding non-pharmacological countermeasures, the first one to mention is certainly sleep itself. Indeed, it has been shown that taking naps is beneficial, and helps to enhance cognitive (Lovato & Lack, 2010) and physical performance (Blanchfield et al., 2018; Waterhouse et al., 2007) in the context of both sleep deprivation and sleep restriction.

In particular, naps of 10-60 minutes duration seem to be enough to mitigate negative impairments in neurobehavioral functioning and alertness following one night of sleep restriction (Gillberg, 1984; Takahashi & Arito, 2000; Tietzel & Lack, 2001), with benefits in subjective alertness lasting up to 1 h following a 10-min nap (Tietzel & Lack, 2001). Moreover, longer naps have been shown to be more effective in increasing behavioural cognitive performance than those of shorter duration following sleep restriction, with more hours of sleep restriction being more detrimental on performance irrespectively of nap duration (Anderson et al., 2000; Maislin et al., 2001).

For sleep deprivation instead, longer naps might be more effective and with more long-lasting benefits (Schweitzer et al., 2006). Even though, the effects of naps on subjective sleepiness are not clear, reporting (Helmus et al., 1997; Naitoh et al., 1981) or not (Dinges et al., 1988; Dinges et al., 2000) high levels of alertness, it is evident that naps ranging between 15 minutes and 2 hours duration following 36-88 hours of sleep deprivation increase cognitive performance (Dinges et al., 1988; Dinges et al., 2000; Lamond & Dawson, 1999; Perlstein et al, 2001). Furthermore, naps seem to be more effective if placed during the first part of the sleep deprivation period, before accumulating considerable sleep debt (Dinges et al., 1988; Mullaney et al., 1983).

In the context of physical exercise, only two studies have examined the effects of 20-30 min afternoon naps following one night of sleep restriction (< 7 h sleep), showing beneficial effects on both endurance (Blanchfield et al., 2018) and sprint running performance (Waterhouse et al., 2007). However, no objective measurements of sleep were collected (e.g. through the use of actiwatches) causing possible limitations to the final results. Further research certainly needs to be conducted to better quantify the effect of diurnal naps and its length of action on physical performance and to subsequently identify the most effective nap duration and time of the day both after sleep restriction and sleep deprivation.

Rest Breaks

Rest breaks from work and cognitive activities are other countermeasures with controversial findings. It has been shown that having breaks of 5-20 min duration during testing sessions after prolonged sleep deprivation (i.e. 54-64 h) improves cognitive performance and alertness (Heslegrave & Angus, 1985; Pigeau et al., 1995). However, their effects seem to be transient and of a small magnitude (Rogers et al., 2003).

Physical Activity

It has been found that short periods of physical activity (e.g. 5-min walking) decrease sleepiness during night work shifts and following one night of sleep restriction (Bonnet

& Arand, 1998; Pallesen et al., 2010), but its effects do not seem to be beneficial following longer periods of sleep deprivation (i.e. 40-64 h) (Kushida, 2006).

Other countermeasures

Other stimulants, such as noise, cold air and bright light have also been found to be efficient countermeasures for sleep deprivation and mental fatigue (Khalafi, 2014; Phipps-Nelson et al., 2003; Reyner & Horne, 1998; van den Berg & Landström, 2006), even though their effect seems to be limited and temporary (Kushida, 2006).

Pharmacological countermeasures

The pharmacological countermeasures currently known in the scientific literature are synthetic stimulant medications, whose aim is to promote wakefulness and maintenance of normal levels of performance by counteracting sleep deprivation and fatigue-related decrements in cortical arousal. Modafinil, methylphenidate and dextroamphetamine are among the most used ones. They are all wakefulness-promoting drugs, mainly used in clinical settings to treat excessive daytime sleepiness or fatigue associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorders (Wesensten et al., 2012). Several studies have looked into the effects of these drugs not only from a clinical perspective, but also during sleep deprivation and sustained operations (e.g. military operations) (Wesensten et al., 2012).

Caffeine

One of the most popular and widely accepted countermeasures, highly used in situations during which sleep loss cannot be avoided, is certainly caffeine. Caffeine, is a wakefulness-promoting natural substance contained in many beverages, such as coffee, tea and coke, and food, such as chocolate (Kushida, 2006), which acts as an A1 and A2A adenosine receptor antagonist in the central nervous system and interacts with dopamine receptors (Cauli & Morelli, 2005; Davis et al., 2003; Ferré, 2016; Fisone et

al., 2004; Rossi et al., 2010). It seems that the main areas of the brain involved in wakefulness promotion are the hypothalamus which in turn projects to the cortex, basal forebrain and reticular activating system (Mitler & O'Malley, 2005), where greater levels of adenosine seem to inhibit the basal forebrain arousal system (Schwartz & Roth, 2008). Moreover, it seems that a block of the adenosine receptors on GABA neurons by caffeine might also contribute to a further inhibition of those hypothalamic neurons involved during sleep (Strecker et al., 2000).

It has been extensively demonstrated, both in multiple laboratory and field studies, that caffeine, if properly provided, increases wakefulness (Jr et al., 1997; Kamimori et al., 2000; Penetar et al., 1993), improves mood and have positive effects on cognitive performance (Lagarde et al., 2000; Lumley et al., 1987; Penetar et al., 1993; Rosenthal et al., 1991; Schweitzer et al., 2006; Sicard et al., 1996; Van Dongen et al., 2001) during both periods of sleep deprivation and sleep restriction. Indeed, significant increments in vigilance levels have been shown after caffeine administration following sleep restriction (De Valck & Cluydts, 2001; Lumley et al., 1987; Rosenthal et al., 1991). Studies on the effects of caffeine following prolonged sleep deprivation have found similar results, with decrements in subjective levels of sleepiness (Keister & McLaughlin, 1972), enhanced mood (Penetar et al., 1993), higher levels of alertness (Bonnet & Arand, 1994; Kamimori et al., 2000; Penetar et al., 1993; Stivalet et al., 1998; Wesensten et al., 2002) and increased sustained attention (Dinges et al., 2000; Rogers et al., 2001), divided attention (Zwyghuizen-Doorenbos et al., 1990), vigilance (Zwyghuizen-Doorenbos et al., 1990), logical reasoning (Bonnet & Arand, 1994), working memory (Dinges et al., 2000) and choice reaction time (Lorist et al., 1994). Moreover, it has been demonstrated that combining caffeine with naps have also positive effects on cognitive performance during one day of sleep deprivation (Bonnet & Arand, 1994a, 1994b, 1995) which have been found to be greater than caffeine intake alone (Dinges et al., 2000; Rogers et al., 2001). The same results have been shown when caffeine is combined with bright light (Jr. et al., 1997).

The effects of caffeine during sleep restriction and sleep deprivation have also been investigated based on the dose administered. The main findings suggest a synergy between beneficial dose and amount of sleep deprivation. It has been shown that lower

doses (100-150 mg) are sufficient to overcome the negative effects of one-night sleep deprivation (Kamimori et al., 2005; Lagarde et al., 2000), whereas medium/high doses (200-600 mg) are needed when sleep deprivation is more extended (Lieberman et al., 2002; Tharion et al., 2003). Furthermore, it has also been demonstrated that high doses (300-600 mg) do not improve cognitive performance more than medium doses, suggesting that high doses might not be necessary (Lagarde et al., 2000). Several studies have also found that as sleep deprivation prolongs, higher doses of caffeine are needed to obtain the same beneficial results provided by lower doses during less protracted sleep deprivation (Bonnet et al., 1995; Wesensten et al., 2002).

Caffeine is also widely used in sport. Although most of the studies in the literature reported beneficial effects of caffeine during endurance exercise activities (McLellan et al., 2016), to the best of my knowledge only a few studies have investigated the effects of caffeine on endurance exercise performance in association with sleep deprivation. In particular, it has been shown that caffeine seems to be an effective strategy to overcome the negative effects of sleep deprivation on endurance exercise, restoring performance levels back to rested-state levels (McLellan et al., 2004a; McLellan et al., 2005; McLellan et al., 2007). However, the present studies have only been conducted in military contexts and caffeine dosages have not been normalised for soldiers' body weight. Further research needs to be conducted in order to better understand the role played by caffeine in association with sleep deprivation and endurance exercise performance and its effects in relation to the different inter-individual responses to caffeine, which seem to be genetically, environmentally, and epigenetically-dependent (Pickering & Kiely, 2018).

Modafinil

Modafinil is a synthetic stimulant accepted for the treatment of excessive daytime sleepiness related to narcolepsy, obstructive sleep apnea, attention deficit disorders, depression, cocaine addiction, fatigue-/sleepiness-induced diseases and shift work sleep disorders (Wesensten et al., 2012). It is well known for its psychoactive and euphoric effects alongside positive changes in mood and feelings (Jasinski, 2000; Makris et al.,

2007; Rush et al., 2002). However, its precise mechanism of action is not fully known yet. It is suggested that modafinil acts via the stimulation of the adrenergic system, in particular the alpha 1 adrenoceptor (Duteil et al., 1990). Specifically, enhanced electrical activity between neurons has been found, indicating that modafinil might be involved in an ad hoc potentiation of the central nervous system catecholaminergic signaling (Beck et al., 2008). Moreover, modafinil has also been shown to stimulate alertness by blocking the reuptake of noradrenaline in sleep-promoting neurons (Gallopin et al., 2004) and by weakly inhibiting dopamine reuptake (although modafinil is not a dopamine receptor agonist) (Volkow et al., 2009).

Modafinil has been investigated on healthy individuals. The main results suggest that repeated administration of modafinil (from 100 to 400 mg per dosage) during prolonged sleep deprivation increases alertness and cognitive performance (Wesensten et al., 2012). In particular, it has been demonstrated that, as in the case of caffeine, it reduces subjective feelings of sleepiness and fatigue (Baranski et al., 1998; Pigeau et al., 1995), increases objective and subjective alertness (Hughes et al., 2001; Wesensten et al., 2002), improves reaction time (Baranski et al., 1998; Brun et al., 1998; Pigeau et al., 1995; Wesensten et al., 2002), sustained attention (Hughes et al., 2001; Wesensten et al., 2002), short-term memory and grammatical reasoning (Brun et al., 1998) during prolonged sleep deprivation.

It has been shown that multiple administration of modafinil in the dosage of 100 mg increases the above mentioned cognitive functions (Baranski et al., 2002; Bodenmann et al., 2009; Stivalet et al., 1998). However, this dose seems not to be able to maintain baseline levels of cognitive performance as repeated doses of 200 mg or higher do (Batéjat & Lagarde, 1999; Caldwell et al., 2000; Lagarde & Batejat, 1995). Moreover, whereas a single dose of 200 mg has been suggested for reestablishing resting levels of performance after one night of sleep deprivation (Batéjat et al., 2006; Dagan & Doljansky, 2006; Gill et al., 2006; Thomas & Kwong, 2006; Wesensten et al., 2002), 400 mg of modafinil are needed following two or more nights of sleep deprivation (Hart et al., 2006; Huck et al., 2008; Killgore et al., 2008; Wesensten et al., 2002).

Compared to other synthetic stimulants, modafinil is associated with less side effects (Rogers et al., 2003). In particular, it has been associated with less sleep disturbances during recovery sleep (Buguet et al., 1995) and less amount of recovery sleep needed (Edgar & Seidel, 1997; Pigeau et al., 1995). Moreover, it has also been found that subjective and objective effects of modafinil are more similar to those of caffeine than those of amphetamines (Warot et al., 1993). In particular, although modafinil has been authorised in certain divisions of the United States military to maintain alertness during prolonged operations, Wesensten and colleagues have found that 600 mg caffeine have the same beneficial effects on performance and alertness compared to 200 and 400 mg modafinil during sleep deprivation in healthy adults (Wesensten et al., 2002). Nevertheless modafinil effects seem to last longer (Killgore et al., 2008; Wesensten et al., 2005a).

Methylphenidate and Dextroamphetamine

Methylphenidate and dextroamphetamines are generally used for the treatment of attention deficit hyperactivity disorder, narcolepsy and emotionally unstable patients, such as individuals with a history of alcoholism or drug addiction. It has been shown that these wakefulness-promoting drugs are able to increase vigilance and executive functioning levels (Caldwell et al., 1995; Caldwell et al., 2000; Magill et al., 1998; Pigeau et al., 1995). However, because of their high potential for addiction, either of them have not been approved as countermeasures to use for behavioural deficits associated with sleep deprivation (Rogers et al., 2003).

3.9 Can recovery sleep overcome the effects of sleep deprivation on cognitive and endurance exercise performance?

As previously mentioned, sleep is the main effective countermeasure used to mitigate the negative effects of sleep deprivation and sleep restriction. It has been demonstrated that nights of recovery sleep following acute and chronic lack of sleep are beneficial to

increase impaired cognitive performance caused by nights of sleep deprivation and sleep restriction (Balkin et al., 2005; Belenky et al., 2003a; Corsi-Cabrera et al., 1996; Drummond et al., 2006; Lorenzo et al., 1995; Rosa et al., 1983; Rupp et al., 2009; Wesensten et al., 2005b). However, whether or not recovery sleep and/or the duration/kinetics of recovery can restore cognitive performance to baseline levels is still controversial.

Indeed, whereas one night of recovery sleep seems to be sufficient to reestablish baseline levels of response-inhibition performance following two nights of total sleep deprivation (Drummond et al., 2006), it has been demonstrated that 3 days of recovery sleep (i.e. 8 h of sleep) do not bring cognitive performance back to stable levels (although decreased) following both chronic mild and moderate sleep restriction (i.e. 5 and 7 h sleep) (Belenky et al., 2003a). Moreover, it seems that both negative effects of prolonged sleep restriction on alertness and cognitive performance and how subsequent recovery sleep improves them depends on the amount of habitual sleep obtained before sleep restriction (Balkin et al., 2005; Rupp et al., 2009; Wesensten et al., 2005b). These findings suggest that days/weeks of sleep debt might have generated some adaptive changes which minimize the counteracting effects of recovery sleep (Belenky et al., 2003).

To the best of my knowledge, the effects of nights of recovery sleep on endurance exercise performance following sleep deprivation and sleep restriction have never been tested yet. The only two studies present in the literature have investigated the effects of 20-30 min afternoon naps after one night of sleep restriction (i.e. less than 7 h sleep), showing beneficial effects on both endurance (Blanchfield et al., 2018) and sprint running performance (Waterhouse et al., 2007). However, future research is crucial in order to identify the role played by full nights of recovery sleep in the field of sport and endurance exercise performance.

3.10 Summary and conclusions

Sleep deprivation and sleep restriction are widespread issues in our modern society and can be defined as periods of total and partial lack of sleep respectively. These forms of

sleep debt have been extensively investigated and current findings suggest that they both have similar detrimental effects on subjective sleepiness and cognitive performance. Negative effects on behaviour induced by lack of sleep have been linked with neural activity changes and specific molecular and cellular processes. Several countermeasures, such as caffeine, modafinil and recovery sleep, have been demonstrated to counteract the detrimental effects of sleep deprivation and sleep restriction on cognitive performance.

However, the effects of sleep deprivation and sleep restriction on endurance exercise performance are still relatively unknown. The greater results indicate that whereas sleep restriction seems not to affect endurance exercise performance, sleep deprivation looks harmful, particularly during endurance activities lasting longer than 30 minutes. As in the case of mental fatigue, decrements in endurance exercise performance following sleep deprivation have been related to higher ratings of perceived exertion and no relevant alterations on cardio-respiratory parameters.

Yet, the results in this field are still controversial and further research is essential to better explain the role played by sleep deprivation and sleep restriction on endurance exercise performance and to investigate the neurobiological mechanisms underneath that. In the following chapters I intend to cover some of the gaps present in the current literature. In particular, I explore the effects of recovery sleep following acute sleep deprivation on endurance cycling performance and I test the effects of a new training intervention aimed at counteracting the effects of sleep deprivation and making people more resilient to lack of sleep in the context of the endurance exercise performance.

Chapter 4

The Effects of Mental Fatigue on Half-Marathon Performance: a Field Experiment.

Main finding: Mental fatigue has an inconclusive effect on prolonged endurance performance (lasting more than 45 min) and pace, RPE or HR.

4.1 Abstract

Mental fatigue is a psychobiological state caused by prolonged and demanding cognitive activity. It was previously demonstrated that mental fatigue has negative effects on perception of effort and endurance performance during laboratory tests lasting between 3 and 45 minutes. However, the effect of mental fatigue on endurance performance lasting more than 45 minutes is unknown. The main aim of the current study was to investigate the effects of mental fatigue on ratings of perceived exertion (RPE), heart rate (HR), pace and performance during a half-marathon race in amateur runners.

Forty-six amateur long-distance runners (means ± SD: age 43.8 ± 8.6 yr, body mass 73.5 ± 6.7 kg, height 1.76 ± 0.06 m, $\dot{V}O_{2peak}$ estimation 46.0 ± 4.1 ml/kg/min) were randomly allocated to either a group performing a 50-min mentally-fatiguing task before the half-marathon, or a control group (reading magazines for 50 min). All subjects completed psychological questionnaires and fatigue scales before and after the experimental treatment, and after the half-marathon. Time, pace, heart rate and RPE were measured during the race.

Runners who performed the mentally-fatiguing task completed the half-marathon approximately four minutes slower (106.20 ± 12.36 min) than the control group (102.45 ± 10.21 min) (Cohen's d = 0.367; p = 0.265). Although performance was

not significantly different between the two groups, an equivalence testing analysis revealed that the presence of a true effect of mental fatigue large enough to be considered worthwhile at the population level cannot be excluded (t (40.88) = 0.819, p = 0.791).

In conclusion, as expected, because of low statistical power, the data collected do not provide reliable evidence that mental fatigue reduces longer-term endurance performance. However, despite no significant differences between the two groups, equivalence testing suggests that the hypothesis that mental fatigue is harmful to half-marathon performance in amateur runners cannot be rejected.

4.2 Introduction

Mental fatigue has been defined as a psychobiological state caused by prolonged and demanding cognitive activity (Boksem & Tops, 2008; Craig et al., 2006; Ricci et al., 2007). Mental fatigue is an extremely complex phenomenon characterized by tiredness, changes in mood, and reluctance to carry on a task (Matthews & Hancock, 2017). It has been previously demonstrated that mental fatigue is a common condition in people affected by some chronic diseases, such as chronic fatigue syndrome, cancer, multiple sclerosis and anxiety-based disorders (Chaudhuri & Behan, 2000b; Chaudhuri & Behan, 2004; Siegert & Abernethy, 2005). However, nowadays acute manifestation of mental fatigue is an extensive problem which negatively affects the entire population (Boksem & Tops, 2008; Craig et al., 2006; Ricci et al., 2007).

The negative effects of mental fatigue on cognitive performance have been widely studied and recognized (Lorist et al., 2005; van der Linden & Eling, 2006; van der Linden et al., 2003a). It has been shown that mental fatigue has a negative behavioural effect on vigilance, working memory and other executive functions such as inhibitory control and problem solving (Lorist et al., 2005; van der Linden & Eling, 2006; van der Linden et al., 2003a). These impairments seem to be confirmed from a psychophysiological perspective as well. Several studies, indeed, have found consistent mental-fatigue-related changes in brain activity (using both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI)), such as reductions in ERNs

amplitude and alterations in the ACC activity over time, which in turn result in compromised error monitoring and performance adjustment failures (Barch et al., 1997; Boksem et al., 2005; Cook et al., 2007; Lorist et al., 2000; Lorist et al., 2005; Ten Caat et al., 2008).

Nonetheless, in the last decade it has been shown that a mentally fatigued state impairs also physical performance and more precisely endurance exercise performance, defined as any kind of exercise lasting longer than 75 seconds during which the aerobic energy system is the most solicited one (Gastin, 2001) (see systematic review by (Van Cutsem et al., 2017b)).The first study ever conducted on this topic has demonstrated that a prolonged and systematic repetition of mentally-fatiguing tasks impairs endurance performance during a high-intensity time to exhaustion cycling test (Marcora et al., 2009). With this experiment the authors have also provided important evidence that impairments caused by mental fatigue in endurance performance are associated with higher RPE rather than with alterations in physiological responses. Though still limited, there is a growing body of studies that confirm a moderate negative effect of mental fatigue on perception of effort and endurance performance in trained, physically active, healthy populations and in normal ambient conditions (Brownsberger et al., 2013; MacMahon et al., 2014; Marcora et al., 2009; Martin et al., 2015; Pageaux et al., 2014; Pageaux et al., 2013; Smith et al., 2015, 2016). These results seem not to be the case among professional cyclists, who possibly have greater resistance to the negative effects of mental fatigue compared to recreational cyclists (Martin et al., 2016) and in the heat, where the brain is perhaps already under stress due to the extreme environmental conditions (Van Cutsem et al., 2017a). Further studies need to be conducted in order to confirm these first findings.

Endurance exercise performance is generally assessed through either the use of time to exhaustion or time trial tests (Pageaux & Lepers, 2016). The effects of mental fatigue on endurance performance have been investigated using these protocols lasting between 3 and 45 minutes during cycling (Brownsberger et al., 2013; Marcora et al., 2009; Martin et al., 2015; Smith et al., 2016; Van Cutsem et al., 2017b) and running (MacMahon et al., 2014; Pageaux et al., 2014; Smith et al., 2016). However, the effect of mental fatigue on endurance performance lasting more than 45 minutes is unknown.

Furthermore, these experiments have always been conducted in standardised indoor environments such as laboratories (Brownsberger et al., 2013; Marcora et al., 2009; Martin et al., 2015, 2016; Pageaux et al., 2014; Pageaux et al., 2013; Smith et al., 2015; Van Cutsem et al., 2017b) and indoor track and field (MacMahon et al., 2014; Smith et al., 2016) (i.e. explanatory trials) and there is no evidence about the role played by mental fatigue in outdoor settings and during endurance races and mass-start competitions (i.e. pragmatic trials). A laboratory context is completely different from a mass-start competition one and it might inevitably influence athletes from psychological and pacing perspectives for examples. This is why a pragmatic approach, in other words a translation from ideal laboratory conditions into practice (in this case a real race), would be as important as explanatory trials in the understanding of the effects of mental fatigue on endurance performance.

In order to have a more ecologically valid insight of the effects of mental fatigue on endurance performance, the main aim of the current study is to investigate the effects of 50-min mentally-fatiguing task on RPE, heart rate, pace (i.e. speed) and performance (time) during an official half-marathon race (see *Run4Science* section below) in amateur runners. It has been hypothesized that a mentally fatigued state induced by the task has a negative effect on RPE, pace, heart rate and performance during the race compared to the control condition. Specifically, since a half-marathon is a closed-loop kind of exercise (i.e. time trial), it has been hypothesized the same RPE values for lower running pace in the mental fatigue condition compared to the control condition. This would allow participants to maintain reasonable ratings of perceived exertion and therefore to complete the race (MacMahon et al., 2014; Pageaux et al., 2014; Smith et al., 2016). However, because the kind of design used in our study does not include a baseline test for performance, a drastic decrease in statistical power was also expected. Therefore, differently to what has been shown in the previous above-mentioned studies, no effect on performance through the use of the traditional null hypothesis significance testing analysis was predicted to be found. For these reasons and to have a better understanding of the data collected, another alternative statistical approach, called Two One-Sided Tests (TOST) equivalence testing analysis (Lakens, 2017; Lakens et al., 2018) has also been used (see *Statistical Analysis*).

4.3 Methods

Subjects recruitment and inclusion criteria

Forty-eight male amateur long-distance runners were recruited through the Run4Science half-marathon race advertisements. Two participants in the experimental treatment were excluded from this study due to injury and premature exhaustion during the race (see Table 1 for subjects' characteristics). The total number of participants was tested throughout three years, during the same annual competition, in the following dates: 12th of April 2015, 24th of April 2016 and 2nd of April 2017. Before participating in the experiment all subjects were informed about the study protocol and signed a written, informed consent. All procedures used were approved by the Department of Neurological, Neuropsychological, Morphological and Movement Sciences, Ethics Committee from the University of Verona (Italy) and were conducted in conformity with the Declaration of Helsinki.

Subjects eligible for this study were involved in regular running aerobic training, free of any known disease, injury and medical treatment. In order to have a homogeneous fitness level, the recruited runners were first asked to complete a training-competition history questionnaire and a physical activity rating scale (PA-R) (Ross & Jackson, 1991). Only those runners with a physical activity rating above 6 were included in the experiment.

Subjects included in the study were provided with an information document in which all the study procedures were described. However, they were not aware of the real aim and the hypotheses of the experiment. Subjects were told that the study aimed to investigate the effects of two different kinds of cognitive activities on a half-marathon race.

One week prior to the half-marathon, runners were familiarized with the use of the 100-point rating of perceived exertion (RPE) scale developed by Borg (Borg, 1998) and other questionnaires and scales (see *Psychological Questionnaires*). In particular,

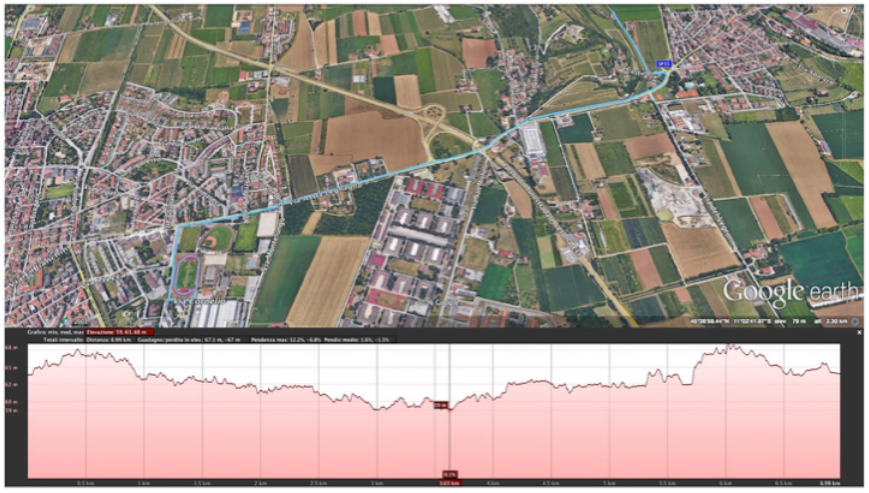
participants were given standard written instructions about the 100-point RPE scale, in which low, high and intermediate anchor points were identified and described. They were also informed to drink around 35 ml of water per kg of body weight, to sleep at least 7 hours, to refrain from alcohol consumption and to avoid strenuous exercise within the 24 hours preceding the experiment. Participants were also asked not to consume any caffeine and nicotine for at least 3 hours before the experiment.

Subjects randomisation and Study Protocol

A randomised, between-group, posttest-only experimental design was used. Participants were randomly asked either to perform a 50-min mentally-fatiguing task immediately before the half-marathon (experimental treatment) or to read some magazines for the same amount of time, always prior to the competition (control treatment). Prior to the race, in order to minimize the effect of maximal oxygen consumption ($\dot{V}O_{2peak}$) on half-marathon performance, participants were randomly allocated to treatment (using the coin tossing method) after being ranked on the basis of their estimated $\dot{V}O_{2peak}$. $\dot{V}O_{2peak}$ was estimated using a validated multiple regression equation (Jackson et al., 1990), which takes into account the following variables: subjects' PA-R (Ross & Jackson, 1991), Body Mass Index (BMI), gender and age (See Table 1).

The study took place at the School of Sport and Exercise Sciences, University of Verona (Italy). Both psychological and cognitive task interventions were carried out in a standardised lecture room. The half-marathon race took place in proximity to the School (See Picture 1.A and 1.B for the course). The race is part of the Run4Science (See *Run4Science* for more details about the event).

A



B

Picture 4.1. The 7-km circuit course (A) and the outdoor track where the race started and the data collection points took place (B).

On the race day all participants were asked to arrive at 07:00 am and in a fasted state. A standardised breakfast, consisting of orange juice and 3/4 melba toasts with jam/honey (the precise energy intake was not calculated) was provided by the organisers in the main Sport Hall of the School of Sport and Exercise Sciences, close to the race starting point. Participants were required to wear their running clothes prior to the commencing of the experiment. The experiment started at 8 am. Subjects were divided into two groups and asked to sit down either in the front (mental fatigue group) or the back (control group) of the lecture room. In order to verify that participants had followed all the instructions previously given, they were asked to complete a pre-experiment checklist. Participants were also asked to inform researchers about any acute illness, infection and/or injury and to give notice of any medication/drug taken.

Participants were required to complete a mood questionnaire and two fatigue-related scales (See *Psychological Questionnaires*). They were then asked to perform either the mental fatigue task or the control one for 50 minutes (see *Treatment*). Immediately after the task subjects were required to complete the same mood questionnaire and fatigue scales completed at baseline. In order to assess subjective workload related to the cognitive task and motivation and expectations related to the half-marathon race, participants completed a workload-related multidimensional scale, a motivation questionnaire and a race-related expectation scale respectively (See *Psychological Questionnaires*).

Immediately after the treatment and the psychological questionnaires participants performed the half-marathon race. The course was a controlled 7-km circuit to be completed three times (See Picture 1.A). The starting point was located inside the University outdoor track (See Picture 1.B). At the end of each lap athletes were required to run on the track and pass through the start, where times and RPE were collected. Participants were equipped with a shoe race chip through which partial (7 and 14-km laps) and final (21 km) times were taken. RPE was measured using the 100-point scale (Borg, 1998), as it was the official scale chosen by the organisers for the race. Two big posters of the same scale were placed in proximity of the starting point at 50-meter distance between each other. Subjects were instructed to look at the scale twice before telling the researchers their RPE. Subjects' HR and pace were continuously collected

throughout the entire race using GPS watches (Polar V800, Polar Electro Oy, Kempele, Finland). Participants were asked to do a 10-min warm-up immediately before the race. Participants were free to drink ad libitum during the race.

Finally, at the end of the half-marathon each participant was asked to go back to the lecture room and to fill in the same mood questionnaire and fatigue scales completed before and after the treatment. Participants were also required to complete the workload multidimensional scale related to the half-marathon race (See *Psychological Questionnaires*).

Treatment

Experimental Treatment

In order to induce mental fatigue, the experimental group performed 50-min cognitive demanding tasks (Axon Sports, USA) on a tablet screen (iPad Mini 2, Apple, California, USA). The tasks used (which have not been validated yet) are part of the Axon Sports Cognitive Assessment, a new neurocognitive application to measure aspects of cognitive function sensitive to change. The treatment consisted of five consecutive blocks of 10-mins (i.e. 50 minutes in total). The cognitive tasks used within each 10-min block were a simple response task and a search response task. The simple response task and the search response task were used as measures of psychomotor speed and inhibitory control (i.e. prevention of a motor response) respectively. In the simple response task participants were required to detect and press a visual stimulus (a green target) appearing randomly in the centre of the screen. The simple response task was the first task participants were asked to perform within each 10-min block. The total duration of the simple response task in each block was 45 seconds with a randomized stimulus frequency of 500 ms and 1500 ms. The search response task was the second task. Participants were asked to detect and press a green target (go visual stimulus) and not to respond to a red target (no-go visual stimulus). Both stimuli appeared randomly in different positions on the screen. A bleep sound was elicited in case of incorrect response to increase subjects' speed and accuracy. The total duration of the search

response task in each block was 9 minutes and 15 seconds with a randomized stimulus frequency of 750 ms and 1000 ms.

Control Treatment

The control group was asked to read some magazines for 50 minutes, as considered a leisure relaxing activity (Kirsch & Guthrie, 1984). Participants were continuously monitored by the researchers to guarantee compliance with both treatments.

Run4Science

Run4Science is one of the biggest endurance field-based scientific events, a pragmatic trial used by scientists to study the effect of interventions in real-life conditions (i.e. running races). It is organised by the University of Verona, in collaboration with the Italian Athletics Federation (FIDAL) and with the patronage of the city council. Run4Science takes place annually since 2014 and involves several Italian, but also international universities. The event has been developed in order to study endurance running performance under different physiological, biomechanical and psychological aspects. It generally runs in April, the period of the year with the most appropriate ambient conditions for endurance competitions in Italy (atmospheric condition ranges found in the three-year experiment: temperature: 20.5-24.2 °C; humidity: 35%-53% RH; barometric pressure: 1013-1029 hPA). Run4Science consists of different running races which may vary depending on the research protocols (generally between 5.0 km and 42.2 km) and it involves approximately 200 amateur runners, aged between 20 and 90 years. The different races are performed on the same route, starting at different time frames in the morning (depending on the experiments procedures). The route is located 5 km away from Verona city centre and presents a maximum of 35 m vertical gain (1.8% maximal slope).

Psychological Questionnaires

Mood. The Brunel Mood Scale (BRUMS) (Terry et al., 2003) was used as a measurement to evaluate subjects' mood. This questionnaire is a shorter version of the Profile of Mood States (POMS) and it consists of 24 items (e.g. tired, anxious, nervous, confused, energetic, active) to be answered on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Items are allocated into six specific subscales: anger, confusion, depression, fatigue, tension and vigour. Each subscale includes 4 related items and can reach a score between 0 and 16.

Mental and Physical Fatigue. Two Visual Analogue Scales (VAS) (Wewers & Lowe, 1990) were used to assess subjective mental and physical fatigue. The VAS used is a 100-mm horizontal line divided into 20 half centimetres intervals (Gift, 1989). Subjects were asked to circle one of the 20 line intervals for both scales based on their actual mental and physical fatigue state. The total range of scores is between 0 and 20. The line ends are anchored by descriptors defining the extreme feelings of fatigue: "no fatigued at all" and "extremely fatigued".

Workload. The multidimensional scale NASA Task Load Index (TLX) (Hart & Staveland, 1988) was used to estimate subjective workload that participants experienced both during the cognitive task and the half-marathon. Participants were required to complete it immediately after each task (i.e. cognitive task and half-marathon). The NASA TLX includes six subscales which determine workload: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort and Frustration. Subjects were asked to circle one of the 20 line intervals on each of the six scales at the point which matched their experience. Each line has two endpoint descriptors "very low" and "very high" that describe the scale. The performance-related subscale goes from "good" on the left to "poor" on the right.

Motivation. Intrinsic motivation and success motivation scales (Matthews et al., 2001) were used to assess motivation related to the half-marathon race. Each scale includes 7

items to be scored on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = somewhat, 3 = very much, 4 = extremely). The total range of scores for each scale is between 0 and 28.

Expectations. The same VAS (Gift, 1989; Wewers & Lowe, 1990) used to measure mental and physical fatigue was used to measure participants' expectations related to the half-marathon race. Subjects were asked to circle one of the 20 line intervals based on how well they expected to perform their race. The total range of scores is between 0 and 20. The line ends are anchored by descriptors defining the extreme expectations: "much better than my personal best" and "much worse than my personal best". A third descriptor "my personal best" was added to the centre of the VAS in order to facilitate subjects answer.

Statistical Analysis

2 – 3 mixed-model ANOVAs (group x time) were used to analyse differences in RPE, heart rate, pace and running time between the two groups. When the assumption of sphericity was not met, the Greenhouse-Geisser correction was used. Significant main effects were followed up using simple contrasts with the α-level adjust via Bonferroni's correction. Independent t-tests were used to analyse between groups differences in the half-marathon performance (race time). In order to control for baseline differences, mood, mental fatigue and physical fatigue difference scores between baseline and post-treatment measurements were calculated.

The Shapiro-Wilk test, histograms, Q-Q plots and boxplots were used to check for all data normality. The non-parametric Mann-Whitney test was run to compare cognitive- and half-marathon-related workload, mood items (apart from vigour) and subjective feelings of physical fatigue. Statistical significance was accepted at $P < 0.05$ level. All data are presented as means ± SD, unless otherwise stated. The SPSS (version 23.0; SPSS, Chicago, IL) statistical package was used for all data analyses.

In addition to a traditional hypothesis testing approach, a Two One-Sided Tests (TOST) equivalence testing analysis (Lakens, 2017; Lakens et al., 2018; Schuirmann,

1987) was also used to statistically reject effects of mental fatigue on half-marathon performance large enough to be considered worthwhile. The smallest effect size of interest (SESOI) was decided a priori, with its lower equivalence bound (Δ_L) and upper equivalence bound (Δ_U) set to -1 and 1 minute respectively (raw equivalence bounds). Δ_L and Δ_U corresponded to 1% of the control group performance, which is equivalent to the smallest worthwhile change for half- and full marathons (Hopkins & Hewson, 2001).

4.4 Results

Participants characteristics

Participants' features (general and per group) are reported in Table 4.1.

Table 4.1. *Participants features (N = 46)*

	Mental Fatigue Group (*N* = 22)	Control Group (*N* = 24)	Total Participants (*N*= 46)	Total Range
Age (years)	43.1 ± 10.0	44.4 ± 7.2	43.8 ± 8.6	20.3 – 59.0
Height (m)	1.76 ± 0.07	1.77 ± 0.06	1.76 ± 0.06	1.55 – 1.89
Weight (kg)	74.0 ± 7.2	73.0 ± 6.4	73.5 ± 6.7	60.0 – 87.0
BMI (kg/m^2)	23.9 ± 1.8	23.3 ± 1.6	23.6 ± 1.7	20.8 – 27.1
PA-R	6.8 ± 0.5	6.9 ± 0.3	6.8 ± 0.4	6 – 7
Estimated $\dot{V}o_{2peak}$ (ml/kg/min)	45.9 ± 4.8	46.0 ± 3.6	46.0 ± 4.1	35.8 – 56.2
Training/Week (h)	5 ± 3	5 ± 3	4 ± 2	1 – 15
Training/Year (weeks)	45 ± 7	46 ± 5	45 ± 6	30 – 52

BMI, Body Mass Index; PA-R, Physical Activity Scale; $\dot{V}o_{2peak}$, maximal oxygen uptake. Data are shown as means ± SD.

Manipulation Checks

The analysis revealed that the difference score between ratings of mental fatigue (VAS) at baseline and post-treatment were significantly higher in the mental fatigue group compared to the control group (p = 0.012), showing a greater increase in the experimental group immediately after the treatment (Figure.4.1). No significant difference score changes were found in ratings of physical fatigue (VAS). The NASA TLX completed immediately after the treatment showed a trend toward significant higher values of mental demand in the experimental group (*Mdn* = 42.50) compared to the control group (*Mdn* = 25.00) (U = 176.50, z = - 1.93, r = - 0.30, p = 0.053) (Figure.4.2A). The multidimensional scale also revealed that the mental fatigue group (*Mdn* = 47.50) perceived significantly higher ratings of effort than the control group (*Mdn* = 25.00) (U = 164.00, z = - 2.21, r = - 0.32, p = 0.027) (Figure.4.2B).

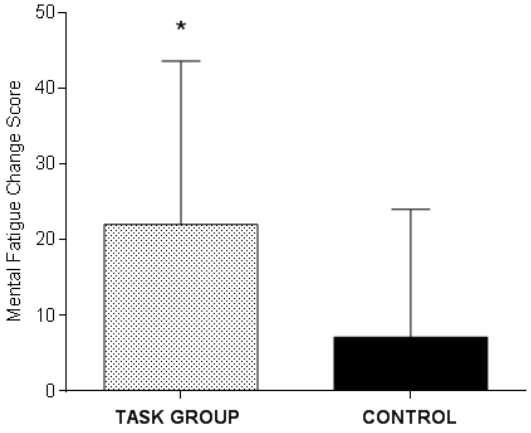
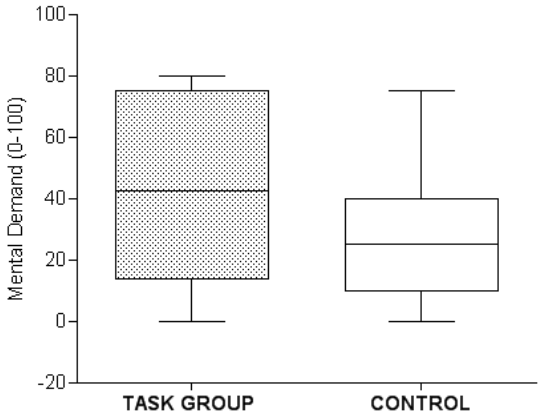


Figure. 4.1. Effect of cognitive demanding task on subjective ratings of mental fatigue. Data are displayed as change score means ± SD. * Significant effect of the experimental treatment (p < 0.05).

A



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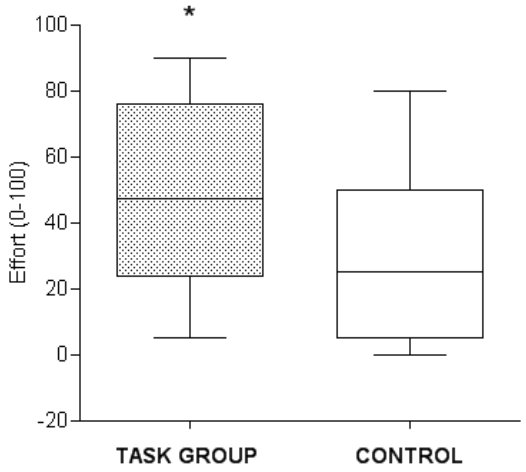


Figure. 4.2. Box plot graphs showing the distribution of mental demand (A) and effort (B) values (NASA TLX) after cognitive treatment. Groups are presented as boxes whose length represents the interquartile ranges. The horizontal bar within the boxes indicates the median. Horizontal lines outside the box show the largest and smallest observations. * Significant effect of the experimental treatment ($p < 0.05$).

Effects of Mental Fatigue on Motivation and Expectations of the race

Intrinsic motivation (mental fatigue group 23.0 ± 2.5; control group 23.1 ± 3.0, p = 0.919) and success motivation (mental fatigue group 16.4 ± 3.1; control group 16.1 ± 3.3, p = 0.802) did not vary significantly between the two groups. Expectations related to the half-marathon performance also did not differ significantly between experimental and control groups (mental fatigue group 43.2 ± 22.4; control group 45.2 ± 14.1, p = 0.713).

As expected a priori, the null hypothesis significance testing analysis showed no statistical difference between the two groups. However, runners who performed the mentally-fatiguing task completed the half-marathon approximately four minutes slower (106.20 ± 12.36 min) than the control group (102.45 ± 10.21 min) (Cohen's $d = 0.367$; $p = 0.265$) (Figure.4.3). Moreover, the TOST procedure revealed no significant equivalence ($t(40.88) = 0.819$, $p = 0.791$) (Figure.4.4), concluding that the presence of a true effect of mental fatigue large enough to be considered worthwhile at the population level cannot be excluded.

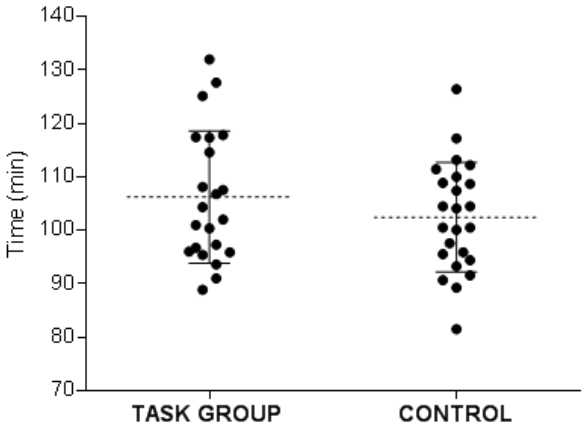


Figure. 4.3. Effect of cognitive demanding task on final race time (mental fatigue group: 106.20 ± 12.36 min; control group: 102.45 ± 10.21 min). Data are displayed as single plots. Horizontal lines represent means (open lines) and SD (solid lines).

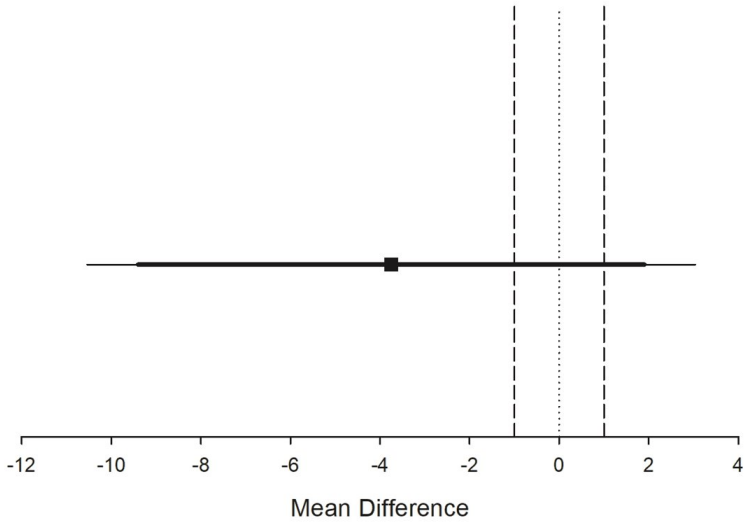
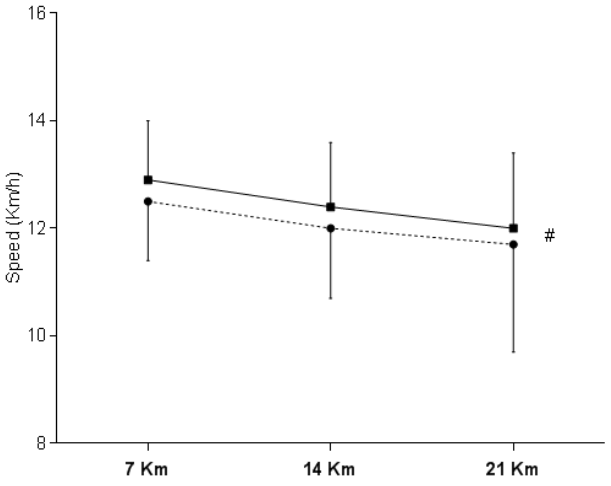


Figure. 4.4. Performance Mean Difference between control and mental fatigue group (-3.75 min). The thick horizontal lines indicate the 90% confidence intervals from the TOST procedure, 90% CI [-9.404; 1.904], whereas the thin horizontal lines indicate the 95% confidence intervals from null-hypothesis significance tests, 95% CI [-10.536; 3.036]. The dotted vertical line indicates the null hypothesis, the dashed vertical lines indicate the equivalence bounds in raw score (Δ_L = -1 min; Δ_U = 1 min).

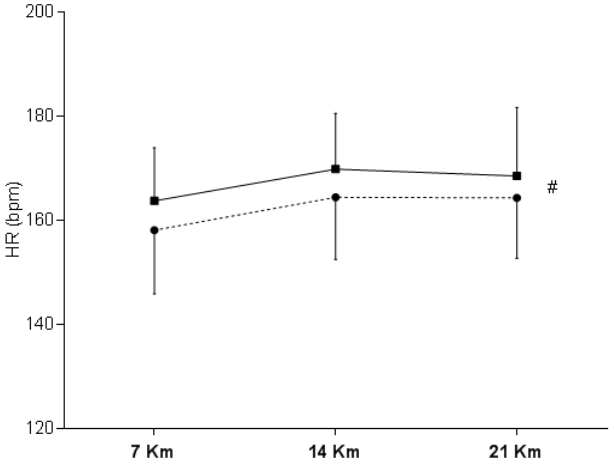
Effects of Mental Fatigue on pace, HR and RPE

No significant interactions on pace (p = 0.910), HR (p = 0.829) and RPE (p = 0.582) were found. Running pace showed a significant decrease over time (p < 0.001) in both groups, but no significant differences between the two groups (Figure.4.5A). HR measurements also showed a significant increase over time (p < 0.001) but no significant changes between the experimental and control group (Figure.4.5B). RPEs significantly increased throughout the race in both groups (p < 0.001) (Figure.4.5C). However, no significant alterations were found between the two conditions.

A



B



C

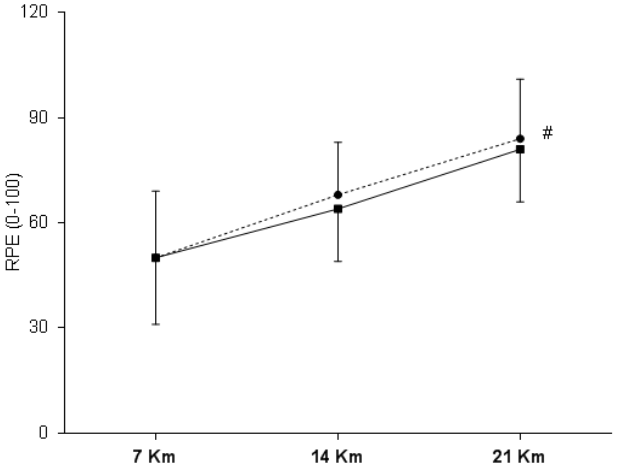


Figure. 4.5. Group mean ± SD alterations in the parameters of pace (A), HR (B) and RPE (C) measured during the half-marathon race at 7, 14 and 21 km in mental fatigue (open line) and control group (solid line). # Significant main effect over time ($p < 0.05$).

4.5 Discussion

The traditional statistical analysis revealed that mental fatigue seems not to have a significant negative effect on half-marathon performance. Indeed, in contrast with our first hypothesis, pace, heart rate and performance did not show any significant impairment after a 50-min mentally fatiguing task compared to the control group. Although a traditional hypothesis testing approach was used, the results were expected not to be significant. Indeed, the ideal sample size calculated a posteriori (G*Power software) using the effect size of the treatment on performance (Cohen's $d = 0.367$) was of 388 (194 per group), a number that could have never been reached in three years of data collection. Moreover, the TOST equivalence testing analysis used, showed that the hypothesis that the true effect is at least as extreme as 1% performance change (Fig.2), which is considered to be the smallest worthwhile change for half- and full marathons, cannot be rejected (Hopkins & Hewson, 2001b).

Markers of Mental Fatigue

Contrary to previous findings (MacMahon et al., 2014; Marcora et al., 2009), no decrements in positive mood were detected after the prolonged cognitively demanding task. No reductions in cognitive performance were also found throughout the task. In agreement with a previous study (Pageaux et al., 2014), higher values of mental demand and effort (NASA TLX) found after the mentally-fatiguing task showed a greater workload in the experimental group compared to the control group. Moreover, significantly greater increases of subjective feelings of mental fatigue (VAS) immediately after the experimental treatment indicated a state of mental fatigue.

Effects of Mental Fatigue on Performance, Pace, Heart Rate and RPE during the Half-Marathon Race

As expected from the sample size calculation for this experiment, the statistical analysis showed that mental fatigue did not have a significant negative effect on the half-marathon performance. These results would be in opposition to our hypothesis for this study and to what previous laboratory/indoor-based studies found in shorter-term endurance performance (MacMahon et al., 2014; Marcora et al., 2009; Pageaux et al., 2014; Pageaux et al., 2013; Smith et al., 2016). However, as stated by more than 800 scientists in a recent Comment in Nature, finding a p value larger than 0.05 or a confidence interval including zero does not necessarily mean that there is 'no difference', 'no effect' or 'no association' (Amrhein et al., 2019). In the current study, a visual inspection of the data suggests that the mental fatigue group completed the race approximately 4 minutes slower than the control group with an effect size of 0.367 (Cohen's *d*) and that the same trend was noticeable during each single data collection. Even though performance was not significantly different between groups, the current experiment showed similar effect size compared to previous within-subject and lab-based studies (Marcora et al., 2009; Pageaux et al., 2014). In addition to that, the TOST equivalence testing analysis used (Lakens, 2017; Lakens et al., 2018; Schuirmann, 1987) showed that the hypothesis that mental fatigue is harmful or even beneficial to the half-marathon performance in amateur runners cannot be rejected, underlining again that it would be misleading to conclude that mental fatigue did not have any effect on the half-marathon performance on the base of statistical significance thresholds only. All these results may indicate that the lack of significance in the half-marathon performance between the two groups was most probably due to a lack of statistical power. In such kind of field study, indeed, the design used would have necessitated a much larger sample size (i.e. the sample size calculated using the G*Power software was 388 in total), whereas the real sample size available was very limited (i.e. 48 participants in total) (see *Limitations*).

The present study also showed that pace significantly decreased throughout the half-marathon in both groups. Even though no differences were found between the two

conditions, running pace in the mental fatigue group was on average 3% slower than in the control group. The statistical analysis also revealed that heart rate values were 3% lower throughout the entire competition in the mental fatigue group. This result might have reflected the slower running pace caused by a possible mental fatigue state. Moreover, in agreement with our second hypothesis, RPE significantly increased over time, but did not change between the two groups at each stage of the race (7, 14 and 21 km). These results would recall findings from other investigations where previous studies showed the same RPE values for lower running velocities/power outputs in a mental fatigue state during both running (MacMahon et al., 2014) and cycling (Martin et al., 2016) time trials. This could indicate that participants in the mental fatigue group decreased their running pace in order to maintain affordable values of RPE and therefore finish their race. These findings are also comparable with what Marcora and colleagues found during an opened-loop type of exercise (i.e. time to exhaustion test) (Marcora et al., 2009). In this case, mentally-fatigued participants perceived higher levels of effort for fixed intensities compared to the control group. Since no adjustment in velocity/power output can be made during time to exhaustion tests, subjects obviate fatigue and increasing ratings of perceived exertion through an earlier disengagement from the task (see *Potential Mechanisms*).

Potential Mechanisms

The results obtained can be explained with the psychobiological model of endurance performance (Marcora et al., 2008). This model is based on the motivational intensity theory (Brehm & Self, 1989; Wright, 2008) and suggests that exercise tolerance is limited by cognitive and motivational aspects rather than by cardiorespiratory and muscle energetics mechanisms (Marcora et al., 2008; Marcora et al., 2009). According to Marcora's model, perception of effort and potential motivation (defined as the maximum effort a person is willing to exert to satisfy a motive (Wright, 2008) are the limiting factors of exercise tolerance. In the current study no difference on either intrinsic or success motivation related to the half-marathon performance was found, with participants' expectations matching their actual performance. These results are in

line with previous findings (Marcora et al., 2009; Pageaux et al., 2013) and suggest that no changes in motivation was probably due to the fact that the half-marathon was an official race, which kept participants in the mental fatigue group highly motivated. A mental fatigue state indeed, would generally restrict people from perceiving further effort, unless there is a reward (in the present case, winning the race) (Boksem et al., 2006; Lorist et al., 2000; van der Linden et al., 2003a). Since potential motivation did not negatively affect the final time of the half-marathon race in the experimental group, perception of effort could have played a crucial role in pacing.

In addition to potential motivation and perception of effort, closed-loop endurance exercises, such as a half-marathon, are also influenced by other factors. During this type of exercise, the primary purpose is to complete a certain distance in the shortest time possible (or to cover the biggest distance possible over a set time). In order to do so athletes need to self-regulate their pace continuously throughout the entire race and choose the highest one, which would allow them to reach the main goal (i.e. complete the race in the shortest time possible). The main goal would not be reached and a premature task disengagement/exhaustion would occur if they stop or suddenly decrease their pace prior to the end of the race. Based on the psychobiological model, the awareness of the overall exercise distance/time, of the exercise distance/time left and the experience of perception of effort during previous exercise at different intensities and durations are three other important elements that could regulate self-paced endurance exercise and avoid premature exhaustion (Marcora, 2010). Pageaux and colleagues demonstrated that 30 minutes of mentally-fatiguing task (i.e. response inhibition task) had a negative effect on 5-km time-trial running performance due to a reduction in subjects' average pace (Pageaux et al., 2014). In the mental fatigue condition, participants performed 6% slower than in the control one. Decrements in performance were associated with higher RPE. Moreover, no alterations in physiological parameters were found immediately before and during the time trial. Considering that participants were aware of the total and remaining distances to complete and that the variable related to previous exercise experiences was controlled, the authors concluded that the slower running pace in the experimental group was a conscious decision for balancing the negative effect of mental fatigue on perception of

effort and avoiding premature exhaustion. Even though the factor related to earlier participants' experience/memory could not be controlled, our study showed similar results, suggesting that also longer-term endurance performance might be limited by perception of effort. However, this is the first study conducted on endurance exercise lasting more than 30 minutes and during a real race, and therefore other mechanisms limiting performance such as central and peripheral fatigue cannot be excluded. It has been demonstrated that mental fatigue does not exacerbate neuromuscular fatigue during endurance exercise of short duration (Pageaux et al., 2015). However, it is also known that neuromuscular fatigue is task dependent (Millet & Lepers, 2004). Further investigations are required in order to better understand the role played by mental fatigue on longer-term endurance performance, such as half-marathons, marathons and ultra-endurance competitions. Additional cardiorespiratory and neuromuscular parameters should be monitored during this type of exercise. This would allow an examination on whether longer-term endurance performance under a mentally-fatiguing state is limited by other factors other than perception of effort.

Limitations

The present study shows several limitations that could have interfered with all the final results: 1) for practical reasons the experimental design used did not involve any baseline measurement (posttest-only experiment); 2) the randomisation was based on runners predicted $\dot{V}O_{2peak}$ and not real values of their maximum oxygen consumption; 3) the small number of subjects (i.e. 22 and 24, mental fatigue and control group respectively) might have limited the power of the findings (as suggested by the visual inspection of the data and the results found using the TOST equivalence testing analysis); 4) the results showed no decrease in cognitive performance (i.e. reaction time and accuracy) during the mentally-fatiguing task and no variations in mood immediately after. The task might have been too short and consequently might have not induced high levels of mental fatigue in the experimental group.

4.6 Conclusions and practical applications

In conclusion, because of low statistical power, the data collected do not provide reliable evidence that mental fatigue reduces endurance performance. However, the equivalence testing analysis indicates that the hypothesis of a true effect of mental fatigue to half-marathon performance in amateur runners cannot be excluded, suggesting that the current results are most probably in line with previous lab-based findings.

From a practical perspective it may be prudent for athletes to avoid any mentally-fatiguing tasks before and during the first part of an endurance race and to adopt specific pacing strategies. As suggested in the study by Pageaux et al, indeed, race-related pacing strategies do not seem to be affected by mental fatigue (Pageaux et al., 2014).

Additional studies will be required to draw a firmer conclusion on the null hypothesis and provide more precise estimates of the effects of mental fatigue on endurance performance during outdoor, official, mass-start competitions. The quantification of the expected negative effect of mental fatigue on longer-term endurance performance will be the first step to develop interventions aimed at reducing mental fatigue and thus improve endurance performance, such as the Brain Endurance Training.

Chapter 5

The Effects of One-Night Sleep Deprivation and One-Night Recovery Sleep on Endurance Cycling Performance

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Main finding: 25-h sleep deprivation does not affect endurance performance and single night recovery sleep appears adequate after 25-h sleep deprivation to recover cognitive performance.

5.1 Abstract

It has been demonstrated that sleep deprivation (SD) might negatively affect endurance performance; however, whereas it has been shown that recovery is quick for cognitive performance, no physical performance data are available on how long it takes to recover from SD as yet. Therefore, the aim of the study was to investigate the acute effects of SD and recovery sleep on endurance performance by evaluating exercise and cognitive performance changes. It was hypothesised that 25-h SD would impair both endurance exercise and cognitive performance and that the following night of recovery sleep would be enough to restore baseline levels of performance. The final results of this study might provide relevant information on the potential applications of recovery sleep in endurance exercise performance.

Twenty-six amateur cyclists and triathletes (means ± standard deviation: age 30.5 ± 8.8 yr, body mass 72 ± 9 kg, height 1.77 ± 0.08 m, $\dot{V}O_{2max}$ 55.3 ± 4.9 ml/kg/min) were randomly allocated to two groups (SD and Control (CON)) and tested over three consecutive days. After baseline testing on Day 1, subjects in the SD group were instructed not to sleep for 25-h (SD condition) on Day 2, and then sleep normally the following night (recovery sleep condition) (Day 3). Subjects in the CON group were required to sleep normally throughout the entire experiment and to attend the same

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testing sessions. Endurance performance during a 20-min Time-Trial (TT) was measured after 40 minutes of cycling at 60% of participants' $\dot{V}O_{2max}$ every morning on Day 1, Day 2 and Day 3. EEG measurements and questionnaires were taken to assess sleepiness. A 10-min psychomotor vigilance test was also used to assess cognitive performance.

Ratings of sleepiness revealed a trend for a significant effect of SD (group × day interaction) (p = 0.050). However, a 2-way mixed model ANOVA revealed no significant group × day interaction effect of SD on TT work. A main pairwise comparison across days showed a decline on Day 2 (Day 1 298.5 ± 43.7 kJ, Day 2 292.5 ± 45.1 kJ, p = 0.002) and a subsequent improvement on Day 3 compared to Day 2 (Day 3 301.9 ± 46.0 kJ, p = 0.009). A significant group × day interaction effect also showed significant impairments and subsequent improvements in reaction time (RT) in the SD group following SD (p < 0.001) and recovery sleep (p = 0.002), respectively. Significant differences between SD and CON groups were also found on Day 2 (p = 0.007).

In conclusion, in the context of three consecutive bouts of endurance exercise, where cumulative fatigue and pacing strategy may play a role, one-night SD did not affect physical performance. As in previous studies, cognitive performance declined after SD and restored to baseline levels with one-night recovery sleep. The current results suggest that trained adults can maintain their physical performance after one-night SD and that one-night recovery sleep is sufficient to recover from cognitive performance impairments due to one-night SD.

5.2 Introduction

SD can be defined as a brain state caused by at least 24 hours of continuous wakefulness (Wesensten, 2012), and it is generally distinguished from sleep restriction (i.e. partial lack of sleep) and sleep fragmentation (i.e. interrupted sleep) (Boonstra et al., 2007; Jones & Harrison, 2001). It has been shown that sleep debt can be associated with different pathological origins (Tobaldini et al., 2017). Nevertheless, it has become a

common condition in our modern societies affecting millions of healthy people (Hafner et al., 2017; Leonard et al., 1998; Sparks et al., 2001), especially in industrialized countries, where working hours and night shifts have been drastically increased (Wesensten et al., 2012).

SD is a very common phenomenon occurring among soldiers (e.g. during prolonged military operations) and athletes (e.g. during ultra-endurance competitions). It has been extensively demonstrated that SD increases subjective feelings of sleepiness and fatigue and negatively affects individuals' mood (Belenky et al., 2003; Dinges et al., 1997; Jewett et al., 1999; Leonard et al., 1998). Moreover, it is also evident that SD has a detrimental effect on cognitive performance. From a behavioural perspective indeed, it has been shown that SD causes clear deficits in vigilance and sustained attention (Goel et al., 2013; Lim & Dinges, 2010; Lowe et al., 2017), in particular during vigilance-related tasks (e.g. Psychomotor Vigilance Task (PVT)), where significant increments in simple reaction times have been found (Belenky et al., 2003; Dinges et al., 1997; Jewett et al., 1999). Finally, SD has also been found to negatively affect several executive functions, including working memory (Chee et al., 2006), logical reasoning (Harrison & Horne, 2000), decision making (Harrison & Horne, 2000), planning (Nilsson et al., 2005) and learning skills (Gosselin et al., 2005).

Decrements in behavioural cognitive performance due to SD have been associated with a decreased activity and function in several specific areas of the brain (Boonstra et al., 2007). Main results from neuroimaging studies have suggested that the prefrontal cortex, area associated with executive functions, attention and arousal, together with other regions (e.g. parietal cortex and some subcortical regions, such as the thalamus), seem to play a key role when individuals encounter sleep loss (Mu et al., 2005; Muzur et al., 2002; M. Thomas et al., 2000). More precisely, these areas of the brain are subjected to a reduction in activity following SD, which have been shown to further decline during prolonged cognitive tasks (Asplund & Chee, 2013; Drummond et al., 2005; Thomas et al., 2000; Zhu et al., 2018), and to partially come back to wakeful resting levels following recovery sleep (Wu et al., 2006). Moreover, EEG experiments conducted on the topic have observed a spectral power shift toward lower frequencies, in particular a general reduction in alpha activity (8-12 Hz) and an increment in theta

activity (4-8 Hz) following SD (Boonstra et al., 2007; Cajochen et al., 1995; Finelli et al., 2000), concluding that a prevalence of slow-wave activity might provide an index of cortical deactivation and sleepiness (Borbély, 1982; Borbély et al., 1981; Brunner et al., 1993; Cajochen et al., 1995). Furthermore, the same changes in the EEG activity along the anterior-posterior axis have been reported, confirming a main local effect of SD in the prefrontal areas (Boonstra et al., 2005; Horne, 1993).

Whilst extensive research has been conducted on SD and cognitive performance, the number of studies investigating the effects of sleep loss on exercise performance, specifically on endurance exercise performance are still limited and the findings often contradictory (Fullagar et al., 2015; Thun et al., 2015). Several studies have found that endurance exercise performance, defined as any aerobic-based exercise performance lasting more than 75 seconds (Gastin, 2001), might be negatively affected by SD (Fullagar et al., 2015; Thun et al., 2015). In particular, it has been demonstrated that 25-50 h of continuous wakefulness causes decrements in endurance running, walking and cycling exercise performance, during constant-workload time to exhaustion tests (Martin, 1981; Martin & Chen, 1984; Temesi et al., 2013), an incremental test (Azboy & Kaygisiz, 2009) and a distance TT (Oliver et al., 2009). However, contrasting results have also been shown (Azboy & Kaygisiz, 2009; Pickett & Morris, 1975; Racinais et al., 2004) and future investigation is required to better understand the role played by SD on endurance exercise performance. Moreover, the reasons why SD might negatively affect endurance exercise performance are also still unclear. Several findings have shown significant negative effects on RPE (Bond et al., 1986; Martin, 1981; Martin & Gaddis, 1981; Oliver et al., 2009; Symons et al., 1988; Temesi et al., 2013) and no evident cardio-respiratory parameters alterations following SD (Azboy & Kaygisiz, 2009; Martin & Haney, 1982; Martin, 1981; Mougin et al., 1989, 1991; Oliver et al., 2009; Plyley et al., 1987), suggesting that perception of effort might be the limiting factor of endurance exercise performance during a sleep-deprived state (Temesi et al., 2013).

One of the main effective ways to counteract SD is sleep itself. Indeed, it has been demonstrated that nights of recovery sleep following SD are beneficial to increase cognitive performance (Balkin et al., 2005; Belenky et al., 2003; Corsi-Cabrera et al.,

1996; Drummond et al., 2006; Lorenzo et al., 1995; Rosa et al., 1983; Rupp et al., 2009; Wesensten et al., 2005b). However, the effects of recovery sleep on endurance exercise performance following SD have never been tested as yet.

Therefore, the aim of this study was to investigate the acute effects of one-night SD and the following night of recovery sleep on endurance performance by evaluating exercise and cognitive performance changes. Specifically, it has been hypothesized that 25-h SD would impair both endurance exercise and cognitive performance and that the following night of recovery sleep would be enough to restore performance rested levels. In order to objectively assess sleepiness, a valid and sensitive resting EEG test (i.e. Alpha Attenuation Test (Stampi et al., 1995)) has been used. In agreement with previous studies (Alloway et al., 1997; Lakocevic et al., 2013; Stampi et al., 1995), it has been hypothesised a reduction in the Alpha Attenuation Coefficient (i.e. alpha mean power ratio between eyes closed/eyes open) in the frontal area following SD, and a subsequent increase after the night of recovery sleep.

5.3 Methods

Participants

Twenty-six trained cyclists and triathletes (means ± SD: age 30.5 ± 8.8 yr, body mass 72 ± 9 kg, height 1.77 ± 0.08 m, $\dot{V}O_{2max}$ 55.3 ± 4.9 ml/kg/min) undergoing more than 3 hours of moderate to high-intensity cycling training per week were recruited. Subjects were also selected on the basis of their chronotype and sleep quality/disturbances over a one-month period before the experiment. Chronotype and quality of sleep were assessed using the Horne and Ostberg "morningness-eveningness" questionnaire (MEQ) (Horne & Ostberg, 1976) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) respectively. Only "moderate evening, intermediate and moderate morning type" (MEQ score between 30 and 70), "good-sleeper" (PSQI < 5) subjects were included in the study. Subjects with pulmonary, cardiovascular or metabolic diseases and those unable to perform the required exercises were excluded. Prior to the experiment participation all subjects were informed about the study protocol and signed an informed consent

form. All the procedures used were approved by the School of Sports and Exercise Sciences Ethics Committee and were conducted in conformity with the Declaration of Helsinki.

Experimental Design

A randomised, controlled, between-group, experimental design was used. Participants were randomly allocated into two independent groups and asked either not to sleep for one night (i.e. total of 25 hours of SD) and to recover from SD the night after (recovery sleep) (experimental treatment) or to sleep normally throughout the entire experiment (control treatment). The intervention was carried out at the School of Sport and Exercise Sciences, University of Kent, Medway Campus. Both exercise and cognitive testing were conducted in the Psychobiology Laboratory of the School. The night of SD took place in a quiet room of the same building.

All subjects were asked to attend the laboratory on four separate visits throughout the experiment (*Familiarisation* and three *Experimental Visits* on *Days 1-3*) (See *Testing Procedures* and Fig.1 for more details). The *Familiarisation* visit was carried out between 3-6 days prior to the experiment. The three experimental visits were conducted after one night of normal sleep (*Day 1*, baseline condition), after one night of SD (experimental group) or normal sleep (control group) (*Day 2*, SD condition), and after one night of recovery sleep (experimental group) or normal sleep (control group) (*Day 3*, recovery sleep condition). These visits were conducted in three consecutive days. All visits commenced at 8:00 am and carried out between 8:00 and 11:00 am, time frame during which lack of sleep seems to have the most negative impact on cognitive function (Mollicone et al., 2010).

In order to avoid postprandial thermogenesis effects (Brondel et al., 1999; Zammit et al., 1992) and to limit inter-individual variability among participants (Bougard et al., 2009), subjects were asked not to eat in the 12 hours before the experimental visits. Nevertheless, in order to avoid the risk of hypoglycaemia during exercise testing (Sedliak et al., 2007), participants have been provided with a standardised light breakfast prior to the experimental visits. To assure that meals eaten

and hydration status would not have affected SD (Smith et al., 1993) participants were instructed to maintain their habitual diet and to drink an amount of water equal to 35 ml/kg of body mass per day. Caffeine and alcohol were prohibited in the 12 hours before each visit. Participants were asked to maintain their habitual physical activity throughout the experimental period and to avoid strenuous activity during the 24 h prior to each testing. Personal 3-day food, sleep and physical activity diaries were given to subjects in order to monitor their dietary, sleep and physical activity behaviour during the experiment. A monetary reward (£100 in Amazon voucher) was given to all participants who completed the experiment.

Testing Procedures

Familiarisation

During this visit, participants were informed about the testing procedures and were subjected to an initial health screening consisting of a PAR-Q questionnaire. In order to verify that our participants followed all the instructions previously given, they were asked to complete a pre-experimental checklist. They were also required to inform researchers about any acute illness, infection and/or injury and to give notice of any medication/drug taken. Eligible subjects signed an informed consent form. Following the collection of the main anthropometric measurements (weight and height), subjects were then asked to execute a ramp incremental test on a cycle ergometer (Cyclus2, RBM elektronik-automation GmbH, Leipzig, Germany). Prior to the testing, participants were required to do a 5-min warm-up at 100 W. The test commenced immediately after the end of the warm-up, starting from 100 W and increasing the work rate by 30 W/min, at a constant rate of 1 W every 2 seconds, until exhaustion. Participants were asked to maintain a preferred but relatively constant pedalling cadence. Exhaustion was defined when pedalling cadence dropped below 60 rpm, despite strong verbal encouragement. Participants were only allowed to see their cadence during the test. No further feedback related to their performance was given. Pulmonary gas exchange measurements were collected breath-by-breath throughout the

entire test (MetaLyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany). Finger capillary blood samples (i.e. 10 µl) were taken before and immediately after the test (within 60 s; exhaustion condition). Blood lactate concentrations were measured (Biosen; EFK Diagnostics, London, UK) as an indicator of maximal effort (Howley et al., 1995). HR was collected throughout the entire test (Polar V800, Polar Electro Oy, Kempele, Finland). RPE was taken every minute using Borg's 15-point scale (Borg, 1998). Participants were given standard instructions about the scale. Moreover, anchoring procedures for determining the low and high anchor points in the scale were used during the incremental test (Noble & Robertson, 1996). The work rate that would require 60% of participants $\dot{V}O_{2max}$ was then calculated. Finally, subjects were familiarised with all the testing protocols and procedures used in the *Experimental Visits*.

Experimental Visits

Testing procedures were identical in each experimental visit. Participants were asked to attend the laboratory at 08:00 am. In order to verify that participants followed all the instructions given during the *Familiarisation* visit, they were required to complete a pre-experimental checklist. At this point, subjects' weight was checked and a standardised breakfast given. Breakfast consisted in one glass (150 ml) of orange juice (32 kcal, Tropicana Trop 50, Tropicana Products, Chicago, Illinois, USA) and two energy bars (90 kcal per bar, Special K, Kellogg Company, Battle Creek, Michigan, USA).

In order to assess sleepiness and mood, subjects were asked to complete the Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) and the Brunel Mood Scale (BRUMS), respectively (Terry et al., 2003) (See *Psychological Questionnaires* for more details). Prior to both cognitive and exercise testing, participants were required to wear an electroencephalography (EEG) cap (See *EEG procedures* for more details). Resting EEG measurements were collected. Specifically, subjects were asked to complete the 12-min Alpha Attenuation Test (AAT) (Stampi et al., 1995), a valid and sensitive method to assess decrements in alertness due to sleep deprivation (See *Cognitive Testing*

for more details). Subjects were then required to perform a 3-min Stroop Test and a standard 10-min PVT, as objective measurements of cognitive performance impairments produced by sleep loss (Balkin et al., 2004; Basner & Dinges, 2011) (See *Cognitive Testing* for more details).

Finally, participants were asked to perform a cycling testing. Following a 3-min warm-up at a preferred intensity, subjects were required to complete a motivation questionnaire related to the cycling testing to be performed immediately after (See *Psychological Questionnaires* for more details). The exercise testing consisted of a 40-min cycling pre-load at 60% of subjects VO_{2max} followed by 20-min TT. The two cycling bouts have been inter-spread by 5-min resting. Prior to each TT, subjects were instructed to give their best performance and to do as much work as possible. Participants were allowed to see the time left. No verbal encouragement was given. Participants were not aware of their performance throughout the entire experiment. Finger capillary blood samples were collected at rest (immediately before the test), at 8-min intervals during the constant-workload pre-load bout and immediately after the TT (within 60 s from the end of the test). Blood lactate concentrations were analysed. RPE and ratings of feeling were collected every 5 minutes throughout the entire test using the Borg's 15-point scale (Borg, 1998) and the bipolar Feeling scale (Hardy & Rejeski, 1989). Heart rate was collected continuously during the test using a heart rate band (V800, Polar Electro Oy, Kempele, Finland).

In order to estimate the subjective workload perceived, participants were asked to complete the validated multidimensional scale NASA-TLX (Hart & Staveland, 1988) immediately after the cycling testing. In order to assess any change in sleepiness and mood between the beginning and the end of the visits, they were required to complete again both the Karolinska Sleepiness Scale and the BRUMS (See *Psychological Questionnaires* for more details).

A monetary reward of £300, £200 and £100 in Amazon vouchers were given to the first, second and third best TT performances in each group (average of the three TT testing).

Sleep Procedures

All participants were asked to sleep normally (i.e. 7/8 hours) the night before the first experimental visit on *Day 1*. In order to limit sleep inertia effects (Tassi & Muzet, 2000), subjects were required to wake-up at around 07:00 am and to attend the laboratory at 08:00 am. Following the first visit, subjects were allowed to leave and they were either required not to sleep for 25 hours (SD condition) or to sleep normally at home (control condition) during the night prior to the second visit (i.e. *Day 2*). Participants in the SD group were asked to spend the night of SD (from 08:00 pm to 08:00 am the morning after) in the student hub of the School of Sports and Exercise Sciences. In order to avoid any napping, food consumption and use of caffeinated beverages, participants were strictly monitored by one member of the research staff. During the night subjects were allowed to spend their time in no-cognitive demanding activities such as reading magazines, watching movies, playing video games and having a conversation with the researcher (Plukaard, 2015; Shortz et al., 2015). At 02:00 am participants were allowed to eat one energy bar (90 kcal, Special K, Kellogg Company, Battle Creek, Michigan, USA). The following morning, on *Day 2,* all participants were asked to attend the second visit at 08:00 am. Subjects were then allowed to leave the laboratory. They were asked to sleep at home during the upcoming night and to attend the third and last visit the morning after, on *Day 3,* always at 08:00 am. Participants in the SD group were allowed to go to sleep earlier (i.e. from 09:00 pm onwards), but to always wake up at 07:00 am. All subjects were instructed not to take any nap during the three experimental days. A wrist actigraph device (AW Spectrum PRO, Philips Respironics, Murrysville, Pennsylvania, USA) was used to monitor and quantify participants' sleep-wake activity. Participants were asked to wear the device for the entire duration of the experiment (i.e. from 08:00 am the day before the beginning of the experiment).

EEG procedures

EEG data were collected using a wireless 32-channel cap (g.Nautilus EEG system, g.tec Medical Engineering GmbH, Schiedlberg, Austria) with an active, gel-based Ag/AgCl electrode technology (g.LADYbird; g.tec Medical Engineering GmbH, Schiedlberg, Austria). The 10-20 international system was used for the electrodes placement in the cap, with the reference placed on the right earlobe and the ground electrode on the AFz site. Sampling frequency was set up at 500 Hz with 12-bit resolution. A 0.5 Hz – 30 Hz bandpass and a 48 – 52 Hz notch filter was also applied. Electrode impedances were checked prior to testing and maintained to < 30 kΩ. EEG data were transmitted wireless (i.e. Bluetooth system) via the 2.4 GHz band through a receiver connected to a computer. The Matlab software (R2014a, Mathworks, Natick, Massachusetts, USA) was used for data acquisition and analysis.

Cognitive Testing

AAT. The AAT was used to assess objective decrements in alertness due to SD (Stampi et al., 1995). Participants were asked to sit down in the laboratory (which was normally lit (100-150 lux), remain relaxed but awake (Stampi et al., 1995) and to look at a fixation point (i.e. white asterisk on a black background) on a computer screen in front of them (Zunini et al., 2013). The test consists of alternating 2-min eyes closed with 2-min eyes opened for 12 minutes. EEG was recorded continuously throughout the entire test. In order to avoid noise in the EEG signal, subjects were instructed to avoid blinking and to refrain from moving and contracting any facial muscles.

Stroop Test. A 3-min Stroop Test was used as an objective measure of vigilance impairments produced by sleep loss (Balkin et al., 2004). The test included a block of 25 randomly selected trials. The visual stimulus used was either an incongruent colour word (i.e. colour word not corresponding to colour ink; 20 trials) or a congruent colour word (i.e. colour word corresponding to colour ink; 5 trials). Participants were required to press the button of a response pad (RB-730, Cedrus Corporation, San Pedro,

California, USA) corresponding to the colour ink appearing in front of them on a computer screen. Five colours were used for this test: white, red, green, yellow and blue. Words appeared in the centre of the screen on a black background in an Arial Rounded MT font, bold style, 18 font size. The duration of the stimulus appearance on the screen was infinite. A white fixation point (i.e. five aligned asterisks) preceded the stimulus in the same position on the screen on a black background in an Arial rounded MT font, bold style, 36 font size. The duration of the fixation point on the screen was 500 ms. Participants were asked to be as fast and accurate as possible in their response. They were also required to complete a practice trial (i.e. 25 randomly selected trials) at any visit, immediately before testing. The Stroop Test used was generated and run using the E-Prime 2.0 software (Psychology Software Tools, Inc, Pennsylvania, USA).

PVT. The computerised version of the 10-min PVT was also used to assess vigilance reductions induced by SD (Balkin et al., 2004; Basner & Dinges, 2011). Subjects were instructed to press the keyboard button "spacebar" with their preferred hand as soon as a visual stimulus appeared in the centre of a computer screen. Participants were asked to be as fast as possible in their response throughout the entire test. The visual stimulus was a fixed graphic bullseye on a white background. The inter-stimulus interval (i.e. period between a response and the next stimulus) was randomized and varied from 2,000 to 10,000 ms. Reaction times were considered valid only if ≥ 150 ms. Responses < 150 ms were considered as false starts (i.e. errors of commission). Responses ≥ 500 ms were counted as lapses (i.e. errors of omission). Wrong responses (i.e. pressing another button in the keyboard) and no responses (i.e. > 30,000 ms) were also treated as errors. Feedbacks (i.e. reaction time in ms) were provided after each response and appeared centrally on the screen for 1,000 ms prior to the new stimulus. In case of responses < 150 ms, a message "false start" was displayed. Simple RT (ms), response speed (1/RT), false responses (< 150 ms) and minor lapses (≥ 500ms) were assessed as sensitive measures to SD (Basner & Dinges, 2011). The PVT was generated and run using the E-Prime 2.0 software (Psychology Software Tools, Inc, Pennsylvania, USA).

Psychological Questionnaires

Sleepiness. The Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) was used to assess subjective levels of sleepiness before and after the experimental visits. The scale consists of 9-point Likert scale (where 1 = extremely alert, 2 = very alert, 3 = alert, 4 = rather alert, 5 = neither alert nor sleepy, 6 = some signs of sleepiness, 7 = sleepy, but no effort to keep awake, 8 = sleepy, some effort to keep awake, 9 = very sleepy, great effort to keep awake, fighting sleep).

Mood. The BRUMS (Terry et al., 2003) was used as a measurement to evaluate subjects' mood before and after the experimental visits. This questionnaire is a shorter version of the POMS and it consists of 24 items (e.g. tired, anxious, nervous, confused, energetic, active) to be answered on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Items are allocated into six specific subscales: anger, confusion, depression, fatigue, tension and vigour. Each subscale includes four related items and can reach a score between 0 and 16.

Workload. The multidimensional scale NASA TLX (Hart & Staveland, 1988c) was used to estimate the subjective workload experienced during the cycling testing. The NASA TLX includes six subscales: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort and Frustration. Subjects were asked to circle one of the 20 line intervals on each of the six scales at the point which matched their experience. Each line has two endpoint descriptors "very low" and "very high" that describe the scale. The performance-related subscale is reversed going from "good" on the left to "poor" on the right.

Motivation. Intrinsic motivation and success on task motivation scales (Matthews et al., 2001) was used to assess motivation related to the cycling testing. Each scale includes 7 items to be scored on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = somewhat, 3 = very much, 4 = extremely). The total range of scores for each scale is between 0 and 28.

EEG Data Analysis

The EEG analysis was done at the sensor level. EEG data were analysed using SPM v12 (statistical parametric mapping, Wellcome Trust, London, UK). Data was filtered for 0.5-30 Hz using 7th order Butterworth filter, downsampled to 128Hz, and montaged based on average electrode activity. Then, eye-blinks were removed using activity of the Fp2 electrode. Spatial confounds were indicated based on Singular Value Decomposition (SVD) mode and sensor data was corrected using Signal-Space Projection (SSP) correction mode. A maximum of two components of spatial confounds was removed from the EEG data.

Our main interest was in the activity in electrode Fz and frequency band of low-Alpha (9-11 Hz). The section of the interest was extracted from the data. Time-frequency analysis was conducted on a frequency range of 0.5-15 Hz using Morlet wavelet transformation with 7 wavelet cycles. Time-frequency data was then rescaled to log-ratio based on 100 ms activity prior to the beginning of each data section. Finally, data was averaged over time and frequency band.

Statistical Analysis

2-way mixed-model ANOVAs (group × day) were used to analyse differences in endurance exercise performance (i.e. work (kJ), primary outcome variable) and cognitive performance (i.e. PVT and Stroop task, secondary outcome variables). 3-way mixed-model ANOVAs (group × day × time or condition) were used to analyse physiological and perceptual responses and EEG activity (thirdly outcome variables). When the assumption of sphericity was not met, the Greenhouse-Geisser correction was used. Significant interaction effects were followed up using Post hoc Tukey's HSD adjusted *t*-tests. The Shapiro-Wilk test, histograms, Q-Q plots and boxplots were used to check for all data normality. Statistical significance was accepted at $p < 0.05$ level. All data are presented as means ± SD, unless otherwise stated. The SPSS (version 24.0; SPSS, Chicago, Illinois, USA) statistical package was used for all data analyses.

5.4 Results

Participants characteristics

Participants' features (general and per group) are reported in Table 5.1. Participants' sleep data are reported in Table 5.2.

Table 5.1. *Participants features (N = 26)*

	SD Group (N = 13)	CON Group (N = 13)	Total Participants (N= 26)	Total Range
Age (years)	31.1 ± 9.6	29.8 ± 9.3	30.5 ± 8.8	19.0 – 51.0
Height (m)	1.75 ± 0.07	1.75 ± 0.10	1.77 ± 0.08	1.59 – 1.92
Weight (kg)	73.8 ± 9.7	69.4 ± 6.8	72.4 ± 8.6	58.0 – 90.0
$\dot{V}o_{2max}$ (ml/kg/min)	54.2 ± 5.1	56.4 ± 4.6	55.3 ± 4.9	47.0 – 65.3

$\dot{V}o_{2max}$, maximal oxygen uptake. Data are shown as means ± SD. No differences between SD and CON group features ($p > 0.05$).

Table 5.2. *Total amount of sleep hours per group at Day 1, Day 2 and Day 3*

	Day 1 (h)	Day 2 (h)	Day 3 (h)
SD Group (N = 11)	6.7 ± 0.7	0.0 ± 0.0	8.7 ± 1.1
CON Group (N = 12)	6.7 ± 0.9	7.1 ± 1.0	7.0 ± 1.0

SD Group, sleep deprivation group. CON Group, control group.
Data are shown as means ± SD. Due to technical problems with the actiwatch, data from three participants were not recorded.

Manipulation checks

Subjective ratings of sleepiness prior to and following each visit revealed significant group × day interaction effects of SD (sleepiness pre, p = 0.005; sleepiness post, p = 0.010) (Figure. 5.1). Follow-up analyses indicated greater pre- and post-visit levels of sleepiness following SD compared to baseline in the SD group (sleepiness pre, p = 0.012; sleepiness post, p = 0.001). Subsequent decrements in levels of sleepiness were

also found following recovery sleep in the SD group (sleepiness pre, p = 0.045; sleepiness post, p = 0.004). Significantly higher levels of sleepiness were found in the SD group compared to the CON group on Day 2 (sleepiness pre, p < 0.001; sleepiness post, p = 0.040).

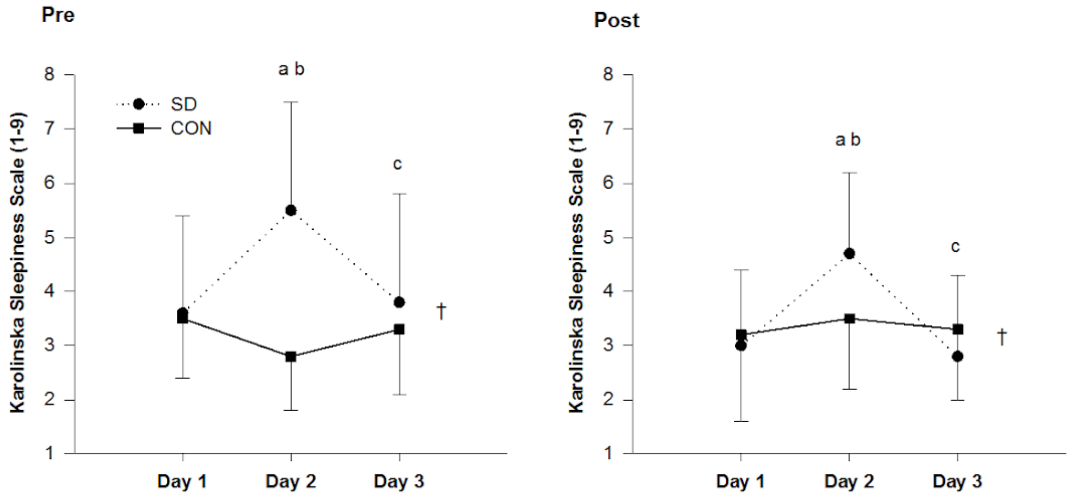
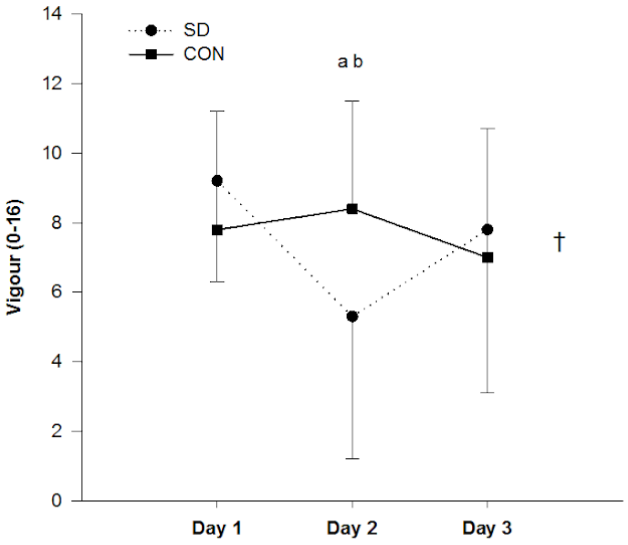


Figure. 5.1. Group mean ± SD changes in the subjective levels of sleepiness Pre and Post testing measured at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). † = significant group × day interaction effect (p < 0.05); a = SD group different from Day 1 (p < 0.05); b = SD group different from CON group at Day 2 (p < 0.05); c = SD group different from Day 2 (p < 0.05).

Subjective vigour and fatigue (BRUMS) prior to the visits showed significant interaction effects (vigour, p = 0.038; fatigue, p < 0.001) (Figure. 5.2), with less vigour (p = 0.005) and greater fatigue (p = 0.001) following SD and lower fatigue following recovery sleep (p = 0.024) in the SD group. No significant increments in vigour were found following recovery sleep (p = 0.139) in the SD group. Higher rates of fatigue were found at Day 3 compared to Day 2 in the CON group as well (p = 0.030). Significantly higher fatigue was observed in the SD group compared to the CON group following SD (p < 0.001). A significant difference in vigour was also found between groups at Day 2 (p = 0.041). The NASA TLX completed immediately after the cycling testing showed no significant group × day interaction effect.

A



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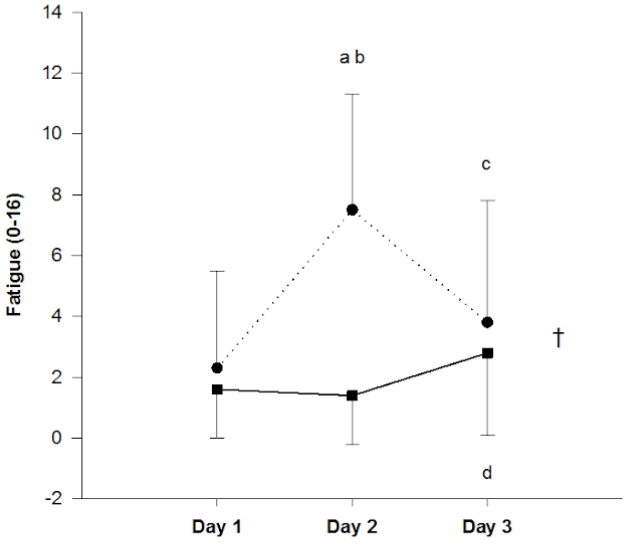

Figure. 5.2. Group mean ± SD alterations in the subjective levels of vigour (A) and fatigue (B) measured at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). † = significant group × day interaction effect ($p < 0.05$); a = SD group different from Day 1 ($p < 0.01$); b = SD group different from CON group at Day 2 ($p < 0.05$); c = SD group different from Day 2 ($p < 0.05$); d = CON group different from Day 2 ($p < 0.05$).

Motivation

Whereas, success in the task (i.e. cycling test) motivation did not vary significantly (p = 0.948), a group × day interaction effect on intrinsic motivation was found ($p < 0.001$) (Figure. 5.3). A post-hoc analysis revealed no significant differences between groups throughout each visit. However, lower levels of intrinsic motivation were reported in the SD group on Day 2 compared to Day 1 ($p = 0.001$) and Day 3 ($p = 0.001$).

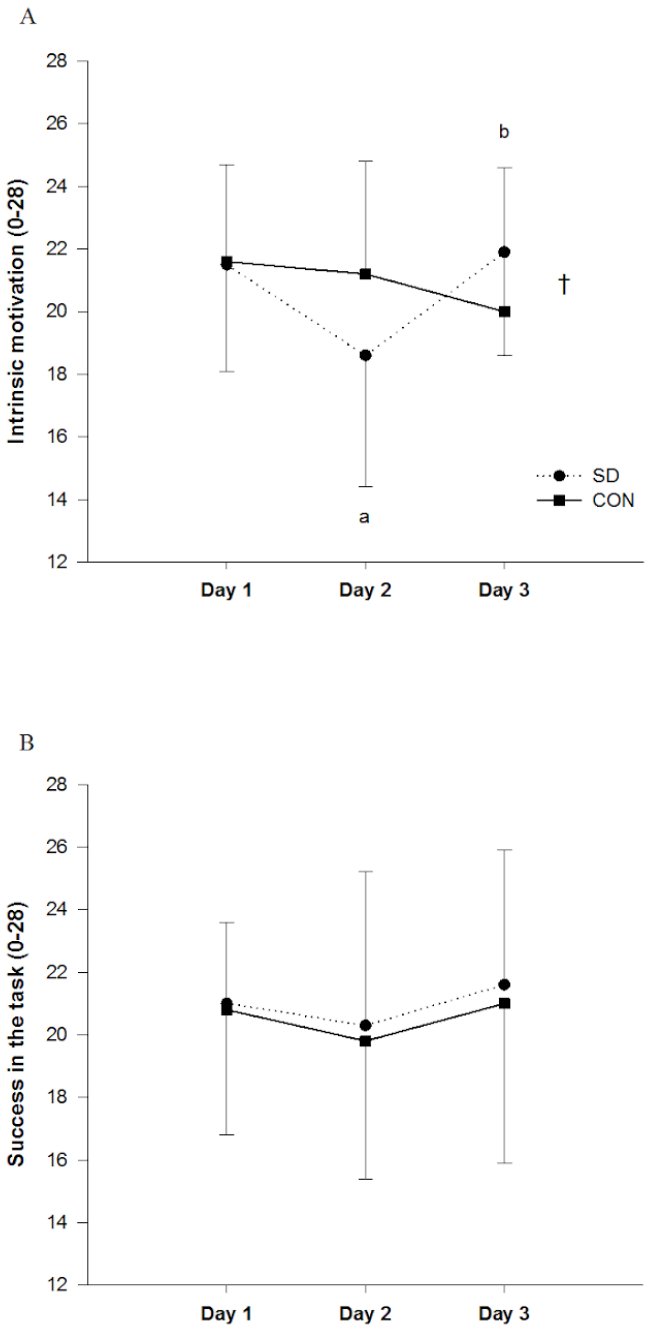

Figure. 5.3. Group mean ± SD alterations in intrinsic motivation (A) and success in the task motivation (B) measured at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). † = significant group × day interaction effect ($p < 0.001$); a = SD group different from Day 1 ($p < 0.001$); b = SD group different from Day 2 ($p < 0.001$).

Pre-load perceptual and physiological responses (Figure. 5.4)

A significant group × day interaction was found on RPE (p = 0.013) for SD. Post-hoc analysis revealed a trend for higher RPE in the SD group compared to the CON group on Day 2 (p = 0.060). Moreover, higher RPE was found in the SD group on Day 2 compared to Day 1 (p = 0.023). Although lower ratings of perceived exertion on Day 3, no significant differences were shown between SD and recovery sleep condition (p = 0.085).

A significant group × day interaction effect was also found on ratings of feeling (p = 0.040) for SD. Significantly lower ratings of feeling were found in the SD group compared to the CON group on Day 2 (p = 0.024). Significant decrements following SD (p = 0.013) and subsequent increments following recovery sleep (p = 0.032) were also shown in the SD group. No significant group × day × time interactions were found both on RPE (p = 0.118) and ratings of feeling (p = 0.307).

HR measurements did not show any significant group × day interaction (p = 0.744), but a significant group × day × time interaction effect was found (p = 0.047). No significant group × day or group × day × time interactions effects were found on lactate measurements.

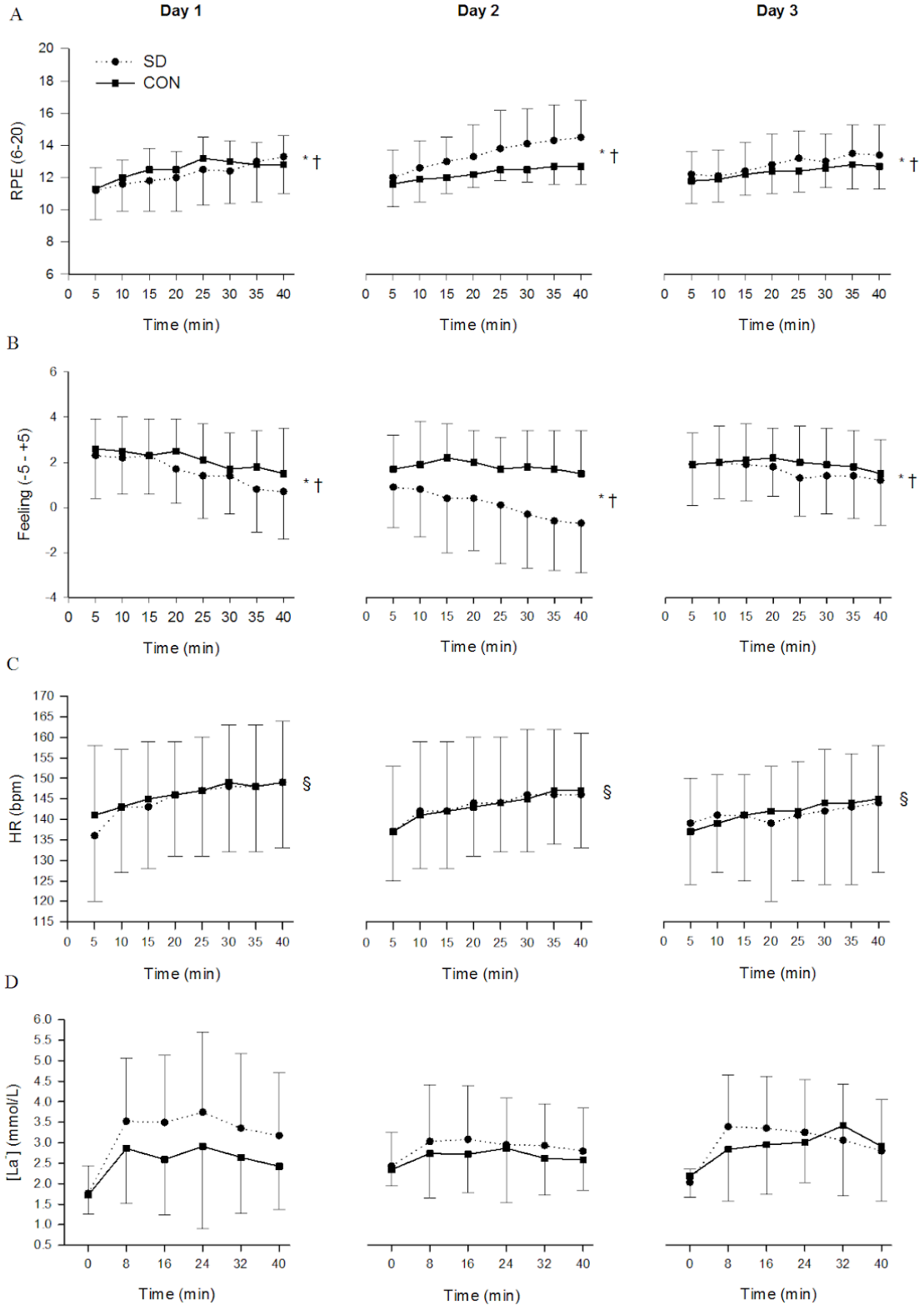

Figure. 5.4. Group mean ± SD changes in RPE (A) feeling (B) HR (C) and blood lactate concentrations (D) measured during the 40-min constant pre-load at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). * = significant main effect of time ($p < 0.05$); † = significant group × day interaction effect ($p < 0.05$); § = significant group × day × time interaction effect ($p < 0.05$).

TT performance (Figure. 5.5)

A 2-way mixed model ANOVA (group × day) revealed no significant interaction effect of SD on TT work (p = 0.126). However, a main effect of day was found (p < 0.001) and the main pairwise comparison across days (from the ANOVA analysis) showed a decline on Day 2 (Day 1 298.5 ± 43.7 kJ, Day 2 292.5 ± 45.1 kJ, p = 0.002) and a subsequent improvement on Day 3 compared to Day 2 (Day 3 301.9 ± 46.0 kJ, p = 0.009).

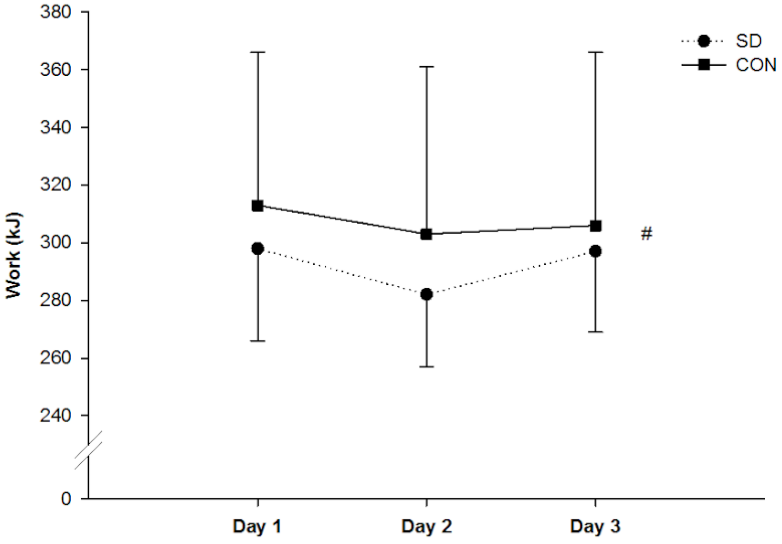

Figure. 5.5. Group mean ± SD Work (kJ) variations measured during the 20-min TT at Day 1, Day 2 and Day 3 in SD (open line) and CON group (solid line). # = significant main effect of Day (p < 0.001). See text for follow-up tests.

TT perceptual and physiological responses (Figure. 5.6)

Whereas RPE and ratings of feeling during the TT did not show any significant interaction for SD, a significant group × day interaction on HR was found (p = 0.027). Follow-up analysis revealed that lower HR values were found in the SD group on Day 2 compared to Day 1 (p < 0.001) and compared to Day 3 (p = 0.005). The CON group also showed significant decrements on HR compared to baseline (Day 1 vs Day 2, p = 0.018; Day 1 vs Day 3, p = 0.001).

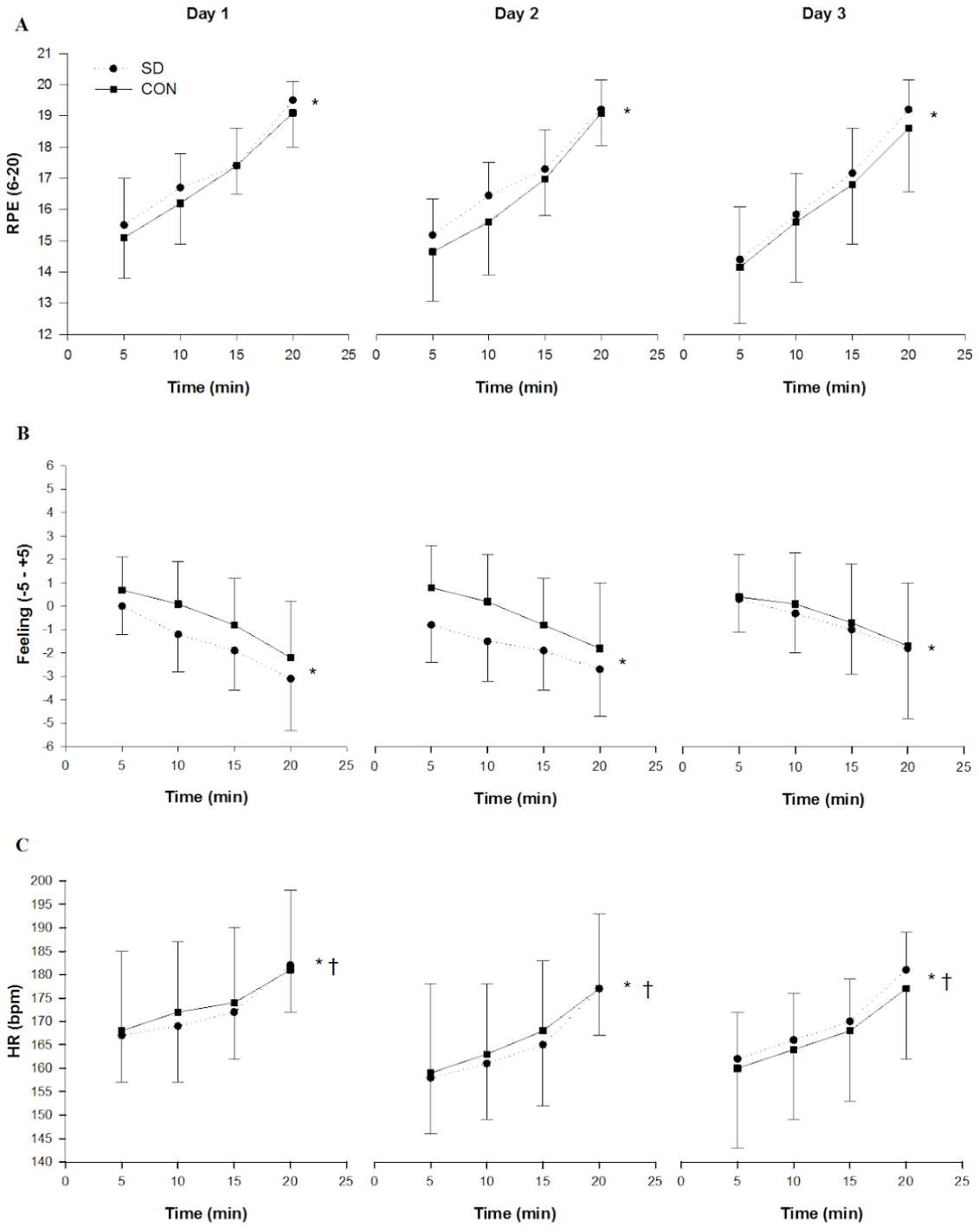

Figure. 5.6. Group mean ± SD changes in RPE (A) feeling (B) and HR (C) measured during the 20-min TT at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). * = significant main effect of time ($p < 0.05$); † = significant group × day interaction effect ($p < 0.05$).

Cognitive performance (Figure. 5.7)

Mean RT in the PVT showed a significant group × day interaction effect for SD ($p < 0.001$). Follow-up analysis indicated significant impairments in the SD group following SD ($p < 0.001$) and subsequent improvements following recovery sleep ($p = 0.002$). Significant differences between SD and CON groups were also found on Day 2 ($p = 0.007$).

1/RT ($p < 0.001$) and number of lapses ($p = 0.045$) also showed significant group × day interaction effects. Specifically, follow-up analysis on 1/RT found significant decrements on Day 2 compared to Day 1 ($p < 0.001$) and significant increments on Day 3 compared to Day 2 ($p = 0.003$) in the SD group. Moreover, lower 1/RT was found in the SD group compared to the CON group on Day 2 ($p = 0.008$).

Number of lapses was significantly higher in the SD group compared to the CON group ($p = 0.034$). Significant differences were found between Day 1 and Day 2 in the SD group ($p = 0.049$), whereas no significant differences were shown between Day 2 and Day 3, always in the SD group ($p = 0.080$).

No significant performance changes were found in the Stroop task.

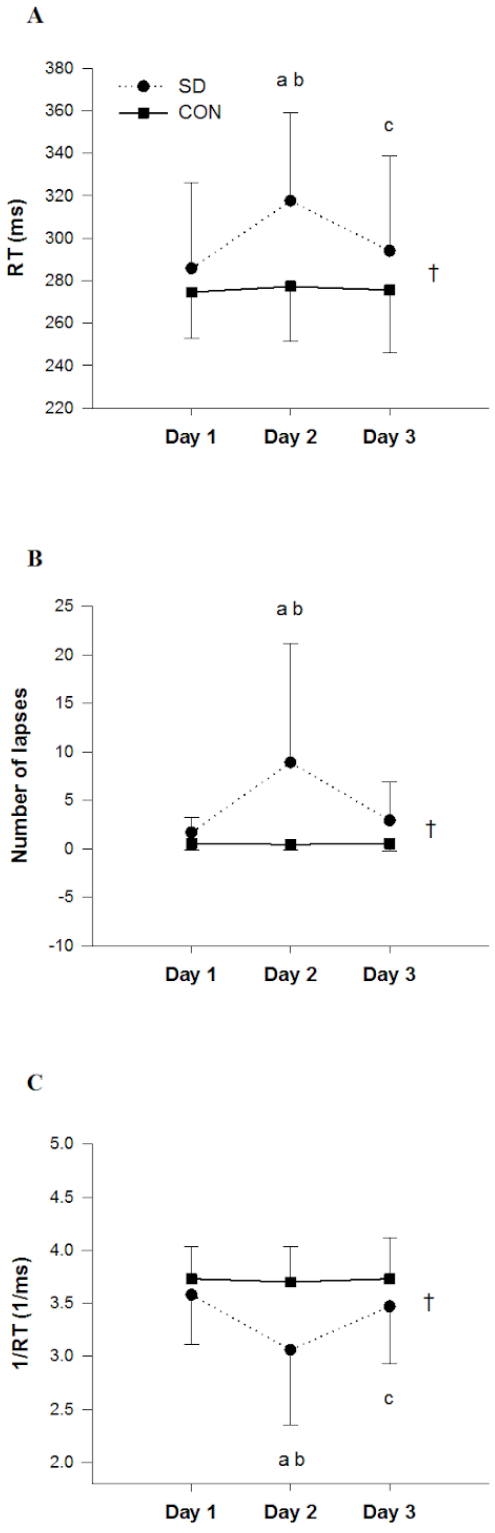

Figure. 5.7. Group mean ± SD changes in RT (A), number of lapses (B) and 1/RT (C) measured during the PVT at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). † = significant group × day interaction effect ($p < 0.05$); a = SD group different from Day 1 ($p < 0.05$); b = SD group different from CON group at Day 2 ($p < 0.05$); c = SD group different from Day 2 ($p = < 0.01$).

AAT

EEG data from only 8 and 6 participants in the SD and CON group, respectively, were taken into consideration for the analysis. Data from the remaining subjects were excluded for different reasons, such as bad EEG recording, too many artefacts, and considerable changes between sessions (i.e. more than 2 SD above/below the mean).

A significant group × day interaction effect was found on the normalised alpha power ratio eyes closed/open in the Fz channel (p = 0.039). Normalisation was done by dividing Day 2 and Day 3 values by Day 1 values. A post-hoc analysis showed that the alpha power ratio in the SD group was significantly lower at Day 2 compared to Day 1 (t (7) = -3.871, p = 0.003). This decrease in power was followed by a subsequent increase on Day 3, which, however, was not significantly different from Day 2 (t (7) = -1.571, p = 0.08) (Figure. 5.8 and 5.9).

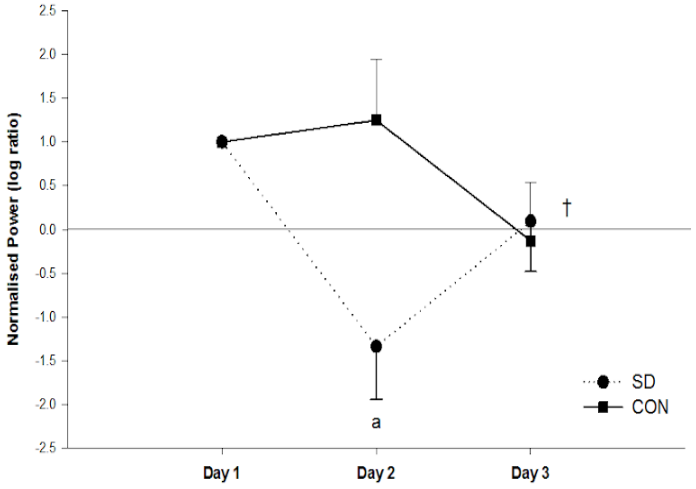

Figure. 5.8. Group mean ± Standard Error of the mean (SE) changes of channel Fz in the normalised alpha power activity ratio during the AAT measured at Day 1, Day 2 and Day 3 in the SD group (open line) and CON group (solid line). † = significant group × day interaction effect (p < 0.05); a = SD group different from Day 1 (p < 0.01).

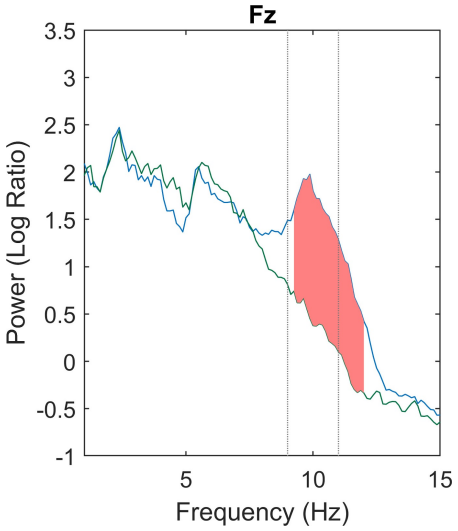

Figure. 5.9. Changes of power activity at the Fz channel over 0.5-15 Hz range of frequency between eyes open (green line) and eyes closed (blue line). The red area shows significant differences between the activity during eyes open and closed ($p < 0.05$). The vertical grey lines define the lower-alpha band (9-11 Hz). Data in this figure are collapsed over visit and condition.

5.5 Discussion

The main finding of this study revealed that, whereas one night of SD has negative effects on cognitive performance and the following night of recovery sleep brings cognitive performance levels back to baseline, one night of SD seems not to be detrimental on endurance exercise performance during a 20-min cycling TT in the context of three consecutive days of TTs. In support to our main hypothesis, though, negative alterations during the 40-min constant-intensity pre-load have been found following one night of SD on both perception of effort and affective valence. Moreover, these findings are in conjunction with no significant alterations in HR and lactate concentrations. The current results have also shown that one night of recovery sleep after one night of SD is beneficial, inducing a return to baseline values of RPE (even though it does not statistically differ from the SD condition) and a significant improvement in subjective feelings during the same bout of submaximal exercise.

Markers of SD and recovery sleep

In agreement with previous studies (Belenky et al., 2003; Dinges et al., 1997; Jewett et al., 1999), an increase in subjective ratings of sleepiness after one night of SD followed by a subsequent decrease after the night of recovery sleep has been detected. Although no significant changes in the NASA-TLX have been found, significantly greater levels of fatigue and lower levels of vigour (BRUMS) following SD have also been shown, confirming a state of sleepiness and fatigue in the SD group. Moreover, subsequent significant decrements in levels of fatigue and higher levels of vigour (although not significant) following one night of recovery sleep suggests that one night of recovery sleep might be enough to recover from one night of SD from a subjective perspective.

From an objective perspective, the AAT has revealed a decrease in the alpha mean power ratio eyes closed/open (Alpha Attenuation Coefficient) at the Fz channel following SD, with the alpha activity during eyes closed lower and during eyes open higher compared to resting state. These results confirm a decrease in alertness level at Day 2, following one night of SD, and a subsequent increase at Day 3, following one night of recovery sleep.

Motivation in the endurance exercise task

In the present study no differences on success in the exercise-task motivation have been observed. However, significantly lower levels of intrinsic motivation have been reported at Day 2 following SD, compared to the one shown at Day 1 and Day 3. These findings suggest that SD might have caused substantial drops in participants' intrinsic interest for the task. However, the external monetary reward might have preserved participants' success in the task motivation, essential to accomplish high performance (Matthews et al., 2001).

Effects of SD and recovery sleep on the 40-min constant pre-load

Whereas, no alterations in HR and lactate concentrations have been found, perception of effort and affective valence assessed during the 40-min constant-intensity pre load have been negatively affected by one night of SD, with averagely higher ratings of perceived exertion and worse ratings of feeling throughout the entire test. The present findings are in agreement with previous experiments (Martin & Haney, 1982; Martin, 1981; Martin & Gaddis, 1981; Mougin et al., 1991), confirming the efficacy of acute SD on perceptual responses during sub-maximal endurance exercise and adding further evidence on the primary role played by perception of effort on endurance exercise performance (Temesi et al., 2013). Further research is crucial to understand the reasons why perceived exertion is higher in sleep deprived subjects. The most probable explanations have already been provided in the context of mental fatigue by (Marcora et al., 2009). Being lack of sleep, one of the main determinants of mental fatigue, a sleep-deprived state itself might affect those central processing of sensory inputs which produce perception of effort during exercise (Marcora, 2009). Moreover, it can also be hypothesised that SD might alter specific cortical regions, such as the ACC (Paus, 2001), whose changes of activity have been shown to be correlated with RPE variations both under hypnosis manipulations during physical exercise and motor imagery (Williamson et al., 2006; Williamson et al., 2001, 2002). EEG and neuroimaging studies on SD and during endurance exercise are required to confirm these speculations.

Effects of SD and recovery sleep on the 20-min TT

The statistical analysis has shown that SD did not negatively affect the 20-min TT performance, highlighting the same performance pattern between the two groups throughout the three repeated bouts of endurance exercise. Even though in line with some previous experiments (Azboy & Kaygisiz, 2009; Pickett & Morris, 1975; Racinais et al., 2004), these results are in contrast with our main hypothesis, suggesting that one night of SD is not enough to significantly impair endurance exercise performance the following morning. Interestingly, a main pairwise comparison across days has revealed

a performance decline on Day 2 and a subsequent improvement on Day 3. Several reasons might explain the current results.

The first and perhaps most evident explanation is that acute SD does not affect endurance cycling performance during a TT. This is in contrast with what has been previously found during a 30-min running TT after 30-h of SD (Oliver et al., 2009). These results suggest that acute SD may have a different impact based on the type of endurance exercise performed. In particular, cycling activity might be less sensitive to performance impairments induced by SD, due to its general lower level of fatigability. Indeed, it has been demonstrated that, for exercise bouts of the same intensity and duration, cycling reaches lower levels of central fatigue and induces less muscle damage than running (Lepers et al., 2000; Lepers et al. 2002; Millet et al., 2002; Millet et al., 2003). It might be hypothesised that also a mental fatigue state induced by SD, as in the case of physical fatigue, can be task dependent. Nevertheless, future research needs to be conducted in order to investigate the effects of SD based on the kind of sport and physical activity performed.

Another plausible explanation is subjects' sensitivity to SD. It has been found a considerable intervariability among physically active people regarding the effects of acute SD on endurance exercise performance, with individual performance changes varying from +4% to -40% following SD (Martin, 1981; Oliver et al., 2009). Consequently, the subjects recruited in the present study might not have been vulnerable enough to SD.

Another possible reason is that the kind of experimental design used might have significantly influenced the findings of our study. Due to our interest in investigating the effects of recovery sleep on endurance exercise performance, subjects have been allocated into two independent groups and required to perform the same cycling task three times, in three consecutive days. This, along with the fact that participants were aware of their group condition since the familiarisation visit (due to participants' organisational reasons), might suggest that some psychological factors could have limited the performance results of the CON group. Indeed, even though at a less extent, it seems that the CON group has followed the same performance pattern of the SD group, in particular at Day 2, with a 3.2% drop in performance, versus a 5.4% decrease

in the SD group. Considering that SD has been demonstrated not to alter individuals pacing during TT (Oliver et al., 2009), and that performance alterations have not been found before in the context of consecutive days of TT (Feli et al., 2006; Hickey et al., 1992), the CON group might have refrained from giving their best at Day 2 (confirmed by a statistical trend between Day 1 and Day 2 ($p = 0.067$)). Moreover, they might also have been influenced by the so-called "last ride effect" in the last TT at Day 3 (Hickey et al., 1992).

This performance pattern adopted by the CON group might not have allowed to see any significant group x day interaction effect in the analysis of the ANOVA. However, if the SD group alone is considered, simple paired t-tests have revealed a significant negative effect on performance following SD ($p = 0.004$) and a return to baseline levels of performance following recovery sleep ($p = 0.001$), significance that could not be found in the CON group. In addition to that, it is important to underline that a drop of 5.4% in endurance cycling performance is a remarkable alteration considering that the smallest worthwhile change in laboratory environments testing cycling performance is ~ 1.25% (Hopkins et al., 1999; Paton & Hopkins, 2006).

To the best of our knowledge, this is the first study testing the effects of recovery sleep following SD on endurance exercise performance. A similar design has been used to test the effects of SD and following recovery sleep during a cycling all-out TTE, showing no differences in performance (Hill et al., 1994). However, because of its short duration (i.e. less than 75 s), the exercise chosen cannot be defined as an endurance type of exercise (Gastin, 2001) and therefore it is not comparable with our results. Moreover, the presence of no control condition or group might have limited the findings of that experiment. Further investigations need to be done in order to better understand the role played by acute SD and recovery sleep on endurance exercise performance and the possible influence that pacing strategy might have in the context of three consecutive days of physical tasks.

Effects of SD and recovery sleep on cognitive performance

As expected, one-night of SD has negatively affected PVT performance by increasing simple reaction time and the number of lapses in the SD group compared to the CON group. Moreover, the following night of recovery sleep has resulted in being beneficial to restore baseline performance levels. These results are in line with previous studies which have demonstrated clear decrements in vigilance and sustained attention following SD and/or SR (Adam et al., 2006; Doran et al., 2001; Goel et al., 2013; Jewett et al., 1999; Lim & Dinges, 2008, 2010; Van Dongen et al., 2003b), and a rapid recovery to well-rested performance levels after one night of normal sleep (Adam et al., 2006).

Contrary to the PVT findings, no performance impairments have been found in the Stroop task. Previous literature has shown that SD can have negative effects on Stroop Task. However, it is still not clear which aspect of this task performance is mainly affected. Indeed, it seems that whereas reaction times and errors, as in the case of the PVT, are negatively influenced (Lingenfelser et al., 1994; McCarthy & Waters, 1997; Stenuit & Kerkhofs, 2008), response inhibition is not impaired by SD (Cain et al., 2011; Sagaspe et al., 2006). In the current study, not even the vigilance and attention aspects of the Stroop Task have been affected. This might be due to the use of a very short version of the Stroop Task. Indeed, compared to the above mentioned studies, in which a higher number of task trials have been used (i.e. between 50 and 200 trials), the Stroop Task performed in the current experiment consisted of 25 trials only. This might also suggest that inhibitory control may be more relevant to endurance performance, however, further research is required to confirm this hypothesis. Finally, another possible limitation of the task used is the structure of the task itself, which did not include any neutral stimulus (i.e. non-word stimulus), as used in previous studies (Cain et al., 2011; Sagaspe et al., 2006).

5.6 Conclusions

In conclusion, one night of SD did not decrease endurance exercise performance during a TT, showing that maximal endurance exercise performance seems to be more robust to 25-h SD than vigilance. However, both 40-min submaximal endurance exercise and cognitive performance have been negatively affected by SD and positively recuperated by one night of recovery sleep.

Further research is still required to better understand the controversial effects of SD and recovery sleep on endurance exercise performance. Indeed, the quantification of a recovery sleep effect is essential in the field of sport and exercise and can be translated into evidence-based advice to trainers and athletes interested in reducing the negative effects of a sleep-deprived state during training and endurance/ultra-endurance competitions.

Chapter 6

Brain Endurance Training to enhance endurance exercise performance in physically-inactive males: a pilot study.

Main finding: 6 weeks Brain Endurance Training does not improve endurance exercise performance (TTE) or RPE during submaximal exercise or cognitive performance in sedentary males.

6.1 Abstract

It has been previously demonstrated that mental fatigue impairs endurance exercise performance. Brain Endurance Training (BET) is a new training strategy aimed at improving resistance to fatigue during endurance exercise by using acute mental fatigue as a training stimulus. It consists in systematic repetitions of prolonged and demanding cognitive tasks used to increase resistance to mental fatigue. The first and only study conducted revealed that the inclusion of BET into a typical aerobic training program significantly improves endurance exercise performance. The purpose of the current pilot study was to investigate the effects of BET alone on endurance exercise and cognitive performance. It was hypothesised that BET alone would improve both endurance exercise and cognitive performance by reducing perception of effort.

Twenty healthy physically-inactive young males (means ± SD: age 25.5 ± 7.3 yr, body mass 82 ± 20 kg, height 1.76 ± 0.09 m, $\dot{V}O_{2peak}$ 33.2 ± 6.7 ml/kg/min) were randomly allocated with a 1:1 ratio to either the BET or the control (CON) group. Participants in the BET group were asked to undergo a 6-week BET training consisting in performing a Go-No Go task three times per week, one hour per session. Subjects in the CON group were required to spend the same amount of sessions and time, surfing

the internet. A cycling time to exhaustion (TTE) test at a moderate to high-intensity domain and a 1-h Simon Task were carried out before and immediately after the training period.

The results of the current pilot study showed that the use of BET alone seems not effective to improve endurance exercise (BET: pre-training 1778 ± 493 sec, post-training 1723 ± 508 sec; CON: pre-training 1356 ± 307 sec, 1434 ± 683 sec) and cognitive performance in physically-inactive young males, revealing no significant group × visit interaction effect of BET on TTE and Simon Task (i.e. reaction time and accuracy) ($p > 0.05$). Further research is crucial to investigate the neurobiological mechanisms underlying BET and to better understand its efficacy alone or in combination with different physical training programs as well as in different kinds of population.

6.2 Introduction

In the past decade, it has been extensively demonstrated that mental fatigue, defined as a psychobiological state caused by prolonged periods of demanding cognitive activities (Boksem & Tops, 2008), impairs endurance exercise performance (Van Cutsem et al., 2017b). In particular, it has been shown that the main factor by which mental fatigue would limit endurance exercise performance is perception of effort rather than cardiorespiratory and/or muscle energetics mechanisms (Marcora et al., 2009f).

In this context, the Brain Endurance Training (BET) has been proposed (Marcora et al., 2015). BET is a new training strategy aimed at inducing chronic resistance to fatigue during endurance exercise by using acute mental fatigue as a training stimulus. It consists of systematic repetitions of prolonged and demanding cognitive tasks used to increase resistance to mental fatigue and hence improve endurance exercise performance. In Marcora and colleagues' study (Marcora et al., 2015), 35 physically active males were randomly allocated into two groups (BET and control). Both groups were trained on a cycle ergometer for 60 min at 65% of their $\dot{V}O_{2max}$ three times per week for twelve weeks. Whilst cycling, the BET group was required to perform a cognitive task (i.e. AX-CPT task) on a computer screen. The

results revealed that the inclusion of BET into a 12-week aerobic training program significantly reduced RPE and increased endurance performance by +126% during a cycling time to exhaustion test (TTE) compared to baseline, whereas the control group, who joined the aerobic training program only, improved their performance by +42% (Marcora et al., 2015).

The mechanism underneath this result possibly relates to the crucial role that perception of effort plays on endurance exercise performance (Marcora & Staiano, 2010; Marcora et al., 2008). It has been demonstrated that perception of effort is strongly associated with the Anterior Cingulate Cortex (ACC) (Williamson et al., 2001, 2002), prefrontal area of the brain highly activated by demanding cognitive tasks (Boksem & Tops, 2008), and that the brain is subjected to plasticity (i.e. it is able to adapt to different stimuli, both structurally and functionally) (Kolb & Whishaw, 1998). Consequently, BET might be able to increase the training load of the brain and induce adaptations in the ACC (and most probably in other relevant cortical areas). These adaptations in turn, might reduce the perception of effort and hence increase endurance exercise performance (Marcora et al., 2015).

In psychology and neuroscience, cognitive training programs consisting of the repetition of shorter cognitive tasks interposed by resting periods (e.g. Flanker, Stroop and Go-No-Go tasks) have been investigated. However, these training strategies have been studied with the aim of increasing specific executive functions, such as inhibitory control (Spierer et al., 2013), working memory (Melby-Lervåg & Hulme, 2013) and attention (Tang & Posner, 2009) and not improving resistance to mental fatigue.

The aim of the current pilot study is to investigate for the first time the effects of BET alone on endurance performance. It has been hypothesised that BET alone would improve performance during a prolonged demanding cognitive task and during endurance exercise by reducing perception of effort. Healthy physically-inactive young males have been tested in order to control for any potential physical-exercise-related performance improvements. The results of this study might potentially change the way endurance athletes are physically and cognitively trained and might also help injured athletes to have a faster recovery.

6.3 Methods

Participants, eligibility criteria and pre-registration

Twenty healthy physically-inactive males, aged 18-45 were recruited (means ± SD: age 25.5 ± 7.3 yr, body mass 82 ± 20 kg, height 1.76 ± 0.09 m, $\dot{V}O_{2peak}$ 33.2 ± 6.7 ml/kg/min). Being a pilot study, the optimal sample size has been estimated using the stepped rules of thumb method for the pilot trial sample size when the standardised effect size for the main trial is medium ($0.3 \leq \delta < 0.7$), the power 80% and the significance 5% (two-sided) (Whitehead et al., 2016). Based on these assumptions, the recommended pilot trial sample size per group for this study was 10.

Subjects were subjected to an initial screening consisting of a health questionnaire (PAR-Q), and the leisure and occupational physical-activity level scales (Saltin & Grimby, 1968). Subjects with pulmonary, cardiovascular, metabolic or neurological/mental health disorders, injuries and those unable to perform the required exercises and cognitive tasks were excluded. Moreover, subjects who scored more than 3 points on the Saltin and Grimby scales were defined not eligible for participation and therefore excluded, as considered physically active. Prior to the study participation, all subjects were informed about the study protocol and signed a written informed consent form. All the procedures used have been approved by the School of Sport and Exercise Sciences Ethics Committee and have been conducted in conformity with the Declaration of Helsinki. All the procedures and protocols used were pre-registered and available at the AsPredicted.org website.

Experimental Design

A randomised, controlled, between-group, experimental design was used. Participants were randomly allocated with a 1:1 ratio to two independent groups, BET (experimental group) and CON (control group). Testing visits as well as the training intervention were carried out at the School of Sport and Exercise Sciences, University of Kent, Medway

Campus, in the psychobiology laboratory and in a standardized seminar room, respectively. The training intervention consisted of a 6-week training programme. Testing sessions were undertaken twice, before and after the 6-week training intervention. In total, all participants were involved in the experiment for 10 weeks.

All the physical sessions were separated by at least 48 hours of recovery. In order to minimize the effects of circadian rhythms, testing and training sessions were performed at the same time of day (±2 hours). All participants were required to refrain from the consumption of alcohol in the 24 hours before each visit. They were also instructed to avoid any caffeine for at least 12 h before both testing and training sessions. Moreover, subjects were asked to maintain their habitual diet and sedentary lifestyle, to drink an amount of water equal to 35 ml/kg of body weight per day and to sleep for at least 7 hours. In order to monitor participants' physical activity behaviour during the whole experiment, a daily physical activity diary and the leisure and occupational physical-activity level scales by (Saltin & Grimby, 1968) were completed at the end of each training week by our subjects. A monetary reward (£200 in Amazon voucher) was given to all participants.

Testing Procedures

Participants were asked to attend the laboratory on seven separate occasions throughout the entire study, one week before the training intervention (i.e. *Week 1*; see *Pre-Training Testing*) and one week after the training intervention (i.e. *Week 8*; see *Post-Training Testing*).

Pre-Training Testing (Week 1)

Visit 1: Screening, Informed Consent, $\dot{V}O_{2max}$ Test

Participants were subjected to an initial health screening consisting of a PAR-Q questionnaire and asked to complete the Leisure and Occupational Physical Activity Level Scales (Saltin & Grimby, 1968). In order to verify that our participants followed

all the instructions previously given, they were asked to complete a pre-experimental checklist. They were also required to inform researchers about any acute illness, infection and/or injury and to give notice of any medication/drug taken. Eligible subjects were asked to sign an informed consent form. Following the collection of the main anthropometric measurements (weight and height), subjects were then asked to execute a step incremental test on a cycle ergometer (Corival, Lode B.V., Groningen, The Netherlands) until subject's volitional exhaustion. Prior to the cycling test, participants were required to do a 2-min warm-up at an unloaded pedalling. The test commenced immediately after the end of the warm-up, starting from 20 W and increasing the work rate by 20 W every minute until exhaustion. Participants were asked to maintain a preferred but relatively constant pedalling cadence. Exhaustion was defined when pedalling cadence dropped below 60 rpm for more than 5 seconds, despite strong verbal encouragement. Participants were only allowed to see their cadence during the test. No further feedback related to their performance was given. Pulmonary gas exchange measurements were collected breath-by-breath throughout the entire test to determine $\dot{V}O_{2peak}$ and 1st and 2nd Ventilatory Thresholds (VT) (MetaLyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany). Peak Power Output (PPO) was also detected. Finger capillary blood samples (i.e. 10 µl) were taken immediately after the test (within 60 s; exhaustion condition). Blood lactate concentrations were measured (Biosen; EFK Diagnostics, London, UK) as an indicator of maximal effort (Howley et al., 1995). HR was collected throughout the entire test (Polar V800, Polar Electro Oy, Kempele, Finland). RPE was asked every minute. In order to assess participants' mood changes and motivation related to the exercise testing, subjects were asked to complete the Brunel Mood Questionnaire (BRUMS) (Terry et al., 2003) and a motivation scale (Matthews et al., 2001) just before commencing the test.

Visit 2: Familiarisation

Participants were familiarised with a TTE at a moderate to high-intensity domain (Mezzani et al., 2013). The intensity chosen was the power output equivalent to the 50% between the 1st and 2nd VT (Mezzani et al., 2013) and evaluated during *Visit 1*. The

intensity was then adjusted in order that all subjects would have lasted approximately between 20 and 30 minutes. Subjects were also familiarised with the cognitive testing protocol, the BET (if participants were allocated in the BET group), and the questionnaires/scales used throughout the whole experiment.

Visit 3: Cognitive Test

Subjects were required to perform a Simon Task. The task consists in an arrow appearing consecutively either on the right or on the left of a fixed "+", located in the centre of a computer screen. Participants were asked to press the button corresponding to the letter "f", whenever the arrow pointed toward left and to press the one corresponding to the letter "j", whenever the arrow pointed towards right, no matter the position of the arrow on the screen. The task consisted in 6 x 10-min blocks to be performed consecutively. Each block was interspersed by two 0-10 rating scales on fatigue and effort perceived (See *Psychological Questionnaires*). Subjects were also asked to complete the BRUMS (Terry et al., 2003) immediately before and after the task. Motivation was also assessed using a motivation scale (Matthews et al., 2001) prior to the cognitive task. Finally, in order to estimate subjective participants' workload, participants were asked to complete the multidimensional scale NASA-TLX (Hart & Staveland, 1988) immediately after the task.

Visit 4: Time to Exhaustion Test

In order to measure endurance performance participants were asked to perform the same TTE as in the familiarisation visit. They were required to maintain a preferred but relatively constant pedalling cadence. Exhaustion was defined when pedalling cadence dropped below 60 rpm for more than 5 seconds. No verbal encouragement was given. Participants were only allowed to see their cadence during the test. No further feedback related to performance was given. Prior to the testing, participants were asked to do a 3-min warm-up at 20 W. HR was continuously measured throughout the entire test (Polar V800, Polar Electro Oy, Kempele, Finland). RPE and ratings of feeling were

collected one minute after the beginning of the test, every 3 minutes during the entire test, and at exhaustion using the Borg's 15-point scale (Borg, 1998) and the bipolar Feeling scale (Hardy & Rejeski, 1989), respectively. Fingertip capillary blood samples were collected immediately before and after the TTE and at the 6th minute during the test (i.e. when the steady state should occur) and blood lactate concentrations were measured. In order to assess mood and motivation related to the TTE, subjects were required to complete the BRUMS (Terry et al., 2003) and a motivation scale (Matthews et al., 2001) just immediately before the exercise testing (after the warm-up). The multidimensional scale NASA-TLX (Hart & Staveland, 1988) was also used immediately after the test to measure subjective workload.

Post-Training Testing (Week 8)

Post-Training testing always started 3-5 days after the last training session.

Visit 5, 6 and 7

Visit 5, 6 and 7 procedures were identical to *Visit 1, 3 and 4,* respectively. Participants were asked to maintain a sedentary lifestyle throughout the entire experiment. Therefore, no meaningful changes in the $\dot{V}O_{2peak}$ (measure of cardio-respiratory fitness) were expected between pre-training and post-training tests. In order to assess individual changes in $\dot{V}O_{2peak}$, the Reliable Change Index (RCI) was used (Heaton et al., 2001; Marcora & Bosio, 2007). The RCI calculated was equal to 5.98 ml/kg/min. A change score representing the difference in $\dot{V}O_{2peak}$ (i.e. post-training – pre-training), was calculated for each participant. If the change score was larger than the RCI, which means that it unlikely occured by chance (e.g. possible improvements due to physical training), participants were excluded from the experiments.
The same individuals' TTE intensities used during Visit 4 were adopted during *Visit 7*. Moreover, immediately before starting the TTE at *Visit 7*, participants were required to complete a bipolar likert scale (Boot et al., 2013; Devilly & Borkovec, 2000) to check for participants' performance expectations (See *Psychological Questionnaires*).

A monetary reward of £300, £200 and £100 in Amazon vouchers were given to the first, second and third best cognitive performances in each group (average of individual's pre- and post-training performance). The same prizes were given to the best three TTE performances in each group.

Training Intervention

The training intervention consists of a 6-week cognitive training program (Weeks 2-7). Participants were required to train 3 times per week, for a total of 18 training sessions. The duration of each training session was 60 minutes. Participants were not aware of the real purpose of the study and of being involved in a proper cognitive training program. It was told to them that the purpose of the experiment was to investigate the effects of different cognitive activities on physiological responses to exercise in physically-inactive people. Participants were randomly allocated either in the BET or in the CON group. Subjects in the BET group were asked to perform a Go-No Go task (Axon Sports, USA) on a tablet screen (iPad Mini 2, Apple, California, USA), during which it was required to detect and press a green target (i.e. green dot, go visual stimulus) and not to respond to a red target (i.e. red dot, no-go visual stimulus). The task could be easily customised through the BET app interface. To make the task boring and more cognitively demanding, after several pilot trials performed by our research group, it was decided to set up the task at a low intensity, with a random stimulus frequency appearance included between 1 sec (minimum rate) and 2 sec (maximum rate). The expiration rate was set up to 3 sec from when the target appears. Moreover, the amount of No Go targets was set up at 20% (in the first three weeks) and 30% (in the second three weeks) out of the total amount of targets appearing on the screen. All targets appeared randomly in different positions on the screen, one at a time. A bleep sound was elicited in case of incorrect response or lack of correct response. A single training session included three blocks of 20 mins to be performed consecutively. At the end of each block, feedback on performance was provided to the participants. All the data was saved and stored in a cloud database automatically. In order to keep participants' motivation high, a £20 Amazon voucher was given to the best participant of the week,

every week. A performance score, which considered both accuracy percentage and mean reaction time (i.e. accuracy * 1000 / reaction time), was calculated for every single session and then averaged weekly. Subjects in the CON group were asked to attend the sessions and to spend the same amount of time surfing the internet (passive activity). Participants were continuously monitored by a researcher to guarantee compliance with both treatments.

Psychological Questionnaires

Mood. The BRUMS (Terry et al., 2003) was used as a measurement to evaluate subjects' mood before and after the cognitive testing and prior to the cycling tests. This questionnaire is a shorter version of the POMS and it consists of 24 items (e.g. tired, anxious, nervous, confused, energetic, active) to be answered on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Items are allocated into six specific subscales: anger, confusion, depression, fatigue, tension and vigour. Each subscale includes four related items and can reach a score between 0 and 16.

Workload. The multidimensional scale NASA TLX (Hart & Staveland, 1988) were used to estimate the subjective workload experienced during both TTE and cognitive testing. The NASA TLX includes six subscales: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort and Frustration. Subjects have been asked to circle one of the 20 line intervals on each of the six scales at the point which matched their experience. Each line has two endpoint descriptors "very low" and "very high" that describe the scale. The performance-related subscale is reversed going from "good" on the left to "poor" on the right.

Motivation. Intrinsic motivation and success on task motivation scales (Matthews et al., 2001) were used to assess motivation related to both cycling and cognitive testing. Each scale includes 7 items to be scored on a 5-point Likert scale (where 0 = not at all, 1 = a

little, 2 = somewhat, 3 = very much, 4 = extremely). The total range of scores for each scale is between 0 and 28.

Effort and Fatigue. Two 0-10 rating scales were used to assess perceived effort and fatigue during the Simon Task, at the beginning of the task and at the end of each 10-min task block. In particular, participants were required to answer the questions "How effortful was the task?" and "How fatigued are you in this moment?" and to type the number corresponding to their state. The total range of scores is between 0 and 10. The line ends are anchored by descriptors defining the extreme feelings of effort ("no effortful at all" and "extremely effortful") and fatigue ("no fatigued at all" and "extremely fatigued").

Expectations. A Bipolar Likert Scale (Peabody, 1962) was used immediately before performing the TTE at *Visit 7* to check for participants' expectations. Participants were asked the following question: "In comparison to your previous time to exhaustion test, how do you think you will perform today?". The scale goes from -5 to +5 and it is anchored by some descriptors: much worse (-5), fairly worse (-3), equal (0), fairly better (+3) and much better (+5).

Data analysis

The step incremental test was used to determine the $\dot{V}O_{2peak}$, measured as the highest value of a 30-sec moving average. The power outputs corresponding at the first and second ventilatory thresholds (i.e. VT1 and VT2) were obtained by using three different measurement criteria. VT1 was determined as: 1) the first unequal increment in carbon dioxide production ($\dot{V}CO_2$) from a visual investigation of $\dot{V}CO_2$ vs $\dot{V}O_2$ single plots; 2) the increment in $\dot{V}E/\dot{V}O_2$ with none in $\dot{V}E/\dot{V}CO_2$; 3) the increment in end-tidal O_2 partial pressure ($PETO_2$) with no fall in end-tidal CO_2 partial pressure ($PETCO_2$). VT2 was determined as: 1) the first unequal increment in carbon dioxide production ($\dot{V}CO_2$) from a visual investigation of $\dot{V}E$ vs $\dot{V}CO_2$ single plots; 2) the increment in $\dot{V}E/\dot{V}CO_2$; 3) the decrement in end-tidal CO_2 partial pressure ($PETCO_2$). The power output

corresponding to the 50% of the total workload between VT1 and VT2 was calculated and used as fixed intensity for the TTE test. A script created with the MATLAB package (R2017a Mathworks, Natick, Massachusetts, USA) was used to do this analysis.

In order to investigate the effects of BET on RPE, ratings of feeling and HR during the TTE, the iso-time method was used (Blanchfield et al., 2014). Each of these variables were firstly linearly interpolated and then extrapolated second by second. Subsequently, the shortest TTE across groups and tests was considered and 5 time points corresponding to the 20%, 40%, 60%, 80% and 100% of that test identified. All the other TTE were segmented based on the time points detected in the shortest TTE. A final time point corresponding to the time at exhaustion was also evaluated for all tests. The time points obtained were used to extract the variables for the following statistical analysis (See *Statistical Analysis* for more details). A script created with the MATLAB package (R2017a Mathworks, Natick, Massachusetts, USA) was used to do this analysis.

All data were screened for outliers (i.e. ± 3 SD above or below the mean) in order to check for transcription or input errors. If verified, outliers were not excluded.

Statistical Analysis

2-way mixed-model ANOVAs were used to test group × test interactions in $\dot{V}O_{2peak}$, endurance exercise performance (TTE) and cognitive performance (Simon Task, i.e. mean reaction time and accuracy). 3-way mixed-model ANOVAs (group × test × iso-time) were used to analyse perceptual (RPE and feeling) and physiological responses (HR) during the TTE. A 2-way mixed-model ANOVA was used to test group × test interactions in perceptual (RPE and feeling) and physiological responses (HR) at exhaustion during the TTE. When the assumption of sphericity was not met, the Greenhouse-Geisser correction was used. Significant interaction effects were followed up using simple contrasts, with the α-level adjusted via Bonferroni correction. The Shapiro-Wilk test, histograms, Q-Q plots and boxplots were used to check for all data normality. Statistical significance was accepted at $p < 0.05$ level. All data are presented

as means ± SD, unless otherwise stated. The SPSS (version 23.0; SPSS, Chicago, IL) statistical package was used for all statistical analyses.

6.4 Results

Participants characteristics

Participants' features (per group, pre- and post-training) are reported in Table 6.1.

Table 6.1. *Participants features (N = 20)*

	Pre-Training		Post-Training	
	BET (N = 10)	CON (N = 10)	BET (N= 10)	CON (N = 10)
Age (years)	22.5 ± 3.3	28.5 ± 9.1		
Height (m)	1.74 ± 0.11	1.78 ± 0.04	1.73 ± 0.11	1.79 ± 0.05
Weight (kg)	76.3 ± 20.4	87.2 ± 18.1	75.4 ± 20.5*	87.2 ± 17.1
PPO (W)	202.9 ± 49.6	201.3 ± 16.4	202.2 ± 48.2	197.3 ± 17.0
$\dot{V}o_{2peak}$ (ml/kg/min)	35.2 ± 7.0	31.1 ± 6.2	34.6 ± 8.1	28.9 ± 6.2*

PPO, peak power output. $\dot{V}o_{2peak}$, peak oxygen uptake. Data are shown as means ± SD. ***** **=** Pre-Training vs Post-Training ($p < 0.05$).

Cardio-respiratory fitness measurement ($\dot{V}O_{2peak}$) and TTE performance

$\dot{V}O_{2peak}$ values did not reveal any significant group × visit interaction effect. A main reduction was found in the post-training intervention visit compared to baseline (p = 0.011).

No significant main effect on visit and group × visit interaction effect were found in the TTE performance (Figure. 6.1). Subjects expectations related to the TTE performance did not differ between the two groups (p = 0.668).

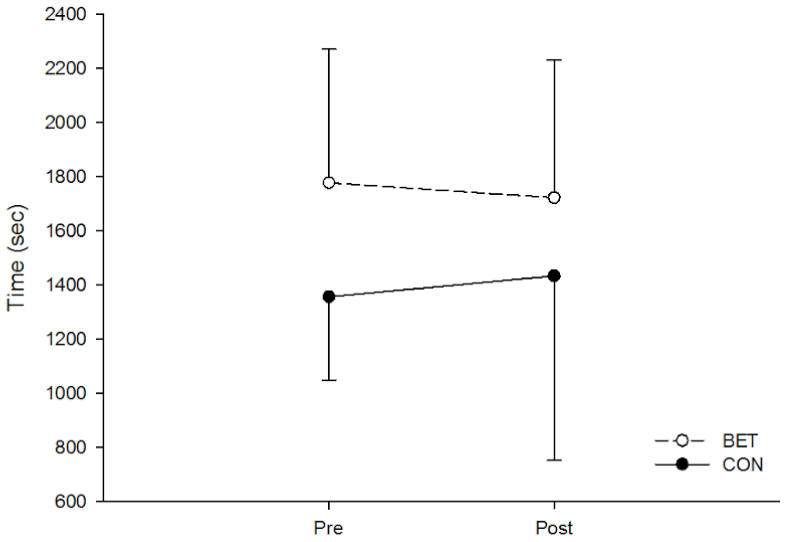

Figure. 6.1. Group mean ± SD time (sec) variations measured during the TTE pre- and post-training intervention in BET (open line) and CON group (solid line).

TTE perceptual and physiological responses

RPE values revealed a significant main effect at iso-time ($p < 0.001$) and a group × visit interaction effect ($p = 0.038$) (Figure. 6.2A). Ratings of feeling values also showed a significant main effect at iso-time ($p < 0.01$) and a group × iso-time interaction effect ($p < 0.01$) (Figure. 6.2B). HR values showed a main effect at iso-time ($p < 0.001$) and a main effect between groups ($p = 0.028$) (Figure. 6.2C). No significant effects were found at exhaustion.

Lactate measurements showed a main effect on time ($p < 0.001$). However, no significant interaction effects were found.

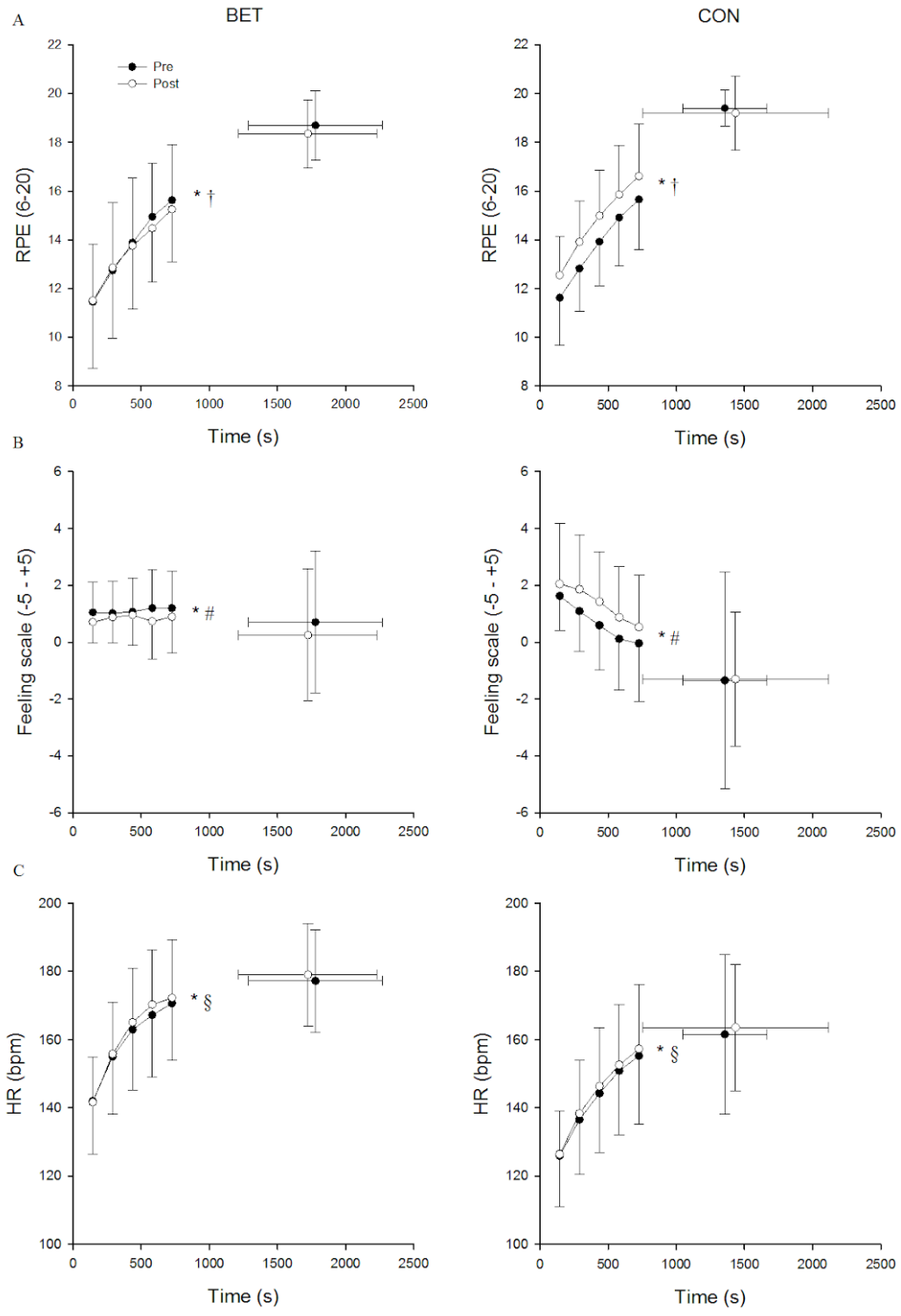

Figure. 6.2. Group mean ± SD changes in RPE (A) feeling (B) and HR (C) at 20%, 40%, 60%, 80%, 100% of the shortest TTE test (absolute iso-time method; see Data Analysis section of this chapter for further details) and at exhaustion, pre (black circle) and post (white circle) training intervention, in the BET (left panel) and CON (right panel) group. * = significant main effect at iso-time ($p < 0.01$); † = significant group × visit interaction effect ($p < 0.05$); # = group × iso-time interaction effect ($p < 0.01$); § = significant main effect between groups ($p < 0.05$).

Cognitive performance

Median RT in the Simon Task showed a significant main effect on visits ($p < 0.01$) and on time ($p < 0.001$) (Figure. 6.3). No significant group × visit interaction effect was found. Median RT of congruent and incongruent stimuli also showed main effects on visits (congruent RT, $p = 0.01$; incongruent RT, $p = < 0.001$) and time (congruent RT, $p < 0.001$; incongruent RT, $p = 0.001$), however no interaction effects were detected.

Total accuracy also showed a significant main effect on visits ($p = 0.038$) and on time ($p < 0.001$) (Figure. 6.3). Accuracy of the congruent responses indicated a main effect on visits ($p = 0.046$) and on time ($p < 0.001$), whereas accuracy of the incongruent responses showed a main effect on time only ($p < 0.01$). No group × visit interaction effects were found on accuracy.

Fatigue and effort rating scales completed throughout the cognitive task revealed a significant main increase of effort and fatigue on time ($p < 0.001$). A significant main effect between groups was found on ratings of fatigue ($p < 0.01$), revealing general higher levels of fatigue in the CON group. No interaction effects were found.

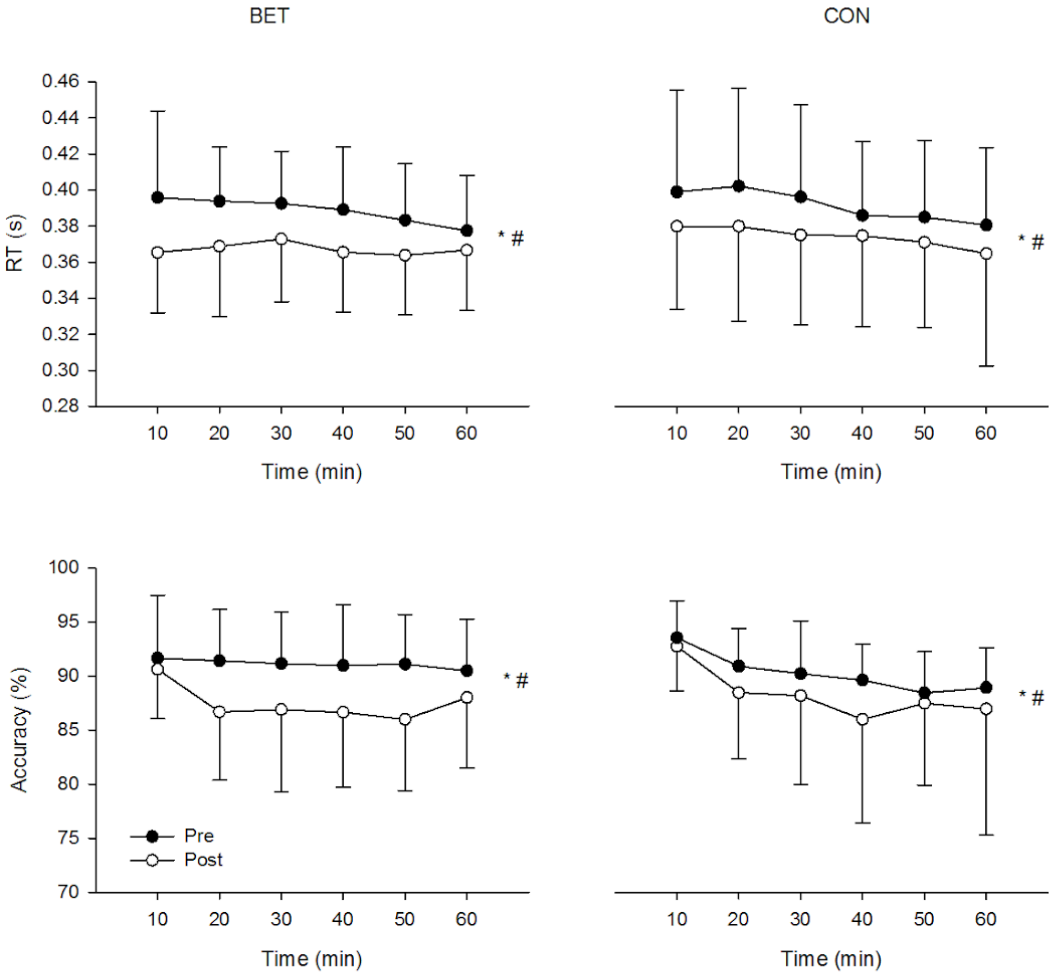

Figure. 6.3. Group median ± SD changes in RT (s) and group mean ± SD changes in accuracy (%) measured during the Simon Task Pre (black circle) and Post (white circle) training intervention, in the BET (left panel) and CON (right panel) group. * = significant main effect on time ($p < 0.001$); # = significant main effect on visits ($p < 0.05$).

Motivation, mood and subjective workload

Both intrinsic motivation and success in the task motivation related to the TTE did not vary significantly between groups and over visits. No difference in success in the Simon Task motivation was also found. However, a significant main decline in intrinsic motivation was reported at the post-training intervention visit compared to baseline ($p = 0.008$). The BRUMS completed before the TTE and the Simon Task, and the NASA TLX completed immediately after did not show any significant difference.

BET

No improvements in the Go-No Go Task performance (i.e. RT and accuracy) were found in the BET group.

6.5 Discussion

The main results of this training study showed that the use of BET alone is not effective to improve endurance exercise performance in sedentary healthy young males. In contrast to our main hypothesis indeed, it seems that BET is beneficial only if used in combination with physical training (Marcora et al., 2015). The current results also revealed no BET efficacy in improving cognitive performance.

BET and endurance exercise performance

Being this the second experiment ever conducted on the topic, only some speculations can be done to explain the results found. Firstly, the present study involved physically-inactive individuals who have hardly ever practiced physical activity. Based on their lack of experience in physical tasks, as well as on the perceptual and physiological results found, it is possible that our participants were neither highly motivated nor completely aware of the effort perceived during both the $\dot{V}O_{2max}$ Test and TTE. Consequently, some of them might not have reached their real exhaustion, causing limitations to the findings. More familiarisation with the cycling testing and perceptual scales might have been necessary and needs to be considered for future studies.

On the other hand, it can also be hypothesised the presence of a belief bias effect (Dube et al., 2010; Evans et al., 1983), for which the subjects might have acted and performed based on their internal beliefs and knowledge throughout the 8-week experiment. All the possible precautions have been taken in order to avoid this kind of biased response, such as blind the subjects from the real aim of the experiment and

check for their performance expectations, however, this possibility cannot be totally excluded.

Another possible explanation is the type of task used. Differently from the previous BET study, where the AX-CPT task was used (Marcora et al., 2015), in the current pilot study a different cognitive task (i.e. Go-No Go Task) has been performed. The Go-No Go task might not have induced enough adaptations at the brain level as the AX-CPT task did, which would let us think of a BET efficacy task dependency. Moreover, compared with Marcora and colleagues' experiment, which showed an improvement both after six and twelve weeks of concurrent BET and physical training program (Marcora et al., 2015), the six weeks of BET alone in our study might not have been enough to generate sufficient training load on the brain and see any endurance exercise performance improvement. Future research is certainly required to better understand the efficacy of different cognitive tasks used as BET and the most effective duration (with and without the combination of a physical task).

The results found in the current experiment suggest that BET might not induce enough adaptations at a brain level by itself. Previous literature has demonstrated that performing two tasks (i.e. physical and cognitive combined) at the same time is more cognitively demanding than the execution of a single task only, as they cause cognitive motor interference between each other (Al-Yahya et al., 2011; Blakely et al., 2016; Bourke, 1996; Darling & Helton, 2014; Epling et al., 2016; Green & Helton, 2011). Cognitive motor interference refers to performance impairments occurring in one or both tasks (i.e. physical and/or cognitive tasks) performed simultaneously (Epling et al., 2016). Very little research has been done on the topic and no chronic studies have been conducted yet. Nevertheless, these findings might suggest that the combination of BET and physical training could possibly generate higher training loads than BET alone, enabling significant structural and functional adaptations of those cortical areas involved with physical and cognitive effort, such as the prefrontal cortex and the ACC (Shenhav et al., 2017).

It has also been shown that physical activity improves cognitive performance by inducing neurogenesis (i.e. structural changes) in different areas of the brain (Hötting & Röder, 2013). In particular, several studies have demonstrated a significant increase in

attention (Hawkins et al., 1992) and different executive functions (Colcombe et al., 2004; Holzschneider et al., 2012; Smiley-Oyen et al., 2008; Voelcker-Rehage et al., 2011) following an aerobic training intervention, which seems to be associated with increased activity of the prefrontal and parietal areas and with decreased activity of the ACC (i.e. improvement in conflict regulation) (Colcombe et al., 2004, 2006). Furthermore, studies conducted on both animals (Fabel et al., 2009) and humans (Fabre et al., 2002; Holzschneider et al., 2012) have revealed that structural and functional adaptations at the brain level seem to be bigger when physical and cognitive training are combined. These results might also explain the inefficacy of a BET intervention alone, and suggest that physical training may play a primary role in preparing the brain to be more sensitive to cognitive stimulation (e.g. BET). Further studies need to be conducted in order to investigate the role of dual-task training in the context of BET and endurance exercise performance and the importance of neurogenesis when physical and cognitive training interventions are combined.

Finally, recent studies have demonstrated that the BDNF (i.e. neurotrophic factor belonging to the neurotrophin family of growth factors and aimed at promoting neuronal longevity and synaptic plasticity at the brain level (Fortune et al., 2019)) increases following exercise tasks in rats and that this enhancement seems to be associated with subsequent cognitive functions improvements, such as memory and learning (Bechara & Kelly, 2013; Gomez-Pinilla et al., 2008). These findings, although coming from animal studies, further indicates that physical exercise might be essential in the context of BET, as exercise-related increments in BDNF may promote structural and functional changes in those brain areas associated with effort and fatigue.

BET and perceptual responses

Despite no performance improvements, a significant group × visit interaction effect has been found in RPE. This might suggest that BET alone could have possibly reduced the increase in RPE found in the control group following the 6-week intervention. However, this reduction was not big enough to induce significant adaptations at a performance level and therefore, this assumption would certainly need further confirmation.

In general, however, the perceptual values collected during the TTE show some abnormalities, which are not corroborated by any performance effect. As already mentioned above, given the total inexperience of the population tested in this field, more familiarisation sessions might have been necessary.

BET and cognitive performance

The current results have also found that six weeks of BET did not improve cognitive performance during the Simon Task. As in the case of the endurance exercise performance, the duration of the training intervention and the use of BET alone, might not have been enough to induce brain adaptations and therefore increase cognitive performance and resilience to fatigue.

Moreover, there is empirical evidence showing that Go-No Go task training interventions improve the same inhibitory control task performance. However, these positive effects on performance seem not be transferable to other inhibitory control tasks, such as the Flanker task (Thorell et al., 2009). These findings are in line with our experiment, which revealed no significant improvement in the Simon task performance following six weeks of BET using a Go-No Go Task as a training stimulus.

Finally, motivation might have also played a central role in these results. Indeed, a significant main decline in intrinsic motivation has been found during the post-training cognitive visit compared to baseline. This decrease of motive may have possibly limited the cognitive performance findings during the Simon Task.

Limitations

The current pilot study shows some limitations that may have interfered with the final findings: 1) the majority of the individuals recruited for this experiment had never practiced any kind of physical activity before. Therefore, considering their total inexperience in endurance exercise tasks until exhaustion, more than one familiarisation session would have been ideal; 2) a belief bias effect (Dube et al., 2010; Evans et al., 1983) might also have affected the results of the present study. Indeed, even though

participants were blinded from the real aim of the study and from the treatment allocation, subjects may have performed based on their internal beliefs and knowledge; 3) the results showed no improvements in cognitive performance throughout the 6-week BET program, meaning that the type, duration and frequency of the cognitive task chosen might not have been demanding enough to cause significant adaptations at the brain level.

6.6 Conclusions

To conclude, BET alone seems to be ineffective to improve both endurance exercise and cognitive performance in sedentary healthy males. However, further research needs to be conducted in order to investigate the neurobiological mechanisms underlying BET and to better understand its efficacy alone or in combination with different physical training programs as well as in other populations, such as females, elite endurance athletes and injured athletes. This study has just started to build up important knowledge and give new insights on the effects of BET on endurance performance.

Chapter 7

Sleep Deprivation Training to Reduce the Negative Effects of Sleep Restriction on Endurance Exercise Performance: a Single Case Study.

Main finding: RPE during exercise after SDT is lower, which might lead to improved performance. Cognitive performance is not improved by SDT.

7.1 Abstract

Sleep deprivation is a mentally fatiguing condition characterized by continuous and prolonged lack of sleep, which is very common in ultra-endurance sporting disciplines. At present, stimulants such as caffeine are the only effective strategy used to reduce the negative effects of sleep deprivation on human performance. In this study an additional strategy has been proposed, which consists in systematic repetition of bouts of sleep deprivation (sleep deprivation training, SDT) to make the brain more resilient to the negative effects of lack of sleep on endurance performance.

It has been hypothesized that SDT would reduce the negative effects of sleep deprivation on endurance exercise performance on a 63-year-old ultra-endurance male runner. The athlete was required to undergo a 6-week SDT, consisting of one night of sleep deprivation per week, in combination with his regular exercise training programme. Testing visits were conducted over five consecutive days, both pre- and post-SDT, during which the subject was asked to run for 2-h at a constant speed and to perform a PVT. Visits were conducted under sleep and non-sleep conditions alternately.

A visual inspection of the data revealed that the use of SDT in combination with physical training seems to be beneficial on both perception of effort and affective valence in the context of five consecutive days of 2-h running at a constant pace, as well

as on mood state and workload perceived. Nevertheless, the data did not show any evident effect of SDT on cognitive performance during a PVT.

The results of this case study provided some initial information in relation to the effects of SDT on endurance exercise performance. SDT might be used to help athletes to counteract the negative effects induced by lack of sleep during endurance and ultra-endurance events. However, future research is crucial.

7.2 Introduction and study purpose

Mental fatigue has been defined as a psychobiological state caused by prolonged demanding cognitive activity (Boksem & Tops, 2008). It has been previously demonstrated that mental fatigue negatively affects perception of effort and endurance exercise performance (Van Cutsem et al., 2017b). Recently, an innovative kind of training called BET, has been proposed (Marcora et al., 2015). The BET consists in a systematic repetition of mentally fatiguing tasks aimed at increasing resistance to mental fatigue and hence improving endurance exercise performance (Marcora et al., 2015). The results of this novel study has revealed that the inclusion of BET into a typical aerobic training program significantly reduces RPE and improves endurance exercise performance (Marcora et al., 2015).

Sleep deprivation is a mentally fatiguing condition characterized by continuous and prolonged lack of sleep (Ackerman, 2011; Boonstra et al., 2007; Jones & Harrison, 2001), which is very common in ultra-endurance sporting disciplines. Although findings in the literature are still controversial (Fullagar et al., 2015), it has been demonstrated that sleep deprivation also negatively affects both, perception of effort and endurance exercise performance (Bond et al., 1986; Martin, 1981; Martin & Gaddis, 1981; Oliver et al., 2009; Symons et al., 1988; Temesi et al., 2013). At present, stimulants such as caffeine (McLellan et al., 2004b; McLellan et al., 2007) and modafinil (Wesensten et al., 2002), as well as naps (Blanchfield et al., 2018; Waterhouse et al., 2007) are the only effective strategies used to reduce the negative effects of sleep deprivation on human performance. Here an additional strategy is proposed: use a systematic repetition of

bouts of sleep deprivation (sleep deprivation training, SDT) to make the brain more resilient to the negative effects of sleep deprivation on perception of effort and endurance exercise performance.

The aim of the current study was to evaluate the effects of SDT in one ultra-endurance athlete. In particular, it has been hypothesized that SDT would increase resistance to the negative effects of sleep deprivation on endurance exercise performance. To the best of my knowledge this is the first study investigating sleep deprivation as a form of training aimed at reducing the negative effects of a sleep deprived state during endurance performance and conducted in the context of intermittent bouts of sleep deprivation. Previous experiments have investigated the effects of prolonged sleep deprivation and restriction which may have prevented any possible adaptation on physical performance (Castellani et al., 2006; Welsh et al., 2004). However, some indirect support comes from studies showing positive effects of SDT in patients with depression (Bunney & Bunney, 2013).

SDT is a form of BET, and as such, it is based on the same rationale for which perception of effort would play a crucial role in limiting endurance exercise performance (Marcora & Staiano, 2010; Marcora et al., 2008; Oliver et al., 2009; Temesi et al., 2013). Indeed, it has been demonstrated that perception of effort during exercise is clearly associated with specific areas of the brain, in particular with the activity of the ACC (Williamson et al., 2001, 2002). Considering that the brain has the capability to adapt both structurally and functionally in response to a stimulus (i.e. brain plasticity) (Kolb & Whishaw, 1998), the use of SDT in combination with endurance exercise training programs might increase the training load and induce adaptations at the brain level. These potential adaptations in the brain, in turn, might cause a reduction in perception of effort and a consequent improvement in endurance exercise performance.

7.3 Methods

Subject

A healthy, 63-year-old ultra-endurance male athlete participated to the current case study (See Table.1 for subject characteristics). The subject was a well-trained runner (i.e. average of 11 training sessions per week), who competed to 3 half-marathons, 9 marathons and 98 ultra-marathon events in total. The subject was a good sleeper (score of < 5 in the Pittsburgh Sleep Quality Index (Buysse et al., 1989)) and a definite morning person (score of 73 in the Ostberg "morningness-eveningness" questionnaire (Horne & Ostberg, 1976)). Prior to taking part in the experiment, the athlete was informed about the all experimental protocol and signed an informed consent form. All the procedures used were approved by the School of Sports and Exercise Sciences Ethics Committee and were conducted in conformity with the Declaration of Helsinki.

Study Design

The subject was required to attend the laboratory for testing on six separate occasions (*Pre-SDT Familiarisation* and *Pre-SDT Experimental Visits*), prior to the training intervention and on other six occasions (*Post-SDT Familiarisation* and *Post-SDT Experimental Visits*), immediately after the training intervention. The *Familiarisation* visits were carried out 48 hours prior to the experimental visits. The *Pre-SDT Experimental Visits* were conducted after one night of normal sleep (*Visit 1*, baseline condition), after one night of sleep deprivation (*Visit 2*), after one night of recovery sleep (*Visit 3*), after one night of sleep deprivation (*Visit 4*) and after one night of recovery sleep (*Visit 5*), respectively. The same sleep procedures were applied for the *Post-SDT Experimental Visits*. All the visits were conducted in five consecutive days (pre and post training intervention) and carried out in the Psychobiology Laboratory at the School of Sport and Exercise Sciences, University of Kent, Medway Campus (See *Testing Procedures* for more details). The nights of sleep deprivation took place in a

quiet room of the same building, whereas the nights of sleep were spent in a quiet room outside the university campus (i.e. hotel room) (See *Sleep Procedures* for more details). All visits commenced at 8:00 am and carried out between 8:00 am and 11:00 am, time frame during which lack of sleep seems to have the most negative impact on cognitive function (Mollicone et al., 2010). In order to avoid postprandial thermogenesis effects (Brondel et al., 1999; Zammit et al., 1992), the participant was required not to eat before any experimental visit. Nevertheless, in order to avoid the risk of hypoglycaemia during exercise testing (Sedliak et al., 2007), the subject was provided with a standardised light breakfast prior to the experimental visits. To assure that meals eaten and hydration status would not have affected sleep deprivation (Smith et al., 1993) the participant was instructed to maintain his habitual diet and to drink an amount of water equal to 35 ml/kg of body weight per day. The subject was not allowed to consume any caffeine and alcohol in the 12 hours before each visit and to practice any strenuous physical activity in the 24 hours before.

The training intervention consisted of a 6-week SDT during which the participant was asked to follow his habitual physical training programme as well as not to sleep one day per week (See *Training Intervention* for more details). In order to monitor dietary, sleep and physical activity behaviours during the entire experiment, the subject was required to complete food, sleep and physical activity diaries. The participant was involved in the experiment for a total of 10 weeks.

Testing Procedures

Pre-SDT Familiarisation

The participant was subjected to an initial screening consisting of a PAR-Q questionnaire and was informed about the testing procedures, including possible risks and benefits. In order to verify that the subject followed all the instructions previously given, he was asked to complete a pre-experimental checklist, to inform the researcher about any acute illness, infection and/or injury and to give notice of any medication/drug taken. Following the collection of the main anthropometric measurements (weight and height), the subject was asked to execute a submaximal step

incremental test for lactate threshold determination on a motorised treadmill (Pulsar 3P; h/p/cosmos Sports and Medical, Nussdorf-Traunstein, Germany), during which the speed was increased by 1 km/h every 4 minutes starting from 9 km/h, with a 1-min rest period between the stages (Australian Institute of Sport, 2014). Finger capillary blood samples were taken at baseline and at the end of each 4-min step (during the 1-min rest period between stages). Blood lactate concentrations were measured (Biosen; EFK Diagnostics, London, UK) to determine the lactate thresholds of our participant. The test stopped when blood lactate reached values just above 4 mmol/L. After 30 minutes resting, the participant was asked to complete another step incremental test for VO_{2max} determination on the same ergometer. The test commenced at a speed equivalent to 4 km/h lower than the critical speed (i.e. last speed completed in the submaximal test) which was increased every minute by 0.5 km/h until volitional exhaustion (i.e. the participant was not able to maintain a fixed running speed, despite verbal encouragement). No performance feedback was given to the participant in both tests. Prior to the testing, the subject was required to do a 10-min warm-up at his preferred speed. Three minutes resting was then given to the subject before the test commenced. Pulmonary gas exchange measurements were collected breath-by-breath throughout the entire tests (MetaLyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany). HR was collected throughout the entire testing (Polar V800, Polar Electro Oy, Kempele, Finland). RPE was taken at the end of each step in both tests using Borg's 15-point scale (Borg, 1998). The participant was given standard instructions about the scale. Moreover, anchoring procedures for determining the low and high anchor points in the scale were used during the incremental test (Noble & Robertson, 1996). The subject was then familiarised with the cognitive testing protocol and the different questionnaires and scales used during the *Experimental Visits*. In order to enable our subject to recover from the morning testing, familiarisation with the physical testing protocol was conducted in the afternoon (See *Pre-SDT Experimental Visits* for the testing protocols description).

Pre-SDT Experimental Visits (1-5)

Testing procedures were identical in each experimental visit. In order to verify that the participant followed all the instructions given during the *Pre-SDT Familiarisation* visit, the subject was required to complete a pre-experimental checklist. At this point, subjects' weight was checked and a standardised breakfast given. Breakfast consisted in one glass (150 ml) of orange juice (32 kcal, Tropicana Trop 50, Tropicana Products, Chicago, Illinois, USA) and two energy bars (90 kcal per bar, Special K, Kellogg Company, Battle Creek, Michigan, USA). In order to assess sleepiness and mood, the subject was asked to complete the Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) and the Brunel Mood Scale (BRUMS), respectively (Terry et al., 2003) (See *Psychological Questionnaires* for more details). The participant was then required to perform a standard 10-min PVT, as an objective measurement of cognitive performance impairments produced by sleep loss (Balkin et al., 2004; Basner & Dinges, 2011) (See *Cognitive Testing* for more details). Finally, the participant was asked to perform a running testing. Following a 10-min warm-up at a preferred intensity, the subject was required to complete a motivation questionnaire related to the running testing to be performed immediately after (See *Psychological Questionnaires* for more details). The exercise testing consisted of a 2-hour simulation race at a constant running speed corresponding at the subject's average speed adopted during his past ultra-endurance competitions (i.e. 11 km/h). The subject was aware of the exercise duration before and throughout the entire test, however no verbal encouragement was given. Finger capillary blood samples were collected at rest, immediately before and after the test (within 60 s from the end of the test). Blood lactate concentrations were analysed (Biosen; EFK Diagnostics, London, UK). RPE and ratings of feeling were collected every 10 minutes throughout the entire test using the Borg's 15-point scale (Borg, 1998) and the bipolar Feeling scale (Hardy & Rejeski, 1989). Heart rate was collected continuously during the test using a heart rate band (V800, Polar Electro Oy, Kempele, Finland). The subject was allowed to drink water ad libitum throughout the testing. To monitor his hydration status, the total intake of water and his body weight before and after the test were taken. In order to estimate the subjective workload perceived, the

participant was asked to complete the validated multidimensional scale NASA-TLX immediately after the 2-hour running testing (see *Psychological Questionnaires* for more details). In order to assess any change in sleepiness and mood between the beginning and the end of the visits, he was also required to complete again both the Karolinska Sleepiness Scale and the BRUMS (see *Psychological Questionnaires* for more details).

Post-SDT Familiarisation

The same identical procedures adopted during the *Pre-SDT Familiarisation* were used.

Post-SDT Experimental Visits (1-5)

The *Post-SDT Experimental Visits* procedures were identical to the ones used in the *Pre-SDT Experimental Visits*.

Sleep Procedures

Sleep procedures were identical in the pre- and post-training blocks of testing (*Pre- and Post-SDT Experimental Visits (1-5)*). The subject was asked to sleep normally (i.e. 7/8 hours) the night before the first visit (i.e. *Visit 1,* baseline conditions). In order to limit sleep inertia effects (Tassi & Muzet, 2000), the participant was required to wake-up at around 07:00 am and to attend the laboratory at 08:00 am. Following *Visit 1*, the subject was allowed to leave and asked not to sleep the following night, prior to the second visit (i.e. *Visit 2*, sleep deprivation condition). The following morning, the subject was required to attend *Visit 2*, always at 08:00 am. The participant was then allowed to leave the laboratory and asked to sleep at his hotel room during the upcoming night. He was then asked to attend the third visit (i.e. *Visit 3*, recovery sleep condition) the morning after. The participant was allowed to go to sleep earlier (i.e. from 09:00 pm onwards), but to always wake up at 07:00 am. Following *Visit 3*, the subject was asked to follow the same sleep procedures before *Visit 4* (sleep deprivation condition) and *Visit 5* (recovery sleep condition). The participant was required to spend the nights of sleep

deprivation in the student hub of the School of Sports and Exercise Sciences, from 08:00 pm to 08:00 am. In order to avoid any napping, food consumption and use of caffeinated beverages, the participant was strictly monitored by one member of the research staff. During the nights of sleep deprivation the subject was allowed to spend his time in no-cognitive demanding activities, such as reading magazines, watching movies, playing video games and having a conversation with the researcher (Plukaard, 2015; Shortz et al., 2015). At 02:00 am participants were allowed to eat one energy bar (90 kcal, Special K, Kellogg Company, Battle Creek, Michigan, USA). The subject was instructed not to take any nap throughout the entire duration of the experiment, except from the day following the SDT session (See *Training Procedures* for more details). A wrist actigraph device (AW Spectrum PRO, Philips Respironics, Murrysville, Pennsylvania, USA) was used to monitor and quantify sleep-wake activity of the participant. The subject was asked to wear the device during the days in which the experimental visits were conducted (the actigraph was given to the participant during the familiarisation visits).

Training Procedures

In addition to the traditional physical training programme, the subject was required not to sleep once per week (SDT) for 6 weeks. It was assumed that such a frequency would have permitted sufficient recovery between one sleep deprivation night and the next one. The purpose was to physically train in a sleep-deprived and brain-fatigued state the day following the night of sleep deprivation. For this reason, the subject was asked not to sleep during the day. He was allowed to take only one 30-60-min nap the day after sleep deprivation or to go to sleep earlier the following night. The participant was required to spend the sleep-deprived nights at home and he was allowed to spend his time in no-cognitive demanding activities, such as watching television, reading magazines, playing video games and/or listening to music (Plukaard, 2015; Shortz et al., 2015). To ensure that the participant did not fall asleep during the nights of sleep deprivation, he was required to send an email to the researcher every hour. In order to avoid overtraining the subject was monitored for the entire duration of the training

intervention through the use of questionnaires, scales and specific equipment. In particular, in order to assess daytime levels of sleepiness, the subject was asked to complete the Epworth Sleepiness Scale (Johns, 1991) (See *Psychological Questionnaires* for more details) at the end of each day during the 6-week training intervention. Moreover, in order to assess overall weekly mood, the participant was required to complete the BRUMS at the end of each week (Terry et al., 2003). As previously mentioned, the participant was provided with a wrist actigraph device to monitor sleep-wake activity, as well as with a GPS watch (Polar V800, Polar Electro Oy, Kempele, Finland) to track the running training session. In order to quantify the training load, the session RPE was asked at the end of each running session (Foster et al., 2001).

Cognitive Testing

PVT. The computerised version of the 10-min PVT was used to assess vigilance reductions induced by SD (Balkin et al., 2004; Basner & Dinges, 2011). The subject was instructed to press the keyboard button "spacebar" with his preferred hand as soon as a visual stimulus appeared in the centre of a computer screen. The participant was asked to be as fast as possible in their response throughout the entire test. The visual stimulus was a fixed graphic bullseye on a white background. The inter-stimulus interval (i.e. period between a response and the next stimulus) was randomized and varied from 2,000 to 10,000 ms. Reaction times were considered valid only if ≥ 150 ms. Responses < 150 ms were considered as false starts (i.e. errors of commission). Responses ≥ 500 ms were counted as lapses (i.e. errors of omission). Wrong responses (i.e. pressing another button in the keyboard) and no responses (i.e. > 30,000 ms) were also treated as errors. Feedbacks (i.e. reaction time in ms) were provided after each response and appeared centrally on the screen for 1,000 ms prior to the new stimulus. In case of responses < 150 ms, a message "false start" was displayed. Simple RT (ms), response speed (1/RT), false responses (< 150 ms) and minor lapses (≥ 500ms) were assessed as sensitive measures to SD (Basner & Dinges, 2011). The PVT was generated

and run using the E-Prime 2.0 software (Psychology Software Tools, Inc, Pennsylvania, USA).

Psychological Questionnaires

Sleepiness (experimental visits). The Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) was used to assess subjective levels of sleepiness before and after the experimental visits. The scale consists of 9-point Likert scale (where 1 = extremely alert, 2 = very alert, 3 = alert, 4 = rather alert, 5 = neither alert nor sleepy, 6 = some signs of sleepiness, 7 = sleepy, but no effort to keep awake, 8 = sleepy, some effort to keep awake, 9 = very sleepy, great effort to keep awake, fighting sleep).

Sleepiness (SDT). The Epworth Sleepiness Scale (Johns, 1991) was used to assess subjective daytime levels of sleepiness, every day, during the 6 weeks of training intervention. The scale consists of one question referring to eight different soporific situations ('How likely are you to doze off or fall asleep in the following situations, in comparison to just feeling tired?') to be answered on a 4-point Likert scale (where 0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). If some of the situations were not experienced, the answer should be based on how much these activities would have affected the subject. The total range of score is between 0 and 24.

Mood. The BRUMS (Terry et al., 2003) was used as a measurement to evaluate the subject's mood before and after the experimental visits and weekly during the SDT intervention. This questionnaire is a shorter version of the POMS and it consists of 24 items (e.g. tired, anxious, nervous, confused, energetic, active) to be answered on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Items are allocated into six specific subscales: anger, confusion, depression, fatigue, tension and vigour. Each subscale includes four related items and can reach a score between 0 and 16.

Workload. The multidimensional scale NASA TLX (Hart & Staveland, 1988c) was used to estimate the subjective workload experienced during the cycling testing. The NASA TLX includes six subscales: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort and Frustration. The subject was asked to circle one of the 20 line intervals on each of the six scales at the point which matched their experience. Each line has two endpoint descriptors "very low" and "very high" that describe the scale. The performance-related subscale is reversed going from "good" on the left to "poor" on the right.

Motivation. Intrinsic motivation and success on task motivation scales (Matthews et al., 2001) was used to assess motivation related to the running testing. Each scale includes 7 items to be scored on a 5-point Likert scale (where 0 = not at all, 1 = a little, 2 = somewhat, 3 = very much, 4 = extremely). The total range of scores for each scale is between 0 and 28.

7.4 Results

Subject characteristics

Athlete's features and physiological parameters pre- and post-training intervention are reported in Table 7.1.

Table 7.1. *Ultra-Endurance Runner characteristics and physiological parameters pre- and post-training intervention.*

	Pre-SDT	Post-SDT
Age (years)	62	63
Height (m)	1.66	1.66
Weight (kg)	56	58
BMI (kg/m^2)	20	21
Peak Velocity (km/h)	16.2	16.5
$\dot{V}o_{2max}$ (ml/kg/min)	46.0	43.6
HR_{max} (bpm)	164	156
2 mmol/l La threshold (km/h)	12.5	13.1
4 mmol/l La threshold (km/h)	13.7	14.3

BMI, body mass index. $\dot{V}o_{2max}$, maximal oxygen uptake. HR_{max}, maximal heart rate. bpm, beats per minute. mmol/l, millimoles per litre. La, lactate.

Manipulation checks and motivation

Subjective ratings of sleepiness before and after each visit and pre- and post-SDT seems not to be considerably altered (see Table 7.2). The total amount of sleep recorded by the actigraph device is reported in Table 7.3. Subjective fatigue and vigour (BRUMS) (Figure. 7.1) show general reduced levels of fatigue and more stable levels of vigour in the post-SDT visits compared to baseline after sleep deprivation and recovery sleep.

The workload perceived (NASA TLX) during the 2-h simulation running race seems to be lower following SDT. Specifically, subjective ratings of mental demand,

physical demand, effort and frustration appear to be lower and less variable throughout the post-SDT visits (Figure. 7.2).

Intrinsic motivation and success in the task motivation related to the 2-h simulation running race seem to be more stable over the post-SDT visits compared to those at baseline (Figure. 7.3).

Table 7.2. *Ratings of Sleepiness Pre- and Post-Experimental Visits, Pre-SDT and Post-SDT*

	Sleepiness Pre-SDT (1-9)				
	Visit 1	Visit 2 (SD)	Visit 3	Visit 4 (SD)	Visit 5
Pre-Visit	2	3	4	2	3
Post-Visit	2	6	2	4	2
	Sleepiness Post-SDT (1-9)				
	Visit 1	Visit 2 (SD)	Visit 3	Visit 4 (SD)	Visit 5
Pre-Visit	2	4	3	3	3
Post-Visit	4	6	3	3	2

SDT, sleep deprivation training. SD, sleep deprivation.

Table 7.3. *Total amount of sleep Pre-SDT and Post-SDT*

	Amount of sleep (h)				
	Visit 1	Visit 2 (SD)	Visit 3	Visit 4 (SD)	Visit 5
Pre-SDT	6.5	0	8.7	0	8.4
Post-SDT	6.4	0	7.3	0	8.5

SDT, sleep deprivation training. SD, sleep deprivation.

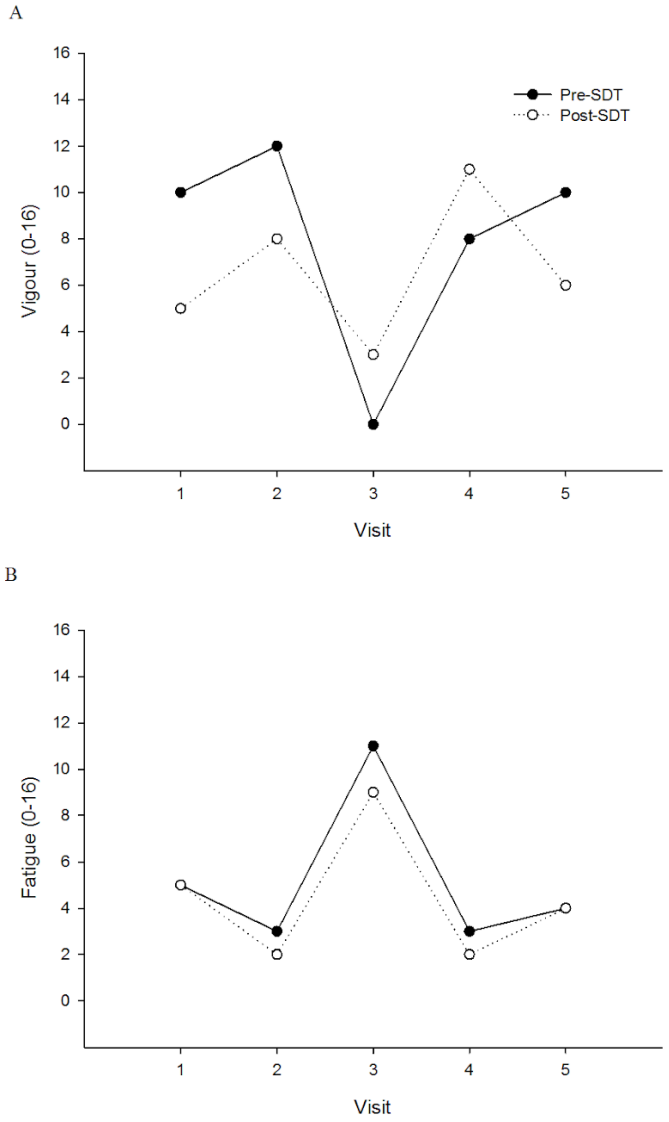

Figure. 7.1. Alterations in the subjective levels of vigour (A) and fatigue (B) measured at Visit 1-5, pre- (solid line) and post-training intervention (open line).

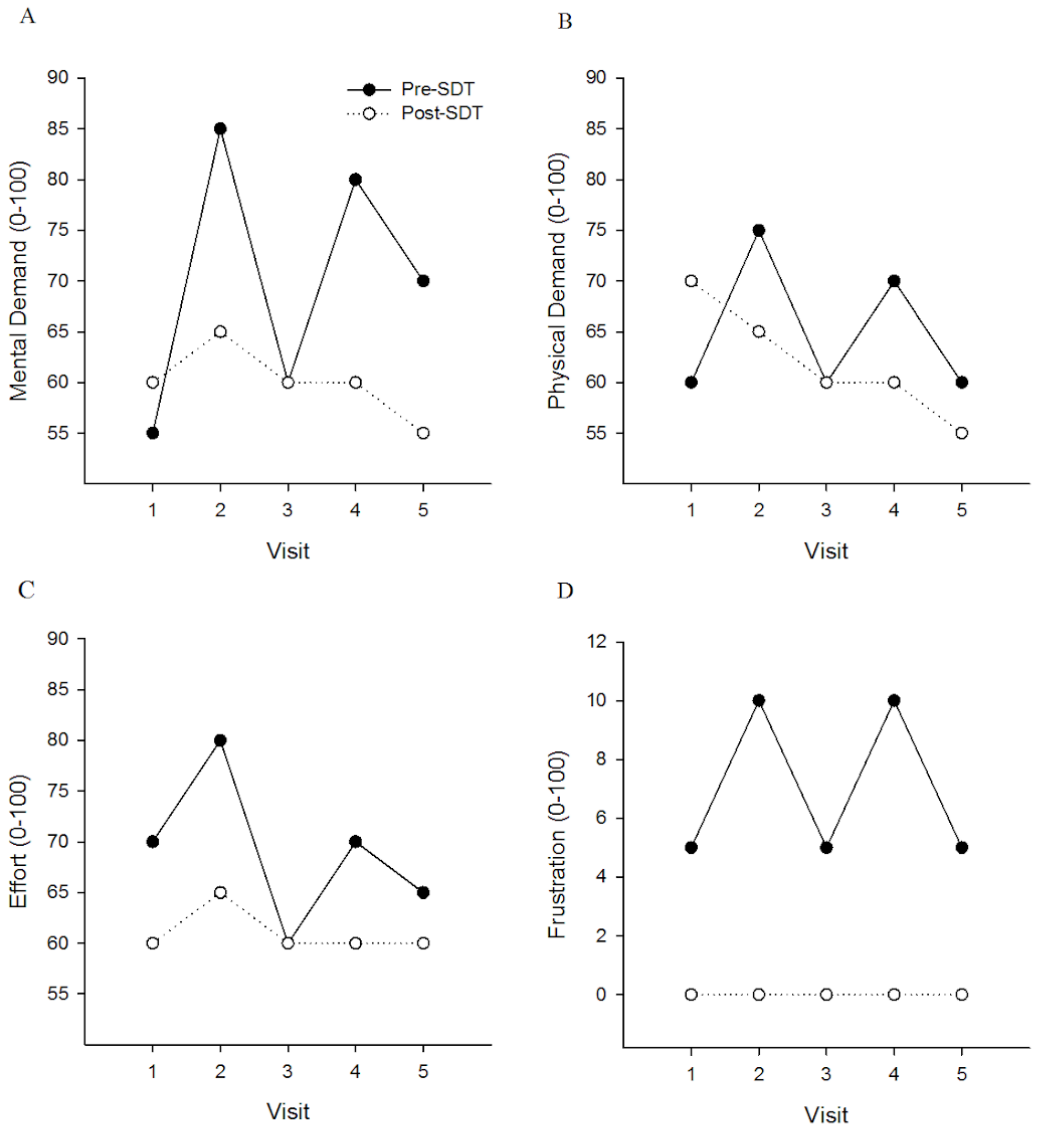

Figure. 7.2. Alterations in the subjective ratings of mental demand (A), physical demand (B), effort (C) and frustration (D) measured after the 2-h simulation running race at Visit 1-5, pre- (solid line) and post-training intervention (open line).

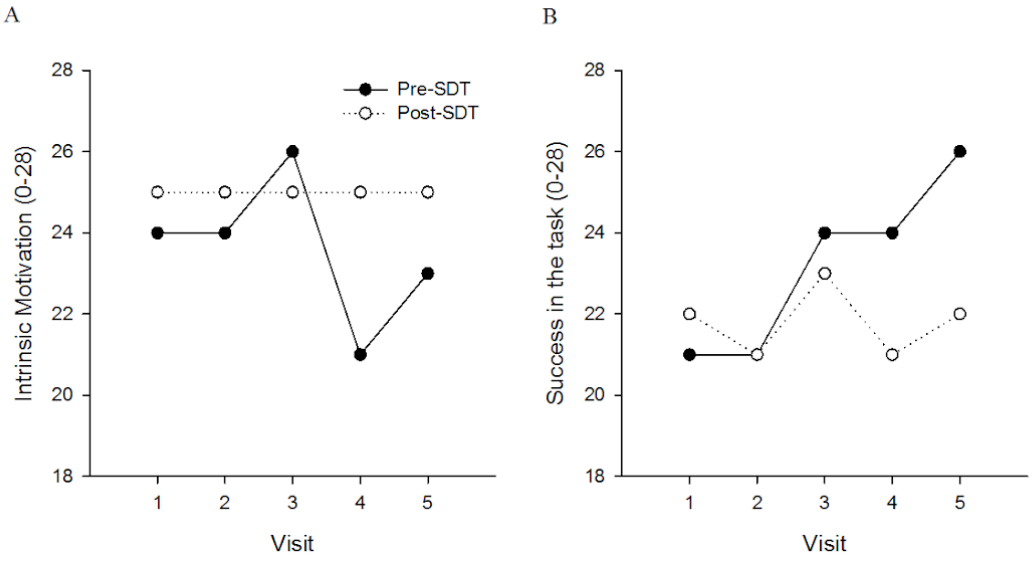

Figure. 7.3. Changes in intrinsic motivation (A) and success in the task motivation (B) measured at Visit 1-5, pre- (solid line) and post-training intervention (open line).

Perceptual and physiological responses

Average RPE, ratings of feeling and HR collected during the 2-h simulation running race are displayed in Figure. 7.4. Final values of the same parameters are displayed in Figure. 7.5. Lower RPE and higher ratings of feeling are reported during the 2-h simulation running races following 6-week SDT compared to baseline. In particular, mean RPE values decrease from 13.2 (pre-SDT) to 12.8 (post-SDT) at Visit 2, and from 13.0 (pre-SDT) to 12.3 (post-SDT) at Visit 4 (sleep deprivation conditions). Lower ratings of perceived exertion are also observed at Visit 3 (12.5, pre-SDT; 12.1, post-SDT) and Visit 5 (12.5, pre-SDT; 11.8, post-SDT) (recovery sleep conditions). RPE values collected at the end of the running testing are even lower, both under sleep deprivation (Visit 2: 14.5, pre-SDT; 13.5, post-SDT; Visit 4: 14.0, pre-SDT; 13.0, post-SDT) and recovery sleep conditions (Visit 3: 13.0, pre-SDT; 12.5, post-SDT; Visit 5: 13.5, pre-SDT; 12.5, post-SDT). Averagely higher ratings of feeling are also reported following the 6-week training intervention. However, differences are evident during Visit 4 and 5 only. Higher HR values are observed after the 6-week SDT following the nights of recovery sleep.

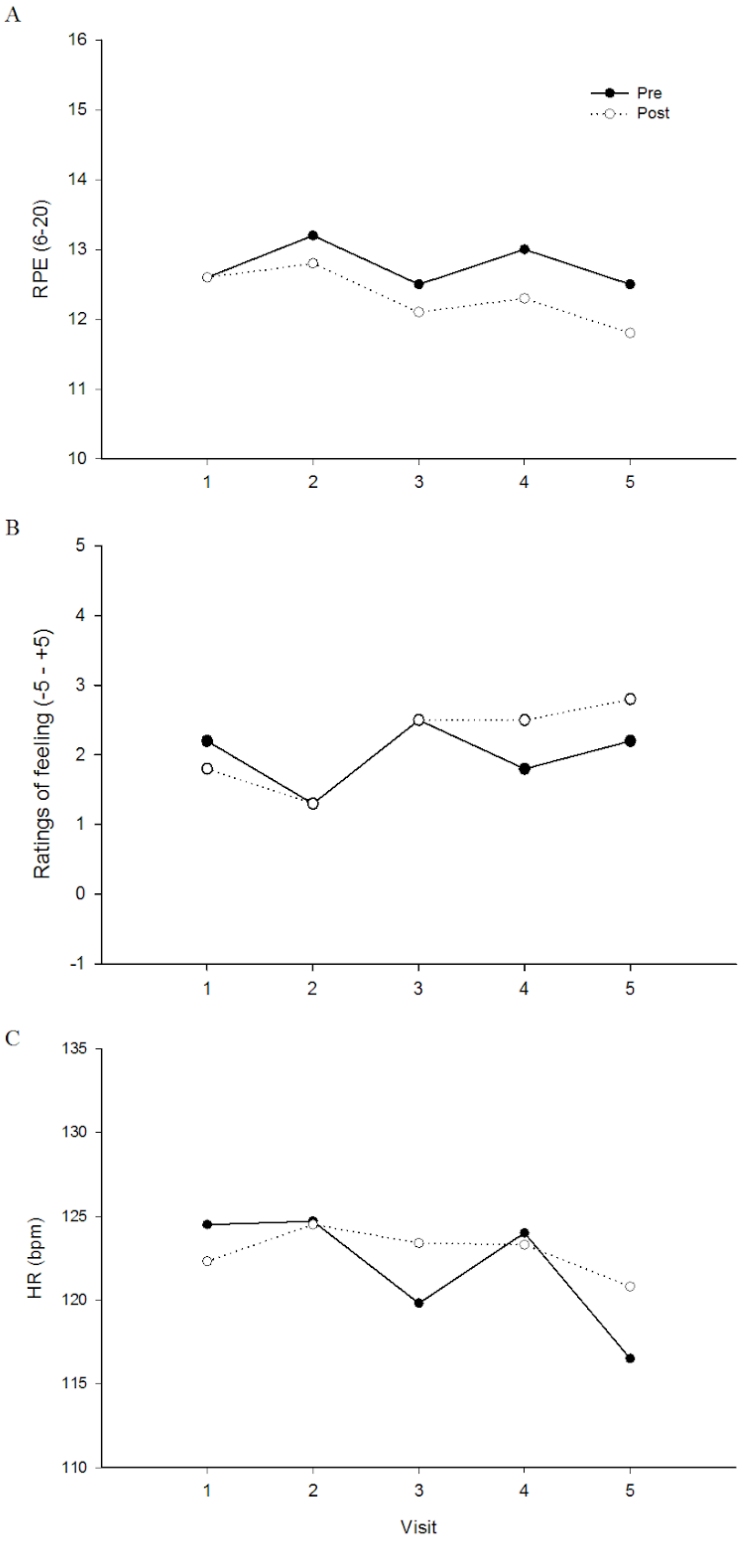

Figure. 7.4. Mean changes in RPE (A) ratings of feeling (B) and HR (C) measured during the 2-h simulation running race at Visit 1-5, Pre-SDT (solid line) and Post-SDT (open line).

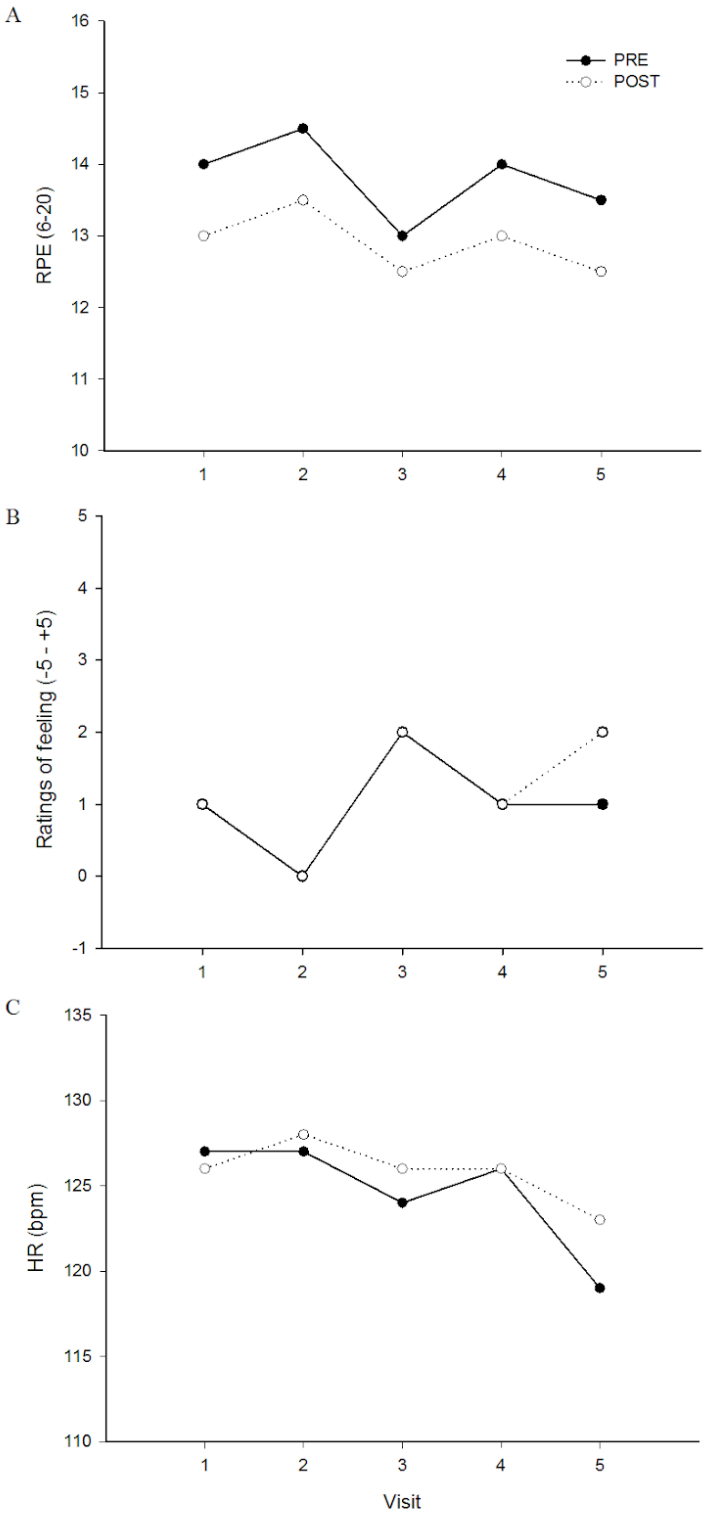

Figure. 7.5. Final values of RPE (A) ratings of feeling (B) and HR (C) measured during the 2-h simulation running race at Visit 1-5, Pre-SDT (solid line) and Post-SDT (open line).

Cognitive performance

Mean changes in RT and number of lapses in the PVT are shown in Figure. 7.6. The results show general lower mean reaction times, but higher variability in the number of lapses following SDT.

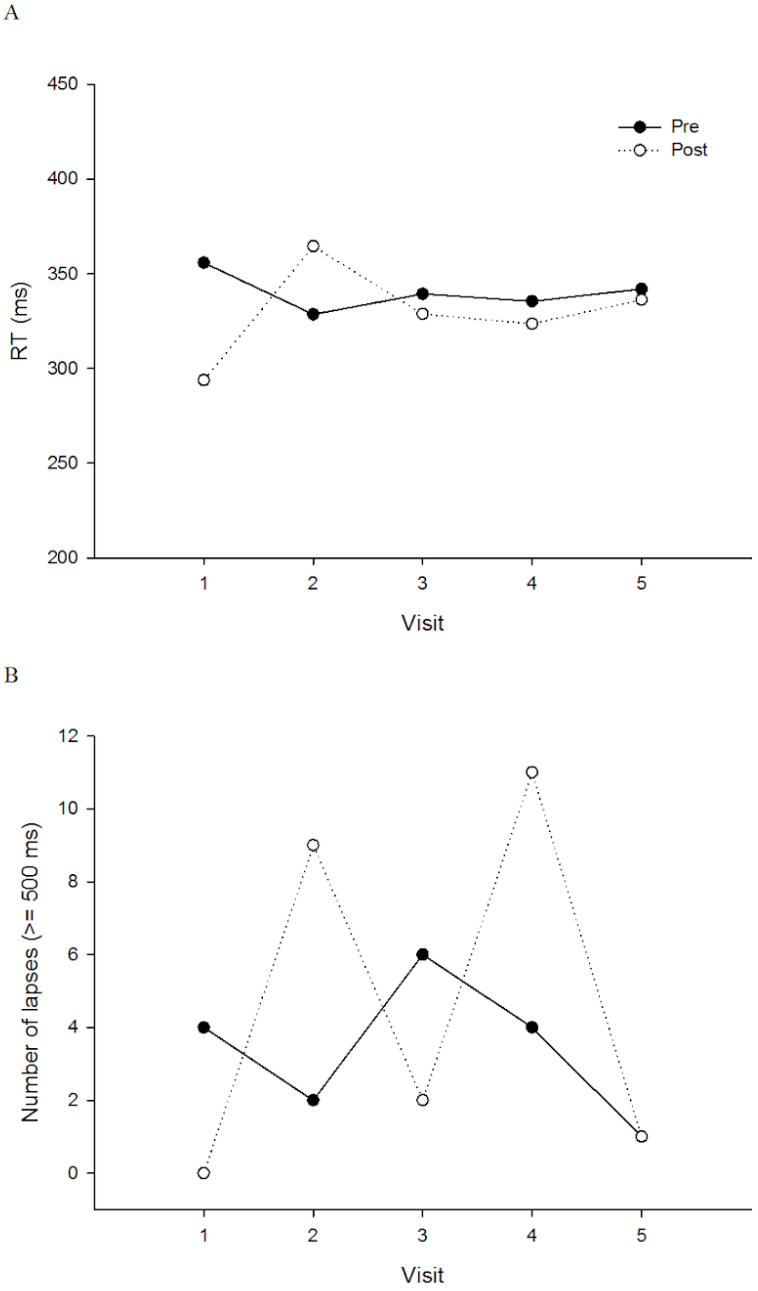

Figure. 7.6. Mean changes in RT (A) and number of lapses (B) measured during the PVT at Visit 1-5, Pre-SDT (solid line) and Post-SDT (open line).

Training

Weekly subjective level of sleepiness (Epworth Sleepiness Scale), vigour and fatigue (BRUMS) measured during the 6-week SDT are reported in Table 7.4. In particular, lower ratings of sleepiness and levels of fatigue are shown throughout the SDT program.

Table 7.4. *Weekly subjective level of sleepiness, vigour and fatigue measured during the SDT.*

	SDT					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Sleepiness (0-24)	8.1	7.9	6.6	4.2	4.0	3.8
Vigour (0-16)	12	10	8	12	8	8
Fatigue (0-16)	5	3	2	0	2	2

SDT, sleep deprivation training.

7.5 Discussion

The combination of SDT with physical training seems to be beneficial on endurance exercise performance in an ultra-endurance athlete. Indeed, the main results of the present case study showed that 6 weeks of SDT seems to be effective on both perception of effort and affective valence in the context of five consecutive days of 2-h simulation running races and alternated nights of sleep deprivation and recovery sleep. Finally the data showed no SDT evident efficacy in improving cognitive performance during a PVT.

Sleepiness, mood state, workload and motivation

Although subjective levels of sleepiness during the pre- and post-SDT experimental visits did not substantially change, the ultra-endurance athlete has reported general reduced levels of fatigue in the post-SDT visits compared to the baseline ones, both

following the nights of sleep deprivation and the nights of recovery sleep. Moreover, the level of vigour appears to be more stable after the training intervention, suggesting less urge to sleep.

Interestingly, lower ratings of perceived workload have also been observed. In particular, subjective ratings of mental demand, physical demand, effort and frustration were reduced and in general more stable throughout the five visits. These data could possibly indicate that a systematic repetition of sleep deprivation bouts may induce resilience to the negative effects that acute sleep deprivation has on mood state and ratings of perceived workload.

The same effect has been observed on motivation. Indeed, both intrinsic and success in the task motivation are not necessarily higher than those reported at baseline, however they are clearly more similar over the five visits, no matter the sleep condition. The ratings of sleepiness and levels of fatigue reported weekly during the SDT, would also confirm a general lower negative impact of sleep deprivation.

Perceptual responses during the 2-h simulation running race

Lower RPE and higher ratings of feeling have been reported during the 2-h simulation running races following 6-week SDT compared to baseline. It has been previously demonstrated that acute sleep deprivation has a negative effect on RPE during sub-maximal endurance exercise (Martin & Haney, 1982; Martin, 1981; Martin & Gaddis, 1981; Mougin et al., 1991). The present data are in line with these findings, showing higher ratings of perceived exertion following sleep deprivation. However, these impairments seem to be lower following 6 weeks of SDT, suggesting that this innovative training strategy might counteract the negative effects of sleep deprivation on perceptual responses during endurance exercise and possibly improve performance itself. Chronic adaptations of those brain regions associated with mental fatigue and perception of effort variations, such as the ACC (Williamson, 2015) and the supplementary motor area (Zenon et al., 2015), might be implicated. Nevertheless, further research is crucial to better understand the efficacy of SDT on endurance

exercise performance and to investigate the potential neurobiological adaptations associated with that.

Finally, it is important to underline the fact that it is unknown how much the physical training program conducted by the athlete during the 6-week intervention might have affected perceptual responses by itself. The athlete indeed, seemed to be more trained (see Table 7.1) and this may have influenced the results.

SDT and cognitive performance

The present findings have also shown that six weeks of SDT seemed not to improve cognitive performance during the PVT. In particular, whereas general lower mean reaction times have been found, higher variability in the number of lapses have been observed following SDT. It might be hypothesised that the duration of the training intervention might not have been enough to induce positive effects on cognitive performance or that SDT might affect longer cognitive tasks only. However, future research is crucial.

Limitations

The present case study shows some limitations that may have interfered with the final findings: 1) the individual was not strictly monitored during the SDT, and consequently he may have fallen asleep during the nights of sleep deprivation; 2) the sleep-wake activity of the individual was not recorded during the 6-week training intervention; 3) the athlete was not blinded from the real aim of the study. This may have affected his internal beliefs and therefore his performance; 4) it is important to underline that this is a single case experiment, and as such, can only provide a descriptive overview of the data collected.

7.6 Conclusions

The results of this case study provide some initial information on the effects of SDT on endurance exercise performance. Clearly, data collected from one subject only cannot explain and predict the effects of SDT on endurance and ultra-endurance athletes populations. Nonetheless, this protocol might help athletes to reduce the negative effects of sleep deprivation during endurance events and to improve the chance of completing ultra-endurance races. Further research needs to be conducted in order to investigate the effects of SDT on endurance performance and its efficacy in combination with other strategies used to counteract the effects of sleep deprivation, such as caffeine consumption. Moreover, the multiple performance testing protocol used to simulate an ultra-endurance event seems to be a feasible way to both monitor ultra-endurance performance and measure the effects of SDT on endurance exercise performance during acute state of sleep deprivation.

Chapter 8

General Discussion

8.1 Main Findings

The present PhD Thesis intended to investigate the effects of mental fatigue and sleep deprivation primarily on endurance exercise performance, as well as on the associated perceptual and physiological responses. Since mental fatigue and sleep deprivation have been studied both acutely and chronically, the main findings have been differentiated and discussed separately, based on these two permutations. It is important to remember that, although defined as two distinct phenomena, sleep deprivation and mental fatigue are closely interconnected and present some overlapping mechanisms. Therefore, mental fatigue and sleep deprivation findings have been discussed together. The effects on cognitive performance have not been covered in this chapter as they are not the principal findings of my PhD and they have been widely studied and documented in the literature already.

Acute effects of mental fatigue and sleep deprivation on endurance performance

Even though previous studies have investigated the acute effects of mental fatigue and sleep deprivation on endurance exercise performance already, during my doctoral research program two innovative experiments have been proposed. The aim has been to provide novel insight into the role played by acute mental fatigue and sleep deprivation on endurance exercise performance, by testing more ecologically valid physical tasks, such as a proper running race (Chapter 4) and a typical cycling training session (Chapter

5). Moreover, the role of recovery sleep on endurance exercise performance following acute sleep deprivation has been properly investigated for the first time (Chapter 5).

The main findings of my two acute studies suggest that both mental fatigue and sleep deprivation do not significantly impair endurance exercise performance. These results are in contrast with previous laboratory/indoor-based experiments (MacMahon et al., 2014; Marcora et al., 2009; Martin, 1981; Martin & Chen, 1984; Pageaux et al., 2014; Pageaux et al., 2013; Smith et al., 2016; Temesi et al., 2013).

Although certain markers of mental fatigue and sleep deprivation measured during the two studies confirmed states of mental fatigue and sleepiness in the experimental groups, the results obtained using the traditional statistical analysis seem to indicate that 50 minute of mentally-fatiguing tasks and 25 hours of sleep deprivation are not enough to induce changes on endurance exercise performance. It is possible that the duration of the cognitive task and the amount of hours of sleep deprivation needed to induce significant impairments are possibly higher than the one used in these two experiments.

However, it is important to highlight that non-significant results (i.e. $p > 0.05$) do not necessarily mean lack of effect (Amrhein et al., 2019). The alternative statistical analysis used in the field experiment (i.e. TOST equivalence testing analysis) (Lakens, 2017; Lakens et al., 2018; Schuirmann, 1987) provided important evidence in that sense, confirming that the hypothesis of a non effect of mental fatigue cannot be rejected (Chapter 4). In addition to that, a visual inspection of the data suggests that both mental fatigue and sleep deprivation could have possibly had detrimental effects on endurance exercise performance. Specifically, individuals in the experimental groups impaired their endurance exercise performance by 6% (mental fatigue group) and by 5.4% (sleep deprivation group), both worthwhile performance changes (Hopkins et al., 1999; Hopkins & Hewson, 2001; Paton & Hopkins, 2006). Moreover, a medium effect size of 0.367 (Cohen's *d*) has been found in the field experiment (Chapter 4), showing important similarities with previous laboratory studies (Marcora et al., 2009; Pageaux et al., 2014). As the kind of design used for these two experiments (i.e. between-group and between-group posttest-only designs) required larger sample sizes, the results might have been affected by a lack of statistical power (See Limitations for more details).

Acute effects of mental fatigue and sleep deprivation on perceptual and physiological responses during endurance exercise

The perceptual responses investigated during the two acute studies revealed a clear common pattern. In general, whereas no changes in RPE and ratings of feeling during self-paced types of exercise (i.e. half-marathon competition and 20-min cycling TT) have been found (Chapter 4 and 5), significantly higher ratings of perceived exertion and lower ratings of feeling during a constant-intensity endurance exercise (i.e. 40-min cycling pre-load) have been reported (Chapter 5). These findings are in line with previous experiments investigating the effects of mental fatigue and sleep deprivation on TT performance, which have shown the same RPE values for lower running speeds and cycling power outputs (MacMahon et al., 2014; Martin et al., 2016; Oliver et al., 2009). This suggests that in order to maintain affordable values of RPE and finish the exercise task, mentally-fatigued and sleep-deprived individuals might decrease their pace during self-paced endurance exercise. Higher levels of RPE have also been found during constant-intensity type of exercise, as in previous studies (Marcora et al., 2009; Martin & Haney, 1982; Martin, 1981; Martin & Gaddis, 1981; Mougin et al., 1991; Pageaux et al., 2013), which gives further demonstration of the key role played by perception of effort on endurance exercise performance and pace regulation when individuals are mentally-fatigued and/or sleep-deprived.

The most likely explanation is that an acute mentally-fatiguing state, either caused by a cognitive demanding task or lack of sleep might affect those central processing of sensory inputs which produce perception of effort during exercise (Marcora, 2009). Moreover, functional alterations of specific areas of the brain, whose changes of activity are correlated with RPE variations (Williamson et al., 2001, 2002, 2006), such as the ACC (Williamson, 2015) and the supplementary motor area (Zenon et al., 2015) might also be hypothesised. EEG and neuroimaging studies on acute sleep deprivation and mental fatigue during exercise tasks are required to better understand

the role of perception of effort on endurance exercise performance and the neurobiological mechanisms underneath that.

From a physiological perspective, no alterations in HR and lactate responses have been found, suggesting once again that endurance exercise performance seems to be limited by cognitive and motivational aspects rather than by cardiorespiratory and muscle energetics mechanisms in a mentally-fatiguing state (Marcora et al., 2008; Marcora et al., 2009). These results are in line with the psychobiological model of endurance exercise performance (Marcora et al., 2008), which recognises perception of effort and potential motivation (i.e. the maximum effort a person is willing to exert to satisfy a motive (Wright, 2008)), as the main limiting factors of endurance exercise performance. Interestingly though, lower values of HR have been observed during 2-h constant-intensity running following sleep deprivation (Chapter 7). These findings are in agreement with past experiments (Holland, 1968; Martin & Gaddis, 1981) and suggest that lack of sleep might act differently from a mental fatigue state induced by prolonged and demanding cognitive tasks, affecting the activity of the sympathetic and parasympathetic nervous systems on the heart during exercise.

Chronic effects of mental fatigue and sleep deprivation on endurance performance

The chronic experiments conducted during my doctoral research program on mental fatigue and sleep deprivation aimed at investigating a new training strategy, consisting in using acute bouts of mental fatigue/sleep deprivation as a training stimulus to induce chronic resistance to fatigue during endurance exercise and hence improve endurance performance (Chapter 6 and 7).

The main results showed that the use of Brain Endurance Training alone is not effective to improve endurance exercise performance in sedentary healthy young males (Chapter 6). As suggested from the only study present in the literature, Brain Endurance Training seems to have a positive effect only if used in synergy with aerobic training (Marcora et al., 2015). Moreover, it has also been observed that the use of Sleep Deprivation Training in combination with a physical training program in an ultra-endurance runner seems to be beneficial on perception effort and affective valence

in the context of five consecutive days of prolonged running testing, during which nights of sleep deprivation and recovery sleep have been alternated (Chapter 7). This is the first time that such a multiple performance testing protocol has been used. I believe this can also be an innovative way to test athletes and to assess performance in those sport events lasting consecutive days, such as ultra-endurance competitions and multiple stage races.

The present findings might suggest that these training strategies are not effective if used alone, as they may not induce enough adaptations of those brain regions involved with effort, such as the ACC (Shenhav et al., 2017) and the supplementary motor area (Zenon et al., 2015). Indeed, previous studies have shown bigger structural and functional adaptations at the brain level when physical and cognitive training are combined (Fabel et al., 2009; Fabre et al., 2002; Holzschneider et al., 2012).

Chronic effects of mental fatigue and sleep deprivation on perceptual and physiological responses during endurance exercise

Whereas the Brain Endurance Training seem not to show any chronic effect on RPE and ratings of feeling (which further suggests that the use of cognitive training alone might not be sufficient to induce significant effort-based adaptations at the brain level) (Chapter 6), the effects of Sleep Deprivation Training in combination with physical training are in line with what has been previously found in relation to the Brain Endurance Training (Marcora et al., 2015) (Chapter 7). Lower ratings of perceived exertion and higher ratings of feeling have been observed during prolonged constant-speed running testing following 6 weeks of training intervention. These improvements have been found both following the nights of sleep deprivation and recovery sleep, suggesting that this kind of training might counteract the negative effects of mental fatigue and/or sleep deprivation on perceptual responses during endurance exercise, facilitate the exercise recovery and potentially improve performance.

Finally, no physiological alterations have been found following the Brain Endurance Training. However, higher HR values have been observed after the Sleep

Deprivation Training, suggesting that sleep deprivation and mental fatigue might act differently on the heart activity during exercise.

To summarise, the main findings presented above suggest that mental fatigue and sleep deprivation affect endurance exercise performance both acutely and chronically in a very similar way, and that perception of effort seems to play a key role in that. These results have highlighted once again the strong link between these two phenomena and the urge to investigate their overlapping mechanisms in association with their potential cause-effect relationship.

8.2 Limitations

The experiments conducted show several limitations which might have affected the final results of this thesis. The first limitation refers to the sample size tested in the study described in Chapter 4. Indeed, the small number of subjects used might have limited the power of the findings. This has also been suggested by a visual inspection of the data and by the results obtained using the TOST equivalence testing analysis.

The sample size limitation present in this experiment was expected, as directly associated with the intrinsic limitations that traditional statistical significance testing has itself (Amrhein et al., 2019). Indeed, in this classical statistical analysis the true effect size is zero (null hypothesis). As the hypothesis of a true effect size exactly equal to zero is statistically impossible and the lack of effect can only be rejected but not statically corroborated, the possibility of a true effect even when $p > 0.05$ needs to be considered (Amrhein et al., 2019). In order to overcome this limitation, the TOST equivalence testing analysis has been used (Lakens, 2017). This statistical approach allows testing for the absence of an effect big enough to be considered meaningful. However, this analysis is not without any limitation either. Indeed, since specific guidelines on how to determine equivalence boundaries are absent at the moment (Lakens, 2017), they had to be chosen by the researcher. Even though all the suggestions and recommendations available in the literature have been considered

(Lakens, 2017; Lakens et al., 2018), the lack of a methodological criteria to set the boundaries might have caused some limitations in the findings.

A sample size limitation is also evident in Chapter 7. Indeed, a single case study can only give a descriptive overview of the data collected, and since no statistical analysis could be done, final conclusions on the effects of Sleep Deprivation Training should not be drawn.

Some limitations are also related to the experimental designs used. For practical reasons, a between-group design (Chapter 5 and 6) and a posttest-only (i.e. subjects have not been tested at baseline, but only after the treatment) with control group design have been utilized (Chapter 4). Consequently, preexisting differences between groups might have distorted the results of the present experiments (Morris, 2008). Alternative experimental designs, such as crossover and pretest-posttest control group designs, as well as using bigger sample sizes, could be potential methodological alternatives aimed to counteract lack of homogeneity and individual variability in such kind of experimental designs. Another valid option would be to conduct more studies and subsequently run a meta-analysis.

A common limitation present in all studies of this thesis is associated with participants recruitment. Due to the practical impossibility to standardise the testing periods within the same menstrual-cycle phase among potential female participants, only male individuals have been tested. Since hormonal state variations due to ovarian cycle and oral contraceptives in females have been demonstrated to significantly interfere with cognitive and physical performance (Constantini et al., 2005; Kimura & Hampson, 1994; Wright & Badia, 1999), the current results cannot be translated to women (i.e. gender bias). Therefore, future research needs to be conducted to investigate the same research questions in the female population. Another important limitation always related to subject recruitment is present in Chapter 6. The study involved physically-inactive individuals who had never practiced any kind of physical activity before, meaning lack of experience and motivation, which can be translated into physical performance failure (i.e. not reaching the real exhaustion during the TTE). More familiarisation sessions need to be considered for future experiments.

Studies discussed in Chapter 4, 5 and 6, present a possible limitation in the kind of treatment chosen. The type, duration and frequency of the cognitive tasks used to induce mental fatigue and sleep deprivation indeed, might not have been enough to cause significant adaptations at the brain level. Future research is certainly required to better understand the most effective tasks, durations and frequencies.

Subjects' knowledge of treatment allocation in the Chapter 5 study might also have affected physical and cognitive performance as well as self-reported measures. For obvious reasons, sleep conditions could not be blinded to participants and therefore performance bias could not be controlled (Juni, 2001). Moreover, a potential belief bias effect might have been present in the training experiments reported in Chapter 6 and Chapter 7 (Dube et al., 2010; Evans et al., 1983). The subjects, indeed, might have behaved based on their internal beliefs and knowledge throughout the entire experiment. Even though participants in Chapter 6 were not aware of the real purpose of the experiment and were blinded from the treatment of the other group (and vice versa), their performance could have been biased by their own expectations.

Finally, in order to remove any bias associated with my awareness of treatment allocation, it has been decided not to use any verbal encouragement during the physical tasks. This decision however, might have limited the performance outcome of my participants. Indeed, it is well known that verbal encouragement improves performance in several endurance tasks (McCormick et al., 2015).

8.3 Conclusions and directions for future research

In general, the experiments conducted during my doctoral research program have explored new, untested research questions, and therefore much more research is needed before definitive evidence-based recommendations can be made.

Because of the methodological issues related to the research design used and the sample size selected, the first study (Chapter 4) does not provide reliable evidence that mental fatigue reduces endurance exercise performance. Therefore, additional studies are required to give more precise estimates of its effects during outdoor, mass-start competitions in running and other endurance disciplines. Field studies can be

challenging and difficult to conduct, as the number of variables to control are higher than the ones present in more standardised environments, such as laboratory settings. Nevertheless, having a more ecologically valid insight of the role played by mental fatigue on endurance exercise performance is essential for advising athletes and coaches on the best strategies to adopt before and during competitions. Alternative experimental designs, such as crossover and pretest-posttest control group designs, as well as using bigger sample sizes, could be potential methodological alternatives aimed to counteract the lack of statistical power found in my experiment. Another valid solution would be to conduct more studies during real competitions and subsequently run a meta-analysis. Moreover, the use of alternative statistical analyses are also suggested in such a field study context. The quantification of the effects of mental fatigue during official races is also crucial to develop interventions aimed at reducing mental fatigue and improve endurance performance, such as the brain endurance training.

Several directions for future research have emerged from the acute sleep deprivation study (Chapter 5). The literature on the effects of sleep deprivation on endurance exercise performance is still controversial. In my experiment 25 hours of lack of sleep seems not to be detrimental during a 20-min cycling TT. On the contrary, perception of effort and affective valence have been negatively affected during a constant-intensity cycling preload and positively recuperated by one night of recovery sleep. Further investigations are certainly required to clarify the role played by acute sleep deprivation on endurance exercise performance based on the amount of sleep deprivation (i.e. one night might not be enough) and the type of exercise (e.g. closed-loop and opened-loop, self-paced and fixed-paced) and discipline (e.g. running, cycling, swimming) performed. Moreover, additional research is essential to quantify the effect of recovery sleep in the field of sport and to investigate its role in combination with other sleepiness-related countermeasures, such as caffeine. A better understanding of the role played by recovery sleep, indeed, would help trainers and athletes to counteract sleep deprivation during endurance/ultra-endurance competitions.

The findings also showed that sleep deprivation seems to induce heart rate reductions. The mechanisms underneath this phenomenon might be associated with unbalanced alterations in the activity of the sympathetic and parasympathetic nervous

systems, however, future research is essential. Furthermore, the single case study (Chapter 7) has confirmed the same trend and has also revealed potential adaptations in the HR variability following the sleep deprivation training, reinforcing the idea that heart rate might be an important physiological marker in this context. Further experiments would need to confirm these results.

Regarding the training study discussed in Chapter 6, the results suggest the inefficacy of BET alone in improving endurance exercise performance. These findings together with the ones obtained by Marcora and colleagues (Marcora et al., 2015) provide initial evidence that the combination of BET and standard aerobic training seems to be the most effective strategy to improve endurance exercise performance compared to the two training interventions alone. However, this is the second study ever conducted on the topic and more research is certainly required to better understand the efficacy of BET alone and when combined with physical training. Moreover, future studies should investigate the neurobiological mechanisms and the brain adaptations underlying the effects of BET on perception of effort and endurance performance as well as its efficacy in other populations such as females, elite endurance athletes and injured athletes.

Finally, future work should be considered in order to explore the effects of SDT on endurance exercise performance (Chapter 7). The results of the single case study provided an initial descriptive overview, however, proper experimental studies are required. Further research should also investigate the potential neurobiological mechanisms and adaptations underlying this innovative training strategy and its efficacy alone and in combination with physical training as well as with other sleep deprivation countermeasures, such as caffeine. In general, future EEG and fMRI studies would be essential to identify acute and chronic structural and functional brain adaptations induced by mental fatigue and sleep deprivation in the context of endurance performance.

In conclusion, the findings of my doctoral research program do not provide statistical evidence of a negative effect of mental fatigue and sleep deprivation on endurance exercise performance during an official half-marathon competition and a standard cycling training session. However, from a practical perspective, it may be

prudent for athletes to avoid any cognitive demanding task before and during the first part of any endurance/ultra-endurance race and to adopt specific pacing strategies until further research would clarify these results. Moreover, even though the present findings suggest that amateur athletes can maintain their physical performance after one-night sleep deprivation, it is recommended to sleep adequately the night before, as the effects might differ among individuals. Nonetheless, whereas BET alone seems to be ineffective in sedentary people, the addition of BET or SDT into a typical physical training program are suggested in preparation for an endurance/ultra-endurance event. These training interventions indeed, might help athletes to reduce the negative effects of mental fatigue/sleep deprivation during endurance events and to improve the chance of completing ultra-endurance races.

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