THE EFFECT OF EXERCISE-INDUCED PAIN ON ENDURANCE PERFORMANCE, AND STRATEGIES TO MITIGATE ITS IMPACT

Thesis submitted at the University of Kent
in fulfilment of the requirements of the degree for
Doctor of Philosophy

by

Ali Astokorki
PhD School of Sport and Exercise Science and Sports Therapy
School of Sport and Exercise Sciences
University of Kent

March 2017

﴿*Over every possessor of knowledge is one [more] knowing*﴾

{Quran, Surah Yusuf, 76}

Acknowledgements

I would like to express my sincere gratitude to my exceptional supervisor and valued mentor Dr. Lex Mauger. The thesis would not have been possible without his patience, encouragement and immense scientific knowledge. Dr. Mauger's continuous support and guidance was unwavering over the last three years and his advice and feedback helped me immeasurably to develop as a writer and scientist. I could not have had a better supervisor and mentor for my PhD study. I would also like to thank the Human Capacity Development Program (HCDP), which has supported me through a scholarship program to fund my PhD study.

It is my pleasure to thank James Hogg, Laura Obeng, and Dr. Andy Galbraith, who gave me access to the laboratory and research facilities. Without they precious support it would not have been possible to conduct this research. I am also grateful to all the staff members of the department (School of Sport & Exercise Sciences) for their full participation and assistance, especially Ruth Brown, Nicola Johnson, Professor Samuele Marcora, Dr. Glen Davison and Dr. James Hopker.

I owe my deepest gratitude to Dr. Akram, who assisted and supported me so that I could study in the UK. I would also like to show my gratitude to colleagues at School of Sport & Exercise Sciences who were always available to support me and participate for studies (Hawbeer, Hawkar, Warhel, Borja, Chiara, Tony, Luca, Stephen, Lauren, Irisz, Kat, Sarah, Anna, Jamie, Andre, Emily, Corinna, Paul, and Anees). I would also like to thank the two sisters Megan and Lauren Judge, who helped me with collected data for the two experimental chapters of the thesis.

It is an honour for me to thank Angela Koch from the Student Learning Advisory Service at University of Kent who helped me to develop my academic writing skills.

I am indebted to my father-in-law, Mr. Salahaddin Rashid, who supported and funded me over two years during financial difficulties arising from the political situation in the Kurdistan region. Without his help, I would not have been able to complete my PhD study in the timescale requested.

Finally, I would like to thank my lovely family: Hiba, the exceptional and unique partner of my life; Lara, a princess of my family; Hussein, my little hero who would never let me study.

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°C	-	Degree Centigrade
°F	-	Degree Fahrenheit
1RM	-	One repetition maximum
5-HT	-	Serotonin
ACC	-	Anterior cingulate cortex
ADP	-	Adenosine diphosphate
AI	-	Anterior insular
ANOVA	-	Analysis of variance
ASICs	-	Acid-sensing ion channels
ATP	-	Adenosine triphosphate
B[La]	-	blood lactate concentration
BG	-	Basal ganglia
BKN	-	Bradykinin
BRUMS	-	Brunel Universal Mood States
CG	-	Central Governor
CGM	-	Central Governor Model
CGRP	-	Calcitonin gene-related peptide
CI	-	Coefficient of variation
cm	-	Centimetre
CMC	-	Central motor commands
CMD	-	Central motor drive
CNS	-	Central nervous system
CON	-	Control group
COX	-	Cyclooxygenase
CPT	-	Cold pressor test
CR	-	Category Ratio
DH	-	Dorsal horn
DOMS	-	Delayed-onset muscle soreness
DPC	-	Dorsolateral prefrontal cortex
DRG	-	Dorsal root ganglia
EEG	-	Electroencephalogram
EIP	-	Exercise-induced pain

EMG	-	Electromyography
FP	-	Fixed power test
GET	-	Gas-exchange threshold
GXT	-	Graded Exercise Test
H^+	-	Hydrogen
HITT	-	High-intensity interval training
HR	-	Heart rate
HTM	-	High threshold mechanoreceptors
Hz	-	Hertz
IASP	-	International Association for the Study of Pain
IFC	-	Interferential current stimulation
Kg	-	Kilogram
Km	-	Kilometre
kPa	-	kilopascal
La	-	Lactic acid
MAIA	-	Multidimensional Assessment of Interoceptive Awareness
MAOD	-	Maximal accumulated oxygen deficit
Min	-	Minute
mm	-	Millimetres
Mmol/L	-	Millimoles per Litre
MPQ	-	McGill Pain Questionnaire
MQ	-	Mood Questionnaire
MS	-	Motivational system
MVC	-	Maximal voluntary contraction
N/m^2	-	Newton per square metre
NGF	-	Nerve growth factor
NO	-	Nitric oxide
nPGi	-	Nucleus paragigantocellularis
NSAIDs	-	Nonsteroidal anti-inflammatory agents/analgesics
PAG	-	Periaqueductal gray
PGE_2	-	Prostaglandin E_2
PGI_2	-	Prostacyclin I_2
PGs	-	Prostaglandins
pH	-	Potential of hydrogen
PO	-	Power output

PO/PI	-	parietal operculum/posterior insula
PO_{mean}	-	Mean power output
PO_{peak}	-	Peak power output
PPO	-	Peak power output
PPT	-	Pain pressure threshold
R^2	-	R squared
RPE	-	Rating of perceived exertion
RPM	-	Revolutions per minute
RVM	-	Rostral Ventromedial Medulla
S	-	Second
S1	-	Primary somatosensory cortex
S2	-	Secondary somatosensory cortex
SaO_2	-	Saturation of Oxygen
SC	-	Spinal cord
SP	-	Substance P
SSES	-	School of Sport & Exercise Sciences
T	-	Transmission cells
TENS	-	Transcutaneous electrical nerve
TT	-	Time trial
TTE	-	Time to exhaustion
TXA_2	-	Thromboxane A_2
VA	-	Visual Analog
VAL	-	voluntary activation level
VCO_2	-	Carbon dioxide output
VE	-	Minute ventilation
VO_2	-	Oxygen consumption
VO_{2max}	-	Maximal oxygen consumption
VO_{2peak}	-	Peak Oxygen consumption
VPL	-	Ventral posterolateral thalamic nucleus
VPM	-	ventral posteromedial nucleus
VR	-	Virtual reality
W	-	Watt
Wpeak	-	Peak power output
Yrs	-	Years
μs	-	Microsecond

Publications and presentations arising from the thesis

Articles published in peer reviewed journals:

Astokorki, A. H. Y., & Mauger, A. R. (2016). Tolerance of exercise-induced pain at a fixed rating of perceived exertion predicts time trial cycling performance. *Scandinavian Journal of Medicine & Science in Sports*. doi: 10.1111/sms.12659.

Astokorki, A.H.Y., Mauger A.R. (2017). Transcutaneous electrical nerve stimulation reduces exercise-induced perceived pain and improves endurance exercise performance. *European Journal of Applied Physiology.* doi: 10.1007/s00421-016-3532-6.

Oral communications:

Astokorki, A.H.Y., Mauger A.R. (2015). An investigation into the analgesic effects of transcutaneous electrical nerve stimulation and interferential current on exercise-induced pain and performance. *Endurance Research Conference, Kent 2015.*

Astokorki, A.H.Y., Mauger A.R. (2016). The effect of compassional hyperalgesia on exercise-induced pain during endurance cycling performance. *European College of Sports Science Conference, Vienna, Austria.*

Astokorki, A.H.Y., Mauger A.R. (2017). Transcutaneous electrical nerve stimulation inhibits central pain transmission and limits the development of peripheral muscle pain during cycling time trial performance. *The British Association of Sport and Exercise Sciences Student Conference, Plymouth, UK, 2017.*

General Abstract

This thesis was supervised by Dr. Lex Mauger
(University of Kent, UK)

Exercise-induced pain (EIP) is a natural consequence of exercising intensely, and results due to an accumulation of endogenous algesic substances, an increase in muscular pressure and muscular distortion or tissue damage. However, the presence of EIP may have negative consequences for exercise and endurance performance, brought about by the physiological and/or psychological effect of pain. EIP has not been widely addressed in sport and exercise science research, and much of the contemporary literature has ignored its potential role in endurance exercise performance, despite the wide acknowledgement it gains in interviews with athletes, coaches, exercise scientists and health and fitness practitioners. Therefore, more empirical research needs to be completed that explores the role of EIP in endurance performance, and the physiological and/or psychological contribution it may make to fatigue and work rate regulation. Therefore, the main purpose of this thesis was to examine the effect of EIP on endurance exercise performance, and identify strategies to mitigate its impact in various endurance exercise tasks. Consequently, this thesis consists of 5 experimental studies, as outlined below.

The 1st experimental study (Chapter 3) assessed the relationship between traditional experimental measures of pain (the cold pressor test (CPT) and algometry), EIP tolerance and participants' performance of a 10 mile (16.1 km) cycling time trial. The primary finding was that no correlation was found between experimental pain measures and TT performance (mean pain in CPT; $R = 0.222$; time lasted in the CPT; $R = -0.292$; PPT; $R = -0.016$). However, there was a significant correlation between EIP tolerance and TT performance ($R = -0.83$, $P < 0.01$). Correlation analysis revealed significant ($P < 0.01$) relationships between TT completion time and VO_{2max} ($R = -0.816$, $P < 0.001$), PPO ($R = -0.864$, $P < 0.001$), GET ($R = -0.454$, $P = 0.009$), and RPE tolerance ($R = -0.736$, $P < 0.01$). Hierarchical multiple regression for physiological parameters (VO_{2max}, GET and PPO) revealed that a significant model emerged ($F_{(1,30)} = 88.586$, $P < 0.01$) when only PPO was used to predict TT completion time. PPO explained 74.7% variance (R Square = 0.747, Adjusted R Square = 0.739, ΔR Square = 0.747, $F_{(1,30)} = 88.586$, $P < 0.01$, Beta = - 0.864).

Stepwise regression for pain and RPE predictor variables (mean pain in CPT, time lasted in the CPT, PPT, EIP tolerance, and RPE tolerance) revealed that all variables with the exception of time lasted in CPT and RPE tolerance contributed to a predictive model. EIP tolerance predicted TT completion time and explained 69.4% variance (R Square = 0.694, Adjusted R Square = 0.684, ΔR Square = 0.694, $F_{(1, 30)} = 68.075$, $P < 0.01$, Beta = - 0.833), PPT explained additional 4% variance (R Square = 0.040, Adjusted R Square = 0.716, ΔR Square = 0.040, $\Delta F_{(1, 29)} = 4.390$, P = 0.045, Beta = - 0.886), and mean pain in CPT also explained additional 4.4% variance (Square = 0.044, Adjusted R Square = 0.754, ΔR Square = 0.044, $\Delta F_{(1, 28)} = 5.543$, P = 0.026, Beta = - 0.881). Therefore, EIP tolerance, PPT and mean pain in CPT explained 77.8% variance in TT completion time. Regression analysis for pain and physiological predictor variables (mean pain in CPT, PPT, EIP tolerance, VO_{2max}, PPO, GET) revealed that a significant model ($P < 0.01$) emerged when only PPO (Adjusted R Square = 0.739) and EIP tolerance (ΔR Square = 0.075) were used to predict TT performance. Therefore, PPO and EIP tolerance explained an overall 82.2% variance in the model. This study demonstrated for the first time that tolerance of EIP provides a good predictor of endurance performance, whereas traditional measures of pain do not. It is suggested that participants who are able to tolerate a greater pain for longer time period, are able to maintain a higher work rate and therefore finish the endurance performance task faster. The results suggest that EIP plays a crucial role in endurance performance, and that a high tolerance for EIP provides an important role as a predictor of endurance athletic performance. Finally, this study demonstrates that psychological variables (in this case pain tolerance), should be considered alongside physiological (e.g. VO_{2max}, lactate threshold, exercise economy) variables, in identifying the determinants of endurance performance.

The 2nd experimental study (Chapter 4) examined the effect of mirror visual feedback on EIP during isometric performance. Specifically, mirror visual feedback was used to deceive participants about the difficulty of the exercise task they were engaging in. It was hypothesised that increasing perceived task difficulty would increase expectation of EIP and reduce time to exhaustion, whereas decreasing perceived would elicit the opposite effect. The results supported the study hypothesis, and showed that the deception of task difficulty in the Experimental group led participants to produce significantly longer times to exhaustion when they thought the task was easier than it was, and significantly shorter times to exhaustion when they thought it was harder than it was ($F_{(1,40)} = 4.293$, P = 0.045). The ANOVA revealed a significant main effect of condition for EIP during the TTE test

($F_{(1, 40)} = 8.736$, $P = 0.005$), and a significant interaction effect of EIP between groups for each time condition were observed ($F_{(1,40)} = 7.163$, $P = 0.011$). The ANOVA revealed a significant main effect of condition for RPE during the TTE test ($F_{(1, 40)} = 33.403$, $P < 0.001$), and a significant interaction effect of RPE between groups for each time condition ($F_{(1,40)} = 13.367$, $P < 0.001$). This was accompanied by significantly higher EIP and RPE when they thought the task was harder than it was, and significantly lower EIP and RPE when they thought the task was easier than it was. This is the first experimental study using the mirror box technique as a strategy to moderate EIP during isometric contractions. The results suggest that perceptions about exercise have a consequence for the EIP arising from them, supporting the psychological and subjective dimensions of pain perception.

Previous experiments investigating transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to elicit analgesic effects in a variety of conditions. Considering the emerging experiments and application of these techniques on exercise and the potential benefits of these strategies to mitigate of EIP impact, the 3rd experimental study (Chapter 5) investigated the effect of TENS and IFC on EIP during single limb, submaximal isometric contraction in healthy volunteers. The primary finding was that the ANOVA revealed a significant difference in the time to exhaustion between conditions ($F_{(2, 34)} = 6.763$, $P = 0.003$). Pairwise comparisons revealed a significantly different TTE time between TENS (10 min 49 s ± 6 min 16 s) and SHAM conditions (7 min 52 s ± 2 min 51 s) ($P = 0.031$) and between IFC (11 min 17 s ± 6 min 23 s) and SHAM conditions ($P = 0.02$). No significant difference between TENS and IFC conditions was observed ($P > 0.05$). The ANOVA also revealed a significant main effect of condition for exercise-induced pain during the TTE test ($P = 0.035$). No significant changes in rating of perceived exertion (RPE) were found between the three conditions ($P > 0.05$). A 3 x 8 (condition x iso-time) ANOVA revealed a significant interaction effect for exercise-induced pain over time between conditions during the TTE test with lower pain intensity in the TENS and IFC conditions ($F_{(3.4, 58.4)} = 3.671$, $P = 0.013$). No interaction and main effects for RPE were found between the three conditions ($P > 0.05$). For the MVC, paired-sample *t*-tests demonstrated that MVC was significantly reduced following the TTE in the Sham ($t_{(17)} = 9.069$, $P < 0.001$), TENS ($t_{(17)} = 7.037$, $P < 0.001$) and IFC conditions ($t_{(17)} = 8.558$, $P < 0.001$). No significant differences between conditions were found for the pre-MVC ($F_{(1.4, 23.4)} = 1.758$, $P = 0.188$) or the post-MVC ($F_{(2, 34)} = 1.499$, $P = 0.238$). This is the first experiment investigating the analgesic effect of TENS during exercise that uses a randomised, crossover and placebo controlled design. This experiment demonstrated for

the first time that eliciting a reduction in EIP through TENS resulted in an improvement in single limb exhaustive exercise. An additional novel finding from this study was that the reduced EIP and improved endurance performance occurred despite no effect on RPE. The results suggest that TENS and IFC can elicit an analgesic effect on EIP, and that this reduction in muscle pain can improve time to exhaustion performance in the absence of changes to perceived exertion. The results suggest that EIP is a limiter of endurance performance in single limb exhaustive exercise, and questions the notion that changes to RPE must always occur when endurance performance is affected.

The 4th experiment (Chapter 6) sought to apply the results obtained in the 3rd experiment to the performance of a 10-mile cycling TT in trained cyclists. The novel finding was that the ANOVA revealed a significant difference in completion time between conditions ($F_{(2, 42)} = 6.597$, $P = 0.003$). Pairwise comparisons revealed that participants performed a significantly faster TT ($P = 0.001$) in the TENS condition (29 min 6 s ± 3 min 20 s) compared to the SHAM (29 min 39 s ± 3 min 34 s) condition. There were no significant differences ($P = 0.872$) between the IFC condition (29 min 28 s ± 3 min 34 s) and the SHAM, or the TENS and IFC conditions ($P = 0.116$). The ANOVA also revealed a significant main effect of condition for power output ($F_{(2, 38)} = 3.48$, $P = 0.041$), mean HR ($F_{(1.38, 29.06)} = 4.016$, $P = 0.042$) and mean B[La] ($F_{(1.49, 31.37)} = 7.54$, $P = 0.004$). There was a significant difference in the mean EIP between conditions during the TT ($F_{(2, 44)} = 4.210$, $P = 0.022$). Paired *t*-tests revealed that participants perceived significantly less pain during the TENS condition (3.5 ± 1.8) than in the sham condition (4.0 ± 2.0) ($t_{(21)} = 3.037$, $P = 0.006$). No differences were observed between the TENS and the IFC condition (3.8 ± 1.9) or the IFC and Sham condition ($P > 0.05$). No significant differences in mean RPE were found between conditions during the TT ($P > 0.05$). Interestingly, this study also showed that TENS elicits an analgesic effect on EIP and improves the TT performance, whereas IFC technique does not elicit any reduction of EIP and consequently has no effect on whole-body endurance performance. This experiment demonstrated the first time that TENS intervention significantly improved completion time of the cycling TT, and that this was attained by the cyclists sustaining a greater power output (PO), heart rate (HR) and blood lactate (B[La]). Regardless of the increased physiological stress and metabolic rate induced by the higher PO, participants perceived EIP in the TENS strategy alongside in the absence of a difference in RPE between conditions. The improvement in dynamic endurance was probably the result of reduction in EIP for a given load. This is the first experiment showing that a TENS intervention can be used to elicit this analgesia to EIP,

and suggests that there may be scope for TENS to be used during exercise in those where EIP negatively effects their engagement in physical activity.

The final experiment in this thesis (Chapter 7) examined the effect of mood and emotional state on EIP and endurance performance. The use of painful images prior to endurance cycling performance was used to negatively affect mood, which was hypothesised to increase EIP. The primary finding was that the ANOVA revealed a significant difference in completion time between conditions ($F_{(2, 40)} = 8.480$, $P = 0.001$). Pairwise comparisons revealed that participants performed a significantly faster TT ($P = 0.003$) in the pleasant condition (29 min 38 s ± 4 min 35 s) and the neutral condition (29 min 39 s ± 3 min 34 s) compared to the painful condition (30 min 19 s ± 5 min 7 s). There were no significant differences between the neutral condition and the pleasant ($P = 1.000$). The ANOVA also revealed a significant difference in PO ($F_{(2, 40)} = 6.318$, $P = 0.004$), mean HR (($F_{(2, 40)} = 4.502$, $P = 0.017$) and mean B[La] ($F_{(2, 40)} = 5.724$, $P = 0.007$) between conditions during the TT cycling performance, but no significant effect of condition for mean RPE or EIP ($P > 0.05$). In the FP, a significant main effect of condition for EIP ($F_{(2, 40)} = 4.363$, $P = 0.019$), but no difference for RPE, HR or B[La]. This experiment demonstrated the first time that painful images negatively affect mood and elicit a compassionate hyperalgesia response to exercise. The results demonstrate that an increased pain sensation during exercise (induced via compassional hyperalgesia) can decrease TT performance, and highlights there is an emotional element to the processing of EIP that can be influenced by compassional hyperalgesia. This is probably the consequence of 'top-down' processing increasing the pain sensation elicited by a given 'bottom-up' stimulus. These results highlight the importance of maintaining a positive mood and emotional state prior to and during exercise.

The experimental studies performed as part of this thesis provides unique empirical evidence to advance scientific knowledge and understanding of the phenomenon of EIP. This thesis provides further new insights into how different interventions both alleviate and exacerbate EIP, which subsequently influences endurance exercise performance. Furthermore, considering the lack of knowledge regarding the testing and role of EIP in exercise, this thesis contributes to and enhances scientific understanding for how to test for and control these variables.

CHAPTER 1

INTRODUCTION
AND LITERATURE REVIEW

Pain perception has long been linked to success in sport and it is well-considered that intense and repetitive muscle contraction causes a noxious environment in the muscle that elicits 'exercise-induced pain' (EIP) (Mauger et al., 2010; Dannecker & Koltyn, 2014). However, this concept is not well explored or identified in the most prominent models of endurance performance. Endurance exercise performance can be defined as the capacity of an organism (e.g. muscular, cardiovascular) to utilise itself during exercise such as cycling, running, swimming or aerobic exercise that is performed for an extended period of time (Rogers & Roberts, 1997). Exercise performance involves an integrated process of numerous physiological and psychological determinants. According to Joyner and Coyle (2008) the key physiological determinants of endurance exercise are maximal oxygen consumption VO_{2max}, lactate threshold and economy of movement (Joyner & Coyle, 2008). The key psychological determinants of endurance exercise include self-efficacy (Martin & Gill, 1991), perfectionism, achievement goals, and personal goal setting (Stoeber, Uphill & Hotham, 2009), use of psychological strategies (Houston, Dolan & Martin, 2011), positive affect (Renfree et al., 2012), and self-talk (Blanchfield et al, 2014), mental fatigue and self-control (Inzlicht & Marcora, 2016) (McCormick, Meijen & Marcora, 2015). This review will only consider the physiological and the specific psychological determinants that interact with the physiological and how these can influence exercise performance in relation to pain.

Therefore, the aim of this literature review is to classify and further describe the key components involved in the explanations and limitations of fatigue, including the following psycho/physiological models, central governor model, anticipatory-RPE regulation model, afferent feedback model, psychological models and the limiting effect of pain on endurance performance. To provide a context to these models in relation to pain, a broader background and introduction to the anatomy and physiology of pain, nociception and pain perception process in the spinal cord and brain levels, theories and thoughts of pain perception, causes of pain, modulation and assessment of pain will be reviewed. Ultimately, this review will work towards reviewing current understanding of the role and importance of exercise-induced pain as a contributor to fatigue and how this may be influence decisions to alter work-rate during exercise.

I. Fatigue

Fatigue is a very complex process, which is likely multifactorial and never absolute (Fitts, 1994; Gandevia, 2001). Whilst the precise mechanisms underpinning its aetiology are still today not fully understood, it is well-accepted that maximising power output or speed while

limiting fatigue is the key determinant of success in endurance exercise (Joyner & Coyle, 2008). Our basic knowledge and understanding of fatigue has generally arisen from laboratory methodologies that require the participant to produce a maximal voluntary contraction or the use the time to exhaustion tests at a fixed intensity, where 'fatigue' occurs at task failure following a fatiguing task or intervention (Ament & Verkerke, 2009). In these instances, muscle fatigue is more closely aligned to a particular point in time where an inability to produce a given force occurs (Mauger, 2014). Accordingly, while these methodologies have the ability to establish causes of fatigue such as an increased concentration of deleterious metabolites and substrate depletion (Coyle et al., 1983; Kent-Braun, 1999), and reduced neural drive to the muscles and task failure (Gandevia, 2001), they are perhaps not truly demonstrative of the demands of 'real-life' endurance performance. Indeed, where completion time is the measure of success in actual endurance performance, athletes are not required to produce maximal contractions and rarely cease exercising during or following the event (Mauger, 2014). Rather, it is the athlete's ability to regulate their own work rate during an endurance event and their physiological capacity to maintain a high work rate, that will determine optimal performance (Mauger et al., 2009). A consequence of this is that different methodological and theoretical approaches are applied to both fixed intensity and self-paced exercise, despite the psychophysiological requirements for these being potentially different. This thesis will attempt to discuss fatigue and endurance performance in the context of both methodologies.

1. Explanations of Fatigue in Endurance Performance

Most previous studies addressing determinants of fatigue during exercise have shown that endurance exercise performance is limited by several physiological determinants, with maximal oxygen consumption (VO_{2max}), lactate threshold and efficiency being the most recognised (Lucia et al., 1999; Balmer, Davison & Bird, 2000; Jeukendrup, Craig & Hawley, 2000; Lucia, Joyos & Chicharro, 2000; Laursen, Shing & Jenkins, 2003; Joyner & Coyle, 2008). In addition to this, biomechanical (positioning) (de Koning, Bobbert & Foster, 1999; Jeukendrup, Craig & Hawley, 2000; Garside & Doran, 2000), environment (wind, temperature, altitude and humidity) (Lucia et al., 1999; Balmer, Davison & Bird, 2000; Jeukendrup, Craig & Hawley, 2000; Lucia, Joyos & Chicharro, 2000; Kay et al., 2001; Laursen, Shing & Jenkins, 2003), mechanical and psychological variables have also been suggested as important contributors. Ultimately, the capability of the athlete to tolerate or sustain a high power output during endurance performance is limited by the capability of the athlete to resist fatigue (Abbiss, 2005), and so factors which affect this

are all important. However, whatever exactly causes this fatigue is debated. Indeed, for at least the last 90-100 years, explaining fatigue during endurance performance has been a major investigation for sport and exercise scientists (Hill, Long & Lupton, 1924). However, despite various models of fatigue being proposed, no single model has been agreed upon (Noakes, 2000). This is likely because the cognitive, biomechanical, biochemical, and physiological models used to understand exercise fatigue and the adaptations that correlate or boost athletic performance are diverse (Brooks et al., 2000; Noakes, 2000; Hampson et al., 2001; Hunter et al., 2003), as are the various forms of exercise to which these are relevant (Kay et al., 2001; Tordi et al., 2003).

1.1 Models in Endurance Performance

1.1.1 Central Governor Model (CGM)

In 1997, the presence of a Central Governor was suggested by Tim Noakes, in his Central Governor Model (CGM), as shown in Figure 1.1. The CG is suggested to exist as a series of networks based in the central nervous system (CNS), that take into account the information about energy supply, current various physiological demands and motivational states to ensure that exercise terminates prior to a catastrophic biological failure (Noakes, 2005, 2012). Consequently, the primary purpose of the CG is to serve as a protective function. Noakes et al. (2001) proposed that muscle recruitment is determined centrally, and used as a method by which to prevent biological failure arising from anaerobisis (Hampson et al., 2001; Lucia et al., 2003). This notion was originally based on a brain-heart feedback loop to prevent cardiac failure, but was then expanded to the whole body in later updates to the CGM (Noakes 2000, 2011). The conception of the CGM likely arose from the original work by Ulmer (1996) on Teleoanticipation. This theory suggests that athletes have to regulate their energy consumption per unit of time with respect to a finishing point, so as to avoid both early fatigue and achieve optimal race time (Ulmer, 1996). Ulmer suggested that changes in exercise intensity are proposed to be controlled by a continuous feedback system where afferent signals that contain information on force, displacement, time and muscular metabolism are fed back to the brain via somatosensory pathways. Based on motor learning and the anticipated exercise bout, the brain is then able to use afferent signals from the muscles, as well as feedback from other organs, in order to alter intensity and optimise performance (Ulmer, 1996). While these principles form the basis for the CGM, the CGM emphasises internal judgement of expectations of exercise (prior experience, knowledge of distance/duration, environment etc.) against the reality of exercise (i.e. the given physiological state of the body). If these two sets of information are

incompatible with the successful completion of the exercise, then this results in an altered 'sensation' of fatigue. This is what is ultimately suggested to lead to changes in work rate. Indeed, it is the description of fatigue as a sensation, or emotion, which really sets the CGM apart from other models of endurance performance. Peripheral metabolites are not merely energy substrates or inert metabolic by-products, neither are they simply the sole or absolute regulators of the entire complex system. Instead they serve together to assist in the determination and constant resetting of the pacing strategy. Because of this reference to the importance of pacing in the CGM, much of the supporting literature for its existence has come from studies where pacing strategies have been examined. Indeed, a study by Amann and colleagues (2006) into various levels of hypoxia on pacing showed that within less than 60 s of exposure, participants altered their pacing strategies without their knowledge of changes to the environmental change. Activity of the electromyographic signal (EMG) was reduced along with power output, suggesting that the power output reduction on exposure to hypoxia related to a central motor drive reduction, a key tent of the CGM (Noakes, 2011).

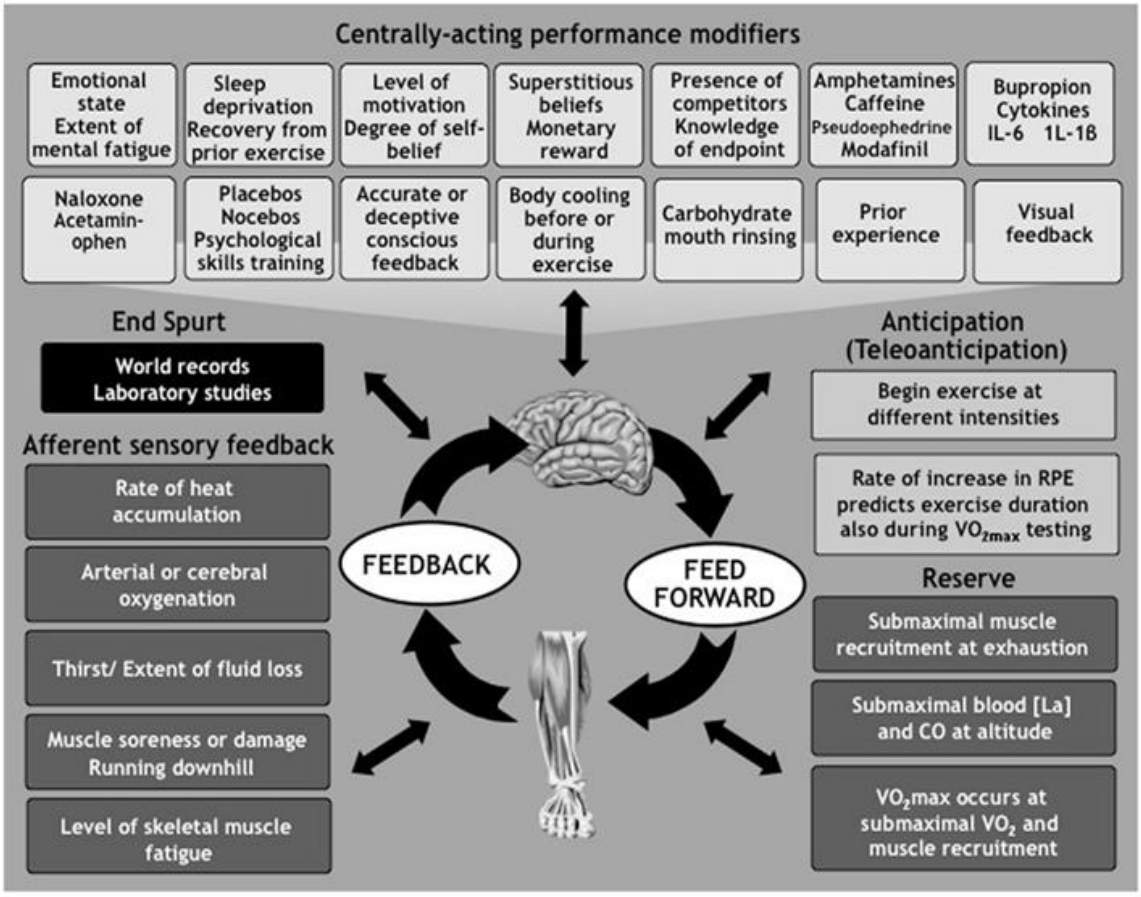


Figure 1.1 The most recent form of the Central Governor Model of Exercise Regulation proposed that the brain regulates exercise performance by continuously modifying the number of motor units that are recruited in the exercising limbs. From Noakes, 2011, p. 26.

A key observation used by supporters of the CGM is the presence of an 'end-spurt' – the last 5-10% of the race where competitors speed up despite experiencing the greatest levels of fatigue (Bartlett, Gratton & Rolf, 2006; Tucker, Lambert & Noakes, 2006*b*). This phenomenon is used as evidence for the presence of both pacing strategies and for the maintenance of a metabolic reserve capacity until the end of endurance events (Bartlett, Gratton & Rolf, 2006). Subjects performing the end spurt show a parallel increased activity of EMG in the skeletal muscle recruitment (Tucker et al. 2004, 2007; Ansley et al., 2004*b*), indicating that the end spurt results in an increased central motor drive (as anticipated by the CGM). In this context, the end-spurt is possible because the athlete knows the end-point is near and an increased work rate can be achieved because the risk to a dangerous imbalance in homeostasis is reduced. Therefore, despite the greater accumulation of deleterious metabolites that are proposed to cause peripheral fatigue, the athlete is still able to increase work rate. Whilst this notion provides an interesting alternative to the traditional models of fatigue, it completely ignores more recent propositions relating to how W' is expended in relation to critical power during endurance events (Chidnok et al., 2013). Indeed, if W' is not completely expended by the end of the event, the athlete's end sprint likely just reflects the athlete using their remaining W', which is possible if a sufficient amount of the previous exercise is completed below critical power (Fukuba & Whipp, 1999).

A further key base of evidence supporting the CGM are studies which demonstrate an ergogenic effect despite eliciting no change in the peripheral parameters associated with performance. There is convincing evidence that certain drugs, such as amphetamines, which act solely on the brain, are capable of modifying the extent of skeletal muscle reserve and serve to increase power output and consequently, endurance performance (Swart et al., 2009). Additionally, even mild analgesics such as paracetamol are capable of increasing power output in self-paced exercise (Mauger et al., 2010) or extending the time a fixed power output can be maintained (Mauger et al., 2013). These studies demonstrate that there are clearly other variables, alongside those influencing oxygen supply/utilisation, that limit endurance performance, and that many of these involve a role for the brain. Indeed, there are a long list of parameters which show a change in exercise performance independent to cardiovascular factors, including; the use of placebos (Beedie, Stuart, Coleman & Foad, Beedie, Coleman & Foad, 2007; Foad, Beedie & Coleman, 2008; Trojian & Beedie, 2008); music (Barwood et al., 2009; Lim, Atkinson, Karageorghis & Eubank, 2009); prior experience (Mauger, Jones & Williams, 2009); self-belief (Micklewright, Papadopoulou, Swart & Noakes, 2010); time deception (Morton, 2009); psychological skills training

(Barwood, Thelwell & Tipton, 2008); knowledge of the endpoint (Wittekind, Micklewright & Beneke, 2009); mental fatigue (Marcora, Staiano & Manning, 2009); cooling of the palms (Kwon et al., 2010); glucose ingestion (Chambers, Bridge & Jones, 2009; Rollo, Cole, Miller & Williams, 2010; Gant, Stinear & Byblow, 2010); cerebral oxygenation (Nybo & Rasmussen, 2007; Rupp et al., 2008; Seifert, Rasmussen, Secher & Nielsen, 2009; Billaut et al., 2010; Rasmussen et al., 2010*a*, 2010*b*); pseudoephedrine (Pritchard-Peschek, Jenkins, Osborne & Slater, 2010), naloxone (Sgherza et al., 2002), and bupropion (Roelands et al., 2008, 2009; Roelands & Meeusen, 2010) and self-control (Inzlicht & Marcora, 2016).

However, the CGM has been widely criticised, largely because it is considered to be untestable (Inzlicht & Marcora, 2016), and therefore questionable as to whether it can be considered a true theory at all. Proposing theories in science that are unfalsifiable is a problem because the well-accepted hypothetico-deductive model of scientific reasoning is based on being able to objectively test key hypotheses that can be shown to be false. This is how knowledge and understanding progresses, by developing new theories that get progessivly closer to the truth (Popper, 2005). The CGM is so vast and complex, and potentially includes a role for every physiological and psychological variable, that almost any observation can be explained by it (Marcora, 2008). This also raises questions as to whether it actually progresses our understanding of endurance performance in a meaningful way. Whilst some of the criticism the CGM receives is perhaps justified, it cannot be ignored that since its conception in 1998, there has been a considerable shift in the way endurance performance studies are conducted (towards a self-paced, whole-body model) and a paradigm shift towards a recognition about the importance of the brain.

1.1.2 Anticipatory-RPE Regulation Model

Much of the development of the CGM occurred between 2002-2008, where the main authors included Tim Noakes, Ross Tucker and Alan St. Clair Gibson (St Clair Gibson et al., 2006). However, from 2009 it appears as though Tim Noakes continued to revise the CGM, whereas Ross Tucker developed his own model. He termed this the Anticipatory-RPE Model (Tucker, 2009), in which the primary foundation is that the conscious perception of effort regulates exercise and protects the athlete as well as ensuring optimal performance under all conditions. This model attributes its name due to the notion that athletes utilise previous knowledge and experience of exercise duration/distance, in an anticipatory process, and use psychophysiological feedback for regulation of pacing strategy and performance during the exercise (Tucker, 2009). They key construct here is

that the athlete knows the end-point of the exercise, as without it an appropriate pacing strategy cannot be formed. However, when the exact end-point is not known, provided the athlete has sufficient experience of the exercise so that it can be estimated, a competitive pacing strategy can be formed (Mauger et al., 2009). Therefore, it appears as though prior experience is important, because it partly allows the athlete to better balance the projected exercise endpoint against remaining energy reserves. This model appears to play an important role in regulation of exercise performance under various environmental conditions (Tucker et al., 2006; Swart et al., 2009), as the initial setting of exercise intensity is gained from sensory afferent input from different external/environmental cues (Nielsen et al, 2001; Nybo & Nielsen, 2001*a*,*b*; Rasmussen et al., 2004) and physiological systems are utilised by the brain to predict the duration of exercise that could be safely sustained without harm (Tucker et al., 2006). The physiological afferent inputs largely rely on the exercise intensity (Noakes & St Clair Gibson, 2004; Noakes, Gibson & Lambert, 2005) and environmental conditions such as temperature and inspired partial pressure of oxygen (Tucker et al., 2006). Initially, the rate of increase in RPE is set to predict an initial 'safe' work rate, and this is termed the "template RPE'' (Tucker, 2009). During intense exercise, afferent information from various physiological systems (which is interpreted by the brain) is responsible for generating the conscious RPE, which is compared to the subconscious template and results in adjustments to power output if rate of RPE increase is not compatible with the likely duration of exercise (Tucker, 2009).

The split between the CGM and Anticipatory-RPE Model has caused some confusion, and it is not altogether clear where the two models differ significantly. Indeed, aside from the initial proposition of the Anticipatory-RPE Model (Tucker, 2009), there is little reference to it in subsequent studies. Similar criticisms to the CGM can be levelled at the model, and given its similarity, they will be considered as synonymous for the purposes of this thesis.

1.1.3 Sensory Afferent Feedback Model

Afferent feedback along spinal and supraspinal circuitries is integrated with central motor commands (CMC) and is contributed to by the activity of underling voluntary contractions of the muscle (Nielsen, 2016). With the onset of exercise, thermal, chemical and mechanical stimuli alter various intramuscular receptor activity, such as metaboceptive or nociceptive, which is specifically reflected in the firing rate of large- and small-diameter primary afferents, including group I/II and group III/IV, respectively (Garland, 1991; Garland & Kaufman, 1995; Amann & Dempsey, 2016; Nees et al., 2016). In the addition to the muscle fatigue which develops during prolonged exercise through

the accumulation of muscle metabolic by-products, the neural afferent feedback that occurs in addition to this is thought to mediate a reflex inhibition of alpha motor neurons involved in contracting single muscles at spinal and supraspinal levels (Gandevia et al., 1990; Gandevia, 2001). The central fatigue that ensues for this is the basis for the sensory afferent feedback model (see Figure 1.2) (Amann & Dempsey, 2008; Amann & Secher, 2010), as the somatosensory feedback associated with peripheral muscle fatigue inhibits central motor drive (CMD) and thereby limits endurance exercise performance (Amann et al., 2013).

Amann and Dempsey (2016) claim that the rate of peripheral fatigue development is associated with increasing neural afferent feedback from locomotor muscles to the central nervous system (CNS). This feedback exerts an inhibitory influence central motor drive regulation, which is manifested in the observed muscle power output. This serves to limit the peripheral fatigue development level (i.e. a primarily central limitation of exercise), in order to avoid unbearable effort/ "pain" and maintain a 'critical threshold' (Amann, et al., 2006, 2007). The key series of studies supporting this model come from Markus Amann's group, where complete afferent block is attained through the use of lumbar injection of fentanyl (Amann et al., 2006, 2007). In these studies, when afferent feedback is blocked, a greater level of peripheral fatigue ensues, suggesting that afferent feedback is required to prevent terminal levels of peripheral fatigue from occurring. In these studies, it is observed that participants have ambulatory problems on conclusion of the exercise (likely due to the severe peripheral fatigue), which suggests a potential protective function of the afferent feedback. Additionally, when afferent feedback is blocked by using fentanyl, participants show a disregard for physiologically sensible pacing strategies. Indeed, in these studies participants select an extreme positive pacing strategy, which results in a power output that cannot be maintained. This also suggests that the afferent feedback during exercise provides useful information regarding pacing strategy. Despite these fentanyl studies showing compelling evidence for the importance of afferent feedback, there are criticisms with this design. Most notably, the exercise pressor reflex is heavily dependent on afferent feedback, and participants in these studies likely suffered from impaired cardiovascular control which would have exacerbated peripheral fatigue through decreased oxygen saturation. Furthermore, the injected fentanyl could have also have migrated to the respiratory centre in the brain, which could explain why SaO_2 was severely impeded in the fentanyl condition, and then could have exacerbated the level of peripheral fatigue the participants experienced. Although these criticisms have substance, the sensory-afferent feedback model provides a testable construct, and provides important evidence to suggest

that sensory-afferent feedback is almost certainly required to set a pacing strategy, even if it is potentially not a primary cause of fatigue.

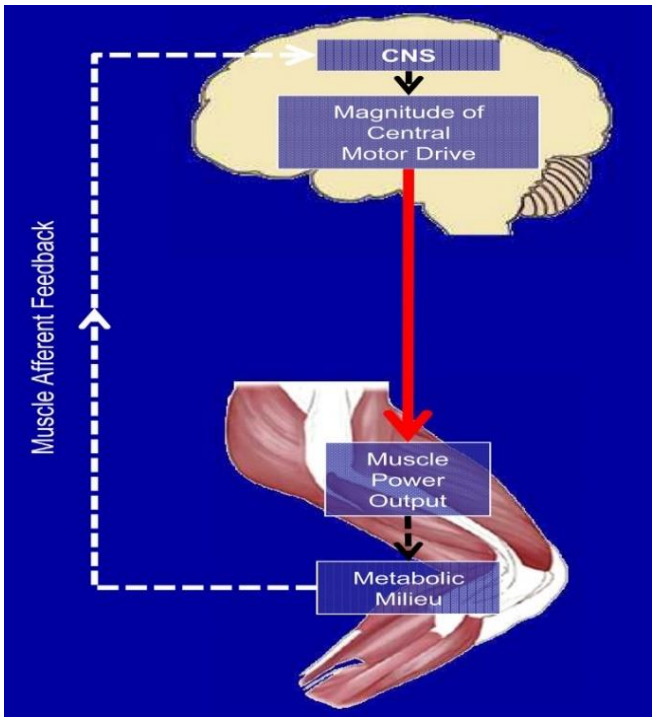


Figure 1.2 Schematic illustration of the suprapinal reflex inhibition model of endurance exercise performance proposed by Amann and colleagues (2008, 2009). From Amann & Dempsey, 2009, 2010, p 454.

1.1.4 Psychobiological Model of Endurance Performance

An alternative to the cardiovascular, afferent feedback and Central Governor models has been recently provided, which places primary emphasis on perception of effort. This model is termed the "Psychobiological model" (Marcora, 2007, 2008*a*, 2008*b*, 2009, 2010, Marcora, Bosio & de Morree, 2008; Marcora & Staiano, 2009*a*, 2010*b*). This model gives greater attention to perception of effort and motivational factors than its predecessors, and explains how both of them influence the conscious decision-making process during endurance exercise performance (Smirmaul et al., 2013). The Psychobiological Model states that fatigue is solely a balance between perception of effort and motivation, and that an athlete's decision to terminate exercise is a conscious choice rather than a mechanical failure. However, the premise of this model is not well accepted by both Hill's classical model (i.e. the cardiovascular/anaerobic model) (Noakes 1988, 1997, 1998, Bassett & Howley, 1997) and proponents of physiology based determinants of endurance performance.

The basis of the Psychobiological model is dependent on the intensity of motivation, as proposed by Brehm and Self (1989), which comprises of two major concepts: "potential

motivation" and "motivation intensity". Potential motivation is an individual's maximum effort available to satisfy a motive, whilst motivation intensity is the actual amount willing to be expended (Wright, 2008). Brehm's theory of motivational intensity postulates that athletes will exert effort in a task for as long as they remain motivated. When the level of effort required to maintain task, intensity goes above the level of motivation required, the individual will terminate the task (Wright, 2008). Therefore, according to the Psychobiological model, exhaustion during intense exercise is a procedure of task disengagement, in which athletes will exercise until perception of effort increases to a critical level in excess of the potential motivation. This model provides a valid explanation of performance change observed when purely psychological parameters are manipulated (e.g. mental fatigue) (Marcora, Staiano & Manning, 2009; Pageaux, Marcora & Lepers, 2013). It also explains what would usually be called physiological fatigue, through the increased effort required to drive a fatigued limb (Marcora, Bosio & de Morree, 2008). Recently, Pageaux et al. (2014) also explored its validity in explaining regulation of work rate in self-paced exercise, where endurance performance was altered by manipulated through a psychological intervention (i. e. mental fatigue).

To provide a theoretical framework for how the Psychobiological model can explain the conscious regulation of endurance performance, Marcora (2010) states that there are five key cognitive/motivational factors that are important: perception of effort, potential motivation (described above), knowledge of the distance/time to cover, knowledge of the distance/time remaining, previous experience/memory of perception of effort during exercise of varying intensity and duration (Brehm & Self, 1989; Marcora, 2010). According to the Psychobiological model, factors 3 to 5 are self-regulated tasks and can explain the "end-spurt" phenomenon (Marcora, 2008) or why athletes begin various races at variety of paces (Josephet al., 2008). Since perception of effort (factor 1) is such a key element in the Psychobiological model, a deeper categorisation is essential, and in particular the exact mechanism of the perception of effort. The modern interpretation is that the perception of effort is thought to be dependent on efferent and afferent signals (Hampson et al., 2001; Meeusen, 2009). However, evidence put forward by Marcora (2009), suggested that the sense of effort is centrally generated and independent of afferent sensory feedback from skeletal muscle and other interoreceptors such as pain and temperature. Rather, it is suggested that perception of effort is the result of the conscious awareness of the corollary discharge associated with the central motor command transmitted to the active muscles (Ross & Bischof, 1981; Marcora, 2009; de Morree, Klein & Marcora, 2012). However, manipulation of the perception of effort can also be generated

from altered central processes during sustained intense exercise (Sacco et al., 1999). Thus, sensory afferent feedback from the active muscles may influence perception of effort, but only indirectly. Consequently, Marcora (2010) has defined the perception of effort as ‘‘the conscious sensation of how hard, heavy and strenuous a physical task is’’, and is the essential determinant of the Psychobiological model (Pageaux, 2014). Indeed, according to this model, the self-regulation of pacing is principally determined by the effort perceived (Pageaux, 2014). Thus, when perception of effort is increased by muscular (de Morree & Marcora, 2013) or mental fatigue (Pageaux et al., 2014), or decreased pharmacologically (Watson, Jenkinson, Kazmierski & Kenakin, 2005), the athlete will constantly alter their pace to compensate.

There is a large body of experimental studies supporting the Psychobiological model (for example; Marcora, Bosio & de Morree, 2008; Haggard, 2008; Marcora, Staiano & Manning, 2009; de Morree, Klein & Marcora, 2012; de Morree & Marcora, 2013; Pageaux & Marcora, 2013; Blanchfield et al., 2014; Pageaux et al., 2014; Inzlicht & Marcora, 2016). However, there are criticisms of these studies, and the model as a whole too. Firstly, the model is suggested to be ‘simpler’ (and therefore more valid) than the CGM, however this relies on the basis of perception of effort being solely the result of the corollary discharge. It is perhaps misleading to suggest the Psychobiological model is inherently simple because of mechanistic basis of perception of effort, because even if afferent feedback is indirectly important, it will affect perception of effort and thus adds multiple layers of complexity. Furthermore, if muscle fatigue requires a greater central motor command to drive the limb, then classical explanations of human performance (e.g. oxygen supply/demand) remain just as important because they will set the boundaries of muscle fatigue. The redefining of perception of effort (i.e. excluding the role of pain, discomfort and dyspnoea) instructions to participants also poses problems, as it limits the degree to which prior studies can be interpreted through the Psychobiological model. Indeed, most previous research uses a definition of RPE that includes discomfort or pain (Noble and Robertson, 1996), and so comparisons of RPE data in these studies are hard to make. However, it has been demonstrated that participants can identify and rate pain and RPE separately (Cook et al., 1997, Pageaux 2016), and so studies that focus on these constructs should attempt to do this by using separate scales. In this thesis, such an approach is taken. However, when this is done caution should be taken in comparing RPE data to previous studies that do not take this approach. Finally, motivation is a construct which is notoriously hard to accurately measure in the laboratory, which makes it very difficult to truly test one of the key tenets of this model.

1.1.5 Pain Limitation of Endurance Performance

Muscle pain is a common experience during exercise, with pain threshold in working muscles occurring at nearly 50% of an individual peak power output (Cook et al., 1997). However, studies have given peculiarly little focus to exercise-induced muscle pain (EIP), which is often raised by coaches, commentators, and athletes as a key factor in endurance performance. Indeed, it is often proposed that athletes who are better able to overcome or tolerate muscle pain during exercise will be more successful, and it is commonly stated as a key inhibitory factor during intense exercise (Mauger, 2013). EIP is also an important feedback source in the maintenance of exercise intensity and is consequently important for athletic performance (O'Connor & Cook, 2001; Bantick et al., 2002; Eccleston & Crombez, 1999; Crombez et al., 1998; Davis et al., 1997). This indicates a need to better understand pain perception during exercise.

1.2 Pain

1.2.1 The Definition of Pain

The International Association for the Study of Pain (IASP), defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage," (Merskey & Bogduk, 1994). This definition is the conclusion over several centuries of ideas and achievements that have further explored the concept of pain. From a neurobiological perspective, a distinction must be made between the perception of pain and the reception of signals provoked by specialised sensory receptors in peripheral tissues of the body (e.g., skeletal muscle) and central nervous system tissues (spinal and supraspinal neurons). This process is so-called "nociception", arising from the individual stimulus-response of "noxious stimuli" (Black, 2012).

1.2.2 Sensory Neurons of muscle pain: Anatomy and physiology

Sensory neurons innervating skeletal muscle fibres are categorised into four primary groups in terms of size, conduction velocity, and myelination (Lloyd & Chang, 1948). Group I and II fibres are myelinated sensory nerve fibres with a large-diameter, and have the highest conduction velocity of all the nerves in the body, and play an important role in proprioception (Taylor & Finn, 2014). Group III and IV fibres are myelinated and unmyelinated sensory nerve fibres with a small-diameter, and have a lower conduction velocity, respectively, corresponding to A∂ and C fibres of the cutaneous tissue (Willis & Coggeshall, 2012). There is additional evidence that groups III and IV, but not groups I

or II, respond to application of noxious thermal, chemical and mechanical stimuli to the muscle, representing that they convey nociceptive input from the muscle (Mense, 1977; Pickar, Hill & Kaufman, 1994). Nociceptive bare nerve endings of group III and IV fibres are distributed throughout the muscle, and terminate in the connective tissue, fat, extrafusal and intrafusal muscle fibres, as well as the adventitia of both arterioles and venules (Walro & Kucera, 1999). The majority of these nerves terminate as free nerve endings in the adventitia of blood vessels in skeletal muscle of mammals, a perfect location for blood sampling of metabolites released as a by-product of muscle contraction (Stacey, 1969). In addition, the fascia around muscle may cause symptoms of muscle pain. Nociceptive fibres innervate the fascia (Tesarz et al., 2011), which are activated both by noxious chemical and mechanical stimuli (Taguchi, Matsuda, Tamura, Sato & Mizumura, 2005; Taguchi et al., 2013). These nociceptive muscle afferents can also be activated by muscle contractions (Itoh & Kawakita, 2002; Taguchi et al., 2005).

Emerging from a muscle, nociception, mechanoreception and proprioception project to various layers of the spinal cord (Davis et al., 1989; Ozaki & Snider, 1997). Nociceptive nerve fibres subsequently signal to the brain through the spinothalamic tract (Foreman, Schmidt & Willis, 1979), where these fibres terminate in the thalamic nucleus submedius, ventral posterolateral nucleus (VPL) (Kniffki & Mizumura, 1983), and anterior paraventricular nucleus of the thalamus (Kawakita et al., 1993; Min, Zhang, Zwiers & Hegerl, 2011). Muscular pain excites or stimulates multiple brain regions, such as the anterior cingulate cortex, dorsolateral prefrontal cortex, the insula, and primary and secondary somatosensory cortex (Peyron, Laurent & Garcia-Larrea, 2000). However, muscular pain also sensitises the brain regions that are related with emotional processing, such as orbitofrontal cortex, parahippocampus, bilateral amygdala, hippocampus, superior temporal pole and caudate (Takahashi et al., 2011; Cheng & Lee, 2011).

1.2.3 Pain Signal Transduction

Muscle afferent feedback neurons are well-known for perceiving the condition of connective tissue (Mense, 1977; Mense & Meyer, 1985; Pickar et al., 1994; Mense & Craig, 1988), while cutaneous afferent neurons carry information about the external noxious environment around/in the muscle (Mense & Craig, 1988). Muscle afferents have a poor spatial resolution in comparison to cutaneous afferents, with mechanical fibres supporting multiple receptors as far as 2-cm apart (Kumazawa & Mizumura, 1977). In a clinical context, this matches the description of muscle pain as being diffusive and hard to localise (Mense, 1991). However, muscles are equipped with sensory fibres that are

activated by mechanical stimuli and capable of detecting noxious pressure, non-noxious pressure, and grading force of muscle contractions (Mense & Meyer, 1985). In addition to mechanical forces, muscle afferent neurons are attuned to the by-products released during sustained muscle contraction or under ischemic conditions (Sacchetti, Lampugnani, Battistini & Mandelli, 1980). Thermal stimuli can also be sensed in the muscle (Hertel, Howaldt & Mense, 1976; Kumazawa & Mizumura, 1977), but rises in temperature due to muscle activity are relatively small and do not approach the range that would stimulate heat nociceptors (Saltin et al., 1968; Brooks et al., 1971).

Muscles themselves come under significant strain during exercise, which creates a unique metabolic environment that can be sensed by the afferent neurons (Li et al., 2003, Dessem et al., 2010). During exercise the muscle may also become damaged, which results in significantly more pain than non-damaging muscle (Faulkner, Brooks & Opiteck, 1993; Proske & Morgan, 2001; Gibson et al., 2009; Martin et al., 2009). The damaged muscle results in the recruitment of macrophages and neutrophils (Malm et al., 2000; Tidball, 2005) and the release of a wide range of biochemicals (including: serotonin, bradykinin, prostaglandin E_2, prostacyclin I^2 (PGI_2), thromboxane A_2 (TXA_2), and nerve growth factor (NGF) (Shah, Phillips, Danoff & Gerber, 2005; Ernberg et al., 1999; Murase et al., 2010; Urai, Murase & Mizumura, 2013).

1.2.4 Nociception and Pain processing: Peripheral to Central Mechanisms

The pain signal during exercise is usually instigated by stimulation of the peripheral nociceptors, the free (bare) nerve endings which exist in and around the small arterioles, arteries and veins, connective tissue and muscle fibres (Stacey, 1969). These Type III afferent nerve fibres (also known as A-delta fibres) synapse primarily on cell bodies in the dorsal root ganglia (Cerveto et al., 1976). Nociceptive Aδ fibres are stimulated by high threshold noxious pressure and their activation in muscle level results in an aching, dull, or cramp (Marchettini et al., 1996). Type IV afferent nerve fibres (also known as cutaneous C-fibres) are unmyelinated, end solely in free nerve endings (Stacy, 1969), and respond to various noxious chemical stimuli (Mense, 1993).

Nociceptive muscle afferents can be stimulated by mechanical pressure or chemical or thermal stimuli (Tadaki, Kumazawa, Mizumura & Tadaki, 1981). Implementation of a noxious stimulus to a nociceptor results in generating an electrical signal (Koltzenburg & Handwerker, 1994). When the stimulus is sufficiently great, then the electrical signal may exceed a threshold value, resulting in the generation of an action potential and the release

of neurotransmitter that is conveyed alongside the axon to the dorsal horn in the spinal cord (Black, 2012). In addition, a nociceptor may also be excited or sensitised by a given stimulus. During the sensitisation, the building of a noxious substance may lower the activation threshold of the nociceptor (O'Connor & Cook, 2001). Therefore, after the receptor has been sensitised, less input is required to cause activation (Mense, 2003).

Receptors that respond to mechanical stimuli are called "high threshold mechanoreceptors (HTM)" and require high intensities of tissue-threating mechanical pressure to respond to stimuli for muscle nociceptors, such as squeezing or pinching the muscle (Kumazawa & Mizumura, 1977). As a result, weak mechanical pressure stimuli (such as during most forms of exercise) are not perceived as muscle pain because the stimulus is not sufficiently large to activate HTM muscle receptors (Mense, 2003). In addition to mechanical pressure, a host of chemical substances directly sensitise and activate muscle nociceptors (Kumazawa & Mizumura, 1977). These biochemical substances include protons (hydrogen ions), bradykinin, serotonin, histamine, potassium, substance P, prostaglandin E, cytokines, and adenosine triphosphate (ATP) (Mense, 2009). During a single bout of exercise, not surprisingly, many of these algesic substances are released and produced in response to tissue damage and inflammatory processes that may occur as a consequently of exercise-induced muscle pain. These substances may also sensitise HTM's, thus lowering the magnitude of the mechanical pressure required for them to fire.

1.2.5 The Cause of Pain by Noxious Biochemicals

1.2.5.1 Protons (hydrogen ions)

During intense exercise, muscle ischemia, tissue damage and inflammation often occur alongside an increase in the concentration of protons, or hydrogen (H^+) and a decrease in tissue pH (Hood et al., 1988, Issberner et al., 1996). The activation of proton-sensitive nociceptive fibres is a likely contributor for exercise-induced pain (Black, 2012). Tonic, low-force contractions can lead to increased ischemia of skeletal muscles and result in a lowering of muscle pH via accumulation of lactic acid (La) that disassociates into lactate and H^+ ions (Black, 2012). Dynamic exercise at a moderate to high intensity such as cycling or running can also lead to enhanced production of lactic acid, resulting in cramp-like or aching pain experienced during intense exercise (Black, 2012). Intramuscular injection of an acidic solution of pH 5.2-6.0 elicited a moderate-intensity pain that activated more that 50% of mechanosensitive afferent nociceptors and led to increased sensitivity to mechanical pressure (Hoheisel et al., 2004). H^+ ions signal along acid-sensing ion channels (ASICs) (Sluka et al., 2003; Canessa, 2007; Stockand et al., 2008), which are

stimulated when the extracellular pH decreases to ≤ 7 (Benson et al, 2002; Hesselager, Timmermann, & Ahring, 2004). ASIC3 homomeric channels are thought to play a crucial role in central sensitisation to noxious stimuli and are found in the dorsal root ganglion of the spinal cord (Price et al., 2001).

1.2.5.2 Adenosine triphosphate (ATP)

In muscles, ATP serves as the primary energy source for exercise metabolism (Green, 1997). ATP is rapidly metabolized into adenosine, and damage to muscle cells may lead to membrane dissemination and result in the release of adenosine, ATP, or both (Black, 2012). Adenosine receptor antagonists, specifically A_1, and A_2 receptors, are thought to be a crucial element in the nociception in human pain modulations (Sawynok, 1998; Millan, 1999; Sawynok & Liu, 2003; Sawynok, 2006).

Previous studies have shown that injection of a dose of ATP into the muscle as a stimulus for non-nociceptive and nociceptive muscle group IV receptors in animals (Reinöhl et al., 2003; Hanna & Kaufman, 2004), produces painful stimuli in humans (Mørk et al., 2003). Injection of ATP into human subjects in the trapezius muscle induces pain at rest and mechanical hyperalgesia (Mørk et al., 2003), but low dose ATP into the thumb does not cause pain (Pollak et al., 2013). A study by Mørk et al. (2003) showed that no muscle hyperalgesia occurs despite the use of a much higher concentration of ATP. The interpretation for this difference is unclear, and perhaps represents differences in metabolism, the muscle injected, or volume of injection.

1.2.5.3 Bradykinin (BKN)

One of the most important products of a series of pathophysiological processes and potent activator of skeletal muscle nociceptors is Bradykinin (BKN) (Beck & Handwerker, 1974). BKN has been long recognised as one of the most potent pro-inflammatory substances (Nishimura et al., 2002) and endogenous algesics (Steranka et al., 1988). Its actions have been most intensively considered in the periphery (Kozma, Ahmed, Best & Lim, 1995), although there is arising evidence that BKN may also play a crucial role within the central nervous system (CNS) following tissue damage, inflammation, and infection (Walker, Perkins & Dray, 1995). BKN is a polypeptide substance related to a precursor in the plasma globulin fraction and a separate system in tissues (e.g. muscular) (Silva, Beraldo & Rosenfeld, 1949). It is formed in response plasma extravasation, ischemia and when certain factors involved in the clotting system are activated (Webster & Pierce, 1963). Therefore, it is formed in response to tissue damage directly and other states common to exercise,

such as hypoxia, ischemia and acidification (Black, 2012). Additionally, at the tissue damage site, BKN promotes all the features of the acute inflammatory response including noxious stimuli and increased blood flow (Walker, Perkins & Dray, 1995). Group III and IV nociceptors in skeletal muscle are activated by BKN and injections of BKN into the muscle have been shown to be mildly painful (Kaufman et al., 1982; Babenko et al., 1999). BKN exerts its action by acting on the bradykinin B2 receptor and activating a G protein that regulates intracellular metabolic changes (Bandell et al., 2004). This change leads to excitability of free nerve ending in dorsal root ganglia (sensitisation) (Mense & Gerwin, 2010). BKN also plays a crucial role in sensitising nociceptors in skeletal muscle (Dray & Perkins, 1993, Babenko et al., 1999). Excitation of the B1 and B2 receptors alters the resulting action potential of nociceptive afferents and can enhance their sensitivity to other noxious stimuli, such as serotonin (5-HT) (Hu et al., 2004). In addition, BKN enhances the production of prostaglandins, which are crucial inflammatory mediators that also function to excite or sensitise nociceptors and prolong and enhance the effect of BKN (Mense, 1981).

1.2.5.4 Serotonin (5-HT)

Serotonin (5-HT) is a monoamine neurotransmitter with wide range of functions in the nervous system and throughout the body (Tecott et al., 1995). 5-HT is much like BKN, in that it activates both III and IV afferent fibres in skeletal muscle (Mense, 1977). Injections of 5-HT into the muscle in sufficiently large doses have been shown to result in noxious stimuli, whilst in lower doses, serotonin functions to activate nociceptors to BKN, leading to a greater noxious stimuli response to a given dose (Babenko et al., 1999). Animal experiments have been also found that 5-HT is a direct mediated to muscle pain and a hyperalgesic agent (Taiwo YO & Levine, 1992).

1.2.5.5 Substance P (SP)

SP is an endogenous neuropeptide, that acts as a neurotransmitter and neuromodulator (Harrison & Geppetti, 2001; Datar, Srivastava, Coutinho & Govil, 2004), and is found in skeletal muscular nociceptive fibres and in neuron of the dorsal root ganglion (Mense, Hoheisel & Reinert, 1996). Release of SP is induced by noxious stimulation and induced by exercise and inflammation (Lind, Brudin, Lindholm & Edvinsson, 1996). Several lines of evidence indicate that SP and calcitonin gene-related peptide (CGRP), co-localized with prostaglandins (PGs), serotonin, bradykinin and nitric oxide (NO), contribute to the generation of noxious stimulation and hyperalgesia (McMahon, Lewin & Wall, 1993;

Meller & Gebhart, 1994). SP interacts with the neurokinin-1, -2, and -3 receptors, and is known to increase the release of other algesic agents, such us histamine and PGE_2 (Levine, Fields & Basbaum, 1993, O'Connor & Cook, 1999). In experimental and clinical studies, Anand and Bley (2011) indicate that depletion of SP in nociceptive afferent fibres is correlated with the substance capsaicin, and has been shown to attenuate the perception of pain in response to chemical and mechanical stimuli (Hoheisel et al., 2004).

1.2.5.6 Prostaglandin E_2

Prostaglandin E_2 (PGE_2) is a cyclooxygenase (COX) product, and is associated with inflammatory pain (Kuehl & Egan, 1980; Harvey et al., 2004). Nonsteroidal anti-inflammatory agents/analgesics (NSAIDs), inhibit COX-1 and/or COX-2, and repress inflammatory pain by attenuating prostanoid generation, mainly PGE_2, in patients suffering from migraine, osteoarthritis, rheumatoid arthritis, and gout (Kawabata, 2011). PGE_2 exhibits very little action on nociceptors but plays very important role in activating or sensitising nociceptors to Bradykinin and other substance stimuli (Mense, 1981). NSAIDs, such as ibuprofen and aspirin blunt of the action of the COX-1 enzyme (Vane, 1978) and thus function to limit inflammation and resulting tissue damage (Black, 2012) and consequently pharmacological intervention downstream and upstream signals of PGE_2 may serve as novel strategies for the reduction of pain during exercise (Trappe et al., 2001; Motl, O'Connor, & Dishman, 2003; Peterson et al., 2003; Motl et al., 2006; Hudson et al., 2008; Mauger et al., 2010; Trappe et al., 2011).

1.2.6 Nociception and Pain Processing in the Levels of Spinal Cord and Brain: Pathways of Pain Perception

Following stimulation of peripheral nociceptive fibres in skeletal muscle an electrical signal is conveyed through afferent fibres to the spinal cord (SC) (Kumazawa, Mizumura & Tadaki, 1981). The SC subsequently conveys the electric signal to the brain, where it is perceived as pain. Early theories regarding pain pathways, which date back to Descartes (1644), present a widely accepted view of pain that nociceptive fibres convey input signals from the periphery to the brain as along simple cables. The early anatomists (e.g. Bell, 1824) and neurophysiologists (e.g. Muller, 1833; Von Frey, 1896; Sherrington, 1906) outlined the classic picture of pain (Descartes, 1644), and provided a framework for how pain was relayed to the spinal cord and brain from the periphery. Advances in immunohistochemistry, genetics and neuroimaging have allowed scientists to look more

closely at the spinal cord and brain to gain an insight into how the stimulation of peripheral nociceptive fibres are processed at the level of spinal cord and brain, where it is ultimately perceived as painful. These techniques have confirmed that pain perception involves a series of complex connections from a peripheral receptor to the spinal cord and brain. Ultimately it is an integrative and complex sensation that is processed and modified in multiple regions (Melzack & Wall, 1965).

Input from afferent nociceptive fibres synapse at the dorsal root ganglia (DRG) and the dorsal horn, primarily at laminae I and II, but also in laminae V (Mense, 1993). When the intensity of the stimulation is sufficiently large enough, it will produce a postsynaptic 'excitability' output that is conveyed to supraspinal areas along one of numerous projection nerve tracts. Within the DRG in the SC, afferent nociceptive fibres and projection neurons communicate utilising a host of amino acid and peptide neurotransmitters such as glutamate and substance P (Miller, 1999; DeLeo, 2006). They will also possess neurotransmitter receptors for endogenous opioids, which play a crucial role in pain processing and especially hypoalgesia (Black, 2012).

Relying on the type of nociceptor sensitised or activated, a stimulus is conveyed along the spinal cord to various regions within the brain via contralateral spinothalamic, spinohypothalamic, spinomesencephalic, spinorecicular, spinoparabrachial, and dorsal column tracts (Millan, 1999). The spinothalamic tract consists of two separate tracts, a neospinothalamic (lateral) tract, which projects along the medulla oblongata to the ventral posterolateral thalamic nucleus (VPL), and a paleospinothalamic (medial) tract, which projects to the reticular formation in the brainstem, the periaqueductal gray (PAG), hypothalamus, amygdala, and parts of the thalamus (Millan, 1999). Sending signals from Aδ fibres may be transmitted through neospinothalamic and result primarily in fast, sharp pain, whilst sending signals from C fibres through the paleospinothalamic tract are thought to be responsible for dull, aching pain. Through the spinoreticular tract, nociceptive inputs transmit signals to the reticular formation and synapse in the nucleus paragigantocellularis (nPGi) and medial thalamus, which inputs to the locus coeruleus (Millan, 1999). The spinomesencephalic tract travels to the PAG, much more like spinothalamus, and the PAG provides inputs limbic system pathways such as anterior cingulate cortex (ACC) and amygdala (Black, 2012).

Understanding of pain-related inputs is not in any way comprehensive, as numerous different brain regions have been shown to be stimulated or activated during processing of pain. However, this reveals the complex nature of the processing of noxious inputs at the spinal cord and supraspinal levels. Activation of the primary and secondary somatosensory

cortex via thalamocortical projections can provide information regarding the location and intensity of a painful stimulus. Other regions, such as the PAG, ACC, and amygdala, may provide information regarding the affective and emotional aspect of pain (Black, 2012).

1.2.7 Theories and Thoughts of Pain Perception

Numerous theories have been postulated to explain the process of pain perception, yet none of these can account for all features of the perception of pain, which demonstrates its complexity (Moayedi & Davis, 2013). The four most popular theories of perception of pain are the Specificity, Intensity, Pattern, and Gate Control Theories of Pain (Figure 1.7), and will be outlined here.

1.2.7.1 The Specificity Theory of Pain

The specificity theory of pain states each somatosensory modality (touch and pain) is separately encoded in pathways (Dubner, Sessle & Storey, 1978; Craig, 2003; Perl, 2007; Ma, 2010). Therefore, this theory proposes that pain is processed by a specific neuronal pathway (as a unique sensory experience) (see Figure 1.3. 1A). For example, the model suggests low threshold mechanoreceptors are encoded in non-noxious mechanical stimuli, which are related to primary sensory neurons that project to "mechanoreceptive" secondary sensors in the spinal cord or brain. A higher threshold mechanoreceptive sensor is projected to secondary neurons in the brain regions (Moayedi & Davis, 2013), which would be stimulated by a nociceptor through noxious stimuli, which would project to higher "pain" centres in the brain. Whilst specificity theory was perhaps the most dominant explanation of pain perception in the mid 1900's, its popularity reduced following the postulation of Gate Control Theory in 1965 (Melzack & Wall, 1965).

1.2.7.2 Intensity Theory of Pain

Intensity Theory of Pain conceptualises that pain is not truly a unique sensory experience, but defines pain as an emotional experience when a stimulus sufficiently stronger than usual occurs (Plato, 1998). In 1859, Naunyn showed that a sub-threshold stimuli for sense of touch induced pain in individual patients with syphilis who had disintegrating dorsal columns [cited in Dallenbach (1939)]. They described this as unbearable pain when this stimulus was reproduced 60-600 times. Arthur Goldscheider further advanced the Intensity Theory, when he proposed a neurophysiological model to describe this framework (see Figure 1.3. 1B) (Moayedi & Davis, 2013) which suggested that the increase in sensory

afferent processing would produce a summation effect. Intensity theory originally competed with specificity theory, but lost support when specialist fibres (later coined nociceptors) for sensing pain were identified.

1.2.7.3 Pattern Theory of Pain

This theory ignores findings of specialised nerve endings "receptors" that produce pain, and instead suggests that a specific combination of stimuli and a particular pattern of neural firing elicits a given pain perception (Nafe, 1929) (see Figure 1.3. 1C). Goldschneider (1920) suggested that there were no specific receptors for pain or separate system for perceiving pain, and instead sensory receptor nerves respond to damaging stimuli and other non-damaging stimuli such as touch lead to painful or non-painful experiences as a factor of outcome of variances in the patterns of the signals transmitted through the central nervous system [cited in Moayedi & Davis, 2013].

1.2.7.4 Gate Control Theory of Pain

In 1965, the Gate Control Theory of Pain was proposed by Melzack and Wall and provided a model that could support the apparently divergent concepts of the Specificity and Pattern Theories (see Figure 1.3. 1D). The model suggests that signals projected by primary afferent fibres from stimulus of the cutaneous tissue are conveyed to three regions within spinal cord: the dorsal column, the substantia gelatinosa and a group of cells termed transmission cells (T) cells. Melzack and Wall proposed that the 'gate' is the substantia gelatinosa, which modulates sensory information transmission from the primary afferent fibres to the central (T) cells. This gating mechanism in the dorsal horn modulates the T-cell and influences the activity in large-diameter (A-delta nerve fibre) and small-diameter (C-fibres) fibres. Large-fibre activity tends to inhibit transmission (or closes the gate) whilst small-fibre activity tends to facilitate transmission (or opens the gate). Activity from descending tract fibres that initiate in supra-spinal regions and project to the dorsal horn could also modulate this gate. Once nociceptive information reaches a critical "threshold" that surpasses the inhibition provoked, it "opens the gate" and activates pathways that lead to the pain experience and its associated patterns of behaviour (Melzack & Wall, 1965).

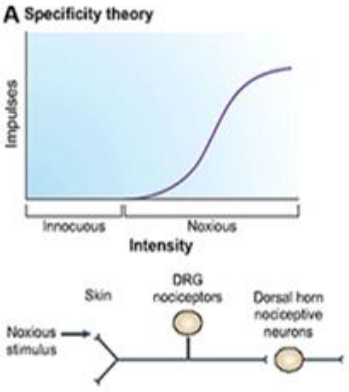
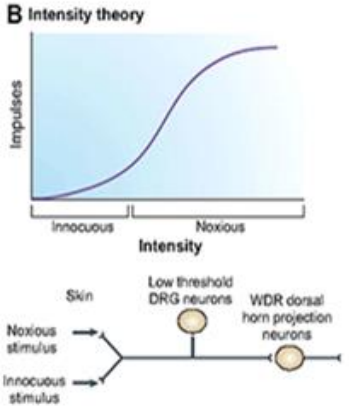
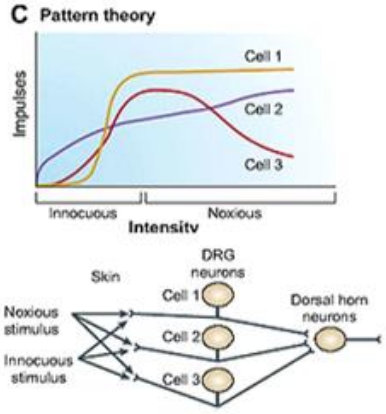


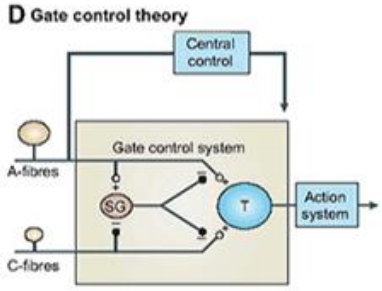
Figure 1.3 Schematic diagrams of pain theories. ***A***: Based on the Specificity Theory of Pain; each modality (touch and pain) is encoded in separate pathways. Touch and pain stimuli are encoded by specialized sense organs. Impulses for each modality are transmitted along distinct pathways, which project to touch and pain centres in the brain, respectively. DRG, dorsal root ganglion.



B: based on the Intensity Theory of Pain; there are no distinct pathways for low- and high-threshold stimuli. Rather, the number of impulses in neurons determines the intensity of a stimulus. The primary afferent neurons synapse onto wide-dynamic range (WDR) 2nd-order neurons in the dorsal horn of the spinal cord, where low levels of activity encode innocuous stimuli, and higher levels of activity encode noxious stimuli.



C: The Pattern Theory of Pain posits that somatic sense organs respond to a dynamic range of stimulus intensities. Different sense organs have different levels of responsivity to stimuli. A population code or the pattern of activity of different neurons encodes the modality and location of the stimulus.



D: The Gate Control Theory of Pain proposes that both large (A-fibres) and small (C-fibres) synapse onto cells in the substantia gelatinosa (SG) and the 1st central transmission (T) cells. The inhibitory effect exerted by SG cells onto the primary afferent fibre terminals at the T cells is increased by activity in A-fibres and decreased by activity in C-fibres. The central control trigger is represented by a line running from the A-fibre system to the central control mechanisms; these mechanisms, in turn, project back to the Gate Control system. The T cells project to the entry cells of the action system. +, excitation; -, inhibition. Figure is reproduced with permission from Perl (2007), p. 74.

1.2.8 Pain Modulation and Mechanisms

The localisation of allodynia and hyperalgesia at the muscle during exercise illustrated how the spinal cord (SC) and brain can exert a modulatory effect on how inputs from peripheral nociceptors are perceived (Mehler, 1962). In addition to receiving nociceptive input from ascending peripheral sites, nociceptive projection neurons in the dorsal horn (DH) in the SC receive nociceptive inputs from a host descending brain regions that play a crucial element in the modulation of pain (Suzuki, Rygh & Dickenson, 2004). This complex neural network of connections allows for the combination of signals from multiple tissues and can exert both inhibitory and excitatory effects on the signal of nociceptors and modulate perceptions of a noxious stimulus (Black, 2012).

The original proposals in Melzack and Wall's 'gate-control theory of pain', suggests that non-nociceptive input from afferent fibres activate interneurons at the SC level which inhibit the nociceptive projection neurons activity, thus blunting the nociceptive input from the peripheral tissues. This theoretical framework helped elucidate a variety of complex phenomena, such as why a balm that irritates the skin around a painful bruise or cut may provide temporary pain relief, and why thoughts and emotions influence pain perception (see Figure 1.8). The periaqueductal gray (PAG) is well-known to control nociceptive inputs and perception of pain through its interactions with both ascending and descending projections from numerous sites (Ossipov, Morimura & Porreca, 2014). Stimulation of the PAG has also been shown to result in analgesia without affecting attention, alertness, or motor control in response to non-nociceptive stimuli (Mayer & Price, 1976). The PAG integrates ascending nociceptive stimuli with descending nociceptive inputs from hypothalamus, amygdala, insula, and ACC (Brooks & Tracey, 2005). Between the PAG and the rostral ventromedial medulla (RVM), bidirectional connections also exist (Brooks & Tracey, 2005), and form what is termed 'PAG-PVM system'. Electrical stimulation of RVM or the PAG amygdala produces analgesia (Hosobuchi, Adams & Linchitz, 1977; O'Conner & Cook, 1999), and some analgesics work via nerve signals from the RVM to the SC via the RVM. The RVM is a principal source of serotonin release, and serotonin has been shown to cause inhibition of nociceptive neurons in the DH (Jordan et al., 1978). In addition, the RVM has neurons that synapse on nociceptive projections of nerves in the spinothalamic tract and may attenuate nociceptive inputs by inhibiting excitatory interneurons or activating inhibitory interneurons. The PAG-PVM system and amygdala also contain high concentrations of receptors for endogenous opioids and exogenous opiates (Yaksh, Yeung & Rudy, 1976; Fields, Bry, Hentall & Zorman, 1983; Rossi et al., 1994; Waters & Lumb, 1997; Heinricher, Tavares, Leith & Lumb, 1999). Consequently,

systemic administration of exogenous opiates in the PAG has been shown to induce analgesia (Fields, 2004) and endogenous opioids such as enkephalins, endomorphins, and beta-endorphins are likely to play a crucial element in pain modulation in the SC as well as the brain and afferent nociceptive fibres in the periphery (Stratton, 1982; Straneva, 2002). During exercise, levels of endogenous opioids have been shown to increase, particularly in response to high intensity exercise (Goldfarb & Jamurtas, 1997), leading to the suggestion that endogenous opioids may play a role in exercise-induced analgesia (Janal, Colt, Clark & Glusman, 1984; Pertovaara, Huopaniemi, Virtanen & Johansson, 1984).

To summarise, the perception of pain starts with the sensitisation of peripheral nociceptors, central nociceptors, or both. Muscular nociceptors generally exist in and around the small arterioles, arteries and veins, and connective tissue found in skeletal muscular tissues. These nociceptive signals are conveyed to the DH of the SC through type III or IV afferent nerve fibres and respond to a host of noxious biochemicals, mechanical pressure, and thermal stimuli. Nociceptive signals are subsequently conveyed to the brain along several tracts where multiple regions are involved in its processing, including the thalamus, hypothalamus, reticular formation, PAG, ACC, and amygdala. Pain sensations may be modulated in these regions by endogenous and exogenous substances (e.g., opioids and other analgesic drugs) as well as by neural input from other tissue (e.g., afferent input from tissue deformation associated with muscular contractions). Thus, the perception of pain represents the end product of a complex and integrative sensation of both inhibitory and excitatory signals in which processing can occur in both ascending and descending pathways.

In addition to physiological pain modulation, a number of studies have found that psychological manipulations are also capable of modulating pain perception by acting on processes within the nervous system, brain and spinal nociception (Fields, 1999, Rhudy et al., 2013). It has now been shown that a number of variables (including: emotional context, attentional state, empathy, attitudes and expectations, hypnotic suggestions, and the placebo response) can alter both pain processing in the brain and pain perception (Turner, Loeser, Deyo & Sanders, 1994; Rainville et al., 1999; Price, 2000; Villemure & Bushnell, 2002; Linde et al., 2007). Several clinical and experimental studies demonstrate that individuals report significantly lower pain intensity when they are distracted from the noxious stimulation (Villemure & Bushnell, 2002; Apkarian, Bushnell, Treede & Zubieta, 2005; Loggia, Mogil & Bushnell, 2008). At the cerebral cortex level, neuroimaging studies indicate that distraction from pain decreases noxious stimulus responses in both sensory

(including primary and secondary somatosensory cortices) and limbic cortical regions (including anterior cingulate cortex and insular cortex) (Apkarian et al., 2005). In experimental studies, mood and emotional state also alter pain perception, with a positive effect of mood or emotions following presentation of pleasant images, music, relaxing odours and humorous films, normally decreasing the perception of pain, whist negative mood or emotions, induced by unpleasant images increases the perception of pain (Price, 2000; Villemure & Bushnell, 2002). It has also been shown that placebo analgesia is associated with reduced activity of certain regions of the brain, including anterior cingulate cortex, the thalamus and insula. Increased activity of brain regions associated with pain also occurs when there is an anticipation of pain, leading to an increased pain perception (Wager et al., 2004). In summary, variables such as mood, emotion, distraction and deception can alter pain perception irrespective of the size of the nociceptive stimulus. This helps demonstrate that pain is subjective and that there is an emotional element to pain.

1.2.9 Assessment of Pain

Pain perception is a complex, multifaceted experience that is subjective and relative to the individual. Therefore, the evaluation of pain perception is a challenge when it comes to how to assess it. Whilst it has been suggested that there is no single 'best' assessment of pain during and following exercise (O'Connor & Cook, 1999), there are several commonly used methods for assessment of pain that have been shown to provide accurate, reliable, and valid information regarding certain dimensions of pain. These methods include subjective measures of pain or magnitude and objective measures of pain tolerance and pain threshold.

1.2.9.1 Pain Threshold

Pain threshold is defined as the minimum stimulus input required to be perceived as 'painful'. Pressure, thermal, and electrical stimuli are generally used to investigate pain thresholds (Melchers & Andersson, 1973; Jensen, Karoly & Braver, 1986; Hargreaves et al., 1988; Droste et al., 1991). In an experimental trial, the intensity of noxious stimuli is decreased or increased in a stepwise, incremental manner. During "descending" trials the stimulus is initially set above the pain threshold and then gradually lowered until the stimulus is no longer perceived as a painful, and during "ascending" trials, noxious intensities below pain threshold are initially applied and then intensity is gradually increased until the stimulus is perceived as a painful (Black, 2012). This procedure has its roots in signal detection theory and scaling methods, and readers are referred to Gracely

and his colleagues (Gracely, Lota, Walter & Dubner, 1988; Gracely & Kwilosz, 1988) as well as Wall and Melzack (1999) for further complete explanations of the methodology underlining these techniques.

In exercise-related research, the most common method used for determining the pain threshold is the use of manually applied pressure or force to numerous points on the muscle or another anatomical structure (e.g., finger) (Black, 2012). Delayed-onset muscle soreness has repetitively shown to lower the pain pressure threshold (Baker et al., 1997; Dannecker, Hausenblas, Kaminski & Robinson, 2005; Maridakis, O'Connor, Dudley & McCully, 2007; Hedayatpour, Falla, Arendt-Nielsen & Farina, 2008). Whilst intra-individual and inter-individual differences can exist in threshold measures, the measurements can provide meaningful information regarding the peripheral and central sensation during and following exercise, and they can also be useful in determining the influences of various analgesic interventions (Black, 2012).

1.2.9.2 Pain Tolerance

Pain tolerance represents the maximal level (greatest) of noxious stimuli an individual is able to tolerate (O'Connor & Cook, 1999). Perhaps it is difficult and unethical to acquire a true assessment of pain tolerance in human subjects, as application of the largest noxious stimuli could result in substantial tissue damage (Black, 2012). Assessment of a true 'pain tolerance' could be measured by application of a hot, cold and electrical stimuli as well as application of mechanical pressure (O'Connor & Cook, 1999; Black, 2012). However, given the potential for tissue damage, applications more often involve examining the length of time an individual can or will tolerate a noxious stimulus, such as submersion of the hand in ice water (e.g., cold pressor test) and application of a mechanical stimulus (e.g., algometer). Measuring pain tolerance with this technique often imposes maximum exposure to the noxious stimulus, thus setting a maximum amount the possible length of tolerance time (O'Connor & Cook, 1999). Pain tolerance is perhaps more relevant to endurance performance than pain threshold, as most endurance exercise occurs above the intensity at which pain threshold occurs. Therefore, the duration of pain, or level of pain, that someone is willing to engage in is the key aspect.

1.2.9.3 Pain Intensity Ratings

Subjective measures of pain intensity can be assessed for any noxious stimulus that exceeds an individual's pain threshold. Multiple questionnaires and scales have been developed to assist in the quantification of pain intensity. Tools such as the Visual Analog

(VA) scales, Category Ratio (CR) scales, and magnitude estimation, at the level of groups and at the level of individuals are commonly used. VA scales comprise a line (typically 50-100 mm in length) with verbal presenters "worst pain imaginable" at the right end and "no pain" at the left end. Individuals are instructed to point a vertical mark on the line so that the distance from the left edge anchors the pain being experienced in a given part of the body at that moment, as shown in Figure 1.9a. The distance in millimetres (mm) from the left edge of the line to the mark is used as the pain score. The VA scale is most popular in both research and clinical settings because of its ability to obtain a rapid rating and ease of use. VA scales possess inherent ratio properties, provide valid and reliable assessment of intensity of pain (Revill, Robinson, Rosen & Hogg, 1976; Jensen et al., 1986; Cook et al., 1997), and have been shown to be sensitive to interventions that provide analgesia. Numerical or category ratio (CR) scales are also commonly used, especially to assess intensity of pain during the dynamic exercise performance (O'Connor & Cook, 1999). In study by Cook et al. (1997), a CR scale was established by combining the verbal presenters from the perception of pain profile (Tursky, Jamner & Friedman, 1982) with structures of the easily administered 0 - 10 CR Borg scale (Borg, 1990). The 0 - 10 CR pain intensity scale is "numbered 0 - 10. The verbal anchors and numerical vales for the scale are as follows; 0 no pain at all, ½ very faint pain, 1 weak pain, 2 mild pain, 3 moderate pain, 4 somewhat strong pain, 5 strong pain, 7 very strong pain, 10 extremely intense pain (almost unbearable)" (Cook et al., 1997). The category ratio scales are shown in Figure 1.9b. The administration of the category ratio (CR) scale in assessing pain, like the VA scales, have been shown to be both reliable and valid tools in assessing intensity of pain and values of peak pain during intense exercise (Cook et al., 1997). Despite the efficiency for assessing the intensity of pain, the nature of the numerical scales may introduce some bias. Because of their fixed-end-point these scales elicit difficulties for measuring the effect of treatment on pain conditions. An individual who rates the intensity of pain during exercise as higher than the plausible category scales will not be capable of providing the higher rating of pain during a subsequent condition, even when individual experiences greater intensity of pain. To resolve this issue, when it is necessary, the 0-10 CR scale allows individuals to choose a number above 10 and thus overcomes the fixed-end-point problem associated with typical category ratio scales. This scale has been shown to perform in a similar manner to VA ratio scales (Cook et al., 1997).

Generally, a limitation of the use of single VA, numerical, or category scales in the measurement of pain intensity is that these scales observe pain as a unidimensional experience missing qualities besides intensity. The experience of pain clearly involves

other dimensions, such as emotional and unpleasantness. Assessment tools beyond VA and category scales may be needed to better capture the totality of the experience of pain.

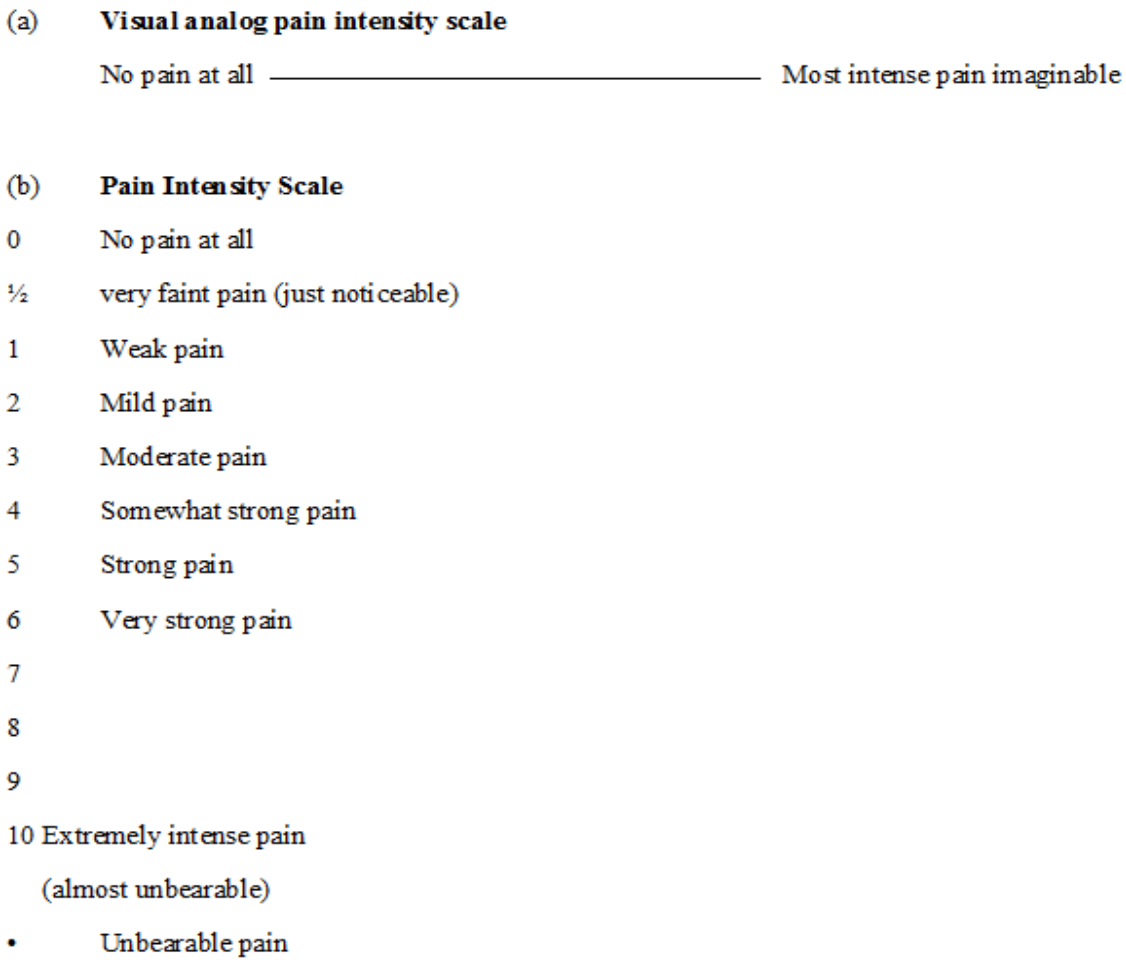


Figure 1.4 Scales for assessing pain intensity a: Visual Analog scale. B: Category-ratio scale (Cook et al., 1997).

1.2.9.4 Multidimensional Assessment of Pain

In addition to intensity, assessing pain has an affective component (Singer et al., 2004). Intensity is measured via a sensory dimension (Duncan, Bushnell & Lavigne, 1989), whilst the affective dimension can provide information regarding the quality and location (e.g., aching, dull, sharp) of the pain regarding how unpleasant or bothersome the experienced pain may be (Price, 2000). Individual rating of both the affective and sensory dimensions can be acquired to provide a much more complete measurement of the pain an individual is experiencing (Price, 2002). Scales of the affective dimension have not been extensively used when evaluating pain perception during and following exercise, but the scales of this type could provide more detailed information about the efficiency of various treatments

for pain conditions. For instance, a pharmacological treatment with, for example ibuprofen, could attenuate the intensity of delayed-onset soreness but might not attenuate it sufficient to reduce how unpleasant or bothersome of pain was during a particular moment. Another instrument that has been established to measure pain in a multidimensional manner is the McGill Pain Questionnaire (MPQ) (Melzack, 1975). The MPQ is a multidimensional measure that has the ability to describe the diverse pain dimensions. It classifies pain into three unique dimensions: affective, evaluative, and sensory. It provides valuable information on the sensory and affective quality of pain experience as well as pain intensity and location, and is able to discriminate between various pain problems (Reading, 1984). The MPQ has been shown to be both valid and reliable (Reading, 1982; Wilkie et al., 1990). The MPQ is commonly used in clinical and research tools and can provide useful information regarding the nature of the experience of pain during exercise (Black, 2012). However, obtaining repeated reporting on the MPQ during exercise can be difficult, because it requires participants complete multiple components and therefore requires significant attention over a prolonged period, which may not be practical during exercise.

1.3 Pain: Psychological Perspectives

The basis for categorising pain as a psychological phenomenon is provided by the distinction between pain and nociception (Baum, 1997). Nociception indicates the processing of neurophysiological events that activate nociceptors, which are then experienced as pain (Turk & Melzack, 2000). Initiation of the brain processing and nociceptive pathways contribute to the experience and awareness of the biological substrates, and in turn this suggests that pain should be described as psychological phenomenon (Hadjistavropoulos & Craig, 2004). Motivational and emotional aspects are central to understanding the nature of pain (Price, 2000), and these are particularly important constructs in exercise too.

1.3.1 The Influence of Emotion, Attention and Mood on Pain

Mood, emotion and attentional state are probably the most significant psychological factors believed to influence pain modulation (Villemure & Bushnell, 2002). The hypothesis of motivational priming (Lang, 1995) suggests that a negatively or positively valence stimulus activates the defensive or the appetitive part of motivational system (MS) so that a new stimulus-response is increased if its valence is compatible with stimulated part of MS and diminished if it is incompatible (Kenntner-Mabiala et al., 2007). The International Affective Picture System (IAPS) provides a standardised set of images

stimuli, which systematically vary on the dimensions of valence and arousal and can be a useful methodological tool for affect induction (Lang, Bradley & Cuthbert, 1995). Indeed, much of the research supporting the psychological components of pain has used the IAPS to induce changes in mood. Kenntner-Mabiala and Pauli (2005) used the IAPS to assess pain response to electrical stimulation following the presentation of positive, neutral, and negative images. They found that positive images were shown to associate with lower pain and lower N150 amplitudes recorded compared to negative images stimuli. This demonstrates that a psychological intervention, unrelated to the nociceptive stimuli, was capable of eliciting both a neurophysiological and perceptual change. Further evidence in support of motivational priming is provided by studies using the cold pressor test (CPT), where observing positive images compered to negative images caused an increase in pain threshold (Meagher, Arnau, & Rhudy, 2001) and in tolerance of pain (Meagher, Arnau, & Rhudy, 2001). Therefore, the observation that emotional image valence can modulate pain may be useful tool to explore the nature of 'exercise-induced pain' (EIP).

In addition to the effect of emotion on pain, attention is perhaps the most considered variable that influences pain and nociception (Villemure & Bushnell, 2002). Focusing an individuals' attention on the pain stimulus has generally been shown to exacerbate the perception of pain (Levine, Gordon, Smith & Fields, 1982), whereas distributing attention from pain stimulation decreases the perception of pain (Miltner, Johnson, Braun & Larbig, 1989; Lautenbacher et al., 1998; Miron, Duncan & Bushnell, 1989). However, there is also evidence that the influence of attention on pain is based on whether the individual focuses on the affective or the sensory aspects of pain. Ahles et al. (1983) instructed individuals to attempt to express emotions or to focus on the sensory aspects of pain during the CPT task. The investigators observed that focusing attention on the sensory aspects, in comparison to affective aspects, was related to less distress. Moreover, focusing attention on emotional pain sensations results in more pain reports than when focussed on the sensory aspects during cold pressor test (Bishop, 1999).

Mood state may also alter pain perception, as it is associated with motivation and performance. In experimental studies, enhancing mood by observing pleasant stimuli such as humorous films or music commonly decreases perception of pain (Cogan, Cogan, Waltz & McCue, 1987; Zelman, Howland, Nichols & Cleeland, 1991; Good, 1996; Weisenberg, Raz & Hener, 1998; de Wied & Verbaten, 2001; Meagher et al., 2001; Marchand & Arsenault, 2002). Contrariwise, decreased mood increases perception of pain (Zelman et al., 1991; Weisenberg et al., 1998; de Wied & Verbaten, 2001; Meagher et al., 2001). However, the interpretation of these studies is difficult, as they may not be able to control

the effect of focusing attention, a factor known to alter nociceptive transmission in spinal cord and affect the experience of pain (Villemure & Bushnell, 2002). Indeed, the pain modulation arising from mood changes be a result from the variation in attention, as an emotional response can be directly caused by level of attention (Öhman, Flykt & Esteves, 2001).

1.4 Exercise Induced Pain (EIP)

Pain is a relatively common experience for people who exercise, and is often associated with the 'burning' sensation in muscles or the dull ache of muscle soreness or cramps (Friden, Sjöström & Ekblom, 1983; Schwane, Watrous, Johnson & Armstrong, 1983; Jones, Newham, Round & Tolfree, 1986; Newham, 1987; Clarkson & Sayers, 1992; Miles & Clarkson, 1994; Cook et al., 1997). Pain emanating from the muscle contractions during exercise is very common, and athletes can easily distinguish the sensation of dull ache of muscle soreness from that of exertion (Armstrong, 1984; Clarkson & Tremblay, 1988; Clarkson & Hubal, 2002). Pain of this kind is termed 'exercise-induced pain' (EIP), and has been shown to increase in-line with exercise intensity, expressed as either a percentage of peak oxygen consumption or peak power output during cycling exercise (Cook et al., 1997). Following exercise cessation, muscular pain does not immediately cease, rather, it appears to decrease in an exponential manner over several minutes (Black, 2012). This decrease very closely imitates the decrease in oxygen consumption and rating perceived exertion (RPE) (Cook et al., 1997). Pain perception during high-intensity cycling performance has been described as intense, sharp, exhausting, burning, pulling, tiring, rasping, and cramping (Miles & Clarkson, 1994), and it appears likely that other types of aerobic exercise performance would elicit similar pain perception (Cook et al., 1997). This naturally occurring pain that is the consequence of intense and prolonged exercise has been shown to elicit a reproducible pain threshold of nearly 50% of peak oxygen consumption or peak power output, suggesting that high-force muscle contractions or high-intensity exercise are not necessary to provoke muscular pain (Weiser et al., 1973; Cook et al., 1997). Muscular pain can be provoked during very short bouts of exercise, as brief as 8-seconds (Cook et al., 1997), but tends to be likely more distinct during longer bouts of exercise (Black, 2012).

1.4.1 The Aetiology of Exercise Induced Pain

The experience of muscle pain tends to elicit large inter-subject variability with similar modes, relative exercise durations, and exercise intensities. This raises the question of what

nociceptive mechanisms are underlying or responsible for EIP. The exact mechanisms of muscle pain resulting from intense and prolonged exercise are still not yet known. However, the aetiology of EIP suggests that it may arise from either (or a combination of) accumulation of noxious biochemical, increased intramuscular pressure, or deformation of tissue due to muscular contractions (Mauger, 2014). Exercise, especially high-intensity exercise, leads to a build-up of metabolic by-products such as those discussed in Section 2.4, which stimulate and sensitise type III and IV afferent nociceptive fibres (Mense, 2009). However, muscular pain is generally related with work rate conditions where low-force, repetitive, tonic muscular contractions are performed (Mense, 2009). The low-force muscular contractions may generate enough force to overcome 'systolic blood pressure' and result in occlusion of the blood vessels that carry oxygen-rich blood to the working muscular and remove venous blood containing metabolic by-products such as lactic acid and other noxious biochemicals (Black, 2012). During exercise, some of those other noxious biochemicals may play a crucial element in the experience of pain (Cook et al., 1997). Intense exercise has been shown to increase the release of histamine, potassium, and prostaglandin E_2 (PGE_2) (Rotto, Hill, Schultz, & Kaufman, 1990), and has also been shown to increase interstitial fluid or tissue fluid level of BKN and adenosine in skeletal muscular (Langberg et al., 2002). Increased serotonin levels in the brain have also been associated with exercise (Caperuto et al., 2009), and exercise has been shown to increase the level of substance P concentrations in the ventral horn of the spinal cord (Wilson et al., 1993; Lind et al., 1996). Whilst none of these findings provides direct evidence for whether accumulation of these noxious biochemicals underpins the naturally occurring muscle pain experienced during exercise performance, at least they demonstrate a conceivable association. Additionally, the findings that EIP increases with longer durations of exercise and does not decrease immediately following exercise propose that muscular pain may build-up as accumulation of noxious biochemicals and drop as the biochemical levels are gradually removed during recovery (Cook et al., 1997). In short duration exercise that is of high intensity (e.g. HITT), there is likely a significant accumulation of these metabolites over a short period of time, and such exercise has been shown to cause significant amounts of pain (Foster et al., 2014). It may be that because this exercise is of shorter duration, a greater amount of pain is able to be tolerated by the athlete. Conversely, in moderate duration exercise, these noxious biochemicals still accumulate but at a slower rate and so cause a smaller level of pain but for a longer duration (Mauger et al., 2010). Because exercise of this sort goes on for longer, it is likely that only a lower magnitude of pain can be tolerated. However, in both this short and moderate duration exercise, interventions

which serve to reduce pain appear to improve performance (Foster et al., 2014; Mauger et al., 2010). In very long duration exercise (i.e. that takes place below the gas exchange threshold), it is likely that a minimal level of noxious metabolites will accumulate, and so the mechanism of EIP is less clear here. However, some evidence exists suggesting that noxious biochemicals are not solely responsible for naturally occurring EIP. For instance, administration of aspirin was not found to reduce EIP, which would reduce PGE_2 levels during cycling exercise (Cook et al., 1997). Furthermore, exercise induced muscle leg pain has been shown to occur after only 8-seconds of cycling, which would potentially limit the biochemicals accumulated (Cook et al., 1997). These results propose that such accumulation is not a requirement for eliciting EIP. Another possible mechanism for EIP is increased intramuscular pressure associated with muscular contractions and force production. If force levels are sufficiently high, the rise in intramuscular pressure and the mechanical deformation of muscle could be enough to stimulate the HTM nociceptive afferent fibres (Black, 2012). Mechanically, stimulation of HTM muscle receptors by high-force muscular contractions could be responsible for the experienced of pain during high-intensity, short term exercise (Mense & Gerwin, 2010). These mechanisms, alongside a likely higher level of muscle damage, may provide the basis of EIP during longer duration exercise.

1.4.2 Use of Exercise Induced Pain for Regulating Exercise Performance

Exercise induced pain may play a key role in the maintenance of exercise intensity and consequently important for athletic performance (O'Connor & Cook, 2001; Bantick et al., 2002; Eccleston & Crombez, 1999; Davis et al., 1997). A review of pain perception during exercise by Mauger (2013) suggested that muscular pain is a crucial factor in the work-rate regulation (Mauger, 2013). This indicates that the different perceptions of pain that present among certain types of exercise should be studied further. Because understanding of the nociceptive mechanisms underpinning EIP may be a relatively limited, as a better understanding of the mechanisms and assessments of muscular pain that underpin EIP may lead to the development of more effective methods to improve endurance performance.

While many bouts of exercise, especially moderate-high-intensity exercise, result in a noxious environment in the exercising muscles, certain components of pain, such as pain threshold, are altered during exercise. Numerous studies have shown a reduced pain response to noxious electrical stimuli of the arm (Feine et al., 1990), finger (Droste et al., 1991), and dental pulp (Pertovaara, Huopaniemi, Virtanen & Johansson, 1984;

Kemppainen et al., 1985, 1986; Paddon-Jones & Abernethy, 2001) during exercise and that this attenuated sensitivity may occur in a dose-dependent manner with exercise intensity (i.e., greater stimulation is required to induce pain at higher exercise intensities). Furthermore, Kosek and Ekholm (1995) demonstrate the threshold of mechanical pressure required to induce muscular pain is reduced during isometric and static contractions. Several studies have demonstrated increases in pain threshold to heat, compression ischemia, mechanical pressure, and electrical stimulation of the dental pulp subsequent to exercise (Koltyn, 2000). The analgesic effects of exercise occur more often after high-intensity exercise, are most commonly pronounced immediately succeeding exercise, after gradually dispersing with time (Koltyn, 2000, 2002). While the physiological mechanisms of the analgesic effects observed during exercise are not fully understood, numerous illuminations have been suggested. Exercise, especially vigorous and strenuous exercise (> 60% of VO_{2peak}) lasting longer than 30-min, is known to result in the release of endogens opioids such as beta-endorphins, that could function to moderate pain intensity at a peripheral level and in central nervous system. Administration of opioids such as naloxone have yielded mixed results, some studies eliciting blunting or preventing of analgesia during exercise (Haier et al., 1981; Janal et al., 1984; Droste et al., 1988) and other finding no such effect (Janal et al., 1984; Olausson et al., 1986; Droste et al., 1991). These outcomes indicate that both non-opioid and opioid mechanisms may play a role exercise-induced analgesia. A second possible explanation could be provided by Melzack and Wall's (1965) 'gate-control theory', with the noxious stimuli (small fibres input) being blocked by other non-nociceptive input during exercise. When there is much more activity of large afferent fibres (non-nociceptors) in comparison to the activity of small afferent fibres (nociceptors), the gate blocks some level of the pain signals that pass through to the brain so that individuals tend to perceive less pain. Another possible mechanism could be that the distraction of exercise focuses attention away from noxious stimuli and can lead to exercise-induced analgesia (McCaul & Malott, 1984; Fillingim, Roth & Haley, 1989). The increase in heart rate and respiration has also been suggested to cause increases in pain threshold by drawing perceptual attention away from noxious stimuli (Fuller & Robison, 1993). The key point to take from this, is that assessment of pain during exercise is complex, and methods of experimentally induced pain (e.g. algometry) do not necessarily represent the challenges athletes face in terms of tolerating pain during exercise.

1.4.3 Use of Exercise Induced Pain Tolerance for limiting Exercise Performance

The concept that natural muscle pain limits exercise or athletic performance is fascinating but experimentally unclear and puzzling. It appears, perhaps, that exercising with intense pain could lessen motivation to exercise, leading an individual to reduce exercise intensity to reduce pain or prevent further increases in pain intensity. It has been suggested that pain sets ultimate limits on the performance of athletes during training and competition and consequently athletes with the greatest (largest) pain tolerances could perform at a higher percentage of their maximal capabilities and outperform athletes with lower pain tolerances (O'Connor & Cook, 1999). Despite these beliefs, relatively few studies have attempted to explain the role of pain in exercise and performance.

The majority of studies investigating exercise performance neglect to report pain perception during exercise, and this is despite the fact that EIP is a well-documented phenomenon. Cook et al. (1997) demonstrated an intensity of pain threshold for quadriceps muscle group during cycling performance of nearly 50% of VO_{2peak}, and pain increased with exercise intensity until participants reached exhaustion. Although this study does not necessarily show that it was the lack of tolerance to the EIP that caused the cyclists to stop (for this was not the intention of the study), it does show a clear association between exercise intensity and pain perception. It is logical therefore, that athletes must be able to tolerate a lot of pain in order to maintain high work rates which are needed for a good exercise performance. However, many participants indicated that even though they experienced very strong muscle pain during the cycling task, muscular pain did not play a role in their exercise cessation. There is experimental evidence that proposes that competitive athletes may be considerably tolerant to some forms of pain than non-competitive athletes, and that the stage of the season may dictate the level of painful training engaged in and consequently affect the perception of pain (Scott & Gijsbers, 1981). A study by Anshel and Russell (1994) speculated that the capacity of an athlete to tolerate EIP is an important aspect in endurance exercise performance, and there is agreement between coaches, athletes and some researchers that EIP tolerance can limit different types of exercise performance (O'Connor, 1992; Cook et al., 1997; Kress & Statler, 2007).

1.4.4 Manipulation of Exercise Induced Pain within Exercise Performance

In experimental studies, the manipulation of EIP could also yield insight into its role in exercise performance. Ingestion of caffeine has been consistently shown to enhance exercise performance in the form of both increased work completed in a fixed period of time and increased exercise time to exhaustion (for example; Keisler & Armsey, 2006; Ganio et al., 2009). In addition, multiple studies have demonstrated reduced EIP following caffeine consumption (Molt et al., 2003; O'Connor et al., 2004; Molt et al., 2006; Gliottoni & Molt, 2008; Gliottoni et al., 2009; Gonglach et al., 2015). A study by Jenkins et al. (2008) investigated the time trial performance (TT) in trained cyclists who were administrated a placebo or multiple low doses of caffeine and also measured EIP during the TT. The study found that EIP did not differ between the placebo and caffeine conditions, but that TT performance increased with caffeine. While these findings agree with those of Cook et al. (1997) that muscular pain may not be a primary limiting factor in exercise performance, a second elucidation may actually support a role for pain in determining exercise performance. Similar findings in a study by Mauger et al. (2010) showed that acetaminophen improves performance of a 10-mile cycle TT through an increased power output, but at the same level of the rating perceived exertion and muscle pain intensity. The study supports the notion that exercise is regulated by the perception of pain, and increased tolerance of pain can improve work rate during prolonged exercise. In another study by O'Connor and Cook (2001), participants adapted their work-rate during cycling exercise so that muscle pain intensities remained constant over a period of 20-30 minutes. It is plausible that the cyclists in the studies by Mauger et al. (2010) and Jenkins et al. (2008) self-selected (self-paced) a work-rate during the TT that produced a muscle pain intensity that was near the maximum intensity they could tolerate or endure while continuing to exercise. Thus, the protocol of experiments could have masked the analgesic effects of acetaminophen or caffeine, but allowing work rate to vary.

Numerous studies have also examined the impact of pain on exercise by attempting to increase the perception of pain during exercise through administration of opioid antagonists such as naloxone. Administration of naloxone should increase perception of pain during exercise (Sgherza et al., 2002), which would be expected to reduce time to exhaustion. In an experimental study of administration of naloxone prior to exhaustive treadmill running, administration of naloxone led to increased pain as assessed via the McGill Pain Questionnaire (MPQ) (an increase of 30% in overall pain intensity) and reduced exercise time to exhaustion (Surbey et al., 1984). Another experimental study by

Paulev et al. (1989), found increased pain intensity during a 120-min running task, but exercise performance was not compromised. Additional experimental evidence considering the role of exercise-induced muscle pain can be assembled from studies examining performance in the presence of delayed-onset soreness or pain (DOMS). Decreased performance in short-duration exercise (20-30 s) (Sargeant & Dolan, 1987; Byrne & Eston, 2002), 5-min cycling exercise (Twist & Eston, 2009), and 30-min running TT (Marcora & Bosio, 2007) has been shown following the induction of DOMS. Whilst these studies reported a potential association between the presence of muscular pain and exercise performance, it is difficult to demonstrate conclusively whether pain is the primary cause of the decreased exercise performance in these studies, as damaged muscle can also lead to decreased joint range of motion and decreased capacity of muscles to generate force. Therefore, the use DOMS studies to explore the fatigue/pain relationship should be treated with caution. Other methods to induce pain during exercise include carrageenan (Diehl et al., 1988; Radhakrishnan, Moore & Sluka, 2003), hypertonic saline (Ro et al., 2007), acidic saline (Sluka et al., 2001), and mustard oil (Han et al., 2008). While these examples go some way to mimicking and exacerbating the sensation of EIP the methods of inducing EIP in these studies are limited and there still remains a need to seek a unique technique to apply the whole-body exercise. Thus, whist it appears perhaps that exercise-induced muscle pain may play some role in limiting exercise capacity, very few experimental studies have been able to determine the individual effects of pain sensation compared with other crucial factors on exercise performance. Given that exercise performance can be influenced not only by a host of physiological factors but also psychological factors, further studies attempting to determine the contribution of pain sensation to exercise performance is necessary.

1.4.5 Role of Exercise Induced Pain in Self-Pace Exercise Performance

The role of exercise-induced pain in pacing strategies during endurance exercise performance is even less well established than its role on general performance. It is known that the sensation of pain accompanies intense exercise, and so it has been suggested that this sensation is utilised to moderate and judge the work rate (Mauger, 2014). In sport coaches and athletes' description about their performance and training, it appears that exercise pain tolerance is important for the regulation of pace, in which it contributes to the ultimate decision up or down regulate pace. The role of pain in these pacing decisions are not suggested to supersede the multitude of other factors known to contribute to pacing in endurance performance, but rather contributes to these. According to this proposition,

athletes change their work rate to moderate the level of pain perception (alongside a host of other sensations, such as RPE), with increases and/or decreases in work rate to manage the perception of pain to a level that the athlete is willing to tolerate (Mauger, 2014). These ideas are supported by investigations that have utilised analgesia during self-paced exercise to enhance performance (Mauger et al., 2010; Foster et al., 2014), and in these novel studies cyclists seem to be able to maintain a higher power output under conditions of analgesia. A key observation of these studies is that perception of pain remained the same (in comparison to the control condition) throughout the exercise, suggesting that the cyclists were willing to tolerate a given level of pain, and that changes in power output were made to achieve this. These findings are corroborated by recent studies that have used caffeine to induce an analgesic effect. Indeed, Gonglach et al. (2015), showed that EIP is likely used as a regulator of exercise intensity when power output can be selected by the participant. But, caffeine is known to elicit a range of other ergogenic effects (Keisler & Armsey, 2006) which could conceivably explain the observed differences in power output, so the conclusions of this study need to be treated with some caution. However, ingestion of other analgesics, such as aspirin and codeine has not produced enhancements in athletic performance (Ray & Carter, 2007; Hudson et al., 2008). These studies used a fixed intensity exercise model, and this may have affected the impact of the analgesic effect during exercise. Alternatively, the different mechanism of action of aspirin and codeine may not be effective for EIP.

Whilst several studies have investigated the relationship between pain perception and athletic potential, many of these have tended to use experimental pain, such as thermal pain (e.g. the cold pressor test) (for example; Janal et al., 1994; Ruble et al., 2005) and pressure pain (via algometry) (for example; Cook et al., 1997; Vaeter et al., 2015) to test their hypotheses. The importance of EIP may be misrepresented in these studies, as the interrelationship between nociception and pain perception pathways is a highly complex process, and follow different processing pathways by different types of painful stimuli and subsequently provoke very different responses (Olesen et al., 2012). Muscle pain arising from repetitive strain and intense exercise, which is associated with endurance performance, is likely induced through a combination of deformation of tissue, release of noxious metabolites and increased intramuscular pressure associated with muscle contractions (Ellingson et al., 2014), which is distinct from these traditional measures of pain induction. In order to appropriately understand the role of EIP on exercise performance, the experimental pain should emulate the variety of factors caused by EIP. For example, algometry may be a useful tool for assessing particular hyperalgesia of

muscles such as fibromyalgia (de Carvalho et al. 2012) and delayed onset muscle soreness (Close et al., 2006), but this does not sufficiently replicate EIP.

2. Overview/General Conclusion of Literature Review

Muscle fatigue is a very complex and multifactorial process (Fitts, 1994; Gandevia, 2001), and it is well-accepted that maximising power output or speed while limiting fatigue is the key determinant of success in endurance exercise (Joyner & Coyle, 2008). Substrate depletion, increased concentration of deleterious metabolites during prolonged strenuous exercise (Coyle et al., 1983; Kent-Braun, 1999), and reduced neural drive to the muscles (Gandevia, 2001) are all well-accepted models to explain this process of fatigue. However, they do not adequately explain how exercise intensity of regulated in self-paced exercise, or why performance is improved independently of any physiological manipulation. Indeed, where completion time is the measure of success, athletes are not required to produce maximal contractions and rarely cease exercising during or following the event (Mauger, 2014). Rather, it is the athlete's ability regulate their own work-rate during the endurance event, that determines their success (Mauger et al., 2009). How this is achieved is a puzzle that still remains to be explained. Limitations and explanations of fatigue in previous literature suggests that endurance exercise performance may be limited by several physiological determinants, with maximal oxygen consumption VO_{2max}, lactate threshold and efficiency interacting to produce race velocity (Lucia et al., 1999; Balmer, Davison & Bird, 2000; Jeukendrup, Craig & Hawley, 2000; Lucia, Joyos & Chicharro, 2000; Laursen, Shing & Jenkins, 2003; Joyner & Coyle, 2008). Whilst this is undoubtedly true, there are further unanswered questions that remain. New models of endurance performance, such as the CGM and Psychobiological Model attempt to answer these, and have gone some way to change the way we think about limitations of endurance performance. However, other markers such as pain, which are generated during prolonged exercise and are suggested to be important for performance, remain largely unexplored. The literature review has attempted to compile the most important studies on endurance performance in pain, to demonstrate current understanding and highlight areas that remain to be explored. Consequently, this thesis will seek to further knowledge in this area, by addressing the following aims in a collection of 5 experimental studies.

2.1 Purposes and Outline of the Thesis

The overall purpose of this thesis is to examine and establish the importance of EIP on endurance performance. Through 5 novel studies, the thesis will explore the following aims and hypotheses.

Chapter 3 Experimental 1st study:

Tittle: Tolerance of exercise-induced pain at a fixed rating of perceived exertion predicts time trial cycling performance.

Aim: To compare the predictive capacity of experimental pain and exercised-induced pain (EIP) on exercise performance.

Hypothesis: Experimental induction of pain will be a poor predictor of time trial cycling performance, whereas EIP tolerance will be a strong predictor of time trial cycling performance.

Chapter 4 Experimental 2nd study:

Tittle: Task deception using a Mirror Box can influence perceptual measures and the time-to-exhaustion of an isometric voluntary contraction

Aim: To establish whether deception of exercise task difficulty will change pain response and affect endurance performance.

Hypothesis: Increasing perception of task difficulty will increase EIP and decrease endurance performance. Decreasing perception of task difficulty will decrease EIP and increase endurance performance.

Chapter 5 Experimental 3rd study:

Tittle: Transcutaneous electrical nerve and interferential current stimulation reduce exercise-induced muscle pain and improve time to exhaustion performance

Aims: To investigate whether reducing nociceptive afferent feedback at the spinal level during a sustained single limb, submaximal isometric contraction will reduce pain perception and improve time to exhaustion.

Hypothesis: Reduced nociceptive afferent feedback will result in reduced perceived pain and an increase in time to exhaustion.

Chapter 6 Experimental 4th study:

Tittle: Transcutaneous electrical nerve stimulation inhibits central pain transmission and limits the development of peripheral muscle pain during cycling time trial performance.

Aims: To establish whether reducing nociceptive afferent feedback at the spinal level during cycling exercise will improve endurance performance.

Hypothesis: Reduced nociceptive afferent feedback will result in improved endurance cycling performance.

Chapter 7 Experimental 5th study:

Tittle: The effect of compassional hyperalgesia on exercise-induced pain during endurance cycling performance.

Aims: To examine whether changes in mood will affect pain perception and exercise performance.

Hypothesis: Negative mood will increase pain perception and reduce endurance performance. Positive mood will decrease pain perception and improve endurance performance.

CHAPTER 2

GENERAL METHODS

2.0 Introduction

The intention of this chapter is to define and describe the major and consistent methodologies used in the experimental studies reported in the following chapters. The particular protocols of the individual experiments are also detailed in the methods section of each chapter. All data collection for these experiments and all analyses which comprise this thesis were collected in the laboratories of the School of Sport and Exercise Sciences of the University of Kent.

2.1 Recruitment and Ethical Approval

Prior to the commencement of each study, ethics were approved by the University Ethics Committee (University of Kent). Before participating in each study, an information sheet (see example in Appendix A) was given to the participants, which explained and outlined the study details and scope of the participants' involvement in the study. Participants who were interested in participating in the studies then contacted the researcher and further information was given if so required. Prior to use of any equipment or measurements being taken, participants were required to complete a health questionnaire (see Appendix A). Those participants who were then interested in participating in the study filled out a written consent form (see example in Appendix A). The participants were informed that all data would be unidentifiable and that they had the right to withdraw from the experiment at any time. Prior to all experimental visits, participants were asked to abstain from the ingestion of alcohol (48 h prior), and asked to refrain from any vigorous exercise (24 h prior), caffeine (8 h prior) and analgesics (6 h prior) prior to any test visit (Lu, Lai & Chan, 2008). All visits were separated by 2-5 days. All data was collected at the School of Sport and Exercise Sciences University of Kent .

2.2 Pre-test Measurement and Familiarisation

All participants performed at least one familiarisation session of the experimental procedures performed in each study. This was to help reduce any learning effect and improve test reliability. In their first laboratory visit, all participants were measured for their height and weight. Height was measured using a stadiometer (Stadiometer, Holtain Ltd, Crosswell, Crymych, Dyfed, UK), with the participant being asked to remove their shoes and stand upright with heels and toes together and their back to the stand. Participants were encouraged to stand tall and look straight ahead. Height was then measured to the nearest millimetre. Body mass was assessed using a heavy-duty Seca

770 floor digital scale (Seca, Hamburg, Germany). Participants removed their shoes and stood on the scales. Body mass was measured to the nearest 100 g. All participants were fully familiarised with the rating of perceived exertion (RPE) using the Borg (6-20) (Borg, 1998) scale and pain scale (Cook et al., 1997), that pain should be anchored to exercise-induced pain (i.e. numeric values given relative to their experience of muscle pain). Details of scale familiarisation are given in Section .3.11

2.3 The Validity and Reliability of Data Collection Tools

In measurement and collection of data, the major pieces of equipment used throughout this thesis (including: Velotron, Lode Excalibur, The Metalyzer 3B, Biosen EFK and Polar RS400) have been shown to be valid and reliable (i.e. consistency and accuracy) in these sorts of tests (Sporer & McKenzie, 2007; Weber & Schneider, 2001; Meyer et al., 2001; Davison et al., 2000; Engström et al., 2012). This section will provide detail of these for the major pieces of equipment used throughout this thesis.

2.3.1 Velotron

The Velotron (Velotron, Racermate, Seattle, WA, USA) has been shown to be vaild and reliable in the sorts of tests used in the studies in this thesis (Sporer & McKenzie, 2007). The Velotron manufacturer reports the following specifications; generates variable load range from 5 to 2000 W, accuracy of ±1.5% and repeatability of ±0.2 % or better, smooth electronic shifting controlled from handlebar or remote gear-shift lever, set virtual gears to mimic the chain ring combinations on any bicycle.

2.3.2 Lode Excalibur

In experimental research, the reliability of the Lode Excalibur (Lode Excalibur, Lode Medical Technology, Groningen, The Netherlands) has been assessed by Weber and Schneider (2001). In the experimental studies in this thesis, the Lode Excalibur was used to deliver the maximal incremental test to determine VO_{2max} and peak power output (PPO). The manufacturer reports the following specifications; workload range of 8-2500 W, maximum rpm independent constant load of 180 rpm, minimum rpm independent constant load of 25 rpm, workload accuracy below 100 W of 2 W, workload from 100 to 1500 W, accuracy of 2 %, and workload over 1500 W, accuracy of 5 %, maximum operational temperature 40 °C, minimum operational temperature 14 °C (minimum temperature at which the device will work within specification).

2.3.3 The Metalyzer 3B

Using the Metalyzer 3B (Cortex Biophysik GmbH, Leipzig, Germany), an athlete's performance can be precisely assessed using parameters such as the maximum oxygen uptake (VO_{2max}) at a maximum heart rate (HRpeak) and respiratory thresholds. The MetaLyzer 3B has been tested for validity and reliability by Meyer et al. (2001). This device has been reported to have the following specifications; volume transducer: range: 0.1 – 12 l/s, resolution: 7 mL, accuracy: 2%, O_2 analyser: range: 0 – 35 % O_2, t90: 100 ms, accuracy: 0.1 Vol.%, CO_2 analyser: range: 0 – 13 % CO_2, t90: 100 ms, accuracy: 0.1 Vol.%, temperature sensor: range: -55 °C - +155 °C, accuracy: 1° C, and pressure sensor Type: range: 200 – 1050 mbar, accuracy: 1.8%.

2.3.4 Biosen *EFK*

The Biosen (Biosen, EFK Diagnostics, London, England) has widely been used to test blood, plasma or serum to provide lactate and glucose values quickly and precisely in clinics. Test-retest reliability of the Biosen has been established by Davison et al. (2000), who showed a high level of reliability for this device ($R^2 = 0.995$). This device has been reported to have following specifications by the manufacturer; multi-lingual touch screen display with step by step instructions, 20 µl blood, plasma or serum sample required for analysis, results in 20-45 seconds, enzymatic-amperometric method using chip-sensor technology, measuring range, glucose 0.5–50 mmol/L (9–900 mg/dL); Lactate 0.5–40 mmol/L (5–360 mg/dL), imprecision: CV ≤1.5 % (12 mmol/L), and innovative needle and exchanger design eliminates cross contamination.

2.3.5 Polar RS400

The validity of HR measured by Polar RS400 has been assessed by Engström et al. (2012), with correlation coefficients ranging from 0.97 to 1.00. The Polar RS400 has been reported to have the following technical specifications by the manufacturer; operating temperature: -10 °C to +50 °C / 14 °F to 122 °F, accuracy of heart rate monitor: ± 1% or 1 bpm, whichever larger. Definition applies to stable conditions, heart rate measuring range: 15-240.

2.4 Assessments of Test Performance

2.4.1 The Graded Exercise Test (GXT)

During the 1st, 3rd, and 5th studies, all participants visited the laboratory prior to the experimental visits to complete a maximal incremental test to determine their VO_{2peak} or VO_{2max} and peak power output (PO_{peak}). On a cycle ergometer (Lode Excalibur, Lode Medical Technology, Groningen, The Netherlands), participants initially completed a 5-10 min warm-up at 75 W, followed by an incremental ramp protocol which started at 100 W and increased by 30 W $2 \bullet min^{-1}$ until volitional exhaustion or when cadence dropped 5 RPM below the participants' self-selected cadence. Participants were given instructions to rate their perceived exertion (Borg, 1998) on the 6-20 scale, and to report perceived pain intensity (Cook et al. 1997) 15 s prior to the end of each stage. Oxygen consumption during the test was collected through online gas analysis (Cortex Metalyser 3B, Cortex GmbH, Lepzig, Germany), and heart rate was recorded through a telemetric device (Polar RS400, N2965, Finland). VO_{2max} was determined by a visible plateau in oxygen consumption with a standard increment in exercise intensity, at or around the point of volitional exhaustion. All GXT's conducted demonstrated such a plateau.

2.4.2 Assessments of VO_{2max}

During the 1st, 3rd, and 5th studies, using the cycle ergometer (Lode Excalibur, Lode Medical Technology, Groningen, The Netherlands), oxygen consumption and other ventilatory and gas exchange responses throughout the GXT (VE, VCO_2 and RER) were collected through online gas analysis by the Cortex Metalyser (Cortex Metalyser 3B, Cortex GmbH, Lepzig, Germany). A volume transducer and sample line running from the Cortex Metalyser were attached to a turbine (Cortex Metalyser 3B, Cortex GmbH, Lepzig, Germany), which in turn was tightly secure to a face mask worn by the participants. The facemask covered the mouth and nose and was available in different sizes. To achieve a stable seal and ensure a tight-fitting mask seal around the face placed in right position, the experimenter temporarily positioned their hand over the turbine while asking the subject to expire, if the mask is properly fitted, it would be an airtight seal. The Cortex MetaLyzer was interfaced to a computer installed with Metasoft software (3B, Cortex GmbH, Lepzig, Germany). The Metalyzer automatically recorded ambient pressure and air temperature prior to each test. During a test, the software continuously captured ventilatory data, which were subsequently averaged over a 30 s time periods. The MetaLyzer- Metasoft interface also allowed the direct capture of HR data from a polar HR monitor (Polar RS400, Polar

Electro Oy, Kempele, Finland). All data captured by the Metasoft software were then exported and stored as an Excel spread sheet.

Approximately one hour prior to testing, the Metalyzer was calibrated in accordance with the manufacturers' recommendations.

2.4.3 Assessment of Peak Power Output (PPO)

During the 1st, 3rd, and 5th studies, power output was assessed using the cycle ergometer (Lode Excalibur, Lode Medical Technology, Groningen, The Netherlands) peak power output was defined as the highest PO averaged over 30 s in the GXT. For instance, as the GXT started at 100 W and increased by 30 $W \cdot min^{-2}$ a participant who terminate cycling after 10-min and 15 s would have PO_{peak} of 265 W. Previous studies have been shown that PO_{peak} is a stronger indicator of endurance cycling performance than VO_{2max} (Lucia et al., 2001a).

2.5 Assessment of Endurance Performance

2.5.1 Endurance Performance of a 10-Mile cycling Time Trial (TT)

During the 1st, 3rd, and 5th studies, in order to provide a measure of endurance performance, on the cycle ergometer (Velotron, Racermate, Seattle, WA), participants were instructed to work at a self-selected intensity in order to complete the 10-mile (16.1-km) cycling time trial (TT) in the fastest possible time. Participants could change gear and cadence to vary their PO, and they could see the distance they had completed but were given no information on performance or physiological parameters (e.g. PO, HR, time elapsed). Participants were asked to report RPE and perceived pain every km. A fingertip sample of blood was acquired every 4-km for analysis for blood lactate concentration (B[La]). If participants required a fan, it was placed in a standardised position in front of the them during the entire duration of the endurance performance of a 16.1-km cycling time trial. Participants were given a 10-min cool-down following completion at a self-selected intensity.

2.6 Assessment of Mood Questionnaire (MQ)

During 3rd and 5th studies, The Brunel Mood Scale (BRUMS) was used in order to identify the participants' mood prior to and follow the experimental tasks. BRUMS developed by Terry et al. (2003) to measure current mood "How do you feel right now?" prior to and following the experimental tasks. This questionnaire has been adapted to create a shorter 24 items (e.g., "angry, uncertain, miserable, tired, nervous, energetic") divided into six

subscales: confusion, tension, anger, fatigue, vigour and depression. The items are answered on a 5-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely), and each subscale, with four relevant items, can achieve a raw score in the range of 0 to 16.

2.7 Assessment of Blood Lactate Concentrations [B(La)]

10 µl samples of capillary blood were taken from the thumb of the participants for measurement of blood lactate concentrations (Biosen, EFK Diagnostics, London, England). The site was first cleaned with an alcohol swap and allowed to dry. The thumb was then punctured using an automated instrument (Hemocue, Angelholm, Sweden), which inserted a sterile needle to a depth of 2.25 mm. Gentle pressure was then applied to the thumb tip, the initial blood wiped clear and a sample of arterialised whole blood (25 µL) was collected in a heparinised tube (Microvette CB300, Sarstedt, Germany). Blood lactate concentration was measured during RPE clamp (1st study), fixed power (3rd study) every 2-minutes, and every kilometre during endurance performance of a 16.1-km cycling time trial (1st, 3rd, 5th studies).

2.8 Assessment of Perceptual Parameters

2.8.1 Assessment of Rating Perceived Exertion (RPE)

Perceived exertion was measured during the incremental test (1st, 3rd, 5th studies), RPE clamp (1st study), fixed power (3rd study) every 2-minutes, for the time to exhaustion tests every 30 s (2nd study) and every 45 s (4th study) and for endurance performance of a 16.1-km cycling time trial (1st, 3rd, 5th studies) every kilometre using the 15 points RPE scale (Borg, 1998), as shown in Figure 2.6. Standardised explanations of the scale were given to each participant in the first visit of each study prior to the warm-up. Briefly, participants were asked to rate how much effort was required to drive the limb/s. Standardised instructions for the RPE scale were given to each participant (see Appendix C).

2.8.2 Assessment of Exercise-Induced Pain (EIP)

Exercise-induced pain was measured during the incremental test (1st, 3rd, 5th studies), RPE clamp (1st study), fixed power (3rd study) every 2-minutes, for the time to exhaustion tests every 30 s (2nd study) and every 45 s (4th study) and for endurance performance of a 16.1-km cycling time trial (1st, 3rd, 5th studies) every kilometre using the Cook scale (Cook et al., 1997), as shown in figure F.6. Standardised instructions for the scale were given to

each participant in the first visit of each study prior to the warm-up. Briefly, participants asked to rate the feelings of pain and discomfort, and not to report other pains they may have experienced (e.g., seat discomfort). Participants were also asked to not use this rating as an expression of perceived exertion. Standardised instructions for the scale were given to each participant (see Appendix C).

CHAPTER 3

EXPERIMENTAL 1st STUDY

Tolerance of exercise-induced pain at a fixed rating of perceived exertion predicts time trial cycling performance

Ali HY. Astokorki[1], Alexis R. Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK

Published in *Scandinavian journal of medicine & science in sports*
Accepted for publication 19 January 2016
DOI: 10.1111/sms.12659

I. ABSTRACT

INTRODUCTION: Pain has long been linked to success in sport and it is well-recognised that intense and repetitive muscular contraction, which is consistent with endurance performance, causes 'exercise-induced pain' (Dannecker & Koltyn, 2014; Mauger et al. 2010). Pain has an important role in protecting the body from damaging stimuli through avoidance behaviour, and so pain during exercise may contribute to task disengagement or reductions in work rate that are manifested in the athlete's pacing strategy (Mauger, 2014). Therefore, pain tolerance (the maximum level of perceived pain someone is able to tolerate) and threshold (the level at which a stimulus is initially perceived as pain) may be significant factors in successful endurance performance. Therefore, the purpose of this study is to compare the predictive capacity of experimental pain and exercised-induced pain (EIP) on exercise performance. **METHODS:** Thirty-two recreationally active male (n= 23) and female (n= 9) participants were recruited. Participants completed measures of pain tolerance by cold pressor test (CPT), pain pressure threshold via algometry (PPT), and EIP tolerance using an RPE-clamp trial. A VO_{2max} test provided traditional predictors of performance (VO_{2max}, gas-exchange threshold (GET), peak power output (PPO)). Finally, participants completed a 16.1-km cycling time trial (TT). **RESULTS:** No correlation was found between experimental pain measures (CPT, PPT) and TT performance. However, there was a significant correlation between EIP tolerance and TT performance ($R = -0.83$, $p < 0.01$). Regression analysis for pain and physiological predictor variables (mean pain in CPT, PPT, EIP tolerance, VO_{2max}, PPO, GET) revealed that a significant model ($p < 0.01$) emerged when only PPO (Adjusted R Square = 0.739) and EIP tolerance (ΔR Square = 0.075) were used to predict TT performance. **CONCLUSION:** These findings suggest that EIP tolerance is an important factor in endurance performance. However, PPT and CPT have limited ability to assess this relationship, and so their use in EIP research should be treated with caution.

Keywords: Fatigue; Exercise; Perceived Exertion; Pacing

II. INTRODUCTION

The physiological determinants of endurance performance are well established, with maximal oxygen consumption (VO_{2max}), the so-called 'lactate threshold' and energetic exercise costs (economy) considered the most important (Joyner & Coyle, 2008). Whilst these factors are critical to a successful endurance athlete, the sole focus on physiological mechanisms ignores the fact that work rate regulation (pacing) is ultimately controlled by the brain (Ulmer, 1996). Consequently, perceptual markers, such as rating of perceived exertion (RPE), have been suggested to be equally important as traditional physiological components (Tucker, 2009), or even in some cases, the sole determinant (Marcora, 2010). However, whilst the recognition that effort perception is integral to endurance performance is an important step forward in providing a more holistic understanding of endurance performance, there are other perceptions generated during intense exercise that may also be involved. Pain has long been linked to success in sport and it is well-recognised that intense and repetitive muscular contraction, which is consistent with endurance performance, causes 'exercise-induced pain' (EIP) (Dannecker & Koltyn, 2014; Mauger et al., 2010). Pain has an important role in protecting the body from damaging stimuli through avoidance behaviour, and so pain during exercise may contribute to task disengagement or reductions in work rate that are manifested in the athlete's pacing strategy (Mauger, 2014). Therefore, pain tolerance (the maximum level of perceived pain someone is able to tolerate) and threshold (the level at which a stimulus is initially perceived as pain) may be significant factors in successful endurance performance.

Although pain is a universally recognised perception, it is less well-known that different types of pain are sensed and processed very differently. Indeed, pain is now generally classified into three basic groups: neuropathic, inflammatory, and nociceptive (Dannecker & Koltyn, 2014; Ellingson et al., 2014), each of which may arise from different stimuli, may be perceived differently, and so exert a different response. This is important because the widely accepted definition of pain suggests that it is ultimately a subjective sensation, which is largely independent of the level of present or impending tissue damage (Olesen et al., 2012). Whilst several studies have investigated the relationship between pain and exercise, many of these have tended to use experimental pain, such as thermal pain (e.g. the cold pressor test) (for example; Janal et al., 1994; Ruble et al., 2005) and pressure pain (via algometry) (for example; Cook et al., 1997; Vaeter et al., 2015) to test their

hypotheses. Despite these techniques having excellent validity and reliability in studies of clinical pain, they inadequately represent the aetiology of EIP, and thus will likely be processed and reacted to very differently (Olesen et al., 2012). Exercise-induced pain likely arises from the build-up of a variety of noxious biochemicals (including; serotonin, bradykinin, histamine, potassium, hydrogen ions, adenosine, prostaglandins, and substance P combined with increased intramuscular pressure) (O'Connor & Cook, 1999). Consequently, in order to test the relationship between the tolerance of pain during exercise and endurance performance, it is important to replicate the type of pain that is consistent with EIP. Because EIP might provide important perceptual information that informs the exerciser whether to elect to stop exercising or increase or decrease their work-rate (Mauger, 2013), valid data that establishes this relationship may be of use for exercise practitioners looking to improve adherence to exercise routines and for coaches looking to educate and improve the performance of their athletes.

Therefore, the purpose of this study was to assess the relationship between traditional experimental measures of pain (the cold pressor test (CPT) and algometry), EIP tolerance and participants' performance of a 16.1-km cycling time trial. It was hypothesized that experimental induction of pain would be a poor predictor of time trial cycling performance, whereas EIP tolerance would be a strong predictor of time trial cycling performance.

III. MATERIALS AND METHODS

Participants

Thirty-two recreationally active male (n= 23) and female (n= 9) participants who exercised regularly (3 h or more per week) were recruited for this study. None of the participants were trained cyclists. The participants' mean age, height and body mass were 29 ± 6 yrs, 173.9 ± 10.1 cm and 73.2 ± 14.6 kg, respectively. Prior to participation in the study, an information sheet was given to the participants stipulating what they were asked to do. The participants were informed that all data would be unidentifiable and that they had the right to withdraw from the experiment at any time. Following this, they were asked to complete the inclusion/exclusion criteria checklist followed by an informed consent form. Participants were excluded from the study if they had Reynaud's syndrome, diabetes (types I and II), cardiovascular disease, open cuts on their hands or any bleeding disorders. All

participants provided informed consent before volunteering for the study and the research was approved by the local Ethics Committee (University of Kent). Before all experimental visits, participants were asked to refrain from any vigorous exercise 24 hours prior to the laboratory visits, and asked to refrain from the ingestion of alcohol, caffeine and analgesics 48 h, 8 h and 6 h prior to any visit (Lu, Lai & Chan, 2008). Participants reported to the laboratory on three separate visits, each separated by 2-5 days.

Procedures

After a separate familiarisation session of the experimental pain procedures and RPE-clamp test, in their first visit participants completed an assessment of pain tolerance using the cold pressor test (CPT) and pain pressure threshold (PPT) via algometry. Following this, participants undertook an assessment of aerobic capacity by completing a cycle-based VO_{2max} test. Finally, participants undertook a familiarisation of the endurance performance test by completing a self-paced 16.1-km cycling time trial (TT). Pain tests were separated by 30-min and exercise tests separated by 45-min to allow recovery. During the second visit, participants performed a previously described RPE clamp trial (Tucker et al. 2006) on a cycle ergometer. During the final visit, participants completed a final performance 16.1-km TT.

VO_{2max} Test (GXT)

On a cycle ergometer (Lode Excalibur, Lode Medical Technology, Groningen, The Netherlands), participants initially completed a 5-min warm-up at 75 W, followed by an incremental ramp protocol which started at 100 W and increased by 30 W $2 \cdot min^{-1}$ until volitional exhaustion or when cadence dropped 5 RPM below the participants' self-selected cadence. Participants were given instructions to rate their perceived exertion (Borg, 1998) on the 6-20 scale and to report perceived pain intensity (Cook et al., 1997) 15 s prior to the end of each stage. Oxygen consumption during the test was collected through online gas analysis (Cortex Metalyser 3B, Cortex GmbH, Lepzig, Germany), and heart rate was recorded through a telemetric device (Polar Electro, N2965, Finland). VO_{2max} was determined by a visible plateau in oxygen consumption of ≤ 2 $mL \cdot kg^{\cdot -1} \cdot min^{-1}$ with a standard increment in exercise intensity, at or around the point of volitional exhaustion.

Cold Pressor Test (CPT)

Participants were assessed for pain tolerance by using a CPT. This test involves the participant submerging their hand in iced water maintained between 0-2 °C, leading to the stimulation of the sympathetic nervous system and a high level of pain. Participants were asked to keep their hand in the iced water for as long as they could tolerate, although a cut-off time of 7-min was imposed, which was unknown to the participant (Angius et al., 2015). During the immersion, the participants reported their pain perception using the Cook numeric pain rating (0-10) scale (Cook et al., 1997). They remained seated throughout the test, which was conducted in a private room with no interference or interaction from the investigator. Before undergoing the CPT, hot/cold sensation tests were completed to ensure the participant could distinguish between hot and cold.

Pain Pressure Threshold (PPT) Test

Participants were assessed for PPT using a pressure algometer (Force Dial FDK, Wagner Instruments, CT, USA), three times, alternating between both thighs using a probe of 1 cm diameter. For the assessment of PPT, participants lay in a supine position and were instructed to report a change in sensation from pressure to weak pain. Force was applied and gradually increased (3 N/cm^2 per s) to the middle part of the rectus femoris on both legs. The rubber footplate of the algometer was held perpendicular to the muscle and the display turned away from the participant. This process was repeated three times for each leg. The average of the two nearest force values for each leg was recorded as the PPT for that limb. The mean of the PPT scores for the two legs was recorded as the participants' pain threshold.

RPE Clamp

Participants were instructed to exercise on the cycle ergometer (Veltron, Racermate, Seattle, WA) at a power output (PO) that was perceived by them to represent an RPE of 16 which corresponded to the verbal cue of between 'hard' and 'very hard', as described previously (Tucker et al., 2006). Participants were required to ride continually at an RPE of 16 and to adjust their PO so that this perceived effort was maintained. Pilot testing demonstrated this protocol to produce increases in perceived pain over time, despite the fixed rating of perceived exertion. The PO measured during the first 3-min of the trial was

averaged and provided the 'initial PO'. The RPE clamp test was terminated when participants' PO dropped to less than 70% of their initial PO (Tucker et al., 2006). Participants provided a pain perception score (Cook et al., 1997), which was recorded every 2-minutes and at the end of the trial.

Time Trial (TT)

Participants completed a 16.1-km TT on the cycle ergometer (Veltron, Racermate, Seattle, WA), as previously described (Mauger et al., 2010). Briefly, participants were required to cycle 16.1-km as quickly as they could, and were not provided with any feedback other than distance completed. Participants were asked to provide their RPE and perceived pain after every km completed. After every 4 km, a fingertip sample of blood was taken to assess the concentration of blood lactate.

Statistical Analysis

All data are reported as means ± SD. Statistical assumptions were checked for linearity, multicollinearity, additivity, independence, homoscedasticity and normality, and accepted unless otherwise stated. The highest VO_2 at the end of the VO_{2max} test was recorded as VO_{2max} and the highest sustained PO in the VO_{2max} test was recorded at the peak power output (PPO). Gas-exchange threshold (GET) was calculated from the VO_{2max} test gas data using the V-slope method (Wasserman et al. 1994). The pain reported on the termination of the RPE-clamp test was recorded as the participants' EIP tolerance. End-RPE was the highest RPE reported in the GXT. The relationship between the physiological parameters, experimental pain tests, EIP tolerance, End-RPE, and TT were established using a Pearson Bivariate two-tailed correlation. Hierarchical regression analysis was used to assess the predictive capacity of the physiological parameters (VO_{2max}, PPO, GET) on TT performance, and following this, stepwise multiple linear regression was used to determine the predictive value of experimental pain (time lasted in CPT, mean pain in CPT, PPT) EIP tolerance and End-RPE on TT performance. Finally, the significant predictors from the pain and physiological parameters were entered into a hierarchical multiple linear regression analysis to assess their predictive capacity of TT performance. All data management and statistical analysis was performed using the statistical package SPSS for

Windows, PC software, version 22 (SPSS Inc., Chicago, IL, USA). The alpha value was set at $P < 0.05$.

IV. RESULTS

All group mean values are reported in Table 3.1. Participants' pacing, physiological and perceptual responses during the TT are displayed in Figure 3.1,2,3,4,5. Correlation analysis revealed significant ($p < 0.01$) relationships between TT completion time and VO_{2max} ($R = -0.816$, $P < 0.001$), PPO ($R = -0.864$, $P < 0.001$), GET ($R = -0.454$, $P = 0.009$), End-RPE ($R = -0.736$, $P < 0.01$) and EIP tolerance ($R = -0.833$, $P < 0.01$). There was no correlation ($P > 0.05$) between measures of experimental pain and TT performance (mean pain in CPT; $R = 0.222$; time lasted in the CPT; $R = -0.292$; PPT; $R = -0.016$), which are displayed in Figure 3.2. Correlation analysis demonstrated significant ($P < 0.01$) relationships between EIP tolerance and GET ($R = 0.473$, $P < 0.01$), VO_{2max} ($R = 0.770$, $P < 0.01$) and PPO ($R = 0.757$, $P < 0.01$).

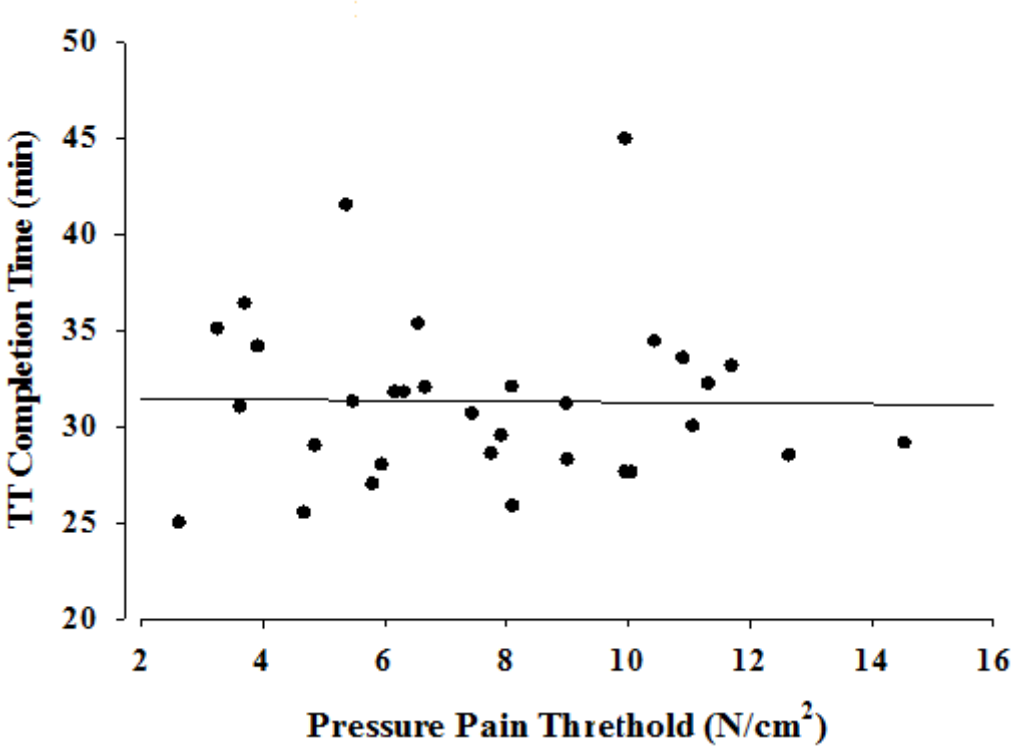


Figure 3.1 Correlation between time trial completion time and combined limb pain pressure threshold ($R = 0.016$, $P > 0.05$).

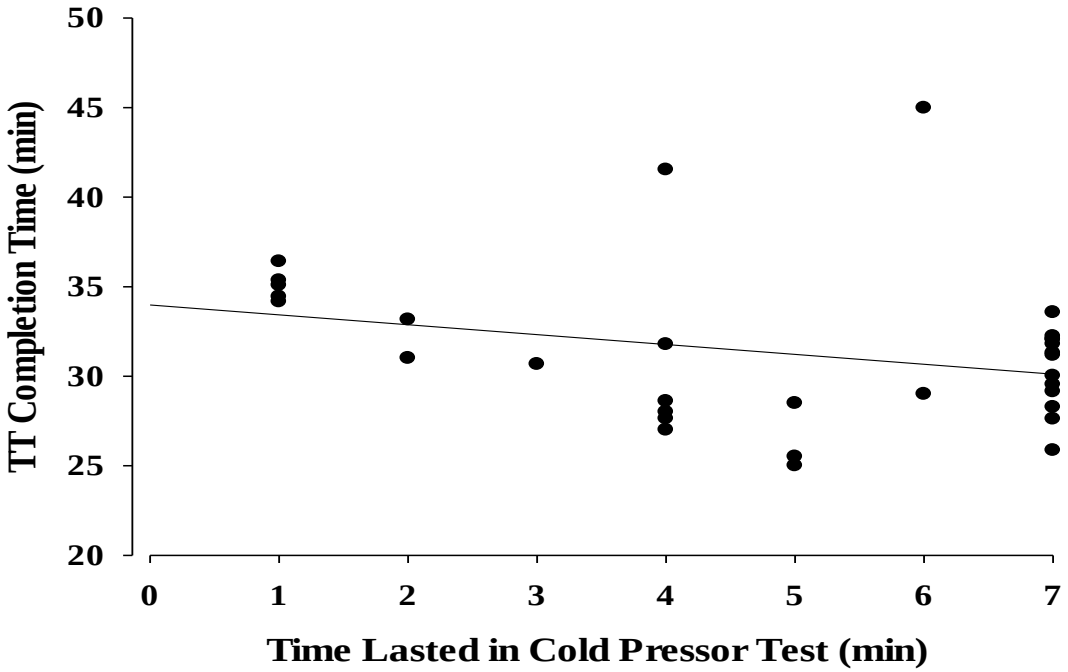


Figure 3.2 Correlation between time trial completion time and time lasted in cold pressor test (R = 0.292, P > 0.05).

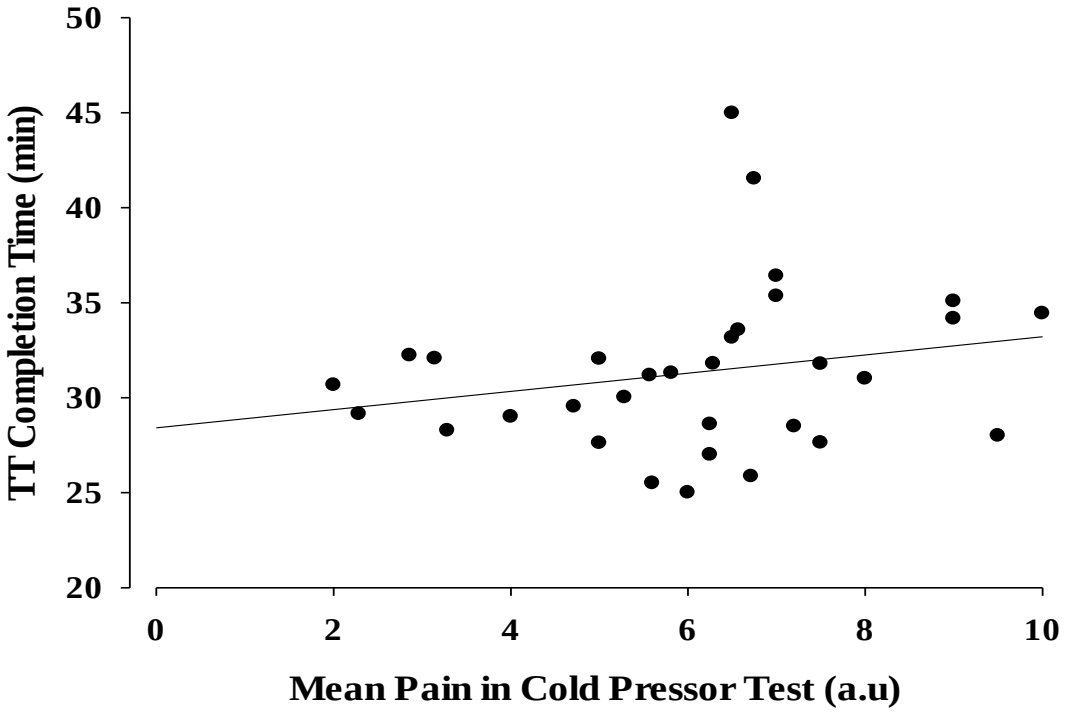


Figure 3.3 Correlation between time trial completion time and mean pain score in cold pressor test (R = 0.222, P > 0.05).

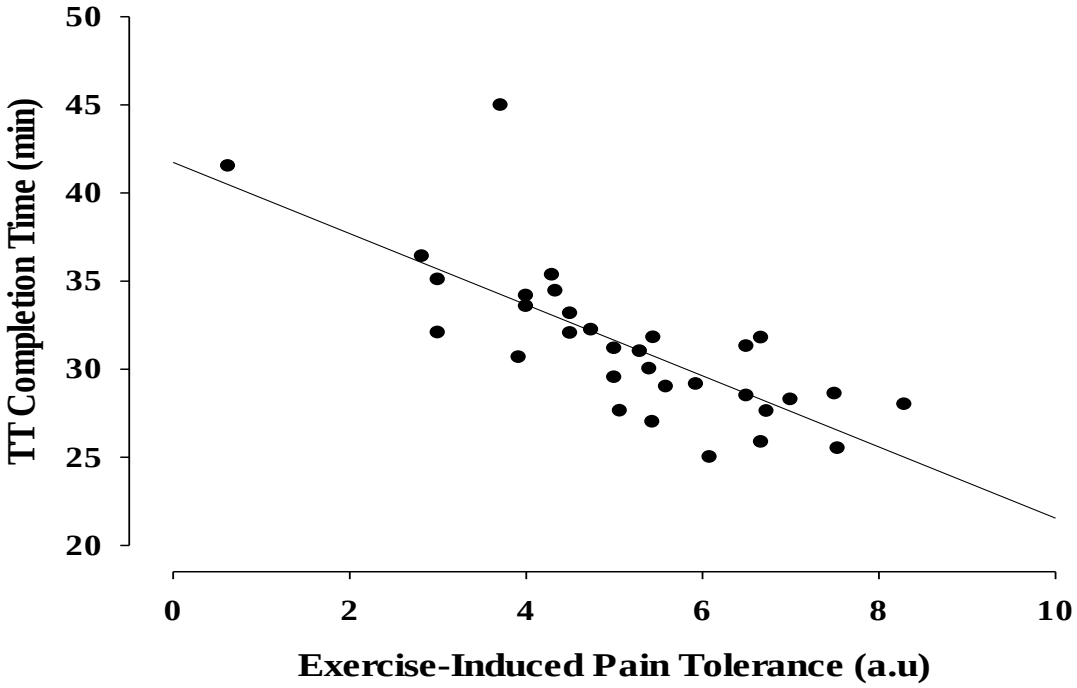


Figure 3.4 Correlation between time trial completion time and exercise-induced pain tolerance (R = 0.833, P < 0.05)

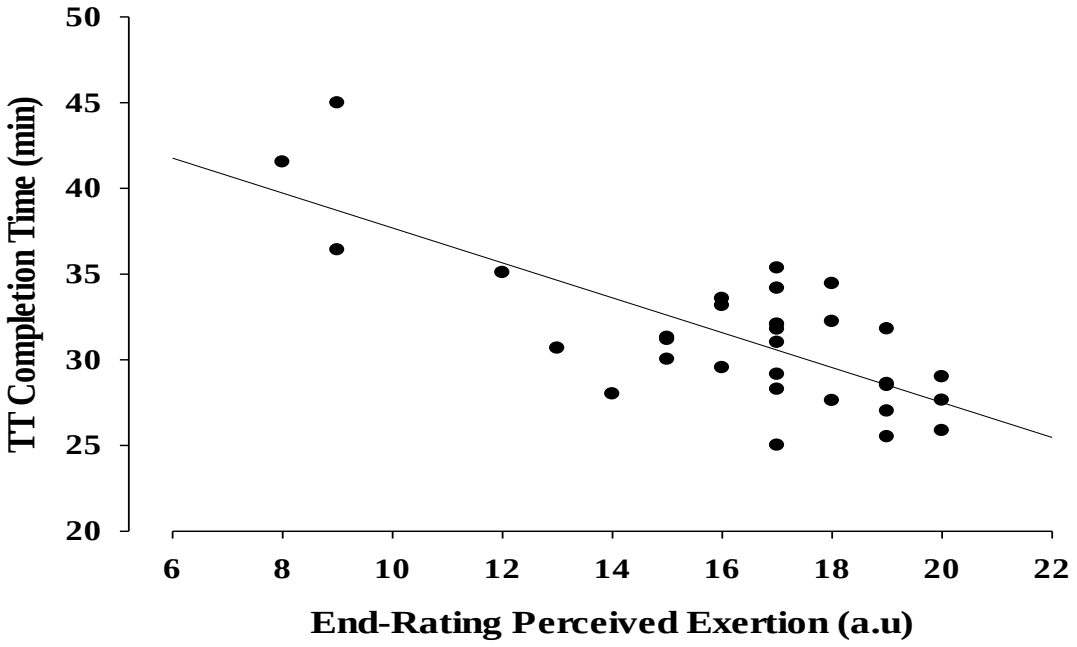


Figure 3.5 Correlation between time trial completion time and (e) end rating perceived exertion (R = -0.736, P < 0.05).

Hierarchical multiple regression for physiological parameters (VO_{2max}, GET and PPO) revealed that a significant model emerged ($F_{(1,30)} = 88.586$, $P < 0.01$) when only PPO was used to predict TT completion time. PPO explained 74.7% variance (R Square = 0.747, Adjusted R Square = 0.739, ΔR Square = 0.747, $F_{(1,30)} = 88.586$, $P < 0.01$, Beta = - 0.864).

Stepwise regression for pain predictor variables (mean pain in CPT, time lasted in the CPT, PPT, EIP tolerance, and End-RPE) revealed that all variables with the exception of time lasted in CPT and End-RPE contributed to a predictive model. EIP tolerance predicted TT completion time and explained 69.4% variance (R Square = 0.694, Adjusted R Square = 0.684, ΔR Square = 0.694, $F_{(1, 30)} = 68.075$, $P < 0.01$, Beta = - 0.833), PPT explained additional 4% variance (R Square = 0.040, Adjusted R Square = 0.716, ΔR Square = 0.040, $\Delta F_{(1, 29)} = 4.390$, P = 0.045, Beta = - 0.886), and mean pain in CPT also explained additional 4.4% variance (Square = 0.044, Adjusted R Square = 0.754, ΔR Square = 0.044, $\Delta F_{(1, 28)} = 5.543$, P = 0.026, Beta = - 0.881). Therefore, EIP tolerance, PPT and mean pain in CPT explained 77.8% variance in TT completion time.

Hierarchical multiple regression for PPO, EIP tolerance, PPT and CPT revealed that a significant model emerged only when PPO and EIP tolerance were used to predict TT completion time. PPO explained 74.7% variance (R Square = 0.747, Adjusted R Square = 0.739, ΔR Square = 0.747, $F_{(1, 30)} = 88.586$, $P < 0.01$, Beta = - 0.547), and EIP tolerance contributed an additional 7.5 % variance (R Square = 0.075, Adjusted R Square = 0.810, ΔR Square = 0.075, $\Delta F_{(1, 29)} = 12.221$, P = 0.002, Beta = - 0.419). Therefore, PPO and EIP tolerance explained an overall 82.2% variance in the model.

Table 3.1 Group mean values across all pain and exercise tests

Variable	Mean ± SD
VO_{2max} (mL/kg/min)	48 ± 8
Anaerobic Threshold (W)	146 ± 43
Anaerobic Threshold (mL/kg/min)	30 ± 6
Peak Power Output (W)	252 ± 66
GXT End-RPE	16.43 ± 3.14
GXT End-pain	6.43 ± 2.70
Mean pain in CPT	6.06 ± 1.98
Time lasted in CPT (min:sec)	4:49 ± 2:14
Pain Pressure Threshold (kPa)	76 ± 29
RPE clamp time to exhaustion (min:sec)	28:35 ± 13:40
Tolerance of Exercise Induced Pain	7.23 ± 2.02
RPE clamp mean pain	5.16 ± 1.59
RPE clamp mean Power Output (W)	171 ± 47
Time trial mean VO_{2max} (mL/kg/min)	39 ± 7
Time Trial mean Power Output (W)	184 ± 57
Time trial end blood lactate (mmol)	9.69 ± 2.28
Time Trial mean pain	4.62 ± 1.47
Time Trial end pain	7.25 ± 2.24
Time Trial mean RPE	14.8 ± 1.9
Time Trial end RPE	18.1 ± 2.
Time trial completion time (min:sec)	31:11 ± 4:28

RPE, rating of perceived exertion; CPT, cold pressor test.

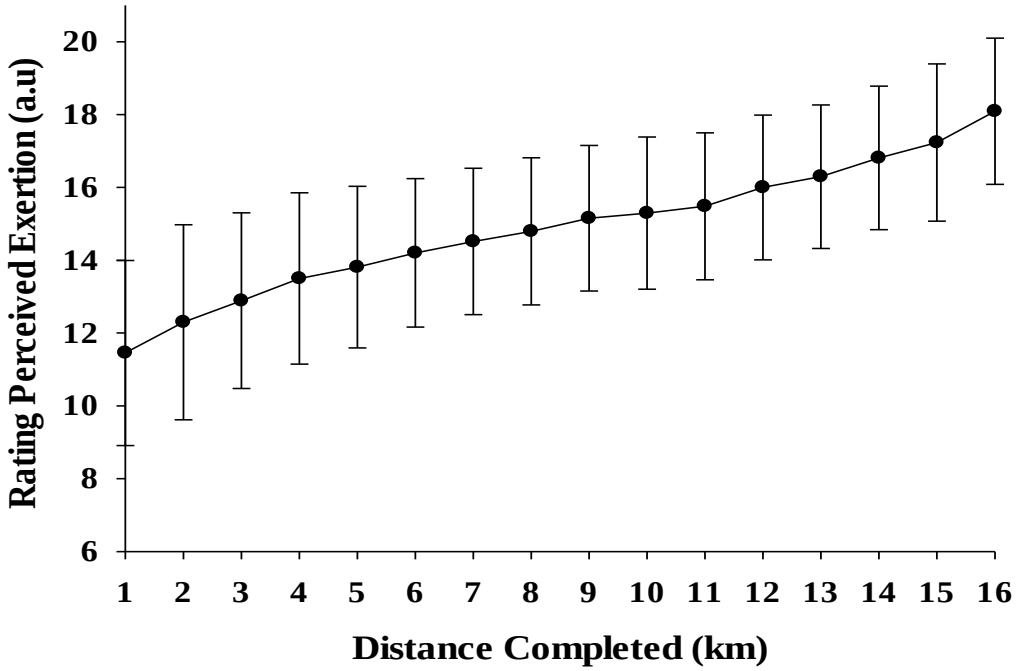


Figure 3.6 Rating perceived exertion profile during the 16.1-km cycling time trial performance.

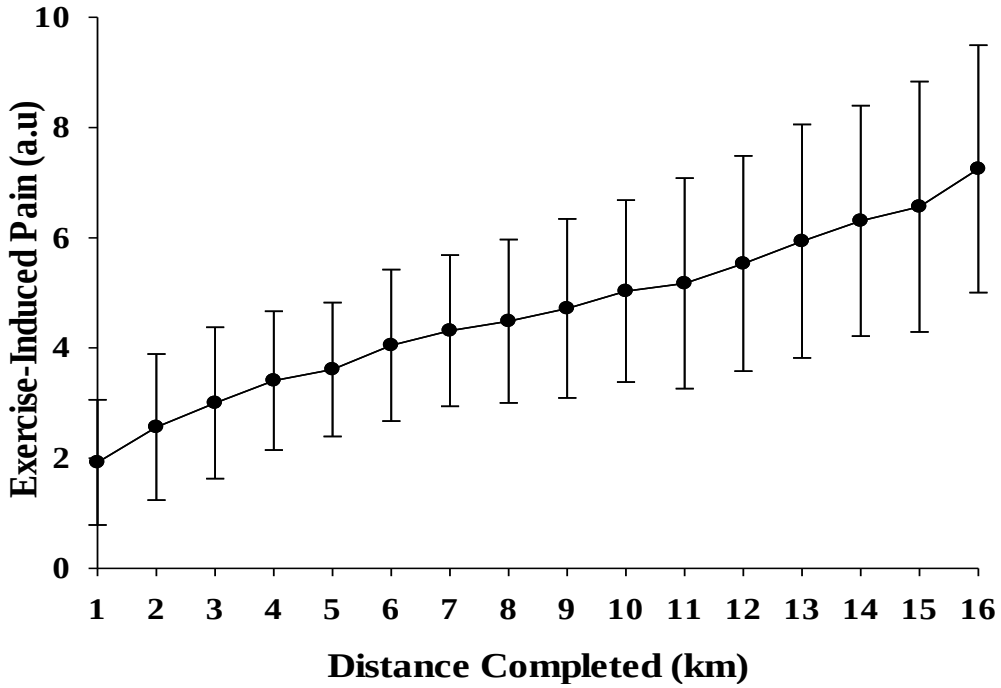


Figure 3.7 Exercise-induced pain profile during the 16.1-km cycling time trial performance.

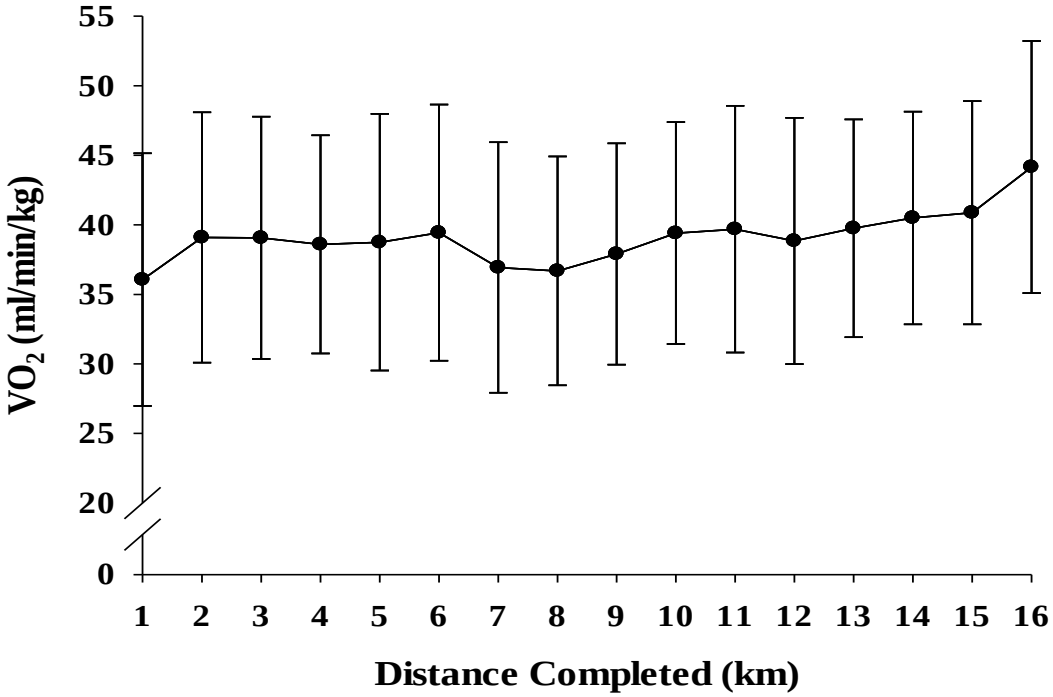


Figure 3.8 VO_2 profile during the 16.1-km cycling time trial performance.

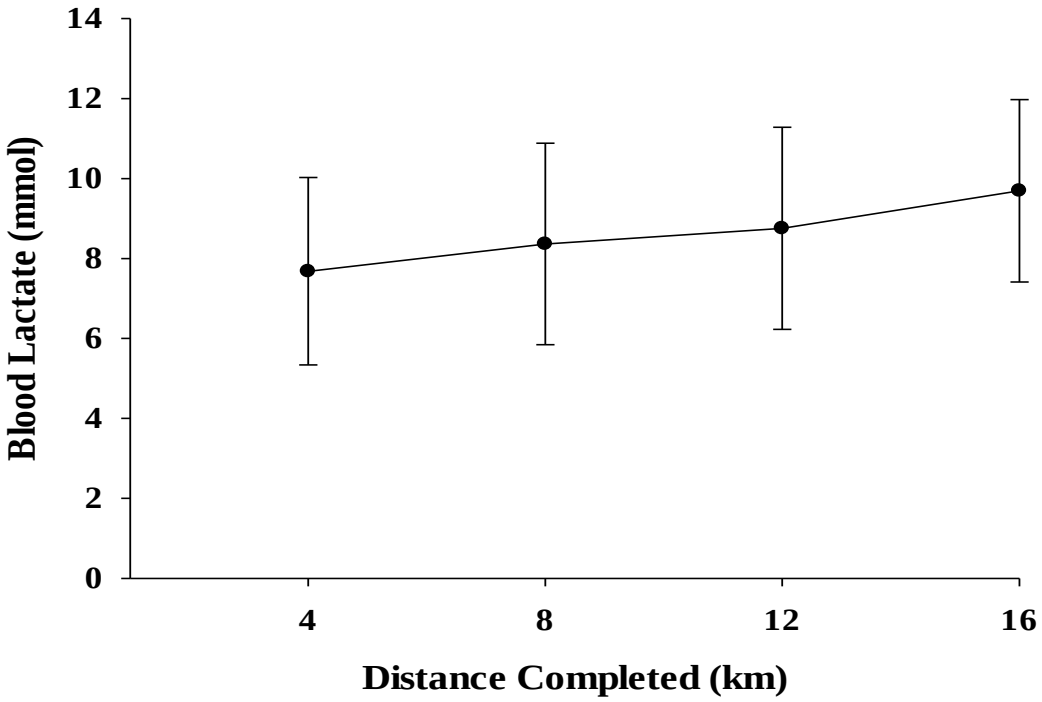


Figure 3.9 Blood lactate profile during the 16.1-km cycling time trial performance.

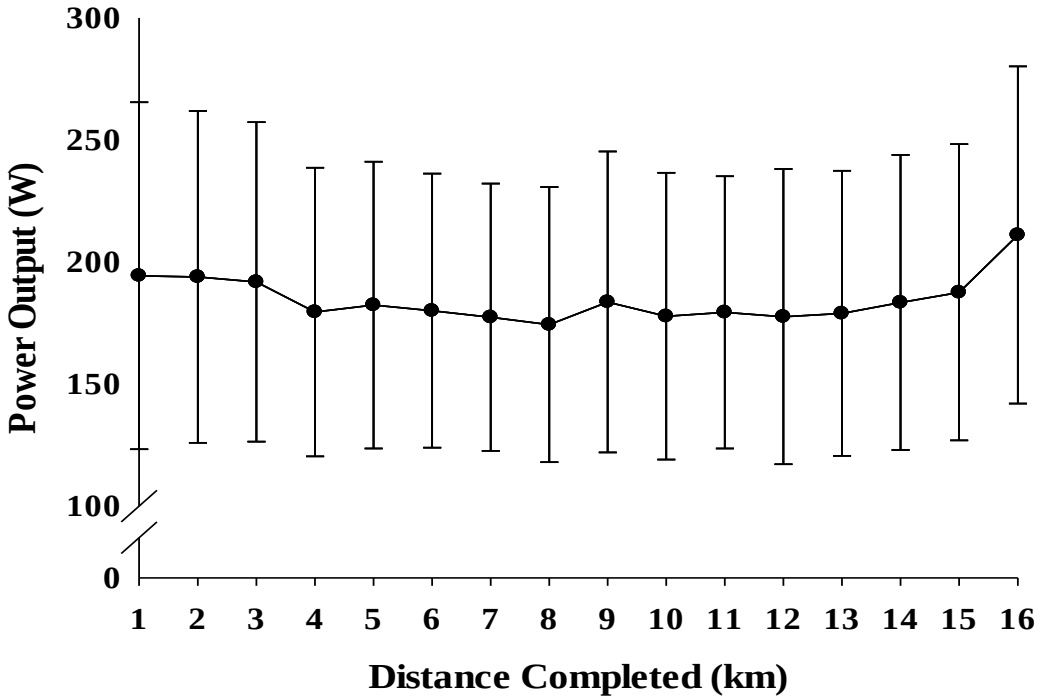


Figure 3.10 Power output profile during the 16.1-km cycling time trial performance.

V. DISCUSSION

The primary aim of this study was to examine the relationship between pain tolerance (CPT duration), pain threshold (PPT), EIP tolerance and cycling time trial performance. The primary and novel finding was that tolerance of EIP explained considerably more variance in cycling TT performance than pain threshold and tolerance assessed through algometry and a CPT (respectively). Therefore, participants who were willing to engage in greater amounts of pain during fixed effort exercise were generally able to produce faster 16.1-km times. This is an important finding, as traditional measures of pain tolerance and threshold (such as algometry and the CPT) are often used to inform discussion on the tolerance of the pain arising from intense exercise. As the results of the current study show that these traditional pain measures explain little variance in endurance performance (compared to tolerance of EIP), it suggests that the importance of a high pain tolerance to endurance performance may have been previously underestimated. This novel finding demonstrates the need to use experimental pain measures which replicate the aetiology of EIP when investigating the role of pain arising from intense exercise. This is further reinforced by

the observation that when combined with physiological predictors of endurance performance (VO_{2max}, PPO, GET), only PPO and EIP tolerance could explain the variation in TT performance. This infers that both tolerance of EIP and physiological parameters need to be taken into account when explaining endurance performance.

The current study is the first to directly use EIP tolerance as a predictor of endurance performance and to demonstrate the importance of using an appropriate method for pain induction in exercise/pain studies. Our data shows that pain tolerance (mean pain in CPT) during a CPT and pain threshold (pressure corresponding to weak pain) via algometry explain only limited variance in endurance performance (4.4% and 4% respectively), which is striking given the variance explained by EIP tolerance (69.4%). When combined with the physiological performance parameters, CPT and PPT had no predictive capacity, whereas EIP was still able to explain an additional 7.5% variance after PPO had explained 74.7% variance in the model. This demonstrates that the method used to induce experimental pain should replicate the type of pain experienced as closely as possible, and may partly explain the lack of agreement in previous research that attempts to explain the relationship between pain and exercise performance. Although the method of inducing EIP in the current study is a step-forward in quantifying its role in endurance performance, developing an experimental pain model which replicates EIP in resting conditions is still important. Although some studies have achieved this through the use of intramuscular saline injection (Khan et al., 2011) or biochemicals (Pollak et al., 2014), these studies are limited and there still remains a need to apply this technique to whole-body exercise. Perception of pain is generally assessed in research through the use of thermal, pressure and electrical stimuli to promote an algesic response. Consequently, it is these methods which have usually been applied to studies that examine the relationship between exercise and pain (Ellingson et al., 2012; Janal et al., 1994; Ruble et al., 2005; Vaegter et al., 2015). This may have misrepresented the importance of EIP, as the pathway between nociception to pain perception is a hugely complex process, and different types of painful stimuli follow different processing pathways and consequently evoke very different responses (Olesen et al., 2012), as our data supports. This is one of the key reasons why particular analgesics are more effective in treating different types of pain. Pain arising from intense, repetitive and rhythmical movement, which is consentient with endurance exercise, is likely produced through a combination of increased intramuscular pressure, release of

noxious metabolites and deformation of tissue associated with muscular contractions (Ellingson et al., 2014). Thus, in order to adequately examine the role of EIP in exercise performance, the experimental pain used should try to emulate the environment and aetiology of EIP as closely as possible. Therefore, whilst algometry may be a useful means to assess specific hyperalgesia of muscles (for example in delayed onset muscle soreness (Close et al., 2006) and fibromyalgia (de Carvalho et al., 2012)), it does not adequately represent EIP, and thus, we recommend that its use in the assessment of this phenomenon should be avoided. The mechanisms causing the perception of pain during a CPT are so far removed from the sensation of EIP (Olesen et al. 2012), that its use is also questionable when assessing the role of pain in exercise performance.

It has previously been suggested that the tolerance of EIP is an important prerequisite for endurance performance (Mauger, 2013, 2104). Whilst this notion is well-supported through interviews with athletes and coaches (Kress & Statler, 2007), given the emphasis placed on this parameter there is comparatively little empirical evidence to convincingly substantiate these beliefs. Whilst studies have been able to demonstrate that EIP is proportional to exercise-intensity (Cook et al., 1997), and that using an intervention to reduce pain (such as caffeine or paracetamol) can improve exercise performance (Astorino et al., 2011; Astorino et al., 2012; Foster et al., 2014; Hudson et al., 2008; Jenkins et al., 2008; Mauger et al., 2010, 2014), the design of these studies generally mean that whilst performance can be improved, differences in pain between conditions are masked (i.e. not different). This may be because participants regulate their intensity based on their pain perception (Mauger, 2014), but therein lies an assumption that the intervention has elicited analgesia, and that it is this analgesia which has allowed an improved performance. This inference is further questioned by studies which employ an analgesic intervention which elicits no change in pain or performance – a common finding when aspirin and dietary ginger are used (Black & O'Connor 2008, 2010; Cook et al., 1997; Hudson et al., 2008). However, studies which increase pain during exercise through intramuscular saline injections (Graven-Nielsen et al. 2002; Khan et al. 2011) and muscle damage (for example; Black & Dobson, 2013) have shown that performance is decreased, thus providing further support for the notion that pain perception influences exercise performance. A recent study (Gonglach et al., 2015) used a novel 'pain-clamp' exercise trial to examine the analgesic effect of caffeine on exercise performance, and further substantiates this view. The use of

the pain-clamp in this study (Gonglach et al., 2015) provides more direct evidence that a reduction in pain can lead to an improved endurance performance. Thus, despite the methodological constraints of previous studies, the majority of the literature is supportive of the concept that pain tolerance is an important pre-requisite to endurance performance. To our knowledge, the data from the current study is the first to meaningfully quantify this relationship, and shows that the recreationally active in this study participants who were willing to engage in greater amounts of pain in a separate exercise trial exhibited better performances in the TT. The linear relationship between perceived pain and work-rate (Cook et al., 1997) likely underpin this observation – if higher work rates produce greater levels of pain, then for a faster completion time an athlete must be willing to endure significant amounts of pain in order to maintain competitive work rates. For the athlete who will not or cannot endure higher levels of pain, they must adhere to lower work rates in order to prevent pain from progressing to intolerable levels - in the current study, participants with worse TT completion times were apparently unwilling to maintain sufficiently high PO in the RPE-clamp because they could not tolerate the pain that this would induce. Although changes in work rate during self-paced exercise may be partly regulated by pain perception (and therefore performance predicted by pain tolerance), the relationship between pain and performance is likely more complex than this. Indeed, it appears that analgesia may only be effective during less painful exercise (Gonglach et al., 2015), and that complete analgesia negatively affects the pacing response (Amann et al., 2009). Therefore, it may be that pain is used to help regulate pacing during exercise (in addition to a host of other variables), but that this regulation is overly conservative so that higher levels of peripheral fatigue could be tolerated (if pain were reduced).

When traditional predictors of endurance performance (VO_{2max}, GET, PPO) were combined with the significant pain threshold/tolerance predictors (EIP tolerance, PPT and time lasted in CPT) in the regression analysis, only PPO and EIP tolerance arose as significant contributors to predicting TT performance. This observation supports the notion that both physiological and psychological components should be accounted for in endurance performance. The factors affecting endurance performance have been well-argued (Joyner & Coyle, 2008; Marcora, 2010; Tucker, 2009), but perhaps the most widely accepted is that of Joyner and Coyle's (2008) model of endurance performance, which uses solely physiological parameters to predict performance. Clearly, these factors are integral

because they provide the limits of the body's 'race velocity'. However, they are unable to explain day-to-day variation between performances, variation between individuals with similar values, and changes in velocity within a race (when even pacing is the optimal strategy). Tolerance of EIP and pain perception during exercise may help explain these issues, because these traditional performance parameters (VO_{2max}, GET, PPO) will partly determine the size of the nociceptive signal for a given velocity. Indeed, EIP arises as a result of the build-up of noxious biochemicals (O'Connor & Cook, 1999) combined with increased intramuscular pressure, and the point at which this increases significantly is partly dependent on the transition from steady-state to non-steady-state exercise. This is because many of these noxious biochemicals are produced when energy is derived from anaerobic sources. However, it is well-known that perceived pain is ultimately a subjective experience, which is not always dependent on the size of the nociceptive signal. Therefore, whilst the physiological parameters of endurance performance may dictate the peripheral conditions for pain, how this is perceived and acted on by the athlete will depend on a multitude of other psychological and perceptual factors (Kress & Statler, 2007). This suggests that endurance performance is not solely a product of the peripheral factors of the Joyner and Coyle (2008) model (which may dictate the state of the peripheral muscle for a given velocity), and that the pain and discomfort arising from the interpretation of the intramuscular environment (and its effect on decision making) should be recognised. However, it should be stated that in the current study, peak power output still explained the greatest variance in TT performance (~75%), with tolerance on EIP pain explaining an additional 7.5%. Therefore, the contribution of EIP tolerance to the endurance performance model (for the participant group for this study) is 10% of that explained by traditional physiological factors. Consequently, physiological capacity is still of primary importance in explaining endurance performance, although the current data suggests a smaller, but nonetheless important role for EIP tolerance. Indeed, in the current study, for a participant in the upper part of the third quartile for TT completion time, performance variation explained by EIP tolerance could be sufficient to move them into the upper second quartile. It is important to note that the participants in the current study, whilst recreationally active, were not trained cyclists. It has previously been suggested that physical activity (Ellingson et al., 2012) and regular, specific endurance training (Scott & Gijsbers, 1981) decrease pain perception. Therefore, the variance in endurance performance explained by EIP

tolerance in this study is likely specific to the participant population and should not be assumed to be similar in trained or highly trained individuals. However, none of the previous studies investigating the differences in pain perception between untrained and trained individuals have used EIP as a measure of experimental pain, and as previously discussed, this limits the understanding of this pain/exercise relationship. Indeed, the relationship between pain threshold/tolerance and training appears complex, with exercise training appearing to improve pain tolerance in some tests (e.g. CPT) but not others (Janal et al., 1994). Therefore, future research should seek to further explore the influence of training on pain perception, using an experimental pain model that replicates EIP.

The lack of previous research discussing the role of pain in exercise performance may be due to the type of exercise task traditionally used in exercise science. In addition, sensation of pain is often measured and discussed as part of perception of effort and fatigue (Sgherza et al., 2002), and this may have affected wider understanding of the specific role of pain. Until relatively recently, research investigating fatigue and perception of effort has tended to rely on time to exhaustion and fixed intensity tests (Mauger, 2013). However, contemporary research has started to use self-paced exercise models, which can elicit a different response and is more applicable to exercise performance (than fixed work rate models). In the current study, it is interesting to note that the end pain scores reached in the RPE clamp trial (where PO was free to vary), and the self-paced TT were very similar (7.23 ± 2.02 and 7.25 ± 2.24 respectively), and that the end pain in the VO_{2max} test (where PO was externally controlled) was much lower (6.31 ± 2.70). This is a similar observation to previous pain studies (Cook et al. 1997), where relatively low pain responses were reported for fixed intensity exercise of moderate intensity and for a maximal incremental test. Therefore, it may be that the nature of self-paced exercise provides conditions where the athlete is able and/or willing to reach considerably higher levels of EIP in comparison to fixed intensity exercise. Therefore, the importance of EIP with respect to performance in fixed intensity exercise may be different to that of self-paced performance, and thus its importance may have been previously underestimated. Future research should seek to use self-paced exercise models to examine the effect of pain on endurance performance.

VI. CONCLUSION

This study demonstrates that EIP plays an important role in moderate duration endurance performance for recreationally active participants, and that a high tolerance for EIP provides an important performance advantage. Because the magnitude of perceived pain depends on a host of factors, not always related to the size of the nociceptive stimulus, it is important that psychological performance parameters (in this case pain), are considered alongside the physiological. When assessing pain threshold and tolerance, it is important to account for the aetiology of the pain type, as this has consequences for its perception. Therefore, when examining the pain-exercise relationship, induction of experimental pain through the CPT and algometry should be avoided, as this bear little relevance to EIP. Consequently, future studies looking to investigate the role of EIP should try to replicate the correct aetiology of pain as closely as possible.

CHAPTER 4

EXPERIMENTAL 2nd ST

Task deception using a Mirror Box can influence the time-to-exhaustion of an isometric voluntary contraction

Ali HY. Astokorki[1], Alexis R. Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK

I. ABSTRACT

INTRODUCTION: Ramachandran's mirror box technique has previously been used to treat pain arising from clinical conditions, by creating an illusion of a hidden limb. We sought to use this technique to deceive participants about the difficulty of an exercise task, to examine whether this deception would moderate exercise-induced pain (EIP) and rating of perceived exertion (RPE), and whether this would influence endurance performance. **METHODS:** 42 participants were allocated into a Control (No Mirror) and Experimental (Mirror) group. In the first experimental visit, all participants performed three separate isometric elbow flexion tasks of 20% of their one repetition maximum (1RM) until exhaustion in both arms simultaneously. In the second visit, participants in the Control group repeated the same task as visit 1. Participants in Experimental group performed the same task but with their arms in a mirror box, and unbeknown to the participant, on two of the tests the hidden arm lifted 15%1RM and 25%1RM. Time to exhaustion, RPE and EIP was recorded for each of the tests. **RESULTS:** The deception of task difficulty in the Experimental group led participants to produce significantly longer times to exhaustion when they thought the task was easier than it was, and significantly shorter times to exhaustion when they thought it was harder than it was ($F_{(1,40)} = 4.293$, $P = 0.045$). The ANOVA revealed a significant main effect of condition for EIP during the TTE test ($F_{(1, 40)} = 8.736$, $P = 0.005$), and a significant interaction effect of EIP between groups for each time condition were observed ($F_{(1,40)} = 7.163$, $P = 0.011$). The ANOVA revealed a significant main effect of condition for RPE during the TTE test ($F_{(1, 40)} = 33.403$, $P < 0.001$), and a significant interaction effect of RPE between groups for each time condition ($F_{(1,40)} = 13.367$, $P < 0.001$). This was accompanied by significantly higher EIP and RPE when they thought the task was harder than it was, and significantly lower EIP and RPE when they thought the task was easier than it was. **CONCLUSION:** This study demonstrates that expectations about task difficulty and its associated perceptions influence subsequent performance. These findings show that EIP and RPE were partly based on the expected task, and exercise performance was positively or negatively impacted by the deception.

II. INTRODUCTION

Ramachandran's mirror box technique (Ramachandran and Rogers-Ramachandran and Cobb, 1996) is a promising intervention that is commonly used to treat hemiparesis following stroke, phantom-limb pain, and complex regional pain syndrome. It can also lead to better motor outcomes, and it is reported to have analgesic benefits on intractable pain conditions (Ramachandran & Altschuler, 2009). The technique involves participants viewing one limb (for example; the left arm) and a reflection of it in the mirror, thus creating the illusion of viewing both arms, despite the fact the participants only see the reflection of their left arm in the mirror. How the mirror box is capable of treating both acute and chronic pain conditions is the matter of debate, largely because the processing of pain throughout the brain is complex and involves multiple primary and secondary regions. Indeed, brain functional imaging of neuronal activity has identified that multiple brain regions are modulated and activated by nociceptive stimuli (Price, 2000). However, some nociceptive regions remain unknown and often processing involves several non-nociceptive activations which reflect secondary processes, such as anticipation, attention, affect, and cognitive aspects of pain perception (Buchel et al., 2002; Coghill et al., 1999; Derbyshire et al., 1997; Rainville et al., 1997). One area of primary importance is the insular cortex, which sustains many connections throughout the brain network, including the primary and secondary somatosensory areas: auditory, visual, motor cortical areas, several thalamic nuclei, amygdalae, basal ganglia (BG), anterior cingulate, prefrontal cortex, and hypothalamus (Black, 2012; Augustine, 1996; Mesulam & Mufson, 1982). This demonstrates the complex nature of pain processing and the different conscious and subconscious components involved in the ultimately subjective experience of pain perception. It is likely that the mirror box is capable of attenuating pain through its effect on the mirror neurons, which are present in cerebral cortical areas of the human brain, and form a section of a complex network that is required for visual information (Rizzolatti & Craighero, 2004). The neurons in the temporal, occipital, frontal, and parietal areas (that contribute to the mirror neurons) in the premotor cortex (Iacoboni et al., 2005) are responsible for the assembly of visual and motor sensory system information and thus may play a vital role in pain as a perceptual and affective phenomenon. It is suggested that in amputees, phantom limb pain can be caused because after amputation the motor output still perceives the limb to be present, but proprioceptive and visual input is absent from the

amputated area. This incongruent information processing may lead directly to pain, and indeed, even in healthy individuals' limb pain can be induced when incongruent information is presented (McCabe et al., 2005). The mirror box essentially works by rectifying the incongruence of the visual and sensory input by creating an illusion of the missing limb. These studies demonstrate that a mirror box is capable of creating (or rectifying) an incongruent environment between expectation and reality.

Intense and repetitive or prolonged muscular contraction produces a metabolic environment in and around the muscle that sensitises and stimulates peripheral nociceptors. The consequence of this is that prolonged exercise causes a level of discomfort and pain that is proportional to exercise intensity and/or exercise duration (Cook et al., 1997). However, in most exercise scenarios there is a host of external factors, independent of the metabolic environment in the muscle (i.e. the size of the nociceptive signal), which have the potential to moderate the overall pain perception or intensity. Indeed, participant's mood, a different level of motivation, or task distraction have all been shown to reduce pain perception in experimental studies (Atlas & Wager, 2012), and these factors are changeable in most forms of exercise. This is important because it is suggested that exercise-induced pain (EIP) can limit or predict endurance performance (Astokorki & Mauger, 2016) and may pose a barrier to engaging in physical activity. Whilst it is difficult to repeatedly and safely reduce the size of the nociceptive signal during exercise (although this has been shown to improve exercise performance using analgesic drugs, it is not recommended as a strategy – Mauger et al., 2010, Foster et al., 2014), there may be scoped to moderate the psychological processing of pain during exercise. However, this possibility has not yet been investigated.

The purpose of the current study was to use the mirror box technique to investigate whether pain arising from exercise could be attenuated by changing participant's perception of the exercise task. The mirror box was used to create the illusion that participants were lifting either a heavier, or lighter mass than they actually were. It was hypothesised that when participants thought they were lifting a heavier mass, pain would be increased and time to exhaustion would be reduced. Whereas when they thought they were lifting a lighter mass, pain would be decreased and time to exhaustion would improve.

III. MATERIALS AND METHODS

Participants:

Forty-two recreationally active, male (n=29) and female (n=13) participants were recruited for this study. Participants' mean age, height and body mass were 23 ± 4 years, 176 ± 10 cm and 70.73 ± 12.5 kg respectively. Individuals suffering from the following conditions were excluded from the study; a history of mental or brain disorders, cardiovascular disorders, types I and II diabetes, and those taking chronic medications that affect the central nervous system. Participants were informed that all data would be unidentifiable and that they had the right to withdraw from the experiment at any time. Following this, they were asked to complete a health questionnaire followed by an informed consent form. The study was approved by the local Ethics Committee of the University of Kent. Participants reported to the laboratory on two separate experimental visits. For 24 h before each visit, participants refrained from any vigorous exercise, and asked to refrain from the ingestion of alcohol, caffeine and analgesics 48 h, 8 h and 6 h prior to any visit (Lu, Lai & Chan, 2008). The time interval between the two experiments was 2-7 days. Following Visit 1, participants were allocated to either a control group (No Mirror) or an experimental group (Mirror). Group allocation was made according to participants' time to exhaustion (TTE) time achieved during Visit 1 so that TTE times were evenly balanced between groups (Mirror = 570 ± 265 s; No Mirror = 571 ± 148 s). This resulted in 21 participants (male = 15, female = 6) in the control group and 21 participants (male = 14, female = 7) in the experimental group.

Procedures

Following a separate familiarisation session of the procedures, in this first visit, participants performed a one repetition maximum (1RM) contraction of the bicep muscle to familiarise them with the isometric time to exhaustion (TTE) exercise task. In a seated position, with their elbow rested on a pad on a table in front of them, participants lifted a series of increasingly heavier dumbbell weights through 90 degrees of elbow flexion (forearm resting on table at 0° followed by elbow flexion to forearm to 90°). Starting weight and weight increments were estimated by experimenter and participant to minimise the number of lifts required to reach 1RM. One to 3-min rest were provided between each contraction so that the participant was adequately rested for each attempt. This process was

repeated for both dominant and non-dominant arms and all participants received strong verbal encouragement throughout each contraction. Following a 20-min period of rest, participants then performed an isometric TTE bicep contraction of both arms at 20% 1RM. Participants held the dumbbells in the required position (elbow joint at 90° with elbow rested on table, with forearm and upper arm each at 45° to table surface) with both arms until they could no longer maintain the contraction. Every 45 s during the TTE, participants were asked to report their muscle pain using a numeric pain rating scale (Cook et al., 1997) and their rating of perceived exertion (RPE) using the Borg (6-20) scale (Borg, 1998). Participants were instructed to report RPE solely as effort to drive the limb (Pageaux et al., 2015) (i.e. independent of pain and discomfort) and that pain should be anchored to exercise-induced pain (i.e. numeric values given relative to their experience of muscle pain).In the second visit, participants were asked to perform a similar TTE task as described above, however participants were required to complete three TTE tests holding 20% of their 1RM in the non-dominant hand and 20%, 25% and 15% of their 1RM in the dominant hand, in a randomised order and with 20-min recovery between each TTE. The No Mirror (Control) group could see both arms, however, the Mirror (Experimental) group performed the task with their arms inside a mirror-box (Ramachandran et al, 1995). The mirror-box consisted of a mirror placed in the sagittal plane between two arm holes. One side of the box was covered allowing participants to only see their non-dominant hand, however due to the mirror placement, the image of the non-dominant hand was superimposed onto the dominant hand so the participants believed they could see both hands. To facilitate this illusion, participants in the Mirror group were given a period of 10-min before the TTE tasks to move their hands simultaneously until they perceived their non-dominant hand as the dominant (i.e. participants only saw their non-dominant hand and its reflection, but perceived the reflection to be their dominant hand). The result of the illusion was that participants in the Mirror Group believed that they were always lifting 20%MVC in both hands, whereas they were actually lifting; 20% and 20%, 20% in the non-dominant hand and 15%, and 20% and 25% in the dominant hand (see Figure 4.1). This illusion was reinforced by the investigator telling the participant that they were replicating the task from Visit 1 three times (i.e. always lifting 20%1RM in both hands). In the same manner as Visit 1, RPE and pain were recorded every 45 seconds. Both groups

were asked to focus on both arms throughout the TTE, however no other verbal encouragement was provided in order to avoid experimenter bias.

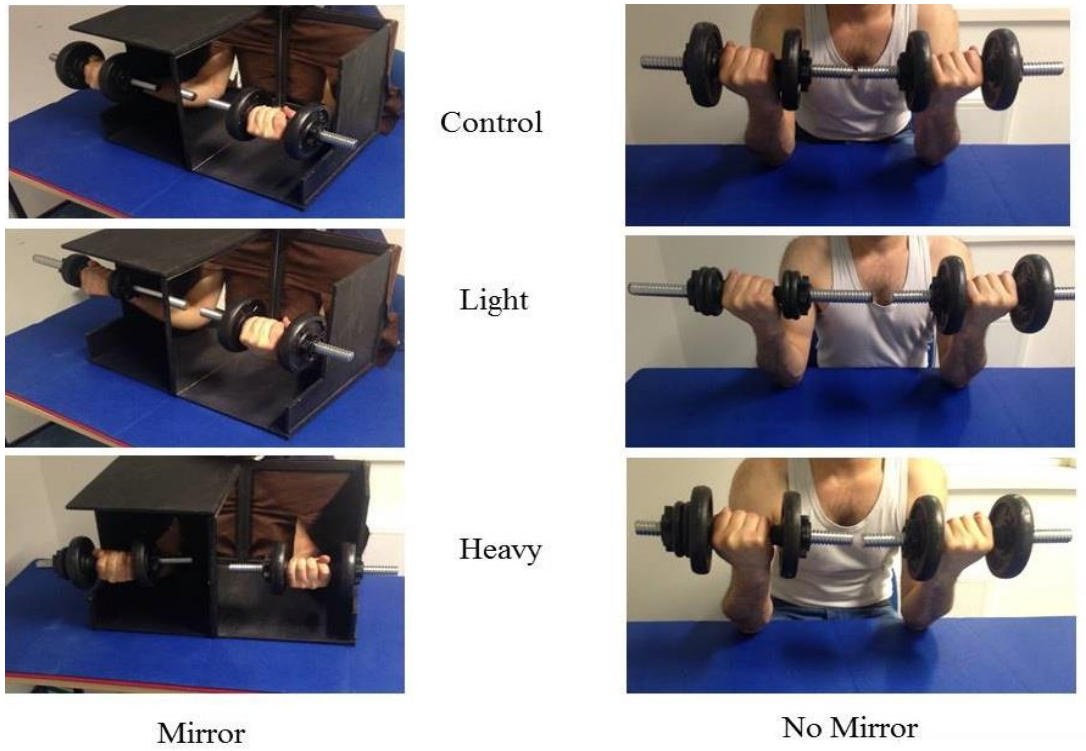


Figure 4.1 Examples of lifted and observed mass in the Mirror and No Mirror conditions.

Statistical Analysis

All data are presented as mean ± SD. Data were checked for standard assumptions (Kruskal-Wallis test and Shapiro-Wilk test) for each statistical test prior to analysis, and none of these were violated. To control for the inter-individual variability of baseline values in TTE that occurred between the two groups (Mirror and No Mirror), comparisons were made according to the percentage change from baseline TTE (20%1RM) to the mass change conditions (15%1RM (Light) and 25%1RM (Heavy)), thus creating two conditions for the analysis of TTE (ΔHeavy and ΔLight) (Tstutsumi et al., 2011). Therefore, to compare TTE time, mean exercise-induced pain and mean RPE between groups for each condition, a 2x2 ANOVA (group (mirror and no mirror) x condition (ΔHeavy and ΔLight) was employed. To compare perceptual measures (exercise-induced pain and RPE) between

conditions over time, the slope method was used to create a single value for pain and RPE to represent a change over time, as described previously (Angius et al. 2016). To do this, individual values of RPE and pain obtained during the TTE were plotted against the absolute TTE time for each condition, the curve for each variable was mathematically fitted by a linear equation to then obtain the slope. Consequently, perceptual values were analysed using a 2x2 ANOVA. All data management and statistical analysis was performed using the statistical package SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, USA). The alpha value was set at $P < 0.05$.

IV. RESULTS

Time to Exhaustion (TTE)*:* The percentage change from baseline TTE to the Light and Heavy conditions is shown in Figure 4.2. The ANOVA revealed a significant main effect of condition for the TTE test ($F_{(1,40)} = 44.113$, $P < 0.01$). A significant interaction effect of TTE between groups (Mirror and No Mirror) for each time condition (ΔLight and ΔHeavy) was observed ($F_{(1,40)} = 4.293$, $P = 0.045$). This demonstrates that participants in the Mirror (Experimental) group performed less well when they thought the mass was heavier than it was (ΔLight), and better when they thought the mass was lighter than it was (ΔHeavy).

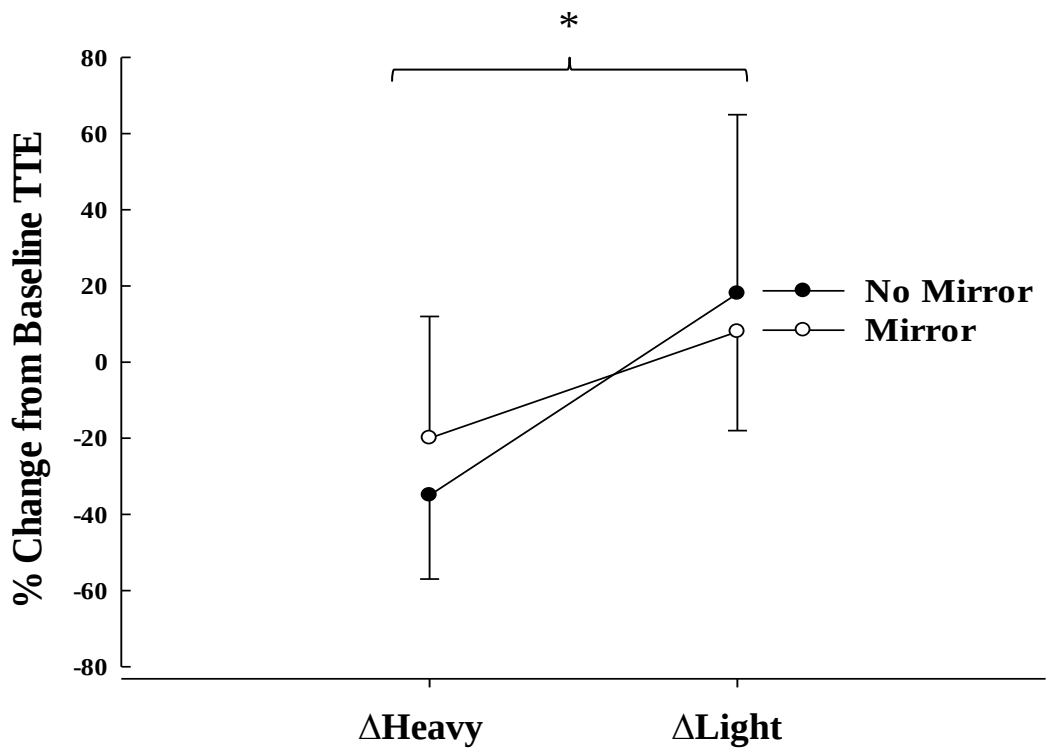


Figure 4.2 TTE elicited a significant difference between conditions. *significantly different between conditions ($P < 0.01$).

Exercise-induced pain (EIP): The ANOVA revealed a significant main effect of condition for EIP during the TTE test ($F_{(1, 40)} = 8.736$, $P = 0.005$), as shown in Figure 4.3. A significant interaction effect of EIP between groups for each time condition were observed ($F_{(1,40)} = 7.163$, $P = 0.011$). This shows that the perceived EIP for participants in the Experimental group was attenuated by the illusion that all masses lifted were the same, as shown in Figure 4.4.

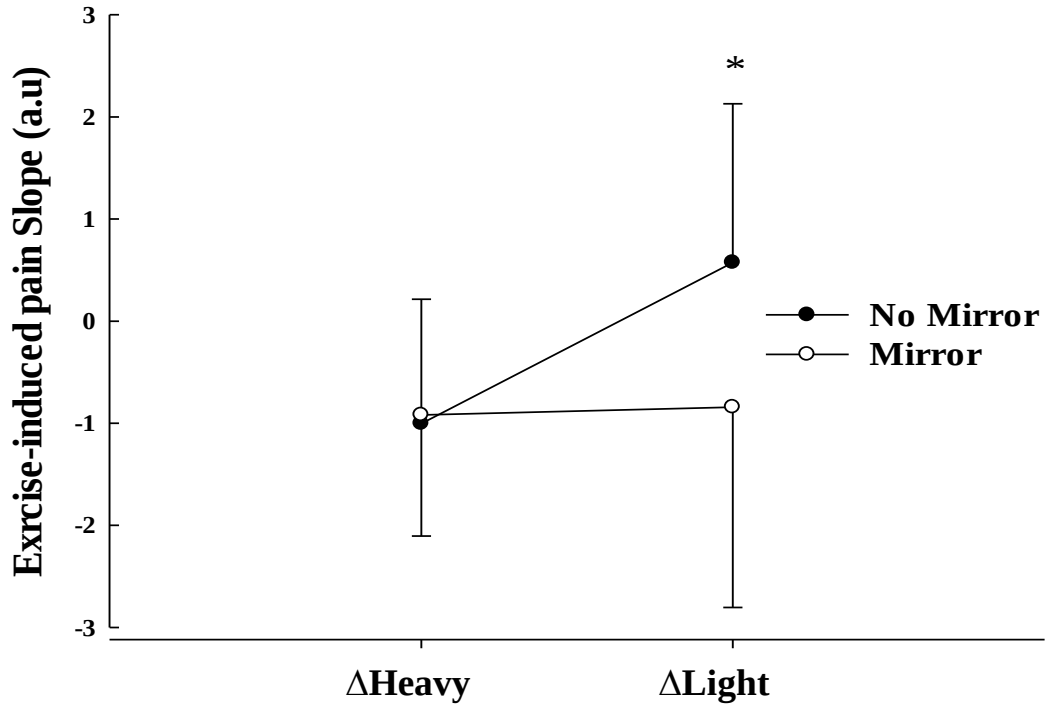
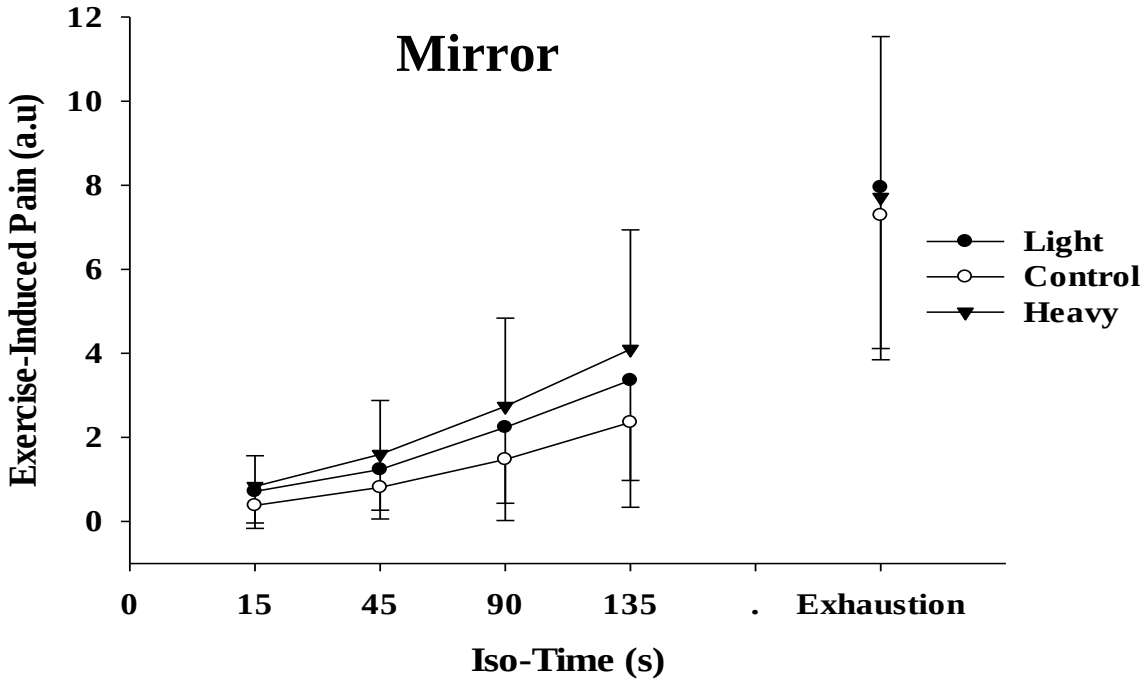


Figure 4.3 Difference in EIP slope from the Control condition to the two mass change conditions, for Mirror and No Mirror groups. *significantly different between conditions ($P < 0.01$).

(a)



(b)

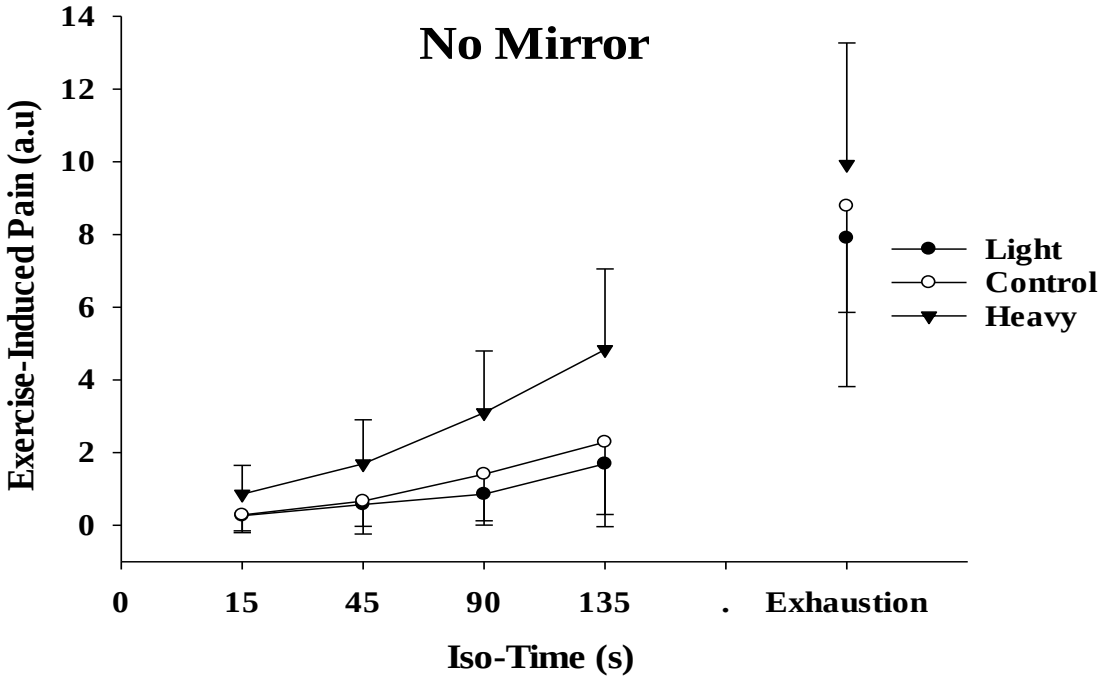


Figure 4.4 The progression of the perceived EIP over time was more similar between conditions in the Mirror group (a) then in the No Mirror group (b). This suggests that the visual dimensions of the lifted mass partly influenced the resulting EIP pain of lifting them.

Rating perceived exertion (RPE): The ANOVA revealed a significant main effect of condition for RPE during the TTE test ($F_{(1, 40)} = 33.403$, $P < 0.001$), and a significant interaction effect of RPE between groups for each time condition ($F_{(1,40)} = 13.367$, $P < 0.001$), as shown in Figure 4.5. This shows that the perceived RPE for participants in the Experimental group was attenuated by the illusion that all masses lifted were the same, as shown in Figure 4.6.

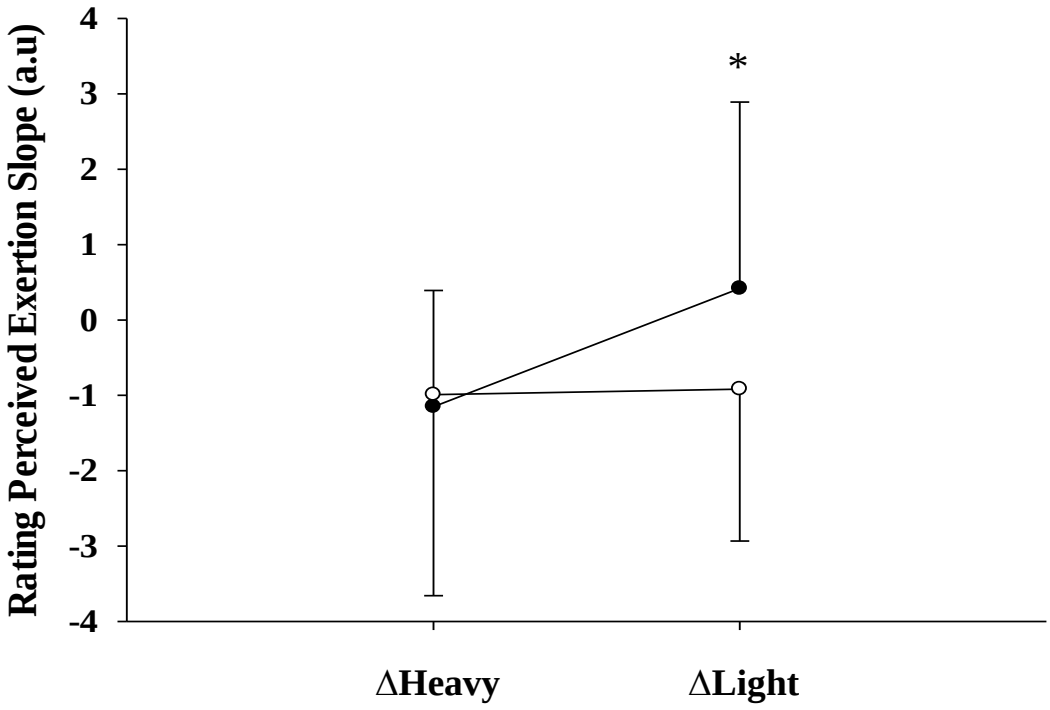
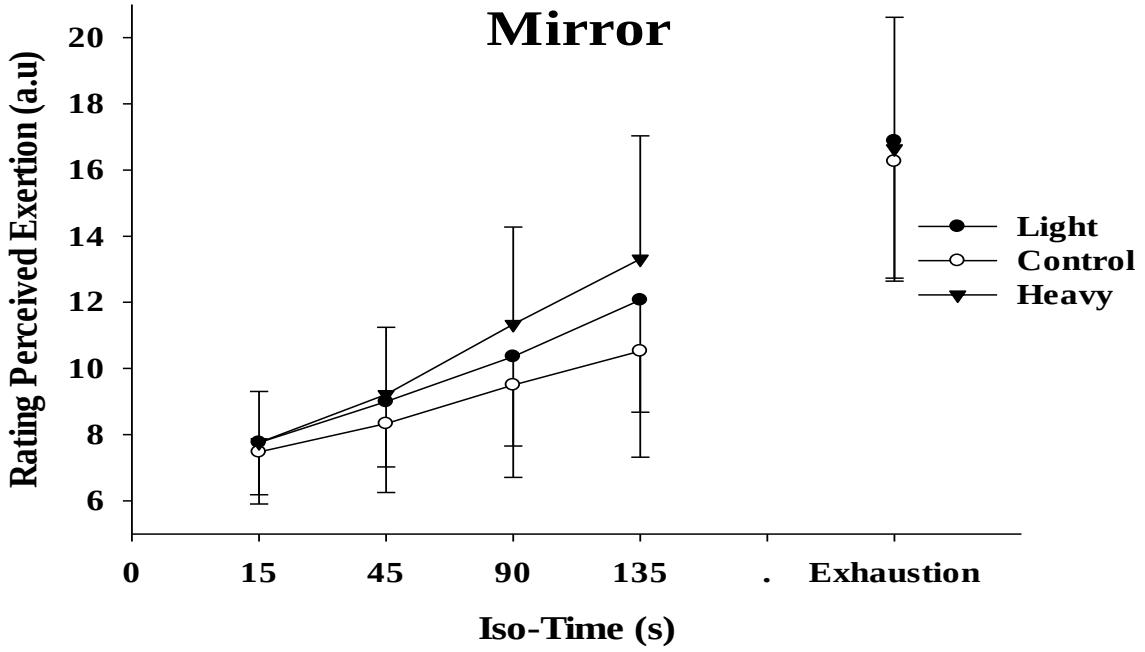


Figure 4.5 Difference in RPE slope from the Control condition to the two mass change conditions, for Mirror and No Mirror groups. *significantly different between condition ($P < 0.01$).

(a)



(b)

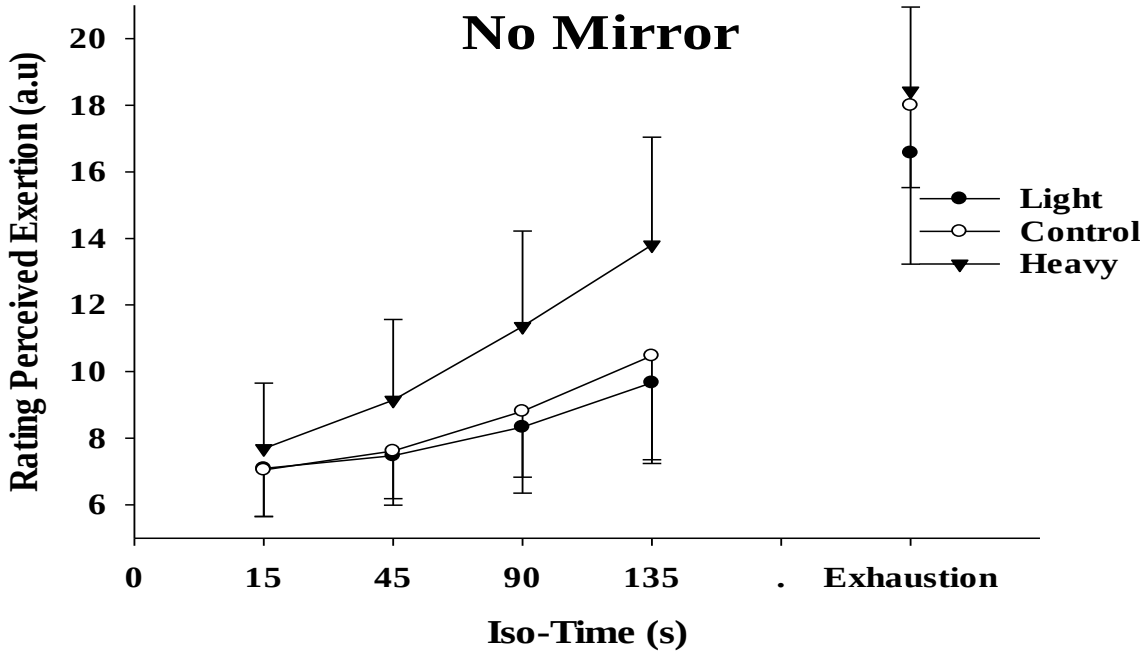


Figure 4.6 The progression of the RPE over time was more similar between conditions in the Mirror group (a) then in the No Mirror group (b). This suggests that the visual dimensions of the lifted mass partly influenced the resulting RPE for lifting them.

V. DISCUSSION

The purpose of this study was to investigate whether deceiving participants about the difficulty of an exercise task using an optical illusion, would be able to moderate perceptual response and change endurance performance. The primary finding was that despite the exercise task being made harder or easier (via increasing or decreasing the mass lifted), an optical illusion which made participants oblivious to this change blunted the effect of the task difficulty on the perceptual measures (EIP and RPE) and resulted in less dramatic changes in endurance performance. To our knowledge, this is the first study demonstrating that deception of task difficulty, via the use of a mirror box, can moderate perceptual response and endurance performance.

In the current study, participants in the Mirror (Experimental) Group believed they were always lifting 20%1RM in both hands, whereas they were actually lifting 5% more or 5% less than this (i.e. 25% 1RM and 15%1RM) in their dominant hand. This created a scenario where participants were completing a task that was significantly harder (25% 1RM) or easier (15%1RM) but were deceived to believe that it was always the same task. Participants in the No Mirror (Control) Group who were aware of the changes in mass (i.e. that the tasks were easier or harder) showed that when a lighter weight was lifted, RPE and EIP rose less steeply and TTE was longer. When a heavier mass was lifted, RPE and EIP rose more steeply and TTE was shorter. Whilst the participants in the Mirror (Experimental) Group showed a similar response, the degree to which the perceptual and performance measures differed between conditions was significantly attenuated. That is, lifting a heavier mass did not increase EIP and RPE, and did not reduce TTE by as great a degree as in the Control group. However, lifting a lighter mass did not reduce EIP and RPE, and did not increase TTE by as great a degree as in the Control group. This suggests that the perception of task difficulty exerts an important influence on perceived effort of lifting a mass, and the EIP arising from muscular contraction. It is likely that the changes to these perceptual measures then caused changes to participants' endurance performance (Marcora & Staniano, 2010; Mauger, 2014).

Whilst it is widely acknowledged that endurance performance is primarily dictated by physiological parameters (Joyner & Coyle, 2008), there is growing understanding that the perceptual response to exercise also forms an important basis for success. Indeed, the psychobiological model argues that endurance performance can be explained solely by

psychological constructs (Marcora, 2010). According to this model, during a time-to-exhaustion test, RPE gradually increases over time so that the task feels increasingly strenuous. The model predicts that people will consciously disengage from the task when their perception of effort has increased to the critical level set by their potential motivation, or, they believe they have attained maximal effort and perceive continuing as being beyond their capability (Marcora & Staiano, 2010; Smirmaul, Dantas, Nakamura, & Pereira, 2013). Therefore, according to this model, any intervention which serves to moderate RPE will have a direct effect on endurance performance. The results of the current study support this, as deceiving participants about the mass lifted attenuated RPE and a consequent change in time to exhaustion was observed. However, the psychobiological model is extreme in that it states that perception of effort (and changes to it) is the sole driver for determining endurance performance. However, it has been proposed that the pain arising from repeated muscle contraction (exercise-induced pain) also forms an important psychophysiological determinant of endurance performance (Mauger, 2014). This concept is directly refuted by the psychobiological model (Marcora, 2010), yet numerous studies demonstrate that changing pain response during exercise has a direct effect on performance (Gonglach et al., 2015; Graven-Nielsen et al., 2002; Mauger et al., 2010; Foster et al., 2014). In the current study, deception of task difficulty moderated the EIP that participants felt, and differences in time to exhaustion were observed between these conditions. Therefore, the results of this study also support the notion that EIP plays an important role in endurance performance, and this can be moderated independently of the magnitude of the nociceptive signal. There was also a similar response for changes in perception of effort however, and so the importance of effort perception alongside pain should also be recognised.

The observation that perceived pain can be influenced by psychological interventions is not new. Indeed, expectation and arousal factors, such as placebo effects and the requirement to focus on an ongoing task, are examples of variables that modulate pain (Wiech, Ploner, & Tracey, 2008). Simple perceptual factors can also influence pain. For example, both reported intensity of pain and neural responses to painful stimuli are reduced when participants look at their own body, compared with when they view a neutral object (Longo, Betti, Aglioti, & Haggard, 2009). This visually induced analgesia demonstrates that acute pain can be modulated by specific visual contexts. The effect of the

psychological intervention in the current study on EIP however, is a new finding, and this may have been due to the anticipation or expectation of pain that participants thought may arise as a result of the mass lifted in the time to exhaustion task. Indeed, when pain is anticipated, patients often report the worsening of pain (Turner et al., 1994), whereas expectation of pain relief usually induces placebo analgesia (Wager et al., 2004). Furthermore, the level of expected pain intensity significantly alters perceived pain when comparisons between two noxious thermal stimuli of almost equal intensity are made (Keltner et al., 2006). In the current study, the participants were well conditioned from Visit 1 to know the expected rate of EIP increase during the 20%1RM TTE task, and so these expectations may have served to influence the actual pain experienced when unbeknown to them the task was made easier or harder in Visit 2. Studies in pain neuroscience suggest that nociceptive brain regions are modulated by stimulus expectancies and even short-term expectations that vary as a function of cue have strong effects on pain perception and pain-evoked responses (Atlas, Bolger, Lindquist & Wager, 2010). These conditioned expectations of pain appear to result in real changes in pain-related processing in the brain, with regions affected including the cingulate, insula, thalamus, lateral prefrontal cortex, orbitofrontal cortex, parahippocampus, and caudate (Atlas & Wager, 2012). Thus, in the current study, despite the nociceptive signal being increased (or decreased) by changing to the mass lifted, an expectation that the EIP would not be different likely resulted in changes to pain-related processing in the brain that caused EIP to change little.

The Mirror Box technique has been shown to be a successful method in treating conditions where movement is impaired or significant pain is experienced with relatively little limb movement (Ramachandran & Altschuler, 2009). The current study also suggests, for the first time, that it is successful in reducing the non-clinical pain related to strenuous physical exercise and that this can improve exercise capacity/performance. However, the practicality of using the Mirror Box to improve physical activity or performance outside of the laboratory in fully mobile populations is perhaps questionable. However, doing so would be advantageous because even moderate levels of exercise elicit some level of pain (Borg, 1998), and symptoms of diseases such as pain and fear of pain may present barriers to physical exercise (Hays & Clark, 1999) in some clinical populations where exercise would be beneficial to their condition. Indeed, regular exercise provides a range of health

benefits, which significantly reduce all-cause mortality (Lee & Skerrett, 2001) and consequently exercise is often prescribed to treat a range of clinical conditions to improve patient outcome (Naci & Ioannidis, 2013). If pain could be reduced during exercise, then this may improve motivation to exercise (Wiech & Tracey, 2013) and help improve rates of adherence to exercise prescription programmes. The results of the current study provide a proof of principle that visual expectations of exercise can influence pain, perception of effort and exercise performance/capacity and so similar interventions that have more real-world practicality may provide an avenue for future study. The rapid development of new technology and the increased affordability of virtual reality (VR) devices may provide this, and future work should seek to identify whether VR can be used in conjunction with exercise to moderate the wearer's perceptual response.

VI. CONCLUSION

This study used the well-established Mirror Box technique to deceive participants about the expected difficulty of an isometric, single-limb TTE task. The Mirror Box created an illusion that deceived participants into believing that the task was the same as previously completed, when in fact it was easier or harder. This purely psychological intervention resulted in reduced EIP and RPE (when participants thought the task was easier), and increased EIP and RPE (when participants thought the task was harder). These manipulations resulted in a better or worse endurance performance respectively.

CHAPTER 5

EXPERIMENTAL 3rd STUDY

Transcutaneous electrical nerve and interferential current stimulation reduces exercise-induced muscle pain and improves time to exhaustion performance

Ali HY. Astokorki[1], Alexis R. Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK

Published as Part I in the *European Journal of Applied Physiology*
Accepted for publication January 2017
DOI: 10.1007/s00421-016-3532-6

I. ASTRACT

INTRODUCTION: Exercise-induced muscle pain (EIP) is believed to arise from a bult-up of endogenous algesic substances, with an increased intramuscular pressure in and around the muscle. Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to elicit analgesic effects in a variety of conditions. However, the relative effectiveness of these two modulations on EIP has not been considered. Therefore, the aim of this study was to investigate whether TENS or IFC elicit an analgesic effect during single limb, submaximal isometric contraction, and whether this improves time to exhaustion. **METHODS:** 18 recreationally active male (n= 11) and female (n= 7) participants were recruited. A single-blind, crossover, randomised design with TENS, IFC, and sham conditions was used (on separate visits). The TENS and IFC were administered on the bicep of the dominant arm, whereas in the sham condition a dummy simulator produced no current. In each condition, participants initially performed 3x5 second maximal voluntary contractions (MVCs) against a load cell. The maximum of the values was used to establish the 20% MVC for the TTE task. The TTE task involved the participant maintaining a 20% isometric MVC of the bicep until task withdrawal. **RESULTS:** The ANOVA revealed a significant difference in the time to exhaustion between conditions ($F_{(2, 34)} = 10.554$, $P < 0.001$). The ANOVA also revealed a significant main effect of condition for exercise-induced pain during the TTE test ($F_{(2, 34)} = 3.690$, $P = 0.035$). No significant changes in rating of perceived exertion (RPE) were found between the three conditions ($P > 0.05$). A 3 x 8 (condition x iso-time) ANOVA revealed a significant interaction effect for exercise-induced pain over time between conditions during the TTE test with lower pain intensity in the TENS and IFC conditions ($F_{(3.4, 58.4)} = 3.671$, $P = 0.013$). No interaction effects for RPE were found between the three conditions ($P > 0.05$). For the MVC, paired-sample *t*-tests demonstrated that MVC was significantly reduced following the TTE in the Sham ($t_{(17)} = 9.069$, $P < 0.001$), TENS ($t_{(17)} = 7.037$, $P < 0.001$) and IFC conditions ($t_{(17)} = 8.558$, $P < 0.001$). No significant differences between conditions were found for the pre-MVC ($F_{(1.4, 23.4)} = 1.758$, $P = 0.188$) or the post-MVC ($F_{(2, 34)} = 1.499$, $P = 0.238$). **CONCLUSION:** The findings of the study suggest that TENS and IFC elicit an analgesic effect for EIP, and that this intervention elicited a significant improvement in time to exhaustion performance in the absence of changes to perceived exertion.

II. INTRODUCTION

Exercise-induced muscle pain is believed to arise from an accumulation of endogenous algesic substances (including: hydrogen ions, potassium, histamine, serotonin, bradykinin, acetylcholine, adenosine and substance P), with an increased intramuscular pressure in and around the muscle (Mense, 1993). These endogenous algesics are released from cells when homoeostasis is disturbed, which is a consequence of intense exercise (Mauger et al., 2010). Therefore, exercise-induced muscle pain is closely bound to both the intensity and duration of the exercise task (Cook et al., 1997). The accumulated algesic substances sensitise, activate, or increase the firing rate of group III and IV afferent muscle fibres, which then convey nociceptive signals regarding actual or potential tissue damage to the brain via the spinal cord (O'Connor & Cook, 1999). It is suggested that the perceived pain arising from this afferent fibre activation, along with increased intramuscular pressure, heat accumulation, and skeletal muscle fatigue, may play a combined role in the regulation of the level of exercise intensity and preservation of a metabolic reserve by the central nervous system (Tucker, 2009). Indeed, the activity of afferent fibres can moderate sensory receptor input, reflex and inhibitory circuit neurons in the spinal cord, neurotransmitters involved in synaptic modulation, and central nervous system efferent output (Bentley, 1996). Consequently, muscle pain may increase afferent neuron inhibition and decrease the ability of the brain to recruit muscles ability to produce force (Graven-Nielsen et al, 2002). Furthermore, as a consequence of the pain, the exercise may also reduce mood (Karsdorp et al., 2013) and make the task psychologically more demanding and less desirable, which may decrease motivation and performance. Therefore, there is likely both a psychological and physiological benefit to reducing muscle pain during exercise.

Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to elicit analgesic effects in a variety of conditions (Marchand et al., 1993; Robinson, 1996; Schmitz et al., 1997). How this analgesia is achieved is debated, but DeDomenico (1987) and Savage (1992) suggest that the electrical principles of TENS and IFC differ, and so the techniques operate through different mechanisms of action. The neurophysiological basis of muscle pain relief from TENS is believed to derive directly from the gate control theory of pain. Accordingly, TENS is proposed to selectively activate Aβ large-diameter afferent fibres by high frequency stimulation, inhibiting constant transmission of nociceptive neurons by generating an afferent barrage of nerve impulses

within the spinal cord (Melzack, 1965; Garrison & Foreman, 1994; Walsh, 1997). However, it is also suggested that the application of TENS burst mode can effectively activate Group III, Aδ and C small-diameter afferent fibres by both high frequency and low frequency bursts applied together. This is suggested to lead to the release of endogenous opioids (Resende et al., 2004; Sabino et al., 2008), and serotonin (Chen, 2010) and a subsequent decrease in pain. IFC utilises a medium frequency alternating current with a various beat frequency (Low & Reed, 1994; Cramp et al., 2000), and combined with a kilohertz cycle duration delivers current to overcome skin impedance and penetrate deep into the muscle. This is believed to reduce pain transmission through gate control mechanisms, release endorphins and increase circulation of opioids (Melzack, 1965; Dounavi, Chesterton & Sim, 2012).

Muscle stimulation using therapeutic current has previously been used in combination with exercise to achieve several aims, including pain relief, facilitated recovery, treatment for urinary incontinence in female athletes and delayed onset muscle soreness (Bolin, 2003; Heyman, De Geus, Mertens & Meeusen, 2009; Rivata et al., 2010; Rocha et al., 2012; Vanderthommen et al., 2012). Given that exercise-induced muscle pain may be a factor affecting exercise capacity and performance, and that therapeutic muscle stimulation has shown promise in the treatment of muscle pain (Tourville, Connolly & Reed, 2006), there may be scoped to use this technique to reduce muscle pain during exercise.

To our knowledge, no studies have considered the effectiveness of TENS and IFC on exercise-induced muscle pain during fatiguing exercise. Therefore, the aim of this study was to investigate whether TENS or IFC elicit an analgesic effect during single limb, submaximal isometric contraction, and whether this improves time to exhaustion.

III. MATERIALS AND METHODS

Subjects

Eighteen recreationally active male (n= 11) and female (n= 7) participants were recruited for this study. The participants' mean age, height and body mass were 25 ± 6 yrs, 176 ± 11 cm and 73.5 ± 16.6 kg, respectively. Prior to participation, an information sheet detailing the study was given to participants, which included an inclusion/exclusion criteria checklist. Participants were excluded from the study if they had history of cardiovascular

disorders (e.g. angina, heart attack, high blood pressure etc.), chronic medications that affect the central nervous system, current pregnancy, bleeding disorders (e.g. haemophilia), deep vein thrombosis, impaired sensation, acute/chronic infection (e.g. tuberculosis), malignancy, recently radiated tissue, skin diseases or severely damaged skin, types I or II diabetes, were using a cochlear implant hearing device or pacemakers, or any other condition that may be a danger to their participation (e.g. muscle injury). Following satisfactory completion of the inclusion/exclusion criteria checklist, all participants provided written informed consent and the research was approved by the University of Kent Ethics Committee. Prior to all experimental occasions, participants were asked to refrain from the ingestion of alcohol 48 h before the laboratory occasions, and asked to refrain from any vigorous exercise (24 h prior), caffeine (8 h prior) and analgesics (6 h prior) prior to any test occasion (Lu, Lai & Chan, 2008). Following a full familiarisation visit, in a single-blind, crossover, and randomised design, all participants completed a TENS, IFC, and sham condition, which were separated by 2-5 days.

TENS and IFC Stimulation

Using a Vectra Genisys multi-waveform stimulator (Chattanooga Group, Hixon, TN, USA), as shown in Figure 5.1, the parameters of biphasic IFC pulses were delivered in a continuous mode with a pulse frequency of 100Hz. For the biphasic TENS pulses, a continuous pattern of stimulation was used, with a pulse width of 300 μs and a frequency of 100 Hz. A bipolar IFC set-up was used in the current study in order to maintain blinding of conditions. Both bipolar and quadripolar IFC have been shown to be equally successful when used to manage pain conditions (Johnson & Tabasam, 1998). The current intensity was adjusted for the TENS and IFC conditions so that participants reached a strong but appropriate intensity without causing any noticeable muscle contraction, whereas in the sham condition a dummy simulator produced no current. The two electrodes were administered on the bicep of the dominant arm that they were at least 2.5 cm apart (this was kept consistent between participants). This location was then recorded and re-used for subsequent testing. The electrode was then removed and the site of installation was cleaned.

Figure 5.1 Elicit a participant performing a TTE by applying TENS intervention on their bicep.

Sham Stimulation

A sham stimulation was used as a placebo-controlled condition. During the sham condition, electrodes were placed in the same locations as the IFC and TENS conditions, but participants received no current and were told "This type of stimulation is supposed to reduce pain by using a subthreshold stimulus that you will not able to perceive". This explanation was strengthened via a visual display of the electrical current on an oscilloscope.

Procedures

During the familiarisation visit, a general health screening was conducted which included a series of tests to ensure that it was safe to administer TENS and IFC to participants. Before undertaking stimulation, participants were tested for sensory discrimination using a sharp and blunt patella hammer, and a skin integrity test to ensure normal skin sensation.

For application of TENS and IFC, the skin of the dominant bicep was cleaned thoroughly prior to electrode placement in order to reduce electrical resistance. Following this, bipolar surface TENS and IFC electrodes were attached to the bicep of the dominant arm. Subsequently, TENS and IFC were applied in order to find the appropriate stimulation intensity for the subsequent test occasions. The current intensity was adjusted until participants reported feeling a tingling sensation without visible muscle contraction and/or muscle pain (i.e. non-painful paraesthesia). During stimulation, and after testing, participants were monitored for signs of skin irritation, nausea, swelling and pain. On completion of stimulation, the current was ramped down before turning off the machine.

On each test occasion, participants were given standard instructions for the numeric pain rating scale (Cook et al. 1997) and rating of perceived exertion (RPE) using the Borg (6-20) scale (Borg, 1998). Pain was anchored according to minimum and maximum pain felt due to exercise-induced pain (EIP). All tests were preceded by a standardized warm-up where participants performed three unilateral (dominant arm) maximal voluntary contractions (MVC) of the elbow flexors against a load cell (Globus Ergo Meter, Globus, Codogne, Italy), which were separated by a 3-min rest. To do this, participants were in a seated position with the forearm resting on a bench and the elbow angle at 90º and the wrist angle at 180º. Each MVC test was performed for 5 s with a rapid increase in force over 1 s, a sustained maximum for 3 s, and a gradual release over the final second. Maximal force was recorded for each MVC. Participants were strongly encouraged to perform maximally throughout each contraction. The maximum of the three values was used to establish the 20% MVC for the time to exhaustion task (TTE) performed in that visit. Following a rest period of 10-min, participants undertook the TTE in the same seated position described for the MVC tests. The TTE task required the participant to maintain a 20% isometric MVC of the bicep until force dropped below the force required for more than 2 s, or when the participant withdrew from the task. During the TTE task, participants were asked to rate their perceived pain and RPE every 30 s. On completion of the TTE task, participants immediately performed a further MVC for assessment of fatigue.

Following the familiarisation visit, all participants returned to the laboratory on three more occasions to perform the experimental sessions using the same protocol described above. In these experimental tests, TENS, IFC or Sham were administered during the TTE tests. Each visit was separated by 2-5 days and were completed at the same time of day (± 2 h).

Statistical Analysis

Prior to statistical analysis, standard assumptions (Kruskal-Wallis test and Shapiro-Wilk test) were checked for each statistical test, and none of these were violated. Time to exhaustion (TTE) was analysed using a repeated measures ANOVA and Bonferroni Pairwise Comparisons. Mean RPE and mean EIP were assessed using an ANOVA with repeated measures and appropriate follow-up paired-sample *t*-tests. Changes in RPE and EIP during each condition were performed using a three-way ANOVA with repeated measures, with follow-up paired samples *t*-tests used to detect differences between conditions when an interaction effect had been observed. All statistical analysis was performed using the statistical package SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data are reported as means ± SD. Statistical significance was accepted when $P < 0.05$.

IV. RESULTS

Time to Exhaustion (TTE): The ANOVA revealed a significant difference in the time to exhaustion between conditions ($F_{(2, 34)} = 6.763$, $P = 0.003$), as shown in Figure 5.2. Pairwise comparisons revealed a significantly different TTE time between TENS (10 min 49 s ± 6 min 16 s) and SHAM conditions (7 min 52 s ± 2 min 51 s) ($P = 0.031$) and between IFC (11 min 17 s ± 6 min 23 s) and SHAM conditions ($P = 0.02$). No significant difference between TENS and IFC conditions was observed ($P > 0.05$).

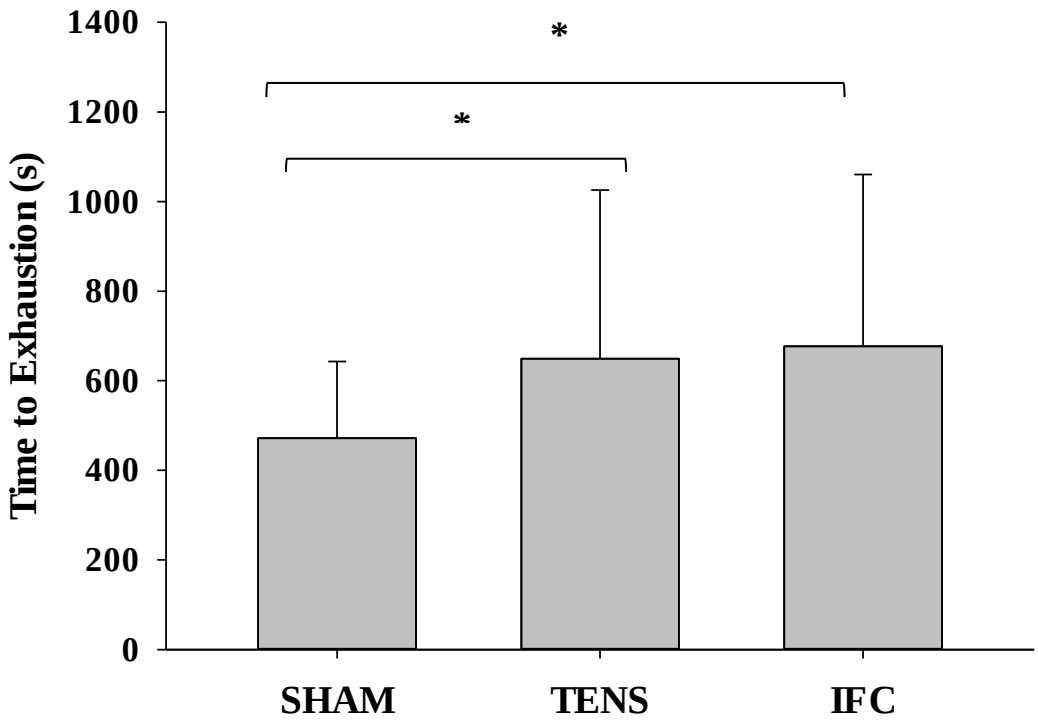


Figure 5.2 TTE elicited a significant difference between conditions. Sham = placebo-controlled, TENS = transcutaneous electrical nerve stimulation, IFC = interferential current. *significantly different from Sham condition ($P < 0.01$).

Exercise-Induced Pain (EIP): The ANOVA revealed a significant main effect of condition for perceived exercise-induced pain during the TTE test ($F_{(2, 34)} = 3.690$, $P = 0.035$), as shown in Figure 5.3. Follow up paired-sample *t*-tests showed a significant difference in mean exercise-induced pain during the TTE tests between the TENS and sham conditions ($t_{(17)} = 2.322$, $P = 0.033$), but no significant differences between the IFC and sham conditions ($t_{(17)} = 1.919$, $P = 0.072$), or the TENS and IFC conditions ($t_{(17)} = -0.466$, $P = 0.647$).

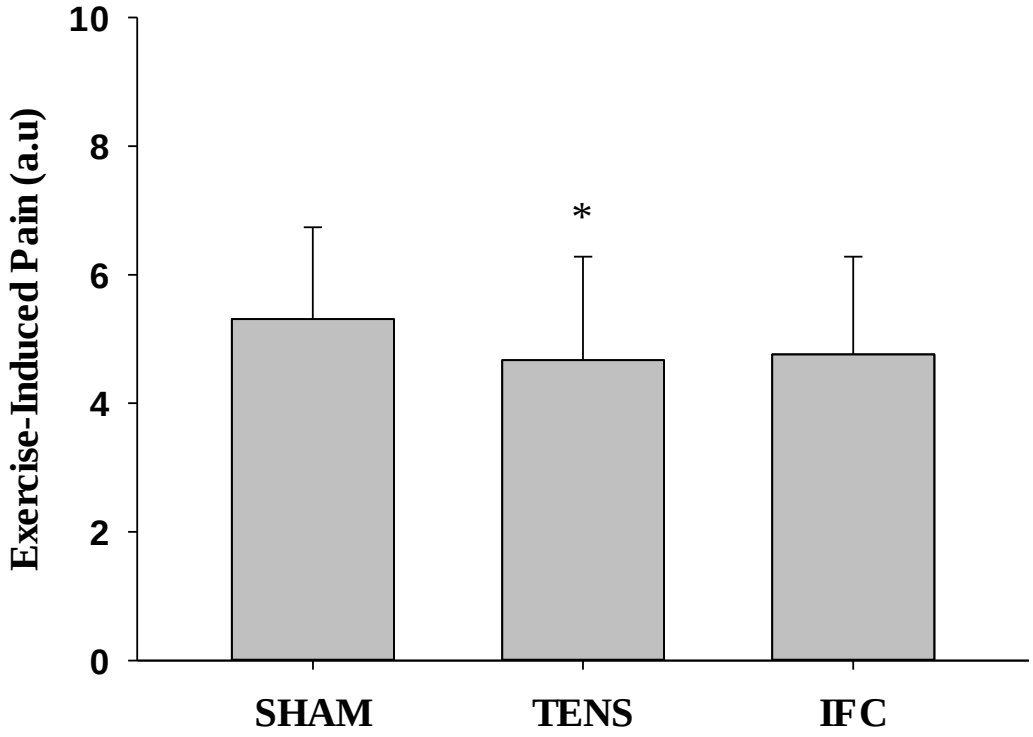


Figure 5.3 Pain scores elicited a significant difference between conditions. Sham = placebo-controlled, TENS = transcutaneous electrical nerve stimulation, IFC = interferential current. *significantly different from Sham condition ($P < 0.05$).

A 3 x 8 (condition x iso time) ANOVA revealed a significant main effect of condition for perceived exercise-induced pain ($F_{(1.24, 19.13)} = 8.39$, $P = 0.006$). There was also a significant main effect for time ($P < 0.001$). There was also a significant interaction effect

for exercise-induced pain over time between conditions during the TTE test ($F_{(3.73, 63.4)}$ = 4.95, P = 0.002), as shown in Figure 5.4. Follow-up paired-sample *t*-tests showed a significantly different pain perception between TENS and SHAM conditions at 120 s ($t_{(17)}$ = 2.482, P = 0.024), 180 s ($t_{(17)}$ = 2.319, P = 0.033), 210 s ($t_{(17)}$ = 3.402, P = 0.003) and 240 s ($t_{(17)}$ = 3.589, P = 0.002. Significant differences were also shown between IFC and SHAM conditions at 120 s ($t_{(17)}$ = 2.482, P = 0.024), 150 s ($t_{(17)}$ = 2.388, P = 0.029), 180 s ($t_{(17)}$ = 2.997, P = 0.008), 210 s ($t_{(17)}$ = 3.298, P = 0.004) and 240 s ($t_{(17)}$ = 2.858, P = 0.011). No differences were found at any time point between TENS and IFC conditions (P > 0.05).

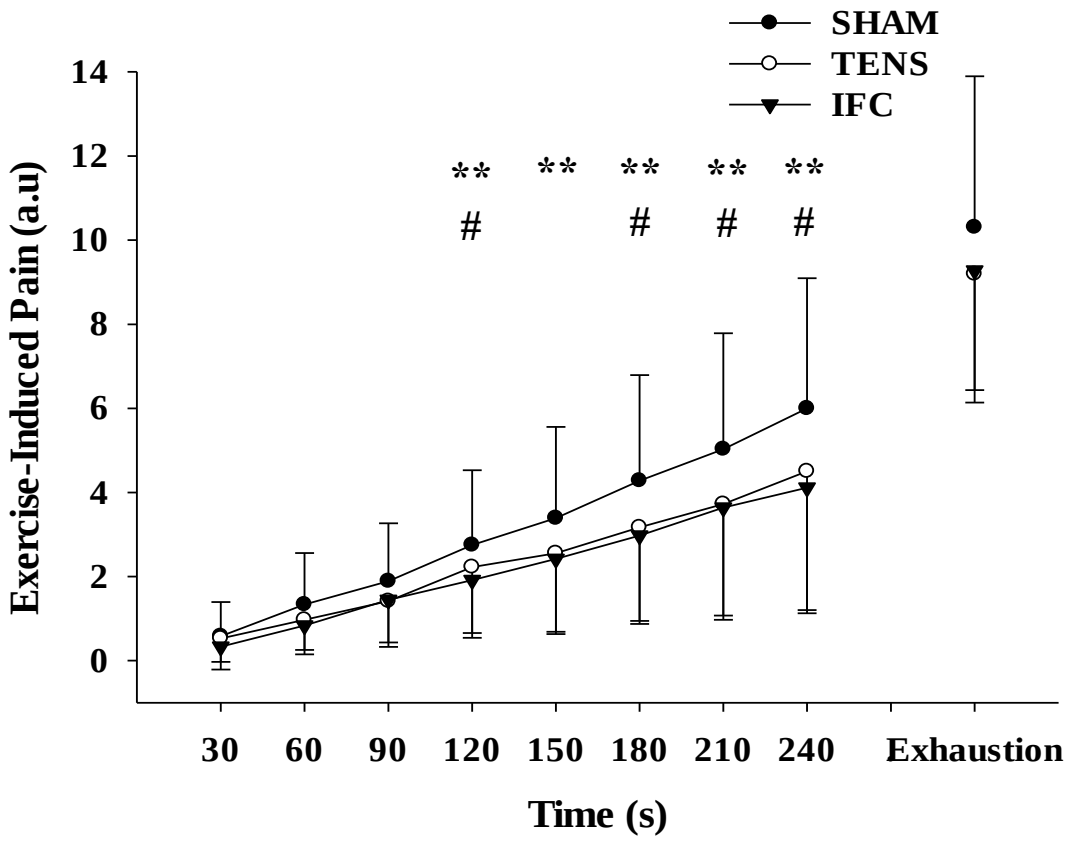


Figure 5.4 Pain scores over time elicited a significant interaction between conditions from 60 - 240 s during the TTE test. ** denotes a significant interaction between sham and TENS. # denotes a significant interaction between sham and IFC. # denotes a significant interaction between TENS and IFC in perceived pain.

Rating Perceived Exertion (RPE): There was no significant main effect of condition ($F_{(2, 34)} = 0.031$, $P = 0.969$) for RPE, as shown in Figure 5.5.

A 3 x 8 (condition x iso time) ANOVA revealed a significant main effect of condition for time ($P < 0.001$), but no main effects ($F_{(2.34)} = 2.706$, $P = 0.081$) or interaction effects for RPE over time during the TTE were observed ($F_{(4.08, 69.39)} = 1.82$, $P = 0.134$), as shown in Figure 5.6.

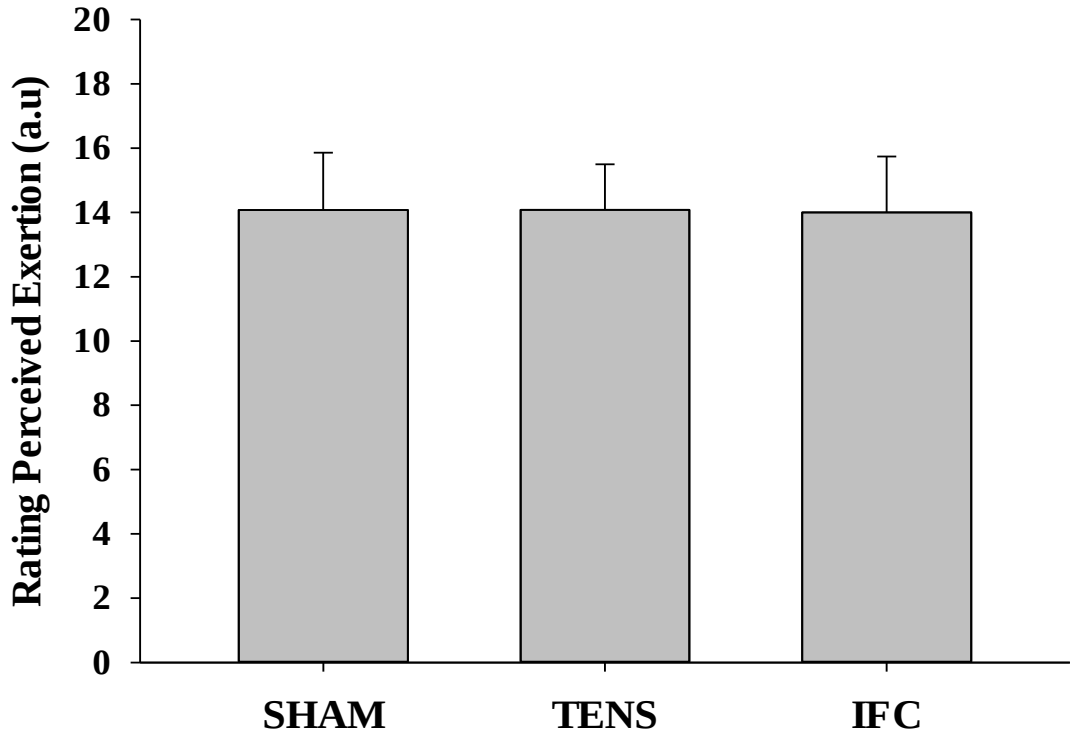


Figure 5.5 RPE scores elicited no significant difference between conditions. Sham = placebo-controlled, TENS = transcutaneous electrical nerve stimulation, IFC = interferential current.

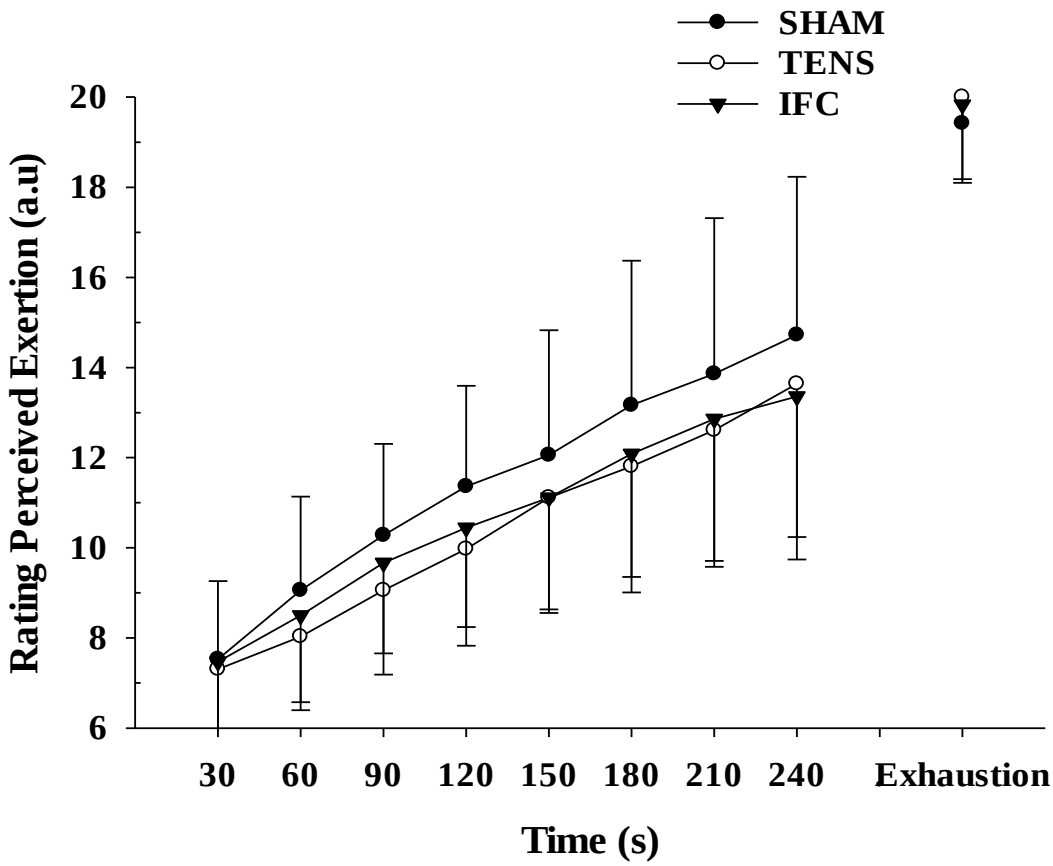


Figure 5.6 RPE scores over time elicited no significant difference between conditions. Sham = placebo-controlled, TENS = transcutaneous electrical nerve stimulation, IFC = interferential current.

Maximal Voluntary Contraction (MVC): No significant differences between conditions were found for the pre-MVC ($F_{(1.4, 23.4)} = 1.758$, $P = 0.188$) or the post-MVC ($F_{(2, 34)} = 1.499$, $P = 0.238$). MVC was significantly reduced following the TTE in the SHAM ($t_{(17)} = 9.069$, $P < 0.001$), TENS ($t_{(17)} = 7.037$, $P < 0.001$) and IFC conditions ($t_{(17)} = 8.558$, $P < 0.001$), as shown in Figure 5.7, suggesting that significant fatigue and performance decrement had occurred in all conditions following the TTE task.

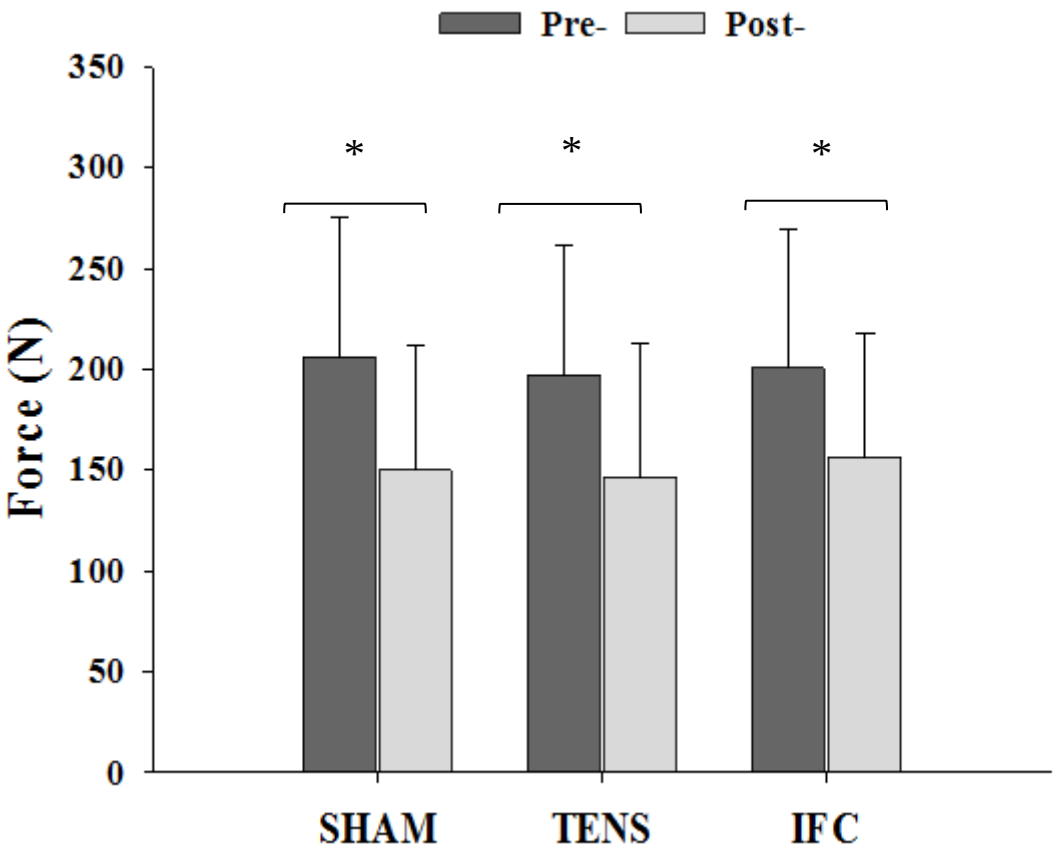


Figure 5.7 MVC pre-and post elicited between conditions. In the sham condition displayed a significantly reduced in MVC pre-and post. TENS condition displayed a significantly reduced in MVC pre-and post. IFC condition displayed a significantly reduced in MVC pre-and post. However, there was no significant difference between conditions for pre-MVC, and no significant difference between conditions for post-MVC.

V. DISCUSSION

The purpose of this study was to investigate whether TENS and IFC can elicit an analgesic effect during a sustained single limb, submaximal isometric contraction in healthy participants. The primary finding of this study was that both TENS and IFC were able to significantly reduce exercise-induced pain, and that this intervention elicited a significant improvement in time to exhaustion performance. To our knowledge, this is the first study utilising a randomised, crossover and placebo controlled design, which shows an ergogenic effect for TENS and IFC. This data also provides support for the notion that exercise-induced pain is a limiter of endurance performance in single limb exhaustive exercise.

It has previously been suggested that the perceived pain arising from prolonged or repetitive muscular contraction may be an important sensation which is used to regulate work rate and influence endurance performance (Mauger, 2014). This exercise-induced pain is caused by one, or a combination of, algesic metabolic by-products, an increased intramuscular pressure and muscular distortion (Dannecker & Koltyn, 2014; Mense, 1993). This noxious environment serves to both sensitise and stimulate both Type III (A-delta fibres) and Type IV (C fibres) small afferents, which convey the nociceptive signal and synapse in lamina I, II and V (Mense, 1993). If a stimulation threshold is met, a postsynaptic output will be produced and transmitted to the supraspinal regions of the brain, where it is processed and interpreted as perceived pain. The type of sustained sub-maximal contraction used in the current study has been shown to produce such a noxious environment, which both inhibits the excitation-contraction coupling process (Kent-Braun, 1999) and elicits a nociceptive signal, as described above. Although pain tolerance has long been linked to athletic potential (Scott & Gijsbers, 1981), it is only relatively recently that a growing body of empirical evidence has provided strong support this notion. EIP may exacerbate fatigue by reducing voluntary activation of the muscle (Kennedy et al. 2013) or by contributing to a host of unpleasant sensations (Kress and Stratler, 2007) that either leads to a decision to reduce work rate or disengage with the task (Mauger, 2014). Whilst the current study cannot identify whether psychological or physiological determinants led to the apparent ergogenic effect of therapeutic muscle stimulation, it does provide further evidence that analgesic interventions during exercise are able to increase time to exhaustion performance. Exercise-induced pain increased as function of time and reached its most intense at the end of the exercise, where near maximal values were

observed. To moderate this pain, without changing the metabolic environment at the muscle, TENS and IFC were used to inhibit the transmission of the nociceptive signal at the spinal level. The TENS intervention appeared to reduce perceived pain, which resulted in a longer time to exhaustion of the sustained isometric contraction and a faster TT time. The analgesic mechanism of TENS and IFC are suggested to be underpinned by the gate-control theory of pain (Sluka & Walsh, 2003). Indeed, when TENS and IFC are applied to produce a strong comfortable and non-painful paraesthesia, large diameter afferents (A-beta fibres) are selectively activated (Sluka & Walsh, 2003). The activation of these large diameter low threshold mechano-receptive nerve fibres could inhibit the nociceptive transmission from small diameter higher threshold nociceptive (A-delta and C) fibres through pre- and post synaptic inhibition in the dorsal horn of the spinal cord (Melzack & Wall, 1967). This would reduce the number of nociceptive signals reaching the higher brain centres and consequently reduce the perceived pain for a given stimulus at the nociceptor. A reduction in the afferent barrage from Type III and IV fibres could also offset the reduction in voluntary activation that is observed during painful exercise (Kennedy et al. 2013), which would likely allow for an improved exercise performance.

Accordingly, in the current study exercise-induced pain increased as function of time and reached its most intense at the end of the exercise, where near maximal values were observed. To moderate this pain, without changing the metabolic environment, TENS and IFC were used to inhibit the transmission of the nociceptive signal. This intervention appeared to induce analgesia which resulted in a longer time to exhaustion of the sustained isometric contraction. The mechanism of analgesia by TENS and IFC are posited to operate lie in the gate-control theory of pain (Sluka & Walsh, 2003). When TENS and IFC are applied at high frequency (~100 Hz), with pulse durations between 300 μs and a pulse amplitude titrated to produce a strong comfortable and non-painful paraesthesia, large diameter afferents (A-beta fibres) are selectively activated (Sluka & Walsh, 2003). According to Gate Control Theory of Pain (Melzack & Wall, 1965), the activation of large diameter low threshold mechano-receptive nerve fibres could inhibit the nociceptive transmission from small diameter higher threshold nociceptive (A-delta and C) fibres through pre-and post synaptic inhibition in the dorsal horn of the spinal cord. This would reduce the number of nociceptive signals reaching the higher brain centres and consequently reduce the perceived pain for a given stimulus at the nociceptor. Whilst, the

mechanism of reduced pain perception observed in the TENS and IFC conditions is perhaps best supported by the gate control mechanisms discussed above, it has also been suggested that analgesia through TENS and IFC may also be explained by the release endogenous opioids (Kalra et al. 2001). Whilst evidence for this mechanism is stronger for low frequency TENS (Sjölund & Eriksson, 1979), more recent studies on animal models also suggest that analgesia by high frequency TENS is reduced by systemic naloxone in high enough does to block μ, δ and κ opioid receptors (Han et al., 1991; Woolf et al., 1980), thus supporting a role for endogenous opioids for both high and low frequency TENS.

The mean reduction in pain (compared to the SHAM condition) elicited by TENS and IFC was approximately 12%, with a stronger effect evident later in the exercise (>30% after 180 s – see Figure 5.3). The greater reductions in pain with TENS and IFC towards the end of exercise are paralleled by the increasingly noxious environment in the muscle and the consequential increased pain. Therefore, the apparent analgesic effect of the stimulation was most noticeable during a noxious environment that elicited a pain intensity of ~4.3 ('somewhat strong pain') and above on the Cook Scale (Cook et al., 1997). It is important to note, that in the familiarisation visits, this scale was anchored specifically according to previously experienced maximum and minimum levels of muscle pain during exercise, rather than a general pain sensation (e.g. dental pain), so as to provide a measure specific to the experiences of EIP. The effectiveness of the analgesia observed in the current study is supported by some studies which have used TENS to reduce pain. Indeed, in a cross-over study investigating neuropathic pain in patients with spinal cord injury, analgesic TENS was shown to elicit a 29-38% improvement on a global relief scale. Furthermore, Bjordal et al. (2003) demonstrated a 26.5% mean reduction in analgesic consumption for post-operative patients following a well-controlled TENS intervention. Salisbury and Johnson (1995) have also shown that TENS increased the cold pain threshold and that IFC decreased cold pain intensity. However, whilst several studies have demonstrated positive analgesic effects of TENS, there are a number of studies that show no such effect (Johnson & Tabasam, 1999; Tabasam & Johnson, 1999; Alves-Guerreiro, 2001; Claydon et al., 2008; Gomes et al., 2014). The numerous systematic reviews and meta-analysis (for example; Hurlow et al., 2012; Simpson et al., 2014; Zeng et al., 2015) on this area suggest that different TENS parameters, patient's groups, outcome measures and a lack of placebo controls and randomisation are the reason for the equivocal findings

for the effectiveness of TENS. Therefore, in the current study the use of a placebo controlled condition, the randomisation of conditions and the controlled exercise intensity between conditions and participants presents a robust experimental design that supports the effectiveness of TENS as an analgesic intervention, and a role for EIP on endurance performance.

The apparent analgesic effect of TENS on EIP observed in the current study, coupled with TENS being a safe, non-invasive and cheap intervention, may have potential implications for improving physical activity behaviour in certain individuals. Exercise and physical activity is known to induce a range of health benefits, which significantly reduce all-cause mortality (Lee & Skerrett, 2001). Exercise is also prescribed to treat a range of disease and clinical conditions to improve patient outcome and increase quality of life (Naci & Ioannidis, 2013; Thomson et al., 2003). Despite this, there are universally low rates of regular exercise participation and low levels of adherence to prescribed exercise protocols (Findorff et al., 2009; Linke et al., 2011). The reasons and risk factors which underpin low activity levels (particularly for at risk populations) are multifactorial, and likely depend personal attributes (demographics, cognitive variables, behaviours) and environmental factors (social environment, physical environment, and characteristics of the physical activity) (Woodward & Berry, 2001). Indeed, obstacles to physical activity for obese and normal weight individuals include low motivational status, self-efficacy, negative learning history with exercising, lack of coping skills, and aversive environmental characteristics such as reduced access to physical activity facilities, high costs of training programs, low social and cultural support, and time barriers (Sherwood & Jeffery, 2000). However, as pain inherently motivates decisions and action (Wiech & Tracey, 2013), and exercise is known to elicit pain (Cook et al., 1997), pain avoidance may contribute to lower physical activity and adherence. This is supported by some studies which demonstrate that symptoms of diseases such as pain and fear of pain present the biggest barriers to physical exercise (Clark; Hays & Clark, 1999). Indeed, Cohen-Mansfield et al. (2003) showed that health problems and pain were the main obstacles to physical exercise in a nondisabled population aged 75–85 years. The reduced EIP elicited by TENS in the current study provides some provisional support for its use as a cheap intervention with the potential to reduce pain for those who find it a barrier to exercise.

A notable observation in the current study is that TTE increased following a reduction in pain, but with no change in RPE between conditions. It has been suggested that RPE is the conscious manifestation of afferent information from a host of afferent physiological systems and external cues, and that this perception of effort is an important determinant of endurance performance (Tucker, 2009). However, the balance of evidence suggests that the primary generator for perception of effort is the collorary discharge (i.e. an internal signal that arises from centifugal motor commands) associated with central motor command (McCloskey, 1981), and that this is independent from afferent feedback (including pain) from the working muscles and other interoceptors (Marcora, 2009; de Morree et al, 2012, 2014). Indeed, feelings of pain and discomfort have often been assessed as part of the perception of effort (Noble & Robertson, 1996), however, numerous studies have shown that pain and effort can be dissociated (Angius et al., 2015; Cook, 1997; O'Connor & Cook, 2001; Pageaux et al., 2015; Astokorki & Mauger, 2016) and are therefore distinct entities. By dissociating perception of effort and EIP in the current study by using separate scales and proving detailed instructions, we were able to observe the individual effects of therapeutic muscle stimulation on EIP and RPE, and the consequent impact on endurance performance. In-line with our hypothesis, a reduction in EIP paralleled an improvement in TTE and TT performance. This finding supports the view that EIP is a contributing factor to task cessation and self-paced performance (Mauger, 2014), but is contrary to the view that endurance performance is primarily determined by perception of effort, as stated by the Psychobiological Model (Marcora, 2010). The view that the generation of RPE from central command underpins the psychobiological model of performance, which postulates that endurance performance is primarily determined by perception of effort (Marcora & Staniano, 2010), (Marcora 2010). Although this model acknowledges that severe pain (from a muscle strain for example) would affect motivation (and therefore inhibit performance), it suggests that muscle pain normally experienced during high-intensity aerobic exercise does not limit performance in healthy humans (Marcora 2010). The results of the current study suggest that 'normal' EIP experienced during exhaustive exercise does affect performance and that it can be moderated independently of perception of effort. These findings support other studies which demonstrate that an analgesic intervention can improve exercise performance in a variety of exercise models (Astorino et al., 2011; Astorino et al., 2012; Foster et al., 2014;

Gonglach et al., 2015; Mauger et al., 2010; Mauger et al., 2014) and strengthens the belief (Kress & Statler, 2007) that tolerance of EIP is an important prerequisite for endurance performance (Mauger, 2013, 2104).

VI. CONCLUSION

The findings of the study suggest that TENS and IFC elicit an analgesic effect on EIP during single limb, submaximal isometric contraction performance, and that this reduction in muscle pain can improve time to exhaustion performance in the absence of changes to perceived exertion. Further studies are needed to identify how TENS or IFC elicits an analgesic effect for EIP, and the psychophysiological underpinning the subsequent improvement in endurance performance.

CHAPTER 6

EXPERIMENTAL 4th STUDY

Transcutaneous electrical nerve stimulation inhibits central pain transmission and limits the development of peripheral muscle pain during cycling time trial performance

Ali HY. Astokorki[1], Alexis R. Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK

Published as Part II in the *European Journal of Applied Physiology*
Accepted for publication January 2017
DOI: 10.1007/s00421-016-3532-6

I. ABSTRACT

INTRODUCTION: Muscle pain is a natural consequence of intense and prolonged exercise and has been suggested to be a limiter of performance and barrier to physical activity. Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to reduce both chronic and acute pain in a variety of conditions. This study was sought to ascertain whether TENS and IFC could reduce exercise-induced pain and whether this would affect endurance exercise performance. It was hypothesised that TENS and IFC would reduce exercise-induced muscle pain and result in an improved endurance exercise performance during whole-body dynamic exercise. **METHODS:** Twenty-tow healthy male and female participants completed a 16.1-km cycle time trial as quickly as they could whilst receiving TENS, IFC and a Sham placebo in a repeated measures, a cross-over, randomized, and placebo controlled design. **RESULTS:** The ANOVA revealed a significant difference in completion time between conditions ($F_{(2, 42)} = 6.597$, $P = 0.003$). Pairwise comparisons revealed that participants performed a significantly faster TT ($P = 0.001$) in the TENS condition (29 min 6 s ± 3 min 20 s) compared to the SHAM (29 min 39 s ± 3 min 34 s) condition. There were no significant differences ($P = 0.872$) between the IFC condition (29 min 28 s ± 3 min 34 s) and the SHAM, or the TENS and IFC conditions ($P = 0.116$). The ANOVA also revealed a significant main effect of condition for power output ($F_{(2, 38)} = 3.48$, $P = 0.041$), mean HR ($F_{(1.38, 29.06)} = 4.016$, $P = 0.042$) and mean B[La] ($F_{(1.49, 31.37)} = 7.54$, $P = 0.004$). There was a significant difference in the mean EIP between conditions during the TT ($F_{(2, 44)} = 4.210$, $P = 0.022$). Paired *t*-tests revealed that participants perceived significantly less pain during the TENS condition (3.5 ± 1.8) than in the sham condition (4.0 ± 2.0) ($t_{(21)} = 3.037$, $P = 0.006$). No differences were observed between the TENS and the IFC condition (3.8 ± 1.9) or the IFC and Sham condition ($P > 0.05$). No significant differences in mean RPE were found between conditions during the TT ($P > 0.05$). **CONCLUSION:** These findings demonstrate that TENS can attenuate exercise-induced muscle pain in healthy volunteers and that consequently significantly improves endurance performance in whole-body dynamic exercise.

Key words: Exercise-induced pain; time to exhaustion; time trial; exercise; gate control theory.

II. INTRODUCTION

The perception of muscle pain involves a complex neurobiological integrated network of peripheral and central mechanisms that are dependent on interactions between top-down and bottom-up information. Of primary importance however, is the nociceptive signal, which arises when A-delta (group III) and C fibres (group IV) are sensitised and stimulated by variety of noxious mechanical, thermal and chemical stimuli (Marchettini et al., 1996). Intense and prolonged muscular contraction elicits such an environment, through the production of bradykinin, hydrogen ions, potassium, prostaglandins and an increased intramuscular pressure (Mense, 1993), and results in what has been termed exercise-induced pain. Consequently, intense and prolonged exercise is often accompanied by sensations of pain and discomfort, which may contribute to a negative affect (Babel, 2015) and present barriers to regular physical exercise (Cohen-Mansfield et al., 2003). Additionally, because the magnitude of exercise-induced pain is proportional to exercise intensity (Cook et al., 1997), and pain represents a powerful stimulus to disengage from the pain-causing behaviour, successful endurance exercise performance may require a high tolerance to pain (Mauger, 2014). Indeed, Astokorki and Mauger (2016) have recently shown that tolerance to exercise-induced pain (but not pressure or thermal pain) predicted cycling performance in untrained men and women. This finding is supported by studies that have sought to reduce pain during exercise and observed an improved endurance performance as a consequence (Astorino et al., 2011; Astorino et al., 2012; Foster et al., 2014; Hudson et al., 2008; Jenkins et al., 2008; Mauger et al., 2010, 2014).

If reducing pain during exercise allows an improved endurance performance, or reduces the unpleasantness of the experience, then an intervention which can achieve this could be of interest to populations where regular exercise would impart a health or performance benefit. Whilst some studies have achieved this through pharmacological intervention, such as paracetamol or caffeine ingestion (Astorino et al., 2011; Astorino et al., 2012; Foster et al., 2014; Hudson et al., 2008; Jenkins et al., 2008; Mauger et al., 2010, 2014), there are negative side-effects associated with this that may offset the benefit of any increased exercise performance or adherence. Furthermore, it should be noted that some evidence exists investigating that the ingestion of other analgesics (aspirin and codeine) has not reduced exercise-induced pain or produced improvements in performance (Roi et

al., 1994; Cook et al., 1997; Ray & Carter, 2007; Hudson, Green, Bishop & Richardson, 2008). Thus, there is a need for alternative methods of analgesia, that can be used during exercise and elicit little or no side-effect and show an improved performance. According to the Gate Control Theory of pain (Wall & Melzack, 1965), perception of pain is not solely due to activation of nociceptors, but is the outcome of modulation of both nociceptive and non-nociceptive inputs. Inhibitory interneurons regulate the transmission of ascending nociceptive information at the substantia gelatinosa, allowing modulation of the nociceptive signal before it has reached the brain level (Melzack & Wall, 1965). Thus, selectively stimulating Aβ large-diameter afferent fibres in the presence of a nociceptive stimulus may serve to reduce the subsequent perception of pain – this is the premise of 'rubbing a bruised shin reduces the pain'. In accordance with this, application of a high frequency electrical stimulation with a pulse amplitude titrated to produce a strong comfortable and non-painful paraesthesia is suggested to activate large diameter afferents (A-beta fibres) (Sluka & Walsh, 2003) and induce mild analgesia (Melzack, 1965; Garrison & Foreman, 1994; Walsh, 1997). This technique is called transcutaneous electrical nerve stimulation (TENS), and when adapted to produce both high-low frequency impulses, interferential current stimulation (IFC). When administered correctly, these techniques are safe, produce no dangerous side-effects and whilst not widely used, have been shown to elicit pain relief, facilitate recovery, treatment for urinary incontinence in female athletes and delayed onset muscle soreness (Bolin, 2003; Heyman, De Geus, Mertens & Meeusen, 2009; Rivata et al., 2010; Rocha et al., 2012; Vanderthommen et al., 2012).

However, no studies have administered TENS or IFC during exercise with the aim of reducing exercise-induced pain. Therefore, the purpose of this study was to establish whether the analgesic effect of TENS and IFC using equal stimulus parameters of frequency, and current amplitude would reduce perceived pain and improve performance of a 10-mile (16.1 km) cycling time trial. It was hypothesised that the TENS and IFC would reduce the exercise-induced pain and would improve completion time when compared to the 'sham' condition.

III. MATERIALS AND METHODS

Subjects

Twenty-two participants (male n=14, female n=8), trained in cycling and triathlon and exercising regularly (> 3 h per week) were recruited for this study. The participants' mean age, height and body mass were 33 ± 8 yrs, 173 ± 7 cm and 71.8 ± 13.3 kg, respectively. Prior to participation, participants were given an information sheet of the study describing what they were asked to do. All data were anonymised and participants were told that they had the right to withdraw from the experiment at any time. Following this, they were asked to complete the inclusion/exclusion criteria checklist and medical health questionnaire. The participants were excluded from the study if they had history of any cardiovascular disorder (e.g. angina, heart attack, high blood pressure etc), chronic medications that affect the central nervous system, pregnancy, bleeding disorders (e.g. haemophilia), deep vein thrombosis, impaired sensation, acute/chronic infection (e.g. tuberculosis), malignancy, recently radiated tissue, skin diseases or severely damaged skin, types I or II diabetes, or were using cochlear implants or pacemakers, or any other condition that may be a danger to their participating in a test (e.g. injury). Following this, all participants were asked to read and sign an informed consent form. The research was approved by Local Ethics Committee at the University of Kent. task. Participants were asked to refrain from the ingestion of alcohol 48 hours, caffeine 8 hours and analgesics 6 hours, and asked to refrain from any vigorous exercise 48 hours, prior to experimental visits (Lu, Lai & Chan, 2008). Participants were also asked to maintain their normal diets and keep regular sleeping hours.

Table 6.1. Group mean values across all perceptual and exercise tests

Variable	**Male**	**Female**	**Total (Fe & M)**
Age (yrs)	33 ± 4	31 ± 6	32 ± 7
Height (cm)	176 ± 4	167 ± 5	173 ± 7
Body mass (kg)	74.36 ± 12.23	60.50 ± 5.05	71.86 ± 13.40
VO_{2max} (mL/kg/min)	55.3 ± 5.3	47.9 ± 8.8	52.5 ± 7.5
Anaerobic Threshold (mL/kg/min)	29.7 ± 6.5	25.5 ± 3.7	28.2 ± 5.9
Peak Power Output (W)	322.4 ± 53.6	207.1± 40.2	280.5 ± 74.4
GXT end pain	7.4 ± 2.7	4.9 ± 1.7	6.5 ± 2.7
GXT end RPE	18.8 ± 1.5	16.3 ± 2.1	18.0 ± 2.0
GXT HR_{max} (beat. min^{-1})	178.2 ± 11.4	177.4 ± 11.4	177.9 ± 11.4

RPE, rating of perceived exertion; GXT, graded exercise test; HR, heart rate

Procedures

Participants attended the laboratory on four separate occasions, each separated by 2-5 days. Visit one involved full familiarisations of the stimulations, perceptual scales, questionnaires and exercise tests. In visits 2-4, participants completed the exercise test (10-mile cycling time trial) in the presence of either TENS, IFC or sham in a counter-balanced and single-blind experimental design.

Familiarisation

On the first visit to the laboratory, participants underwent a general health screening in addition to a test for skin integrity and sensory discrimination using a sharp and blunt patella hammer. All the participants completed the test satisfactorily and agreed to proceed with experiment. To be familiarised with the TENS and IFC stimulation, and to ensure the stimulation induced a strong comfortable and non-painful paraesthesia, participants were briefly administered TENS and IFC. In order to reduce resistance to the electrical current, the skin of the vastus lateralis of both thighs was shaved and cleaned thoroughly before the electrodes were placed on it. Bipolar surface electrodes were placed over the vastus lateralis and the TENS and IFC were applied at high frequency, but low intensity stimulation. To ensure the appropriate intensity for the subsequent test occasions, amplitude was steadily increased until the participant perceived a comfortable tingling sensation but did not experience any muscle pain. The intensity of TENS or IFC was gradually increased in a similar manner, but limited so as to produce no muscle contraction. Stimulation frequency was increased up to 100 Hz with a pulse width of 300 μs – these parameters induced a comfortable tingling sensation, with no muscle pain or contraction in all participants. Throughout all test occasions, participants were monitored for signs of skin irritation, nausea, swelling and pain. Following familiarisation to TENS and IFC, participants were introduced to the numeric pain rating scale (0-10) (Cook et al., 1997) and Borg's (6-20) rating of perceived exertion (RPE) scale (Borg, 1998). Participants were instructed to report RPE solely as effort to drive the limb (Pageaux et al., 2015) (i.e. independent of pain and discomfort) and that pain should be anchored to exercise-induced pain (i.e. numeric values given relative to their experience of muscle pain). After participants confirmed their understanding of the pain and RPE scales, they completed a VO_{2max} test (GXT) after a standardized 10-min warm-up at a self-selected intensity on the

cycle ergometer (Velotron, Racermate, Seattle, WA). An incremental step protocol was utilised, starting at a power output (PO) of 100 W with increases of 30 W. min^{-1}. Participants maintained a self-selected cadence until volitional exhaustion or when they could no longer maintain the required cadence. During the test, gas exchange (Cortex Metalyser 3B, Cortex GmbH, Lepzig, Germany) and heart rate (HR) (Polar Electro, N2965, Finland) were recorded continuously, with RPE and perceived pain recorded at the end of each stage. Throughout the test verbal encouragement was given by the researcher. On completion of the test, participants received a 30-min rest period during which they were familiarised to, and completed, a mood questionnaire (Brunel Universal Mood States (BRUMS) (Terry & Fogarty, 2003). Finally, after the 30-min rest period, participants completed a familiarisation of the self-paced 10 mile (16.1-km) cycling time trial (TT). Participants could change gear and cadence to complete the TT in the fastest time they could, and they could see the distance they had completed but were given no information on performance or physiological parameters (e.g. PO, HR, time elapsed). Participants were asked to report RPE and perceived pain every km. On completion of the TT, participants completed a further BRUMS.

Experimental Visits 2-4

Participants initially completed a BRUMS before performing the TT in the same manner as described above, with the addition of a fingertip sample of blood acquired every 4-km for analysis for blood lactate concentration (B[La]). Throughout the TT participants either received TENS, IFC or sham (placebo-controlled) on the vastus lateralis of both thighs, as shown in Figure 6.1. Prior to the TT, the stimulation electrodes were placed (in the manner described in the familiarisation visit) and current was applied for 5-min, followed by a 10-min warm-up on the cycle ergometer at a self-selected intensity. The parameters of the IFC pulses were delivered in a continuous mode with a pulse frequency of 100Hz (ascertained in the familiarisation visit). For the TENS pulses, a continuous pattern of stimulation was used, with a pulse width of 300 μs and frequency at 100 Hz. As TENS is carried out via two electrodes, bipolar IFC was used to maintain blinding of conditions. Previous studies have shown that bipolar and quadripolar techniques work equally well when used to manage pain conditions (Johnson & Tabasam, 1998). Stimulation was delivered using a Vectra Genisys multi-waveform stimulator (Chattanooga Group, Hixon, TN, USA). In the

sham stimulation, the electrodes were placed on the same muscle site as the TENS and IFC conditions and the machine was turned on but with no stimulation applied. Participants were told, “This type of stimulation is supposed to reduce pain using a subthreshold stimulus that you will not be able to perceive”, which was strengthened via a visual display of the electrical current on an oscilloscope. On completion of the TT, participants completed a BRUMS.

Statistical Analysis

Descriptive data are reported as means ± SD. Standard assumptions (Kruskal-Wallis test and Shapiro-Wilk test) were checked for each statistical test prior to analysis, and none of these were violated. Power output and HR were averaged for every km completed. TT completion time was analysed using a repeated measures ANOVA and Bonferroni Pairwise Comparisons. BRUMS score, PO, B[La], HR, RPE and pain were assessed using an ANOVA with repeated measures and appropriate paired-sample *t*-tests Bonferroni Pairwise Comparisons. Changes in PO, B[La], HR, RPE and pain over time between conditions was examined using a three-way ANOVA with repeated measures and appropriate follow-up paired-sample t-tests. All statistical analysis was performed using the statistical package SPSS for Windows, PC software, version 22 (SPSS Inc., Chicago, IL, USA), and significance was accepted when $P < 0.05$.

IV. RESULTS

Time Trial (TT) Completion Time: The ANOVA revealed a significant difference in completion time between conditions ($F_{(2, 42)} = 6.597$, $P = 0.003$). Pairwise comparisons revealed that participants performed a significantly faster TT ($P = 0.001$) in the TENS condition (29 min 6 s ± 3 min 20 s) compared to the SHAM (29 min 39 s ± 3 min 34 s) condition. There were no significant differences ($P = 0.872$) between the IFC condition (29 min 28 s ± 3 min 34 s) and the SHAM, or the TENS and IFC conditions ($P = 0.116$).

Power Output (PO): The ANOVA revealed a significant main effect of condition for power output ($F_{(2, 38)} = 3.48$, $P = 0.041$). There was also a main effect for distance completed ($P < 0.001$), but no interaction effect ($F_{(30, 570)} = 0.92$, $P = 0.587$), as shown in Figure 6.1.

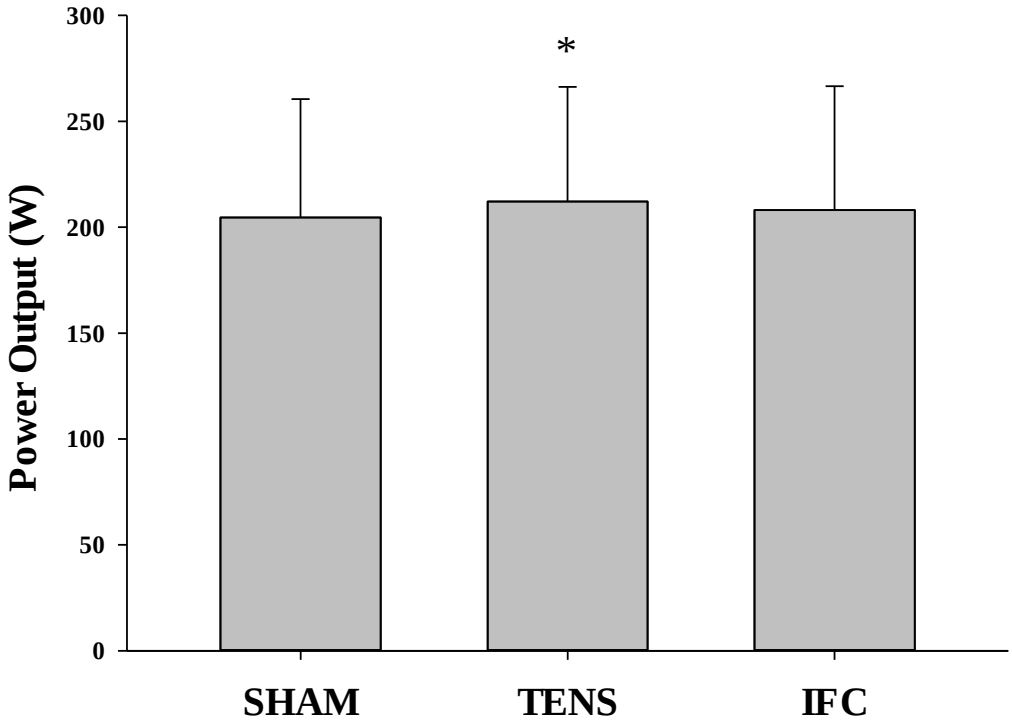


Figure 6.1 Shows the power output differences between conditions. * A significant main effect for condition. Significant differences ($P < 0.05$) between TENS vs. SHAM.

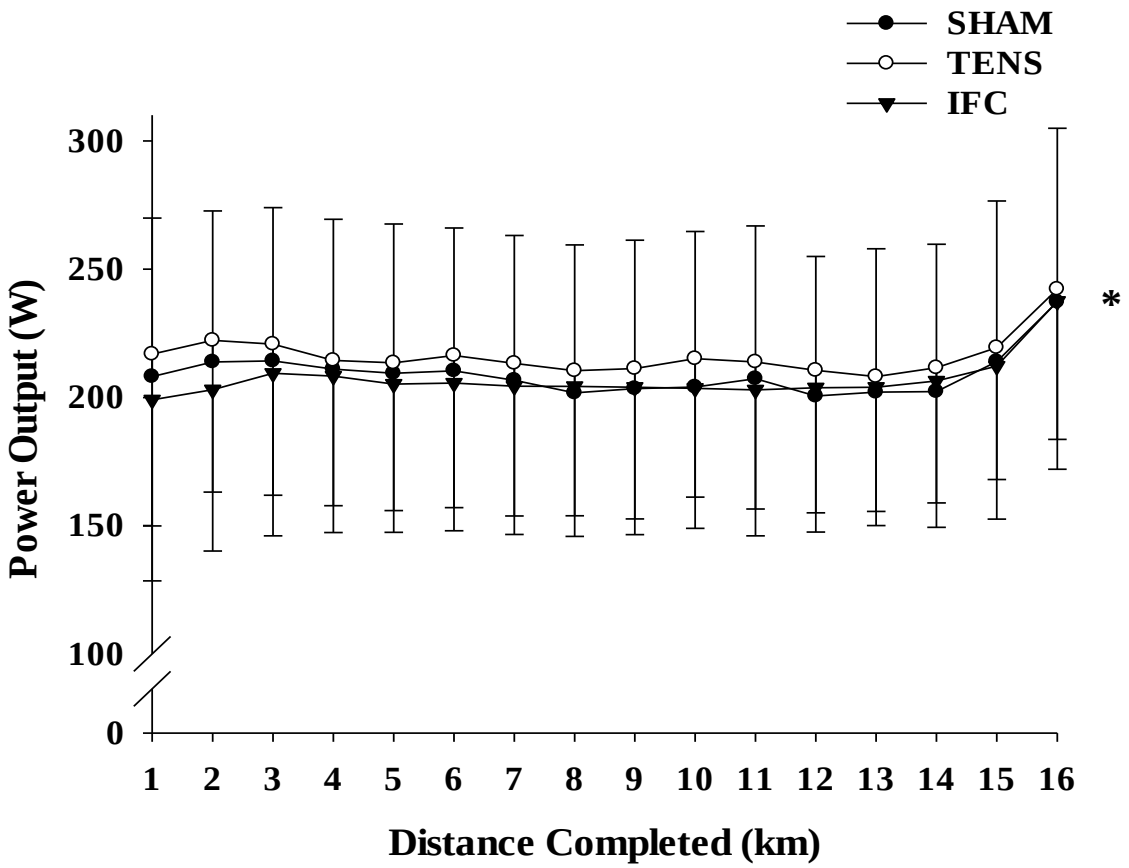


Figure 6.2 Power output profiles during the time trials for TENS, IFC and Sham conditions. ***** denotes a significant main effect for condition ($P < 0.05$).

Rating Perceived Exertion (RPE): No significant main effects for condition were observed ($P > 0.05$). There was a main effect for distance completed ($P < 0.001$), but no significant interaction effect was found ($P > 0.05$), as shown in Figure 6.3.

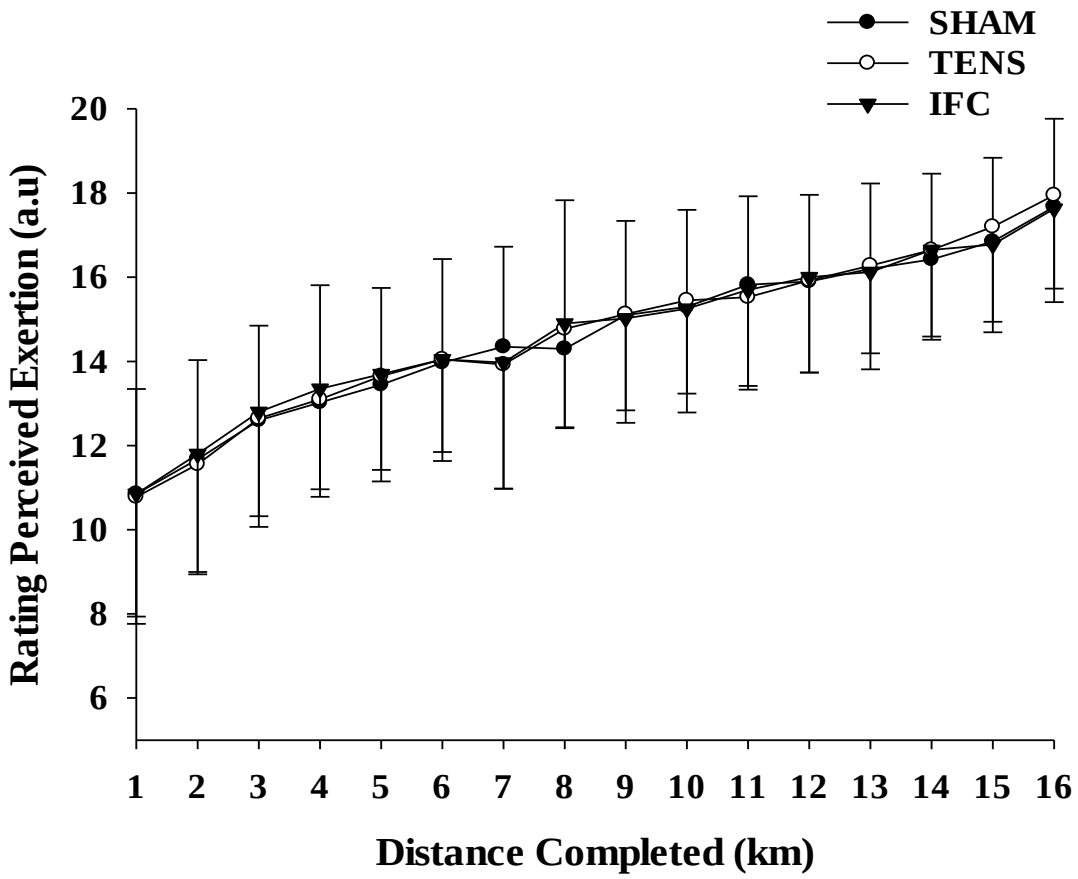


Figure 6.3 Rating perceived exertion profiles during the time trials for TENS, IFC and Sham conditions.

Exercise-induced pain (EIP): There was no main effect of condition for EIP ($F_{(1.41, 29.62)} = 3.60$, $P = 0.054$). There was a significant main effect for distance completed ($P < 0.001$) and a significant interaction effect ($F_{(30, 630)} = 2.04$, $P = 0.001$). Follow-up paired *t*-tests revealed that participants perceived significantly less EIP in the TENS condition compared to the SHAM at the 4th, 6th, 9th, 11th, 12th, 13th and 15th km ($P < 0.05$), as shown in Figure 6.4.

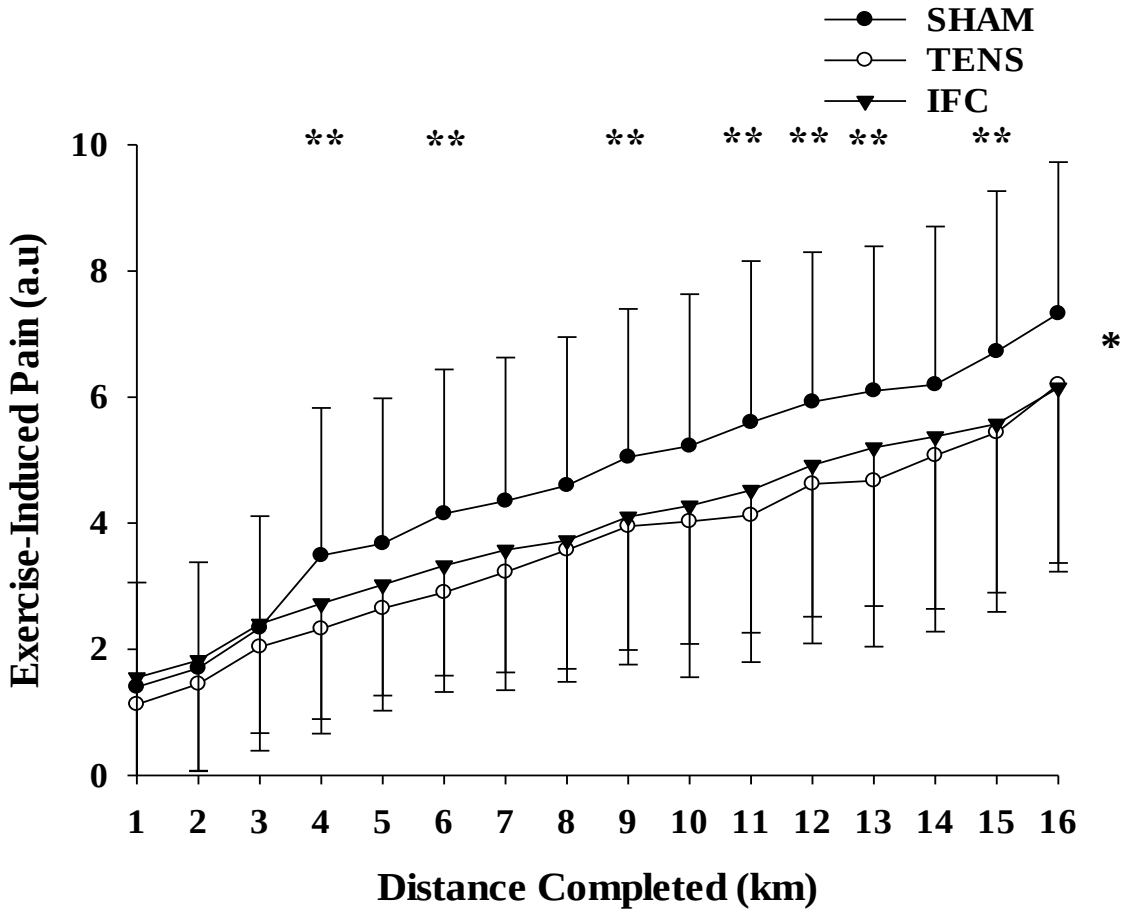


Figure 6.4 Exercise-induced pain profiles during the time trials for TENS, IFC and Sham conditions. ****** denotes a significant interaction between sham and TENS. ***** denotes a significant main effect for condition and time ($P < 0.05$).

Heart Rate (HR): The ANOVA revealed a significant difference in the mean HR between conditions during the TT ($F_{(1.38, 29.06)} = 4.016$, $P = 0.042$). There was a significant main effect for distance completed ($P < 0.05$), and a significant interaction effect was observed ($F_{(1.3, 27.8)} = 3.171$, $P = 0.008$). Follow-up paired-sample *t*-tests showed a significant difference in HR between TENS and SHAM conditions between the 8^{th}-16^{th} km ($P < 0.05$). Additionally, significant differences in HR between IFC and SHAM conditions were observed between the 11^{th}-16^{th} km ($P < 0.05$). There were also significant differences in HR between TENS and IFC conditions during the 9^{th}, 14^{th}, 15^{th} and 16^{th} km ($P < 0.05$). Differences in HR between conditions are shown in Figure 6.5.

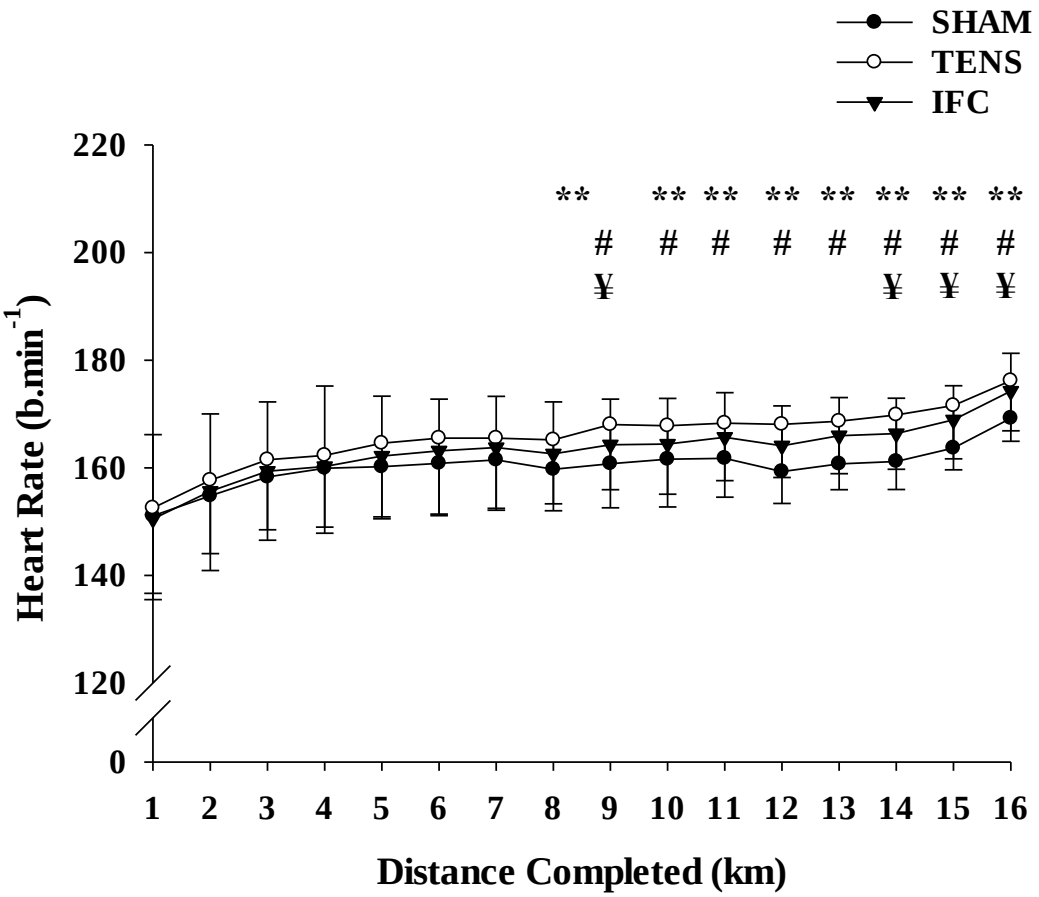


Figure 6.5 Heart rate profiles during the time trials for TENS, IFC and Sham conditions. ****** denotes a significant interaction between sham and TENS. # denotes a significant interaction between Sham and IFC. ¥ denotes a significant interaction between TENS and IFC in HR.

Blood lactate (B[La]): The ANOVA revealed a significant main effect of condition ($F_{(1.49, 31.37)} = 7.54$, $P = 0.004$), a main effect for distance completed ($P < 0.05$) and a significant interaction effect $F_{(3.68, 77.63)} = 3.51$, $P = 0.013$). Follow up paired-sample *t*-tests showed a significantly different B[La] between TENS and SHAM conditions at the 12th km ($t_{(21)} = -2.850$, $P = 0.01$), and the 16th km ($t_{(21)} = -4.370$, $P < 0.001$). There was also a difference in B[La] between IFC and SHAM conditions at the 16th km ($t_{(21)} = -3.632$, $P = 0.002$), and a significant difference in B[La] between TENS and IFC conditions at the 12th km ($t_{(21)} = 2.496$, $P = 0.021$), as shown in Figure 6.6.

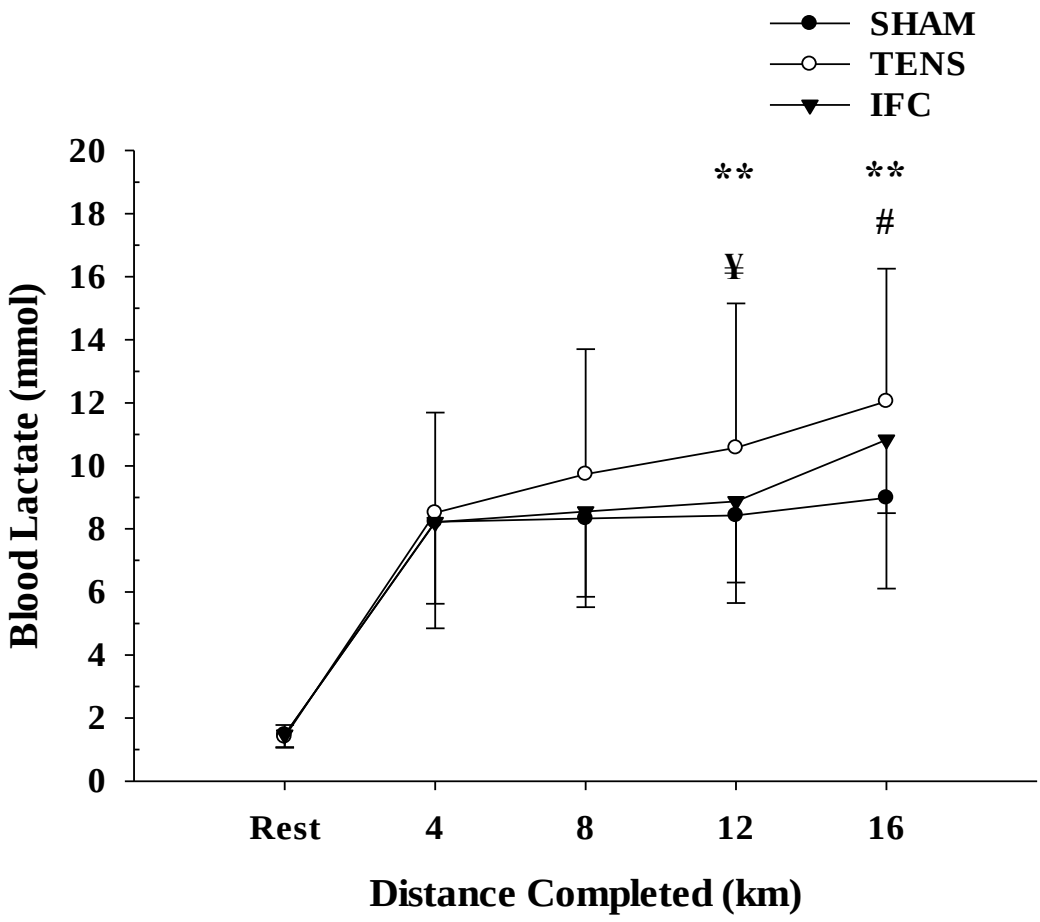


Figure 6.6 Blood lactate profiles during the time trials for TENS, IFC and Sham conditions. ** denotes a significant interaction between sham and TENS. # denotes a significant interaction between Sham and IFC. ¥ denotes a significant interaction between TENS and IFC in B[La].

BRUMS: No differences in mood states were found between conditions pre- or post TT. Paired-sample *t*-tests showed only a significant difference in pre- and post TT for vigour during the TENS condition ($t_{(21)} = -2.114$, $P = 0.047$). No other differences in pre- post mood states were observed.

V. DISCUSSION

The purpose of the study was to determine whether TENS and IFC would improve the performance of a 10-mile cycling TT by reducing exercise-induced pain in trained cyclists. The principal and novel finding of this study was that TENS significantly improved completion time of the cycling TT, and that this was achieved by maintaining a higher PO, HR and B[La]. Despite the increased physiological strain and metabolic challenge induced by the higher PO, participants felt less exercise-induced pain in the TENS condition alongside no change in perception of effort. These findings support previous research which demonstrates that mild analgesia can induce an ergogenic effect in self-paced exercise, but is the first study to show that a TENS intervention can be used to elicit this analgesia to exercise-induced pain.

The TENS intervention in the current study conferred a ~2% average improvement in TT completion time compared to the placebo condition. This was the result of a significantly higher PO (mean of 216 W) that was sustained throughout the TT (see Figure 6.2), which likely led to the observed higher HR and B[La] concentration in the TENS condition. The higher metabolic demand in the TENS condition would have created a greater noxious environment in and around the muscle (evidenced by the higher B[La]), which would have been expected to increase perceived pain. However, the striking finding of this study was that despite the increased nociceptive conditions, participants perceived less pain in the TENS condition. TENS is hypothesised to reduce pain by selectively activating the large-diameter primary afferent fibres (A-beta fibres) (Sluka & Walsh, 2003), which inhibits the nociceptive transmission from small diameter higher threshold nociceptive (A-delta and C) fibres through pre-and post synaptic inhibition in the dorsal horn of the spinal cord (Melzack & Wall, 1965). Additionally, activation of small-diameter afferent fibres through TENS and/or IFC may modulate the transmission of pain through the release of endogenous opioids (Resende et al., 2004; Sabino et al., 2008), and serotonin (Chen, 2010).

Therefore, despite the likely higher stimulation of the nociceptive fibres experienced in the TENS condition of the current study, TENS stimulation may have been able to attenuate the noxious input of nociceptors at the spinal cord level, thereby reducing the overall experience of pain in this condition.

Classically, endurance performance has been explained through a performance model that focusses solely on the physiological mechanisms underpinning maximal oxygen uptake, lactate threshold and exercise efficiency (Joyner & Coyle, 2008). Whilst there is no doubt that these parameters set the basis of performance velocity, they are not capable of explaining differences between race performance, or how work rate is regulated during exercise. Furthermore, the model is not capable of explaining improvements in performance via interventions that have no effect of the maximal oxygen uptake, lactate threshold, and exercise efficiency parameters. A clear example of this is the study of Swart et al. (2009), who showed that highly trained cyclists were capable of sustaining significantly higher work rates under increased levels of metabolic and cardiorespiratory stress for longer when given the amphetamine methylphenidate. This study demonstrates that the exercising body is capable of tolerating a significantly greater physiological strain than is usually achievable is normal conditions, and that this tolerance is likely set by the central nervous system. The Central Governor Model (Noakes 2000, 2011) suggests that endurance performance is regulated through a complex comparison between perceived demands of the exercise (knowledge of end-point, environmental conditions, course topography), knowledge of own physiological capability and current demands of the exercise (via afferent feedback). This internal calculation is set with the primary aim of avoiding a disturbance to homeostasis to a level that would result in damage to the body. Support for this model is underpinned by studies which have shown that changes to factors influencing the internal calculation (e.g. distance knowledge (Mauger et al., 2009), competition (Corbett et al., 2012), central processing (Swart et al., 2009)) can improve endurance performance. However, Amann et al. (2009) suggest that a difference in endurance performance is primarily dependent on afferent feedback from the periphery. In this Afferent Feedback Model, metabolic changes in the muscle results in a reduced or impeded central motor drive that elicits central fatigue. This system is suggested to act as a safety mechanism, so that central motor drive restricts the development of peripheral locomotor fatigue to an individual critical threshold, and that this level of restriction is at

least partly based on muscle afferent feedback. The studies by Amann and colleagues (2009) using fentanyl and epidurals support this notion, although there are some inherent methodological flaws arising from complete blockade of afferent feedback in these study design (e.g. migration of fentanyl above the site of blockade, effect on exercise pressor reflex). The Psychobiological Model of endurance performance (Marcora, 2009) suggests that motivation and perception of effort (RPE) are the sole determinants of endurance performance. In this model, RPE is the product of central command (via the collorary discharge) and completely independent of afferent feedback. Increased central drive is required in the presence of muscle fatigue, and so RPE increases with task duration. Disengagement from the task occurs when the RPE is greater than the motivation for the task. This model is supported by studies that show that changes to RPE are able to change endurance performance, and that RPE is a product of the central motor drive (Pageaux et al., 2015). The results from the current study show an improvement in performance via an intervention that likely reduced nociceptive signal past the spinal level. This allowed a higher PO to be sustained, alongside a reduced level of pain but no change in RPE. Central command would likely have been higher in the TENS condition (increased PO and a higher level of muscle fatigue) compared to the sham condition, and according to the psychobiological model, this should have resulted in an increased RPE. As this was not the case, the results of this study cannot be explained by the psychobiological model. However, the reduced afferent feedback experienced in the TENS condition may have either reduced the conscious awareness of the demands of the task, and/or moderated the debilitative cortico-spinal effects that a sustained higher PO would usually elicit. Consequently, the findings of the current study are best explained by the central governor model or the afferent feedback model.

The 30 s improvement in completion time (~2% faster than sham) observed in the TENS condition, whilst small, is likely meaningful. Indeed, for riders of similar ability competing in amateur 10-mile TT races, a 30 s improvement in completion time would usually result in several places higher in the rider rankings. As there are no known side-effects with TENS that may affect exercise, the change in performance observed in the current study can be exclusively attributed to the analgesic effect. This finding provides support for the notion that tolerance of exercise-induced pain is a determinant of endurance performance (Astokorki & Mauger, 2016), and that moderation of it confers a performance advantage

(Mauger, 2014). Astokorki and Mauger (2016) have recently shown that when combined with physiological performance parameters, tolerance of exercise-induced pain was able to explain an additional 7.5% variance after PPO had explained 74.7% variance in endurance performance. Mauger et al. (2010) have also shown that mild analgesia using paracetamol improves 10-mile TT performance to a similar degree observed in the current study. Whilst the current study supports the theoretical importance of exercise-induced pain to endurance performance, the practicality (and ethical implications) of using TENS as an ergogenic aid is perhaps less impactful. However, even moderate levels of exercise elicit some level of pain (Cook et al., 1999), and symptoms of diseases such as pain and fear of pain present the biggest barriers to physical exercise (Clark; Hays & Clark, 1999) in some clinical populations where exercise would be beneficial to their condition. Indeed, regular exercise provides a range of health benefits, which significantly reduce all-cause mortality (Lee & Skerrett, 2001) and consequently exercise is often prescribed to treat a range of clinical conditions to improve patient outcome (Naci & Ioannidis, 2013; Thomson et al., 2003). If pain could be reduced during exercise, then this may improve motivation to exercise (Wiech & Tracey, 2013) and help improve rates of adherence to exercise prescription programmes. Therefore, the results of the current study have particular relevance to populations who engage in exercise for health benefit (rather than endurance performance), because TENS could provide a cheap, safe and non-invasive means of reducing obstacles for exercise engagement.

VI. CONCLUSION

This study demonstrates that electrical nerve stimulation through TENS can elicit an analgesic effect during exercise and improve the performance of a 10-mile cycling TT. Despite a higher PO, B[La] and HR, TENS reduced perception of pain during exercise, in the absence of a difference in RPE between conditions. These findings provide some insight into the pain pathways involved in the transmission of exercise-induced pain, and support the notion that tolerance of pain is an important determinant of endurance performance.

CHAPTER 7

EXPERIMENTAL 5th STUDY

The effect of compassional hyperalgesia on exercise-induced pain during endurance cycling performance

Ali HY. Astokorki[1], Alexis R. Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK

I. ABSTRACT

INTRODUCTION: Pain is an unpleasant, subjective experience that includes sensory and emotional components. Several studies have shown that observing other's pain can enhance the intensity of painful stimuli (compassional hyperalgesia), likely through changes in mood. This phenomenon was used in the current study to investigate the degree to which negative mood may affect exercise-induced pain and endurance performance. **METHODS:** Twenty-one participants, trained in cycling, completed 5 laboratory visits. The first two visits assessed aerobic capacity (VO_{2max} test) and fully familiarised participants with the fixed power (FP) and time trial (TT) tests. In the subsequent three visits, in a counter-balanced manner, participants performed a FP and TT. Immediately prior to these, participants viewed a collection of images from the International Affective Picture System database that were either pleasant, unpleasant (painful) or neutral. Participants were asked to rate each image with respect to affective valence and their level of emotion. During the TT and FP, participants were asked their EIP, RPE and had measures of HR and B[La] recorded. **RESULTS:** Rated the subset of painful images with significantly higher values for emotional pain compared to the pleasant images and neutral images ($P<0.05$), and also rated each subset of images as different from one another for affectice valence ($P<0.05$). The ANOVA revealed a significant main effect of condition for TT performance ($F_{(2, 40)} = 8.480$, $P = 0.001$), PO ($F_{(2, 40)} = 6.318$, $P = 0.004$), HR ($F_{(2, 40)} = 4.502$, $P = 0.017$), and B[La] ($F_{(2, 40)} = 5.724$, $P = 0.007$) during the TT cycling performance, but no significant effect of condition for mean RPE or EIP ($P > 0.05$). The FP, a significant main effect of condition for EIP ($F_{(2, 40)} = 4.363$, $P = 0.019$), but no difference for RPE, HR or B[La] was found. The mood states, a significant effect of condition for depression, tension, anger, and confusion following viewing the images ($P < 0.05$), but no differences for fatigue and vigour were observed. **CONCLUSION:** The results of this study demonstrate that viewing painful images prior to exercise decreased TT performance. This study demonstrates that there is an emotional element to the processing of EIP that can be influenced by compassional hyperalgesia.

II. INTRODUCTION

Pain is an unpleasant, subjective experience that includes sensory and emotional components (Rainville, 2002). The sensory components of pain involve the transmission of signals from peripheral receptors through somatosensory to thalamic nuclei (VPL, VPM, S1, S2, and the posterior parietal regions) and, consequently, from these regions to cortical limbic pathways including the anterior cingulate cortex (ACC) and the anterior insular (AI) (Price, 2002). The emotional components of pain relate to perceptions of the unpleasantness of pain and primarily comprise of a complex system of neurophysiological networks in the brain, and involve several regions near the edge of the cortex which are associated with mood and instinct (Price, 2000; Boggio, Zaghi & Fregni, 2009), this region also controls the basic core of emotions (fear, pleasure, anger) which influence observation, memory, movement, and cognition which are combined to yield insights into the thoughts and feelings of others (Ickes, 1997). These basic emotions primarily involve the limbic system (Boggio et al., 2009). The cortical limbic pathway is known to integrate nociceptive input with information about the overall body status, and in turn regulates the affect attributed to pain (Price, 2002). Indeed, this affective component of pain depends upon neurophysiological systems that are anatomically distinct, at least partially, from those involved in the sensory perception of pain (Duquette, Roy, Lepore, Peretz & Rainville, 2007). In this regard, emotions and mood form an important element of pain, and changes in these have been shown to result in a different experience of perceived pain (De Wied & Verbaten 2001; Meagher et al., 2001).

At the neural level, several studies have described the sensation of pain without apparent noxious stimulation, and have shown that observing other's pain emotionally can enhance the intensity reports to painful stimuli – an effect termed compassional hyperalgesia (de Wied & Verbaten, 2001; Wunsch et al., 2003; Godinho et al., 2006; Loggia et al., 2008; Godinho et al., 2012). The International Affective Picture System (IAPS) suggests using hyperalgesia as a comprehensive term for all cases of increased pain sensitivity, since it is so often difficult to distinguish whether it is capable of activating nociceptors (Loeser & Treede, 2008). It is believed that the dorsolateral prefrontal cortex (DLPFC) plays a crucial role in physical, somatosensory pain perception, and its role in emotional pain, through exertion control on the perception of pain by modulating cortical and subcortical pathways (Lorenz, Minoshima & Casey, 2003; Godinho et al., 2006; Freund, Stuber, Wunderlich, &

Schmitz, 2007; Bar et al., 2007; Borckardt et al., 2007). Besides these regions, however, the neural activity of midbrain and ventral inferior frontal gyrus is also believed to be involved in the processing of pain and negative emotions, and is associated with the neural basis of empathy for pain response (Kober et al., 2008; Fan et al., 2011; Buhle et al., 2013). Intense exercise causes a noxious environment in the muscle which elicits 'exercise-induced pain' (EIP), and tolerance of this sensation has been associated with endurance performance (Dannecker & Koltyn, 2014; Mauger et al. 2010). The athlete's 'grimace' can be frequently observed in a variety of events, and partly represents the obvious pain and effort that the athlete is going through (Kress & Stratley, 2007). Indeed, there have been cited incidents where athletes have appeared to exaggerate or hide their facial expressions during an event in an attempt to deceive their opponents about how they are faring (Fotheringham, 2001). However, it has perhaps not been considered how observing someone else's pain during exercise, may affect one's own perceptions. If the intensity of the pain stimuli observed from others changes our own pain processing of pain and the way we experience it (Lamm et al., 2007), then this may affect decisions to alter work-rate due to a different pain perception (Mauger, 2014).

Therefore, the purpose of this study was to examine whether a moderation of the emotional response to pain via the use emotional pain evoking images, effects pain perception during endurance performance. It was hypothesised that painful images would induce hyperalgesia and reduce endurance cycling performance.

III. MATERIALS AND METHODS

Participants

Twenty-one male (n = 13) and female (n = 8) participants, trained in cycling (>3 h exercise per week) were recruited for this study, with characteristics detailed in Table 1. Before participating in this study, participants were given a brief of the study (information sheet) describing exactly what they were asked to do. Participants were informed that a series of potentially distressing images would be viewed in this study. Ten images (4 painful, 3 neutral, 3 pleasant) were presented to participants before taking part in the study so that they were aware of the type of image that would be viewed if they decided to participate. The participants were aware that all data would be unidentifiable and that they had the

right to withdraw from the study at any time without being required to provide a reason or an explanation. Following this, they were asked to complete the inclusion/exclusion criteria checklist and then asked to sign an informed consent form. Individuals suffering from the following conditions were excluded from the study: pregnancy, psychological disorders, history of fainting, bleeding disorders (e.g. haemophilia), types I or II diabetes, history of brain disorders, clinically significant or unstable medical, neuropsychiatric, or chronic pain disorder, history of substance abuse or dependence, history of brain surgery, tumour, or intracranial metal implantation, or be taking chronic medications that affect the central nervous, and history of heart disorders. All participants provided informed consent prior to volunteering for the study. Before all experimental visits, participants were asked to refrain from any vigorous exercise 24 hours before the laboratory visits, and asked to refrain from the ingestion of alcohol, caffeine and analgesics 48 h, 8 h and 6 h before any experimental visit (Lu, Lai & Chan, 2008). The experimental protocol was approved by the local Ethics Committee (University of Kent). Participants reported to the laboratory on five separate visits, each separated by 2-5 days.

Table 7.1 Participant mean values for anthropometric characteristics, cardiovascular and performance parameters, and mean ratings for image subsets for Affective Valance and Emotional Pain.

Variable	**Male**	**Female**	**Total (F & M)**
Age (yrs)	31 ± 7	29 ± 8	31 ± 7
Height (cm)	183 ± 9	166 ± 6	176 ± 12
Body mass (kg)	78.54 ± 15.73	59.50 ± 5.90	71.29 ± 15.82
VO_{2max} (mL/kg/min)	56.7 ± 8.9	49.5 ± 10.8	54.0 ± 10.1
Anaerobic Threshold (W)	164.4 ± 53.1	116.5 ± 30.9	146 ± 51
Peak Power Output (W)	336.1 ± 56.5	214.6± 51.2	290 ± 81
GXT end pain	7.9 ± 1.7	5.3 ± 2.6	6.9 ± 2.4
GXT end RPE	18.0 ± 1.5	17.0 ± 2.6	17.6 ± 2.0
GXT HR_{max} (beat. min^{-1})	181 ± 12	173 ± 18	180 ± 15

Image with respect (score)	**Pleasant**	**Neutral**	**Painful**
Affective Valence (1-9)	1.70 ± 0.80	3.88 ± 1.1	6.57 ± 0.93
Emotional pain/no pain (1-9) *	1.25 ± 0.30	1.33 ± 0.4	6.06 ± 1.30

RPE, rating of perceived exertion; GXT, graded exercise test; HR, heart rate; * Rating image based on emotional pain perceived and not feelings of disgust/unease

Table 7.2 Participants mean values for multidimensional assessment of interoceptive awareness questionnaire

Variables	values
Noticing	3.46 ± 0.85
Not-Distracting	3.31 ± 1.21
Not-Worrying	2.32 ± 0.83
Attention Regulation	3.33 ± 0.58
Emotional Awareness	3.22 ± 0.89
Self-Regulation	3.36 ± 2.43
Body Listening	1.59 ± 1.34
Trusting	3.57 ± 0.63

Procedure

Seventy-five images categorised into three subsets (painful, pleasant, and neutral), were shown via a PowerPoint Presentation on three separate experimental conditions (visits 3-5). Both painful and pleasant images had somatosensory content (i.e. illustrated athletes in painful or pleasant situations). The painful images (n = 25) presented emotionally disturbing images demonstrating athletes in pain (e.g. a severe injury). Pleasant images (n = 25) presented athletes enjoying cycling, exercising or joyful situations. The neutral subset (n = 25) presented a photo that included complex visual stimuli with no particular emotional content (e.g. a photo of a garden). Where appropriate, images (40%) were taken from the International Affective Picture System (IAPS) (Lang et al., 2001) according to IAPS criteria in terms of valence and arousal, which have previously been validated for their valence score (Boggio et al., 2006, 2008). As a limited number of relevant images (i.e. pain occurring in sporting situations) were present on the IAPS database, the remaining images were obtained from the internet. In this study, the image stimulus was presented sequentially within a slide show over the course of the exercise tasks, in an analogous manner to numerous pain studies which utilise the same technique (e.g. Boggio et al., 2009; Godinho et al., 2011; Godinho et al., 2011). Briefly, participants viewed a computer screen at a comfortable distance of approximately 60 cm. A standardised set of instructions were utilised to explain the procedure of the study, and they were informed that a series of images would be viewed. It was highlighted that participants should rate each image based on the emotional pain felt and not feelings of disgust or unease. The

three subsets of images were presented on separate visits in a counterbalanced and randomised order. Each subset presented a total of 25 images (15 images were viewed before the fixed power test and 10 images before the time trial). Each image was viewed for 30 s, as shown in the schematic in Figure 7.1. Immediately after viewing each image, participants were asked to rate each image with respect to affective valence (1 = pleasant, 9 = unpleasant) (Avery et al., 2007) and their level of emotional pain while viewing the images (1 = comfortable/no pain, 9 = uncomfortable/pain) (Bär, et al., 2007).

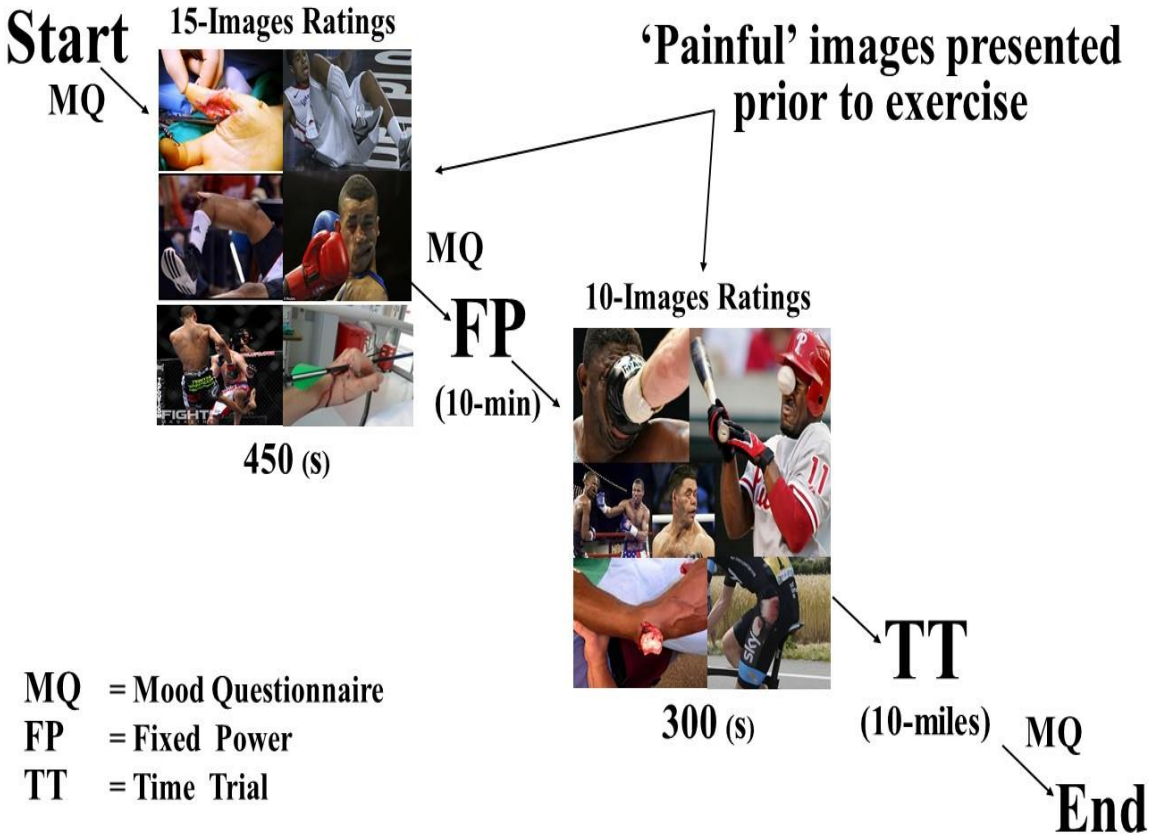


Figure 7.1 Overview of study design. Participants completed 5 visits to the laboratory (Each visit separated by 48 h).

In their first laboratory visit, participants completed a familiarisation of viewing images and providing a rating for these, and were then were given a Multidimensional Assessment of Interoceptive Awareness questionnaire (MAIA) created by Mehling et al. (2012). This questionnaire was used in order to identify the participants' awareness of uncomfortable, comfortable, and neutral body sensations, tendency not to ignore or distract oneself from sensations of pain or discomfort, tendency not to worry or experience emotional distress with sensations of pain or discomfort, ability to sustain and control attention to body sensations, awareness of the connection between body sensations and emotional states, ability to regulate distress by attention to body sensations, active listening to the body for insight, experience of one's body as safe and trustworthy. This questionnaire has been divided into eight subscales (including: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening and trusting. The items are answered on a 0 to 5-point scale (0 = never and 5 = always). Following this they were given standard instructions for the numeric pain rating scale (0-10, Cook et al. 1997) and rating of perceived exertion (RPE) using the Borg (6-20) scale (Borg, 1998) and a mood questionnaire (Brunel Universal Mood States; MQ) (Terry & Fogarty, 2003). Following this, participants commenced an assessment of aerobic capacity by performing a cycling-based VO_{2max} test. Power output was assessed using the cycle ergometer. Heart rate was continuously displayed using a Polar Vantage XL heart rate monitor (Polar Electro Oy, Kempele, Finland). Prior to the test, the ergometer was adjusted for each participant and the setting was recorded to allow reproduction at each subsequent visit. Expired gases were assessed using an online gas analyser (Cortex Biophysik GmbH, Leipzig, Germany) throughout the test. Following a rest period of 30-min, participants then performed a familiarisation of the exercise performance task described in Visit 2.

During the second visit, participants completed a second familiarisation MQ, followed by a second familiarisation of the exercise performance tasks. These involved a fixed power test (FP) where participants cycled against a fixed power equivalent to 70% of the maximal aerobic power (determined from GXT) for 10-min, maintaining a self-selected cadence throughout. The cadence was recorded to allow reproduction at each subsequent visit. The FP test was designed to be non-exhaustive, so that participants could report RPE and perceived pain every 2-minutes to allow an analysis of the perceptual effect of the experimental intervention, and to allow them to be able to complete the subsequent

performance trial. 5-min following the completion of the FP, participants completed the endurance performance test - a self-paced 16.1-km cycling time trial (TT) (Velotron, Racermate). Participants were instructed to complete the distance as quickly as possible, and to report RPE and perceived pain every km. After the TT, participants were given a 10-min cool-down at a self-selected intensity, and then completed a further MQ.

Visits 3-5 formed the experimental data collection. In these visits, participants initially completed a MQ followed by the FP and the TT (as described in Visit 2). During these exercise tasks, the computer screen was placed at eye level 60-cm away from participants, and then an image subset group (i.e. neutral/pain/pleasant) was presented. The presented image subset was randomised and counter-balanced across visits 3-5. Fifteen images from the subset were presented prior to FP task for a period of 7-min and 30 s, and 10 images were presented during the rest period between the FP and TT for 5-min (each image was viewed for 30 s). After viewing each image, participants were immediately asked to rate each image and their level of emotional pain while viewing the images. After the TT test, participants completed a final MQ.

Statistical analysis

Prior to statistical analysis, standard assumptions were checked for each statistical test, and none of these were violated, with the exception of completion time for the TT. The reciprocal translocation was used to normalise the distribution of TT completion time, which was then analysed using a repeated measures ANOVA and Bonferroni Pairwise Comparisons. Analysis of mean PO, mean HR, mean B[La], RPE and mean exercise-induced pain were performed using an ANOVA with repeated measures and appropriate follow-up paired-sample *t*-tests or pairwise comparisons. Changes in PO, HR, B[La], RPE and exercise-induced pain during each TT and FP condition were assessed using a three-way ANOVA with repeated measures and appropriate follow-up paired-sample *t*-tests. All statistical analysis was performed using the statistical package SPSS version 22 for Windows programs (SPSS Inc., Chicago, IL, USA). Descriptive data are reported as means ± SD. Statistical significance was accepted when $P < 0.05$.

IV. RESULTS

Image Ratings: Participants rated the subset of painful images with significantly higher values for emotional pain compared to the pleasant images and neutral images (P<0.05). Participants also rated each subset of images as different from one another for affective valence (P<0.05), as shown in Figure 7.2.

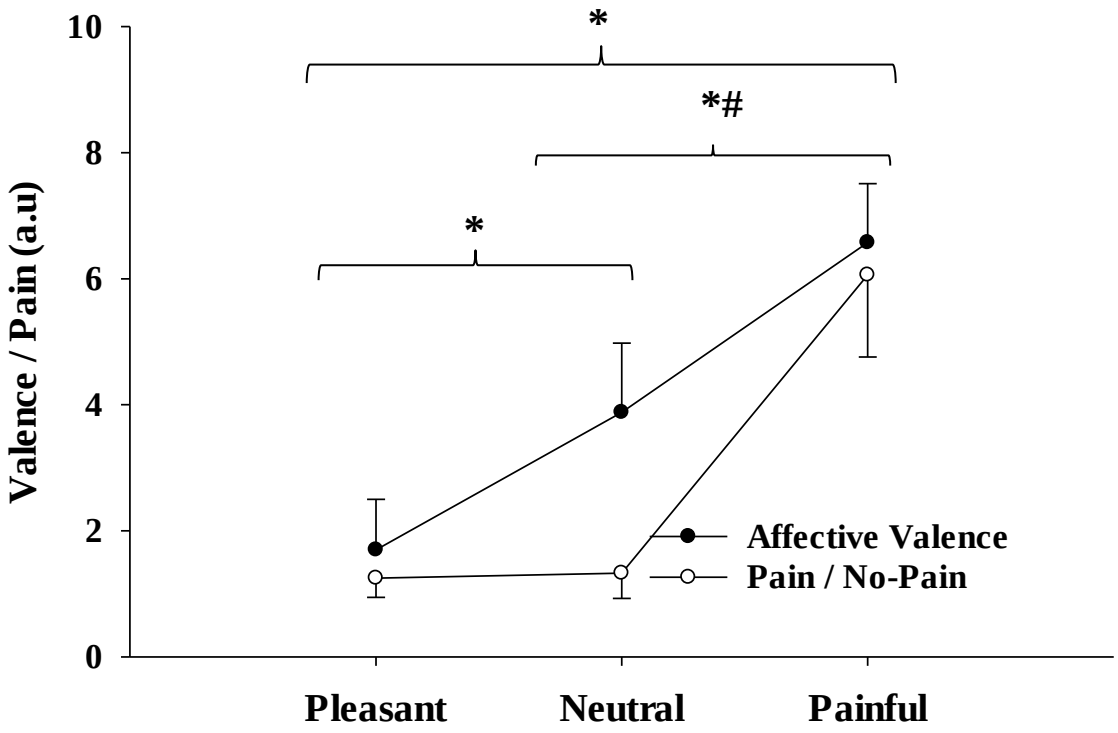


Figure 7.2 Shows differences between conditions for rating of affective valence and emotional pain perceived. * denotes significant difference between conditions for affective valence (P<0.05). # denotes significant difference between conditions for pain/no-pain.

Time Trial Task (TT)

Completion Time: The ANOVA revealed a significant difference in completion time between conditions ($F_{(2, 40)} = 8.480$, $p = 0.001$). Pairwise comparisons revealed that

participants performed a significantly faster TT (P = 0.003) in the pleasant condition (29 min 38 s ± 4 min 35 s) and the neutral condition (29 min 39 s ± 3 min 34 s) compared to the painful condition (30 min 19 s ± 5 min 7 s). There were no significant differences between the neutral condition and the pleasant (P = 1.000).

Power Output (PO): The ANOVA revealed a significant main effect of condition for PO during the TT cycling performance ($F_{(2, 40)} = 6.318$, P = 0.004), as shown in Figure 7.3. Follow-up tests showed a significant difference in mean PO between pleasant and painful image conditions ($t_{(20)} = 3.493$, P = 0.002) and between neutral and painful image conditions ($t_{(20)} = 2.939$, P = 0.008), but no significant differences between pleasant and neutral image conditions was found ($t_{(20)} = 0.560$, P = 0.581). There was also a main effect for distance completed (P < 0.001), but no interaction effect ($F_{(30, 600)} = 0.847$, P = 0.702), as shown in Figure 7.4.

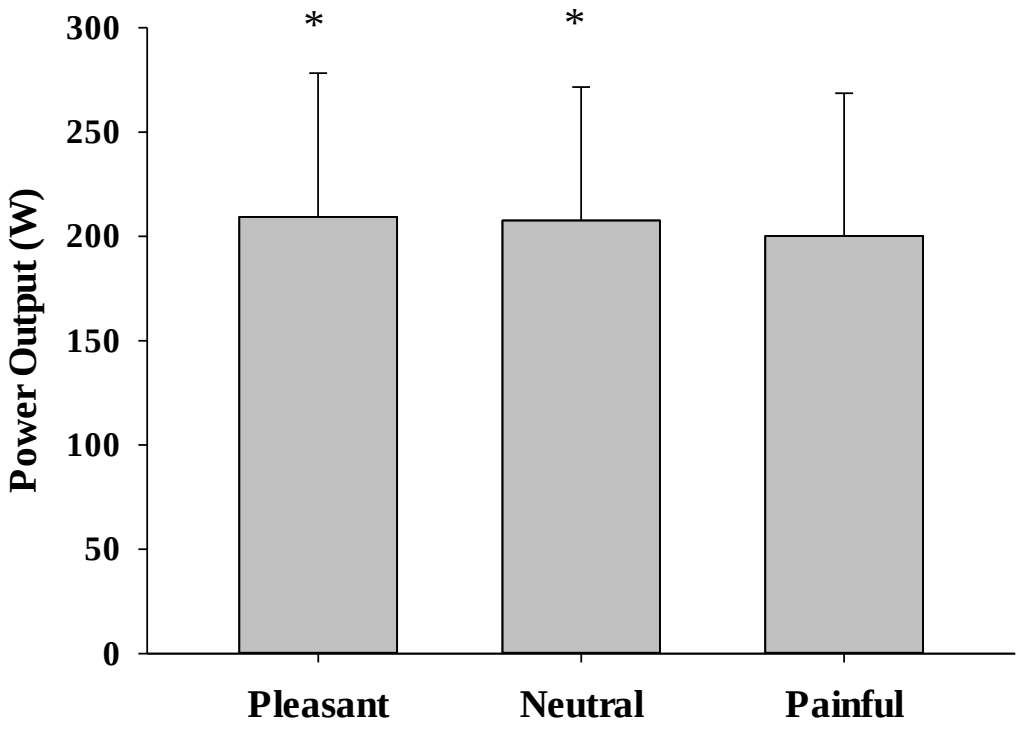


Figure 7.3 Shows the power output differences between conditions. * A significant main effect for condition. Significant differences (P < 0.05) between pleasant vs. painful, and neutral vs. painful.

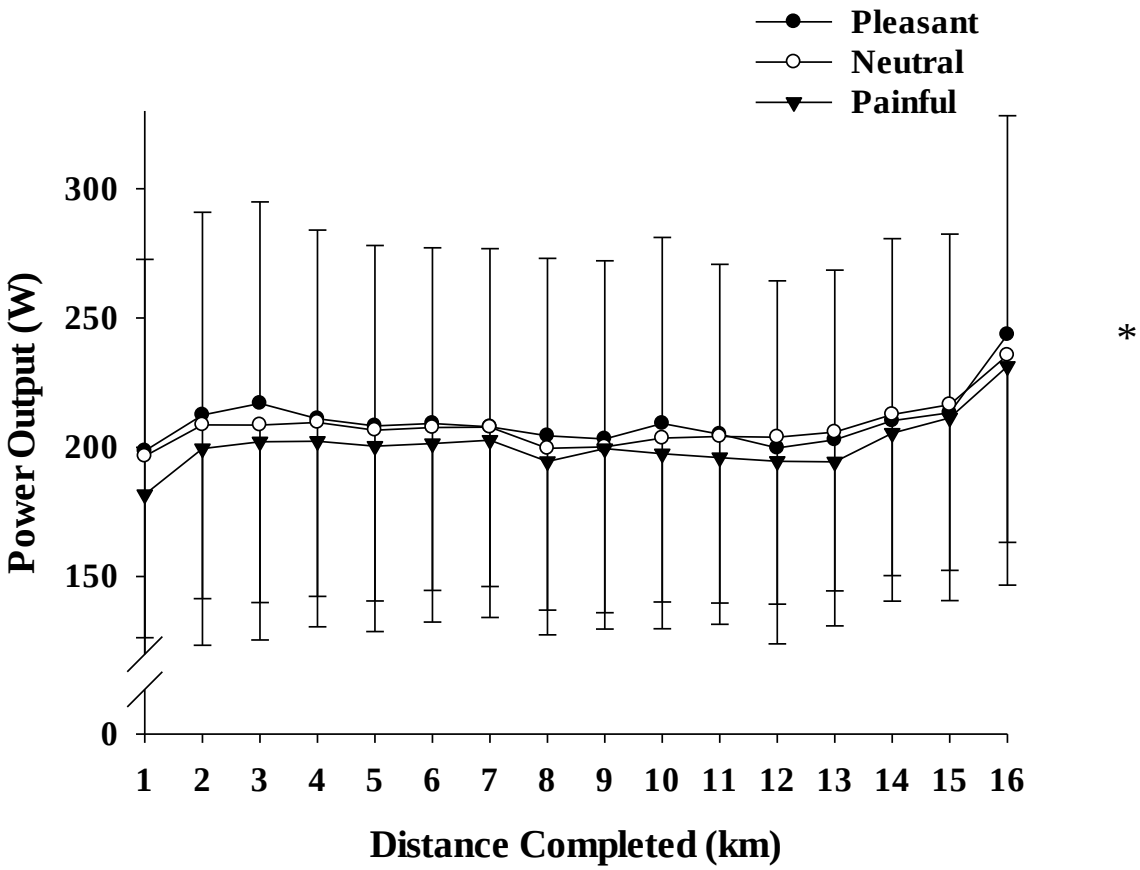


Figure 7.4 Power output differences between conditions over time. Although there was a significant difference in mean PO between conditions, no significant interaction effects for PO over time between conditions during the TT were observed ($P > 0.05$), indicating that the intervention did not effect pacing strategy selection. *significantly different between condition ($P < 0.05$).

Heart Rate (HR): The ANOVA revealed a significant difference in the mean HR between conditions during the TT ($F_{(2, 40)} = 4.502$, $P = 0.017$). There was a significant main effect for distance completed ($P < 0.05$), but no significant interaction effect was found ($P > 0.05$), shown in Figure 7.5.

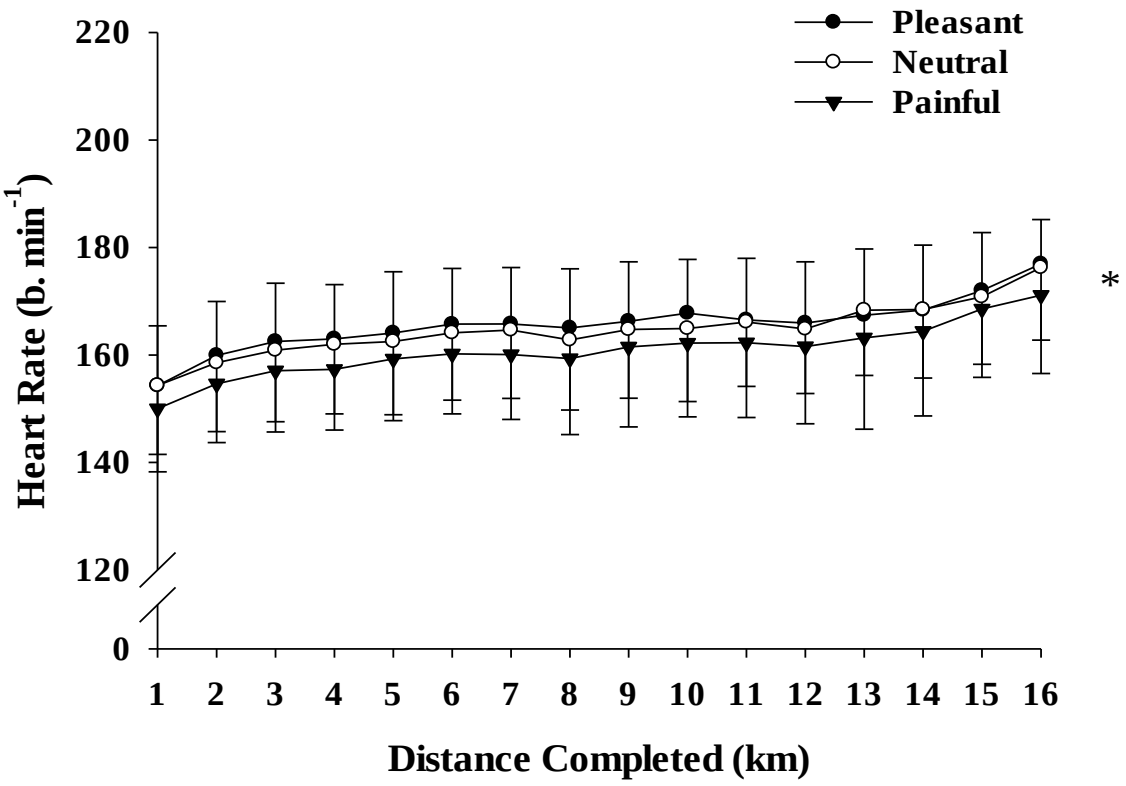


Figure 7.5 Heart rate differences between conditions over time. Although there was a significant difference in mean HR between conditions, no significant interaction effects for HR over time between conditions during the TT were observed ($P > 0.05$). *significantly different between condition ($P < 0.05$).

Blood lactate (B[La]):The ANOVA revealed a significant main effect of condition for mean B[La] during the TT ($F_{(2, 40)} = 5.724$, $P = 0.007$), a main effect for distance completed ($P < 0.05$), but no significant interaction effect ($P > 0.05$), as shown in Figure 7.6.

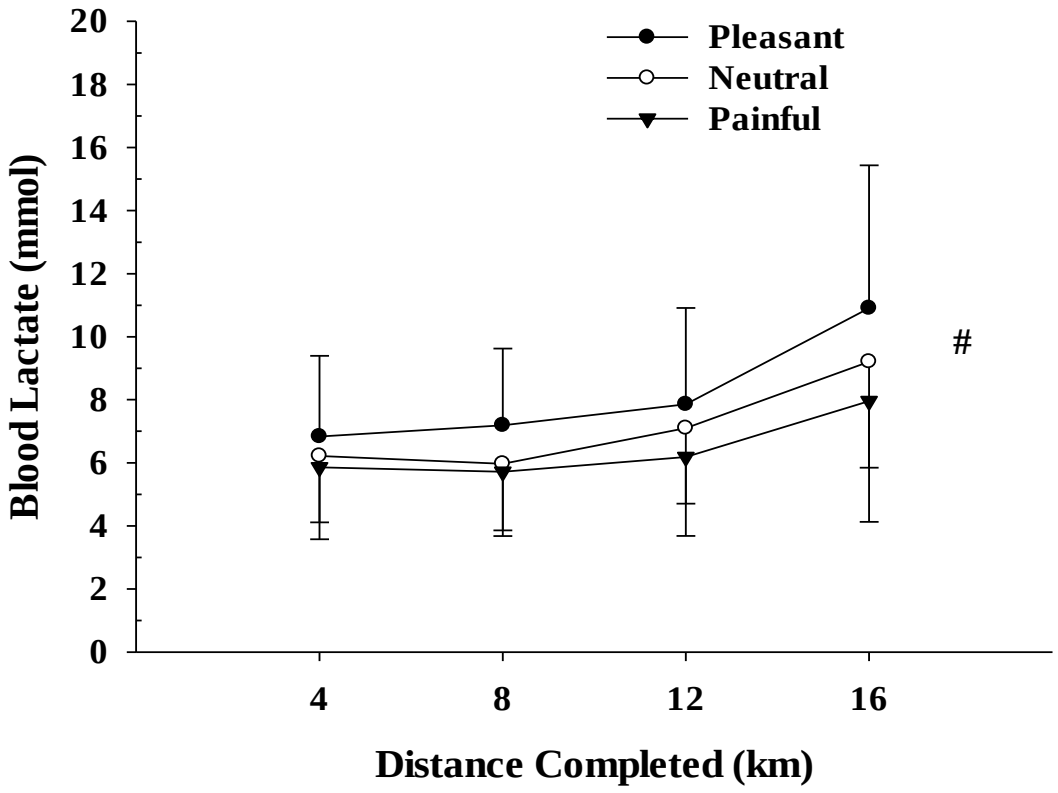


Figure 7.6 Blood lactate differences between conditions over time. # denotes a significant difference between pleasant and unpleasant image conditions, and a significant difference between neutral and unpleasant image conditions during the TT.

Perceived Exertion: No significant main effects for condition were observed ($P > 0.05$). There was a main effect for distance completed ($P < 0.001$), but no significant interaction effect was found ($P > 0.05$), as shown in Figure 7.7.

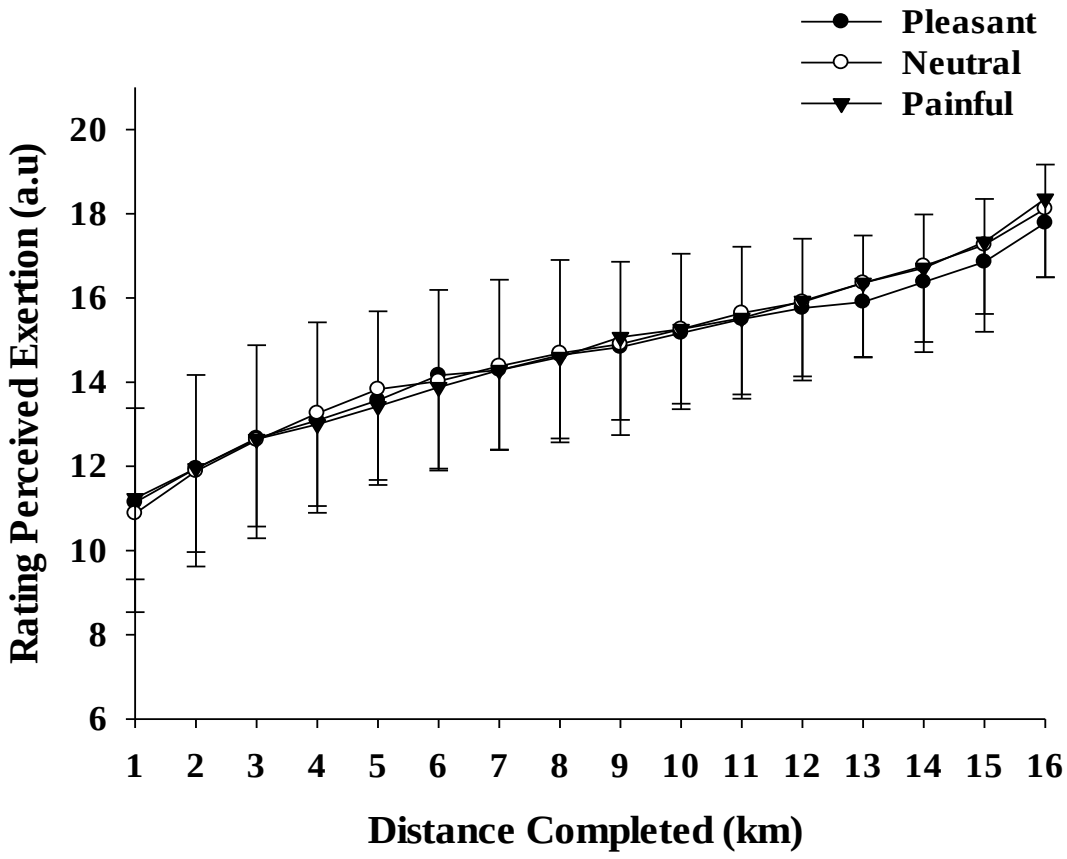


Figure 7.7 No differences between conditions for RPE during the TT.

Exercise-induced pain (EIP): No significant main effects for condition were observed ($P > 0.05$). There was a main effect for distance completed ($P < 0.001$), but no significant interaction effect was found ($P > 0.05$), as shown in Figure 7.8.

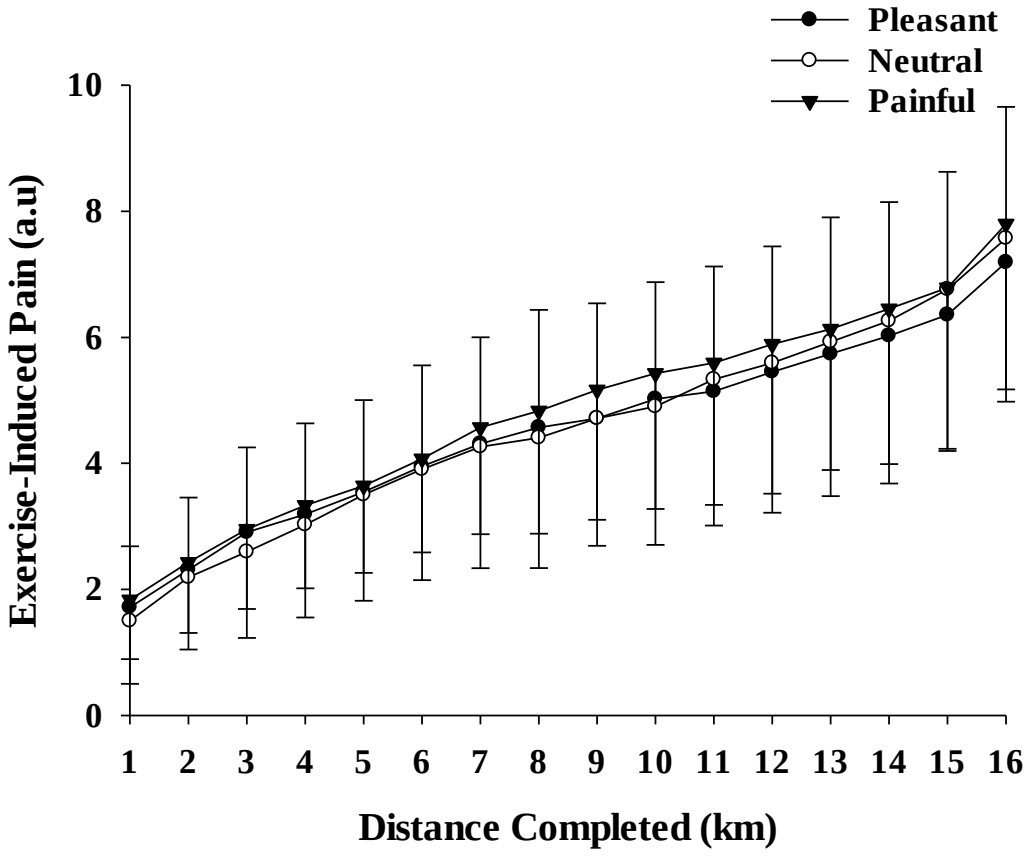


Figure 7.8 No differences between conditions for EIP during the TT.

Fixed Power Task (FP)

Heart Rate (HR): No significant main effects for condition were observed ($P > 0.05$). There was a main effect for time completed ($P < 0.001$), but no significant interaction effect was found ($P > 0.05$) during the FP test, as shown in Figure 7.9.

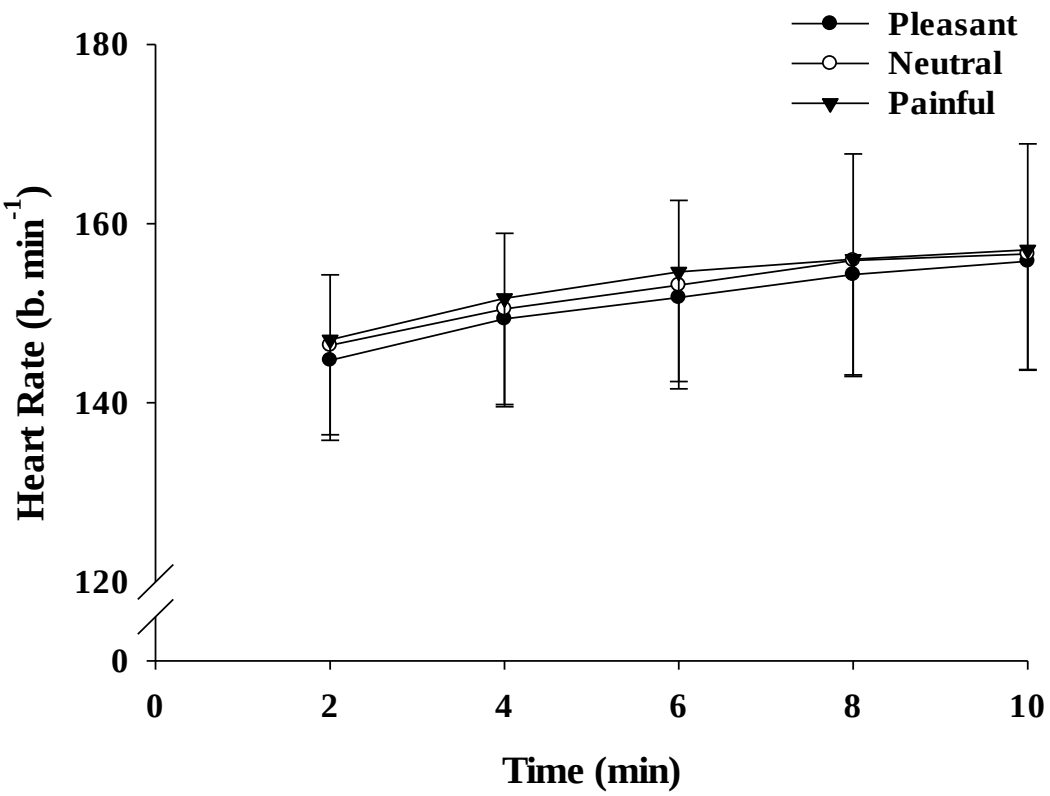


Figure 7.9 No differences between conditions over time for heart rate during the FP test.

Exercise-induced pain (EIP): There was main effect of condition for EIP ($F_{(2, 40)} = 4.363$, $P = 0.019$). There was a significant main effect for time completed ($P < 0.001$). Following-up tests showed a significant difference in EIP between pleasant and painful image conditions ($P = 0.015$). No significant difference between pleasant and neutral image conditions ($P = 0.308$), or between neutral and painful image conditions was found ($P = 0.098$). The ANOVA revealed no significant interaction effects for EIP ($P > 0.05$), as shown in Figure 7.10.

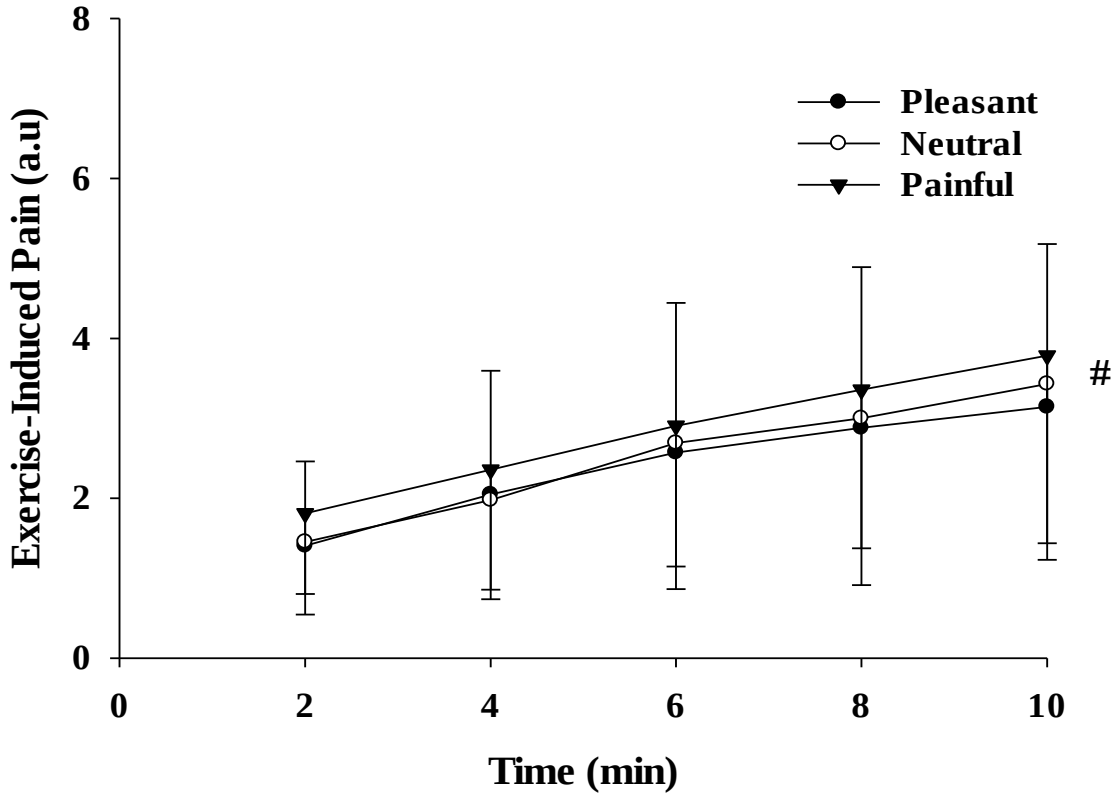


Figure 7.10 EIP differences between conditions during the FP test. # denotes a significant main effect for condition on EIP.

Percieved Exertion (RPE): No significant main effects for condition were observed ($P > 0.05$). There was a main effect for time completed ($P < 0.001$), but no significant interaction effect was found ($P > 0.05$) during the FP test, as shown in Figure 7.11.

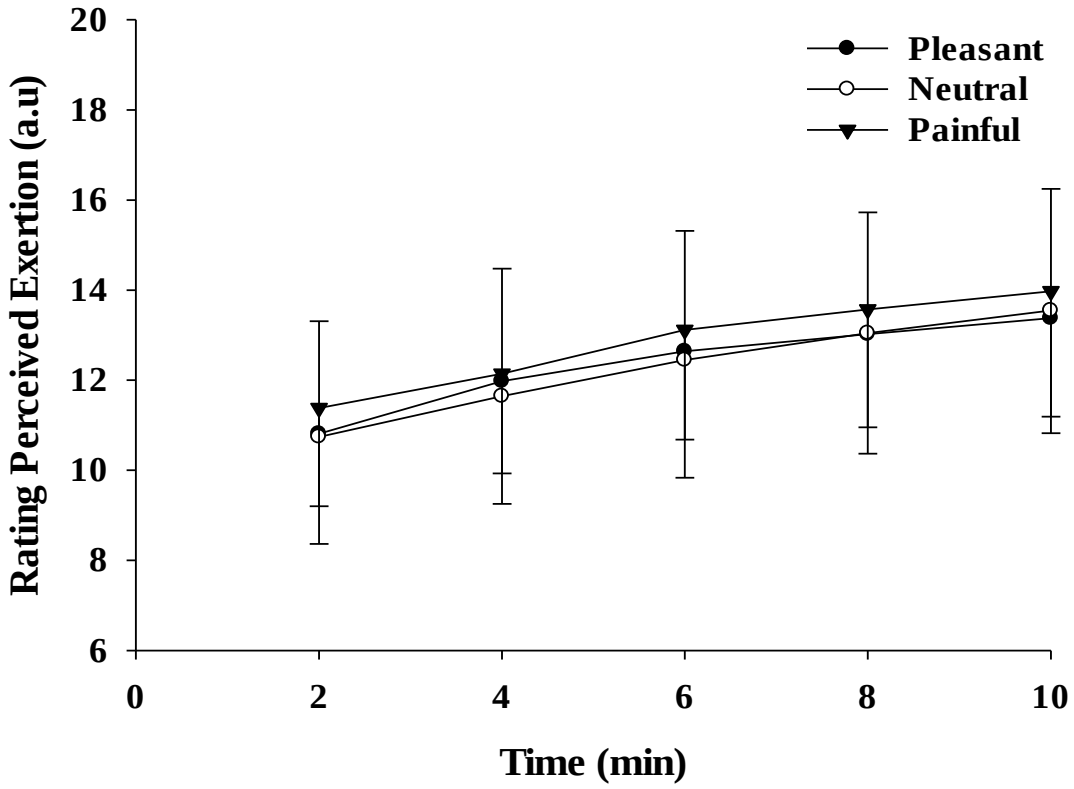


Figure 7.11 No differences between conditions over time for RPE during the FP test.

Blood Lactate (B[La]). No significant main effect of condition or interaction effects for B[La] was found (P > 0.05) during the FP test, as shown in Figure 7.12.

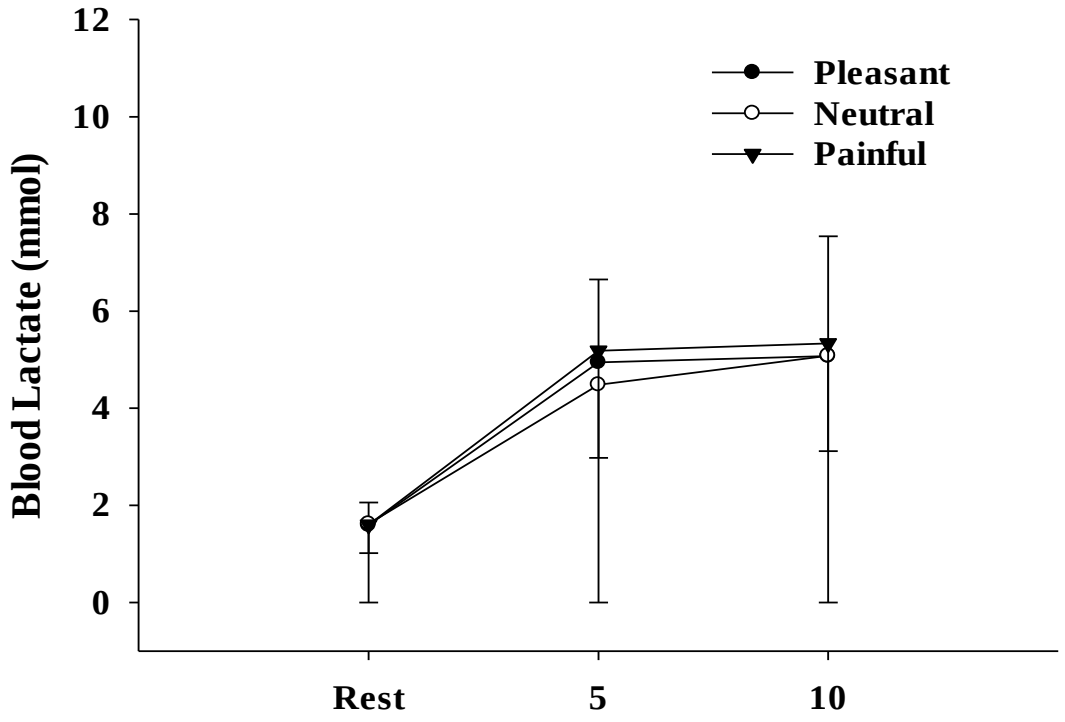


Figure 7.12 No differences between conditions for blood lactate during the FP test.

Mood States (BRUMS):

Table 7.3 Participant mean values for mood states (depression, tension, anger and confusion).

	Pleasant		Neutral		Painful	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Depression	1.10 ± 2.28	0.71± 1.55	1.14 ± 2.43	1.43± 2.68	1.57 ± 2.36	2.43± 2.82*
Tension	1.86 ± 2.85	0.90 ± 1.34	1.33 ± 2.18	1.48 ± 2.54	1.38 ± 2.27	3.29± 3.85*
Anger	1.29 ± 2.39	1.14 ± 2.85	1.67 ± 2.31	1.38 ± 2.91	1.81 ± 3.08	2.38±3.63*
Confusion	0.95 ± 1.80	0.86 ± 1.82	1.00 ± 1.82	0.71 ± 1.95	2.19 ± 2.42	2.24±3.02*

* A significant different between pre-and post.

V. DISCUSSION

The primary finding of this study was that viewing a set of images that elicited a significant degree of emotional pain prior to exercise, exacerbated the level of perceived pain experienced for a given exercise intensity, and this resulted in endurance performance being negatively impacted. When a set of images were presented that depicted painful sporting situations (in comparison to neutral or pleasant images), participants rated cycling at 70% of their peak PO as significantly more painful, despite no change in any physiological response or perception of effort. This increased pain then likely resulted in a longer time trial performance, arising from a self-selected power output that was significantly lower and a consequently lower mean HR and B[La]. These findings suggest that there is a significant emotional element to EIP, which if exacerbated can lead to an increased perception of pain despite no change in the nociceptive signal.

Pain sensation can be separated into a sensory-discriminative and an affective-motivational component (Treede, Kenshalo, Gracely & Jones, 1999). The sensory-discriminative component (i.e. nociception or sensory pain) informs the individual about the location, modality, and intensity of stimuli. The affective-motivational component (i.e. pain unpleasantness or emotional pain) refers to the emotional responses to a painful stimulus, or accompanying feelings of fear, disgust, exhaustion, sadness, and anxiety. These sensations motivate the individual to escape or reduce the source of pain, and thus provide an important protective function. Numerous studies have previously demonstrated that the sensation of pain can be present without any apparent noxious stimulation, and that pain perception and the intensity of the noxious stimuli are not necessarily directly proportional (Keltner et al., 2006). This observation is consistently demonstrated where observing others' pain can enhance the intensity reporting of painful stimuli – an effect termed compassional hyperalgesia (Godinho et al., 2006). Importantly, this shows that changes to the affective-motivational component of pain can moderate the sensory-discriminative component. It is suggested that the unpleasant emotional mood states elicited by viewing others' pain augment the sensory experience of pain, whereas pleasant emotional states diminish it (Meaghar et al. 2001). Therefore, for compassional hyperalgesia to be elicited, changes in mood relevant to unpleasant emotional states need to be elicited. The manipulation check data in the current study (i.e. differences in response to the pre/post MQ) indicate that the targeted emotional states were stimulated by the image subsets (i.e.

depression, tension, anger and confusion all significantly increased following viewing the Painful images), which is a consistent response to this type of intervention (Meaghar et al., 2001). Indeed, De Wied and Verbaten (2001) and Meagher et al. (2001) both found that exposing subjects to painful images negatively affected emotional state, and this reduced the tolerance of a cold pressor test. Wunsch et al. (2003) further showed that unpleasant images depicting painful scenes, led to increased intensity and unpleasantness judgement of thermal stimuli. These effects were subsequently suggested to be specifically related to the particular observation of painful scenes, as non-painful images that were equally unpleasant did not induce hyperalgesia (Godinho et al., 2006). The results of the current study replicate these previous findings, and demonstrate that a negative emotional state, induced by emotionally painful images, can increase intensity of EIP. This is an important observation, because it has previously been suggested that EIP is processed and perceived very differently to traditional models of experimental pain (Angius et al., 2015), and therefore it is not necessarily expected that the same interventions bring about the same effects with these different types of pain. Indeed, transcranial direct current stimulation of the motor cortex has previously been shown to reduce the intensity of pain associated with a cold pressor test, but did not have any analgesic effect on exercise induced pain (Angius et al., 2015). As the motor cortex is more associated with the sensory-discriminative aspect of pain (Boggio et al, 2008, 2009), combined with the current findings this may also suggest that EIP is strongly influenced by the affective-motivational component.

The experience of pain is represented in memory through learning and life experiences, as with other affective states, and this association between pain experience and particular situations is perhaps one of the most important systems to promote survival (Gendolla, 2012). Pain-priming results in increased pain intensity for a given painful stimuli and an activation of the memory network, suggesting an activation of the mental representations about past experience of pain (Silvestrini, 2015). Viewing painful images prior to exercise performance may therefore activate the memory networks regarding previously painful exercise situations, and therefore create expectancy that the imminent task will be painful. An alternative explanation is that focus on painful images prior to exercise may change attention during exercise so that more focus is put on the painful aspects of it, resulting in a higher pain rating for a given nociceptive stimuli (Meagher et al., 2001).

In the current study, the FP test was designed to assess whether the intervention resulted in a change in perceptual response (i.e. pain and RPE) for a given exercise intensity. The subsequent TT was then performed to assess whether the predicted change in perceptual response would elicit a change in endurance performance. This experimental design was necessary to fully explore the research question, because it has previously been shown that whilst changes in perceptual responses to an intervention can be observed in fixed intensity exercise, in self-paced exercise (such as a TT), participants tend to maintain a fixed progression in perceptual parameters at the expense of changes to work rate (Mauger et al., 2010, Mauger, 2014; Tucker, 2009). Thus, the TT provided a true measure of self-paced endurance performance, whilst the FP task helped demonstrate that the intervention elicited the predicted perceptual response. It is noteworthy that the intervention resulted in no changes to RPE, and a significant change to EIP in the FP task. This provides further evidence that EIP and RPE can be partitioned, provided participants are given adequate instructions and familiarisation with the two scales (Pageaux, 2016). Of further note, is that despite no apparent effect of the intervention on RPE, performance of the TT was affected by the intervention. This supports the findings from Chapters 5 and 6, that endurance performance can be moderated by changes in pain perception, independently to any change in RPE. This further question the validity of the psycho-biological model of endurance performance, which suggests that RPE is the sole determinant of endurance performance and that the normal pain sensation associated with exercise has no role in performance.

VI. CONCLUSION

In conclusion, this study has shown that there is a strong emotional element to EIP, and that this can be moderated by manipulating mood. In the current study, this was achieved be presenting participants with a series of emotionally painful images, and this caused an effect called compassional hyperalgesia. In support of the previous experimental chapters, perception of pain proved to be a determinant of endurance performance, as when more pain was felt for a given exercise intensity (due to compassional hyperalgesia), cycling time trial performance was negatively affected.

CHAPTER 8

GENERAL DISCUSSION

8.1 General discussion

Exercise-induced pain is a naturally experienced phenomenon and arises as consequence of intense and prolonged exercise. However, it has been suggested to have a negative effect on endurance performance. Despite this, the study of exercise-induced muscle pain during athletic performance has received limited attention. Therefore, the main purpose of the thesis was to provide further empirical evidence to advance scientific knowledge and understanding of the phenomenon of EIP; primarily by comparing experimental pain measures (CPT, PPT) to the sensation of and tolerance to EIP (Chapter 3), and to consider strategies to mitigate the impact of EIP as means of understanding its mechanisms. These interventions included those which have both a top-down (mirror visual feedback (Chapter 4), compassional hyperalgesia (Chapter 7)) and bottom-up effect (TENS and IFC (Chapter 5 and 6)). As a result, this thesis demonstrates that:

I) EIP plays a crucial factor in endurance performance and can even predict performance in time trial cycling (1st study in Chapter 3);

II) A high tolerance of EIP provides an important pre-requisite for successful endurance performance (1st study in Chapter 3);

III) Top-down control and psychological factors linked to task expectation have a large influence on the magnitude and impact of EIP during endurance performance (2nd study in Chapter 4);

IV) Decreasing the magnitude of the nociceptive signal, independently to any change in RPE, provides an analgesic effect on EIP and results in an improved endurance performance in both single limb and whole-body exercise (3rd study in Chapter 5, 4th study in Chapter 6);

V) The impact of pain during exercise can be affected by mood, with a decreased mood resulting in an increased pain sensation (induced via compassional hyperalgesia) and decreased endurance performance (5th study, Chapter 7).

VI)

Overall, this thesis represents original work, which makes a significant contribution to advancing the scientific knowledge in the area of pain and exercise performance.

The primary purpose of the 1st experimental study performed in Chapter 3 was to examine the relationship between pain threshold/tolerance induced by traditional experimental inductions of pain, tolerance of EIP, and endurance performance. Whilst several studies have previously investigated the relationship between experimental measures of pain and exercise performance, many of these have used experimental pain, including thermal, pressure and electric stimuli to test their postulates that pain threshold/tolerance predicts exercise capacity. However, these traditional measures of experimental pain poorly reflect the nociceptive pathway and sensation of EIP, and so in this study it was important to create a test that could measure tolerance specifically to EIP. Accordingly, we found that 'RPE clamp' (Tucker et al., 2006) adequately induced EIP, and tolerance to it could be assessed by the level of EIP reached in the test. This experimental study (Chapter 3) demonstrated for the first time that tolerance of EIP could be used as a predictor of endurance cycling performance, whereas traditional pain measures did not. This reveals the importance of using an appropriate method for pain measurement in the area of exercise induced pain studies. This experimental study (Chapter 3) provides new evidence for the need to consider the link between pain and performance. Indeed, athletes who are capable of pushing harder and longer are commonly the ones who are successful. Thus, this study laid the framework for the rest of the thesis, and confirmed that endurance exercise is partly regulated by the perception of pain, a higher pain tolerance can enhance exercise capacity. It is suggested that EIP might provide important perceptual information to the brain regarding the state of the exercising periphery, which informs the exerciser whether to increase or decrease their work-rate and thus avoiding impending tissue damage. However, this assumes that pain perception purely dependent on the size of the nociceptive signal and this is known not to be the case. Indeed, pain has a significant subjective element and psychological component (Hansen & Streltzer, 2005). There is no doubt that physiological factors will ultimately limit a successful endurance athlete (Joyner & Coyle, 2008), but the sole emphasis on physiological mechanisms ignores the fact that regulation of exercise appears to be ultimately regulated by the brain (Ulmer, 1996). Some models such as the CGM (Noakes 2000, 2011) and Psycho-biological model (Marcora, 2007, 2008a, 2008b, 2009, 2010, Marcora, Bosio & de Morree, 2008; Marcora & Staiano, 2009a, 2010b) try to address this, but the role of EIP in these models is either ignored or dismissed. The results of 1st study suggest that EIP plays a key role in endurance performance, but whether this

is predominantly due to the size of the nociceptive signal (and therefore perhaps a secondary perception, related to the sensation of peripheral fatigue but otherwise unimportant) or due to the psychological unpleasantness associated but not necessarily proportional to the nociceptive signal, was unknown. Consequently, experimental studies 2-5 were designed to investigate the physiological and psychological impact of EIP, and specifically to try to separate the impact of these two facets during endurance performance.

The primary purpose of the experimental 2nd study in Chapter 4 was to use the mirror box technique to alter perceptions of the exercise task. It was hypothesised that when participants believed the task to be easier or harder, performance would be better or worse (respectively) and this would be paralleled by the perception of less or more pain (respectively). The results of this study confirmed the hypothesis, with participants reporting that both increases in both EIP and RPE over time were less affected by task difficulty when participants were deceived of the change in task demands. This is an important finding because processing of pain is interpreted and perceived by the brain by a complex neurological network (Peyron, Laurent & Garcia-Larrea, 2000), yet simple factors appear to be able to influence the neural (and consequently perceptual) responses to painful stimuli (Mancini, Longo, Kammers & Haggard, 2011). This shows that EIP is partly a subjective experience (in the same manner as experimental pain), and its perception can be affected by the expectation of pain. Therefore, mirror visual feedback could be important in the developments of therapeutic strategies for those who suffer increased pain during exercise or movement. Although this study provides insight into the psychological element of EIP, and shows that it responds in a similar manner to intervention previously tested on experimental pain, the changes in endurance performance could not be solely attributed to differences in EIP. Indeed, RPE was affected in the same manner by the intervention, and RPE has previously been identified as a key limiter to endurance performance. Thus, this study alone cannot present the change in EIP as the driver for the change in TTE, as this could equally be explained by changes to RPE.

The 5th experimental study performed in the Chapter 7 further explored the psychological aspects of EIP, and how these may drive the change in performance associated with EIP. Painful images were used to induce compassionate hyperalgesia, which has previously been shown to affect pain perception. Compassionate hyperalgesia was produced, which led to negative mood and an increased EIP for a given cycling intensity. The unique experimental design of this study then showed that this hyperalgesia led to a decrease in endurance performance. It is likely that the induced compassional hyperalgesia activated pain circuitries that transiently amplified participants' perception of pain. Indeed, fMRI experiments have shown that regions of the brain associated with coding the intensity and location of pain are affected when observing another person in pain (Jackson et al., 2006; Lamm et al., 2007). This study suggests that EIP can be similarly affected by this phenomenon. An important finding of this study was that EIP was exacerbated and that this occurred alongside a decreased endurance performance. Crucially, no change in RPE was observed. Combined with the results from 1st study, this shows that EIP exerts an impact on endurance performance independently of perception of effort. This novel finding suggests that the notion that RPE is the sole limiter of endurance performance, as predicted by the Psychobiological model, is incorrect, and that changes to perception of effort do not have to occur for endurance performance to be affected. It may be that such a finding has not previously been observed because feelings of pain and discomfort are usually included in the general instructions for RPE. However, it has been shown people can distinguish between perception of effort and pain, and so studies should seek to use the two scales independently (Pageaux, 2016). This methodological approach was used in this thesis, and doing so appears to have provided new insight into the importance of perception of effort and pain in endurance performance.

Where 2nd and 5th studies were designed to investigate the psychological, top-down aspects of EIP, 3rd and 4th studies were designed to explore the bottom-up, afferent feedback component of EIP, and how moderating the magnitude of this feedback may alter performance. In Chapter 5, the 3rd experimental study investigated the effects of transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) on EIP during single limb, submaximal isometric contractions in healthy participants. Although

TENS and IFC are both well-known as non-invasive non-pharmacologic therapies, that have been shown to be more effective than placebo to elicit analgesic effects in a variety of conditions (Marchand et al., 1993; Robinson, 1996; Schmitz et al., 1997; Facci et al., 2011), this is the first study investigating the potential analgesic effect of TENS and IFC on the perception of EIP during a sustained single limb, submaximal isometric contraction in healthy participants. The primary and novel finding was that both TENS and IFC were able to significantly reduce the perception of EIP, and that this intervention elicited a significant improvement in time to exhaustion performance (TTE). To our knowledge, this is the first study using a randomised, crossover and placebo-controlled design, which shows an ergogenic effect for TENS and IFC, and the results provide an interesting insight regarding the psychological and physiological mechanisms involved in the generation of pain perception during single limb exercise. It is suggested that exercise-induced muscle pain is caused by an accumulation of endogenous algesic substances, with an increased intramuscular pressure and muscular distortion (Mense, 1993; Dannecker & Koltyn, 2014). The accumulated endogenous algesic substances (including: hydrogen ions, potassium, histamine, serotonin, bradykinin, acetylcholine, adenosine and substance P) activate and stimulate both Group III (A-delta fibres) and Group IV (C fibres) small afferents, which then transmit nociceptive signals (regarding actual or potential tissue damage stimuli) and synapse in lamina I, II and V in the spinal cord and then to the supraspinal regions of the brain, where it is processed and interpreted as pain (Mense, 1993; O'Connor & Cook, 1999). Sustained sub-maximal isometric contractions used in this experimental study (Chapter 5) have been shown to yield endogenous algesic substances, which both prevent or inhibit the excitation-contraction coupling process (Kent-Braun, 1999) and provoke a nociceptive signal. To mitigate the impact of this metabolic environment, without changing the endogenous algesic substances, TENS and IFC were utilised to reduce the transmission of the nociceptive signal arriving in the brain. The mechanisms behind this intervention is postulated to operate through the Gate-Control Theory of Pain (Sluka & Walsh, 2003), as shown in Figure 8.1. According to this theory, Melzack and Wall (1965) suggest the spinal cord comprises a neurological "gate" that either allows pain signals or blocks them to pass through to the brain. Small-diameter afferent fibres (pain signal) and large-diameter afferent fibres (tough, pressure, other senses) both synapse at the dorsal horn and carry the transmission of nociceptive information up the spinal cord to the brain. When there is more

activity of large afferent fibres in comparison to the activity of small afferent fibres, individuals tend to perceive less pain. Indeed, when TENS and IFC was applied during time to exhaustion task in this experimental study (Chapter 5), individuals experienced less EIP via activating large afferent fibres much more than small afferent fibres activity. This intervention appeared to induce analgesia which resulted in a longer time to exhaustion of the sustained isometric contraction. The most striking observation to emerge from the data in this experimental study (Chapter 5) is that TTE increased following a reduction in perception of EIP, but in the absence of changes to RPE between conditions. A variety of evidence suggests that the primary generator for RPE is the collorary discharge associated with central motor command (McCloskey, 1981), and is independent from afferent feedback (in this case pain) from the exercising muscles and other interceptors (Marcora, 2009; de Morree et al, 2012, 2014). Marcora and Staniano (2010) postulated that the sole determinant of endurance performance is primarily the RPE. Marcora (2010) also states that perception of muscle pain naturally experienced during high-intensity aerobic exercise does not influence endurance performance. However, the results from the study in Chapter 5 suggest that the nature of EIP perception experienced during exhaustive exercise task does limit performance and that it can be moderated independently of RPE in healthy participants. Other studies support that these findings demonstrate that an analgesic intervention (such as, paracetamol or caffeine) are able to improve exercise performance in a variety of exercise models (Mauger et al. 2010; Astorino et al. 2011; Astorino et al. 2012; Foster et al. 2014; Mauger et al. 2014; Gonglach et al. 2015) and support that tolerance of EIP is an important factor in determining endurance performance (Mauger, 2013, 2104; Astokorki & Mauger, 2016). The results conclude that TENS and IFC elicit an analgesic effect for EIP, and that this reduction in EIP perception can improve time to exhaustion performance in the absence of changes to perceived exertion. However, the limitation of this experimental study (Chapter 5) is that it could be argued that single limb exercise creates a metabolic and nociceptive environment that is different to that seen in whole-body exercise. Therefore, the analgesia elicited by TENS and IFC may not be ergogenic in whole-body exercise. To address this, a follow-up study was conducted to examine the efficiency of TENS and IFC in cycling exercise.

In Chapter 6, the 4th experimental study aimed to assess whether the ergogenic effect of TENS and IFC observed in Chapter 5 would be replicated in cycling exercise. This is the first study to investigate the effect of TENS and IFC on perception of during whole-body dynamic exercise. The primary and novel finding of this experimental study (Chapter 6) was that TENS improved performance of the cycling TT (~ 2%), and that this was achieved by sustaining a higher power output, heart rate and blood lactate concentration. Despite the increased physiological strain and metabolic lactic acidosis cause induced by the higher PO, participants perceived less EIP in the TENS condition alongside no change in RPE. The greater power output result in the higher metabolic demand in the TENS intervention, which would have produced a greater noxious environment in and around the exercising muscles, which would have been experienced as more EIP. However, the most striking result in this experiment performed in Chapter 6 was that despite the higher noxious environment caused, participants perceived less EIP in the TENS intervention. These findings suggest that during this dynamic whole-body endurance exercise, the participants were able to tolerate a greater rate of accumulation of muscle metabolites and physiological strain than usually experienced in normal conditions (a placebo control). This data provides support for the notion that tolerance of EIP is one of the likely variables that is used to help regulate exercise intensity, perhaps to avoid physiological harm. Indeed, it has been suggested by the Central Governor Model that endurance performance is regulated through a complex integrative system of control that balances perceived demands of the exercise via afferent feedback, and capacity of the physiological system. However, there are other models that could also explain the observed ergogenic effect. In the Afferent Feedback Model, metabolic changes in the exercising muscle produces increased afferent feedback that results in a reduced or impeded central motor drive (i.e. central fatigue). It is plausible that the TENS intervention impeded the afferent feedback at the spinal cord (in accordance with gate control theory), which would have reduced the size of the afferent feedback and consequently offset the reduction in central motor drive. However, the findings of this study (Chapter 6), and those presented in Chapters 5 and 7, suggest that the Psychobiological model is not able to explain the limitations to endurance performance in all scenarios. Each of these three studies demonstrate that exercise performance was affected by the experimental intervention, but with the absence of any change to RPE. Whilst TENS attenuated the perception of EIP and improved performance in this

experimental study (Chapter 6), IFC did not reduce pain or improve performance (despite this occurring in the previous chapter with single limb exercise). A reason for this may be the intrinsic factors of the IFC intervention used to stimulate a large group of quadriceps femoris muscles during dynamic whole-body exercise, as this was not the same as the IFC intervention that stimulates a small group of muscles (single limb) used in the previous experimental study. Indeed, two stimulation channels for the IFC intervention were used to activate quadriceps femoris muscles rather than four channels. Consequently, this may not have been sufficient to stimulate the whole quadriceps femoris muscles and to reduce pain and subsequently improved performance.

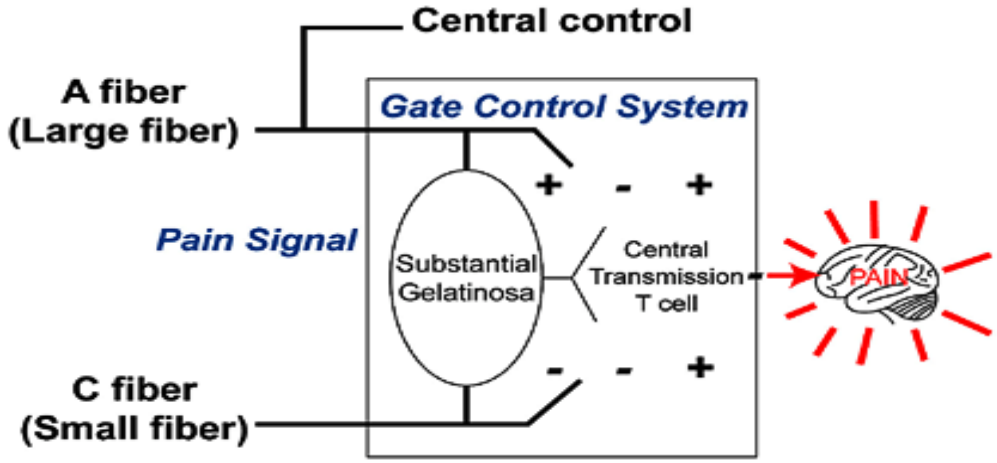


Figure. 8.1. The circuit diagram of the gate-control theory of pain perception as proposed by Melzack and Wall (1965). According to the theory, they proposed that the transmission cells [T cells] originally thought to be cells of the spinothalamic tract activate neural mechanisms that produce pain perception, i.e., T-cell activity is interpreted by the central nervous system as pain. A gate cell, or G cell (originally thought to be cells of the substantia gelatinosa), can modulate the activity in afferent pathways (of both large and small fibres) to the T cell, before it gets to the T cell. The G cell activity is, in turn, modulated by activity in both large and small primary afferent fibres. Specifically, barrages in both large and small fibres excite the T cell (drive its membrane voltage toward the critical firing level), whereas the same barrages in large fibres excite the G cell to discharge and the same barrages in small fibres inhibit the G cell discharge (drive its membrane voltage away from the critical firing level). Activity in the G cell inhibits (reduces or blocks) transmission from both large and small fibres to T cells. Cortical and subcortical influences on the gate control mechanism, called "Central Control" in the figure, are indicated in the diagram of Figure 8.1.

8.2 Conclusion and perspectives

In conclusion, the experimental studies in this thesis provide new insight into how EIP affects exercise endurance performance, and how some strategies can mitigate its impact. Each experiment in this thesis provides an important contribution to this field, by exploring and adding to the existing knowledge base. Overall, this thesis has demonstrated that EIP plays a key role in exercise performance, and a higher tolerance of EIP is one of several determinants of endurance performance, mainly because it facilitates awareness of the physiological state of muscle and subsequently assists to regulate pacing during moderate prolonged exercise. By reducing pain through psychological or physiological interventions, endurance performance is improved, whereas increasing pain through a psychological intervention worsens endurance performance. These are important findings, because pain during intense exercise has previously escaped significant attention in the empirical literature. Where there has been a focus on this, experiments have largely assessed pain through the use of thermal, pressure and electrical stimuli to promote an algesic response, which as shown in this thesis, are perhaps not appropriate for exploring EIP. To address in this, the experiments of this thesis were designed in such a way as to maintain the mechanisms causing EIP, and to explore interventions that are able to offset the effect of this. The interventions used to reduce pain and improve exercise performance in this thesis may have implications for populations where EIP poses a barrier to physical activity. Indeed, devices like TENS are cheap, easy to use and portable, and the results from this thesis suggest it can elicit a meaningful analgesic effect during exercise. Although there is clearly a physiological component to EIP, this thesis also shows that there is an important psychological element, which can be affected by parameters such as mood and expectation. This suggests that people's psychological approach to exercise and competition may have consequences for their perceptions during the exercise. This psychological element should not be ignored.

8.3 Limitations

All the experimental studies in this thesis utilised a sample of recreationally active, healthy male and female participants who exercised regularly (3 h or more per week) were recruited. None of the participants were highly trained cyclists. As such interpretation of our findings of this thesis should be restricted to matching populations. It is possible that highly trained or sedentary groups would show a different response to EIP, therefore, these studies should be repeated with a highly trained or sedentary cohort that would assist further explanation about the internal protective mechanism of afferent feedback and the central governor regulation of exercise intensity.

8.4 Implications and directions for future studies

The primary results of the experimental studies that consist of this thesis have implications for the instruction and interpretation of EIP during endurance exercise performance. An awareness of potential changes in perceived pain during intense exercise may practically assist athletes, coaches, exercise scientists and health and fitness practitioners to consider advice given to their charges. EIP has a strong psychological component, so there is scope to look to strategies that can help athletes and individuals better tolerate this pain. Indeed, it may be that engaging in particularly painful training to condition the exerciser psychologically could be an effective strategy that could be investigated with a training study.

The influence of pain expectation has become the focus of scientific investigation within recent years. Whilst this thesis has extended the examination of this theme via mirror visual feedback, several essential questions remain unanswered. Although the results of mirror study (Chapter 4) give us a better understanding of the importance of how our expectations of pain affects the experience of pain, one of the limitations of this study is that brain activity was not measured. A functional magnetic resonance imaging study or use of electroencephalogram (EEG) would allow the recording of how specific areas of the brain may be differently affected when different expectations of the exercise are presented. Expectation of pain has been shown to enhance responses to non-painful somatosensory stimulation in the anterior cingulate cortex (ACC) and parietal operculum/posterior insula (PO/PI), both of which may play roles in regulating pain-dependent behaviour

(Sawamoto et al., 2000). Whether a similar effect occurs during exercise would be an interesting study to further explore.

This thesis has shown that TENS and IFC can reduce pain and improve endurance performance. However, the theoretical explanation for why this occurs cannot be confirmed. To assess whether the Afferent Feedback model provides an appropriate explanation, a follow-up study using transcranial magnetic stimulation (TMS) and peripheral stimulation to assess neuromuscular parameters including voluntary activation level (VAL) and cortical silent period (CSP) would allow this theory to be tested. Of further interest, would be to identify why IFC did not elicit a change in performance in cycling exercise. To assess this, a stronger IFC protocol could be applied and a measure of circulating endogenous opioids.

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Appendices

APPENDIX A
EXAMPLES OF AN INFORMATION SHEET, CONSENT FORM AND HEALTH QUESTIONNAIRE

School of Sport & Exercise Sciences, University of Kent, The Medway Building, Chatham Maritime, Kent. ME4 4AG.

Ali Astokorki

Tel No: 01634 888903 ***e-mail:*** *ahya3@kent.ac.uk*

PARTICIPANT INFORMATION SHEET

Title of Study: An investigation into the analgesic effects of transcutaneous electrical nerve stimulation and interferential current on exercise-induced pain and cycling performance

Dear Participant,

Thank you for showing an interest in participating in the study. Please read this information sheet carefully before deciding whether to participate. If you decide to volunteer I would be grateful of you for your participation. If you decide not to take part there will be no disadvantage to you of any kind and I thank you for considering our request.

What is the aim of the project?

The aim of this study is to examine how transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) affect pain and cycling performance.

What types of participants are needed?

We are seeking to recruit 15 males and females (who cycling for more than 3 hours a week) aged between 18 and 44. To take part, you must not be within a pregnancy, type I or II diabetes, bleeding disorders (e.g. haemophilia), using a cochlear implant hearing device,

have a history of heart disorders, or be taking chronic medications that affect the central nervous system.

Transcutaneous electrical nerve stimulation (TENS) is a method of pain relief in which a special device transmits low-voltage electrical impulses through electrodes on the skin. This device is non-invasive and safe with no side-effects compared with pharmacological analgesic modalities.

Interferential Current Therapy (IFC) is a non-invasive therapy indicated for the symptomatic relief from, and management of pain. It provides a safe and effective alternative to pharmacological approaches to pain control. IFC is similar to TENS, but involves passing a moderate frequency weak electrical current across the surface of the skin. You may not be able to tell the difference between TENS & IFC. Although noticeable, it is not painful but will block the transmission of pain messages at the spinal cord level. This interferential stimulation is concentrated at the point of intersection, deep in the tissues, between the electrodes.

Assessment of suitability/safety for administering electrical stimulation

Before undergoing stimulation, on the first visit you will be tested for sensory discrimination test by using a sharp and blunt patella hammer. During stimulation, and after testing, you will be monitored for signs of skin irritation, swelling and/or pain in the tested area and nausea. On completion of stimulation, current will be ramped down before turning off the machine.

Assessment of Blood Lactate

During the time trial test, we will obtain a measure of blood lactate every 4km of the 16.1km trial. This will involve a small prick on the finger/thumb in order a draw a few drops of blood for analysis. This may cause some discomfort, but is not very painful. You may find that you have a slight bruise for a few days after.

What will my participation involve?

The study requires you to come into the laboratory at Medway Park on four separate visits. In total, the time of these combined sessions will not exceed 4 hours over approximately

two weeks. The first visit will last approximately an hour, the second, third and fourth visits will take approximately 45-minutes each, separated by 2-5 days.

Visit 1

A general health screening will be conducted and your height and weight will be taken. This will include a series of tests to ensure it is suitable to administer TENS and IFC to you. Following these tests, bipolar surface TENS and IFC electrodes will be placed over your thigh, and then we will apply TENS and IFC in order to find the appropriate intensity for the following visits for three minutes. The current intensity will be adjusted until you report feeling a tingling sensation without causing muscle contraction and/or muscle pain. Following this, you will complete an exercise test to exhaustion (VO2max test). This will involve cycling against a progressively increasing intensity until you can no longer continue. Following a rest period of 30-min, you will complete a familiarisation of mood questionnaire (MQ) and you will undertake a familiarisation of the endurance performance test by completing a self-paced 16.1-km cycling time trial (TT). You will be asked to give a rating of perceived exertion (RPE) and perceived pain every km. After the TT test, participants will complete the MQ for the second time.

Visit 2

During this visit, you will complete the MQ and you will then perform the TT (as described in Visit 1). During these exercise tasks, they will be employed to TENS (as described above), sham (placebo), or IFC (in a randomised order) during the whole TT test. After the TT test, participants will complete the MQ for the second time.

Visit 3

During this visit, you will perform the same protocol as described in Visit 2 but with one of the 2 remaining randomised (sham/IFC/TENS) applies.

Visit 4

During this visit, you will perform the same protocol as described in Visit 2 but with the 1 remaining randomised (sham/IFC/TENS) applies.

What are the risks associated with the experiment?

During cycling exercise

There may be shortness of breath and aching muscles during the exercise due to effort being undertaken. Water can be provided when carrying out the testing. There are no risks associated with this outside of the normal risks of moderate cycling exercise.

During TENS and IFC

There are some risks of TENS and IFC, which are small, but include nausea, fainting, skin irritation and electrical burns. Our participant exclusion criteria protect against some of these, and the pre-tests we will perform in the first visit will also minimise risk. Although unlikely, if you are effected by any of these adverse effects we will withdraw you from the study and recommend that you visit your GP.

Requirements or abstentions imposed upon the participants prior to and after the experiment

Prior to your lab visits, please do not ingest caffeine 6 hours prior, large quantities of food 3 hours prior, or alcohol 24 hours, or heavy exercise 24 hours prior to testing. This is very important as it may affect the results. Please try to keep your diet the same prior to each test.

If I decide to start the study can I change my mind?

Your decision to participate in this research is entirely voluntary and you can withdraw at any time without penalty against you. If you are a University of Kent student, your decision to participate or withdrawal will have no influence upon any judgements made of your academic performance.

Will my confidentiality be protected?

The researchers might use information gained from this study in scientific journal articles or in presentations. However, your results will remain anonymous and your individual data will not be able to be identified. At no time will names be given or information about you with regards to lifestyle etc. If this changes at any point, consent will have to be given by you and you are completely allowed to say yes or no with the information.

How can I get information about the study?

You will be able to get information about your results and the study findings by contacting Ali Astokorki.

What if I have questions?

If you have questions about this research project, please contact the research supervisor, Dr Lex Mauger – lm415@kent.ac.uk

School of Sport & Exercise Sciences, University of Kent, The Medway Building, Chatham Maritime, Kent. ME4 4AG.

Ali Astokorki

Tel: 01634 888903 **email: ahya3@kent.ac.uk**

If you have any queries please contact: **Ali Astokorki (see above)**

Participant Identification Number for this trial:

CONSENT FORM

Title of Study: An investigation into the analgesic effects of transcutaneous electrical nerve stimulation and interferential current on exercise-induced pain and cycling performance

Please initial box

1- I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

2- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

3- I understand that any personal information that I provide to the researchers will remain strictly confidential. ☐

4- I agree to have a small sample of blood taken for the purposes of this research. ☐

5- I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

HEALTH QUESTIONNAIRE

Name……

Date of Birth…… Age……

Please answer these questions truthfully and completely. The sole purpose of this questionnaire is to ensure that you are in a fit and healthy state to complete the exercise test.

ANY INFORMATION CONTAINED HEREIN WILL BE TREATED AS CONFIDENTIAL.

SECTION 1: GENERAL HEALTH QUESTIONS

Please read the 8 questions below carefully and answer each one honestly: check YES or NO.

	YES	NO
1. Has your doctor ever said that you have a heart condition or high blood pressure?	□	□
2. Do you feel pain in your chest at rest, during your daily activities of living, or when you do physical activity?	□	□
3. Do you lose balance because of dizziness or have you lost consciousness in the last 12 months? (Please answer NO if your dizziness was associated with over-breathing including vigorous exercise).	□	□
4. Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	□	□
If yes, please list condition(s) here:		
5. Are you currently taking prescribed medications for a chronic medical condition?	□	□
If yes, please list condition(s) and medications here:		
6. Do you currently have (or have you had within the past 12 months) a bone, joint or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please	□	□

answer NO if you had a problem in the past but it *does not limit your ability* to be physically active.		
If yes, please list condition(s) here:		
7. Has your doctor ever said that you should only do medically supervised physical activity?	□	□
8. Are you, or is there any chance you could be, pregnant?	□	□

If you answered NO to all of the questions above, you are cleared to take part in the exercise test

Go to SECTION 3 to sign the form. You do not need to complete section 2.

If you answered YES to one or more of the questions in Section 1 - PLEASE
GO TO SECTION 2.

SECTION 2: CHRONIC MEDICAL CONDITIONS

Please read the questions below carefully and answer each one honestly: check YES or NO.

		YES	NO
1.	**Do you have arthritis, osteoporosis, or back problems?** If YES answer questions 1a-1c. If NO go to Question 2.	□	□
1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□

1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebrae (e.g. spondylolisthesis), and/or spondyloysis/pars defect (a crack in the bony ring on the back of the spinal column)?	□	□
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	□	□
2.	**Do you have cancer of any kind?** If YES answer questions 2a-2b. If NO, go to Question 3.	□	□
2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head and neck?	□	□
2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	□	□
3.	**Do you have heart disease or cardiovascular disease? This includes coronary artery disease, high blood pressure, heart failure, diagnosed abnormality or heart rhythm.** If YES answer questions 3a-3e. If NO go to Question 4.	□	□
3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□
		YES	**NO**
3c.	Do you have chronic heart failure?	□	□
3d.	Do you have a resting blood pressure equal to or greater than 160/90mmHg with or without medication? Answer YES if you do not know your resting blood pressure.	□	□
3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	□	□
4.	**Do you have any metabolic conditions? This includes Type 1 Diabetes, Type 2 Diabetes and Pre-Diabetes.** If YES answer questions 4a-4c. If NO, go to Question 5.	□	□
4a.	Is your blood sugar often above 13mmol/L? (Answer YES if you are not sure).	□	□

4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, OR the sensation in your toes and feet?	□	□
4c.	Do you have other metabolic conditions (such as thyroid disorders, current pregnancy related diabetes, chronic kidney disease, or liver problems)?	□	□
5.	**Do you have any mental health problems or learning difficulties?** This includes Alzheimer's, dementia, depression, anxiety disorder, eating disorder, psychotic disorder, intellectual disability and down syndrome. If YES answer questions 5a-5b. If NO go to Question 6.	□	□
5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□
5b.	Do you also have back problems affecting nerves or muscles?	□	□
6.	**Do you have a respiratory disease?** This includes chronic obstructive pulmonary disease, asthma, pulmonary high blood pressure. If YES answer questions 6a-6d. If NO, go to Question 7.	□	□
6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□
6b.	Has your doctor ever said you blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	□	□
6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	□	□
6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	□	□
7.	**Do you have a spinal cord injury?** This includes tetraplegia and paraplegia. If YES answer questions 7a-7c. If NO, go to Question 8.	□	□

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□
7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as autonomic dysreflexia)?	□	□
		YES	**NO**
8.	**Have you had a stroke?** This includes transient ischemic attack (TIA) or cerebrovascular event. If YES answer questions 8a-8c. If NO go to Question 9.	□	□
8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking any medications or other treatments).	□	□
8b.	Do you have any impairment in walking or mobility?	□	□
8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	□	□
9.	**Do you have any other medical condition which is not listed above or do you have two or more medical conditions?** If you have other medical conditions, answer questions 9a-9c. If NO go to Question 10.	□	□
9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	□	□
9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, and kidney problems)?	□	□
9c.	Do you currently live with two or more medical conditions?	□	□
	Please list your medical condition(s) and any related medications here:		
10.	**Have you had a viral infection in the last 2 weeks (cough, cold, sore throat, etc.)?** If YES please provide details below:	□	□
11.	**Is there any other reason why you cannot take part in this exercise test?** If YES please provide details below:	□	□

12.	**Please provide brief details of your current weekly levels of physical activity (sport, physical fitness or conditioning activities), using the following classification for exertion level:** **L = light (slightly breathless** **M = moderate (breathless)** **V = vigorous (very breathless)** **Activity Duration (mins.) Level (L/M/V)** **Monday** **Tuesday** **Wednesday** **Thursday** **Friday** **Saturday** **Sunday**		

Please see below for recommendations for your current medical condition and sign this document:

If you answered NO to all of the follow-up questions about your medical condition, you are cleared to take part in the exercise test.

If you answered YES to one or more of the follow-up questions about your medical condition it is strongly advised that you should seek further advice from a medical professional before taking part in the exercise test.

Please complete the Participant Exclusion Document to assess specific contraindications for participating in this study and hand it to the researcher, before you sign the Consent Form.

SECTION 3: DECLERATION

Please read and sign the declaration below:

I, the undersigned, have read, understood and completed this questionnaire to the best of my knowledge.

NAME: ……

SIGNATURE: ……DATE: ……

SIGNATURE OF PARENT/GUARDIAN: ……

This health questionnaire is based around the PAR-Q+, which was developed by the Canadian Society for Exercise Physiology www.csep.ca

APPENDIX B

RISKS AND ETHICAL ISSUES

If any of the questions in Section IV B is answered 'yes', a full ethics application must be made to the REAG. This also applies for studies not defined as 'research' in the narrow sense, i.e. evaluations/audits, etc. Complete this form and send it to the Faculties Support Office along with supporting documentation: a copy of the full research proposal; any participant information sheets and consent forms; any surveys, interview schedules; any advertising material or proposed website wording.

Overview
Name of Applicant(s)
Ali Astokorki and Dr. Lex Mauger
Contact Details (Please include your UoK address, email and telephone number)
M0-16, Medway Campus, Chatham, ME4 4AG ahya3@Kent.ac.uk 01634 (888903)
Title of Project
An investigation into the analgesic effects of transcutaneous electrical nerve stimulation and interferential current on exercise-induced pain and cycling performance
Lay Summary (Please provide a brief summary of the study)
Neuromuscular electrical stimulation (NMES) is widely recognized as the use of therapeutic electrical currents for purposes of actuating skeletal muscle to increase, or prevent loss, of strength. While previous literature has supported the use of NMES for improving strength in a weak but innervated skeletal muscle, there remains much discussion and disagreement regarding the optimal current waveform for NMES (Bax, Staes, & Verhagen, 2005; Ward, 2009). To better understand the performance capability of electrical currents used for NMES, consistency among stimulus parameters must be considered lest erroneous conclusions be drawn. Transcutaneous electrical nerve stimulation (TENS) and interferential (IFC) are widely recognized therapeutic currents. While these waveforms are capable of stimulating skeletal muscle to produce contraction, variations in the electrophysiologic characteristics of each current have led investigators to compare the magnitude of the effect of each current on skeletal muscle (Snyder-Mackler, Garrett & Roberts, 1989). TENS interventions tend to be described according to the technical characteristics of TENS as 'high frequency, low intensity' (conventional TENS) or 'low frequency, high intensity' (acupuncture-like TENS). This has resulted in unclear reporting of TENS interventions because

it fails to specify the physiological intention of TENS (Dalal, Sheth & Vyas, 2014). In this regard, the physiological intention of conventional TENS is to selectively activate non-noxious skin afferents without simultaneously activating noxious skin afferents as this leads to segmental anti-nociception (Wall, Melzack & Bonica, 1994). Theoretically, high frequency (~10–250 pps), low intensity (non-painful) currents would be most efficient in selectively activating non noxious skin afferent (Hansjuergens, 1986). Interferential current (IFC) is the transcutaneous application of alternating medium-frequency electrical current for therapeutic purpose. It is widely used in physical therapy clinics to provide pain relief in variety of conditions and patients populations (Chipchase, Williams & Robertson, 2009). IFC deliver currents to deep tissues through the use of kilohertz carrier frequency pulses or sinusoidal currents to overcome the impedance offered by the skin. It can be delivered out of phase because very high frequency currents are not uncomfortable for subjects; these currents interfere with each other within tissues at the point where the currents cross (Hansjuergens, 1986).

As described by Melzack and Wall, TENS and IFCs are forms of electro analgesia based on the gate control theory of pain perception. According to this theory, stimulation of large diameter primary sensory afferent cutaneous fibers activates inhibitory interneurons in the spinal cord dorsal horn and thus may ease the transmission of nociceptive signals from small diameter A-delta and C-fibers (Chung et al., 1984). However, as intense exercise is known to elicit feelings pain and discomfort, it is curious that no studies have investigated the effect of transcutaneous electrical nerve stimulation and interferential current in reducing pain during exercise in order to improve performance. Therefore, the purpose of this study is to compare the analgesic effect of TENS and IFC using equal stimulus parameters of phase duration, frequency, and current amplitude. While will also examine whether TENS and IFC reduce pain perception and consequently yield an improvement in time trial cycling performance. It is hypothesized that TENS and IFC would be more effective in reducing pain perception and yield greater cycling performance than sham stimulation. In the sham stimulation, the electrodes are placed on the same muscle site and the TENS machine is turned on, but no current is passed through the electrodes.

Name of Supervisor(s) (If applicable)

Dr Lex Mauger

Application Reference Number (For office use only)

Risks and ethical issues

Please list the principal inclusion and exclusion criteria
Inclusion: Healthy male and female participants Aged 18-44 Appropriate completion of a PAR-Q before exercise Participating in regular cycling (>3 h per week) Exclusion (participants with/having): Using cochlear implant hearing device or pacemakers History of any cardiovascular disorder Chronic medications that affect the central nervous system Pregnancy Type I or II diabetes Bleeding disorders (e.g. haemophilia) Deep vein thrombosis Impaired sensation Acute/chronic infection (e.g. tuberculosis) Malignancy Recently radiated tissue Skin diseases or severely damaged skin
How long will each research participant be in the study in total, from when they give informed consent until their last contact with the research team?
Approximately 2 weeks, which will include a maximum of 5 hours laboratory time
What are the potential risks and burdens for research participants and how will you minimise them? (Describe any risks and burdens that could occur as a result of participation in the research, such as pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Describe what steps would be taken to minimise risks and burdens as far as possible)
The usual risks of vigorous physical exercise are present (out of breath, sweating, discomfort, tiredness), but these are no greater than participants would experience in their day-to-day exercise regime. These risks have also previously been risk assessed and accounted for by the SESS, are minimised by clear experimenter instructions to the subject, thorough warm-up and cool-downs prior to and after exercise, and risk assessment of the subjects through a general health

questionnaire. Subject is allowed to withdraw from the study without needing to give a reason or an explanation. Therefore, these risks are considered minimal, easily addressed, and no different than those posed by any regular physical activity regime. TENS and IFC are generally considered safe with no side-effects compared with pharmacological analgesic modalities. However, electrical current that is too intense or that is used incorrectly can burn or irritate the skin. The electrodes should not be placed over the eyes, heart, brain, or front of the throat. People with heart problems should not use TENS or IFC. The effects of long-term use of TENS or IFC on foetuses are unknown. However, there may be additional side-effects with use of TENS and IFC in pregnancy, bleeding disorders, diabetes or heart conditions. As such, these populations are listed in the study's exclusion criteria. If participants report any serious side-effects following use of TENS or IFC, they will immediately be withdrawn from the study. We will take a fingertip blood sample for analysis of blood lactate from participants immediate testing and then disposal it (thus complying with the Human Tissue Act) and we will remind the subject that he/she has the right to withdraw from the study without needing to give a reason or an explanation.
Please describe what measures you have in place in the event of any unexpected outcomes or adverse effects to participants arising from involvement in the project
All higher risk populations (from exercise) will be excluded from participating in the study. A trained first aider is always on site to give emergency first aid if required. If participants report any serious side effects after testing, they will be recommended to visit their GP.
Will interviews/questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?
No
If yes, please describe the procedures in place to deal with these issues
N/A
What is the potential benefit to research participants?
There are no immediate benefits to the participants
What are the potential risks to the researchers themselves?

None
Will there be any risks to the University? (Consider issues such as reputational risk; researches that may give rise to contentious or controversial findings; could the funder be considered controversial or have the potential to cause reputational risk to the University?)
No
Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants? (If yes, give details and justification). For example, the disturbance of a school child's day or access to their normal educational entitlement and curriculum).
No

Recruitment and informed consent
How and by whom will potential participants, records or samples be identified?
Fifteen recreationally active males and females participants (>3 h exercise per week), aged between 18-44 yrs will be recruited to take part in the study. They will be trained and used to moderate physical activity will be approached as a potential recruitment pool. Participants will be recruited through the use of posters, flyers, emails and word of mouth.
Will this involve reviewing or screening identifiable personal information of potential participants or any other person? (If 'yes', give details)
None
Has prior consent been obtained or will it be obtained for access to identifiable personal information?
No
Will you obtain informed consent from or on behalf of research participants? (If 'yes' please give details. If you are not planning to gain consent, please explain why not).
Yes – full written and verbal informed consent will need to be given by participants. Procedures will be explained to them through a written information sheet and verbally.
Will you record informed consent in writing? (If 'no', how will it be recorded?)

Yes
How long will you allow potential participants to decide whether or not to take part?
A minimum of 24 h will be given to prospective participants to decide whether to participate
What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or have special communication needs? (eg, translation, use of interpreters?)
None – due to funding limitations we cannot provide this service and will consequently only recruit participants who are fluent speakers of English
If no arrangements will be made, explain the reasons (eg, resource constraints)
See above

Confidentiality
In this section personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.
If you will be undertaking any of the following activities at any stage (including in the identification of potential participants) please give details and explain the safeguarding measures you will employ • Electronic transfer by magnetic or optical media, email or computer networks • Sharing of personal data outside the European Economic Area • Use of personal addresses, postcodes, faxes, emails or telephone numbers • Publication of direct quotations from respondents • Publication of data that might allow identification of individuals, either directly or indirectly • Use of audio/visual recording devices • Storage of personal data on any of the following: – Manual files – University computers – Home or other personal computers – Private company computers – Laptop computers

All hard files will be kept in a locked cabinet by the supervisor. All electronic files will be kept on password protected computers by the researchers.
How will you ensure the confidentiality of personal data? (eg, anonymisation or pseudonymisation of data)
Subject number coding. A master code will be kept in a locked filing cabinet by the supervisor (Dr. Lex Mauger). The PhD student researcher will have access by permission to this code.
Who will have access to participants' personal data during the study?
Mauger and Astokorki
How long will personal data be stored or accessed after the study has ended? (If longer than 12 months, please justify)
Personal data will be stored for a period of 6 months, after which time is will be destroyed. De-identified data will be kept for a period of 5 years – this is to allow data to be analysed and written up to allow subsequent publication.
Please note: as best practice, and as a requirement of many funders, where practical, researchers must develop a data management and sharing plan to enable the data to be made available for re-use, eg, for secondary research, and so sufficient metadata must be conserved to enable this while maintaining confidentiality commitments and the security of data.

Publication and dissemination
How do you intend to report and disseminate the results of the study? If you do not plan to report or disseminate the results please give your justification
Conference and/or peer-reviewed paper
Will you inform participants of the results? (Please give details of how you will inform participants or justify if not doing so)
Yes – participants will be given a verbal debrief of their results

Management of the research		
Other key investigators/collaborators. (Please include all grant co-applicants, protocol authors and other key members of the Chief Investigator's team, including non-doctoral student researchers)		
None		
Has this or a similar application been previously rejected by a research Ethics Committee in the UK or another country? (If yes, please give details of rejected application and explain in the summary of main issues how the reasons for the unfavourable opinion have been addressed in this application)		
No		
How long do you expect the study to last?		
• Planned start date: September 2015	• Planned end date: May 2016	• Total duration: 8 months
Where will the research take place?		
Medway Park, University of Kent		

Children
Do you plan to include any participants who are children under 16? (If no, go to next section)
No
Please specify the potential age range of children under 16 who will be included and give reasons for carrying out the research with this age group
N/A
Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves
N/A
If you intend to provide children under 16 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding
N/A

Participants unable to consent for themselves	
Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity? (If yes, the research must be reviewed by an NHS REC or SCREC)	
No	
Is the research related to the 'impairing condition' that causes the lack of capacity, or to the treatment of those with that condition?	
☐ Yes	If 'yes' proceed to next question
☒ No	If 'no' the study should proceed without involving those who do not have the capacity to consent to participation
Could the research be undertaken as effectively with people who do have the capacity to consent to participate?	
☒ Yes	If 'yes' then the study should exclude those without the capacity to consent to participation
☐ No	If 'no' then the inclusion of people without capacity in the study can be justified
Is it possible that the capacity of participants could fluctuate during the research? (If yes, the research must be reviewed by an NHS REC or SCREC)	
No	
Who inside or outside the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?	
Dr Mauger – has been an active researcher for 9 years, including successful NHS project ethics submission and completion of NHS Good Clinical Practice Training	
What will be the criteria for withdrawal of participants?	
If a participant, who has given consent, subsequently loses capacity to give consent, they will be withdrawn from the study. Subjects will be advised that they can withdraw from the study at any time, without any disadvantage to themselves.	

Declaration

To be signed by the Chief Investigator

- I agree to comply, and will ensure that all researchers involved with the study comply with all relevant legislation, accepted ethical practice, University of Kent policies and appropriate professional ethical guidelines during the conduct of this research project
- If any significant changes are made to the design of the research I will notify the Faculty of Sciences Research Ethics and Advisory Group (REAG) and understand that further review may be required before I can proceed to implement the change(s)
- I agree that I will notify the Faculty of Sciences Research Ethics Advisory Group of any unexpected adverse events that may occur during my research
- I agree to notify the Faculty of Sciences Research Ethics Advisory Group of any complaints I receive in connection with this research project

Signed: Name: Ali Astokorki Dr Lex Mauger	Date: / /2016

What to do next
Send your completed form, along with all supporting documentation, to the Faculties Support Office, at fso@kent.ac.uk.

Checklist	
Please ensure you have included the following with your application (where relevant):	
• Full research proposal (current project)	☒
• Participant information sheet	☒
• Consent form	☒
• Covering letter (if relevant)	☐

• Any questionnaires/interview schedules/topic guides to be used • Any approved instruments/measures to be used • Any advertising material to be used to recruit participants • Confirmation that project is covered by UoK insurance policies (if necessary)	☒ ☐ ☒ ☐

APPENDIX C

Instraction for rating perceived exertion and exercise-induced pain

The RPE scale instructions used were the following: "During this test we want you to rate your perception of effort defined as the sensation of how hard you are driving your arm/legs in order to lift the weight/cycle. Look at the scale before you; we want you to use this scale from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion". To help you choose a number that corresponds to how you feel within this range, consider the following. When you do not have the sensation of driving your arm/legs, choose number 6 ("no exertion at all") - e.g. at rest with no contraction. When you have the sensation of driving your arm/legs "hard", choose number 15. Number 20 ("Maximal exertion") corresponds to the feeling of effort when you are exercising maximally (i.e. as hard as you can for that given moment). Try to appraise your perception of effort as honestly as possible, without thinking what the actual physical load is. Don't underestimate your perception of effort but do not overestimate it either. It's your own feeling of effort that's important, not how it compares to other people. What other people think is not important either. Look at the scale and the expressions and then give a number. Any questions? from (Borg, 1998).

The pain scale instructions used were the following: "The scale before you contains the numbers 0 to 10. You will use this scale to assess the perceptions of pain during the exercise test. For this task, pain is defined as the intensity of hurt that you feel as a result of the exercise. Don't underestimate or overestimate the degree of hurt you feel, just try to estimate it as honestly and objectively as possible.

The numbers on the scale represent a range of pain intensity from "very faint pain"(number 0.5) to "extremely intense pain–almost unbearable"(number 10). When you feel no pain, you should respond with the number zero. When the pain from the exercise becomes just noticeable, you should respond with the number 0.5. If you feel extremely strong pain that is almost unbearable, you should respond with the number 10. You can also respond with numbers greater than 10. If the pain is greater than 10, respond with the number that represents the pain intensity you feel in relation to 10. In other words, if the pain is twice as great then respond with the number 20.

Repeatedly during the test, you will be asked to rate your level of pain. When rating these pain sensations, be sure to report only the specific sensations arising from the exercise (e.g.

arm contraction) and not report other pains you may be feeling (e.g., seat discomfort). It is very important that your ratings of pain intensity reflect only the degree of hurt you are feeling arising from the exercise. Do not use your ratings as an expression of fatigue (i.e., inability of the muscle to produce force) or exertion (i.e., how hard is it for you to drive your leg).

In summary, you'll be asked to: (a) provide pain intensity ratings arising from the exercise only; (b) give ratings as accurately as possible; and (c) not under-or-over- estimate the pain, but simply rate your pain honestly. You should use the verbal expressions to help rate your sensations" (Cook et al., 1997).

APPENDIX E

ABSTRACTS AND PUBLISHED PAPERS

An investigation into the analgesic effects of transcutaneous electrical nerve stimulation and interferential current on exercise-induced pain and performance.
Oral presentation at the Endurance Research Conference, Kent, 2-4 September, 2015.

Authors and affiliations

Ali Astokorki[1] and Alexis Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, ME4 4AG, UK

Abstract

Introduction: Transcutaneous electric nerve stimulation (TENS) is the application of low intensity electrical impulses at frequencies between 0-200 Hz, whereas interferential current (IFC) is a medium frequency (3000-5100 Hz) alternated current with a various beat frequency ranging from 0-250 Hz. These methods have been shown to reduce pain in a variety of conditions (Marchand et al., 1993; Robinson, 1996; Schmitz et al., 1997). Compared with TENS, IFC delivers lower impendence of an electrical circuit on skin and subcutaneous tissue, and so IFC should activate deeper fibres than that of TENS (Robertson, Low, Ward and Reed, 1994; Cheing and Hui-Chan, 2003). However, the relative effectiveness of these two modulations on exercise-induced pain (EIP) has not been considered. Therefore, the purpose of this study was to investigate whether TENS or IFC elicits an analgesic effect during EIP and improves time to exhaustion (TTE) performance.

Methods: 18 recreationally active, male (n= 11) and female (n= 7) participants were recruited. A single-blind, crossover, randomised design with TENS, IFC, and sham

conditions was used (on separate visits). The TENS and IFC were administered on the bicep of the dominant arm, whereas in the sham condition a dummy simulator produced no current. In each condition, participants initially performed 3x5 second maximal voluntary contractions (MVCs) against a load cell. The maximum of the values was used to establish the 20% MVC for the TTE task. The TTE task involved the participant maintaining a 20% isometric MVC of the bicep until task withdrawal. During the TTE task, perceived pain and RPE were recorded every 30 seconds.

Results: Analysis of the results revealed that TENS and IFC significantly increased TTE when compared to sham stimulation ($P = 0.003$). ANOVA also revealed a significant main effect of condition for pain intensity during the TTE test ($P = 0.035$). No significant changes in rating of perceived exertion (RPE) were found between the three conditions ($P > 0.05$). A 3 x 8 (condition x iso-time) ANOVA revealed a significant interaction effect for pain intensity during the TTE test with lower pain intensity in the TENS and IFC conditions ($P = 0.013$). No interaction effects for RPE were found between the three conditions ($P > 0.05$).

Conclusion: The findings of the study suggest that TENS and IFC elicit an analgesic effect for EIP, and that this reduction in pain can improve time to exhaustion performance in the absence of changes to perceived exertion.

References:

1. Marchand, S., Charest, J., Li, J., Chenard, J.R., Lavignolle, B. and Laurencelle, L., 1993. Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain*, *54*(1), pp.99-106.
2. Schmitz, R.J., Martin, D.E., Perrin, D.H., Iranmanesh, A. and Rogol, A.D., 1997. Effect of interferential current on perceived pain and serum cortisol associated with delayed onset muscle soreness. *Journal of Sport Rehabilitation*, 6, pp.30-37.
3. Robinson, A.J., 1996. Transcutaneous electrical nerve stimulation for the control of pain in musculoskeletal disorders. *Journal of Orthopaedic & Sports Physical Therapy*, *24*(4), pp.208-226.

4. Robertson, V.J., Low, J., Ward, A. and Reed, A., 2006. *Electrotherapy explained: principles and practice*. Elsevier Health Sciences.
5. Cheing, G.L. and Hui-Chan, C.W., 2003. Analgesic effects of transcutaneous electrical nerve stimulation and interferential currents on heat pain in healthy subjects. *Journal of rehabilitation medicine*, *35*(1), pp.15-19.

Congress of European College of Sports Science Conference,
Vienna, Austria, 6-9, July, 2016.

The effect of compassional hyperalgesia on exercise-induced pain during endurance cycling performance. Oral presentation at the annual congress of European College of Sports Science Conference, Vienna, Austria, 6-9, July, 2016.

Astokorki[1], A.H.Y., Mauger, A.R[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, ME4 4AG, UK

Abstract

Introduction: Pain is an unpleasant, subjective experience that includes sensory and emotional components (Rainville, 2002). Several studies have shown that observing other's pain can enhance the intensity of painful stimuli – an effect termed compassional hyperalgesia (Godinho et al., 2012). Intense exercise causes a noxious environment in the muscle that elicits 'exercise-induced pain' (EIP), and tolerance of this sensation has been associated with endurance performance. It is unknown the degree to which this sensation is effected by top-down processing, such as compassional hyperalgesia.

Methods: Twenty-one participants, trained in cycling, completed 5 laboratory visits. The first visit involved an assessment of aerobic capacity (VO2max test) and a familiarisation of the fixed power (FP) and time trial (TT) tests. The second visit provided a further familiarisation of the FP and TT. In the subsequent three visits, in a counter-balanced manner, participants performed a FP and TT. Immediately prior to these, participants viewed a collection of images from the International Affective Picture System database that were either pleasant, unpleasant (painful) or neutral. Participants were asked to rate each image with respect to affective valence and their level of emotion. During the TT and FP, participants were asked their EIP, RPE and had measures of HR and B[La] recorded.

Results: ANOVA revealed a significant difference in TT performance, PO and HR ($P < 0.05$) between conditions during the TT cycling performance, but no significant effect of condition for mean RPE or EIP ($P > 0.05$). For the FP, a significant main effect of condition for EIP, but no difference for RPE, HR or B[La]. A significant effect of condition for Depression, Tension, Anger, and Confusion following viewing the images ($P < 0.05$), but no differences for fatigue and vigour were found.

Discussion: The results of this study demonstrate that viewing painful images prior to exercise decreased TT performance. This study demonstrates that there is an emotional element to the processing of EIP that can be influenced by compassional hyperalgesia. It is suggested that the dorsolateral prefrontal cortex (DLPFC) plays a crucial role in physical, somatosensory pain perception, and in emotional pain (Borckardt et al., 2007). Future studies should seek to examine cortical changes in the DLPFC during exercise that elicits sensations of pain.

References:

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The British Association of Sport and Exercise Sciences Student Conference,
University of St Mark & St John, Plymouth, England,
United Kingdom, 12-13th April, Conference Title:
"Clinical Exercise Science"

Transcutaneous electrical nerve stimulation inhibits central pain transmission and limits the development of peripheral muscle pain during cycling time trial performance. *The British Association of Sport and Exercise Sciences Student Conference, Plymouth, UK, 14th-13 ,April2017.*

Ali Astokorki[1] and Alexis Mauger[1]

[1] Endurance Research Group, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, ME4 4AG, UK

Introduction: Muscle pain is a natural consequence of intense and prolonged exercise and has been suggested to be a limiter of endurance performance (Mauger et al., 2010, J Appl Physiol, 08, 98-104). Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to reduce both chronic and acute pain in a variety of conditions. However, no studies have administered TENS or IFC during exercise with the purpose of reducing exercise-induced pain (EIP) during cycling time trial performance. Therefore, the purpose of this study was to ascertain whether TENS and IFC could reduce EIP and whether this would affect endurance exercise performance.

Methods: Following University ethics approval, twenty-two healthy male and female participants, trained in cycling, completed 4 laboratory visits. d In the first visit, participants underwent a test for skin integrity and sensory discrimination using a sharp and blunt patella hammer. To be familiarised with the TENS and IFC stimulation, participants were briefly administered TENS and IFC pulses which were delivered at a pulse width of 300 μs and frequency of 100 Hz using a Vectra Genisys multi-waveform stimulator (Chattanooga Group, Hixon, TN, USA). Following familiarisation to TENS and

IFC, participants completed a VO2max test (GXT) and a familiarisation of the time trial (TT) tests. In experimental visits 2-4, participants completed a 16.-km cycle time trial whilst receiving TENS, IFC or a Sham placebo in a repeated measure, a cross-over, randomized, and placebo-controlled design.

Results: ANOVA revealed a significant difference in TT performance; TENS significantly improved (P = 0.003) participants' time trial completion time (~2% improvement) through an increased power output and higher physiological strain (increased heart rate and blood lactate concentration). There was a significant difference in the mean EIP between conditions during the TT ($F(2, 44) = 4.210$, $P = 0.022$). Paired *t*-tests revealed that participants perceived significantly less pain during the TENS condition (3.5 ± 1.8) than in the sham condition (4.0 ± 2.0) ($t(21) = 3.037$, $P = 0.006$). No differences were observed between the TENS and the IFC condition (3.8 ± 1.9) or the IFC and Sham condition ($P > 0.05$). No significant differences in mean RPE were found between conditions during the TT ($P > 0.05$).

Conclusion: These findings demonstrate that TENS can attenuate EIP in healthy volunteers and that this significantly improves endurance performance in whole-body dynamic exercise. g

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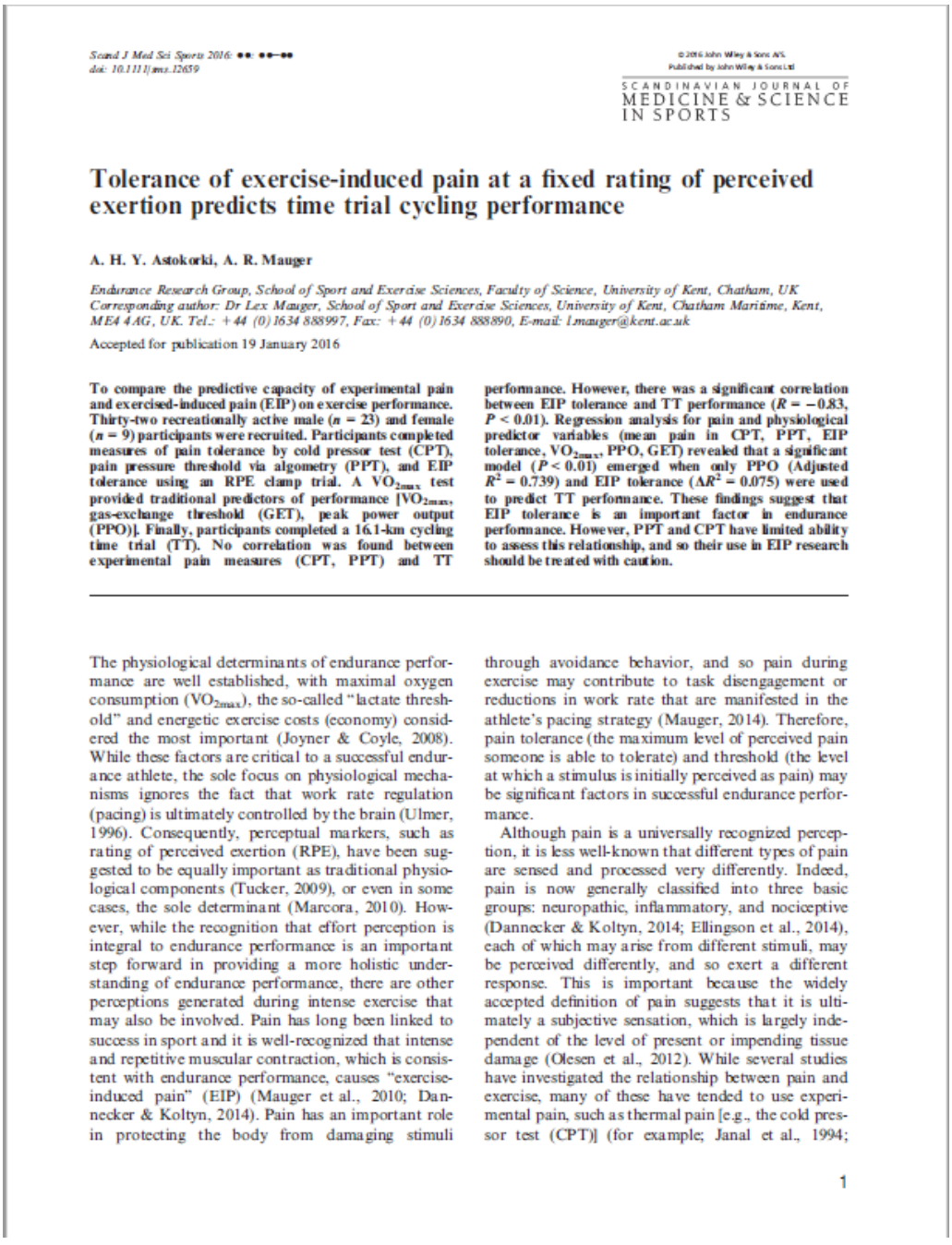


Scand J Med Sci Sports 2016: ●●: ●●–●●
doi: 10.1111/sms.12659

SCANDINAVIAN JOURNAL OF MEDICINE & SCIENCE IN SPORTS

Tolerance of exercise-induced pain at a fixed rating of perceived exertion predicts time trial cycling performance

A. H. Y. Astokorki, A. R. Mauger

Endurance Research Group, School of Sport and Exercise Sciences, Faculty of Science, University of Kent, Chatham, UK
Corresponding author: Dr Lex Mauger, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, Kent, ME4 4AG, UK. Tel.: +44 (0) 1634 888997, Fax: +44 (0) 1634 888890, E-mail: l.mauger@kent.ac.uk

Accepted for publication 19 January 2016

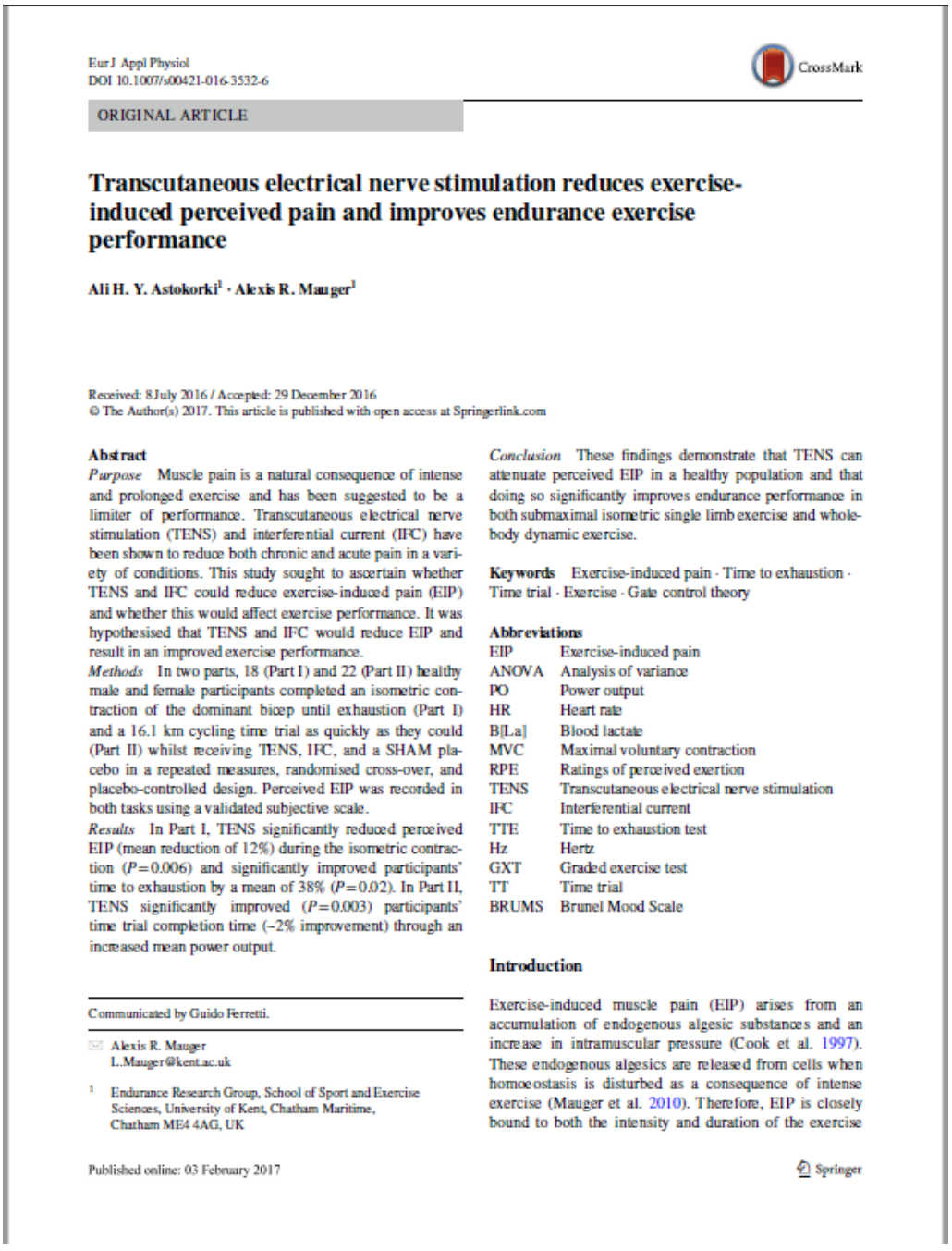
To compare the predictive capacity of experimental pain and exercised-induced pain (EIP) on exercise performance. Thirty-two recreationally active male ($n = 23$) and female ($n = 9$) participants were recruited. Participants completed measures of pain tolerance by cold pressor test (CPT), pain pressure threshold via algometry (PPT), and EIP tolerance using an RPE clamp trial. A VO_{2max} test provided traditional predictors of performance [VO_{2max}, gas-exchange threshold (GET), peak power output (PPO)]. Finally, participants completed a 16.1-km cycling time trial (TT). No correlation was found between experimental pain measures (CPT, PPT) and TT performance. However, there was a significant correlation between EIP tolerance and TT performance ($R = -0.83$, $P < 0.01$). Regression analysis for pain and physiological predictor variables (mean pain in CPT, PPT, EIP tolerance, VO_{2max}, PPO, GET) revealed that a significant model ($P < 0.01$) emerged when only PPO (Adjusted $R^2 = 0.739$) and EIP tolerance ($\Delta R^2 = 0.075$) were used to predict TT performance. These findings suggest that EIP tolerance is an important factor in endurance performance. However, PPT and CPT have limited ability to assess this relationship, and so their use in EIP research should be treated with caution.

The physiological determinants of endurance performance are well established, with maximal oxygen consumption (VO_{2max}), the so-called "lactate threshold" and energetic exercise costs (economy) considered the most important (Joyner & Coyle, 2008). While these factors are critical to a successful endurance athlete, the sole focus on physiological mechanisms ignores the fact that work rate regulation (pacing) is ultimately controlled by the brain (Ulmer, 1996). Consequently, perceptual markers, such as rating of perceived exertion (RPE), have been suggested to be equally important as traditional physiological components (Tucker, 2009), or even in some cases, the sole determinant (Marcora, 2010). However, while the recognition that effort perception is integral to endurance performance is an important step forward in providing a more holistic understanding of endurance performance, there are other perceptions generated during intense exercise that may also be involved. Pain has long been linked to success in sport and it is well-recognized that intense and repetitive muscular contraction, which is consistent with endurance performance, causes "exercise-induced pain" (EIP) (Mauger et al., 2010; Dannecker & Koltyn, 2014). Pain has an important role in protecting the body from damaging stimuli through avoidance behavior, and so pain during exercise may contribute to task disengagement or reductions in work rate that are manifested in the athlete's pacing strategy (Mauger, 2014). Therefore, pain tolerance (the maximum level of perceived pain someone is able to tolerate) and threshold (the level at which a stimulus is initially perceived as pain) may be significant factors in successful endurance performance.

Although pain is a universally recognized perception, it is less well-known that different types of pain are sensed and processed very differently. Indeed, pain is now generally classified into three basic groups: neuropathic, inflammatory, and nociceptive (Dannecker & Koltyn, 2014; Ellingson et al., 2014), each of which may arise from different stimuli, may be perceived differently, and so exert a different response. This is important because the widely accepted definition of pain suggests that it is ultimately a subjective sensation, which is largely independent of the level of present or impending tissue damage (Olesen et al., 2012). While several studies have investigated the relationship between pain and exercise, many of these have tended to use experimental pain, such as thermal pain [e.g., the cold pressor test (CPT)] (for example; Janal et al., 1994;

Astokorki, A.H.Y., Mauger A.R. (2017). Transcutaneous electrical nerve stimulation reduces exercise-induced perceived pain and improves endurance exercise performance. *European Journal of Applied Physiology*, In Press, doi: 10.1007/s00421-016-3532-6. A

full version of the article can be attained as Open Access at the following link: https://link.springer.com/article/10.1007%2Fs00421-016-3532-6



Eur J Appl Physiol
DOI 10.1007/s00421-016-3532-6

ORIGINAL ARTICLE

Transcutaneous electrical nerve stimulation reduces exercise-induced perceived pain and improves endurance exercise performance

Ali H. Y. Astokorki[1] · Alexis R. Mauger[1]

Received: 8 July 2016 / Accepted: 29 December 2016

Abstract
Purpose Muscle pain is a natural consequence of intense and prolonged exercise and has been suggested to be a limiter of performance. Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) have been shown to reduce both chronic and acute pain in a variety of conditions. This study sought to ascertain whether TENS and IFC could reduce exercise-induced pain (EIP) and whether this would affect exercise performance. It was hypothesised that TENS and IFC would reduce EIP and result in an improved exercise performance.
Methods In two parts, 18 (Part I) and 22 (Part II) healthy male and female participants completed an isometric contraction of the dominant bicep until exhaustion (Part I) and a 16.1 km cycling time trial as quickly as they could (Part II) whilst receiving TENS, IFC, and a SHAM placebo in a repeated measures, randomised cross-over, and placebo-controlled design. Perceived EIP was recorded in both tasks using a validated subjective scale.
Results In Part I, TENS significantly reduced perceived EIP (mean reduction of 12%) during the isometric contraction ($P=0.006$) and significantly improved participants' time to exhaustion by a mean of 38% ($P=0.02$). In Part II, TENS significantly improved ($P=0.003$) participants' time trial completion time (−2% improvement) through an increased mean power output.
Conclusion These findings demonstrate that TENS can attenuate perceived EIP in a healthy population and that doing so significantly improves endurance performance in both submaximal isometric single limb exercise and whole-body dynamic exercise.

Keywords Exercise-induced pain · Time to exhaustion · Time trial · Exercise · Gate control theory

Abbreviations

EIP	Exercise-induced pain
ANOVA	Analysis of variance
PO	Power output
HR	Heart rate
B[La]	Blood lactate
MVC	Maximal voluntary contraction
RPE	Ratings of perceived exertion
TENS	Transcutaneous electrical nerve stimulation
IFC	Interferential current
TTE	Time to exhaustion test
Hz	Hertz
GXT	Graded exercise test
TT	Time trial
BRUMS	Brunel Mood Scale

Introduction

Exercise-induced muscle pain (EIP) arises from an accumulation of endogenous algesic substances and an increase in intramuscular pressure (Cook et al. 1997). These endogenous algesics are released from cells when homoeostasis is disturbed as a consequence of intense exercise (Mauger et al. 2010). Therefore, EIP is closely bound to both the intensity and duration of the exercise

Communicated by Guido Ferretti.

✉ Alexis R. Mauger
L.Mauger@kent.ac.uk

[1] Endurance Research Group, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, Chatham ME4 4AG, UK

Published online: 03 February 2017