EXAMINING THE RELATIONSHIP BETWEEN ENDOGENOUS PAIN MODULATION AND EXERCISE

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A thesis by published works submitted for the degree of Doctor of Philosophy

2017

Abstract

The physiological processes that underpin the perception of pain are complex, involving neural systems which act to manipulate the perception of pain through endogenous pain inhibition and facilitation. Dynamic pain assessment, including the conditioned pain modulation (CPM) protocol, allow for the assessment of the efficiency of this endogenous system of pain modulation. Athletes regularly experience pain through the performance of physically demanding tasks and, perhaps as a result of this repeated exposure, are better able to tolerate pain than non-athletes. However, whether athletes possess a more efficient system of endogenous pain modulation, involving enhanced inhibition and/or reduced facilitation, remains to be fully clarified. In addition, although pain is considered an important factor in the performance of physically fatiguing exercise, research to-date has not yet examined whether a more efficient system of endogenous pain modulation is beneficial for endurance exercise performance.

Therefore, the current thesis has two primary research aims: 1) compare the pain modulatory capacity of athletes and non-athletes; and 2) assess the role of endogenous pain modulation in endurance exercise performance. Based on pre-existing literature, it is hypothesised that: 1) athletes will display enhanced pain modulatory capacity when compared to non-athletes; and 2) that an elevated endogenous pain modulatory capacity will result in increased endurance exercise performance.

This thesis includes seven chapters, beginning with an introduction (Chapter I) followed by a literature review (Chapter II), four research papers (Chapters III-VI) and a discussion (Chapter VII). The research papers present four studies which address the primary aims and hypotheses of the thesis. In Study 1 (Chapter III) the endogenous pain modulation

of athletes and non-athletes was compared. As hypothesised, athletes displayed enhanced endogenous pain modulatory capacity when compared to age- and sex-matched non-athletes. Study 2 (Chapter IV) assessed the relationship between endogenous pain modulation and endurance exercise performance. Those displaying elevated endogenous pain inhibitory responses were shown to produce longer endurance times in a sustained muscular contraction. In Study 3 (Chapter V) high-definition transcranial direct current stimulation (HD-tDCS), a form of non-invasive electrical brain stimulation, was examined as a method for the enhancement of endogenous pain modulatory capacity. HD-tDCS was shown to significantly enhance endogenous pain modulatory capacity, offering a method for the experimental manipulation of endogenous pain modulation. Extending upon these findings, HD-tDCS was used in Study 4 (Chapter VI) to examine the effect of enhanced endogenous pain modulation on endurance exercise. Despite successfully increasing endogenous pain modulatory function, HD-tDCS did not increase endurance exercise performance. Therefore, although enhanced endogenous pain modulatory capacity was shown to be related to endurance exercise performance, experimental manipulation of endogenous pain modulation did not cause changes in endurance exercise performance. These findings partially reject the second hypothesis of this thesis and indicate that mediating factors may account for the observed relationship between endogenous pain modulation and endurance exercise.

The findings presented in this thesis are of significant importance to the incremental advancement of knowledge in this field. As previous research has largely failed to utilise dynamic pain assessment, this thesis offers the first comprehensive discussion of the relationship between endogenous pain modulation and exercise. The findings also have significant practical implications, including implications for the treatment of chronic pain, the selection of athletes and the use of novel methods of exercise performance-enhancement.

Publications Arising from this Thesis

1. Flood, A., Waddington, G., Thompson, K., & Cathcart, S. (2017). Increased conditioned pain modulation in athletes. *Journal of Sports Sciences, 35,* 1066-1072. doi: 10.1080/02640414.2016.1210196
2. Flood, A., Waddington, G., & Cathcart, S. (in press). Examining the relationship between endogenous pain modulation capacity and endurance exercise performance. *Research in Sports Medicine*
3. Flood, A., Waddington, G., & Cathcart, S. (2016). High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: a randomized trial. *The Journal of Pain, 17,* 600-605. doi: 10.1016/j.jpain.2016.01.472
4. Flood, A., Waddington, G., Keegan, R. J., Thompson, K. G., & Cathcart, S. (2017). The effects of elevated pain inhibition on endurance exercise performance. *PeerJ, 5,* e3028. doi: 10.7717/peerj.3028

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List of Abbreviations

ACC	Anterior cingulate cortex
CGM	Central governor model
CPM	Conditioned pain modulation
DNIC	Diffuse noxious inhibitory control
DOMS	Delayed-onset muscle soreness
EIH	Exercise-induce hypoalgesia
HD-tDCS	High-definition transcranial direct current stimulation
IASP	International Association for the Study of Pain
LTD	Long-term depression
LTP	Long-term potentiation
NMDA	N-methyl-D-aspartate
NS	Nociception specific
PAG	Periaqueductal gray
RVM	Rostral ventromedial medulla
tDCS	Transcranial direct current stimulation
WDR	Wide-dynamic range

Acknowledgements

I would first like to acknowledge the support that I have received from the members of my supervisory team: Dr Stuart Cathcart, Professor Gordon Waddington, Dr Richard Keegan and Professor Kevin Thompson. I have no doubt that this would not have been possible without your wealth of experience and knowledge. I have learnt a lot from you all and your passion has driven me to overcome the challenges that I have faced along this journey. So I thank you and I look forward to continuing to work with you into the future.

I would also like to thank the academic staff and student members of UCRISE and the Faculty of Health. You have provided a network of support and encouragement over the past three years and I have thoroughly enjoyed working with you. Many thanks also to the Faculty of Health technical support staff for assistance both in and out of the laboratory.

To my family and friends outside of the PhD world, thank you for all of your love and support. You are a central reason for why this PhD rollercoaster has had more ups than downs. For that, and so much more, I will be forever grateful.

Chapter I

Introduction

1.0. Background

Extensive processing throughout the central and peripheral nervous system acts to manipulate the intensity of nociceptive impulses (Millan, 2002). By acting upon nociception, this endogenous modulatory response influences the perception of pain (Nir & Yarntisky, 2015). Therefore, understanding the relative contribution or strength of the competing inhibitory and facilitatory forces involved in endogenous pain modulation holds significant practical value in a variety of settings. For example, the perpetuation of pain symptoms seen in chronic pain sufferers is thought to be due, in part, to a maladaptive endogenous pain modulatory response characterised by enhanced facilitation and/or diminished inhibition (Yarnitsky, 2010). Importantly, dynamic pain assessment protocols, in contrast to the static pain measures of threshold and tolerance, allow for the activation and measurement of endogenous pain modulation (Yarnitsky, 2010). One common dynamic protocol for the assessment of endogenous pain modulation, particularly endogenous pain inhibition, is the conditioned pain modulation (CPM) protocol. This protocol involves the presentation of a noxious test stimulus before and either during or after a noxious conditioning stimulus is applied to a spatially remote bodily region. The degree of change in the perceived intensity of the noxious test stimulus caused by the noxious conditioning stimulus reflects endogenous pain modulation efficiency (Yarnitsky, Granot, & Granovsky, 2014).

Significant individual differences exist in the perception of, and sensitivity to, pain. Highly trained athletes have demonstrated a heightened capacity to tolerate pain when compared to non-athletes (Tesarz, Schuster, Hartmann, Gerhardt, & Eich, 2012). Such

findings suggest that athletes may possess an innate capacity to tolerate high levels of pain. Alternatively, regular engagement in physical activity may reduce pain sensitivity at rest. Longitudinal investigations support this suggestion, with pain tolerance levels increasing after aerobic exercise interventions of twelve (Anshel & Russell, 1994) and six (Jones, Booth, Taylor, & Barry, 2014) weeks. However, when the CPM protocol is used to examine endogenous pain modulation, research to-date has reported both increased (Geva & Defrin, 2013) and decreased (Tesarz, Gerhardt, Schommer, Treede, & Eich, 2013) endogenous pain modulatory capacity in endurance sport athletes when compared to non-athletes. Therefore, it is unclear whether athletes possess more efficient endogenous pain modulation.

In the performance of physically strenuous endurance exercise, pain is a common and natural occurrence (Miles & Clarkson, 1994), with an individual's capacity to endure this exercise-induced pain considered an important factor in determining success (Anshel & Russell, 1994; Mauger, 2013). In support, the central governor model argues that afferent feedback, including nociception, is integrated into either subconscious or conscious pacing decisions which dictate work-rate adjustments during fatiguing endurance exercise (Noakes, 2012). However, the psychobiological model proposes that work-rate regulation is a conscious process independent of afferent feedback from the periphery (Marcora, 2010). Though these viewpoints offer competing theoretical positions, the performance-enhancing effects of analgesic substances such as acetaminophen are well-recognised (Foster, Taylor, Chrismas, Watkins, & Mauger, 2014; Mauger, Jones, & Williams, 2010), suggesting an important role for the perception of pain in the regulation of work-rate during fatiguing exercise.

Despite the apparent role of pain perception in fatiguing exercise tasks, the influence of endogenous pain modulation on endurance exercise performance remains unexamined. It

is possible that an enhanced endogenous pain modulatory response of elevated inhibition and/or reduced facilitation is adaptive for endurance exercise performance. Mauger and colleagues (2010) have previously speculated that the performance-enhancing effects of acetaminophen may be due, in-part, to an increased endogenous pain inhibitory response. However, research to-date has failed to utilise dynamic assessment protocols, such as CPM, to examine the influence of endogenous pain modulation on endurance exercise performance.

In order to comprehensively assess the impact of endogenous pain modulatory capacity on endurance exercise performance, a method for the manipulation of endogenous pain modulation is needed. Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation which allows for the targeted manipulation of neuronal excitability in regions underlying the anodal and cathodal electrodes (Nitsche & Paulus, 2000). tDCS has proven effective for the reduction of pain sensitivity in both chronic (Fregni et al., 2006) and acute (Boggio, Zaghi, Lopes, & Fregni, 2008) pain, with these analgesic effects being partially attributed to a manipulation of endogenous pain modulatory networks (DosSantos, Ferreira, Toback, Carvalho, & DaSilva, 2016). Applying tDCS over the primary motor cortex, Reidler and colleagues (2012) found enhanced endogenous pain modulatory responses in healthy participants. Therefore, tDCS presents as a viable tool for the experimental assessment of the effect of enhanced endogenous pain modulatory capacity on endurance exercise performance.

1.2. Thesis Aims and Structure

This thesis has two primary research aims. To clarify previous mixed findings, the first aim is to compare the endogenous pain modulatory responses of athletes and non-athletes. The second aim is to assess the role of endogenous pain modulation in endurance

exercise performance. It is hypothesised that athletes will display enhanced pain modulatory capacity compared to non-athletes and that an elevated endogenous pain modulatory capacity will result in increased endurance exercise performance. Four chapters present a series of research papers which systematically address the two primary aims and hypotheses of this thesis (see Appendix A). At the time of submission, three of these papers have been published and one is in press. Each paper is presented in the thesis in the style of the journal in which it is published or in press.

In Chapter III the endogenous pain modulatory responses of athletes and non-athletes are compared. The relationship between endogenous pain modulation and endurance exercise is then assessed in Chapter IV. In Chapter V high-definition tDCS (HD-tDCS), a more focal method of tDCS delivery, is examined as a tool for the enhancement of endogenous pain modulatory capacity. Finally, in Chapter VI HD-tDCS applied over the primary motor cortex is used to assess the effects of enhanced endogenous pain modulation on endurance exercise performance. A literature review (Chapter II) outlining the relevant concepts and the current state of the literature precedes the research papers. A summary and general discussion of the findings is presented in a concluding chapter (Chapter VII) which follows the final research paper. A brief introduction and conclusion linking each research paper is presented at the beginning and end of Chapters III-VI.

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Chapter II

Literature Review

2.0. Introduction

This chapter will provide an overview of the current understanding of the physiological mechanisms which underlie the perception of pain, including the involvement of peripheral, spinal and supraspinal structures in the transmission of nociception. The influence of endogenous pain modulatory processes on perceived pain will also be outlined, emphasising the importance of dynamic pain assessment protocols for the assessment of the functioning of the endogenous pain modulatory system. Research findings relating to the pain sensitivity of athletes and non-athletes and the potential role of pain in endurance exercise performance will then be discussed. This review of the literature will highlight the need for additional research to assess the potential differences in the endogenous pain modulatory capacity of athletes and non-athletes as well as the effects of endogenous pain modulation on endurance exercise performance. These related areas of investigation form the two primary research aims of this thesis.

2.1. Historical Perspectives on Nociception and Pain

The current definition of pain from the International Association for the Study of Pain (IASP) (Merskey & Bogduk, 1994) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’. Importantly, this definition acknowledges the subjective nature of the experience of pain. Therefore, care should be taken to distinguish between pain, as a subjective experience, and nociception, defined as ‘the neural process of encoding noxious stimuli’ (Merskey &

Bogduk, 1994). This distinction recognises that pain perception can occur without nociception and conversely, nociception is not sufficient for pain perception. The current definitions follow a long history of debate regarding the nature of the pain experience, spanning millennia (Perl, 2007).

As reviewed in Perl (2007) and Moayedi and Davis (2013), the current understanding of pain is a significant diversion from the historical understanding of the causes underlying the conscious perception of pain. In the posthumously published *Treatise of Man*, Descartes (1664) proposed that a stimulus would pull a thread which would open certain pores on the internal surface of the brain. Animal spirits, contained within these pores, would then flood the muscles and the nerves to activate behavioural (motor) responses. This argument is illustrated in an extensively cited example and image from *Treatise of Man*, which depicts the pain-specific somatosensory pathway proposed by Descartes in a man standing over a fire (Figure 1). This work popularised the specificity theory of pain which proposes that unique or distinct neural structures exist for the reception, transmission and perception of not only pain, but all somatosensory modalities (Moayedi & Davis, 2013). The alternative intensity and pattern theories argue against the idea of specialised neural structures and instead propose that somatosensory experiences are distinguished by the intensity of neural activity or the spatiotemporal relationship between the responses of non-somatosensory-specific neural structures (Perl, 2007).

Figure 1. Descartes (1644) description of the pain pathway: 'If for example fire comes near the foot, minute particles of this fire which as you know move with great velocity, have the power to set in motion the spot of the skin of the foot which they touch, and by this means pulling upon the delicate thread which is attached to the spot of the skin, they open up at the same instant the pore against which the delicate thread ends, just as by pulling at one end of a rope one makes to strike at the same instant a bell which hangs on the other end'.

Little change occurred in the theoretical understanding of pain until the 1960's with the development of the gate control theory (Melzack & Wall, 1965). The gate control theory signified a notable shift in the understanding of pain physiology as it attempted to clarify the opposing positions of the specificity, intensity and pattern theories and better explain the complexity of the pain experience. In particular, the gate control theory responded to Beecher's (1946) observations of soldiers reporting no pain and refusing pain relief despite suffering serious injuries. Gate control theory also accounted for the accumulating evidence that suggested that nociception undergoes significant dynamic modulation which influences

the resulting perception of pain (Yaksh, 1999). According to Melzack and Wall's (1965) original conception of the gate control theory, nociceptive impulses are modulated at the dorsal horn. This modulation can block the transmission of noxious input to spinal and subsequent supraspinal regions, explaining the separation of the conscious perception of pain from the intensity of the noxious stimulus, highlighted in the current IASP definition of pain and Beecher's observations. In addition, by recognising the supraspinal involvement in the gating of nociception, the gate control theory provided a mechanism to explain the influence of psychological factors in the perception of pain. The spinal gating mechanism proposed by Mezack and Wall is displayed in Figure 2.

According to Melzack and Wall (1965), the substantia gelatinosa, a dense arrangement of interneurons contained within the spinal cord, inhibit primary afferents prior to their synaptic connection to ascending spinal transmission neurons. Therefore, the substantia gelatinosa acts as a presynaptic gating mechanism within the spinal cord, modulating nociception. Activity in small diameter primary afferents responding to the presence of a noxious stimulus sends excitatory impulses to the spinal cord and inhibitory impulses to the substantia gelatinosa (Melzack & Wall, 1965). This causes a disinhibition of the primary afferents from the substantia gelatinosa, opening the 'gate' for the transmission of nociception to ascending spinal neurons. Input from large diameter cutaneous afferents responding to non-noxious stimuli such as rubbing or vibration, excite the substantia gelatinosa, elevating its inhibitory effect on small diameter afferents (Melzack & Wall, 1965). This act of 'closing the gate' results in hypoalgesia and explains the analgesic effect of rubbing or applying pressure to a painful area. Therefore, according to gate control theory, nociceptive input to the ascending tracts within the spinal cord is a function of the relative input of both small and large diameter primary afferent fibres.

The involvement of supraspinal regions in the filtering of nociceptive input was acknowledged by Melzack and Wall (1965). They argued that a 'central control trigger' activated supraspinal networks ('Action System' in Figure 2) which, in turn, initiate modulatory processes. Although these supraspinal networks were not elaborated upon, it was recognised that the definitive 'pain centre' was inadequate and that instead a vast network of brain regions are likely involved in pain processing. The neuromatrix theory, a later addition to the gate control theory based on analyses of the physiological mechanisms of phantom limb pain (Melzack, 1989), provided further detail as to the nature of these supraspinal neural networks involved in pain perception. Briefly, the neuromatrix refers to a system of brain regions responsible for the development of a neurosignature, or the manifestation of the conscious awareness of our 'body-self' (Melzack, 2001). Sensory input may contribute to the neurosignature, but it is not necessary. Instead, the neurosignature is a product of the brain (Melzack, 1999). Therefore, according to the neuromatrix theory, the perception of pain is not solely the result of injury or potential injury, but rather the result of a complex interplay of neural activity within the neuromatrix. Melzack (1989) suggests that the neuromatrix is partly in-built, but can also be moulded based on sensory experience through a process of synaptic plasticity.

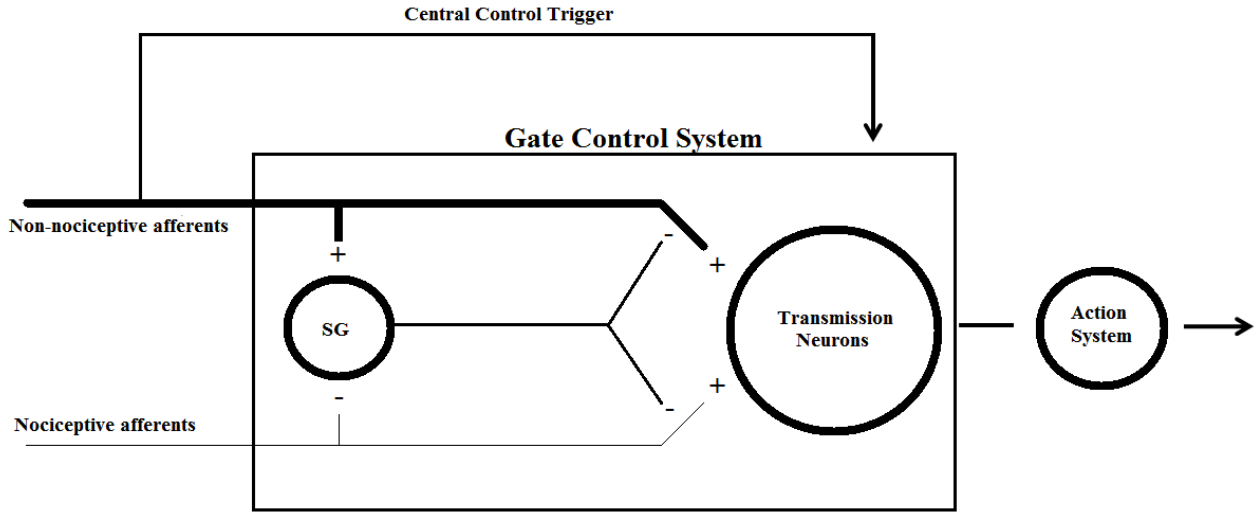

Figure 2. Mechanisms of the gate control theory (from Melzack & Wall, 1965). SG, substantia gelatinosa.

2.2. Physiology of Pain: Ascending Pathways

The following sections discuss the physiological mechanisms involved in the reception of noxious input and the transmission of the resulting nociceptive impulse to supraspinal regions.

2.2.1. Peripheral mechanisms

The conversion of noxious stimuli to a neural impulse is referred to as transduction (Briggs, 2010). This process begins in the most distal regions of peripheral afferent fibres in specialised receptors referred to as nociceptors, which are widely dispersed throughout the body, including the skin, mucosa, deep fascias, visceral organs, muscles, tendons and arteries (Almeida, Roizenblatt, & Tufik, 2004). These receptors are selectively sensitive to noxious input due to their high excitation thresholds (Almeida et al., 2004).

From the receptor, specialised afferent fibres project the neural impulse toward the spinal cord, specifically the dorsal horn (Brooks & Tracey, 2005). Specialised peripheral

afferent fibres were first identified by Sherrington (1906), with subsequent research uncovering further specialisation amongst peripheral fibres. A-delta fibres are myelinated fibres with a diameter of 2-6 μm and a conduction velocity of 12-30 m/s which are selective for noxious input, typically corresponding to rapid, sharp and well-localised pain (Millan, 1999). These fibres can be further separated into type I and type II A-delta afferents. Type I afferents respond strongly to high intensity, noxious mechanical pressure but weakly to noxious thermal or chemical stimuli, unless subject to repetitive stimulation. In contrast, type II fibres possess a lower threshold for noxious thermal stimuli and are, therefore, more receptive to this modality of stimulus (Millan, 1999). Type C peripheral afferent fibres, unmyelinated, thin (0.4-1.2 μm) fibres with slow conduction velocities (0.5-2.0 m/s) also respond to noxious input, but typically result in dull pain often referred to as 'second wave' pain (Millan, 1999). Finally, A-beta fibres are myelinated fibres with a large diameter (> 10 μm) and fast conduction velocities (30-100 m/s). These fibres respond to non-noxious input including touch, vibration and other low-intensity mechanical stimuli (Millan, 1999). Although not directly involved in nociceptive transmission, large diameter A-beta fibres are important for the segmental modulation of nociception proposed by the gate control theory (Almeida et al., 2004).

2.2.2. Spinal mechanisms

Sensory input is transmitted along primary afferent fibres toward the spinal cord, with the terminals of the nociceptor fibres creating synaptic connections with second order neurons of the spinal dorsal horn (Brooks & Tracey, 2005). This synaptic transmission largely relies on the neurotransmitter glutamate and ionotropic type receptors (D'Mello & Dickenson, 2008). According to Rexed's cytoarchitectonic method of spinal cord organisation (Rexed, 1952), the dorsal horn consists of Laminae I through VI (Millan, 1999).

Neurons contained within the dorsal horn can be separated into three distinct categories. First, nociception specific (NS) neurons, found predominately in superficial layers (Laminae I and II), respond exclusively to noxious input (Villanueva, Lopez-Avila, & Monconduit, 2006). These neurons receive input from A-delta and C-type fibres from the periphery (Almeida et al., 2004). Wide-dynamic-range (WDR) neurons are multi-receptive, responding to both noxious and innocuous input from A-beta, A-delta and C-type fibres (Le Bars, 2002). These neurons are located predominately in deeper Lamina of the dorsal horn (Laminae IV-IV) (Villanueva, Lopez-Avila & Monconduit, 2006). Importantly, WDR neurons increase their response frequency from non-noxious to noxious input (Almeida et al., 2004). Due to their graded response and their reception of noxious and innocuous stimuli, WDR neurons are important for the coding of the intensity of the stimulus. Finally, non-noxious neurons, located within Lamina I, II and IV receive innocuous, low intensity input from A-beta and A-delta peripheral afferents (Almeida et al., 2004).

NS, WDR and non-noxious second order neurons can be further classified according to their projection targets. Intrinsic second order neurons are contained within the spinal cord (Todd, 2010). These interneurons include both excitatory and inhibitory interneurons which influence the activity of dorsal horn neurons and produce presynaptic effects on peripheral afferents (Millan, 1999). Those second order neurons which project from the dorsal horn to supraspinal regions are referred to as projection neurons (Todd, 2010). Projection neurons ascend to supraspinal targets via multiple spinal tracts. The anatomy of these ascending tracts is complex, and therefore, a comprehensive presentation is beyond the scope of this review. However, several comprehensive reviews of the ascending spinal tracts involved in the transmission of sensory input (nociceptive and non-nociceptive) are presented elsewhere (Almeida et al., 2004; Millan, 1999). For the transmission of nociceptive input, the

spinothalamic, spinalreticular and spinomesencephalic tract are of particular importance. The spinothalamic tract forms from NS, WDR and non-noxious projection neurons of the dorsal horn. This tract extends from the dorsal horn to the periaqueductal gray (PAG) in the brainstem before ascending to the lateral, posterior medial and central aspects of the thalamus (Almeida et al., 2004). The spinoreticular tract originates mainly from WDR and NS neurons in deeper dorsal horn laminae (Haber, Moore, & Willis, 1982). Axons of the spinoreticular tract project to brainstem structures involved in the modulation of nociceptive circuits (Almeida et al., 2004). Axons of NS, WDR and non-noxious neurons of the dorsal horn also form the spinomesencephalic spinal tract. Within the spinomesencephalic tract, the spinoannular tract projects to the PAG, while the spinotectal tract reaches the superior colliculus (Millan, 1999). Within these tracts, nociceptive input predominately ascends via spinal columns contralateral to the innervating peripheral fibre (Almeida et al., 2004).

2.2.3. Supraspinal mechanisms

Melzack and Wall's (1965) gate control theory and later Melzack's (1999; 2001) neuromatrix theory acknowledged the involvement of supraspinal sites in the processing of nociception. Using neuroimaging techniques, research has discovered consistent neuroanatomical regions involved in the processing of nociceptive input (Ingvar, 1999). Significant nociceptive processing appears to take place in regions of the brain stem, including the PAG, parabrachial area and the rostral ventromedial medulla (RVM) (D'Mello & Dickenson, 2008). Further upstream, the thalamus acts as the main relay site for ascending afferent input, projecting nociceptive afferents towards several cortical regions through distinct lateral and medial tracts (Tracey, 2005). The lateral tract involves projections from the lateral thalamus to the primary and secondary somatosensory cortex and is predominately involved in sensory-discriminative aspects of pain perception (Peyron, Laurent, & Garcia-

Larrea, 2000). Using hypnotic suggestion, Hofbauer, Rainville, Duncan, and Bushnell (2001) demonstrated support for the role of the primary and secondary somatosensory regions in the processing of the sensory aspects of pain. The medial tract, originating in the medial thalamus and projecting to disperse cortical regions including the anterior cingulate cortex (ACC), is responsible for emotional aspects of the pain response (Almeida et al., 2004). The role of the limbic system, especially the ACC, in the emotional aspects of pain has been demonstrated using positron emission tomography (Rainville, Duncan, Price, Carrier, & Bushnell, 1997).

The insula is considered to play a role in the integration of the information processed by the lateral and medial systems (Brooks & Tracey, 2005). However, as discussed in Bushnell and Duncan (1989), this distinction between lateral and medial systems is an oversimplification of complex circuitry, with much overlap occurring in the regions involved in the emotional and sensory aspects of pain. The complexity of supraspinal nociceptive processing is yet to be fully elucidated despite the identification of several cortical and subcortical sites involved in the neuromatrix.

2.3. Physiology of Pain: Muscle Pain

The majority of the research examining the physiology of nociception has focused on nociception of cutaneous origin. Nociception originating in the muscle has unique psychophysiological and neuroanatomical properties. Four distinct primary afferent fibres originate in the muscle and connective tissue. Type I and II afferents are located within muscle spindles and golgi tendon organs and transmit innocuous information regarding muscle stretch and contraction (O'Connor & Cook, 1999). Type III (equivalent to A-delta fibre) and IV (equivalent to C-type fibre) fibres transmit nociceptive input from the wall of arterioles and surrounding connective tissue of skeletal muscle to the spinal dorsal horn via

the dorsal root (Graven-Nielsen & Mense, 2001; Mense, 1993). In contrast to the sharp pain induced via stimulation of cutaneous A-delta fibres, stimulation of type III muscle afferents typically results in the perception of dull, cramp-like pain (O'Connor & Cook, 1999). Type IV fibres also transmit nociceptive impulses with similar perceptual qualities (O'Connor & Cook, 1999). Muscle nociceptors respond to a wide array of stimulation including noxious mechanical, thermal and chemical stimuli (Mense, 1993). Brandykinin, serotonin, potassium and histamine have all been consistently identified as substances released during skeletal muscle activity which activate and sensitise nociceptors in the muscle (Graven-Nielsen & Mense, 2001; O'Connor & Cook, 1999).

At the spinal level, primary afferent fibres originating from the muscles synapse with similar dorsal horn neurons as those innervated via cutaneous nociceptive primary afferents (Millan, 1999). This convergence of input explains the poor localisation of muscle pain compared to cutaneous pain and the phenomena of referred pain, which describes the referral of muscle pain to regions- mainly other deep tissue- which are remote from the source of the noxious stimulus (Mense, 1994). From the dorsal horn, nociception originating in the muscle ascends through the same spinal tracts described above (O'Connor & Cook, 1999). In a comparison of the processing of noxious input from the skin and the muscle, Svensson, Minoshima, Beydoun, Morrow, and Casey (1997) discovered a significant overlap in the supraspinal regions involved. Given the convergence of afferent fibres from the muscle and skin in the dorsal horn and ascending spinal tracts (Millan, 1999), this overlap in supraspinal processing is not surprising. However, noxious stimuli applied to the skin did produce stronger responses in the ipsilateral premotor area, contralateral pre-frontal cortex and secondary somatosensory area, while the ACC was more strongly activated by muscle pain (Svensson et al., 1997). Therefore, despite significant overlap, some unique

psychophysiological responses exist for the processing and perception of nociceptive impulses with origins in the muscle, compared to the skin.

2.4. Physiology of Pain: Endogenous Modulation

The ascending nociceptive pathways presented above suggest a static transmission of nociception toward supraspinal regions. Indeed, this forms the basis for the predictions of specificity theory described above. However, significant modulation of ascending nociception occurs at each level of the nervous system, including at the periphery, the dorsal horn, the spinal cord as well as supraspinal cortical and subcortical levels (Millan, 2002). This modulation is bi-directional, exerting both inhibitory and facilitatory influences on ascending nociceptive input, including nociceptive input originating in the muscle during exercise performance (Heinricher, Tavares, Leith, & Lumb, 2009; O'Connor & Cook, 1999). Endogenous processes which modulate nociception and the resulting perception of pain have clear teleological importance. For example, reduced pain perception resulting from endogenous inhibition of nociception may allow for survival-based behaviours during dangerous or stressful situations. In contrast, increased pain perception from endogenous facilitation of nociceptive input may enhance injury recovery by promoting recuperative behaviours (Heinricher et al., 2009).

The most widely described descending modulatory system originates in the PAG (Pertovaara & Almeida, 2006; Heinricher et al., 2009). As descending pathways from the PAG to the dorsal horn are sparse, the PAG exerts its modulatory control on nociceptive transmission via the RVM (Heinricher et al., 2009). Several populations of neurons within the RVM produce functionally distinct effects on ascending nociception. Off-cells in the RVM inhibit nociception in the spinal dorsal horn while on-cells initiate facilitation (Fields &

Heinricher, 1985). Although recognised as distinct from on- and off-cells, less is known of the role of neutral-cells of the RVM in the modulation of nociception (Heinricher et al., 2009). However, it is possible that these cells undergo phenotypic differentiation into either on- or off-cells in chronic pain states (Miki et al., 2002). From the RVM, projections descend via the dorsolateral funiculus to both superficial and deep laminae of the dorsal horn (Pertovaara & Almeida, 2006). Here descending impulses exert modulatory effects directly by inhibiting or facilitating primary afferent fibres, or indirectly by exciting inhibitory and excitatory spinal interneurons (Pertovaara & Almeida, 2006). In addition, descending projections may modulate nociceptive transmission at dorsal horn projection neurons (Millan, 2002). Although the majority of research has examined the effect of descending supraspinal projections on dorsal horn modulation, ascending efferents from the PAG also modulate nociception in supraspinal regions (Morgan, Sohn, & Liebeskind, 1989).

The modulatory output of the PAG-RVM system is subject to top-down and bottom-up activation. The RVM and PAG receive both direct and indirect innervation from ascending nociceptive input originating from the dorsal horn, creating a spino-bulbo-spinal loop (D'Mello & Dickenson, 2008). Top-down influences on the PAG and RVM originate from dispersed cortical and subcortical regions including the hypothalamus, parabrachial nucleus, nucleus tractus solitarius, amygdala, ACC, insula and orbitofrontal cortex (Brooks & Tracey, 2005; Millan, 2002). The involvement of these supra-spinal regions in the modulation of nociception explains the influence of psychological factors, such as attention and distraction, in the manipulation of pain perception (Briggs, 2010).

2.4.1. Diffuse noxious inhibitory control

Diffuse noxious inhibitory control (DNIC) refers to a distinct endogenous pain inhibitory system causing extra-segmental inhibition of nociception. First defined by Le Bars, Dickenson, and Besson (1979a), DNIC explains the long recognised counter-irritation phenomenon whereby a noxious stimulus temporarily reduces the perceived intensity of a second noxious stimulus applied to a distinct bodily region, with the duration of this inhibition dependent on the type and intensity of the conditioning stimulus. In a series of papers, Le Bars et al. (1979a; 1979b) were the first to experimentally investigate the physiological mechanisms underpinning counter-irritation. In anaesthetized rats, Le Bars and colleagues (1979a) demonstrated significant inhibition of WDR neurons following the application of a noxious stimulus. Of the 68 WDR neurons examined, sixty-seven were inhibited by noxious stimuli presented to diffuse excitatory receptive fields, with some neural responses being completely abolished by the presentation of the noxious conditioning stimulus (Le Bars et al., 1979a). This inhibitory response was not evident following innocuous stimulation (Le Bars et al., 1979a). In a second study, Le Bars et al. (1979b) found that the DNIC did not influence the activity of non-WDR neurons. In addition, the DNIC effect was abolished in decerebrate rats, suggesting the involvement of a complex, likely brainstem-mediated, supraspinal loop in the observed extra-segmental inhibition of WDR neurons (Le Bars et al., 1979b). Subsequent investigation confirmed the role of brainstem structures, particularly the subnucleus reticularis dorsalis, in the DNIC-like effect in humans (Villanueva & Le Bars, 1995). Importantly, lesions of the PAG and RVM did not influence the DNIC-like response, suggesting that the PAG-RVM and DNIC modulatory responses involve distinct physiological mechanisms (Villanueva & Le Bars, 1995).

CPM is the preferred terminology to explain the psychophysiological correlate of DNIC in humans (Yarnitsky et al., 2010). CPM is typically assessed by applying a noxious test stimulus before and either during or immediately after a noxious conditioning stimulus is applied to a remote bodily region. The degree of change in the perceived intensity of the noxious test stimulus following the noxious conditioning stimulus reflects CPM efficiency (Yarnitsky et al., 2010). More recently, the use of CPM assessment has extended beyond the specific examination of the DNIC-like effect described by Le Bars and colleagues (1979a; 1979b), and is now thought to reflect an individual's pain modulation profile. Those with deficient CPM, characterised as pro-nociceptive, display a maladaptive endogenous pain modulatory response of increased facilitatory and/or decreased inhibitory responses for any noxious input (Yarnitsky et al., 2014). Therefore, CPM measurement is now routinely utilised as an assessment of the efficiency of endogenous pain inhibitory mechanisms, referred to as endogenous analgesia (Nir & Yarnitsky, 2015; Yarnistky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). Traditional static measures of pain threshold and tolerance do not allow for such an examination of the capacity of the endogenous pain modulatory system (Yarnitsky, 2010). Therefore, as a dynamic psychophysical assessment tool, CPM is argued to better represent the reality of the pain experience when compared to static pain measures (Yarnitsky et al., 2014).

In addition to the modulatory effects of nociceptive input described by LeBars and colleagues (1979b), CPM assessment also recognises the modulatory effects of the perception of pain (Nir & Yarnitsky, 2015). Using placebo and nocebo interventions, Nir, Yarnitsky, Honigman and Granot (2012) manipulated the perceived intensity of the conditioning stimulus used within the CPM assessment protocol, without changing the intensity of the nociceptive input. These changes in the perceived intensity of the conditioning stimulus

caused changes in the resulting analgesic effect. As the placebo and nocebo interventions produced no change in the physical intensity of the noxious stimulus, this finding suggests that the perception of pain is involved in endogenous analgesia (Nir & Yarnitsky, 2015). Therefore, within the CPM assessment protocol, the perceived intensity of the conditioning stimulus, as well as its physical intensity, is thought to influence the resulting analgesic effect. It is recommended then, that a conditioning stimulus which produces mild to moderate levels of pain is adequate to activate the CPM response, irrespective of the physical intensity of that stimulus (Yarnitsky et al., 2015).

Using the CPM assessment protocol, inter- and intra-individual differences have been observed in endogenous pain inhibitory capacity. For example, chronic pain sufferers have consistently demonstrated pro-nociceptive pain modulation (see Yarnitsky, 2010 for review). Pain inhibitory capacity also appears to decay with age, with some suggesting these decays begin as early as 40 years of age (Grashorn, Sprenger, Forkmann, Wrobel, & Bingel, 2013). Although this age-related decline in pain inhibitory capacity has been presented as an explanation for the increased rates of chronic pain in the elderly (Grashorn, Sprenger, Forkmann, Wrobel, & Bingel, 2013), the direction of causality is yet to be determined. Research examining gender differences in pain modulatory capacity is somewhat mixed, however, some evidence points to reduced CPM levels in females (Popescu, LeResche, Truelove, & Drangsholt, 2010).

2.5. Physiology of Pain: Summary

Current understanding now distinguishes the perception of pain from the intensity of the noxious stimulus and the resulting nociceptive impulse. Following the gate control theory, research has examined the neurophysiology and anatomy of the system/s of nociception

transmission from peripheral, spinal, and supraspinal relay sites. However, this research has also identified the existence of significant modulatory influences which manipulate the intensity of the noxious input throughout the nervous system. Therefore, nociceptive input to supraspinal regions is not the direct result of the intensity of the noxious stimulus, but rather the result of significant endogenous modulation, the capacity of which can be assessed using the CPM protocol.

2.6. Pain and Exercise

Research examining the interaction between pain and exercise is wide-ranging. The following review will consider two domains within this broad research field. First, both the immediate and extended effects of exercise on pain perception will be discussed. Second, the role of pain in the regulation of exercise performance, specifically endurance exercise performance, will be reviewed.

2.6.1. Immediate and prolonged effect of exercise on pain

Acute widespread analgesia immediately following a single bout of physical activity, referred to as exercise-induced hypoalgesia (EIH), is a widely recognised phenomenon typically assessed through pre- and post-exercise pain assessment (see Koltyn, 2000 for review). This hypoalgesic response has been observed following acute isometric, extended aerobic and dynamic resistance exercise tasks (Naugle, Fillingim, & Riley, 2012). The strength of the resulting hypoalgesia is dependent on the intensity of the exercise, with tasks of higher intensity producing stronger EIH (Hoffman et al., 2004; Koltyn, 2002). However, this effect decays quickly following the cessation of the exercise task (Koltyn, 2000). Although the physiological mechanisms of EIH remain unresolved, Vaegter, Handberg, and Graven-Nielsen (2013) suggest that EIH is distinct from the CPM effect outlined above.

In addition to the immediate, transient hypoalgesic effects of a single exercise session, pain sensitivity assessed at rest has been shown to be related to physical activity levels. Ellingson, Colbert, and Cook (2012) found that healthy individuals who met recommended levels of physical activity have reduced pain sensitivity when compared to individuals who engage in lower levels of physical activity. This observed relationship between exercise participation and basal pain sensitivity was accounted for by the level of engagement in vigorous rather than moderate or low intensity exercise. Comparisons between the pain sensitivity of athletes and non-athletes also points to the hypoalgesic effects of regular exercise (Tesarz et al., 2012). Marathon runners display elevated pain tolerance and threshold levels at rest when compared to age- and sex-matched controls (Freund et al., 2013; Johnson, Stewart, Humphries & Charmove, 2012). Increased pain tolerances, but not thresholds, have also been observed in competitive rowers (Ord & Gijsbers, 2003). Interestingly, professional ballet dancers exhibit similarly reduced pain sensitivity (Tajet-Foxell & Rose, 1995). Within athlete populations, high level athletes display elevated pain tolerances compared to low level athletes, and these pain tolerance levels vary according to phase of training or competition (Scott & Gijsbers, 1981).

In addition to observational findings, research implementing exercise interventions has also shown that regular physical activity results in decreased pain sensitivity at rest. For example, Anshel & Russell (1994) delivered a 12 week intervention which required participants to engage in designated exercise tasks three times per week. Pain tolerance levels to noxious pressure were significantly increased at the completion of the 12 week intervention when compared to controls (Anshel & Russell, 1994). Similar findings have been observed more recently following a six week aerobic exercise intervention (Jones et al., 2014).

Recent research has attempted to extend upon these findings by examining the putative relationship between physical activity levels and endogenous pain modulatory capacity, as assessed through the CPM protocol. Such research is important to explain the physiological mechanisms underlying the reports of pain insensitivity in athletes uncovered through static pain assessment protocols (Geva & Defrin, 2013), as well as to account for the potential utility of exercise interventions for the correction of maladaptive endogenous pain modulation in chronic pain sufferers (Vaegter, Handberg, Jorgensen, Kinly, & Graven-Nielsen, 2015). Geva and Defrin (2013) reported enhanced endogenous pain inhibitory responses in highly trained triathletes when compared to normally active controls. In contrast, decreased endogenous pain inhibition in endurance athletes compared to inactive controls was observed by Tesarz and colleagues (2012). These contradictory findings may be due to athlete sampling, with the athletes recruited by Tesarz et al. (2012) reporting low levels of weekly physical activity relative to those recruited by Geva and Defrin (2013). However, findings have been similarly mixed when examining the relationship between physical activity levels and endogenous pain inhibitory capacity in non-athletes. Naugle and Riley (2014) and Umeda, Lee, Marino, and Hilliard (2016) found that those who engage in higher levels of physical activity, particularly vigorous physical activity, display elevated pain inhibition. However, Lemming et al. (2015) and Vaegter et al. (2015) discovered no relationship between endogenous pain inhibition and the physical activity levels of non-athletes. Therefore, further research is needed to compare the pain modulatory capacity of athletes and non-athletes to clarify the relationship between physical activity levels and endogenous pain inhibitory capacity.

2.6.2. Pain as a regulator of performance

The acknowledgement of the role of the brain in the regulation of exercise performance has stimulated substantial research interest into the factors influencing the regulation of exercise work-rate. Much of this research has focussed on the perception of effort as a regulator of performance. Although this research often presents perceived effort as analogous to pain (Pageaux, 2016), relatively little research has specifically considered the potential regulatory role of pain. This distinction between pain and perceived effort is important, given pain has consistently been shown to possess distinct neurophysiological and perceptual qualities (Pageaux, 2016). Despite limited research evidence, anecdotal evidence given through athlete and coach reports and colloquial phrases such as 'no pain, no gain' which describe the pain of performance suggest that pain is an important factor determining endurance exercise performance. In fact, Anshel and Russell (1994, p. 535) argue that the ability to handle pain is 'among the most important features of sporting success.' Exercise-induced pain in non-injured individuals can be divided into three categories; 1) pain occurring during or immediately after exercise; 2) delayed-onset muscle soreness (DOMS); and 3) pain from vigorous, involuntary contractions (cramp) (Miles & Clarkson, 1994). Although DOMS, cramp and pain associated with injury have clear implications for endurance exercise performance, research assessing the role of pain in exercise performance regulation typically refers to the influence of naturally occurring pain arising during the performance of fatiguing exercise.

Current models present differing positions on the factors involved in the regulation of work-rate during fatiguing exercise, with the role of pain in endurance exercise performance being unclear. According to the central governor model (CGM), moment-to-moment pacing decisions are made by a subconscious, centrally located governor which ensures optimal

performance is achieved without threatening bodily homeostasis (Lambert, St Clair Gibson, & Noakes, 2005; St Clair Gibson & Noakes, 2004). During early stage exercise, pacing decisions are based on both internal and external factors, such as prior experience and environmental conditions (Noakes, 2012). After a delay, afferent feedback from the periphery indicating the physiological state of the exercising muscles is integrated into the pacing calculations made by the central governor to manipulate work-rate through either an up- or down-regulation of neural motor drive (St Clair Gibson & Noakes, 2004). The knowledge of the task duration and the remaining duration of the task is also vital for the calculation of an optimal pacing strategy (St Clair Gibson & Noakes, 2004). The importance of conscious processes is also acknowledged, with the conscious perception of fatigue thought to discourage potentially damaging conscious efforts to override subconscious regulation (Noakes, St Clair Gibson, & Lambert, 2005). Nociception is considered an important signaller of the state of the exercising body, and is, therefore, central to the manipulation of work-rate during fatiguing exercise tasks proposed by the CGM (St Clair Gibson et al., 2006). If nociceptive input indicates that the current pace would lead to premature fatigue, the subconscious central governor would adjust efferent neural drive to ensure the safe completion of the task (St Clair Gibson et al., 2006). Although not discussed explicitly, due to the focus on subconscious factors as regulators of work-rate, the CGM suggests that nociception, rather than the perception of pain, plays a role in exercise performance.

Later iterations of the CGM placed added emphasis on conscious factors involved in the manipulation of exercise work-rate (Noakes, 2012), suggesting the importance of the perception of pain for pacing decisions. In fact, Noakes (2012) stated that ‘everything’ can potentially affect athletic performance through brain-derived pacing decisions. In a similar model of exercise regulation proposed by Tucker (2009), work-rate regulation is based on a

pre-determined perceived exertion template. Work-rate is adjusted throughout exercise tasks to align the conscious perception of exertion with the subconscious template (Tucker, 2009). As perceived exertion is explained as a gestalt of afferent feedback (Noakes, 2012), nociceptive feedback is argued to contribute to pacing decisions by influencing perceived exertion.

An alternative model to the CGM is the psychobiological model which is based on motivational intensity theory (Brehm & Self, 1989). According to the psychobiological model, corollary discharges from motor to sensory regions generate the perception of exertion (Marcora, 2009). As muscles fatigue, an elevated central motor command is required to produce the same degree of force, corresponding to an elevation in corollary discharges, increasing the perception of exertion (deMorree, Klein, & Marcora, 2014; Marcora, 2009). In open-loop exercise tasks, where the end-point of the task is unknown, exhaustion occurs when perceived exertion exceeds potential motivation, defined as the level of effort the individual is willing to endure (Smirmaul, Dantas, Nakamura & Pereira, 2013). In tasks with a known end-point, conscious decisions to regulate work-rate are based on the discrepancy between perceived exertion and potential motivation, as well as the knowledge of the task duration, the knowledge of the remaining duration of the task and previous experience (Pageaux, 2014; Smirmaul, Dantas, Nakamura, & Pereira, 2013). As afferent feedback is not considered to be involved in the generation of perceived exertion or the determination of potential motivation (Marcora, 2010; Pageaux, 2014), the psychobiological model argues against the role of afferent feedback, including nociception, for the regulation of exercise performance.

The administration of analgesic substances prior to the performance of fatiguing exercise has been used to experimentally assess the potential role of pain in work-rate

regulation. Acetaminophen, a common pharmacological analgesic, has been shown to significantly improve both time-trial (Mauger, Jones, & Williams, 2010) and repeated sprint (Foster, Taylor, Chrismas, Watkins, & Mauger, 2014) cycling performance. The analgesic effects of caffeine have also been shown to enhance cycling performance (Gonglach, Ade, Bemben, Larson, & Black, 2015). Sgherza and colleagues (2002) reported reduced cycling time-to-exhaustion in an incremental ramp task following the administration of the opioid antagonist, Naloxone. Based on these findings, Mauger (2014) suggests that naturally occurring, exercise-induced pain is central to the formation of a pacing strategy for the regulation of exercise work-rate.

In support, Amann, Proctor, Sebranek, Pegelow, and Dempsey (2009) reported significant increases in central motor command during a 5 km cycling time-trial following the administration of Fentanyl, an opioid agonist. Performance in the first half of the time-trial was also enhanced. However, overall time-trial performance was no different across experimental conditions due to a significantly diminished second-half performance (Amann et al., 2009). At task completion, concentrations of muscle metabolites were also significantly greater in the Fentanyl condition (Amann et al., 2009). These findings highlight pain as a regulator, rather than simply a limiter of exercise performance. Without sensory input to signal the state of the working muscles, central work-rate regulation appears to produce a sub-optimal pacing strategy, leading to excessive peripheral fatigue. Indeed, a central tenant of the CGM is the existence of a peripheral reserve at exhaustion (Noakes & St Clair Gibson, 2004). Therefore, some degree of analgesia may allow access to otherwise inaccessible physiological reserves for the enhancement of performance, while excessive attenuation of sensory input may interrupt the conscious or subconscious calculation of an optimal pacing strategy.

Although the influence of exercise-induced pain on endurance exercise performance remains unclear, reports of the performance-enhancing effects of exogenous analgesic interventions suggest that a greater endogenous capacity to inhibit nociceptive input may be adaptive for exercise performance. For example, an individual with an anti-nociceptive pain profile may experience less pain during fatiguing exercise tasks than those characterised as pro-nociceptive. This in-turn may allow for better access to physiological reserves during fatiguing exercise, resulting in elevated exercise performance. Mauger and colleagues (2010) offer indirect support for this hypothesis, speculating that the performance-enhancing effects of acetaminophen may be due to an elevated descending pain inhibitory response. Also, Astokorki and Mauger (2016) have recently shown that individuals with a reduced sensitivity to exercise-induced pain produce superior cycling time-trial performances. This suggests that the comprehensive assessment of the influence of endogenous pain modulation on endurance exercise performance will require the targeted manipulation of endogenous pain modulatory responses, confirmed using dynamic pain assessment.

2.7. Non-Invasive Manipulation of Pain: Transcranial Direct Current Stimulation

The use of transcranial electrical stimulation for the manipulation of cortical excitability as a mechanism for behaviour modification has seen significant growth in popularity over recent years. tDCS is one method of minimally invasive transcranial stimulation shown to be effective in a wide range of settings, including the treatment of schizophrenia (Brunelin et al., 2012), recovery from stroke (Fregni et al., 2005), as well as the enhancement of cognitive performance (Chi & Snyder, 2011). tDCS is applied through two, typically 25-35 cm^2 moistened sponge electrodes placed on the scalp over the cortical region under investigation. Stimulation results in polarity dependent shifts in cortical excitability, with anodal stimulation typically increasing and cathodal stimulation typically

decreasing neuronal excitation (Nitsche & Paulus, 2000). However, the direction of modulation resulting from tDCS is complex, differing according to the anatomy of the cortical region under investigation (Caparelli-Daquer et al., 2012; Nitsche & Paulus, 2000). The intensity and duration of stimulation also impacts on the resulting direction of neuronal changes, with tDCS administration protocols typically involving 10-20 minutes of stimulation at 1-2 milliamperes (Nitsche et al., 2008). tDCS differs from other transcranial stimulation techniques such as transcranial magnetic stimulation in that it does not induce the rapid depolarisation needed to create action potentials (Nitsche et al., 2008). These sub-threshold excitatory or inhibitory effects of tDCS can be seen not only in the regions underlying the surface anode or cathode, but also in distant cortical and subcortical regions via cortico-cortical and cortico-subcortical functional connectivity (Lang et al., 2005).

The manipulation of neuronal excitability through the application of tDCS is evident both during and briefly after stimulation (Nitsche & Paulus, 2001). Anodal and cathodal stimulation appear to exert their effects during stimulation exclusively through the depolarisation and hyperpolarisation of the resting membrane potential, respectively (Stagg & Nitsche, 2011). Changes in the resting membrane potential are also likely to explain the extended effects of tDCS, particularly anodal tDCS (Leibetanz, Nitsche, Tergau, & Paulus, 2002). These extended effects have also been attributed to events at the synapse, with the blockade of N-methyl-D-aspartate (NMDA) receptors shown to eradicate the after effects of both anodal and cathodal stimulation (Leibetanz et al., 2002). The importance of NMDA receptors in long-term potentiation (LTP) and long-term depression (LTD) synaptic plasticity suggests that tDCS facilitates the strengthening or weakening of synaptic transmission (Stagg & Nitsche, 2011). Therefore, it is argued that heightened neuronal excitability following anodal tDCS is extended beyond the period of stimulation through the sub-threshold

depolarisation of the resting membrane potential, acting on NMDA receptors for the displacement of Mg^{+} to cause LTP-like synaptic strengthening. Diminished neuronal excitability under the cathode is argued to result from hyperpolarisation of the resting membrane potential, causing LTD-like weakening of synaptic connections. The physiological effects induced via tDCS have largely been examined with stimulation of the primary motor cortex. However, similar mechanisms of action have been shown to be involved in the stimulation of other cortical sites, including the primary somatosensory cortex (Rehman et al., 2016) and visual cortex (Antal, Nitsche, & Paulus, 2006), suggesting at least some degree of transferability across distinct cortical targets (Stagg & Nitsche, 2011).

The ability to target specific neural regions and behavioural outcomes is of central importance to the utility of tDCS in clinical and research settings. Bikson and Rahman (2013) review anatomical and functional specificity as the origins of this specificity. Anatomical specificity refers to the ability to guide direct current to certain brain regions while leaving others unaffected (Bikson & Rahman, 2013). tDCS allows for this anatomical specificity through the manipulation of dosage and electrode placement (Peterchev et al., 2012). Technological advancements have allowed for increased anatomical specificity beyond that possible with traditional methods. HD-tDCS is an advanced tDCS technique whereby direct current is delivered through small, disk electrodes arranged in a ring configuration, typically with an active electrode surrounded by four return electrodes. HD-tDCS has been shown to allow for far greater spatial precision than conventional methods, however, neuronal changes beyond the targeted region remain a limitation of the techinque (Caparelli-Daquer et al., 2012; Datta et al., 2009; Kuo et al., 2013). Although anatomical specificity allows for targeted stimulation of specific brain regions, it does not explain the ability to induce specific functional or behavioural changes when stimulating brain regions responsible for multiple

tasks. To account for these functionally specific effects, Bikson and Rahman (2013) outline functional specificity as the modulation of neuronal networks which are already active. This likely occurs through the facilitation of LTP- and LTD-like processes (Bikson & Rahman, 2013). Therefore, through functional specificity, tDCS allows for the targeting of specific functions with no distinct neurophysiological separation.

Of the research examining the effects of tDCS, the analgesic effects have perhaps been the most widely investigated. An early review of the effects of tDCS in chronic pain as well as pain in healthy populations in the Cochrane Collaboration (O'Connell, Wand, Marston, Spencer, & DeSouzer, 2010) found no evidence to support the use of tDCS for the reduction of pain levels in chronic pain sufferers. However, subsequent reviews with meta-analyses (Luedtke et al., 2012; Vaseghi, Zoghi, & Jaberzadeh, 2014) have supported the analgesic effects of tDCS in chronic and experimentally induced pain, highlighting a growing research interest into the putative analgesic effects of tDCS. Despite this accumulating evidence, significant variability in experimental methods for the application of tDCS has resulted in a lack of clarity regarding the optimal protocols for tDCS-induced analgesia. Anodal tDCS over the dorsolateral prefrontal cortex as well as the primary motor cortex has proven most effective for pain control in chronic pain and healthy populations (Boggio et al., 2008; DallAgnol, Pascoal-Faria, Barros, & Correa, 2015; Fregni et al., 2006; Riberto et al., 2011). These analgesic effects have been shown to occur during and immediately after a single session of tDCS (Antal, Terney, Kuhnl, & Paulus, 2010; Reidler et al., 2012) as well as up to several months after repeated stimulation sessions (DaSilva et al., 2012).

tDCS-induced analgesia is considered to occur through the indirect activation of cortical and subcortical neural networks involved in pain modulation, rather than direct action on the primary cortical target of stimulation (DosSantos, Ferreira, Toback, Carvalho, &

DaSilva, 2016). Boggio et al. (2008) argue that the analgesic effects of motor cortical tDCS are due to the descending modulation of thalamic and brainstem activity. Similar explanations for the analgesic effects of tDCS in chronic pain populations have been proposed, with computational modelling suggesting that tDCS over the primary motor cortex acts on maladaptive endogenous pain modulatory processes within the pain neuromatrix which perpetuate pain symptoms in chronic pain (DaSilva et al., 2012). Further neurophysiological investigations have supported these suggested mechanisms of action, with tDCS over the primary motor cortex shown to modulate thalamic activity via cortico-thalamic connectivity (Polania, Paulus, & Nitsche, 2012). Despite these suggestions, only Reidler and colleagues (2012) have investigated the effects of tDCS on endogenous pain modulatory responses, finding that tDCS significantly increased pain inhibition in healthy participants. Additional research, then, is needed to replicate and extend upon the findings of Reidler and colleagues to verify the utility of tDCS for the enhancement of endogenous pain modulatory capacity.

2.7.1. Transcranial direct current stimulation-induced analgesia for performance-enhancement

Results of research assessing the capacity for tDCS to enhance endurance exercise performance through the manipulation of pain have been mixed. Cogiamanian, Marcegli, Ardolino, Barbieri, and Priori (2007) reported enhanced time-to-exhaustion in a submaximal isometric contraction following tDCS of the motor cortex. Although no pain assessment was conducted, the authors speculated that the observed performance-enhancing effects of the tDCS intervention may be attributed to a reduced perception of pain. In contrast, Kan, Dundas, and Nosaka (2013) found no improvement in endurance exercise performance or exercise-induced pain following tDCS of the motor cortex. Angius, Hopker, Marcora and

Mauger (2015) reported that although tDCS of the motor cortex resulted in analgesia for pain induced via cold water immersion, no changes in exercise-induced pain or endurance exercise performance were evident. While these findings highlight the importance of pain aetiology, the influence of endogenous pain modulation on endurance exercise performance remains unexamined due to the exclusive use of static pain measures to-date.

2.8. Summary

This review of the current state of the literature highlights the need for additional research to not only consider endogenous pain modulation when assessing the relationship between pain and exercise, but also adequately assess endogenous pain modulatory capacity by utilising dynamic assessment methods. Two specific areas require additional investigation. First, although research suggests that athletes are better able to tolerate pain than non-athletes (Tesarz et al., 2012), it remains unclear whether athletes possess greater endogenous pain modulatory capacity. Second, pain is argued to be involved, either directly or indirectly, in the regulation of work-rate during fatiguing exercise (Mauger, 2014). However, research to-date has failed to assess the impact of endogenous pain modulatory capacity on endurance exercise performance. These two areas of investigation form the basis of the current thesis, as is evident in the thesis aims and hypotheses outlined below.

2.9. Project Aims and Hypotheses

The current thesis aims to compare the endogenous pain modulatory capacity of athletes and non-athletes and assess the impact of endogenous pain modulatory capacity on endurance exercise performance. It is hypothesised that athletes will display enhanced pain modulatory capacity when compared to non-athletes and that an elevated endogenous pain modulatory capacity will result in increased endurance exercise performance. A series of four

studies are presented which systematically address these primary research aims and hypotheses.

2.9.1. Study 1: Increased conditioned pain modulation in athletes

The aim of Study 1 was to utilise the CPM assessment protocol to compare the endogenous pain inhibitory responses of well-trained athletes with non-athletes engaged in moderate levels of physical activity. It was hypothesised that athletes would display elevated pain inhibitory responses when compared to non-athletes.

2.9.2. Study 2: Examining the relationship between endogenous pain modulation capacity and endurance exercise performance

The aim of Study 2 was to assess the relationship between endogenous pain inhibitory responses and endurance exercise performance. It was hypothesised that those exhibiting elevated endogenous pain inhibition would produce superior endurance exercise performance.

2.9.3. Study 3: High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: a randomized trial

The aim of Study 3 was to examine the effect of HD-tDCS on endogenous pain inhibitory responses, as assessed through the CPM protocol. It was hypothesised that active HD-tDCS over the primary motor cortex would enhance endogenous pain inhibition.

2.9.4. Study 4: The effects of elevated pain inhibition on exercise performance

Study 4 assessed the impact of experimentally enhancing endogenous pain inhibition on endurance exercise performance. It was hypothesised that elevated pain inhibition would result in enhanced endurance exercise performance.

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Chapter III

Increased Conditioned Pain Modulation in Athletes

3.0. Preface

The efficiency of the endogenous pain modulatory responses of athletes relative to non-athletes is unclear. While Geva and Defrin (2013) have reported increased endogenous pain inhibitory responses in athletes, Tesarz and colleagues (2013) have reported reduced endogenous pain inhibitory responses in athletes. The following chapter presents a published study comparing the endogenous pain modulatory efficiency of highly trained athletes to recreationally active non-athletes. This study attempts to clarify previously mixed findings by restricting athlete recruitment to high-level athletes and implementing a sequential CPM testing protocol, recommended as a clearer representation of endogenous pain modulatory capacity.

3.1. Published Paper

Flood, A., Waddington, G., Thompson, K., & Cathcart, S. (2017). Increased conditioned pain modulation in athletes. *Journal of Sports Sciences, 35,* 1066-1072. doi: 10.1080/02640414.2016.1210196

FORM E: DECLARATION OF CO-AUTHORED PUBLICATION CHAPTER

Declaration for Thesis Chapter 3

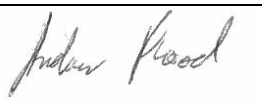
Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, data collection, data analysis, manuscript preparation.	80%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Contributor is also a student at UC Y/N**
Stuart Cathcart	Contributed to study design and manuscript preparation.	N
Gordon Waddington	Contributed to study design and manuscript preparation.	N
Kevin Thompson	Contributed to study design and manuscript preparation.	N

Candidate's Signature		**Date** **07/02/2017**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
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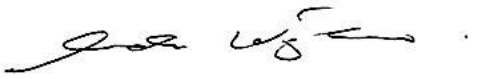
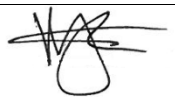
Signature 1		**Date** 23/02/2017
Signature 2		02/03/2017
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Increased conditioned pain modulation in athletes

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Abstract

The potential relationship between physical activity and endogenous pain modulatory capacity remains unclear. Therefore, the aim of the current study was to compare the pain modulatory responses of athletes and non-athletes. Conditioned pain modulation (CPM) was assessed in 15 athletes and 15 non-athletes at rest. Participation was restricted to pain-free males between 18 and 40 years of age. To measure CPM capacity, a sequential CPM testing protocol was implemented, whereby a test stimulus (pressure pain threshold [PPT]) was presented before and immediately after a conditioning stimulus (4-min cold-pressor test). Pain intensity ratings were obtained at 15-s intervals throughout the cold-pressor task using a numerical rating scale. Athletes demonstrated higher baseline PPTs compared to non-athletes ($P = .03$). Athletes also gave lower mean ($P < .001$) and maximum ($P < .001$) pain intensity ratings in response to the conditioning stimulus. The conditioning stimulus had a stronger inhibitory effect on the test stimulus in athletes, showing enhanced CPM in athletes compared to non-athletes ($P < .05$). This finding of enhanced CPM in athletes helps clarify previous mixed findings. Potential implications for exercise performance and injury are discussed.

Introduction

Research has shown consistent support for an immediate, albeit temporary reduction in pain sensitivity following physical exercise (Kodesh & Weissman-Fogel, 2014; Koltyn, 2002; Naugle, Fillingim, & Riley, 2012). In contrast, the long-term effects of regular physical activity on pain perception are unclear. For example, despite concluding that athletes appear to have a higher tolerance for pain, in a meta-analysis conducted by Tesarz, Schuster, Hartmann, Gerhardt, and Eich (2012), only five of the 12 studies analysed revealed a significant difference between athletes and non-athletes' pain tolerance, with the remaining studies showing no significant difference between the two groups. Differences in athletes and non-athletes' pain thresholds showed similarly mixed results.

Pain perception is the result of competing inhibitory and facilitatory mechanisms working in endogenous modulatory circuits (Nir & Yarnitsky, 2015). This complexity of the pain experience is not accounted for with the use of static measures such as pain threshold and tolerance (Nir, Granovsky, Yarnitsky, Sprecher, & Granot, 2011). The extensive use of such measures in the examination of athletes' pain capacity may explain the mixed findings seen to-date.

Conversely, dynamic measures of pain assessment account for this complexity in the pain experience (Nir & Yarnitsky, 2015). In diffuse noxious inhibitory control (DNIC), noxious stimuli applied to one region of the body inhibit the activity of dorsal horn neurons situated in spatially remote receptive fields (LeBars, 2002). DNIC has been described in animals to involve a complex spino-bulbo-spinal loop devoid of higher brain centre involvement (Dahan, Niesters, & Sarton, 2012). Conditioned pain modulation (CPM) is the preferred terminology when describing the DNIC-like effect in humans as it acknowledges

that, in addition to the spino-bulbo-spinal loop, pain inhibition in humans involves top-down influences from higher order brain systems (Brock, Olesen, Valeriani, Arendt-Nielsen, & Drewes, 2012; Moont, Crispel, Lev, Pud, & Yarnitsky, 2011; Weissman-Fogel, Sprecher, & Pud, 2008). When compared to static measures of pain threshold and tolerance, CPM testing protocols have been identified as potentially better predictors of the clinical experience of pain and allow for greater insight into endogenous pain processing systems (Arendt-Nielsen & Yarnitsky, 2009; Edwards, Ness, Weigent, & Fillingim, 2003; Yarnitsky, Granot, & Granovsky, 2014). Therefore, the use of CPM testing protocols may clarify our understanding of the potential differences in pain capacity between athletes and non-athletes.

Limited research has examined the effect of regular physical activity on CPM. Geva and Defrin (2013) found that highly trained athletes had significantly more efficient CPM, characterised by greater pain inhibition, than normally active controls. In support, heightened physical activity levels have been shown to correlate with enhanced pain inhibitory capacity in healthy, non-athlete populations (Naugle & Riley, 2014; Umeda, Lee, Marino, & Hilliard, 2016). Tesarz, Gerhardt, Schommer, Treede, and Eich (2013), however, found decreased CPM in athletes compared to non-athletes. Despite the use of the CPM testing protocols, methodological differences in the test paradigm (sequential versus parallel) as well as the pain induction techniques and sample populations may explain the conflicting results.

It is clear that additional research is needed to help clarify the differences between athletes and non-athletes in pain perception and CPM. This study aims to compare the CPM capacity of athletes and non-athletes. It is hypothesised that athletes and non-athletes will differ in pain inhibitory capacity, demonstrated by changes in CPM.

Methods

Participants

A total of 30 participants, with equal numbers of athletes and non-athletes, volunteered and were deemed suitable for participation. Although a-priori power calculation was not conducted, the sample size is in-line with previous research in this area (see Geva & Defrin, 2013). Athletes were recruited from regional sporting clubs from a range of sports including cycling (n = 5), triathlon (n = 2), swimming (n = 2), football (n = 3), weightlifting (n = 1) and martial arts (n = 2). Individuals training for at least 10 h per week and competing at, or above the top tier of their local competition were included in the athlete sample. Non-athletes were defined as individuals who engaged in amateur physical exercise for no more than 4 h per week. Participants' demographic information is displayed in Table 1. Due to known age (Grashorn, Sprenger, Forkmann, Wrobel, & Bingel, 2013) and (Popescu, LeResche, Truelove, & Drangsholt, 2010) gender-related differences in pain modulation capacity, only males between 18 and 40 years of age were included in the study. In addition, specific criteria excluded individuals with current pathology to the hands, sufferers of diseases with the potential to cause neural damage such as diabetes, and sufferers of chronic pain. The study protocol was approved by the University of Canberra Human Research Ethics Committee (Project Number 14-115). Participant-informed consent was obtained following a full explanation of the study, including the methods, aims and roles of participants.

Table 1

Demographic variables of athletes and non-athletes

	Athletes (n = 15)	Non-athletes (n = 15)	P-value
Age (years)	24.40 (5.28)	23.40 (3.81)	0.68
Training hours ($h \cdot week^{-1}$)	14.80 (5.02)	2.07 (1.10)	< 0.001
Sessions (sessions per week)	8.53 (3.96)	2.00 (1.13)	< 0.001

Data is presented as the mean(SD).

Training hours: Self-reported hours of weekly training/physical exercise.

Sessions: Number of self-reported training/physical exercise sessions per week.

Measures

CPM

CPM is calculated by examining the effect of a conditioning stimulus (CS) on the perceived intensity of a noxious test stimulus (TS) (Yarnitsky et al., 2010). There are two common forms of CPM assessment. The parallel CPM protocol involves the presentation of a TS before and during the presentation of a CS applied to a remote region. In the sequential protocol, however, the TS is presented before and immediately after the CS. As this CPM protocol is argued to be influenced to a lessened degree by cognitive factors such as distraction, it has been recommended as a "cleaner" representation of pain inhibition (Yarnitsky et al., 2015). Therefore, the sequential CPM protocol was adopted for use in the current study.

PPT

For the TS, participants were instructed to place their right hand on a table with their palm facing down. Pressure was then gradually applied to the index finger of participants' right hand using a handheld pressure algometer at a rate of approximately 1 kg · s^{-1} (Wagner Force Dial FDK 20). Participants were instructed to verbally report when the pressure being applied to their finger was first perceived as painful. Once pain was reported, pressure was released and participants' PPT was recorded. This procedure was repeated three times, with 20 s separating each measurement. Support for the use of handheld pressure algometers for the assessment of pain thresholds has been presented elsewhere (Kinser, Sands, & Stone, 2009). Prior to testing, participants were familiarised to the PPT protocol using the ring finger of their right hand. Testing began 1 min after familiarisation.

Cold water immersion

The CS involved the immersion of participants' left hand and part of their wrist in a cold water bath for 4 min. The thermostat-controlled water bath maintained the water temperature at 2 ± 1°C. The water was not circulated at any point throughout the task. Participants were instructed to rest their hand gently on a grid (rubber covered metal grid) which was placed at the base of the water bath. This controlled the depth of hand immersion across participants. Participants were instructed to rate their current level of perceived pain at 15-s intervals using a 0–10 numerical rating scale ($NRS_{0–10}$) with descriptive anchors at 0 (*No pain*), 5 (*Moderate pain*) and 10 (*Most intense pain imaginable*). Participants were able to remove their hand from the water bath if the pain became intolerable. In such cases, pain intensity ratings of "10" were carried through the remainder of the 4-min task.

Questionnaires

All potential participants were required to complete two questionnaires. The first comprehensively assessed participants' physical exercise or training routines. This included questions regarding weekly physical exercise/training, number of sessions of physical exercise/training per week and type of physical exercise engaged in. This self-report data was used to exclude volunteers who did not meet the criteria for inclusion into the athlete or non-athlete group.

The second questionnaire assessed eligibility for participation against the specific exclusion criteria outlined earlier, including questions regarding participants' gender and age as well as questions excluding those with current pathology to the hands, sufferers of diseases with the potential to cause neural damage such as diabetes, and sufferers of chronic pain.

Study design

All tests were performed in the same laboratory by the same experimenter. To ensure that the acute analgesic effects of exercise and caffeine did not interfere with the results, participants were instructed to refrain from engaging in physical activity or consuming caffeinated beverages on the day of testing. All participants confirmed that they had adhered to this request. An outline of the study protocol and aims were presented to the participants prior to informed consent being obtained. Volunteers were then required to complete the two questionnaires which assessed their suitability for participation against the exclusion and inclusion criteria and captured participants' weekly physical exercise routines. To limit the effects of hand temperature on pain perception, those that were deemed eligible for participation then immersed both hands in lukewarm water (25 ± 2°C) for 1 min. Participants' PPT (TS) was then assessed on the right hand, followed by cold water

immersion of the opposing hand (CS). Immediately following (< 10 s) the CS, participants' PPT was measured again on the right hand. In those unable to tolerate the 4-min cold water immersion, PPT measurement was taken immediately (< 10 s) after voluntary withdrawal from the task.

CPM magnitude was calculated by subtracting participants' mean PPT before the CS from their mean PPT after the CS. Therefore, higher values represented greater pain inhibition. This absolute-change method of CPM calculation was preferred over the relative-change method as it follows the methods adopted in previous research in this field (Geva & Defrin, 2013; Naugle & Riley, 2014; Tesarz et al., 2013; Umeda et al., 2016).

Statistical analysis

Data analysis was performed using SPSS statistics software for Windows, Version 21. Independent samples *t* tests were used to assess between group differences in CPM magnitude, PPT and CS pain ratings. Due to violations to the assumption of normality, non-parametric Mann–Whitney *U* tests examined differences between athletes and non-athletes on age, number of hours per week of training/physical exercise and number of sessions per week of training/physical exercise. Pearson's *r* correlational analysis was used to assess the relationship between CS pain ratings and CPM magnitude. Non-normally distributed data warranted the use of Kendall's tau-b to test the correlation between pain measures (PPT and CPM) and training/physical exercise levels in both athletes and non-athletes.

As in Tesarz et al. (2013), corrections for multiple comparisons were not implemented due to the exploratory nature of the study. This is also in accordance with the suggestions of Perneger (1998). Therefore, $P < .05$ was considered statistically significant.

Results

Characteristics of the sample

Characteristics of the two groups are displayed in Table 1. Athletes and non-athletes did not differ significantly in age. There were, as expected, significant differences in the reported number of hours of weekly physical activity and number of weekly training/physical exercise sessions between the two groups. Athletes' self-reported level of competition included national (n = 6), state (n = 6) and local top-tier (n = 3) levels of competition.

Relationship between pain and physical activity

Results of the Kendall's tau-b correlational analysis are given in Table 2. In athletes, CPM levels correlated in a positive direction with reported number of training hours per week and number of training sessions per week. Also, correlational analysis indicated a positive correlation between PPT and number of training sessions per week. However, a negative correlation between athletes' PPT and number of training hours per week was observed. Regarding non-athletes, CPM correlated in a negative direction with reported hours per week of physical exercise and number of sessions per week of physical exercise. Similarly, PPT and hours per week of physical exercise shared a negative correlation. Finally, a positive correlation was observed between PPT and number of sessions per week of physical exercise reported by non-athletes.

Table 2

Results from correlational analysis of pain and physical activity levels

	Athletes (n = 15)		Non-athletes (n = 15)	
	Hours	Sessions	Hours	Sessions
PPT	−.03	.35	−.14	.19
CPM	.05	.25	−.39	−.44

*Significant correlation at P < .05.

Data presented refers to the correlational test statistic (τ).

PPT: Pressure pain threshold.

CPM: Conditioned pain modulation.

Hours: Self-reported hours of weekly training/physical exercise.

Sessions: Number of self-reported training/physical exercise sessions per week.

Comparison of PPT

CPM, PPT and ratings of CS intensity for athletes and non-athletes are presented in Table 3. Athletes were found to have a significantly higher mean PPT at baseline compared to non-athletes, $t(28) = 2.27$, $P = .03$. Calculation of Cohen's effect size suggested that this difference was large ($d = .83$).

Table 3

Pain variables of athletes and non-athletes

	Athletes (n = 15)	Non-athletes (n = 15)	P-value
PPT (kg)	8.01(2.67)	6.12(1.80)	0.03
CS ratings (NRS_{0-10})	5.91(1.50)	8.34(1.14)	< 0.001
CS max ratings (NRS_{0-10})	7.83(1.55)	9.67(0.62)	< 0.001
CPM (kg)	1.19(1.12)	0.30(1.04)	< 0.05

Data is presented as the mean(SD).

PPT: Force required to elicit perceived pain.

CS ratings: Mean ratings of pain intensity throughout CS.

CS max ratings: Highest intensity ratings given during CS presentation.

CPM: Difference between PPT before and after CS.

Comparison of CS perceived intensity

The CS successfully induced pain, with all participants reaching, or exceeding perceived intensity ratings of six on the $NRS_{0–10}$ during cold water immersion. In total, eight participants (two athletes and six non-athletes) were unable to tolerate the entire 4-min duration of the CS. Pain intensity ratings during the CS were significantly lower in athletes than in non-athletes, $t(28) = -4.97$, $P < .001$, $d = 1.82$. Also, maximum pain ratings from the CS differed significantly between the two groups, $t(28) = -4.25$, $P < .001$, $d = 1.56$. These differences were shown not to influence CPM magnitude, with correlational analyses finding no relationship between mean CS pain ratings and CPM scores, $r(28) = -.25$, $P = .19$, or maximum CS pain ratings and CPM scores, $r(28) = -.06$, $P = .74$. Therefore, mean CS pain ratings and maximum CS pain ratings were not included as covariates in the comparison of CPM scores between the two groups.

Comparison of CPM

The main analysis found that CPM scores were significantly higher in athletes compared to non-athletes, $t(28) = 2.07$, $P < .05$. According to Cohen's (1988) conventions, this effect ($d = .82$) can be considered large.

Discussion

It was hypothesised that athletes and non-athletes would differ in their pain inhibitory capacity. This hypothesis was supported with results indicating higher CPM scores in athletes compared to non-athletes.

Potential explanations for enhanced CPM

The finding of increased pain inhibition in athletes is consistent with the similar findings of Geva and Defrin (2013). However, Tesarz et al. (2013) found conflicting results of enhanced pain inhibition in non-athletes compared to athletes. One potential explanation for these conflicting findings is the standard of athlete sampled. In the study by Geva and Defrin, athletes included national level triathletes who trained on average 13 h per week. In the current study, 80% of athletes sampled competed at state or national level. Athletes also reported similar levels of weekly training (14.8 h) as those participating in the study of Geva and Defrin. Athletes sampled by Tesarz et al., however, were selected from regional clubs and their level of competition was not reported. Athletes also reported performing substantially less hours of weekly training (9.6 h) compared to the current study and that of Geva and Defrin.

From these findings, it appears as though elevated pain inhibitory capacity is evident only in athletes competing and training at a high level. In fact, the findings of Tesarz et al.

(2013) suggest that athletes performing at lower levels seem to exhibit less efficient pain modulation than non-athletes. In the current study, results from the correlational analysis, although not reaching statistical significance, offer tentative support for this idea of a non-linear relationship between physical exercise and pain modulation. In athletes, those reporting higher training loads were shown to possess more efficient pain modulation. The direction of this relationship was reversed in non-athletes, with non-athletes who reported higher levels of physical exercise displaying reduced pain inhibition. Similarly, recent research evidence suggests that levels of vigorous physical activity, rather than moderate physical activity, are predictive of pain inhibitory capacity (Naugle & Riley, 2014; Umeda et al., 2016). These findings offer preliminary support for the potential inverted-U shaped, or nonlinear relationship between physical activity and pain inhibition. Future research should aim to investigate this further.

The comparison between the current study and previously conducted studies is further complicated by the CPM protocols utilised. Geva and Defrin (2013) adopted a parallel protocol, whereby the second TS and the CS are presented simultaneously. This protocol has been argued to reflect psychological factors involved in pain perception such as attention (Yarnitsky et al., 2015), therefore reducing the clarity of the measure and potentially overestimating the CPM effect. Despite finding similar results to that of Geva and Defrin, a sequential protocol was used in the current study, which more closely replicates that of Tesarz et al. (2013). This protocol, where the second TS is presented after the CS, is seen to be more representative of pain inhibitory capacity than the parallel design (Yarnitsky et al., 2015). Therefore, the current study is the first to demonstrate enhanced CPM in athletes when assessed using a sequential testing protocol.

It is important to note, however, that Tesarz et al. (2013) allowed for a 1-min interval between the removal of the CS and the application of the TS (2-min tonic heat pain). Tesarz et al. may have missed the peak CPM response and instead measured the rate of pain inhibition decay. This is in contrast to the method adopted in the current study, where the second TS was presented immediately after the CS.

The current findings, along with those of Geva and Defrin (2013), demonstrate an elevated pain inhibitory response in athletes. What remains unclear, however, is whether this increased pain inhibitory capacity in athletes is due to their regular exposure to pain through training and performance, or whether it is an innate capability, predisposing individuals to engage in athletic endeavours. Some have argued that pain modulation capacity can be altered by life experiences (Yarnitsky et al., 2014). Indeed, longitudinal examinations of changes in pain tolerance following an extended exercise intervention support this argument (Anshel & Russell, 1994; Jones, Booth, Taylor, & Barry, 2014). This suggests that regular exposure to pain-inducing exercise may strengthen the CPM pathway, resulting in an enhanced pain inhibitory response. However, findings of reduced, rather than enhanced, CPM amongst chronic pain sufferers (Cathcart, Winefield, Lushington, & Rolan, 2010; Lautenbacher & Rollman, 1997) indicate that it is overly simplistic to suggest a direct relationship between regular exposure to pain and increased pain inhibitory capacity. Instead, as indicated by Geva and Defrin (2013), differences in the nature of the pain experienced by athletes and chronic pain sufferers must be considered when comparing the pain modulation of the two groups.

Ultimately, the mechanisms underlying the differences in pain inhibitory capacity between athletes and non-athletes remain unclear. Longitudinal research examining the effect of physical exercise on pain modulation is needed to establish a chain of causality.

Implications

Despite continued debate (Amann & Secher, 2010; Marcora, 2010), the role of pain in exercise performance regulation remains widely accepted (Mauger, 2014). Research has shown that the administration of substances with analgesic properties results in an increased ability to access physiological reserves during fatiguing exercise tasks, leading to enhanced task performance (Foster, Taylor, Chrismas, Watkins, & Mauger, 2014; Mauger, Jones, & Williams, 2010). It is possible then that the enhanced pain inhibitory capacity of athletes allows them to better access physiological reserves during fatiguing exercise, resulting in enhanced performance.

However, according to models of exercise fatigue, a physiological reserve is maintained so as to ensure that the task performance does not threaten internal homeostasis (Tucker & Noakes, 2009). In a study by Amann, Proctor, Sebrank, Pegelow and Dempsey (2009), the injection of fentanyl to reduce the rate of afferent feedback from working muscles resulted in an increase in noxious metabolite accumulation and reported muscle soreness. This suggests that by helping maintain a physiological reserve, pain may be an important factor in limiting performance to a "safe" level, thereby reducing the likelihood of injury. It is possible then that an increased pain inhibitory capacity may be maladaptive for an athlete, predisposing them to an increased injury risk.

These potential implications of enhanced pain inhibition on exercise performance and injury require further examination.

Limitations

Several limitations of the current study must be acknowledged. Athletes were sampled from a range of sports including cycling, triathlon, swimming, football, weightlifting and

martial arts. This potentially limits the clarity of the findings. However, research examining the effect of exercise type on the relationship between pain and exercise has shown mixed results (Ellison & Freischlag, 1975; Ryan & Kovacic, 1966). This suggests that exercise type may not have influenced our results. In addition, we were interested in establishing an understanding of the relationship between exercise and pain modulation capacity, rather than exploring the potential mediating role played by exercise type on this relationship. Despite this, we acknowledge the need for further research to expand on our currently limited knowledge in this area.

Another potential limitation of the current study is the lack of an objective measure of athletes' physical fitness. The clear and significant differences in training/physical exercise routines and competition status signified an adequate disparity between the athletic statuses of the two groups. Therefore, the measurement of participants' physical fitness through an objective measure (e.g., VO_2max) was deemed superfluous to the needs of the study.

The intensity and duration of the CS was selected to ensure an adequate level of pain was experienced by both groups so as to activate CPM. However, athletes rated the intensity of the CS significantly lower than controls and a higher proportion of non-athletes withdrew from the CS prior to the 4-min time period. This difference in pain in response to the CS may have impacted on the magnitude of the inhibition of the TS. Research to date, however, has failed to reach a definitive conclusion as to the effect of the CS intensity on the resulting pain inhibition (Weissman-Fogel et al., 2008), with some arguing that the CPM protocol requires a CS rated as moderately painful before no further activation of CPM can be achieved (Nir et al., 2011). This level of pain was experienced by participants in both groups, with all participants reporting a perceived intensity exceeding five (moderate pain) on the NRS. Also, the findings of the correlational analysis demonstrated no relationship between the pain

intensity ratings given for the CS and the magnitude of pain inhibition. We are, therefore, confident that the CS elicited the desired activation of the CPM pathway and that differences in CS intensity between the two groups did not significantly influence the magnitude of this activation.

PPT assessment was conducted using a manual handheld pressure algometer. The reliability of this method of algometry requires the consistent application of force by the tester. Therefore, this pain assessment technique is open to experimenter bias. Several measures were implemented to reduce the potential for experimenter bias. The tester was familiarised in the use of the device and is experienced in the assessment of CPM using this protocol (Flood, Waddington, & Cathcart, 2016). This experience, according to Kinser et al. (2009), increases the reliability of pain assessment. Also, care was taken to follow recommended protocols for the use of the manual handheld algometer for the measurement of PPT (Jensen, Andersen, Olesen, & Lindblom, 1986; Kinser et al., 2009). Specifically, force was applied perpendicular to the surface of the participants' finger at a consistent rate (1 kg · s^{-1}).

The methods of calculating CPM magnitude must also be considered when discussing the current findings. Previous research examining the relationship between physical exercise and pain inhibition has utilised the absolute-change method of CPM calculation (Geva & Defrin, 2013; Naugle & Riley, 2014; Tesarz et al., 2013; Umeda et al., 2016). Therefore, to better align with this research and allow for clearer comparisons to be drawn, the absolute-change method was preferred in the current study. However, the relative-change method is an alternate method which calculates CPM magnitude as the percentage of change in the perceived intensity of the TS following the presentation of the CS. This method has been offered as a potential alternative to the absolute-change method as it better accounts for

variability in the perceived intensity of the pre-conditioning TS (Yarnitsky et al., 2010). Despite this suggestion, no consensus appears to have been reached regarding the utility of one method of CPM calculation over the other. Future research should continue to examine the utility of these methods for the assessment of pain inhibitory capacity.

Despite conducting multiple comparisons across the two groups, an adjustment of the α-level was not made, with statistical significance remaining at $P < .05$. A correction factor was not used as it is widely noted that the overly conservative nature of these corrections may unnecessarily inflate the possibility of a type II error (Perneger, 1998). In addition, previous research examining differences in pain modulation between athletes and non-athletes have also failed to correct for multiple comparisons (Tesarz et al., 2013). However, due to the increased potential for type I errors, caution should be taken when interpreting the findings of the current study.

Summary

This study aimed to extend upon the work of Geva and Defrin (2013) and Tesarz et al. (2013) by comparing the pain inhibitory capacity of athletes and non-athletes. The findings suggest that athletes have an increased pain inhibitory response, supporting previous research findings of Geva and Defrin, Umeda et al. (2016) and Naugle and Riley (2014). Further research is needed to identify the underlying mechanisms responsible for this observed relationship between physical exercise and pain inhibitory processes.

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3.2. Postface

The primary outcome of the study presented in this chapter confirmed the findings of Geva and Defrin (2013), with athletes shown to possess elevated endogenous pain inhibitory responses compared to recreationally active non-athletes. Interestingly, the relationship between reported levels of physical activity and endogenous pain inhibition differed between the two groups. Higher levels of engagement in physical activity was shown to be related to stronger endogenous inhibitory responses amongst athletes, while those non-athletes who reported higher levels of physical activity displayed reduced endogenous pain inhibition.

It is speculated that highly efficient endogenous pain modulation allows athletes to access otherwise inaccessible physiological reserves during the performance of fatiguing exercise. The following chapters will extend upon this suggestion, utilising both observation and experimental research methodologies to explore the potential influence of endogenous pain modulation on endurance exercise performance.

Chapter IV

Examining the Relationship between Endogenous Pain Modulation Capacity and Endurance Exercise Performance

4.0. Preface

In the previous chapter, it was proposed that a more efficient endogenous pain modulatory response may allow for greater access to physiological reserves during fatiguing exercise, resulting in superior endurance exercise performance. However, this novel suggestion had not yet been explored. The following chapter presents a research report of a paper in press which offers a preliminary investigation into the proposed role of endogenous pain inhibitory capacity in endurance exercise performance. In this study, endogenous pain modulation and endurance exercise performance are assessed in a sample of recreationally active non-athletes. Correlational analysis is then used to determine the potential relationship between endogenous pain modulation and endurance exercise performance.

4.1. Paper in Press

Flood, A., Waddington, G., & Cathcart, S. (in press). Examining the relationship between endogenous pain modulation capacity and endurance exercise performance. *Research in Sports Medicine*

FORM E: DECLARATION OF CO-AUTHORED PUBLICATION CHAPTER

Declaration for Thesis Chapter 4

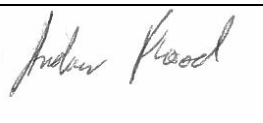
Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, data collection, data analysis, manuscript preparation.	80%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Contributor is also a student at UC Y/N**
Stuart Cathcart	Contributed to study design and manuscript preparation.	N
Gordon Waddington	Contributed to study design and manuscript preparation.	N

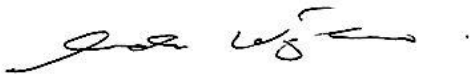
Candidate's Signature		**Date** **07/02/2017**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**University of Canberra**

Signature 1		**Date** 23/02/2017
Signature 2		27/02/2017

Examining the relationship between endogenous pain modulation capacity and endurance exercise performance

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Abstract

The aim of the current study was to examine the relationship between pain modulatory capacity and endurance exercise performance. Twenty-seven recreationally active males between 18 and 35 years of age participated in the study. Pain modulation was assessed by examining the inhibitory effect of a noxious conditioning stimulus (cuff occlusion) on the perceived intensity of a second noxious stimulus (pressure pain threshold). Participants completed two, maximal voluntary contractions followed by a submaximal endurance time task. Both performance tasks involved an isometric contraction of the non-dominant leg. The main analysis uncovered a correlation between pain modulatory capacity and performance on the endurance time task ($r = -.425$, $p = .027$), such that those with elevated pain modulation produced longer endurance times. These findings are the first to demonstrate the relationship between pain modulation responses and endurance exercise performance.

Introduction

It is now widely accepted that psychological factors play a regulatory role in the performance of fatiguing exercise tasks. In particular, perceived exertion has received significant research attention as a performance regulator (Smirmaul, Dantas, Nakamura, & Pereira, 2013; Marcora, 2008; Marcora, 2009). In contrast, the potential role of pain has been somewhat overlooked.

Research findings have offered tentative support for the regulatory role of pain in fatiguing exercise tasks. For example, caffeine has been shown to enhance performance in fatiguing exercise tasks by manipulating exercise-induced pain (Gonglach, Ade, Bemben, Larson, & Black, 2016). Similarly, Foster, Taylor, Chrismas, Watkins, and Mauger (2014) discovered increased cycling performance following the ingestion of acetaminophen, attributing these performance-enhancing effects to a reduction in exercise-induced pain. This supported the similar findings of Mauger, Jones, and Williams (2010) who demonstrated the performance-enhancing effects of acetaminophen in a cycling time trial.

These findings demonstrate improvements in endurance task performance following exogenous manipulation of pain. They also suggest that, without external manipulation, an individual possessing a decreased sensitivity to pain may have a performance advantage during extended performance tasks. This was examined in a recent study by Astokorki and Mauger (2016). In this study, pain measures taken at-rest were not predictive of performance in a subsequent 16.1 km cycling time trial. However, sensitivity to exercise-induced pain was predictive of subsequent time trial performance (Asokorki & Mauger, 2016). As acknowledged by the authors, these findings demonstrate the importance of the method of pain induction when examining the relationship between exercise performance and pain.

Conditioned pain modulation (CPM) is a measure of endogenous pain modulatory capacity (Nir & Yarnitsky, 2015). This dynamic measure reflects the complexity of pain perception, where pain is the product of both inhibitory and facilitatory influences (Brock, Olesen, Valeriani, Arendt-Nielsen, & Drewes, 2012). Therefore, CPM is argued to be more representative of the clinical pain experience when compared to the static measures of pain tolerance and threshold (Yarnitsky, Granot, & Granovsky, 2014). Although exercise-induced pain has been shown to result from a variety of noxious stimuli (see O'Connor & Cook, 1999), it can be assumed that the perception of pain resulting from fatiguing physical activity is subject to central modulatory processing. Therefore, those with highly efficient central pain processing may experience lessened pain at any given work rate or any given level of exercise-induced noxious stimuli.

Some have speculated upon the performance regulatory role of pain modulation, arguing that substances such as acetaminophen (Mauger et al., 2010) and brain stimulation (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007) enhance endurance exercise performance through a manipulation of nociceptive processing. Despite this, the relationship between naturally occurring inter-individual variations in pain modulatory capacity and exercise performance has not yet been examined. Such research would have clear implications for our understanding of the mechanisms underlying the putative performance-regulatory role of pain and the reported performance enhancing effects of analgesic substances such as acetaminophen.

In this exploratory study, we examine the relationship between pain modulatory capacity and endurance time in a submaximal isometric contraction of the knee extensors. It is hypothesised that those with greater pain modulatory efficiency will demonstrate enhanced endurance exercise performance.

Methods

Participants

Twenty-seven males between the ages of 18 and 35 years were recruited for participation from the local university student population. Sampling restrictions were enforced to account for the known age (Grashorn, Sprenger, Forkmann, Wrobel, & Bingel, 2013) and gender (Popescu, LeResche, Truelove, & Drangsholt, 2010) related differences in pain modulation. Participants were recreationally active and were not engaged in competitive sport specifically involving knee-extensor muscles (e.g. cycling or weightlifting). Descriptive information of the sample, including age, height, weight and physical activity level is displayed in Table 1.

Along with restrictions to participants' age, gender and physical activity, chronic pain sufferers, individuals with current pathology to the hands and sufferers of diabetes were excluded from participation. Participants also presented as pain-free on the day of testing.

Table 1

Characteristics of the sample

Variable	Mean ± SD
Age (years)	23 ± 4.07
Height (cm)	181 ± 7.58
Weight (kg)	77 ± 9.26
Physical Activity (MET-min/week)	7158 ± 8844.99
MVC (Nm)	281.15 ± 49.43
Endurance Performance (s)	105.27 ± 43.09
PPT (kg)	9.29 ± 3.27
Removal of CS (s)	119.62 ± 52.37
CPM (kg)	−.67 ± 1.29

MET-min/week, number of minutes spent performing physical activity multiplied by the assigned metabolic equivalent value; MVC, maximal voluntary contraction; Endurance Performance, time to exhaustion in the endurance time task; PPT, pressure pain threshold; Removal of CS, time to removal of the conditioning stimulus at a reported intensity of *7* on the 0-10 rating scale; CPM, conditioned pain modulation.

Measures

Physical Activity Questionnaire

The physical activity habits of participants were assessed using the long, self-administered version of the International Physical Activity Questionnaire (IPAQ). This version of the IPAQ independently assesses physical activity against five domains of activity,

including job-related physical activity, transportation physical activity, housework, recreational physical activity and time spent sitting.

Motivation

Participant motivation relating to the physical performance tasks was assessed using the scale developed by Matthews, Campbell, and Falconer (2001). This scale contains 14-items assessing success motivation and intrinsic motivation as well as a final single item measure of overall motivation. All items are scored against a 5-point Likert scale with descriptive anchors at *0 (not at all), 1 (a little bit), 2 (somewhat), 3 (very much)* and *4 (extremely).*

CPM

Central pain modulatory capacity was assessed using the counter-irritation protocol. This protocol involves the presentation of a noxious stimulus, called the test stimulus (TS), before and immediately after a second noxious stimulus, the conditioning stimulus (CS), is applied to a remote bodily region. The inhibitory effect of the CS on the perceived intensity of the TS reflects pain modulatory capacity (LeBars, 2002).

In the current study, an assessment of participants' pressure pain threshold (PPT) was used as the TS. Participants were instructed to place their left hand on a table with their palm facing downwards. Using a handheld pressure algometer (Model 01163, Lafeyette Instruments, Lafeyette, IN), pressure was then manually applied to the index finger at a rate of approximately 1 kg/s until participants first reported feeling pain. This was performed twice, with the two measures separated by 20-seconds. PPT was recorded as the mean force required to elicit pain in the two trials.

As the CS, a sphygmomanometer cuff was then placed around the participants' right arm, slightly proximal to the cubital fossa. The cuff was gradually inflated (approximately 20mmHg/s) until participants reported feeling pain. The cuff then remained at that level of inflation while participants offered pain intensity ratings at 10-second intervals using a 0-10 numerical rating scale. This numerical rating scale included descriptive anchors at *0* (*No Pain*), *5* (*Moderate Pain*) and *10* (*Worst Pain Imaginable*). Two consecutive ratings at the same perceived intensity, or a reported reduction in perceived intensity, resulted in further inflation of the cuff by approximately 20mmHg. The cuff was fully deflated once a perceived intensity of *7* on the 0-10 numerical rating scale was reported. This protocol ensured that the intensity of the CS resulted in identical levels of perceived pain across participants. Throughout cuff occlusion, participants remained seated, with their right arm resting on a table. Cuff occlusion has previously been shown to successfully inhibit the perceived intensity of a TS for the assessment of CPM (Cathcart, Winefield, Rolan, & Lushington, 2009).

Immediately following the deflation of the cuff, PPT was assessed for a second time, following the methods outlined above. CPM magnitude was calculated by subtracting participants' post-conditioning PPT from their pre-conditioning PPT, with lower CPM scores reflecting greater central pain modulatory capacity. Put simply, greater negative values represent enhanced pain inhibition. Despite this method yielding negative values, it remains the recommended method of calculation (Yarnitsky et al., 2015).

Participants were familiarised to both pain induction methods prior to testing. Sixty-seconds separated familiarisation and the first PPT measure.

Physical Performance

Prior to physical performance testing, participants completed a standardised warm-up consisting of 5-minutes of light cycling on a Monark cycle ergometer (Model 828E, Monark Inc, Varberg, Sweden).

Familiarisation trials were then completed, with participants instructed to perform four, 5-second sub-maximal isometric contractions. Each contraction was separated by 20-seconds.

An isokinetic dynamometer (Humac NORM, Computer Sports Medicine, Stoughton, MA) was used during both familiarisation and physical performance tasks to assess voluntarily produced force of the non-dominant leg in an isometric contraction. Throughout the performance, participants remained in an upright, seated position with a 60^0 flexion of the knee. Adjustments were made to ensure alignment of the dynamometer axis of rotation with the lateral femoral epicondyle of the non-dominant leg.

Maximum Voluntary Contraction (MVC)

To provide a baseline for the endurance time task, two MVC trials were completed. Participants were instructed to contract their non-dominant leg with as much force as possible for 5-seconds. Sixty-seconds separated the two maximal contractions. The peak torque (Nm) achieved from the two contractions was recorded. Torque bars and a countdown timer shown on a computer monitor offered real-time visual feedback to the participants throughout both the MVC and familiarisation trials. The researcher also provided scripted verbal encouragement to the participant throughout the MVC trials.

Endurance Time Task

Endurance time was assessed in a submaximal endurance time task. This task required participants to maintain a target force for as long as possible. The target force was calculated as 35% of the peak force produced in the previous MVC trials. Throughout the performance task, participants received force feedback on a computer monitor, allowing them to monitor their force production against the predetermined target force. To facilitate maximal performance, scripted verbal encouragement was also provided by the researcher throughout the endurance task. Endurance time was recorded as the time until force deviated below the target for three consecutive seconds.

Procedures

Experimental procedures followed those approved by the institutional research ethics board (Project Number: 15-120).

Participants were required to attend the laboratory on one occasion. Prior to the session, they were instructed to refrain from vigorous physical activity for 24-hours. The ingestion of caffeine, alcohol and analgesic medication was also restricted for 8-hours prior to participation.

On arrival, participants were fully informed of the experimental protocol and of their right to withdraw at any point. Assessment against the predefined exclusion criteria was also completed. Once written informed consent was obtained, experimental procedures began.

First, participants' age, weight and height were recorded, along with their physical activity habits. Next, pain modulatory capacity was assessed using the CPM protocol. Participants then completed the warm-up and familiarisation trials, followed by the two MVC

trials and the sub-maximal endurance time task. A period of 60-seconds separated the familiarisation trials from the first MVC trial. Following the second MVC trial, participants rested for 3-minutes before beginning the sub-maximal endurance time task. Participants remained seated throughout all rest intervals. Pain assessment preceded the physical activity tasks to account for the potential hypoalgesic effects of physical activity (Koltyn, 2000).

Statistical Analysis

Twenty-seven participants were included in the analysis. A Pearson's *r* correlation coefficient was calculated to examine the relationship between pain variables (CPM and PPT) and sociodemographic variables of age, height, weight and physical activity level. The relationship between pain and exercise performance (peak MVC force and endurance performance) was also assessed using Pearson's *r* correlational analysis. To control for potential differences in motivational states, Pearson's *r* partial correlational analysis was used to assess the relationship between pain variables and exercise performance while controlling for intrinsic and success motivation. In accordance with existing protocols (Patterson, 2011), total physical activity levels are presented and analysed as MET-minutes per week (see Table 1). Visual inspection of histograms confirmed the assumption of normality for all pain and exercise performance variables, while scatterplots confirmed a homoscedastic and linear relationship between variables. However, data relating to reported levels of physical activity was not normally distributed. Therefore, Kendall's tau-b was used for the correlational analysis of physical activity data. Data for all other sociodemographic variables adhered to the assumptions of parametric procedures.

Data analysis was performed using SPSS statistics software (Version 21, IBM Corp, Armonk, NY). Descriptive information regarding sociodemographic data as well as pain and

performance variables is presented in Table 1. The relationship between pain and performance variables is displayed in Figure 1. $P < .05$ was considered statistically significant. For all correlational analyses, *p*-values along with 95% confidence intervals of the correlation coefficients are given.

Results

Pain and Sociodemographic Variables

Statistical analysis uncovered no significant relationships between CPM and participant age, $r(23) = .075$, $p = .710$, 95% CI [−.31, .44], height, $r(23) = .178$, $p = .375$, 95% CI [−.22, .52], weight, $r(23) = .257$, $p = .196$, 95% CI [−.14, .58] or physical activity level, $\tau = -.043$, $p = .754$, 95% CI [−.42, .34].

Correlations between PPT and age, $r(23) = -.055$, $p = .786$, 95% CI [−.43, .33], height, $r(23) = .223$, $p = .264$, 95% CI [−.17, .56], weight, $r(23) = .318$, $p = .106$, 95% CI [−.07, .62] and physical activity level, $\tau = .043$, $p = .755$, 95% CI [−.34, .42] were also shown to be non-statistically significant.

Motivation

Levels of self-reported success (18.07 ± 5.31) and intrinsic motivation (22.96 ± 2.74) were in-line with previous research (Marcora, Staiano, & Manning, 2009). Therefore, participants were deemed adequately motivated for the completion of the physical performance tasks.

Pain and Endurance Time

Primary correlational analysis uncovered a statistically significant negative relationship between CPM and endurance time, $r(23) = -.425$, $p = .027$, 95% CI [−.69, −.05]. That is, those with higher pain modulatory capacity achieved greater performance in the endurance time task. However, no relationship was seen between baseline PPT and endurance time, $r(23) = .009$, $p = .966$, 95% CI [−.37, .39].

While controlling for success and intrinsic motivation, CPM and endurance time were shown to share a statistically significant negative correlation, $r(23) = -.442$, $p = .027$, 95% CI [−.70, −.08]. As in the unadjusted analysis, no relationship was observed between PPT and endurance time while controlling for intrinsic and success motivation, $r(23) = .004$, $p = .984$, 95% CI [−.38, .38].

Pain and MVC

A positive, non-statistically significant relationship was uncovered between peak MVC force and CPM, $r(23) = .374$, $p = .054$, 95% CI [−.01, .66]. The relationship between MVC performance and PPT was also shown to be non-statistically significant, $r(23) = .218$, $p = .984$, 95% CI [−.18, .55].

While controlling for intrinsic and success motivation, partial correlational analysis showed a positive, non-statistically significant relationship between peak force produced in the MVC trials and pain measures of CPM, $r(23) = .351$, $p = .092$, 95% CI [−.03, .64] and PPT, $r(23) = .283$, $p = .175$, 95% CI [−.11, .60].

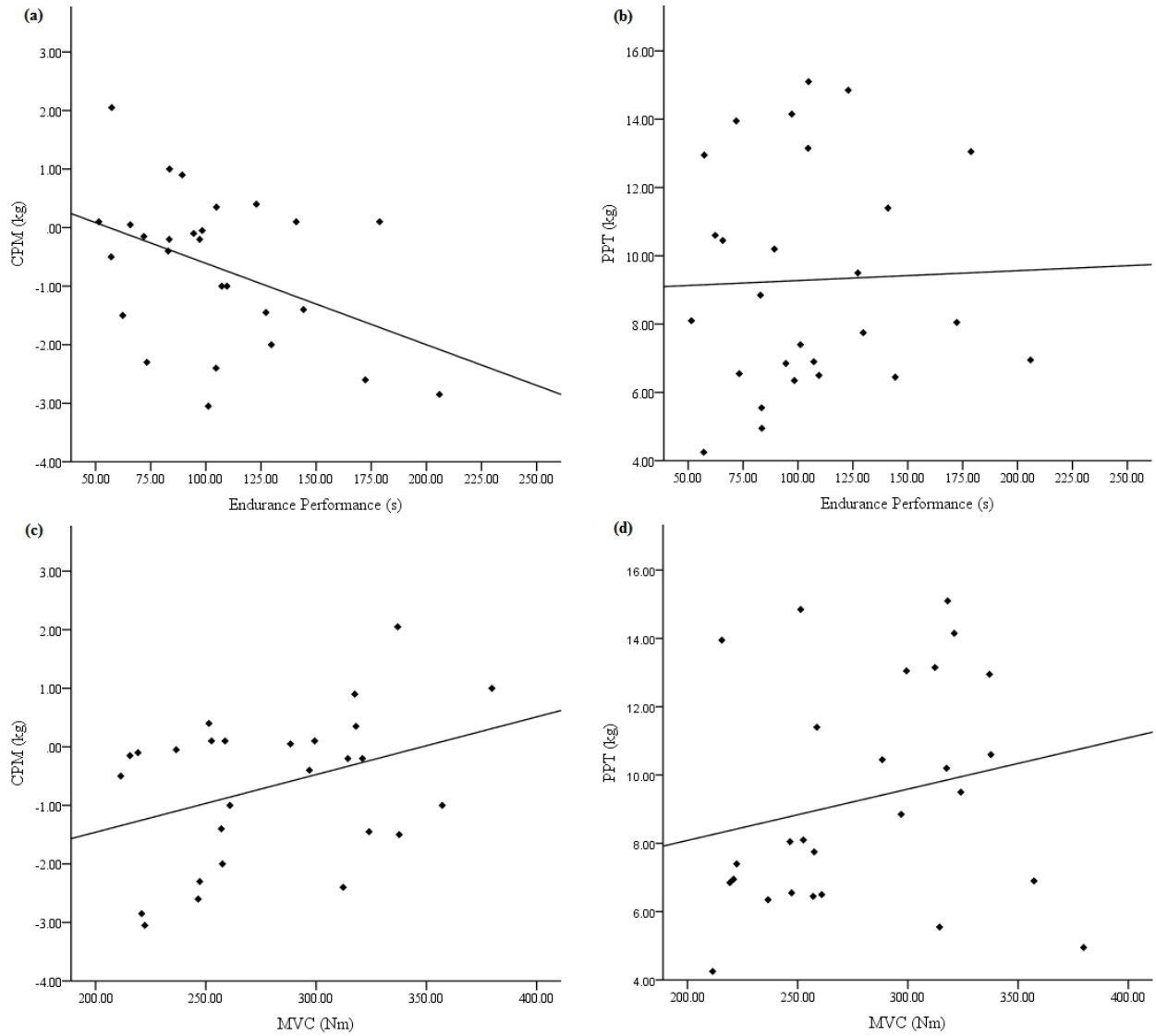

Figure 1. Correlations between (a) endurance performance and CPM ($r = -.425$; $p = .027$), (b) endurance performance and PPT ($r = .009$; $p = .966$), (c) MVC and CPM ($r = .374$; $p = .054$) and (d) MVC and PPT ($r = .218$; $p = .984$)

Discussion

Pain perception is the result of regulatory processing of nociceptive input by endogenous modulatory circuits at both spinal and supraspinal levels (Nir & Yarnitsky, 2015). This modulatory process involves both inhibition and facilitation, with the capacity of these competing influences determining the resulting perception of pain (Nir, Granovsky,

Yarnitsky, Sprecher, & Granot, 2011). The primary aim of the current study was to examine the relationship between pain modulatory capacity and endurance time on a sustained submaximal isometric contraction task. Correlational analysis showed that those exhibiting greater endogenous pain modulatory capacity, characterised by enhanced pain inhibition, performed better on the fatiguing exercise task, with pain modulatory capacity accounting for approximately 18% of the variance in endurance performance. Therefore, the current findings show, for the first time, the relationship between central pain modulation and endurance exercise performance. In fact, to the best of our knowledge, this is the first study to identify the relationship between any method of pain assessment conducted at-rest and exercise performance.

This finding extends upon previous work by Astokorki and Mauger (2016) which demonstrated the relationship between exercise-induced pain and endurance cycling performance. Although not the primary goal of the current study, the finding of no relationship between pain threshold and exercise performance highlights the importance of the method of experimental pain induction when examining the role of pain in exercise performance, a point also identified by Astokorki and Mauger (2016).

Central pain processing has been suggested by others to play a role in exercise-induced pain and exercise performance. For example, Mauger et al. (2010) attributed increases in cycling time trial performance following the ingestion of acetaminophen to an enhanced central pain inhibitory response. Despite this speculation, research has failed to acknowledge the individual differences in pain modulatory capacity and the potential for these differences to influence exercise performance. In this regard, the current findings hold significant value.

It is beyond the scope of the current exploratory project to make definitive conclusions as to why those with greater pain modulatory capacity displayed elevated endurance times. However, models of exercise-induced fatigue such as the teleoanticipation model (Ulmer, 1996) and central governor model (St Clair Gibson & Noakes, 2004) hold some explanatory value. According to these models, exercise performance is regulated by the brain to ensure a physiological reserve is maintained during fatiguing exercise tasks (Noakes, St Clair Gibson & Lambert, 2005; Swart, Lamberts, Lambert, St Clair Gibson, et al., 2009). However, improvements in performance and associated increases in peripheral fatigue (such as elevated blood lactate concentration) following psychological manipulation (Corbett, Barwood, Ouzounoglou, Thelwell, & Dicks, 2012; Jones et al., 2013; Swart, Lamberts, Lambert, Lambert, et al., 2009) suggest that this regulation is overly-conservative and that the physiological reserve can be safely accessed.

Pain has been argued as one factor involved in this performance regulation (Mauger, 2014). As such, manipulations using analgesic substances have predictably resulted in enhanced exercise performance (Foster et al., 2014; Gonglach et al., 2016; Mauger et al., 2010). Following the models described above, it has been suggested that these performance improvements are due to the manipulation of this conservative central performance regulation, allowing the individual to access previously inaccessible physiological reserves (Mauger, 2014). Similarly, the current findings can be argued to demonstrate a greater ability to access physiological reserves in individuals with greater pain modulatory capacity, resulting in an extended endurance time. Without an experimental manipulation of pain modulation capacity or a direct assessment of physiological markers of fatigue, this potential explanation is speculative. Therefore, we encourage additional research into this possible causal explanation.

A surprising and counter-intuitive finding of the current study was the moderately strong, positive correlation between CPM and performance on the MVC trials. Although not reaching statistical significance, this finding suggests that those with a heightened pain inhibitory response produce lower peak forces during a MVC. It is possible that the performance regulatory role of pain inhibition is dependent on the type and duration of the performance task. Additional research is needed to examine the performance regulatory role of pain in maximal tasks of short duration.

Some important limitations must be considered when interpreting the current findings. Pain perception was not assessed during the exercise performance tasks. Therefore, we cannot say with certainty that individuals with efficient pain modulation experienced lessened exercise-induced pain, allowing for their increased performance. Indeed, participants may not have experienced pain during the trial. However, the existence of exercise-induced pain is widely accepted and is a well-recognised result of exercise performance (O'Connor & Cook, 1999). Anecdotal reports from participants also indicated the pain-inducing nature of the endurance time task. Pain assessment was not conducted during the exercise performance to allow participants to focus their attention on maintaining their force output above the target.

As indicated above, the lack of physiological fatigue assessment limits the ability to draw definitive conclusions. In particular, indicators of peripheral fatigue such as blood lactate accumulation may have offered greater insight into the potential increased ability of those with highly efficient pain modulatory capacity to withstand greater levels of physiological fatigue. Such measures were not included to limit the potential for distractions to negatively influence performance in the exercise tasks.

It should be acknowledged that the role of pain in regulating exercise performance is disputed. The psychobiological model argues against the role of afferent feedback in performance regulation, arguing instead for the influence of motivation and neural corollary discharges (Marcora, 2009; Marcora, 2010). Therefore, caution should be taken when considering the current findings in the broader scope of the literature on exercise performance regulation.

Similarly, awareness of pain as a regulator of performance, rather than simply a performance-limiter should be acknowledged. As indicated in the work of Amann, Proctor, Sebranek, Pegelow, and Dempsey (2009), excessive manipulation of afferent feedback seemingly reduces an individual's ability to adequately regulate work rate, resulting in an overly aggressive pacing strategy which threatens the safe completion of a cycling time trial. This suggests the important regulatory role of pain perception. Although improbable, pain inhibitory responses may reach a point of such heightened efficiency that could be detrimental to performance. We encourage further research into this possibility.

The extensive methodological inconsistencies in the assessment of CPM throughout the literature further limit the generalisability of the current findings. For example, the application of noxious stimuli to detection threshold (Reidler et al., 2012) and supra-threshold (Geva, Pruessner, & Defrin, 2014) intensities have previously been utilised as the TS in CPM assessment. The use of PPT measurement was selected for the current study as it is a widely used method for the assessment of CPM efficiency (Lewis, Heales, Rice, Rome, & McNair, 2012). A lack of methodological consistency is also evident in the methods used as the CS. In the current study, cuff occlusion was the preferred method as the CS. This method of pain induction has previously been shown to successfully inhibit the perceived intensity of the TS

(Cathcart, Winefield, Rolan, & Lushington, 2009), and was preferred over alternative methods of noxious heat and cold.

The relationship between the CS intensity (actual and perceived) and the magnitude of the CPM response is also unclear (Pud, Granovsky, & Yarnitsky, 2009). Some have utilised methods whereby the actual intensity and duration, but not the perceived intensity of the CS, is consistent across the sample (Tesarz, Gerhardt, Schommer, Treede, & Eich, 2013). Other methods maintain consistency in the perceived intensity and duration, but not the actual intensity of the CS (Cathcart, Winefield, Lushington, & Rolan, 2010). The current approach varied the duration and actual intensity of cuff occlusion to ensure consistency in the perceived intensity of the CS across participants. This method was utilised to ensure that the induced pain exceeded a moderate level for all participants, following the recommendations of Yarnitsky et al. (2015). However, variations in the actual intensity and the duration of cuff occlusion may have influenced the resulting inhibitory response. Due to these inconsistencies, caution should be taken when generalising the magnitude of inhibition observed in the current study to previous findings.

Both physical performance and pain assessment was conducted by a single researcher. Several methodological considerations were implemented to reduce the potential for experimenter bias. Specifically, feedback provided to the participant during the MVC and endurance trials was either scripted verbal encouragement, or computer generated. This ensured that each participant received the same level of performance feedback and encouragement during the exercise tasks. To further limit the potential for experimenter bias, the duration between the familiarisation, MVC and endurance time trials was also consistent for all participants. For the assessment of pain modulation, the rate of pressure application during PPT measurement followed the recommendations of Jensen, Anderson, Olesen, and

Lindblom (1986), and the rate of cuff inflation adhered to previous methodological approaches (Cathcart, Winefield, Rolan, & Lushington, 2009). This ensured the standardised delivery of both the noxious test and conditioning stimuli for CPM assessment.

Previous research by our group (Flood, Waddington, Thompson, & Cathcart, 2016) as well as others (Geva & Defrin, 2013) has demonstrated heightened pain modulatory capacity in athletes when compared to non-athletes. In contrast, Tesarz, Gerhardt, Schommer, Treede, and Eich (2013) found decreased pain modulatory capacity in endurance athletes compared to healthy, non-athlete controls. Due to these observed differences in pain modulation, caution should be taken when generalising the current findings to athlete populations. Similarly, differences in pain modulation in chronic pain populations further limit the generalisability of the current findings (Lautenbacher & Rollman, 1997).

A final important consideration when interpreting the current findings is the method of target force calculation for the endurance time task. The force required during the muscular endurance assessment was dependent on MVC performance. This is a widely accepted and extensively utilised method for the assessment of muscular endurance (see Cogiamanian et al., 2007; Plaskett & Cafarelli, 2001), and ensures that maximal force generating capacity is accounted for in the measurement of endurance performance. Therefore, using this method, task failure can be considered an indication of maximal endurance, rather than a deficiency in maximal force production capacity. However, the observed correlation between MVC performance and CPM capacity suggests that the target force requirements were reduced for those with heightened CPM. This may explain the correlation between CPM and endurance time. This novel explanation should not be disregarded, and we encourage future research to extend upon the current findings by

utilising the alternative method of a static, pre-determined target force in the assessment of isometric muscular endurance.

Conclusion

The current study is the first to observe a relationship between pain modulation capacity and exercise performance, such that those with heightened pain modulation efficiency have extended endurance times on a submaximal endurance time task. This finding suggests that, although distinct in aetiology from exercise-induced pain, dynamic pain assessment conducted at-rest accounts for a significant proportion of the variability in endurance exercise performance. Additional research is needed before generalisations can be made to an athlete population.

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4.2. Postface

The study presented in this chapter reports a significant correlation between endogenous pain modulation and endurance exercise performance, with more efficient endogenous pain inhibitory responses related to longer endurance times in a fatiguing isometric contraction to exhaustion. It is proposed that a greater endogenous inhibitory response acts as a central manipulator of exercise-induced nociception, reducing the perception of exercise-induced pain and thereby increasing endurance performance. However, such causal inferences cannot be confirmed based on the findings of the current observational study. To better understand the potential impact of endogenous pain modulation on endurance exercise performance, a method for the experimental manipulation of endogenous pain modulation is needed. The following chapter presents HD-tDCS as a potential tool for this purpose.

Chapter V

High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial

5.0. Preface

Increased endogenous inhibitory responses following tDCS over the primary motor cortex have previously been reported by Reidler and colleagues (2012). This suggests that tDCS may be an effective tool for manipulating endogenous pain inhibition, allowing for an examination of the impact of enhanced endogenous pain inhibition on endurance exercise performance proposed in Chapter III. However, methodological concerns, including the use of conventional rather than high-definition tDCS, as well as the use of the simultaneous CPM assessment protocol, limit the conclusions which can be drawn from the findings of Reidler and colleagues. The following chapter presents a published study which attempts to clarify the findings of Reidler and colleagues by adopting an advanced method of neuromodulation in the form of HD-tDCS for the manipulation of endogenous pain modulatory capacity. In contrast to the methods employed by Reidler and colleagues, the more precise sequential CPM assessment protocol is also used in following study to measure endogenous pain modulation.

5.1. Published Paper

Flood, A., Waddington, G. & Cathcart, S. (2016). High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: a randomized trial. *The Journal of Pain, 17,* 600-605. doi: 10.1016/j.jpain.2016.01.472

FORM E: DECLARATION OF CO-AUTHORED PUBLICATION CHAPTER

Declaration for Thesis Chapter 5

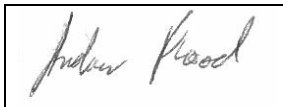
Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, data collection, data analysis, manuscript preparation.	80%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Contributor is also a student at UC Y/N**
Stuart Cathcart	Contributed to study design and manuscript preparation.	N
Gordon Waddington	Contributed to study design and manuscript preparation.	N

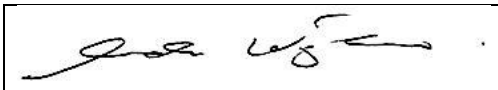
Candidate's Signature		**Date** **07/02/2017**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**University of Canberra**

Signature 1		**Date** 23/02/2017
Signature 2		27/02/2017

High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial

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Abstract

Transcranial direct current stimulation (tDCS) is a form of brain stimulation that allows for the selective increase or decrease in the cortical excitability of a targeted region. When applied over the motor cortex it has been shown to induce changes in cortical and subcortical brain regions involved in descending pain inhibition or conditioned pain modulation (CPM). The aim of the current study was to assess whether activation of pain inhibitory pathways via tDCS of the motor cortex facilitates the CPM response. Elevated CPM after active tDCS of the motor cortex was hypothesized. Thirty healthy male volunteers attended 2 experimental sessions separated by 7 days. Both sessions consisted of CPM assessment after 20 minutes of either active or sham (placebo) tDCS over the motor cortex. CPM capacity was assessed via the pain-inhibits-pain protocol; CPM responses were shown to be elevated after active compared with sham tDCS. This report concludes that tDCS of the motor cortex enhances the CPM response of healthy men. This finding supports the potential utility of tDCS interventions in clinical pain treatment.

Perspective

The use of noninvasive brain stimulation over the motor cortex was shown to enhance the CPM effect. This finding supports the use of tDCS in the treatment of chronic pain, particularly in sufferers exhibiting maladaptive CPM.

Introduction

Transcranial direct current stimulation (tDCS) is a form of brain stimulation shown to induce focal, prolonged and yet reversible shifts in cortical excitability. [28] These shifts are polarity dependent, with anodal tDCS resulting in neuronal hyperpolarization and decreased neuronal excitability. [28] Therefore, tDCS allows for the selective increase or decrease in the excitation of a targeted cortical region.

Support has been shown for the use of tDCS in a wide range of settings including the treatment of depression[4] and the enhancement of memory[16] and problem-solving ability.[10] Similarly, tDCS of the motor cortex can influence pain perception in healthy subjects[5] and chronic pain sufferers.[1]

In an attempt to uncover the underlying mechanisms of this pain-modulating effect, computer modelling and functional imaging have been used to track the current flow and resulting changes in cortical excitation resulting from tDCS of the motor cortex. This research has shown current flows affecting not only the immediate, targeted cortical regions, but also remote regions such as the cingulate cortex, insula, thalamus, and brainstem.[12] It is argued that these remote effects may be due to the modulation of their functional interaction with the motor cortex through cortico-subcortical connectivity.[23]

The facilitation of pain inhibitory pathways may explain the analgesic effects of tDCS of the motor cortex. Diffuse noxious inhibitory control (DNIC) explains the pain-inhibits-pain phenomenon whereby a noxious stimulus applied to one region of the body acts to inhibit the activity of pain-processing dorsal horn neurons in extrasegmental regions.[24] This process has been described in animals to involve a complex spino-bulbo-spinal loop devoid of higher brain center involvement.[11] Conditioned pain modulation (CPM) is the preferred

terminology when referring to this endogenous pain inhibitory process in humans because it acknowledges the influence of top-down activity from higher order brain structures and also bottom-up pain modulation via the spino-bulbo-spinal loop. [7,25,39]

Research on cortical activity during CPM activation in humans has shown prolonged activity in higher cortical structures similar to those affected by tDCS of the motor cortex, including the cingulate, insula, and thalamus.[3,7,11,25,29] It is possible then that the commonly observed analgesic effects of tDCS of the motor cortex may be due to the facilitation and therefore enhanced activation of CPM pathways.

This hypothesis has been previously supported by the findings of Reidler et al,[33] who discovered that anodal tDCS of the motor cortex significantly enhanced CPM. However, methodological issues significantly limit the ability to draw definitive conclusions from the findings of Reidler and colleagues.[33] For example, CPM is typically assessed using the pain-inhibits-pain protocol, whereby one painful stimulus, the conditioning stimulus (CS), inhibits the perceived intensity of a second painful stimulus, the test stimulus (TS), presented to a spatially remote bodily region.[26] In the study by Reidler and colleagues,[33] these 2 painful stimuli were presented simultaneously. The protocol adopted by Reidler and colleagues,[33] referred to as the parallel CPM protocol, has been argued to result in an inflated inhibitory response because it may be influenced by attention or distraction effects.[40]

In addition, low-definition tDCS- such as that used by Reidler et al,[33] administers a constant current typically through 2, 35-cm^2 sponge electrodes.[6,8,27] This approach has been shown to induce widespread changes in cortical activation, thereby reducing the clarity of the resulting behavioural effects.[6,8,14] Recent advancements have led to the development of high-definition (HD) tDCS (HD-tDCS), which uses smaller electrodes arranged in a ring

configuration. This form of stimulation allows for more focal stimulation, with peaks in current flow localized to the area underlying the targeted region.[22]

Thus, the aim of the current study was to examine the effects of HD-tDCS of the motor cortex on CPM in healthy volunteers. It was hypothesized that anodal HD-tDCS targeted at the motor cortex will result in significant increases in the observed CPM effect.

Methods

Participants

Due to the known age-[19] and gender-[30] related differences in CPM capacity, participation was restricted to pain-free men between the ages of 18 and 40 years. Specific criteria excluded individuals with current pathology to the hands, sufferers of diseases with the potential to cause neural damage such as diabetes, as well as sufferers of chronic pain. Individuals were also excluded on the basis of documented contraindications to tDCS (eg, implanted medical devices or history of epilepsy).[13] Thirty participants (mean age 23.9 years) were recruited through advertisements placed throughout the University of Canberra and local community. On the basis of previous research,[33] this sample size was considered adequate. All participants received both stimulation conditions (sham and active) in a randomized, counterbalanced order. Randomization was achieved using a computer-driven random number generator. This ordering was conducted by the principal researcher (A.F.) at the time of participant arrival.

tDCS

HD-tDCS was delivered via a 4 × 1 HD-tDCS multi-channel stimulation interface (Model 4X1-C2, Soterix Medical, New York, NY) attached to a conventional 1 × 1 tDCS

device (Model 1300, Soterix Medical). Electrodes were placed in a 4 × 1 ring configuration using plastic casings inserted into an electroencephalography recording cap. The centre anode electrode was positioned over the area corresponding to C3; an approximation of the location of the left motor cortex on the basis of the international 10/20 electroencephalography system. Return electrodes were placed in a radius surrounding the anode electrode at locations approximately corresponding to Cz, F3, T7 and P3.

Participants' hair underneath the electrode was parted so as to reduce current impedance. Also, conductive gel (Signa Gel; Parker Laboratories Inc, Fairfield, NJ) was injected into the plastic casing beneath the electrode to improve conductance. The HD-tDCS device was used to assess impedance or conductance values before stimulation. Adjustments were made to ensure that these values did not exceed 1.50 quality units.

In the active HD-tDCS condition, 2 mA was delivered for 10 minutes. The HD-tDCS device automatically implemented the ramping method whereby the current intensity is gradually increased to reach the target intensity (2 mA) within 30 seconds, where it is maintained for the desired duration (10 minutes). At the end of this period, current intensity is then gradually ramped back down to 0 mA. This protocol has been shown to induce localized shifts in cortical excitability beyond the stimulation period of up to 6 hours.[22] Similar protocols have been shown to be well tolerated by participants.[6]

In the sham condition, the same protocol was adopted, however, current intensity was ramped up to 2 mA and immediately back down to 0 mA at the start and end of the 10 minute stimulation period. Similar protocols have been shown to produce an effective control condition whereby participants are blinded to their condition.[6,18]

Measures

Pressure Pain Threshold

Participants were instructed to place their right hand on a table with their palm facing down. Pressure was then applied to the index finger of participants' right hand using a handheld pressure algometer (Wagner Force Dial FDK 20; Wagner Instruments, Greenwich, CT). Pressure was increased at a rate of approximately 1 kg/s until the participant reported perceiving pain. When pain was reported, pressure was released and participants' pressure pain threshold (PPT) was recorded in kilograms. This procedure was repeated 3 times, with 20 seconds separating each measurement. PPT was used as the TS in the CPM protocol. Support for the use of handheld pressure algometers for the assessment of pain thresholds has been presented elsewhere.[20] Before testing, participants were familiarized with the PPT protocol using the ring finger of their right hand. Testing began 1 minute after familiarization.

Cold Water Immersion

Participants' left hand and part of their wrist were immersed in cold water for 4 minutes. The water was held in a thermostat-controlled water bath, which maintained the water temperature at 2 ± 1^0C. Participants were instructed to rest their hand gently on a grid (rubber-covered metal grid) which was placed at the base of the water bath. This controlled the depth of hand immersion across participants. Participants were instructed to rate their current level of perceived pain at 15-second intervals using a 0-10 numerical rating scale with descriptive anchors at 0 (No pain), 5 (Moderate pain) and 10 (Most intense pain imaginable). Participants were able to remove their hand from the water bath if the pain became intolerable. In such cases, pain intensity ratings of '10' were carried through the remainder of the 4-minute task. Cold water immersion was used as the CS for the assessment of CPM. This

is a common and well accepted means of inducing counterirritation during CPM assessment.[38]

CPM

The CPM testing protocol included an assessment of participants' baseline PPT (TS) followed by cold water immersion (CS). Immediately after (<10 seconds) the CS, participants' PPT was measured again. PPT measures were taken on the right hand, and the left hand was used for cold water immersion. The inhibitory effect of the noxious CS on the perceived intensity of the TS reflects CPM efficiency.[24] This CPM protocol was conducted after active and sham HD-tDCS. In accordance with accepted protocols, CPM magnitude was calculated by subtracting participants' mean PPT before the CS from their mean PPT after the CS. Therefore, higher values represented greater pain inhibition.

Study Design

The study followed a within-groups design with participants receiving active and sham stimulation in a randomized order. The study consisted of 2 experimental sessions separated by at least 7 days. Both sessions were conducted in a laboratory at the University of Canberra. During the first session, an outline of the study protocol and aims were presented before informed consent was obtained. Eligibility for participation was then assessed against the inclusion and exclusion criteria. Those that were deemed eligible for participation then immersed both hands into lukewarm water ($25 \pm 2^{o}C$) for 1 minute. This reduced the impact of hand temperature on sensory perception and was performed before each session.

Participants then received 10 minutes of either active or sham stimulation. After HD-tDCS, participants' CPM was assessed using the CPM protocol described previously.

The second experimental session included an assessment of CPM after the administration of the remaining HD-tDCS condition.

All tests were performed in the same laboratory by the same experimenter. To ensure that the acute analgesic effects of exercise and caffeine did not interfere with the results, participants were instructed to refrain from engaging in physical activity or consuming caffeinated beverages on the day of testing. All participants confirmed that they had adhered to this request.

Study methods followed those approved by the University of Canberra Human Research Ethics Committee.

Statistical Analysis

Data analysis was performed using SPSS statistics software for Windows, version 21 (IBM Corp, Armonk, NY). Paired samples t-tests compared mean CPM, PPT, and CS ratings as well as maximum CS ratings between the 2 conditions. Pearson r correlational analysis was used to assess the relationship between CS pain ratings and CPM magnitude in active and sham conditions. $P < .05$ was considered statistically significant.

Results

Thirty participants (mean age 23.9 ± 4.56) were deemed eligible for participation and were therefore included in all analyses. The experimental procedure was well tolerated by participants with no reports of negative side effects from HD-tDCS or CPM protocols. Visual inspection of relevant histograms supported the assumption of normality. Table 1 shows all pain measures after active and sham stimulation.

Table 1

Pain variables after active and sham HD-tDCS

Variable	Active HD-tDCS (n = 30)	Sham HD-tDCS (n = 30)
PPT	7.30 (2.86)	6.81 (2.70)
CS ratings	6.73 (2.09)	7.11 (2.00)
CS maximum	8.07 (1.62)	8.50 (1.41)
CPM	0.78 (0.80)	0.19 (0.48)

Note. Data are indicated as mean (SD). The CS ratings are mean ratings of pain intensity throughout CS. CS maximum is the mean of maximum ratings given for the 4-minute CS. CPM is the difference between PPT before and after CS.

PPT

Baseline PPTs were found to be significantly higher following active compared with sham HD-tDCS ($t_{29} = 2.57$, $P = .02$, d = .17).

Cold Water Immersion

Mean pain intensity ratings resulting from cold water immersion were significantly higher after sham stimulation compared with active ($t_{29} = 2.09$, $P < .05$, d = .09). However, maximum pain intensity ratings from cold water immersion were not significantly different after sham compared with active HD-tDCS ($t_{29} = 1.93$, $P = .06$). Correlational analysis showed no significant relationship between mean pain intensity ratings during cold water immersion and CPM magnitude for the active ($r_{28} = .133$, $P = .49$) and sham conditions ($r_{28} = .121$, $P = .53$). Also, no significant relationship was seen between maximum pain ratings during cold water immersion and CPM magnitude for the active ($r_{28} = .191$, $P = .321$) and

sham conditions (r_{28} = .205, *P* = .29). Therefore, ratings of the perceived intensity of the cold water immersion were not included as covariates in the analysis of CPM.

CPM

A stronger CPM response was seen after ative compared with sham stimulation. This difference was statistically significant (t_{29} = 2.57, *P* < .001) and large (d = .92).

Discussion

The aim of the current study was to assess the effect of HD-tDCS on the CPM response in healthy volunteers. HD-tDCS targeted over the motor cortex was shown to enhance the CPM response. In addition, participants' PPTs were also increased after active HD-tDCS.

These findings support those of Reidler and colleagues,[33] who discovered an enhanced CPM response after tDCS of the motor cortex. However, several methodological differences exist in the methods used in the current study and that of Reidler et al.[33] First, HD-tDCS was used in the current study to modulate cortical excitation. This form of stimulation has been shown to increase the focality of current flow under the anodal electrode,[6,8,14] allowing for a more targeted form of stimulation than is possible with the use of conventional tDCS used by Reidler et al.[33] Second, only men between 18 and 40 years of age were included in the current study, reducing the effect of sex- and age-related differences in CPM[19,30] and responsiveness to tDCS.[34] In contrast, Reidler et al[33] included male (n = 6) and female (n = 9) participants from a wider age range (18-64 years), reducing the clarity of their findings. Finally, in contrast to the parallel protocol used by Reidler et al,[33] the sequential CPM protocol involves the presentation of the TS before and immediately after the CS. Using this protocol, the observed pain inhibitory response is reduced, as the potential

influence of attention or distraction is attenuated.[40] Therefore, although the observed inhibitory response is of a lessened magnitude, the sequential CPM protocol is thought to result in a CPM score that is more representative of the pain modulatory process that it is intended to measure.[40] For this reason, the sequential protocol, rather than the parallel protocol adopted by Reidler et al,[33] was preferred in the current study. The current study then, not only supports the findings of Reidler et al, [33] but clarifies and extends their findings by implementing more robust methods of cortical manipulation and pain modulation assessment.

Mechanisms

Reidler and colleagues[33] identified several potential mechanisms through which tDCS and CPM may have additive effects on pain perception. In particular, Reidler et al[33] argued that tDCS of the motor cortex had a top-down inhibitory effect on pain perception, whereas the CPM protocol had a bottom-up effect. Therefore, the authors suggested that tDCS and CPM activation influenced pain perception at different levels of pain processing. Although possible, this explanation largely relies on early conceptualizations of the DNIC-like effect in animals, attributing little to no involvement from higher order brain regions.[11] More recent research, however, has shown that higher order brain regions such as the anterior cingulate cortex, insula, and thalamus all play important roles in the DNIC-like effect, resulting in the distinction between DNIC in animals and CPM in humans.[7,32,35,39] Therefore, we argue that rather than acting on separate levels of pain processing, tDCS facilitates the CPM response by modifying neuronal excitability in CPM-related supraspinal pathways.[12,23]

Implications

The current findings of enhanced CPM after HD-tDCS of the motor cortex have several potentially significant clinical implications. Research has consistently shown

maladaptive CPM in chronic pain sufferers.[9,21] It is currently unclear whether this pronociceptive pain processing is the result of regular exposure to pain or whether maladaptive CPM puts individuals at a greater risk of suffering from chronic pain disorders. Irrespective of this issue of causality, it would appear that adjusting maladaptive CPM may lead to reductions in symptoms of chronic pain. The current research findings suggest that this may be achieved through cortical stimulation of the motor cortex using HD-tDCS. Continued research on the effect of tDCS on maladaptive CPM in chronic pain may uncover the underlying mechanisms of the now commonly accepted analgesic effects of motor cortical tDCS in chronic pain sufferers.[17,15]

Limitations

Several limitations must be recognized prior to drawing conclusions based on the current findings. Importantly, caution should be taken when applying the current findings of enhanced CPM after HD-tDCS to a chronic pain population. To date, only 1 study, conducted by Villamar and colleagues[36] has examined the effect of motor cortical stimulation via tDCS on CPM in chronic pain sufferers. In this study, tDCS was reported to be ineffective in modulating the CPM response of Fibromyalgia patients. Because chronic pain sufferers are consistently shown to exhibit maladaptive CPM, [9,21] it is clear that additional research in this area is needed.

Similarly, only young men were examined in the current study. This inclusion criteria was selected so as to control for the reported reduced CPM efficiency in female participants[2] as well as the age-related differences[19] in pain inhibition capacity. Although this could be considered a strength of the current study, caution should be taken when generalizing these findings outside of the targeted population. In fact, the relative deficiencies in CPM

efficiency among women has been suggested as an explanation for the higher proportion of chronic pain sufferers being female.[31] We encourage future research to extend our findings into this population. Such research would have clear implications for clinical populations.

In the current study, HD-tDCS was administered for 10 minutes at 2 mA. It was assumed that this stimulation intensity, and in particular, the duration was sufficient to induce and maintain changes in cortical excitation throughout the CPM protocol. Although this manipulation was not directly assessed, previous research has shown that 10 minutes of HD-tDCS can have lasting effects of up to 6 hours after stimulation.[22] Because the CPM protocol was performed immediately after the stimulation period (<3 minutes), and was completed within 10 minutes, we are confident that the effects of the HD-tDCS significantly outlasted the time to complete the CPM protocol.

Another potential limitation of the current study was the failure to assess the efficacy of participant blinding protocols. Although no direct measure was utilised, anecdotal reports suggested that the use of the sham HD-tDCS protocol was effective in blinding participants to their condition. In addition, the efficacy of this sham protocol has been consistently shown by others[6,18] as well as our research group (in preparation).

Similarly, the single blinded design, in which only the experimenter was aware of the stimulation condition being administered (sham or active), increased the potential for experimenter bias to influence results. To reduce this possibility, all CPM protocols were standardized, including the rate at which pressure was applied for PPT measurement (1 kg/s) and the intermeasurement intervals.

Statistical analysis showed decreased pain intensity ratings from the CS after active HD-tDCS. It is possible that these differences in CS intensity may have affected CPM

magnitude. However, correlational analysis showed no relationship between CS pain ratings and CPM magnitude. Also, pain intensity ratings reached similarly high levels after active and sham stimulation. Previous research has also failed to adequately identify the potential effects of CS intensity and CPM magnitude.[37] Therefore, we do not anticipate that changes in the perceived intensity of the CS due to HD-tDCS significantly influenced the observed changes in CPM magnitude.

Summary

The findings of the current study suggest that targeted manipulation of the motor cortex via HD-tDCS can increase the CPM response of healthy volunteers. Through adjustments in methodology, in particular the use of a sequential CPM design and HD-tDCS, our findings support and extend previous research conducted by Reidler and colleagues.[33] Despite our speculation, the underlying mechanisms explaining the effect of tDCS on CPM, as well as the clinical implications of the current findings remain unclear. Therefore, continued research on the effects of tDCS on pain perception and CPM, especially in chronic pain populations is needed.

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5.2. Postface

In this study, HD-tDCS resulted in elevated endogenous pain inhibitory responses in healthy participants. This offers support for the earlier findings of Reidler and colleagues (2012) of increased endogenous pain inhibition following conventional tDCS. However, in the current study, participant sampling restrictions reduced the impact of age and gender on endogenous pain modulation capacity. Also, the use of HD-tDCS and sequential CPM assessment allowed for greater precision in the manipulation of neuronal excitability and the assessment of endogenous pain modulatory capacity, respectively. Due to these methodological considerations, the current findings not only support, but also clarify and extend upon the findings of Reidler and colleagues.

Therefore, both the current findings and those of Reidler et al. (2012) support the use of HD-tDCS for the experimental assessment of the impact of enhanced endogenous pain modulatory capacity on endurance exercise performance.

Chapter VI

The Effects of Elevated Pain Inhibition on Endurance Exercise Performance

6.0. Preface

In Chapter IV, endogenous pain modulation was shown to be related to endurance exercise performance. However, an experimental manipulation of endogenous pain modulatory capacity is needed before causal conclusions can be drawn as to the impact of endogenous pain modulation on endurance exercise. Based on the findings of Chapter V, HD-tDCS presents as a tool for this manipulation of endogenous pain modulation. Therefore, in the final study in this series, HD-tDCS is used to assess the impact of heightened endogenous pain modulatory capacity on endurance exercise performance. Importantly, this study employs similar methods to those adopted in the previous chapters for the manipulation of neuronal excitation and the assessment of endogenous pain modulation and endurance exercise performance. This continuity in methodology ensures that the following study acts as a logical extension of the previous works presented in this thesis.

6.1. Published Paper

Flood, A., Waddington, G., Keegan, R. J., Thompson, K. G., & Cathcart, S. (2017). The effects of elevated pain inhibition on endurance exercise performance. *PeerJ, 5,* e3028. doi: 10.7717/peerj.3028

FORM E: DECLARATION OF CO-AUTHORED PUBLICATION CHAPTER

Declaration for Thesis Chapter 6

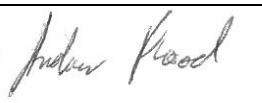
Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, data collection, data analysis, manuscript preparation.	80%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Contributor is also a student at UC Y/N**
Stuart Cathcart	Contributed to study design and manuscript preparation.	N
Gordon Waddington	Contributed to study design and manuscript preparation.	N
Richard Keegan	Contributed to study design and manuscript preparation.	N
Kevin Thompson	Contributed to study design and manuscript preparation.	N

Candidate's Signature		**Date** **07/02/2017**

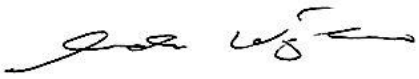
Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**University of Canberra**

Signature 1		**Date** 23/02/2017
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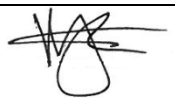
Signature 3		02/03/2017
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The effects of elevated pain inhibition on endurance exercise performance

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Abstract

Background. The ergogenic effects of analgesic substances suggest that pain perception is an important regulator of work-rate during fatiguing exercise. Recent research has shown that endogenous inhibitory responses, which act to attenuate nociceptive input and reduce perceived pain, can be increased following transcranial direct current stimulation of the hand motor cortex. Using high-definition transcranial direct current stimulation (HD-tDCS; 2 mA, 20 min), the current study aimed to examine the effects of elevated pain inhibitory capacity on endurance exercise performance. It was hypothesised that HD-tDCS would enhance the efficiency of the endogenous pain inhibitory response and improve endurance exercise performance.

Methods. Twelve healthy males between 18 and 40 years of age (M = 24.42 ± 3.85) were recruited for participation. Endogenous pain inhibitory capacity and exercise performance were assessed before and after both active and sham (placebo) stimulation. The conditioned pain modulation protocol was used for the measurement of pain inhibition. Exercise performance assessment consisted of both maximal voluntary contraction (MVC) and submaximal muscular endurance performance trials using isometric contractions of the non-dominant leg extensors.

Results. Active HD-tDCS (pre-tDCS, −.32 ± 1.33 kg; post-tDCS, −1.23 ± 1.21 kg) significantly increased pain inhibitory responses relative to the effects of sham HD-tDCS (pre-tDCS, −.91 ± .92 kg; post-tDCS, −.26 ± .92 kg; p = .046). Irrespective of condition, peak MVC force and muscular endurance was reduced from pre- to post-stimulation. HD-tDCS did not significantly influence this reduction in maximal force (active: pre-tDCS, 264.89 ± 66.87 Nm; post-tDCS, 236.33 ± 66.51 Nm; sham: pre-tDCS, 249.25 ± 88.56 Nm; post-tDCS,

239.63 ± 67.53 Nm) or muscular endurance (active: pre-tDCS, 104.65 ± 42.36 s; post-tDCS, 93.07 ± 33.73 s; sham: pre-tDCS, 123.42 ± 72.48 s; post-tDCS, 100.27 ± 44.25 s).

Discussion. Despite increasing pain inhibitory capacity relative to sham stimulation, active HD-tDCS did not significantly elevate maximal force production or muscular endurance. These findings question the role of endogenous pain inhibitory networks in the regulation of exercise performance.

Introduction

Models of exercise intensity regulation, such as the central governor model (CGM), argue that work-rate during the performance of fatiguing exercise tasks is regulated by a centrally derived pacing strategy (St Clair Gibson & Noakes, 2004). The central integration of afferent signals from the periphery is thought to be involved in the calculation of this pacing strategy (Lambert, St Clair Gibson, & Noakes, 2005). An alternative model, the psychobiological model, also suggests that exercise intensity is centrally regulated (Marcora, 2008). However, according to this model, the regulation of work-rate is dependent on the conscious perception of effort and the maximum perception of effort that the individual is willing to withstand (Marcora, Bosio, & de Morree, 2008). As perceived effort is considered to be independent of afferent feedback, the psychobiological model argues that exercise intensity regulation occurs without the involvement of sensory feedback from the periphery (Marcora, 2010).

In an attempt to clarify the role of afferent feedback, research has investigated the effects of experimentally manipulating nociceptive afferents and perceived pain on exercise performance. Acetaminophen, a common analgesic, has been shown to increase cycling performance (Mauger, Jones, & Williams, 2010). Similarly, the ergogenic effects of caffeine consumption have been attributed to the substance's analgesic properties (Gonglach et al., 2015). Naloxone, an opioid antagonist, was shown to decrease time-to-exhaustion in an incremental cycling task (Sgherza et al., 2002). Combined, these research findings offer support for the role of afferent feedback in exercise intensity regulation proposed by the CGM.

Despite this evidence pointing to an important role for pain in the regulation of endurance exercise, an examination of the endogenous processes involved in the central

modulation of nociceptive input is lacking. The perception of pain is dependent on the activity of central endogenous modulatory processing, involving inhibitory and facilitatory mechanisms (Millan, 2002; Nir & Yarnitsky, 2015). Endogenous pain inhibition acts by inhibiting nociceptive input in the central nervous system at both spinal and supraspinal levels, with descending neural pathways with inputs from cortical, subcortical and spinal regions thought to be involved in this modulatory process (Ossipov, Dussor, & Porreca, 2010). Activation of inhibitory pathways has been shown to produce strong, widespread analgesia (Le Bars, Dickenson, & Besson, 1979). Importantly, nociceptive afferents originating in the muscle also undergo extensive endogenous modulation which acts to enhance or diminish the intensity of exercise-induced pain (O'Connor & Cook, 1999).

It is possible that a highly efficient endogenous pain inhibitory system is adaptive for endurance exercise performance. In support of this hypothesis, it has previously been proposed that exogenous interventions which enhance the efficiency of the endogenous pain modulatory system may produce an exercise performance advantage (Angius et al., 2015; Mauger, Jones, & Williams, 2010). However, previous research in this field has been limited by the exclusive use of static measures of pain assessment, such as tolerance and threshold. Advances in pain psychophysics have led to the development of dynamic pain assessment tools which, unlike static measures, allow for the measurement of the efficiency of the endogenous pain modulatory system (Yarnitsky, 2010). Of these assessment tools, conditioned pain modulation (CPM) is the method typically used to assess endogenous pain inhibition. The ability to measure endogenous pain inhibitory capacity offers an opportunity to examine the speculated role of endogenous pain inhibition in exercise performance.

Using the CPM assessment protocol, Flood, Waddington and Cathcart (in press) recently found a significant relationship between endogenous pain modulation and endurance

exercise performance, with those displaying more efficient endogenous pain modulatory responses capable of producing longer endurance times in a submaximal isometric contraction of the knee extensors. Despite these observational findings suggesting a relationship between endogenous pain modulation and endurance exercise performance, it remains unclear whether a more efficient endogenous pain modulatory system results in superior endurance exercise performance. To allow for causal conclusions to be drawn, an experimental manipulation of the endogenous pain modulatory system is required.

Transcranial Direct Current Stimulation (tDCS) presents as a tool which may allow for the manipulation of the endogenous pain modulatory system. tDCS involves the application of a low-intensity electrical current to a targeted cortical region, resulting in polarity dependent shifts in the excitability of underlying regions (Nitsche & Paulus, 2000). These neuronal changes have been shown to persist up to 2 h beyond the stimulation period (Kuo et al., 2013). Conventional methods of tDCS involve the application of a direct current through two, typically 35cm^2, rectangular sponge electrodes. This results in dispersed current flow beyond the targeted region, reducing the clarity of the behavioural observations (Datta et al., 2009). However, computational modelling has shown that an advanced method of tDCS, high-definition tDCS (HD-tDCS), allows for far more focal stimulation, restricting current flow to the targeted region (Kuo et al., 2013).

Recent research has shown that conventional tDCS (Reidler et al., 2012) as well as the more focal HD-tDCS (Flood, Waddington, & Cathcart, 2016) can enhance the efficiency of the endogenous pain modulatory system, causing transient increases in the endogenous pain inhibitory responses of healthy participants, as assessed through the CPM protocol. Through cortico-cortico and cortico-subcortical projections, it is thought that tDCS targeted over the hand area of the motor cortex stimulates descending regions associated with endogenous pain

inhibition, enhancing central pain inhibitory responses and causing widespread analgesia (Flood, Waddington, & Cathcart, 2016). Therefore, by acting upon regions involved in the endogenous pain modulatory system, tDCS presents as a viable tool for the top-down inhibition of ascending exercise-induced nociceptive input.

Using HD-tDCS, the current study aimed to manipulate the efficiency of the endogenous pain modulatory system to assess the influence of enhanced endogenous pain inhibitory capacity on endurance exercise performance. It was hypothesised that HD-tDCS of the hand motor cortex would result in an elevated endogenous pain inhibitory response and increased endurance exercise performance.

Methods

Participants

To control for potential gender (Popescu et al., 2010) and age (Grashorn et al., 2013) related variations in pain inhibitory capacity, 12 healthy, recreationally active males between 18 and 40 years of age were recruited for participation. All participants were recruited from the local University student population. Participants were not engaged in regular strength training programs or competitive sports predominantly involving knee extensor muscles (e.g. cycling, weightlifting). They were also free from symptoms of chronic pain and did not present with contraindications to tDCS (see Villamar et al., 2013).

Participants were instructed to refrain from consuming caffeine or analgesic medications or engaging in vigorous physical activity for at least 24 h prior to the experimental sessions. Adherence to these instructions was confirmed on arrival.

In Cogiamanian et al. (2007), changes in endurance performance following tDCS were assessed across active anodal (n = 9; M = −21.11 ± 5.52), active cathodal (n = 9; M = −35.77 ± 3.39) and control (n = 15; M = −39.33 ± 3.32) conditions. A-priori power analysis based on data presented in Cogiamanian et al. (2007) indicated a total sample of eight participants was needed to uncover a statistically significant difference in endurance time between active and sham conditions with a statistical power of 0.80 at an alpha level of 0.05.

Pain Inhibition Assessment

In the current study, pain inhibitory capacity was assessed using a sequential CPM design, whereby a noxious test stimulus (TS) is presented before and immediately after a noxious conditioning stimulus (CS) is applied to a spatially remote bodily region. This method is in contrast to the simultaneous or parallel CPM design where the second TS and the CS are presented simultaneously. The sequential design was preferred as it has been suggested to provide a clearer indication of endogenous pain modulation (Yarnitsky et al., 2015).

Pressure pain threshold (PPT) assessment was used as the TS. Using a manual pressure algometer (Wagner Force Dial FDK 20, Wagner Instruments, Greenwich, CT), pressure was gradually applied (approximately 1 kg/s) to the dorsal surface of the index finger of participants' non-dominant hand. Participants were instructed to verbally indicate when the pressure first caused pain, at which point the pressure was released and the peak force required to elicit pain was recorded. After 30 s, this assessment was repeated, allowing for an average of the two trials to be calculated. Participants wore a blindfold throughout PPT assessment so as to minimise potential distraction. The use of PPT assessment as the TS in the CPM protocol is well accepted (see Pud, Granovsky, & Yantisky, 2009).

Cuff occlusion of the non-dominant arm was used as the CS. A sphygmomanometer cuff was placed approximately 2 cm proximal to the cubital fossa and gradually inflated (~20 mmHg/s) until participants first reported pain. The cuff then remained at this level of inflation while participants verbally rated their perceived pain level at 10 s intervals using a 0-10 numerical rating scale ($0\text{-}10_{NRS}$). If reported pain remained stable for two consecutive intervals, or if ratings of perceived pain decreased, then the cuff was inflated by ~20 mmHg. Once a perceived pain intensity of *5* on the $0\text{-}10_{NRS}$ was reported, the cuff was fully deflated. Cuff occlusion has previously been shown to be an effective CS for the assessment of pain inhibitory capacity (Cathcart et al., 2009).

Immediately following the removal of the CS, PPT was assessed again. As recommended by Yarnitsky et al. (2015), CPM was calculated by subtracting post-conditioning PPT from pre-conditioning PPT. Therefore, lower CPM values represent enhanced pain inhibitory capacity.

Force Measurement for Exercise Performance Trials

An isokinetic dynamometer (Humac NORM, Computer Sports Medicine, Stoughton, MA) was used to assess force production during maximal voluntary contraction (MVC) and endurance tasks. Participants sat in an upright position perpendicular to the dynamometer while adjustments were made to ensure the correct alignment of the dynamometer's axis of rotation with the lateral femoral epicondyle of the non-dominant leg. To limit movement during force production, participants were fastened to the chair at the shoulders and hip as well as the thigh of the involved leg. Throughout both performance tasks, force was applied by the non-dominant leg, fixed at 90° of flexion, through the padded arm of the dynamometer fastened slightly above the medial malleolus.

Maximal Voluntary Force Production

Three submaximal familiarisation trials were performed 60 s prior to the MVC trials. For MVC assessment, participants were instructed to maximally contract their non-dominant leg for 5 s. Two trials, separated by 60 s, were completed prior to the submaximal fatiguing task. Visual feedback relating to force production and elapsed time was presented on a computer monitor throughout the MVC trials. Scripted verbal encouragement was also provided by the researcher. Peak torque (Nm) from the better of the two trials was taken as the MVC. Pre-tDCS MVC was used to calculate the target force for the fatiguing task.

Muscular Endurance Assessment

For the assessment of muscular endurance, a fatiguing task was performed whereby participants were required to maintain a submaximal isometric contraction at or above 30% of their pre-tDCS MVC force for as long as possible. Task failure was defined as an inability to produce force at or above the target for three consecutive seconds. To promote maximal performance while also limiting the potential for experimenter bias, participants received scripted verbal encouragement throughout the task. Participants also received visual feedback on a computer monitor indicating current and target force. No feedback regarding elapsed-time was given to participants during the fatiguing task.

Direct Current Stimulation

To ensure participant safety, the application of HD-tDCS adhered to the procedural recommendations of Villamar et al. (2013). A HD-tDCS multi-channel stimulation interface (Model 4X1-C2, Soterix Medical, New York, NY) attached to a 1 × 1 low-intensity direct current stimulator (Model 1300, Soterix Medical) delivered 20 min of HD-tDCS. Following the International 10/10 electroencephalography system, electrodes were placed in a 4 × 1 ring

configuration with the centre electrode positioned on the scalp over the hand motor cortex contralateral to the non-dominant side (C3/C4) and return electrodes positioned in a ring around the centre anode at a radius of approximately 5 cm corresponding to Cz, F3/F4, T7/T8 and P3/P4. Electrodes were held in place using an electroencephalography recording cap. Both electrode placement and stimulation intensity replicated the methods used in previous research showing enhanced CPM following HD-tDCS (Flood, Waddington, & Cathcart, 2016). Electrode placement over the hand motor cortex was also chosen to ensure that any functional change in the performance of the leg motor tasks was not due to increased cortico-spinal excitability of the involved limb. HD-Explore software (Version 2.3, Soterix Medical, New York, NY) was used to confirm the focality of the HD-tDCS induced electrical field (Figure 1). For comparison, computational modelling for the conventional $35m^2$ sponge-electrodes is also presented (Figure 1).

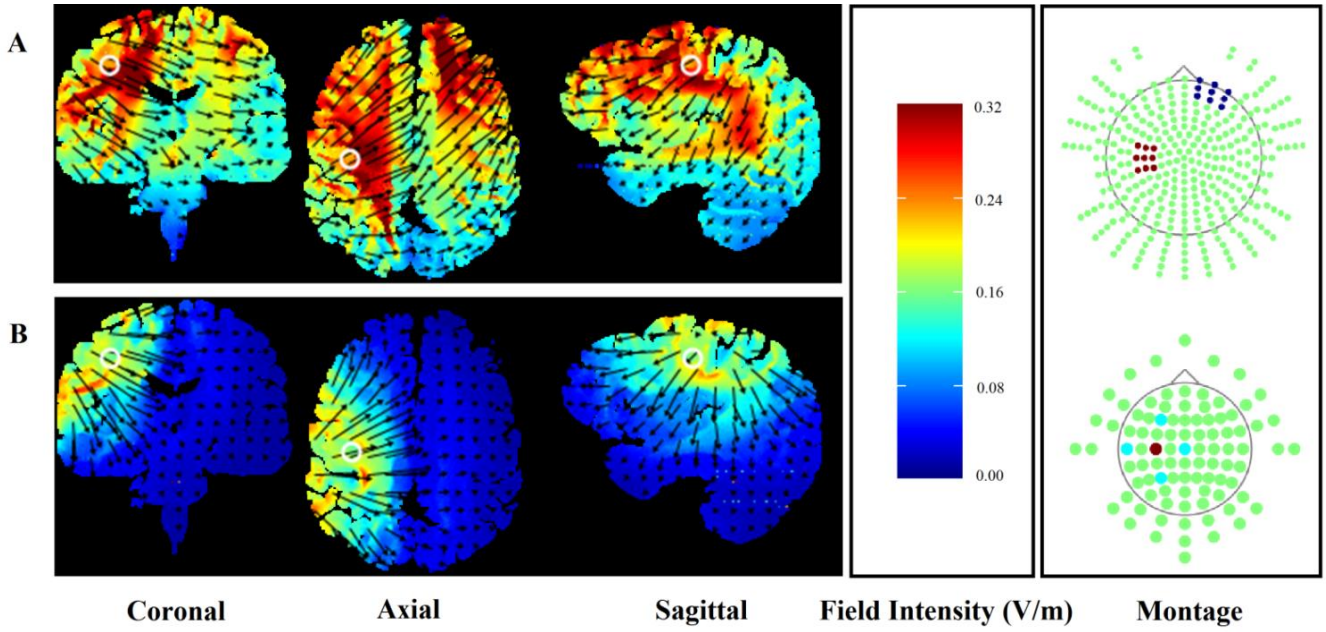

Figure 1. Finite element models of conventional (Panel A) and HD-tDCS (Panel B) of the right hand motor cortex (C3) using HDExplore computational modelling software. Electrode placement is presented with red markers representing anodal and blue markers representing cathodal electrodes. Slice positions are taken at MNI coordinates of −31, −8, and 40 for sagittal, coronal, and axial slices, respectively. A field intensity range of 0.00 - 0.32 was used in both conventional and HD-tDCS models. White circles represent the centre position of each slice while the direction of the current flow is indicated by black arrows.

Participants received both active and sham (placebo) stimulation conditions. The active condition began with an initial 10 s ramping up period, where stimulation intensity was gradually increased from 0 mA to the target intensity of 2 mA. The current then remained at 2 mA for 20 min, followed by a gradual (10 s) ramping down to 0 mA.

Protocols for the administration of sham stimulation followed those of the active condition. However, in the sham condition, stimulation intensity ramped up to 2 mA and then immediately back down to 0 mA at the start and again at the end of the 20 min period.

Previous research has supported the use of similar sham protocols as successful methods for the blinding of participants to their experimental condition (Borckardt et al., 2012). Protocols for the delivery of active and sham stimulation, including ramping periods, were automated by the stimulation device, ensuring consistency throughout the sample.

Motivation

The scale developed by Matthews, Campbell, and Falconer (2001) was used for the assessment of motivation relating to the physical performance tasks. This scale measures success and intrinsic motivation for an upcoming task. All items are scored according to a five-point Likert scale. Higher total scores represent greater levels of motivation for both domains of motivation.

Procedure

Study protocols followed those approved by the local human research ethics committee (Project: 15-261). Prior to testing, written informed consent was obtained. Participants attended two testing sessions separated by at least 1 wk, where they received active or sham stimulation in a randomised counterbalanced order. A single-blind design was adopted, with participants unaware of the ordering of the stimulation conditions.

Motivation, pain inhibition, MVC, and muscular endurance were assessed before and after the HD-tDCS intervention. The calculation of the target force for both pre- and post-tDCS muscular endurance trials was based on pre-tDCS MVC performance. Pre- and post-tDCS physical performance measures were separated by 1 h. During this period, participants rested for 20 min, then underwent 20 min of HD-tDCS followed by post-tDCS motivation and CPM assessment. An additional 4 min rest period separated MVC and endurance trials. See Figure 2 for schematic description of methods.

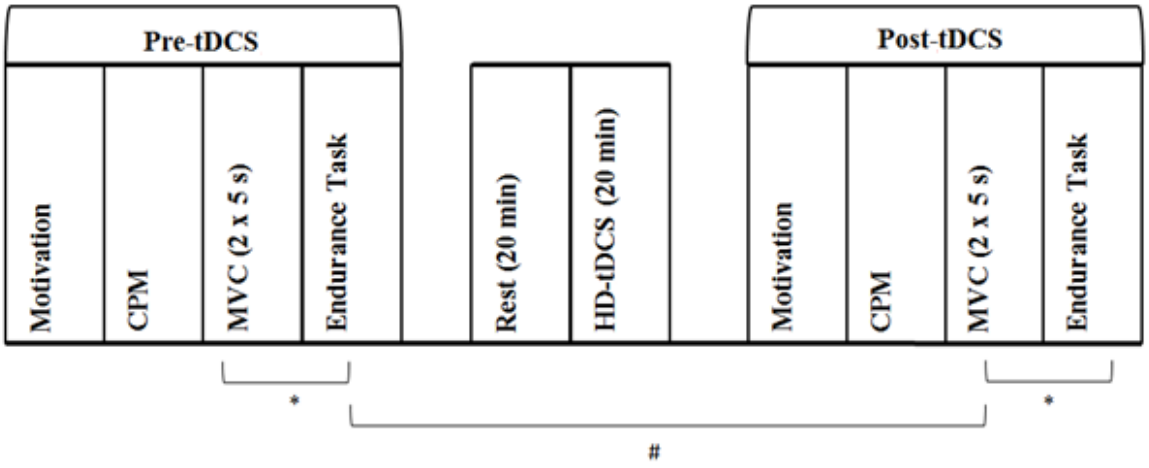

Figure 2. Experimental protocol assessing the effect of increased pain inhibition on exercise performance. First, baseline (Pre-tDCS) measurement of motivation, CPM, MVC and muscular endurance was conducted. The CPM protocol involved PPT assessment before and immediately after cuff occlusion of the opposing upper arm. MVC assessment involved two, 5 s maximal voluntary isometric contractions of the non-dominant leg separated by 60 s. Muscular endurance was assessed as time to failure in a sustained isometric contraction at 30% of peak MVC force. Following a 20 min rest period, 20 min of HD-tDCS at 2 mA was delivered. Motivation, CPM, MVC and muscular endurance were then assessed again (Post-tDCS). A 4 min rest period (*) separated the MVC and endurance trials. Pre- and post-tDCS physical performance assessment was separated by 1 h (#). Participants attended two sessions which differed in the type of stimulation delivered, with active and sham HD-tDCS administered in a randomised, counterbalanced order. Otherwise, experimental protocols for sessions one and two were identical.

Data Analysis

Data analysis was performed using SPSS statistical software (Version 21, IBM Corp, Armonk, NY). For all analyses, $p < .050$ was considered statistically significant. Means and

standard deviations for all dependent variables are presented in Table 1. In accordance with prescribed publication guidelines (APA, 2010), significance values (*p*-values) and effect sizes (Cohen's *d* or partial η^2) are presented for all analyses.

Prior to analysis, assumptions for parametric tests were assessed and confirmed. Paired samples t-tests were used to assess differences in pre-tDCS motivation, pre-conditioning PPT, CPM, MVC and muscular endurance between the two sessions. Two-way repeated measures ANOVAs examined the effect of anodal and sham stimulation on MVC, muscular endurance, pre-conditioning PPT, CPM and motivation with the main factors of time (pre- and post-tDCS) and condition (active and sham). Normalised values were also calculated for peak MVC force (MVC-norm) and muscular endurance (endurance-norm) as (post-tDCS – pre-tDCS) / pre-tDCS. Therefore, these normalised values represent the relative (percentage) change in performance from pre- to post-tDCS, with negative values indicating a reduction in performance. Paired samples t-tests compared MVC-norm and endurance-norm across the two conditions.

Table 1

Mean and standard deviations for pre- and post-tDCS motivation, pre-conditioning PPT, CPM, MVC and muscular endurance across active and sham sessions

	Active		Sham	
	Pre-tDCS	Post-tDCS	Pre-tDCS	Post-tDCS
Intrinsic Motivation	24.92 (1.31)	24.48 (1.73)	24.67 (1.83)	23.92 (2.71)
Success Motivation	16.08 (4.50)	17.25 (4.09)	15.33 (4.40)	15.33 (3.20)
Pre-conditioning PPT	12.95 (4.63)	12.21 (4.26)	12.25 (4.03)	12.73 (4.83)
CPM	−.32 (1.33)	−1.23 (1.21)	−.91 (.92)	−.26 (.92)
MVC (Nm)	264.89 (66.87)	236.33 (66.51)	249.25 (88.56)	239.63 (67.53)
Et (s)	104.65 (42.36)	93.07 (33.73)	123.42 (72.48)	100.27 (44.25)

Data is presented as mean(SD)

Pre-conditioning PPT: Pressure pain threshold prior to the presentation of the conditioning stimulus

CPM: Difference between pre- and post-conditioning PPTs

MVC: Peak torque achieved over the two maximal 5 s contractions

Et: Time to exhaustion in the fatiguing exercise task.

Results

A total of 12 participants (mean age = 24.42 ± 3.85; mean height = 178.50 ± 7.73; mean weight: 81.13 ± 8.61) were included in statistical analysis. Cortical stimulation was well-tolerated by all participants, with no complaints of deleterious responses to the intervention.

Baseline Assessment

Statistical analysis confirmed that pre-tDCS success motivation, $t(11) = .80$, $p = .441$, $d = .17$, intrinsic motivation, $t(11) = .82$, $p = .429$, $d = .16$, pre-conditioning PPT, $t(11) = -.63$, $p = .541$, $d = .16$, CPM, $t(11) = 1.07$, $p = .307$, $d = .52$, MVC, $t(11) = 1.68$, $p = .121$, $d = .20$ and muscular endurance, $t(11) = -1.75$, $p = .109$, $d = .32$ did not differ between the two sessions.

Motivation

Self-reported success and intrinsic motivation (Table 1) exceeded the levels observed in previous research (Marcora, Staiano, & Manning, 2009). Statistical analysis revealed that levels of success motivation did not differ over time, $F(1, 11) = 1.77$, $p = .211$, partial $\eta^2 = .14$, or condition, $F(1, 11) = 2.39$, $p = .150$, partial $\eta^2 = .18$. Similarly, levels of intrinsic motivation did not differ over time, $F(1, 11) = 2.93$, $p = .115$, $d = .21$, or condition $F(1, 11) = 2.71$, $p = .128$, $d = .20$. There was also no significant time x condition interaction effect for success motivation, $F(1, 11) = 1.92$, $p = .194$, partial $\eta^2 = .15$, or intrinsic motivation, $F(1, 11) = .92$, $p = .358$, $d = .08$, indicating that HD-tDCS did not affect participant motivation.

Pain Measures

Pre-conditioning PPTs did not differ significantly as a function of time, $F(1, 11) = .15$, $p = .708$, $d = .01$, or condition, $F(1, 11) = .02$, $p = .893$, $d = .00$. The time x condition interaction effect for pre-conditioning PPT was also non-significant, $F(1, 11) = 1.06$, $p = .324$, $d = .09$.

Although there was no significant main effect of time, $F(1, 11) = .21$, $p = .654$, partial $\eta^2 = .02$, or condition, $F(1, 11) = .31$, $p = .588$, partial $\eta^2 = .03$, on CPM, a statistically

significant interaction effect was uncovered, $F(1, 11) = 5.07$, $p = .046$, partial $\eta^2 = .32$, demonstrating increased endogenous pain inhibition in the active condition relative to the sham condition.

Physical Performance

For MVC force, statistical analysis revealed a significant main effect for time, $F(1, 11) = 9.61$, $p = .010$, partial $\eta^2 = .47$, but not condition, $F(1, 11) = .72$, $p = .415$, partial $\eta^2 = .06$. There was also no significant time x condition interaction for MVC performance, $F(1, 11) = 2.89$, $p = .117$, partial $\eta^2 = .21$. In addition, MVC-norm did not differ significantly between active (−11.24 ± 9.42%) and sham (−.31 ± 15.22%) conditions, $t(11) = 1.91$, $p = .083$, $d = -.89$.

Muscular endurance decreased from pre- to post-tDCS irrespective of condition, $F(1, 11) = 5.75$, $p = .035$, partial $\eta^2 = .34$. However, there was no significant main effect for condition, $F(1, 11) = 2.53$, $p = .140$, partial $\eta^2 = .19$. The reduction in endurance performance from pre- to post-sham stimulation ($M = 23.15 \pm 37.67$ s reduction) was greater than the reduction from pre- to post-active stimulation ($M = 11.58 \pm 15.81$ s reduction). When expressed as a relative change from pre- to post-tDCS, endurance time decreased by 13.30 ± 24.56% following sham stimulation, but only 9.39 ± 12.55% following active. However, both the relative, $t(11) = .68$, $p = .511$, $d = .21$, and absolute, $F(1, 11) = 1.95$, $p = .190$, partial $\eta^2 = .15$, performance advantages gained from active HD-tDCS were not deemed statistically significant.

Discussion

Exercise-induced pain is considered an important factor in exercise performance regulation (Mauger, 2014). With exercise-induced pain being subject to endogenous

modulation (O'Connor & Cook, 1999), the strength of this endogenous modulatory system may be important for exercise performance. The current study aimed to assess this possibility by examining the effect of enhancing the efficiency of the endogenous pain modulatory system on endurance exercise performance.

The current findings demonstrate that active HD-tDCS applied over the hand motor cortex does enhance the efficiency of the endogenous pain modulatory system relative to the effects of sham stimulation, which is in agreement with previous research (Flood, Waddington, & Cathcart, 2016). However, this relative increase in the efficiency of the endogenous pain modulatory system does not result in a concomitant increase in the muscular endurance exercise performance of the non-dominant leg extensors in motivated individuals.

Previous research has speculated upon the potential influence of endogenous pain modulatory capacity on exercise performance. Mauger, Jones and Williams (2010) argue that analgesic substances which produce performance-enhancing effects act by facilitating the endogenous pain modulatory system. In addition, athletes have been shown to possess a more efficient endogenous modulatory response when compared to non-athlete controls (Flood, Waddington, Thompson, & Cathcart, 2016), and a more efficient endogenous pain modulatory system has been shown to be related to superior endurance exercise performance (Flood, Waddington, & Cathcart, in press). Together, these findings suggest that an efficient endogenous pain modulatory system is adaptive for endurance exercise performance. However, the findings of the current study refute this speculation and instead suggest that the efficiency of the endogenous pain modulatory system, assessed through the CPM protocol, does not impact on endurance exercise performance.

Several explanations may account for the current novel findings. Theoretical models of endurance performance, such as the CGM, propose a central regulation of performance

which integrates multiple sensory afferents, including nociception, to ensure that homoeostasis is protected and a physiological reserve is maintained during fatiguing exercise tasks (Lambert, St Clair Gibson, & Noakes, 2005). In contrast, the psychobiological model of endurance performance proposes that afferent signals from the periphery are not involved in the regulation of work-rate during fatiguing exercise (Marcora, 2009). According to this central tenent of the psychobiological model, changes in endogenous pain modulatory capacity should not produce changes in endurance exercise performance. Therefore, the predictions of the psychobiological model offer an explanatory framework through which the current findings may be viewed.

However, caution should be taken when interpreting the current findings as evidence against the proposed role of pain in the regulation of endurance exercise performance. Endogenous inhibition produces extrasegmental modulatory effects at the spinal dorsal horn, where there is significant convergence of nociceptive input with origins in the skin and muscle (Millan, 1999). Therefore, the manipulation of the endogenous pain modulatory system, as shown through the CPM protocol, was expected to produce heightened widespread endogenous hypoalgesia, influencing nociceptive input from the exercising muscles. However, as in-task assessment of muscle pain was not conducted, it is unclear whether the observed relative increase in the endogenous pain inhibitory response induced via active HD-tDCS translated to an increased inhibition of exercise-induced pain. Therefore, the current findings may instead indicate that the endogenous inhibitory networks responsible for the processing of exercise-induced nociceptive input are distinct from the inhibitory networks affected by HD-tDCS of the hand motor cortex. The aetiologically distinct modulatory pathways for the processing of noxious stimuli (mechanical, thermal, etc.) offers indirect support for this possibility (Millan, 2002). Angius et al. (2015) also suggest that

aetiologically distinct pathways are responsible for the processing of exercise-induced nociception and noxious thermal stimuli. We encourage additional research into the neurophysiological pathways specifically responsible for the modulatory processing of exercise-induced pain so as to guide future analgesic interventions for performance-enhancement.

Outside of the effects on the endogenous pain modulatory system, previous research has also directly assessed the ergogenic effects of tDCS. This research has uncovered mixed results. Cogiamanian and colleagues (2007) and more recently Abdelmoula, Baudry, and Duchetau (2016) applied conventional tDCS at 1.5 mA for 10 min over the hand motor cortex. In both studies, the reduction in time-to-exhaustion from pre- to post-tDCS assessment was significantly reduced in the active anodal condition relative to either sham (Abdelmoula, Baudry, & Duchetau, 2016) or control (Cogiamanian et al., 2007) conditions. It is interesting to note that the endurance performance reductions from pre- to post-tDCS in the anodal (21.1% reduction), cathodal (35.7% reduction) and control conditions (39.3%) reported by Cogiamanian and colleagues (2007) were substantially greater than those observed in the current study (active, 9.39 ± 12.55% reduction; sham, 13.30 ± 24.56% reduction). In addition, rather than the sham condition used in the current study, Cogiamanian and colleagues (2007) implemented a control condition which involved no placebo stimulation. These differences in the control conditions used and the degree of fatigue carried from pre- to post-tDCS assessment may explain the discrepancy between the two findings. In contrast to the reported ergogenic effects of tDCS, using similar performance and stimulation protocols, Kan, Dundas, and Nosaka (2013) reported no improvement in muscular endurance following tDCS. The potential performance enhancing effects of tDCS have also been

examined in dynamic, whole-body exercise, with Anguis et al.(2015) finding no significant improvements in cycling time to exhaustion following tDCS over the hand motor cortex.

The potential ergogenic effects of motor cortex targeted tDCS have been attributed, in-part, to increased cortico-spinal excitability to the exercising limb (Cogiamanian et al., 2007). In order to manipulate endogenous inhibitory pathways, without influencing cortico-spinal excitability, the current study assessed performance on a leg motor task after HD-tDCS over the hand area of the motor cortex. The lack of an observed performance improvement offers indirect support for the cortico-spinal excitability explanation of the effects of tDCS on exercise performance.

The use of HD-tDCS rather than conventional methods is a novel approach in the field of exercise performance-enhancement. To-date, no research has examined the ergogenic effects of cortical stimulation using HD-tDCS. This method of cortical stimulation allows for a more targeted delivery of direct current, increasing the spatial focality of the current flow and the resulting neural changes (see Figure 1; Caparelli-Daquer et al., 2012). The exclusive use of conventional sponge-based methods of tDCS delivery limit the conclusions that can be drawn from previous findings, as the current flow and potential cortical regions influenced are widely dispersed (Figure 1). In addition to the targeting of the hand motor cortex, the use of HD-tDCS rather than conventional tDCS may explain the lack of performance advantage observed in the current study. As shown in Figure 1, HD-tDCS resulted in significantly reduced current flow to the somatotopical representation of the leg when compared to conventional tDCS. It is possible that this greater specificity accounts for the failure to replicate the performance advantages reported by Cogiamanian et al. (2007). Therefore, although conventional methods may offer the greatest behavioural effects (i.e. enhanced exercise performance), we suggest that future research should aim to utilise the greater spatial

specificity allowed through the use of HD-tDCS to better understand the supraspinal factors involved in endurance exercise performance.

Limitations

Several limitations of the current study should be noted. The endurance performance task required participants to remain focussed on the computer-displayed force trace and ensure that their force production stayed above the target. Within-task pain assessment was not included as the additional cognitive burden on the participant may have produced a sub-maximal performance. Therefore, as discussed above, we cannot say with certainty that the observed relative increase in endogenous pain inhibitory capacity resulting from active HD-tDCS did reduce exercise-induced pain perception. Future research should attempt to address this limitation through the inclusion of pain assessment both at rest and during the performance of the exercise tasks.

It has been widely reported that the performance of physical activity causes acute widespread hypoalgesia (Koltyn, 2000; Koltyn, 2002; Drury et al., 2004). It is possible that pre-tDCS physical performance may have impacted upon post-tDCS pain assessment. However, the exercise-induced hypoalgesic effect decays quickly after the completion of the exercise task (Koltyn, 2000). Therefore, to account for the potential impact of exercise-induced hypoalgesia, pre-tDCS muscular endurance trials and post-tDCS pain assessment were separated by 40 min (Figure 2). This rest-period was consistent across the two experimental conditions. Statistical analysis confirmed that pain sensitivity returned to resting levels, with pre-conditioning PPTs not differing between pre- and post-tDCS measures.

The spatial specificity of the electrical current applied via HD-tDCS is greater than that of conventional tDCS (Datta et al., 2009). Computational modelling confirmed this

assumption for the current montage (Figure 1). These differences in the distribution of the stimulated neural region resulting from high-definition and conventional tDCS methods limit the potential for comparisons to be made between the current findings and the findings of previous research. In addition, although HD-tDCS allows for greater stimulation specificity, Figure 1 suggests that cortical stimulation may have dispersed beyond the targeted hand motor cortex, potentially inducing unwanted neuronal changes in neighbouring regions. In particular, cortical stimulation may have induced changes in cortico-spinal excitability to the leg motor region. However, previous research has achieved somatotopically specific effects using conventional tDCS (Tanaka et al., 2009), suggesting that the more targeted form of cortical stimulation utilised in the current study was sufficiently localised to the target region. To further clarify the effects of targeted cortical stimulation on motor function, we encourage the examination of tDCS-induced changes in cortico-spinal excitability using methods such as transcranial magnetic stimulation.

Caution should be taken when generalising the current findings to the wider population. The current study sampled only young, pain-free males. Research suggests that pain inhibitory capacity is reduced with age (Grashorn et al., 2013), and that males possess increased pain inhibitory responses (Popescu et al., 2010). In addition, chronic pain sufferers exhibit maladaptive pain inhibition (Lautenbacher & Rollman, 1997). It is possible then that in these populations, the effects of HD-tDCS on pain inhibition and exercise performance may be different to the effects seen in the current study.

Similarly, task duration is an important factor to consider in the generalisation of the current results. The mean endurance time across all conditions was approximately 100 s. The factors influencing performance regulation are argued to be task-specific, particularly dependent on the duration of the task (Abbiss & Laursen, 2008). It is possible then that the

role of endogenous pain inhibition may be more pronounced in longer duration tasks. Indeed, increased cycling performance following acetaminophen ingestion occurred in endurance tasks exceeding 20 min (Mauger, Jones, & Williams, 2010). Future research should continue to examine the potential mediating role of task duration on the factors regulating exercise performance.

No habituation trials were conducted prior to the experimental sessions to ensure a consistency in endurance performance prior to the intervention. The novelty of the performance task may have resulted in the natural performance variations diluting the performance effects of the HD-tDCS intervention. However, statistical analysis demonstrated no significant difference in pre-tDCS endurance time or pre-tDCS MVC force over the two sessions. This suggests that the examination of the performance effects of HD-tDCS were conducted from a stable baseline muscular endurance and MVC assessment.

The current study adopted a single blinded experimental design. In order to minimise the potential for experimenter bias, standardised protocols were implemented for the measurement of both pain and exercise performance. For PPT assessment, rate of pressure application (1 kg/s) and the inter-stimulus interval (30 s) remained consistent for all participants. The rate of cuff inflation for occlusion was also consistent (~20 mmHg/s). To limit the potential for experimenter bias in the exercise performance tasks, performance feedback displayed on a computer monitor was consistent across sessions. Scripted verbal encouragement during the MVC and endurance tasks also accounted for potential experimenter bias.

There is currently a lack of consistency in the CPM methods used for the assessment of pain modulation capacity (Yarnitsky et al., 2015). PPT assessment as the TS in the CPM protocol is widely utilised, however, several alternate methods such as noxious heat are also

used (Pud, Granovsky, & Yarnitsky, 2009). Methodological inconsistencies are also evident in the methods used for the CS. Following previous research methodologies (Cathcart et al., 2009), cuff occlusion was used to inhibit the perceived intensity of the TS. To ensure that the perceived intensity of the CS was consistent for all participants, the actual intensity and duration of cuff occlusion varied. It is possible that these variations in the actual intensity and duration of the CS produced varied inhibitory responses. Due to these methodological inconsistencies, we urge caution when generalising the magnitude of pain inhibition observed in the current study.

Conclusion

The current study found that although HD-tDCS allows for the experimental manipulation of the efficiency of the endogenous pain modulatory system, a more efficient endogenous pain modulatory system does not result in improved endurance exercise performance. This novel finding opposes the argument that a more efficient endogenous pain modulatory system is adaptive for endurance exercise performance. We encourage future research to continue to utilise novel methods of brain stimulation, such as HD-tDCS, to examine the factors involved in exercise performance regulation.

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6.2. Postface

The study presented in this chapter attempted to experimentally manipulate endogenous pain modulatory capacity to clarify the nature of the relationship between endogenous pain modulation and endurance exercise performance reported in Chapter IV. Although endogenous pain modulatory capacity was successfully enhanced, this increased capacity did not cause significant changes in endurance exercise performance. Therefore, it remains unclear why, in the study presented in Chapter IV, those with more efficient endogenous pain modulatory responses displayed superior endurance exercise performance.

Chapter VII

Discussion

7.0. Introduction

This chapter will first summarise the central findings of each research paper presented in the thesis. These findings will then be critically discussed in relation to existing literature and the aims and hypotheses of the thesis stated in Chapter I. In particular, the limited use of dynamic pain assessment in past research will be highlighted to demonstrate the significant and novel contributions of the current findings to the understanding of the interaction between endogenous pain modulation and exercise. An acknowledgement of the limitations of the thesis findings will then be included leading to a discussion of the need for future research to verify and extend upon the findings of this thesis.

7.1. Summary of Main Findings

Nociceptive impulses are manipulated throughout the nervous system by competing inhibitory and facilitatory forces (Millan, 2002). This modulation of nociception affects the intensity of the perceived pain, making the perception of pain a function of the relative contribution of endogenous inhibition and facilitation (Nir & Yarnitsky, 2015). Traditional static measures of pain assessment, including pain tolerance and threshold, do not reflect the efficiency of the endogenous pain modulatory system to manipulate pain perception (Arendt-Nielsen & Yarnitsky, 2009). However, advanced dynamic assessment protocols, such as the CPM protocol, do allow for a determination of endogenous pain modulatory efficiency (Yarnitsky, Granot, & Granovsky, 2014).

Using static pain assessment, athletes have been shown to possess higher pain tolerance levels when compared to non-athletes (Tesarz, Schuster, Hartmann, Gerhardt, & Eich, 2012), suggesting that regular engagement in physical activity can alter the perception of pain at rest. This heightened pain tolerance may be due to a more efficient endogenous pain modulatory response characterised by strong inhibition and/or weak facilitation of nociceptive input. To address this possibility, the first aim of the current thesis was to compare the endogenous pain modulatory responses of athletes and non-athletes using dynamic pain assessment.

The study presented in Chapter III directly addressed the first central thesis aim. In this study, the CPM protocol involving cold water immersion as the conditioning stimulus was used to profile the endogenous pain modulatory capacity of 15 athletes and 15 recreationally active non-athletes. It was hypothesised that athletes and non-athletes would differ in their endogenous pain inhibitory capacity. This hypothesis was supported, with athletes displaying significantly greater endogenous inhibitory capacity when compared to controls. Correlational analysis assessing the relationship between engagement in physical activity and endogenous pain modulatory responses was also conducted. In athletes, those who reported higher levels of training displayed stronger endogenous pain inhibition. Interestingly, this relationship was reversed in non-athletes, with those reporting lower engagement in physical activity displaying stronger endogenous pain inhibitory responses.

Although the findings presented in Chapter III indicated that athletes possess a more efficient endogenous pain modulatory response, characterised by increased endogenous inhibition and/or decreased endogenous facilitation, it remained unclear whether this heightened endogenous pain modulatory capacity is adaptive for exercise performance. Exercise-induced pain has been argued to limit endurance exercise performance capacity

(Mauger, 2014), with hypoalgesic responses to pharmacological substances shown to result in performance improvements in fatiguing exercise tasks (Foster, Taylor, Chrismas, Watkins, & Mauger, 2014; Mauger, Jones, & Williams, 2010). It is possible, then, that the more efficient endogenous system of pain processing reported in athletes in Chapter III, is advantageous for endurance exercise performance. The second aim of the current thesis was to address this possibility by assessing the impact of endogenous pain modulatory capacity on endurance exercise performance.

Observational methods were used in the study presented in Chapter IV to assess the relationship between endogenous pain modulatory capacity and endurance exercise performance. The CPM protocol was again utilised to measure the endogenous pain modulatory responses of 27 recreationally active males. However, in this study cuff occlusion was used as the conditioning stimulus rather than the cold pressor test used in the study presented in Chapter III. Endurance exercise performance was also assessed in a submaximal (35% of maximal voluntary contraction) isometric contraction of the knee extensors. Longer endurance times were observed in those displaying more efficient endogenous pain modulation, suggesting that endogenous pain modulatory efficiency might allow for superior short-term endurance exercise performance, at least in a task involving significant local muscular fatigue and associated progressive pain.

To comprehensively assess the proposed role of endogenous pain modulatory capacity in endurance exercise performance and to establish causality, a tool for the manipulation of endogenous pain modulatory capacity was needed. HD-tDCS is a method of brain stimulation which allows for the selective excitation or inhibition of targeted brain regions (Caparelli-Daquer et al., 2012). HD-tDCS may be an effective tool for the stimulation of the endogenous pain modulatory network, facilitating the endogenous pain inhibitory response. Therefore, in

the study presented in Chapter V, the endogenous pain modulatory capacity of healthy young males was assessed after active and sham HD-tDCS over the hand motor cortex region. HD-tDCS was shown to manipulate endogenous pain modulatory capacity, with active stimulation resulting in significant elevations in endogenous pain inhibitory responses following cold water immersion in the CPM test.

Based on the findings presented in Chapter V, the final study in this thesis attempted to directly evaluate the proposed impact of enhanced endogenous pain modulatory capacity on endurance exercise performance. Endogenous pain modulation and short-term endurance exercise performance were assessed before and after both active and sham HD-tDCS. As in Chapter IV, the CPM protocol involving cuff occlusion was used to determine endogenous pain modulatory capacity and a submaximal isometric contraction of the knee extensors was used to assess endurance exercise performance. HD-tDCS methods also followed the protocols shown to successfully influence endogenous pain modulatory responses in Chapter V. Although HD-tDCS was again shown to increase endogenous pain modulatory capacity, this increased capacity did not produce any change in subsequent endurance exercise performance.

The studies presented in this thesis were designed to provide a systematic examination of the thesis aims and hypotheses as defined in Chapter I. Below, the findings relating to these defined aims and hypotheses will be discussed in the context of existing literature. This discussion will explore the potential explanations and implications of the findings from the series of studies presented in this thesis. An acknowledgement of the limitations of the thesis findings leading to suggestions for future research will also be presented.

7.2. Endogenous Pain Modulatory Capacity of Athletes

As summarised above, the findings presented in Chapter III suggest that athletes possess a more efficient endogenous pain modulatory response when compared to non-athletes. However, the findings of previous research assessing the relationship between endogenous pain modulatory capacity and physical activity levels have been mixed. When compared to non-athletes, both increased (Geva & Defrin, 2013) and decreased (Tesarz, Gerhardt, Schommer, Treede, & Eich, 2013) endogenous pain modulatory responses have been reported in athletes. Correlational analyses comparing endogenous pain modulatory responses and self-reported engagement in physical activity have also uncovered mixed findings. While Naugle and Riley (2014) and Umeda, Lee, Marino and Hilliard (2016) reported significantly more efficient endogenous pain modulation in highly active individuals, Vaegter, Handberg, Jorgensen, Kinly and Graven-Nielsen (2015) reported higher endogenous pain modulatory efficiency in inactive individuals. Lemming et al. (2015) also reported no relationship between endogenous pain modulation and physical activity.

Several potential explanations have been postulated to account for these mixed findings. According to the 'elevated activation level' hypothesis proposed by Tesarz and colleagues (2013), athletes may possess heightened basal activation of the endogenous pain modulatory network, allowing them to endure high levels of daily pain arising through regular physical activity. As the endogenous pain system is constantly functioning at a higher rate, exposure to the CPM testing protocol will produce lower activation of the endogenous pain modulatory response relative to that produced in non-athletes (Tesarz et al., 2013). Although this hypothesis helps explain the counterintuitive findings of apparent reductions in the endogenous pain modulatory efficiency of athletes (Tesarz et al., 2013), it does not

account for the increased endogenous pain modulatory efficiency in athletes reported in Chapter III of the current thesis and Geva and Defrin (2013).

In an attempt to explain these mixed findings, Umeda and colleagues (2016) have recently proposed a novel extension to the 'elevated activation level' hypothesis. They argue that the constant activation of the endogenous pain modulatory system may be dependent on the phase of the competitive season (Umeda et al., 2016). During competition, there may be chronic activation of the endogenous pain modulatory system to manage the pain experienced during this phase of the season. Fluctuations in pain tolerances across the various stages of a competitive season (Scott & Gijsbers, 1981) suggest that similar fluctuations may also occur in the chronic activation of the endogenous pain modulatory system. However, when comparing endogenous pain modulatory capacity across athletes and non-athletes, researchers to-date have failed to report athlete phase of competition, making this explanation highly speculative. This data relating to phase of competition was also not collected in the study presented in Chapter III. Therefore, it is unclear whether the extended 'elevated activation level' hypothesis proposed by Umeda and colleagues accounts for the findings presented in Chapter III.

The exclusive use of observational methods to describe the relationship between regular physical activity and endogenous pain modulation has left the nature of this proposed relationship unclear. It is possible that highly efficient endogenous pain modulation is an inherent characteristic of athletes and highly active individuals, allowing for engagement in regular physical activity. That is, those with more efficient endogenous modulatory responses may be better able to withstand the pain associated with regular physical activity and, therefore, engage more regularly in physical activity (Rhudy, 2013). This explanation, that enhanced pain modulation is an inherent trait predicting future pain experiences, is indirectly

supported by research demonstrating reduced post-operative pain in those displaying an inherently elevated pain modulatory response pre-surgery (Granovsky & Yarnitsky, 2013).

Alternatively, rather than increased endogenous pain modulation being an innate capacity of highly active individuals, regular engagement in physical activity, particularly vigorous physical activity (Naugle & Riley, 2014; Umeda et al., 2016), may cause changes in endogenous pain modulatory capacity. Several explanations provide potential mechanisms through which exercise may exert this effect. Psychological factors, including pain catastrophizing and fear of pain, have been shown to influence endogenous pain modulatory responses (Goodin et al., 2013). It is possible that regular physical activity, causing repeated exposure to noxious input, produces adaptive changes in psychological responses to pain (i.e. reduced pain catastrophizing and fear of pain). This, in turn, may produce a top-down manipulation of endogenous pain modulatory capacity (Goodin et al., 2013). As fear of pain is associated with endogenous pain inhibition and athletes display a reduced fear of pain (Geva & Defrin, 2013), such a psychological explanation may account for the elevated endogenous pain modulatory capacity of athletes reported in Chapter III.

Regular physical activity may also influence endogenous pain modulatory capacity through a manipulation of serotonergic and opioidergic neural systems (Naugle & Riley, 2014). Endogenous modulatory networks rely on serotonergic synaptic transmission (Chitour, Dickenson, & Le Bars, 1982; Kraus, Besson, & Le Bars, 1982; Treister et al, 2011). Also, reduced endogenous pain inhibitory responses following naltrexone administration suggest that endogenous pain modulation is partly dependent on endogenous opioid supply (King et al., 2013; Le Bars, Chitour, Kraus, Dickenson, & Besson, 1981). As regular physical activity is thought to increase the availability of both endogenous opioids (Stagg & Nitsche, 2011) and serotonin (Eyre & Baune, 2012), it is possible that more efficient endogenous pain

modulation in athletes and highly active non-athletes is due to exercise-induced elevations in endogenous opioid and serotonin supply.

Although these potential explanations may account for the increased endogenous pain modulatory capacity of athletes presented in Chapter III, they do not provide an adequate explanation for the mixed findings reported throughout the literature. A non-linear relationship between levels of physical activity and endogenous pain modulatory capacity may better explain the current mixed findings. As shown in Chapter III and the findings of Geva and Defrin (2013), high level athletes who report high levels of weekly training (~14 hours per week) display more efficient endogenous pain modulation than regularly active (~2 hours per week) non-athletes. However, in Tesarz et al. (2013), athletes who report relatively lower levels of weekly physical activity (9.6 hours per week) display weak endogenous pain inhibitory responses compared to inactive individuals. Together, these findings suggest that those who perform either extremely high levels of physical activity or little to no physical activity have higher endogenous pain modulatory efficiency than those engaging in moderate amounts of physical activity. Tesarz et al. have previously suggested a similar non-linear relationship between endogenous pain modulation and physical activity. However, the model proposed by Tesarz and colleagues differs in the proposed nature of this non-linear relationship, arguing instead that engaging in either extremely high levels of physical activity or no physical activity results in reduced, rather than enhanced, endogenous pain modulatory capacity. The validity of this model proposed by Tesarz and colleagues is questionable as it does not reflect the findings of their own research or the findings presented in Chapter III and that of Geva and Defrin.

In summary, by comparing the pain modulatory capacity of athletes and non-athletes, the study presented in Chapter III directly examined the first aim of the current thesis. The

findings of this investigation make a significant contribution to this currently under-investigated field of research by demonstrating heightened endogenous pain modulatory capacity in highly trained athletes. However, the findings presented in Chapter III also highlight the need for future research to utilise dynamic pain assessment protocols to provide a mechanistic explanation for the relationship between pain and engagement in regular physical activity.

7.2.1. Implications

The findings presented in Chapter III have several important implications. Maladaptive endogenous pain modulation has been repeatedly reported in chronic pain sufferers (Yarntisky, 2010), including sufferers of fibromyalgia (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997) and chronic tension-type headache (Cathcart, Winefield, Lushington, & Rolan, 2010). It remains unclear whether such a pro-nociceptive state of endogenous pain modulation precedes or is the result of chronic pain (Granovsky & Yarnisky, 2013). Regardless, the maintenance of chronic pain states may be attributed, in part, to maladaptive endogenous pain modulation. Increased efficiency of the endogenous pain modulatory system in highly trained athletes raises the exciting possibility that regular physical activity may be effective in correcting such maladaptive responses. Indeed, Naugle and Riley (2014) suggest that enhanced endogenous pain modulatory capacity may be the mechanism through which exercise interventions produce positive clinical outcomes in the treatment of chronic pain. However, as discussed in Chapter III, increases in pain modulatory capacity may only be apparent in those engaging in high levels of physical activity. This likely complex, graded effect of physical activity on pain modulatory capacity must be explored further to better inform the use of exercise as a treatment for chronic pain.

The potential implication for the correction of maladaptive endogenous pain modulation relies on the assumption that regular physical activity causes changes in endogenous pain modulatory capacity. As discussed above, the reverse may be true; that heightened endogenous pain modulatory capacity allows for regular engagement in physical activity. Taking this position, Geva and Defrin (2013) suggest that heightened endogenous pain modulatory capacity allows athletes to withstand repeated noxious input arising from regular physical activity. If endogenous pain modulatory capacity is indeed predictive of sporting engagement and success, it is possible that CPM assessment protocols may be useful in athlete selection settings. In addition, endogenous pain modulatory capacity is thought to reflect an individual's ability to respond adaptively to noxious events (Yarnitsky et al., 2008) and has been shown to be associated with the detrimental effects of common injuries in athletes, such as tendinopathy, which often produce significant impairments in function and performance (Peers & Lysens, 2005; Tompra, van Dieen, & Coppieters, 2015). Therefore, not only may stronger endogenous pain inhibitory responses indicate an individual's capacity to withstand the pain associated with athletic endeavours, but it may also indicate a reduced susceptibility to performance-limiting injury and pain. Conversely, heightened efficiency of the endogenous pain modulatory system may reduce the perceived intensity of pain acting to signal impending injury. Although this possibility has not yet been explored, it is possible that in such circumstances, heightened endogenous pain modulation capacity may be maladaptive. Therefore, the utility of pain modulatory assessment in athlete selection is currently unclear, with additional research needed to better understand the relationship between pain modulation and exercise performance.

7.3. Endogenous Pain Modulation and Endurance Exercise Performance

The second aim of this thesis was to assess the impact of endogenous pain modulatory capacity on endurance exercise performance. It was hypothesised that heightened endogenous pain modulatory capacity would be adaptive for endurance exercise performance. This hypothesis was initially supported, with more efficient endogenous pain modulatory responses shown in Chapter IV to correlate with endurance exercise performance. This finding is novel as it is the first to use dynamic pain assessment to determine the relationship between pain and exercise performance. The findings presented in Chapter IV are also the first to report a significant relationship between pain assessment at rest and exercise performance. Importantly, the observed relationship between endogenous pain modulation and endurance exercise performance support previous speculation as to the impact of endogenous pain modulation on exercise performance (Mauger et al., 2010).

The findings of Chapter IV hold particular importance due to the recent questioning of the use of at rest pain measurement in the examination of the relationship between exercise and pain. Astokorki and Mauger (2016) attempted to determine the relationship between exercise performance and pain tolerance levels using both traditional measures (cold pressor test) and aetiologically specific (exercise-induced pain tolerance) methods of measurement. Exercise-induced pain tolerance, measured as perceived pain intensity at exhaustion in a time-to-exhaustion cycling task, was shown to explain a greater proportion of the variance in cycling time-trial performance than traditional pain tolerance assessment methods (Astokorki & Mauger, 2016). From these findings, it was concluded that traditional methods of pain assessment conducted at rest are inappropriate for examining the relationship between pain and exercise (Astokorki & Mauger, 2016). However, limitations in the methods used for pain assessment call into question the conclusions drawn. Specifically, pain tolerance is defined as

‘the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation’ (Merskey & Bogduk, 1994). This point of pain tolerance was not induced by exercise in the study by Astokorki and Mauger. In fact, mean exercise-induced pain tolerance was reported as 7.23, well below the ‘extremely intense pain-almost unbearable’ anchor used to describe a rating of ‘10’ on the scale which was used (Cook, O’Connor, Eubanks, Smith, & Lee, 1997). Therefore, the findings of Astokorki and Mauger instead suggest that the level of pain reported at the cessation of a time-to-exhaustion cycling task predicts subsequent cycling time-trial performance. More work is needed to clarify the significance of such a finding.

Despite these methodological limitations, Astokorki and Mauger (2016) raise the vitally important point that current experimental methods for pain assessment do not adequately reflect exercise-induced pain and are, therefore, inappropriate for determining the relationship between exercise and pain. This point was also highlighted by Pen and Fisher (1994), who argued that traditional experimental pain paradigms do not provide an accurate assessment of exercise-induced pain. The lack of clarity surrounding the potential role of pain in exercise performance may, then, be due to limitations in the methods used to measure pain. The findings presented in Chapter IV support this argument, with pressure pain thresholds shown to be unrelated to endurance exercise performance. However, longer endurance times in those displaying more efficient endogenous pain modulatory responses suggest that dynamic pain assessment protocols may be valid tools for examining the relationship between pain and exercise performance. The findings also indicate that an enhanced endogenous pain modulatory capacity may be beneficial for endurance exercise performance.

To clarify the findings presented in Chapter IV and comprehensively assess the hypothesised influence of endogenous pain modulatory capacity on short-term endurance exercise performance, an experimental examination of the effect of altered endogenous pain

modulatory capacity on endurance exercise performance was needed. In Chapter V, HD-tDCS was shown to allow for this manipulation of endogenous pain modulatory capacity, with stronger endogenous pain inhibitory responses observed following active HD-tDCS over the hand motor cortex. This finding not only supported, but also extended upon the findings of Reidler et al. (2012), who reported that conventional tDCS over the hand motor cortex enhances the efficiency of the endogenous pain modulatory system, as assessed through the CPM protocol.

Several important methodological differences distinguish the study presented in Chapter V from the study conducted by Reidler and colleagues (2012). The primary methodological difference is the use of HD-tDCS over conventional methods of tDCS administration. The value of HD-tDCS over the conventional tDCS approach employed by Reidler et al. was discussed extensively throughout Chapter V and Chapter VI. Briefly, the greater focality of the administered electrical current of HD-tDCS (see Figure 2 in Chapter VI) ensures that the neural changes resulting from transcranial stimulation are far more localised to the targeted region compared to conventional tDCS (Kuo et al., 2013). Therefore, by supporting the findings of Reidler et al. with a more targeted form of stimulation, the findings presented in Chapter V add certainty to the conclusion that HD-tDCS over the hand motor cortex increases CPM responses through the targeted manipulation of the endogenous pain modulatory network.

Together, the findings reported in Chapter V as well as the findings of Reidler and colleagues (2012) support the use of HD-tDCS for the enhancement of endogenous pain modulatory capacity. This effect was replicated in Chapter VI, with HD-tDCS over the hand motor cortex again shown to increase endogenous pain modulatory capacity. However, increased endogenous pain modulatory capacity did not translate to enhanced endurance

exercise performance. Therefore, the findings of Chapter VI, along with those presented in Chapter IV, suggest that although endogenous pain modulatory capacity is related to endurance exercise performance, acute increases in endogenous pain modulatory capacity do not cause concomitant changes in exercise performance.

Several explanations may account for these somewhat conflicting findings. First, distinct neural networks may be responsible for the endogenous modulation of exercise-induced pain. The findings of Angius, Hopker, Marcora and Mauger (2015) support this argument, with tDCS over the hand motor cortex shown to reduce perceived pain arising from cold water immersion without influencing exercise-induced pain. Interestingly, although Angius and colleagues reported that tDCS reduced pain intensity ratings, pain tolerance levels during the same cold pressor test were unaffected. This finding is in contrast to earlier findings of enhanced pain tolerance following tDCS over the hand motor cortex (Zandieh et al., 2013). Combined with their small sample, the findings of Angius et al. require replication in order to clarify the argument that the analgesic effects of tDCS do not apply to exercise-induced pain. However, the findings of Angius and colleagues align with the argument presented in this thesis and by Astokorki and Mauger (2016) that exercise-induced pain has unique qualities which may extend to unique endogenous pain modulatory networks. In summary, it is possible that although the CPM protocol verified that HD-tDCS induces an enhancement in endogenous pain modulatory capacity, the endogenous pain modulatory system involved in the modulation of exercise-induced pain may have been unaffected, explaining the lack of a performance advantage.

Alternatively, potential mediating factors may account for the observed relationship between endogenous pain modulatory capacity and endurance exercise performance, thereby explaining the lack of a performance advantage resulting from an increased endogenous pain

modulatory capacity. Pain catastrophizing is 'an exaggerated negative mental set brought to bear during actual or anticipated pain experience' (Sullivan et al., 2001, p. 53). Catastrophizing thoughts magnify perceived pain intensity (Quartana, Campbell, & Edwards, 2009) including the perception of exercise-induced pain (Weissman-Fogel, Sprecher, & Pud, 2008). High pain catastrophizing also corresponds to weak endogenous pain inhibitory responses (Weissman-Fogel et al., 2008) and is a significant predictor of the experience of pain in athletes (Sullivan, Tripp, Rodgers, & Stanish, 2000). Like endogenous pain modulatory capacity, athletes have also been shown to have lower pain catastrophizing than non-athletes (Geva & Defrin, 2013). Together, this evidence suggests that the relationship between endogenous pain modulatory capacity and endurance exercise performance observed in Chapter IV may be mediated by pain catastrophizing. If so, this would account for the finding of no improvement in endurance exercise performance following the manipulation of endogenous pain modulatory capacity. Manipulating pain catastrophizing, rather than endogenous pain modulatory capacity, may prove effective for the enhancement of endurance exercise performance.

The studies presented in Chapter IV and Chapter VI directly investigated the putative impact of endogenous pain modulatory capacity on endurance exercise performance, hypothesised in Chapter I. Although endogenous pain modulatory capacity was shown to be related to endurance exercise performance, when endogenous pain modulatory capacity was experimentally manipulated, endurance exercise performance was not affected. Therefore, endogenous pain modulation appears to be related to endurance exercise performance, but an acute manipulation of endogenous pain modulatory capacity, using HD-tDCS, may not be effective in improving endurance exercise performance. Potential mediating factors and

distinct neural networks responsible for processing cutaneous and exercise-induced pain may explain these findings.

7.3.1. Implications

A novel finding of the current thesis was the enhanced efficiency of endogenous pain modulatory responses following HD-tDCS of the motor cortex. This finding has potential clinical implications for chronic pain sufferers who, as described above, possess maladaptive endogenous pain modulation (Yarnitsky, 2010). However, further consideration of tDCS protocols for the treatment of chronic pain, specifically stimulation duration and intensity, and electrode placement, is needed to optimise patient outcomes and inform the clinical use of tDCS. Although additional research is needed to verify its clinical utility, preliminary investigations suggest that the observed impact of HD-tDCS on endogenous pain modulation is generalisable to chronic pain sufferers (Spinocchia, Flood, & Cathcart, in submission). This may explain the pain reductions reported in chronic pain sufferers following tDCS over the motor cortex (Antal, Terney, Kühnl, & Paulus, 2010; DalÍAgnol, Pascoal-Faria, Barros, & Corrêa, 2015; DaSilva et al., 2012). Such findings add to the growing interest in the clinical use of transcranial electrical stimulation, evidenced through the recent development of guidelines for the remote delivery of tDCS (Charvet et al., 2015), including the use of tDCS for the out-of-clinic treatment of chronic pain sufferers (Hagenacker et al., 2014).

Although not a primary focus of this thesis, the current findings in relation to the effects of tDCS on endurance exercise performance also hold practical significance. There is some evidence to suggest that tDCS produces performance-enhancing effects (Abdelmoula, Baudry, & Duchateau, 2016; Angius, Pageaux, Hopker, Marcora, & Mauger, 2016; Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007; Okano et al., 2015). However,

others have found no performance improvement following tDCS (Angius et al., 2015: Barwood et al., 2016; Kan, Dundas, & Nosaka, 2013; Muthalib, Kan, Nosaka, & Perrey, 2013). The most widely proposed mechanism through which tDCS may produce a performance advantage is through elevated cortico-spinal excitability (see Cogiamanian et al., 2007). Due to the involvement of the motor cortex in initiating muscular contraction, changes in motor cortical excitability may influence descending motor drive to the exercising muscles to produce changes in exercise performance. In the study presented in Chapter VI, performance in an exercise task involving the knee extensors was assessed after HD-tDCS was applied over the hand motor cortex. This target of stimulation was chosen so as to replicate the cortical target previously shown to enhance endogenous pain modulatory capacity. HD-tDCS over the hand rather than leg motor cortex was also selected to ensure that any performance advantage could not be attributed to changes in cortico-spinal excitability to the involved limb. With muscular endurance of the knee extensors unaffected by HD-tDCS of the hand motor cortex, the findings presented in Chapter VI suggest that increased cortico-spinal excitability is required for tDCS-induced performance enhancement. However, previous research showing significant improvements in muscular endurance following tDCS without accompanying elevations in cortico-spinal excitability (Abdelmoula, Baudry, & Duchateau, 2016; Angius et al., 2016), indicate that the optimal tDCS electrode montage for ergogenic effects remains unclear.

7.4. Limitations and Future Research

This thesis compared the endogenous pain modulatory capacity of athletes and non-athletes and assessed the impact of endogenous pain modulatory capacity on short-term endurance exercise performance. However, future research is needed to confirm and extend the findings presented to gain a greater understanding of the complexities of the pain

experience and the interaction between pain and exercise. Due to the limited use of dynamic pain assessment protocols in exercise and sports science, potential directions for future research in this field are numerous and beyond the scope of this discussion. Therefore, the discussion below highlights several recommendations for future research directions which are considered of primary significance for the progression of knowledge in this field.

The study presented in Chapter III is limited by the use of observational methods. This adds to the exclusive use of observational methods in the research to-date assessing the relationship between endogenous pain modulatory capacity and engagement in regular physical activity (Lemming et al., 2015; Naugle & Riley, 2014; Umeda et al., 2016; Vaegter et al., 2015). As highlighted above and within Chapter III, such observational methods fail to clarify the direction of causality in the observed relationship between endogenous pain modulation and physical activity. In addition, the observational nature of these findings significantly limits the ability to discuss their practical and theoretical implications, including the potential use of CPM protocols in athlete selection and the potential value of exercise interventions for chronic pain treatment. In addition, explanations for the observed differences in the endogenous pain modulatory capacity of athletes and non-athletes are largely speculative as it is unclear whether the heightened endogenous pain modulatory capacity of athletes is acquired or innate. Therefore, it is clear that to advance our understanding of the relationship between exercise and endogenous pain modulation, a longitudinal investigation of the effect of an extended exercise intervention is needed. Methodologies should attempt to replicate those which have previously been used to demonstrate changes in pain tolerance levels following extended exercise interventions (Anshel & Russell, 1994; Jones, Booth, Taylor, & Barry, 2014). As suggested by Rhudy (2013), such a longitudinal investigation should also attempt to investigate the effects of

regular physical activity on psychological factors known to impact upon endogenous pain modulatory capacity, such as fear of pain and pain catastrophizing.

It was speculated above that the relationship between regular physical activity and endogenous pain modulatory capacity may be non-linear. Such an explanation warrants further investigation as it would account for the mixed findings reported throughout the literature. In addition, if the relationship between regular physical activity and endogenous pain modulation was deemed to be non-linear, this may have significant implications in a variety of applied settings, particularly the optimisation of exercise interventions for chronic pain treatment. Therefore, future research should assess the relationship between regular physical activity and endogenous pain modulation at multiple levels of physical activity. Exercise interventions requiring differing levels of weekly engagement in physical activity should also be employed to determine the nature of the potential non-linear relationship between endogenous pain modulatory capacity and regular physical activity.

Exercise type has been argued to influence the degree to which regular physical activity induces changes in pain tolerance at rest. For example, aerobic exercise, but not strength training, has been reported to significantly increase pain tolerance levels at rest (Anshel & Russell, 1994). Ryan and Kovacic (1966) also reported significantly higher pain tolerance levels in contact athletes compared to non-contact athletes and non-athletes. These findings suggest that the relationship between endogenous pain modulation and regular engagement in physical activity may also be dependent on exercise type. As athletes in the study presented in Chapter III were recruited from a wide range of sporting backgrounds, it remains unclear whether exercise type influenced the relationship between physical activity and endogenous pain modulation. Indeed, it is possible that the heterogeneous athlete sample may have reduced the strength of the observed differences in the endogenous pain

modulatory capacity of athletes and non-athletes reported in Chapter III. Future research, then, should consider the effect of exercise type on the relationship between regular physical activity and endogenous pain modulatory capacity.

Due to the effect of pain catastrophizing on the perception of exercise-induced pain and the relationship between endogenous pain modulatory capacity and pain catastrophizing (Weissman-Fogel et al., 2008), it was proposed that pain catastrophizing may mediate the relationship between endogenous pain modulation and endurance exercise performance. Although such a mediating role has been proposed, research to-date, including that presented within this thesis, has not examined this possibility. Therefore, in order to extend upon the findings of the current thesis, future research should include measures of pain catastrophizing, such as the Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995), when exploring the relationship between endogenous pain modulation and endurance exercise performance. Such research is important as psychotherapeutic interventions have been shown to be effective in reducing pain catastrophizing (Sullivan et al., 2000; Sullivan et al., 1995). If pain catastrophizing does influence endurance exercise performance, these interventions may prove to be effective for performance enhancement.

As described above, the effects of HD-tDCS on endogenous pain modulation may have significant implications for the treatment of chronic pain sufferers. However, the restricted sampling of healthy individuals in Chapter V and Chapter VI limits the ability to generalise the current findings to a chronic pain population. As chronic pain sufferers typically exhibit maladaptive endogenous pain modulation, evidenced through weak inhibition and/or strong facilitation (Yarnitsky, 2010), the effects of HD-tDCS on endogenous pain modulatory capacity may differ between chronic pain and healthy populations. In fact, due to the reduced potential for ceiling effects, increases in endogenous

pain modulatory capacity following HD-tDCS may be more pronounced in chronic pain sufferers. Research to-date, however, has failed to assess this possibility. Because of the clear clinical implications and the potential role of endogenous pain modulation in the pain experience of chronic pain sufferers, future research should attempt to examine the effects of HD-tDCS on endogenous pain modulatory capacity in a chronic pain sample.

In the studies presented in Chapter III and Chapter VI, exercise performance capacity was assessed using a time-to-exhaustion task. As a measure of endurance exercise performance, this method requires athletes to maintain a specified target load until volitional exhaustion (Amann, Hopkins, & Marcora, 2008; Laursen, Francis, Abbiss, Newton, & Nosaka, 2007). The time-to-exhaustion task was used as it induces obvious, pronounced and localised exercise-induced pain (Chaffin, 1973). Therefore, the time-to-exhaustion task was appropriate for the assessment of the impact of endogenous pain modulatory capacity on endurance exercise performance. However, the external validity of the task for 'real-world' exercise performance has been questioned, with some arguing that time-to-exhaustion tasks do not reflect endurance exercise events which predominately involve self-selected variations in pace/load to ensure the completion of a task with a defined end-point (Jeukendrup & Currell, 2005). Conversely, Laursen and colleagues (2007) argue that endurance exercise events are often not performed solely at self-selected loads, but instead may require an athlete to match the pace set by a pre-determined strategy or competitor. As performance in such events, then, is dependent on the individual's capacity to maintain a defined load until exhaustion, lab-based assessment using the time-to-exhaustion method may have a high external validity. Nevertheless, caution should be taken when attempting to generalise the findings of this thesis to 'real-world' performance. As has been suggested by others (Amann,

Hopkins, & Marcora, 2008; Laursen et al., 2007), future research should aim to utilise methods which are appropriate for the specific research questions being posed.

7.5. Conclusion

The research direction taken in this thesis was guided by two primary aims: 1) comparing the endogenous pain modulatory capacity of athletes and non-athletes; and 2) assessing the impact of endogenous pain modulatory capacity on endurance exercise performance. As hypothesised, athletes were shown to possess more efficient endogenous pain modulatory responses than non-athletes, clarifying and extending upon previously mixed findings. Although this finding does not indicate whether superior endogenous pain modulation is an inherent trait or an acquired capacity, it does offer a potential explanation as to the mechanisms underpinning the reported pain insensitivity of athletes. In relation to the second thesis aim, endogenous pain modulatory capacity was shown to be correlated with endurance exercise performance, but when manipulated, heightened endogenous pain modulatory capacity from a single session of HD-tDCS did not produce superior exercise performance. These findings may indicate that distinct neural structures are involved in the modulation of exercise-induced pain compared to cutaneous experimentally-induced pain, or that the relationship between endogenous pain modulatory capacity and endurance exercise performance relies on mediating factors.

In the field of exercise science, pain assessment has relied almost exclusively on static assessment measures. By using dynamic pain assessment, the current thesis provides the first comprehensive insight into the interaction between endogenous pain modulation and exercise. The findings presented in the current thesis, then, are not only novel, but also hold significant value for the progression of our understanding of the relationship between pain

and exercise. This has the potential to further optimise the methods used for the identification and selection of athletes who are able to withstand the pain associated with vigorous physical activity, advance the methods of treatment for chronic pain and develop novel methods for exercise performance-enhancement. In this regard, it is hoped that this thesis acts as a catalyst for future research utilising dynamic pain assessment techniques so as to better understand the apparent reciprocal relationship between pain and exercise.

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Appendix A: Progession of Research Papers