The neural basis of the sense of fatigue

Mark Edward Hartman

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The neural basis of the sense of fatigue

by

Mark Edward Hartman

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Kinesiology

Program of Study Committee:
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The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University

Ames, Iowa

2020

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DEDICATION

This dissertation is dedicated to my mother. Thank you for all your incredible support, encouragement, and patience, especially considering that it has taken me 14 years to finish my post-secondary education. I am proud to be your son.
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ACKNOWLEDGMENTS

I owe many thanks to Dr. Ekkekakis. I am extremely grateful to have you as my advisor. The past five years have been the most transformative time of my life, for which you have contributed tremendously. You are one of the most thoughtful, insightful, and intelligent people I know. I cannot thank you enough.

I also want to thank Dr. Pettitt. You have gone to great lengths to help me become successful. I immensely appreciate your guidance over the years. I also want to acknowledge Dr. Lewinski because without your support and unprecedented generosity, I would not be where I am today.

My sincere thanks also go to my committee members: Dr. Sharp, Dr. Clark, Dr. Lang, and Dr. Meyer. Thank you for your guidance and assistance on this project and during my time at ISU. I also want to acknowledge Dr. Smiley. Thank you for your unwavering support and mentorship, both academically and professionally. I am also thankful to Dr. Gillette. Your kindness and willingness to help has been invaluable during times of uncertainty. I sincerely appreciate the care and kindness afforded by Fran Sobotka and DeAnn Pitman. Thank you for all the excellent work you do to support the department.

I also want to express my gratitude to my supportive friends and colleagues who I will miss dearly. Thank you to Jess for being a reliable running partner and for indulging in my erratic discussions on runs. Thank you to Paul for all your knowledge in physiology and for reminding me how to relax on occasion. To Patricia, Jeff, Joey, and Ryan, thank you for your kindness, support, and friendship over the years. I also want to acknowledge Matt. I am very glad to have had you as a lab mate and a great friend during my time at ISU. Finally, to Danielle, I appreciate all your support and sacrifices to help me get to this point. Thank you.
Evidence suggests that the genesis and regulation of the sense of exertional fatigue is rooted within the same neural networks responsible for processing affective responses. One key mechanism proposed to be involved in the sense of exertional fatigue is the interaction between the cognitive inhibitory processes of the dorsolateral prefrontal cortex (DLPFC) and the interoceptive inputs to the amygdala. The primary purpose of this dissertation is to examine the development and progression of exertional fatigue during exercise by examining the interactions between the level of bodily perturbations evoked by the exercise, the activity of the DLPFC (Tissue Oxygenation Index [TOI] percentage), the amygdala (indexed by the acoustic startle eyeblink response [ASER] amplitude), and affective responses (Empirical Valence Scale [EVS] score). The secondary purpose is to modulate the interaction between the DLPFC TOI, the EVS scores, and the ASER amplitudes using transcranial direct current stimulation (tDCS), to explore its potential as a treatment for attenuating the sense of fatigue during physical exertion. Individual differences were also examined. Thirty healthy university students—12 women and 18 men—exercised on a cycle ergometer for up to 20 minutes or until volitional termination at (1) heavy-intensity exercise while receiving sham tDCS on the right and left DLPFC (H-Sham), (2) heavy-intensity exercise while receiving active tDCS (H-Active), (3) severe-intensity exercise while receiving sham tDCS (S-Sham), and (4) severe-intensity exercise while receiving active tDCS (S-Active). The rate of decline in EVS scores was significantly greater during severe-intensity exercise compared to heavy-intensity exercise. The decline in the right and left DLPFC TOI percentages was significantly greater during severe-intensity exercise compared to heavy-intensity exercise, and this decline was larger in the right DLPFC compared to the left DLPFC. During both exercise intensities, the strength of the correlations between EVS scores
and the right and left DLPFC TOI percentages increased as the interoceptive cues intensified. tDCS significantly increased DLPFC TOI percentages and the pattern of the ASER amplitudes. In conjunction with the decline in EVS scores, the drop in TOI was most prominent during severe-intensity exercise when, on average, the right DLPFC TOI dropped below baseline and, therefore, the DLPFC entered a hypometabolic state. Individuals with a higher level of tolerance demonstrated a greater activation of the right DLPFC during the heavy-intensity exercise compared to individuals with lower tolerance. The findings of this dissertation suggest that affective responses during exercise were a function of both the severity of homeostatic perturbations and the level of inhibitory control exerted by the right DLPFC. These results support the model for hemispheric specialization of the right PFC in the cognitive inhibition of displeasure. The regulation of the sense of exertional fatigue is, therefore, likely controlled by the right DLPFC. Exertional fatigue emerged at a defined threshold. Accordingly, the physiological response pattern entered a non-steady-state, accompanied by feelings of greater displeasure (or less pleasure) and high perceived activation. Proximal to the point of termination, the hypometabolic state of the DLPFC and the decline in affective responses were not reversed with active tDCS. As such, near one’s physiological limits, if the deactivation of the DLPFC and the corresponding displeasure serve to protect the body from reaching dangerous levels of perturbation, then this mechanism appears to be immutable. Future work should evaluate the potential of therapies that target the modulation of DLPFC inhibitory control (top–down) or interoceptive sensitivity (bottom–up) networks in relation to types of fatigue (e.g., clinical).
CHAPTER 1. INTRODUCTION

Background and Significance

Defining Fatigue

The definition of fatigue, how it manifests (e.g., in the body or the mind), and how people experience it remains only partially elucidated. Debate around these fundamental issues continues, while scientific progress in understanding fatigue is limited (Pearce, 2006; Rasker, 2009; Saligan et al., 2015; Walker et al., 2019). Despite a wealth of research on the topic, a comprehensive theoretical framework of fatigue remains elusive. In addition, a broadly accepted definition of fatigue has yet to be formulated (Chaudhuri & Behan, 2004). The construct of fatigue has eluded scientific explanation to the extent that researchers have referred to it as an epistemological “enigma” (Pearce, 2006; Rasker, 2009). Scientists have made “little progress in a theoretical and applied understanding of its impact on persons’ lives” (DeLuca, 2005, p. 5).

Nonetheless, fatigue is not a rare phenomenon; it is universal to the human experience. Exertional fatigue is one type of fatigue that people experience on a regular basis. During exhaustive physical exertion or exercise, exertional fatigue manifests as an affective response (valence: pleasure-displeasure), specifically an increase in displeasure (or a decline in pleasure) accompanied by high perceived arousal (Hartman et al., 2019). The physical manifestation of exertional fatigue is a detrimental decline in muscle force production caused by reduced contractility of the muscle fibers (i.e., peripheral fatigue) (Enoka & Stuart, 1992), impaired motor command (i.e., central fatigue) (Bigland-Ritchie et al., 1986; Gandevia, 2001), metabolic perturbation, (Burnley & Jones, 2018), and prefrontal cortex (PFC) deoxygenation (Ekkekakis, 2009a; Robertson & Marino, 2016). During a challenging bout of exercise, the limit of tolerance is due to a multitude of interrelated physical, physiological, and psychological factors.
A different type of fatigue is experienced after the cessation of intense physical exertion (e.g., a challenging exercise bout or demanding manual labor). Post-exertional fatigue is a feeling of low psychological arousal, which is perceived as either pleasant or unpleasant depending on the intensity of the exercise performed and the dispositional traits of the individual (Brand & Ekkekakis, 2018; Ekkekakis, 2003; Ekkekakis & Lind, 2006). For most healthy adults, after challenging exercise, there is an affective “rebound effect,” in which ceasing the exercise feels pleasurable while the exercise itself felt unpleasant. This response is addressed in opponent-processes theory (Solomon & Corbit, 1974), which explains the processes that drive a variety of motivated behaviors (e.g., drug addiction behavior, psychopathological behavior). Displeasure post-exercise also occurs following prolonged low-intensity exertion (e.g., aerobic exercise for long durations or several hours of manual work) (Van Katwyk et al., 2000). Individual traits impact the decline in affect post exercise, such as a person’s psychological tolerance to high-intensity exercise (i.e., individual differences in the highest exercise-intensity that is maintained when the intensity is imposed) and preference for high-intensity exercise (i.e., individual differences in the intensity of exercise that the individual self-selects when given a choice) (Ekkekakis et al., 2008).

Other examples associated with low-arousal fatigue include health-related issues (e.g., lack of sleep, poor diet, stress, psychological and physical disorders, and diseases). Fatigue-like symptoms (e.g., tiredness, drowsiness, lethargy, exhaustion, depression, and low motivation) are associated with many poor health-related behaviors and disorders (DeLuca, 2005, p. 20). When individuals describe non-clinical fatigue, they use words that refer to a general feeling of “tiredness” (Stadje et al., 2016), which is something different than clinical fatigue. Tiredness develops due to a physiological or psychological cause, for example, feeling exhausted after a
long day at work. Tiredness also occurs after participating in a highly demanding mental task that requires prolonged focus, is stressful, and requires cognitive inhibition (Tran et al., 2020). The development and sensation of generally feeling tired can be independent of physical movement and physical impairment.

In clinical practice, fatigue is understood as something broader than a general feeling of tiredness and is also assumed to be different from exertional fatigue. Clinical fatigue can be severely debilitating and can profoundly disrupt physical and mental functioning (Clayton, 2015; Pearce, 2006). Clinical fatigue is among the most prevalent health complaints in the primary care setting (Andrea et al., 2003; Morrison, 1980; Ricci et al., 2007). Clinical fatigue is commonly reported by patients across a variety of disorders including Parkinson’s disease (Karlsen et al., 1999), multiple sclerosis (Fisk et al., 1994) fibromyalgia (Ericsson & Mannerkorpi, 2007), systemic exertional intolerance/chronic fatigue syndrome (SEI/CFS; Wiborg et al., 2010), cancer (Thong et al., 2019), and major depression (Anderson et al., 2003). The causal factors driving the fatigue that is associated with clinical disorders are complex. Fatigue can manifest as a symptom of a disease or as a side-effect of treatments (e.g., chemotherapy, antidepressant medications). Additionally, clinical fatigue can be moderated by specific behaviors. For example, for individuals with SEI/CFS, the completion of a high-intensity exercise bout is often followed by excessive fatigue and feelings of extreme displeasure (i.e., termed "post-exertional malaise") (Hodges et al., 2020; Ohashi et al., 2002). However, not all patients with the aforementioned disorders report symptoms of fatigue. For a minority of patients, fatigue symptoms are relatively mild, and, in some cases, patients are asymptomatic in terms of physiological or self-reported abnormalities (Kocer et al., 2017). It is not clear why levels of fatigue severity vary in certain
individuals with the same underlying disorder. Nevertheless, modern medicine is unable to alleviate fatigue in individuals who experience it.

**Implications of Fatigue**

Fatigue has a considerable impact on modern society. There are economic consequences of fatigue, both at the individual level and at the societal level. In the U.S., approximately 38% of the workforce report significant fatigue at least once during a two-week work period (Ricci et al., 2007). Sixty-six per cent of European workers experience fatigue at the end of most workdays. Depending on its severity, workers with fatigue face extensive healthcare costs (inpatient hospitalization, higher insurance premiums, and expensive prescription medications), accumulate excessive unpaid sick days, and experience job instability (Lin et al., 2011; Reynolds et al., 2004; Stewart et al., 2003). At the macro level, loss in productivity due to fatigue is estimated to cost businesses $136.4 billion annually (Ricci et al., 2007). It is difficult to identify an alternate modern epidemic that affects as many people as fatigue and whose mechanism of action is so poorly understood.

Another implication of fatigue extends to the world of sports performance. Athletes and coaches constantly seek new ways to gain a competitive edge. Delaying the onset or development of fatigue is of paramount importance to athletic success. Athletes strive for peak performance by incorporating new training techniques, integrating advanced technological aids, and adhering to strict dietary regimens. However, most of what is known about peak performance is based on group statistical averages rather than on mechanistic factors specific to each individual (Abdullah et al., 2016). An individual’s response to a given training program or diet is highly variable and unpredictable. A long sought-after goal of sports training is the ability to predict and maximize performance at the individual level (e.g., response to training, signs of approaching “burnout,” and performance readiness) (Harris, 1982; Padgett & Hill, 1989; Scott,
Factors that relate to genetics (Ostrander et al., 2009), diet (Clark & Mach, 2016), stress (Thelwell et al., 2017), and coping skills (Williams et al., 2008) are known to moderate athletic performance. However, because performance moderators derive from group-level averages, predictive validity in relation to a single athlete is low. In contrast to average group effects, a mechanistic theoretical framework of exertional fatigue would benefit coaches and athletes by enabling individual-level predictions. Understanding individual performance factors, such as attenuating an athlete’s fatigue in real time, would help tailor the intervention to optimize the athlete’s response to training, predict and avoid burnout, and maximize the ability to be competitive.

Finally, fatigue indirectly affects the health and well-being of people because it has a detrimental effect on physical activity (PA) behavior. Physical inactivity is rapidly becoming a worldwide health epidemic (Ding et al., 2016; Kohl et al., 2012; Pratt et al., 2015). Globally, physical inactivity is the fourth leading risk factor for all-cause mortality (Kohl et al., 2012). In the U.S., 90–98% of the U.S. population do not meet the minimum PA guidelines, determined using accelerometers (Troiano et al., 2008; Tudor-Locke et al., 2010). Similar inactivity levels have been observed for European citizens (Bassett et al., 2015). On average, approximately 50% of participants drop out of clinical exercise interventions specifically designed to increase participation in exercise within the first six months of the trial (Godin et al., 1995; Gourlan et al., 2016; McEwan et al., 2019; Patnode et al., 2017; Wilding et al., 2016).

Based on survey data, the most common self-reported barriers to not exercising have been summed up as “too much effort,” “no motivation,” “no energy/[feeling] tired,” “not fun,” and “[having] no time” (Ebben & Brudzynski, 2008; Lovell et al., 2010; Vanden Auweele et al., 1997). These statements reflect two themes; firstly, that exercise is perceived as a mostly
negative experience, and, secondly, that exercise results in undesirable levels of exhaustion and tiredness. Both themes relate to the underlying affective (i.e., pleasure–displeasure) qualities of exertional fatigue (Hartman et al., 2019). Just like fatigue, the mechanism that underlies the motivation for participation in exercise or remaining active is poorly understood (Beauchamp et al., 2018; Copeland et al., 2015).

**Current Theories**

Currently, a comprehensive theoretical framework of fatigue does not exist, and the fundamental processes associated with fatigue are poorly understood. Research into fatigue remains at the exploratory stage. For example, a recently funded National Institute of Health (NIH) study identified 932 correlations between various biomarkers in 32 patients with SEI/CFS without applying any a priori hypotheses (Germain et al., 2018). The study did not identify any consistent biomarkers for the disorder. Similarly, Lacerda et al. (2019) assessed over 100 demographic variables in an NIH-funded study to develop a model to predict the likelihood of SEI/CFS. Significant predictors of SEI/CFS were being romantically involved, having frequent colds, and a family history of anxiety. From a statistical perspective, alpha inflation is a concern when numerous exploratory correlational analyses are performed in the absence of a mechanic hypothesis.

Perhaps, a reason for the lack of a mechanistic and theoretical framework for fatigue is that its nature is highly interdisciplinary. Although many scientific fields study fatigue (e.g., biomedicine, cognitive psychology, affective neuroscience, immunology, exercise physiology, exercise psychology, cardiology, pharmacology), interdisciplinary collaboration is rare (Marino et al., 2011). Frequently, fatigue is studied independently and within the conceptual confines and technical language of a single discipline. In clinical practice, fatigue is classified as a medical symptom, and it is usually associated with a systemic condition or disorder (e.g., a chronic
inflammatory condition, pathogenic infection, cancer, autoimmune disorder, cardiovascular disease, neurologic disease, or a sleep or psychological disorder) (Jason et al., 2010; Lambert & Derman, 2000). By contrast, the prevailing view in exercise physiology is that fatigue is defined as reduced muscle output; specifically, “the inability to maintain a given exercise intensity is due to impairment within the active muscles themselves” (Brooks et al., 2005, p. 852) or to the loss of maximal force-generating capacity (Bigland-Ritchie et al., 1986). In the field of psychology, fatigue compromises the performance of cognitively challenging tasks due to a depletion in cognitive resources (Van der Linden et al., 2003; Vohs & Heatherton, 2000) or represents a consequence of dysfunctional beliefs and attitudes (Fry & Martin, 1996; Knoop et al., 2010; Vercoulen et al., 1998). In the field of neurophysiology, fatigue is a phenomenon of the central nervous system (i.e., central fatigue), and it is defined as a significant reduction in efferent motor commands to the active muscles, which results in a decline in force or tension (Gandevia, 2001). Recently, psychobiological definitions of fatigue have emerged within the exercise physiology and psychology subdisciplines. Fatigue is thought to be an emotion that is regulated by the brain to prevent devastating homeostatic disturbances (Gibson et al., 2003; Noakes, 2012; Noakes et al., 2001). Alternatively, fatigue is understood to occur when the muscle force output declines relative to an increase in motor command output or due to a disproportionate increase in corollary discharge (Marcora et al., 2008). Exertional fatigue has also been defined as a high-arousal, negatively valanced affective response evoked by the brain when bodily perturbations approach dangerous levels during episodes of physical exertion (Ekkekakis, 2003; Hartman et al., 2019). The multiplicity of definitions highlights the challenge of delineating fatigue across disciplines, as well as the marked lack of consensus that occurs within disciplines.
In exercise science, fatigue has traditionally been conceptualized as a peripheral phenomenon that is caused by physiological processes from the neck down (Noakes, 2011). Advocates of a cardiorespiratory fatigue model (Dempsey et al., 2008; Krogh & Lindhard, 1913) claim that “ventilation is the limiting factor in aerobic performance at sea level” (Brooks et al., 2005, p. 28). Elsewhere, it has been claimed that cardiac output is the limiting factor (Bassett & Howley, 2000). In other perspectives, exertional fatigue is discussed as muscle fatigue, an exercise-induced reduction in the ability to exert muscle force (Enoka & Stuart, 1992) or a decline in power output (Gandevia, 2001). Note that peripheral fatigue theories offer a reductionistic, single most important fatigue factor, however, these theories do not offer explanations as to how the different peripheral mechanisms coordinate action or relay the fatigue status. The peripheral systems are rarely discussed in terms of integration or coordination, let alone acknowledgement of the role of the brain (Noakes, 2011). Therefore, it is necessary for fatigue theories to address the integration of multiple peripheral systems that interact with the brain.

Support for brain-based fatigue models has grown in the past few decades. Recognition of the hierarchical importance of the brain over peripheral mechanisms is not as controversial as it once was. However, there is still limited evidence on the validity of the brain-based models. Debate continues over whether fatigue is a function of afferent or efferent processes (De Morree & Marcora, 2015, p. 258) and around the relationship between the perception of effort during exercise and fatigue. According to the afferent feedback model, during exercise, afference from the skeletal muscles, heart, and the lungs is processed by the brain to monitor and regulate the internal milieu (i.e., stability of the body’s internal physiology) (Bernard, 1865). The brain generates a sense of fatigue as a way of applying a pacing strategy (Jones et al., 2013; Venhorst
et al., 2018); however, ultimately it forces the cessation of the activity to protect against
dangerous homeostatic perturbations (i.e., when physiological limits are reached). By contrast,
the corollary discharge and psychobiological models posit that a sense of fatigue is an efferent
process that is generated within the motor cortex. The assumption is that fatigue is a perception
of the effort caused by a greater proportional increase in motor cortex activity relative to the
activity or output of the work muscles (Marcora, 2008a). According to this viewpoint, afferent
feedback does not play a role in the sense of fatigue. This proposition is a source of controversy
among exercise researchers (Marcora, 2008b; Meeusen et al., 2009). However, it is reasonable to
assume that both efferent and afferent processes contribute to the sense of fatigue. Additional
research is warranted to distinguish between efferent and afferent processes during episodes of
physical exertion.

The Need for Alternative Methodologies

In a comprehensive review, Ekkekakis (2009) identified several issues that arise when
evaluating fatigue. The first of two key issues identified is that a large percentage of fatigue
studies, clinical fatigue studies in particular, only measure fatigue after it occurs (e.g., in patients
with pre-existing symptoms of fatigue using pre- and post-positron emission tomography [PET]
and single photon emission tomography scans [SPECT]). From a research methods perspective, a
more valid approach would be to experimentally induce fatigue and then measure it as it
transpires. While there are obvious ethical and practical limitations to using a true experimental
design to study clinical fatigue, there are major limitations to what can be understood about
clinical fatigue by using correlational approaches, especially if the interest lies in identifying and
testing the mechanisms. Alternatively, an evaluation of fatigue from its origin to its termination
would allow causal experimental questions to be addressed. The most practical experimental
manipulation of fatigue is likely to involve the production of a large but safe level of acute and
transient fatigue. Different approaches to inducing fatigue via experimental manipulation have been used. In the clinical literature, researchers utilize “imaginal fatigue” protocols, whereby the participants “imagine” feeling fatigued while undergoing a functional magnetic resonance imaging (fMRI) scan (Caseras et al., 2008). Whether a person’s imagination mimics the intensity of actual fatigue and real-world experiences is debatable; however, the results of "imaginal fatigue" studies have not yielded consistent findings. In the psychological literature, when examining non-clinical fatigue, researchers have often utilized highly demanding cognitive tests as a means of inducing a state of mental fatigue. These fatigue protocols involve difficult mental tasks that demand sustained attention over a long duration (e.g., semantic memory tasks) (Thompson-Schill et al., 1997), mental flexibility tasks (Mobbs et al., 2011), and inhibition tests (Xu et al., 2012). Overall, the magnitude of mental fatigue induced by cognitive fatigue tasks is small (McMorris, 2016), and it only reflects one dimension of fatigue (i.e., mental fatigue).

In contrast to cognitive and imaginal tasks, “fatigue protocols” in the exercise literature push the physiological limits of an individual (e.g., incremental cycling exercise performed until volitional termination). The magnitude of fatigue caused by maximal exercise produces large effect sizes for both physical fatigue (Carter et al., 2004; Dawson et al., 2005; Gollnick et al., 1974; Hill et al., 2001; Miller et al., 1987) and psychological fatigue (Hartman et al., 2019; Hogervorst et al., 1996; Welsh et al., 2002). From an experimental and practical perspective, exertional fatigue is transient (in healthy individuals, it dissipates shortly after exercise cessation), and, when relative fitness is taken into account, the magnitude of the fatigue experienced by participants can be nearly standardized (Jamnick et al., 2016; Kirkeberg et al., 2011). Measuring fatigue during its onset, regulation, and termination allows for a holistic assessment of fatigue-related processes that occur in the body and brain. When considering these
factors, it is necessary for researchers to explore the use of exercise as a primary method of studying fatigue in order to advance scientific understanding of this enigma.

The second key brain research issue identified by Ekkekakis (2009) is the slow progress in understanding what takes place in the brain, particularly at the subcortical level, which is virtually off limits owing to the limitations of neuroimaging methods during exercise. For reasons explained in greater detail in Chapter Two, brain activity during exercise is limited to the superficial cortical layers. However, understanding the brain’s response during exercise could never be complete without awareness of the modulatory action and parallel processing that takes place in deep parts of the brain. This is especially relevant for exercise, considering that a large proportion of the brain regions involved in homeostatic processes during exercise (e.g., cardiovascular regulation, respiratory regulation, and hormonal control) are subcortical. One subcortical region in particular, the amygdala, is implicated in the integration of affective (LeDoux, 1986, 1995, 2000) and homeostatic information (Ciriello et al., 1994; Craig, 2002; Roder & Ciriello, 1993), as well as the fatigue associated with brain dysfunction (Chaudhuri & Behan, 2004; Genova et al., 2011). Thus, there is a theoretical basis to suggest that the amygdala may be associated with several important processes in the context of exertional fatigue. To date, no human study has measured the activity of the amygdala during exercise; yet, one study that used mice demonstrated that the utilization of glucose by the amygdala in response to exercise increased by 56% in the central nucleus, 33% in the lateral nucleus, and 18% in the medial nucleus (Vissing et al., 1996). This heightened activity during exercise provides an indication that the amygdala has a functional role in processing exercise-related stimuli, with differential processing within specific nuclei.
In the context of psychophysiology, a variety of sensory, cognitive, and affective processes have been studied using the startle paradigm (Yeomans et al., 2002). Specifically, the acoustic startle eyeblink response (ASER) is an amygdala-mediated reflex that occurs in response to a sudden auditory stimulus at high decibel levels (Hunt & Landis, 1936; Landis & Hunt, 1936). The direct modulatory effect of amygdala activity on the ASER, measured using infrared reflectance oculography or electromyography (EMG) of the eyelid muscles, has been demonstrated in fMRI studies (Eippert et al., 2007; Kuhn et al., 2020). Most importantly, when individuals process affective stimuli, the amplitude of ASER is modulated by content valence, which, in part, is processed by nuclei in the amygdala. Specifically, ASER increases when an acoustic startle stimulus is presented while viewing unpleasant affective images, and it decreases when an acoustic startle stimulus is introduced while viewing pleasant affective images (Balaban & Taussig, 1994; Bradley et al., 1996a, 1996b; Bradley & Lang, 2000; Corr et al., 1997; Lang et al., 1990; Vrana & Lang, 1990). The implications of the ASER highlights the importance of interdisciplinary perspectives because they have the potential to solve novel problems using existing solutions from other fields.

**Theoretical Approach**

Based on available neuroanatomical evidence, the role of afferent feedback is fundamental to exercise regulation. The process by which afferent feedback of the body’s physiological state is encoded and represented in the brain is known as interoception (Craig, 2003). It is well-established that the afferent feedback of bodily homeostasis is processed through interoceptive networks in the brain to produce conscious sensations and guide behavior (Craig, 2002, 2009; Critchley et al., 2004; Edelman, 1989). A wide variety of interoceptors exist throughout the body (e.g., mechanoreceptors, chemoreceptors, thermoreceptors, baroreceptors,
and visceral nociceptors), and they are able to detect changes in homeostasis (Belmonte & Cervero, 1996).

Interoception is a highly adaptive mechanism for two reasons. Firstly, the brain is dependent on the immediate functioning of bodily systems that maintain the internal milieu within a physiological survivable range. Secondly, the long-term survival of organisms depends on their ability to acquire resources from the environment (e.g., food) and fulfill behaviors that promote Darwinian fitness (e.g., reproduction) (Critchley & Harrison, 2013). The brain solves many problems relating to the first objective through autonomic homeostatic regulation (e.g., digestion, thermal regulation, immune function) and without much conscious involvement. However, in most cases, some level of conscious decision-making and deliberate behavior (e.g., seeking food and avoiding impending harm) are required to accomplish both objectives. The brain solves this problem by enabling conscious perceptions of the internal state (e.g., the relative stain on the body) and using this information to inform a conscious decision to take corrective action. Interoception provides the brain with useful information for immediate survival. Threats to survival, such as homeostatic disruptions, enter conscious awareness, and the interoceptive data are encoded as core affective states (Damasio, 1995; Nesse, 1990, 1998). Core affect is the most basic component of all feelings of pleasure and displeasure (Russell & Barrett, 1999), and it is anatomically linked to the processing of exteroceptive (Eippert et al., 2007; Golkar et al., 2012; LeDoux et al., 1988; Ochsner et al., 2012) and interoceptive stimuli (Craig, 2009; Critchley & Garfinkel, 2017). Affective states underlie the motivation to engage in physiologically significant behaviors (e.g., seeking food or avoiding harm) (Craig, 2009) and decision-making (e.g., hunting strategies) (Batson et al., 1992; Damasio, 1995; Kahneman et al., 2000). In the context of exercise, affective states serve to regulate the performance of exercise
(e.g., pacing) (Venhorst et al., 2018), promote evolutionary adaptive exercise behaviors (e.g., moderate-intensity exercise), and prevent maladaptive behaviors (e.g., running until death). Ultimately, affect serves as a protective mechanism that ceases the continuation of activity during high-intensity exercise in an attempt to prevent dangerous levels of homeostatic perturbation. Exertional fatigue fits with the conceptualization of heightened arousal and displeasure during exercise at the limit of a person’s tolerance. Within this framework, volitional termination occurs when the level of fatigue, driven by the increase in displeasure or decrease in pleasure, becomes intolerable, thereby prompting or forcing the individual to stop performing the activity.

The dual-mode theory (DMT) describes the relationship between exercise intensity and affective responses within an interoceptive context (Ekkekakis, 2003, 2009a, 2009b; Ekkekakis & Acevedo, 2006). The DMT builds on interception, the function of which is to promote survival-related behaviors and the sense of the physiological condition of the body (Craig, 2003) within the exercise context. Specifically, the interplay between the cortical and subcortical processes is theorized to drive affective responses during exercise. Since affective responses are the primary method by which the brain consciously monitors the status of its internal milieu via interoception, it follows that this is also the case during exercise. Thus, the DMT proposes that affective responses during exercise are a function of two factors: top–down cortically mediated cognitive factors (e.g., exercise self-efficacy, reappraisal) and subcortical bottom–up affective-encoded interoceptive stimuli. The extent to which each factor influences the affective response changes systematically depending on the exercise intensity. At a relatively low intensity, such as moderate-intensity exercise (i.e., below the ventilatory threshold [VT]), where most individuals report feeling pleasure, cognitive factors account for the majority of variance in the affective
response. Moderate-intensity exercise allows the maintenance of a physiological steady-state; bodily perturbations are minimal, and afferent feedback to the homeostatic subcortical brain regions does not constitute a threat.

As the exercise intensity increases and transitions above the VT, interoceptive cues become increasingly pervasive (i.e., enter conscious awareness) as a function of increased homeostatic perturbations. During heavy-intensity exercise (i.e., above the VT but below the respiratory compensation point [RCP]), the exercise is physiologically more demanding and engages several compensatory mechanisms. For example, the recruitment of less metabolically efficient muscle fibers, such as fast oxidative and fast nonoxidative fibers (e.g., type IIa and type IIb), rapidly deplete the glycogen stores and the level of circulating glucose, which results in the accumulation of metabolic byproducts (e.g., $H^+$ ions, inorganic phosphate[Pi], ammonia [$NH_3$]). In addition, compensatory mechanisms (e.g., ventilation, bicarbonate buffering) must increase in order to re-establish a metabolic steady state. However, the steady state is delayed by 15–20 minutes, depending on fitness, due to the emergence of the pulmonary oxygen uptake ($VO_2$) slow component, and $VO_2$ temporarily lags behind metabolic demand (Burnley & Jones, 2018). These perturbations, induced by heavy-intensity exercise, are detected by the interoceptive receptors (interoceptors). Various gating mechanism determine, based on the severity of the perturbations, when the interoceptive information enters conscious awareness. The point at which the perturbations become exceedingly pervasive to our sensory awareness is the point at which the interoceptive receptors activate the higher-threshold afferent neurons, thus magnifying the interoceptive intensity of the signal received by the subcortical homeostatic regions. Therefore, the interoceptive signals are more salient at higher intensities and exert greater influence on affective responses. It is during heavy-intensity exercise that the interoceptive
factors and cognitive factors will, on average, have a roughly equal influence on affective valence. This equal combination means that heavy-intensity exercise produces heterogeneous affective response patterns in different individuals (i.e., some people report feeling good, and others report feeling bad).

Some of the interindividual differences in affective responses during heavy-intensity exercise can be explained by dispositional trait factors, such as greater preference for or tolerance of high-intensity exercise. For example, individuals with high tolerance typically report experiencing greater pleasure than those with low tolerance (Ekkekakis et al., 2005a). According to the DMT, high-tolerance individuals have increased capacity over low-tolerance individuals to cognitively regulate their affective responses emanating from the interoceptive stimuli. During heavy-intensity exercise, correlations between cognitive variables (e.g., self-efficacy, self-presentational concerns) and affective valence scores are similar in strength compared to those between affect and indices of metabolic strain (e.g., the respiratory exchange ratio, blood acidity, blood lactate concentration) (Ekkekakis, 2003; Ekkekakis et al., 2010).

When the exercise intensity exceeds the RCP, a physiological steady-state can no longer be maintained. Above the RCP, in the severe-intensity domain, increasingly intense afferent signaling from the periphery, caused by severe metabolic perturbations (e.g., the accumulation of metabolites, elevated core temperature, fuel depletion, greater type II muscle fiber recruitment, maximal cardiac output, and the emergence of the VO2 slow component), is detected, in rudimentary form, by the subcortical interoceptive networks (e.g., the nucleus of the solitary tract [NTS], parabrachial nucleus [PB], periaqueductal gray [PAG], paraventricular nucleus [PVN], and ventral lateral medulla [VLM]) and is encoded by the amygdala as a threat to homeostasis (Amaral & Cowan, 1980; Craig, 1996, 2003; LeDoux et al., 1988). These networks relay the
interoceptive information (the dangerous perturbation cues) to the mid-brain (e.g., ventral striatum, dorsal striatum) and cortex (e.g., dorsal anterior cingulate cortex [dACC], ventral anterior cingulate cortex [vACC], medial prefrontal cortex [mPFC], dorsolateral prefrontal cortex [DLPFC]) for conscious awareness either as displeasure or as a decline in pleasure.

For reasons that are not fully understood, activity in the PFC regions, measured using near-infrared spectroscopy (NIRS), typically declines during exercise above the RCP, a decline that often terminates below the baseline values at exercise cessation. The decrease in PFC oxygenation (and, presumably, activity) during severe-intensity exercise physically impairs the ability to regulate affect because the cognitive regulation of affective responses occurs primarily in the PFC regions (Ochsner & Gross, 2005). Therefore, during severe-intensity exercise, affective responses are primarily driven by the bottom–up influence of interoceptive afferent signals, while the amygdala remains unchecked by the PFC. Therefore, affective responses during severe-intensity exercise are primarily driven by the interoceptive stimuli encoded by the amygdala as displeasure or a decline in pleasure. Indeed, nearly all individuals report a decline in affect during severe-intensity exercise. The DMT states that, in the context of exercise, the cortical–subcortical interaction is an evolutionary adaptation designed to detect dangerous homeostatic disturbances that threaten survival. It is speculated that exertional fatigue during severe-intensity exercise is associated with a decline in right PFC activity, which results in impaired ability to regulate affective valence; in other words, the result is compromised ability to regulate feelings of fatigue.

Hemispheric laterality is particularly robust in the cognitive control of emotion, an ability that is primarily associated with the dorsal regions of the PFC. Along with the mPFC and the anterior cingulate, the DLPFC is integrated in a specialized emotional circuit that incorporates bi-
directional projections with subcortical structures (i.e., the amygdala, thalamus, PB, VLM, and PAG). For example, neuroimaging studies in non-exercise contexts have reliably demonstrated activation of the mPFC, DLPFC, and anterior cingulate during attempts to exert cognitive control over negative affect (e.g., through attentional dissociation or cognitive reappraisal), which inhibits activity in the amygdala. These processes have been explained in terms of the regulation of approach–avoidance motivation in response to exteroceptive stimuli (Förster et al., 2001) or alternatively as the regulation of positive–negative affective states in response to exteroceptive (Eippert et al., 2007; Ochsner et al., 2002; Ochsner & Gross, 2005) and interoceptive stimuli (Ekkekakis, 2003, 2009a; Ekkekakis & Acevedo, 2006). In terms of the latter approach, affective states are a function of cortical affective regions (e.g., the DLPFC, mPFC, ACC), subcortical affective regions (e.g., amygdala), and homeostatic regions (e.g., the PB, PAG, VLM, NTS, PVN, insula).

In the clinical literature, a few notable clues exist that may help shed light on the relationships between PFC hemispheric asymmetry, affect, and fatigue. For example, multiple sclerosis patients with severe symptoms of fatigue have reduced glucose metabolism in both hemispheres of the PFC, including the basal ganglia, compared to healthy controls (Roelcke et al., 1997). Similarly, in patients with CFS, reductions in right PFC gray matter volume are correlated with the severity of the patients’ fatigue symptoms (Okada et al., 2004). Furthermore, the activity in the right DLPFC specifically is reduced in CFS patients compared to healthy adults.

**Summary of the Proposed Theoretical Framework**

This dissertation examined the neural basis of exertional fatigue. Exertional fatigue represents a primordial, evolutionarily preserved affective response that is characterized by high arousal and displeasure or by a marked decline in pleasure, the function of which is to cause a
cessation in ongoing exertion, thus protecting the organism from potentially dangerous homeostatic perturbations (Hartman et al., 2019). The utility of this definition is that it provides a foundational interdisciplinary framework for the development of testable, mechanistically based, and novel hypotheses.

The DMT, the theoretical framework initially proposed by Ekkekakis (2003, 2009a, 2009b) and Ekkekakis and Acevedo (2006), laid the foundation for understanding the neural basis of affective responses during exercise. Unlike many brain-based exercises theories, the DMT outlines a specific and succinct neural mechanism that can be tested. The model accounts for the pattern of affective responses observed during exercise across all levels of intensity and considers interindividual differences. Most importantly, in the context of fatigue, the interdisciplinary nature of the DMT bridges a crucial conceptual gap across four major disciplines: exercise physiology, biomedical science, affective neuroscience, and evolutionary psychology. The present study expanded upon this conceptual groundwork and developed a comprehensive theoretical framework for a neural basis of exertional fatigue.

An examination of the interdisciplinary literature suggests that the underlying neural networks involved in the origin and regulation of affective responses significantly overlap with the neural networks associated with homeostatic regulation and clinical fatigue states. According to the affective neuroscience literature, the network of brain areas includes the basal ganglia, the frontal cortex, insula, amygdala, thalamus, and PAG (Davidson, 2001; Etkin et al., 2015; Le Doux, 1986, 1995, 2000; Oosterwijk et al., 2012; Pessoa, 2017; Rosenkranz & Grace, 2001). In the clinical and biomedical literature, fatigue is associated with the functional impairment of a cortical–subcortical circuit that involves the basal ganglia, frontal cortex, thalamus, and amygdala (Caseras et al., 2008; Chaudhuri & Behan, 2004; Genova et al., 2011; Okada et al.,
2004; Roelcke et al., 1997). Relatively little is known about brain functioning during exercise for the reasons expounded in Chapter Two. Exercise-related brain function is limited to the superficial cortical regions (Ekkekakis, 2009a). However, given the available research, what is well-established is that the frontal cortex is significantly involved during exercise and is implicated as having a fundamental role in exertional fatigue (Ekkekakis, 2009a; Robertson & Marino, 2016; Rooks et al., 2010). The frontal cortex, and more specifically the DLPFC and mPFC, are involved in the cognitive control of emotion, and, therefore, the regulation of exertional fatigue, according to the definition proposed by Hartman et al. (2019). Along with the mPFC and the anterior cingulate, the DLPFC is integrated in a specialized emotional circuit that incorporates bidirectional projections with subcortical structures, including the amygdala, thalamus, PB, VLM, and PAG. Thus, the top–down regulation of emotional states is possible because there are direct and indirect pathways between the PFC and the subcortical regions.

Based on empirical evidence, it was theorized that exertional fatigue is influenced jointly by (1) afferent information that converges in the amygdala regarding the physiological condition of the body (i.e., information from chemoreceptors, thermoreceptors, and nociceptors), (2) gating mechanisms (e.g., intensity-coded neural fibers) that permit the flow of interoceptive cues, either to the cortical or to subcortical routes, depending on the stimulus intensity, and (3) inhibitory control exerted by the DLPFC and mPFC. These regions exert regulatory control of the amygdala in accordance with the intentional deployment of a cognitive regulation strategy (e.g., reappraisal) along with a regulatory goal (e.g., the upregulation of pleasure, downregulation of pleasure, upregulation of displeasure, or downregulation of displeasure) (Buhle et al., 2014; Eippert et al., 2007; Ochsner et al., 2002, 2004).
While studies on the hemispheric asymmetry of emotional regulation have produced mixed findings, both hemispheres are involved when individuals intentionally decrease feelings of displeasure evoked by an aversive stimulus (Ochsner & Gross, 2005). Transient episodes (e.g., a severe-intensity exercise bout) and chronic conditions (e.g., clinical depression and SEI/CFS) that cause PFC hypometabolism impair the control by the PFC over the amygdala, which limits the ability to regulate the emotional state. Consequently, without regulatory input from the PFC during exposure to an adverse stimulus, the amygdala remains uninhibited (Davidson, 2000; Davidson, 2001). Thus, it is theorized that exertional fatigue becomes perceptible during physical exertion when regulatory control by the PFC over the amygdala is reduced by transient PFC hypometabolism. It is likely that hypometabolism of the PFC during episodes of exertion relates to a reflexive protective mechanism whereby the amygdala inhibits (bottom–up) the PFC to stop the ongoing exertion (See Figure 1 for a graphical display of the proposed model).

**Purpose**

The proposed theoretical framework was tested using heavy- and severe-intensity exercise as the fatigue-inducing stimuli, performed until volitional termination, while key psychophysiological and self-reported variables were being monitored. Individual differences in the development of exertional fatigue were examined. Lastly, a putative neural mechanism of the framework was tested.

The primary study objective was to determine evidence of a functional relationship between 1) the intensity of bodily perturbations during heavy- and severe-intensity exercise (using VO$_2$ an indication of metabolic strain) (2) activity in the right and left DLPFC (using NIRS), (3) activity in the amygdala (using the ASER), and (4) affective valence (using the empirical valence scale [EVS]) (Lishner et al., 2008). A secondary study objective was to experimentally manipulate the interaction between the DLPFC and the amygdala, using tDCS on
the right and left DLPFC, to determine whether or not this would influence the decline in affective valence during heavy- and severe-intensity exercise.

**Research Hypotheses**

Three research hypotheses were formulated in the current study. Firstly, the assumption was that, during heavy-intensity exercise, but not severe-intensity exercise, anodal tDCS would result in higher EVS scores, higher bilateral DLPFC TOI, and lower ASER compared to sham treatment. During severe-intensity exercise, tDCS would have no effect on these variables.

Secondly, it was hypothesized that affective valence, measured using the EVS, would be directly associated with DLPFC activity, measured using NIRS, and amygdala activity, indexed using ASER, would increase when there was an observed decline in EVS and a decline in DLPFC activity. Specifically, it was hypothesized that during severe-intensity exercise, EVS scores would decline from exercise onset until volitional termination and the decline in affective valence would be associated with decreased DLPFC TOI and an increased ASER.

Thirdly, it was hypothesized that, independent of tDCS, changes in EVS, DLPFC TOI, and the ASER would be associated with individual differences in exercise intensity tolerance, measured using the Preference for and Tolerance of the Intensity of Exercise Questionnaire (Ekkekakis et al., 2005a), such that a greater number of high-tolerance individuals, compared to low-tolerance individuals, would report higher EVS scores, exhibit greater TOI in the DLPFC, and lower ASER activity, during heavy-intensity exercise.
CHAPTER 2. LITERATURE REVIEW

Chapter Overview

Chapter Two contains a literature review of the mechanisms that relate to exertional fatigue and methodologies for its measurement. The interdisciplinary topics addressed include (1) peripheral homeostasis during exercise, (2) interoceptive receptors and primary afferent neurons, (3) the dynamics of cortical–subcortical affective regulation, (4) hemispheric laterality in affective regulation, (5) cortical hemodynamic activity during exercise, (6) indirect measures of subcortical activity, and (7) cortical modulation.

Peripheral Homeostasis During Exercise

Throughout the body, a wide range of intensity-encoding interoceptors (e.g., mechanoreceptors, chemoreceptors, thermoreceptors, baroreceptors, and visceral nociceptors) (Belmonte & Cervero, 1996) support the detection of varying degrees of change in the internal milieu (Cervero, 1994; Cervero & Jänig, 1992; Jänig, 1996). Depending on the magnitude of change, a receptor that responds by firing at a sufficiently high frequency will reach the requisite intensity to activate threshold-sensitive neurons that transmit this information to the brain. For example, both group III and IV (Aδ and C) fibers detect metabolic changes in tissue; low-threshold alpha delta fibers respond to lower levels of firing intensity, and high-threshold C-fibers respond to higher firing rates. Group I (A-fibers) are mechanically sensitive, low-threshold proprioception fibers capable of detecting changes associated with proprioception. Groups III & IV (Aδ and C) fibers have a high threshold and respond to any changes in the physiological condition of all body tissues. C-fibers respond to hypoxia, hypoglycemia, hypo-osmolarity, cutaneous pressure, and the presence of metabolites (Craig, 2002, 2003; Pan et al., 1999; Panneton, 1990; Vallbo et al., 1999). Subsets of these afferent fibers selectively respond to sharp
pain, burning pain, a cool sensation, a warm sensation, itching, touch, and muscle cramping (Craig, 2003). The widespread presence and diversity of interoceptive receptors highlights the inherent necessity of monitoring the internal physiological environment of the body. Notably, various receptors and fibers in the body are attuned to specific perturbations (e.g., an elevation in core temperature, muscle strain, a decrease in tissue oxygenation, fuel depletion, and increased metabolites) that are induced by severe-intensity exercise.

**Stress and Immune Perturbations**

In response to stress—that is, a state of cognitive, emotional, or physical strain resulting from adverse or very demanding circumstances—the subcortical activation of homeostatic regulation modulates a cascade of physiological processes. Examples of stressors include encountering a dangerous animal, prolonged sleep deprivation, social evaluation, and severe-intensity exercise. The response to a stressor includes sympathetic activation of the adrenal medulla, which, in turn, releases epinephrine (E) and norepinephrine (NE) into the bloodstream. In addition, activation of the hypothalamus-pituitary-adrenal (HPA) axis by the PVN of the hypothalamus releases corticotrophin-releasing hormone. This is followed by the secretion of adrenocorticotropic hormone (i.e., from the pituitary gland) and glucocorticoids (i.e., from the adrenal cortex) (Harris, 1951; Selye, 1936, 1938, 1946; Vale et al., 1981, 1982). By readying the required physiological processes for optimal acute peak motor activity (e.g., escape from a predator) to maximize the chances of survival, the stress response has an important evolutionary role to ensure the allocation of metabolic resources is prioritized accordingly (Cohen et al., 2001).

The shift in metabolic priority reduces the activity of “non-essential” bodily activities (e.g., digestion, higher-order cognition, sexual arousal, and anabolic activity or protein repair). Consequently, symptoms of fatigue can occur if certain biological processes are weakened. The
immune system is one of the primary biological systems modulated by the stress response. In response to stress, the immune system plays a key role in mediating symptoms of fatigue through the release of proinflammatory cytokines (e.g., interleukin [IL]-6, IL-1, tumor necrosis factor alpha [TNFα]) and lymphocytes (e.g., B and T cells) (Kiecolt-Glaser et al., 2002). Cytokines have a number of extremely diverse functions, and more than 100 subtypes have been identified. Therefore, their effect on the body varies greatly, and this can include beneficial and harmful effects. In the context of exercise, cytokines partially mediate several processes associated with training adaptation. Cytokines coordinate and regulate various intercellular processes, such as hematopoiesis, angiogenesis, tissue repair, and metabolism (Gleeson, 2007). Many processes by cytokines are vital for survival. For example, cytokines are involved in mobilizing the repair processes to damaged tissue. Chronic elevations in certain cytokines can impair immune function due to increased lymphocyte oxidation resulting from the production of cytokines and associated processes (e.g., HPA activation) (Russell & Ley, 2002). Therefore, the interoceptive processes associated with cytokines are time-dependent and concentration-sensitive, and are moderated by interactions between cytokine subtypes (Shibata, 1990).

Lymphocytes contain affinity-graded adrenergic receptors that respond to increased plasma concentrations of E and NE, which modulate the release of proinflammatory cytokines (Bruunsgaard et al., 1997). The release of proinflammatory cytokines is accompanied by the generation of highly reactive oxygen species (ROS), which contribute to lymphocyte damage, lymphocytopenia, and altered immunity if they remain elevated for too long. The variability of catecholamine receptor affinity across immune cell populations results in the graded activation of these cells, depending on E and NE concentrations. The acute increase in catecholamines allows the immune system to respond rapidly to the physiological demands of the stressor (Buckholtz et
al., 1988). However, the prolonged elevation of catecholamine levels can have negative health consequences if ROS production remains chronically elevated as a consequence of increased immune cell activity. The production of several cytokines, as a result of heightened immune activation, is associated with fatigue symptoms in clinical disorders, bacterial and viral infections, and exercise (Adamson & Billings, 1993; Russell & Ley, 2002).

Many clinical physical stressors (e.g., surgery, trauma, burn, infection) induce a stress response pattern that is similar to that for high-intensity exercise. For example, both stress and high-intensity exercise trigger the subcortical activation of homeostatic regulation centers, sympathetic activation, and activation of the HPA axis. Exercise intensity influences the magnitude of the stress response as lymphocyte concentrations generally increase across moderate-, heavy-, and severe-intensity exercise. However, during prolonged heavy- or severe-intensity exercise performed until volitional termination, lymphocyte concentrations peak at much higher levels than is the case during moderate-intensity exercise (Hoffman-Goetz & Pedersen, 1994). These lymphocytes release plasma IL-6 at an exponential rate that peaks at the point of exhaustion and returns to baseline levels during recovery. After prolonged endurance events (e.g., marathons), the concentration of chemokines (i.e., IL-8, macrophage inflammatory protein 1-alpha [MIP]-1α, and MIP-1β) increases (Niess et al., 2000; Ostrowski et al., 2001). Remarkably, lymphocyte concentration declines below the resting baseline level following high-intensity exercise, which is not the case with moderate-intensity exercise (Ostrowski et al., 1999; Suzuki et al., 2002). The result is the acute impairment of immune function and greater susceptibility to infection after high-intensity exercise.

Following heavy-intensity exercise, the immune system response differs notably from the response mediated by infection. For example, the latter includes an increase in TNFα
concentration, followed by an increase in IL-6 concentration. By contrast, an increase in IL-6 during heavy-intensity exercise is not preceded by elevated levels of TNFα (Pedersen & Febbraio, 2008). While the cytokine response to infection promotes inflammation, the cytokine response elicited by exercise occurs due to the contraction of skeletal muscles and is characterized by anti-inflammatory and metabolic properties. For example, the muscles release anti-inflammatory myokines, such as IL-10, which moderate the inflammatory stress response (de Waal Malefyt et al., 1991).

Nevertheless, exercise intensity that approaches an individual’s physiological limit produces an immune response that more closely resembles the immune response to infection. Following a marathon, for example, TNFα, IL-1 receptor agonist [IL-1RA], and IL-1 beta [IL-1β]) double in concentration, and IL-6 concentration is 50 times greater than resting baseline levels (Hoffman-Goetz & Pedersen, 1994; Ostrowski et al., 2001). Normally, this effect is balanced by the release of cytokine inhibitors (IL-1RA and TNF receptors) and the anti-inflammatory cytokine IL-10. However, depending on fitness-related factors, during high-intensity exercise over a prolonged duration, the release of anti-inflammatory cytokines is attenuated by the release of cortisol (Galbo, 1983; Steinacker et al., 2004). Of the interoceptive receptors that are sensitive to the effects of proinflammatory cytokines released during stress and high-intensity exercise, those that inform the different vagal afferent projections are sensitive to a number of inflammatory mediators. Vagal projections to homeostatic and affective processing brain regions allow monitoring of the body’s immune function (Stead & Bionetwork, 1990). It has been hypothesized that fatigue symptoms associated with major infections (e.g., influenza) are the consequence of the brain’s response to cytokine interoception through the allocation of a large proportion of metabolic resources to immune processes (Krueger & Majde, 1990).
**Metabolic Perturbations**

Several of the metabolic byproducts produced by exercise have inflammatory effects on the body. Disruption to tissue integrity is signaled by responses to changes to the local metabolism (H⁺ ion accumulation); in general, when skeletal muscle demand for adenosine triphosphate (ATP) exceeds mitochondrial ATP production, the muscles increasingly rely on the recruitment of less efficient type II muscle fibers that utilize nonoxidative glycolysis (Jones et al., 2011). Hydrogen ions produced by ATP hydrolysis begin to accumulate in the cytosol when the rate of local mitochondria turnover is maximal (Robergs et al., 2004). Compensatory intracellular and blood/ventilatory buffering processes must engage to expel the H⁺ ions, but H⁺ ion buffering outside of the mitochondria has limited efficiency. As the accumulation of H⁺ ions lowers the blood pH, acidosis leads to impairment of the myosin head cross-bridge, reducing muscle efficiency, and a large enough drop in pH will begin to inhibit phosphofructokinase (PFK), the rate-limiting step in glycolysis (Kjaer et al., 1991). Active skeletal muscle will eventually be unable to contract without ATP and the fuel sources from which it is derived. Therefore, information about localized homeostatic perturbations must be transmitted to the brain before this happens, prompting the brain to cease the activity before catastrophic tissue damage occurs. In fact, the existence of specific chemoreceptors (e.g., carotids that detect H⁺ ions [Biscoe & Duchen, 1990] and purinergic receptors that detect ATP [Harden et al., 1990]) provides evidence that interoception plays a key role in monitoring the internal milieu in order to preserve bodily homeostasis.

**Fuel Depletion**

Muscle glycogen is a major interoceptive cue associated with fatigue. Previous research has assessed the impact of the depletion of skeletal muscle glycogen on fatigue (Ahlborg et al., 1967; Bergström et al., 1967; Hermansen et al., 1967). Exercise performance has been shown to
vary in relation to skeletal muscle glycogen stores (Ahlborg et al., 1967; Carlson et al., 1971; Hargreaves et al., 1987). For example, Rauch et al. (2005) tested the effect of carbohydrate loading and depletion on aerobic cycling time trials. In the study, participants completed two one-hour time trials under glycogen-loaded and glycogen-depleted conditions. As expected, the glycogen-depletion condition resulted in slower performance and lower power output. At the end of each time trial, muscle glycogen concentrations were found to be similar for both conditions; the authors speculated that the brain paced performance relative to the amount of glycogen stored and the maximum depletion rate allowable to complete the trial. The authors noted that a participant’s muscle glycogen levels were never fully depleted in either condition, and there appeared to be a set point beyond which further glycogen depletion in the muscle did not occur. It was proposed that chemoreceptor detection of glycogen metabolites may be responsible for relaying information about glycogen levels and utilization rates to the brain, which, in turn, determined the optimal pacing strategy.

**Perturbations as a Function of Exercise Intensity**

During full-body exercise (e.g., cycling, running, rowing), tolerance varies with intensity and duration. Relative exercise intensities are classified as moderate, heavy, severe, or extreme, based on specific metabolic responses related to allostatic maintenance and the development of peripheral and central fatigue (Burnley & Jones, 2018; Gaesser & Poole, 1996; Whipp, 1994). It has been proposed that exercise intensity should not be defined as a percentage of maximum oxygen uptake (VO\(_{2\text{max}}\)) or maximum heart rate (HR\(_{\text{max}}\)); rather, it should be based on oxygen (O\(_2\)) kinetics as this approach provides deeper insight into the dynamics of homeostasis maintenance during exercise at differing intensities (Gaesser & Poole, 1996).

The *moderate* domain of exercise intensity includes intensities below the lactate threshold (LT), based on lactate exercise protocols, or below the VT, assessed using gas
exchange during incremental exercise protocols. Moderate-intensity exercise is characterized as a metabolic steady state, where the increase in lactate and oxygen uptake stabilizes within two to three minutes of exercise onset and is sustainable for a prolonged period. The removal of metabolic waste products (e.g., H\(^+\) ions, carbon dioxide [CO\(_2\)]) exceeds the rate of accumulation. Moderate-intensity exercise is primarily associated with the recruitment of slow oxidative muscle fibers (e.g., type I) that are fueled primarily by abundantly available free fatty acids (Carter et al., 2002; Jones et al., 2010). Pleasure is the characteristic affective response to moderate exercise. From an evolutionary perspective, the ability and desire to sustain moderate exertion for extended periods must have had some adaptive benefit, driven by selection forces and the development of requisite metabolic processes (Ekkekakis, 2003). This concept has been proposed by several theorists, including Cabanac (2006), who argued that sensory pleasure optimizes muscle efficiency and that positive affect promotes adaptive behavior, while negative affect promotes avoidant behaviors that threaten survival. Therefore, there was an adaptational selection advantage to performing moderate-intensity exercise, such as the primitive human practice of exhaustive hunting, and a mechanism evolved to promote this behavior (i.e., an affective response).

The heavy domain of exercise intensity includes intensity above the VT/LT and up to critical power (CP), measured using the three-minute all-out test or power-duration protocols, or up to the RCP, assessed using gas exchange during incremental exercise protocols. During heavy-intensity exercise, the rate of metabolite removal is equal to the rate of accumulation. In addition to slow-oxidative muscle fibers, additional fast-oxidative and nonoxidative fibers (e.g., types IIa and IIb) are recruited, and these fibers utilize the relatively limited stores of glycogen and circulating glucose. During heavy-intensity exercise, compensatory mechanisms, such as
ventilation, bicarbonate buffering, and muscle fiber recruitment, increase significantly to achieve a metabolic steady state. However, the steady state is delayed by the emergence of the VO$_2$ slow component, where the oxygen uptake lags slightly behind the metabolic demand; this is presumed to relate to the recruitment of type IIa muscle fibers. A steady state is typically achieved within 10–20 minutes, and it can be sustained for minutes to hours, depending on the level of fitness (Burnley & Jones, 2018). The affective response patterns during heavy-intensity exercise are heterogeneous (i.e., some people feel good and some people feel bad) (Ekkekakis et al., 2005a). Interindividual differences in affective responses during heavy-intensity exercise can be explained by dispositional trait factors, such as having a greater preference for or tolerance of high-intensity exercise compared to others. For example, individuals who score high on intensity-tolerance typically report greater pleasure during heavy-intensity exercise than those who score low (Ekkekakis et al., 2005b).

The CP/RCP mark the lower boundary of the *severe* domain of exercise intensity. The upper boundary is defined by exercise intensity during which exhaustion occurs without achieving VO$_{2\text{max}}$. During severe exercise, it is not possible to achieve a steady state because the VO$_2$ slow component rises to the VO$_{2\text{max}}$, followed by exhaustion. Other non-steady state metabolic responses (e.g., lactate, inorganic phosphate, creatine phosphate [PCr], and pH) also occur above the CP (Jones et al., 2008; Jones & Burnley, 2009; Vanhatalo et al., 2010). Severe-intensity exercise extends to the functional limit of muscle fiber recruitment, with the greatest reliance on fast nonoxidative metabolism, and it is characterized by the rapid depletion of glycogen. The accumulation of metabolites and the rapid decline in blood pH activates a negative feedback loop that inhibits several rate-limiting metabolic processes during glycolysis (e.g., PFK inhibition) and beta oxidation (Essén & Kaijser, 1978; Hollidge-Horvat et al., 1999).
Again, the sustainable duration of severe exercise depends on fitness (ranging from two to 40 minutes), but the precise time to exhaustion can be predicted by the curvature of the power–distance relationship using power-duration protocols or by the three-minute all-out test (Burnley & Jones, 2018; Moritani et al., 1981, 1993; Vanhatalo et al., 2007). During severe-intensity exercise, the majority of individuals report displeasure (Ekkekakis et al., 2004, 2005b; Hartman et al., 2019).

Finally, the extreme domain of exercise intensity is defined as intensity that is above the CP/RCP, where termination occurs before the VO$_2$ reaches VO$_{2\text{max}}$ (Hill et al., 2002; Özyener et al., 2001). The metabolic response during the onset of extreme-intensity exercise resembles the trajectory for the severe domain—that is, non-steady states for VO$_2$, PCr, pH, phosphagens, and lactate. However, metabolic demand is so high during extreme exercise that it exceeds the temporal response limit of several metabolic processes (glycolysis, transport of oxygen by hemoglobin, and bicarbonate buffering) (Jones et al., 2008). Some highly trained athletes can sustain extreme-intensity exercise for up to two minutes, corresponding to ~136% of their VO$_{2\text{max}}$ peak power (Hill et al., 2002). In less trained populations, fatigue is reached within 10–30 seconds at approximately 105% of VO$_{2\text{max}}$ peak power (Özyener et al., 2001). While affective responses during extreme-intensity exercise have not been specifically studied, presumably, affective responses would decline universally and at a higher rate during extreme-intensity exercise compared to severe-intensity exercise.

**Interoceptive Receptors and Primary Afferent Neurons**

The dorsal horn of the spinal cord is the ascending point of afferent interoceptive feedback from the viscera. Specifically, interoceptive cues, delivered via the lamina I spinothalamic and vagal afferent tracts, carry information to the homeostatic centers within the brain stem (Craig, 2002). Afferent feedback during exercise plays a critical role in the regulation
of performance and the prevention of damaging perturbations. For example, Amann and Dempsey (2016) showed that pacing ability during a cycling time trial was lost when they injected a pharmacological blocker of afferent neural inputs. In the absence of afferent feedback, metabolic acidosis reaches levels well beyond those achieved without pharmacological blockade. Under normal conditions, afferents detect homeostatic perturbations and relay this information to the brain. Consequently, the authors reported that significant homoeostatic disruption (e.g., blood pH < 7.0 and intracellular muscle glycogen < 25%) was associated with exacerbated fatigue.

In response to a large decline in pH, chemoreceptors fire rapidly at sufficient frequency to activate high-threshold afferent C-fibers, and this is processed in the brain as disruption within the internal milieu. Built-in redundancy causes interoceptive information to travel along two different paths. Firstly, information pertaining to organ function and homeostasis ascends via afferent cranial nerves (primarily the vagus nerve) that terminate within the NTS (Critchley & Harrison, 2013; Ottersen, 1980; Ricardo & Koh, 1978). Secondly, information pertaining to tissue damage from organs, which includes skeletal muscles (Critchley & Harrison, 2013), ascends the dorsal horn of the spinal cord, primarily via the lamina I neurons, and converges with cranial afferents within the NTS (Craig, 1996). Additional processing of interoceptive input occurs in several homeostatic regions, including the PB, which supports essential cardiovascular, respiratory, and metabolic maintenance (Bernard et al., 1996; Craig, 1996; Saper et al., 2002); the PAG, which is associated with affective processing (Silva & McNaughton, 2019) and nociception (Faull et al., 2019); the VLM, which is involved in the regulation of arterial blood pressure and respiration (Ciriello et al., 1994; Roder & Ciriello, 1993; Zardetto-Smith & Gray, 1995); and the PVN, which contributes to cardiovascular, respiratory, and hormonal regulation during exercise (Aggleton et al., 1980; Ottersen, 1980).
Information processed within the homeostatic regions projects to and converges at the amygdala, specifically at the lateral nucleus. Of more than a dozen nuclei in the amygdala, the lateral, basal, central, and medial nuclei are the principal ones. The amygdala encodes the biological significance of interoceptive stimuli (LeDoux, 2000; Phan et al., 2005; Sergerie et al., 2008; Zald, 2003). The functions of the amygdala nuclei are highly specialized. For example, the medial amygdala is associated with motor, olfactory, and sexual function, while the lateral nucleus is involved in affective reactivity (Amaral & Insausti, 1992; McDonald, 1992; O’Keefe & Bouma, 1969; Pandya et al., 1973). As the interoceptive information travels through the amygdala, the nuclei encode the biological significance of the stimulus as either “positive” or “negative” (Whalen, 1998). The lateral amygdala is the first nucleus to receive interoceptive information via projections from the subcortical homeostatic regions (Aggleton et al., 1980; Amaral & Insausti, 1992). Thereafter, the information passes through to the central nucleus of the amygdala and goes on to produce the required physiological responses in several modulatory systems of the autonomic nervous system (e.g., the release of NE, E, dopamine, and acetylcholine), which alters blood pressure, respiration, vasodilation, and constriction (LeDoux et al., 1988). The information also branches to the basal amygdala and projects to higher cortical regions, including the ventral striatum, the mPFC, and the orbital frontal cortex, for conscious processing of the affective significance of the information (Davidson, 2004; Le Doux, 2000).

Notably, the central nucleus of the amygdala receives additional interoceptive projections directly from the spine (Burstein & Potrebic, 1993; Menétrey & De Pommery, 1991) and the spinothalamic tract (Hodge & Apkarian, 1990; Ottersen & Ben-Ari, 1979), and, in so doing, bypasses several other subcortical processing regions (e.g., the PAG, PB, VLM, and PVN) that facilitate the startle response (Amaral & Insausti, 1992; Davis et al., 2008) and control the
autonomic response. This inherent redundancy in the interoceptive networks and the integration of interoception with affective processing is an indication of the biological importance of affect-laden interoception for survival.

**Dynamics of Cortical–Subcortical Affective Regulation**

The amygdala influences cortical processes, and there is evidence of bidirectional projections between the amygdala and the PFC (Turner et al., 1980). In addition to a direct neural connection between the amygdala and the DLPFC (Ghashghaei et al., 2007), the ventromedial PFC has neural connections to both the DLPFC and the amygdala. Both the DLPFC and ventral parts of the mPFC have also been implicated in the downregulation of amygdala function (Bouton, 2004).

In addition, there is substantial evidence of bi-directional communication between the amygdala and PFC (Aggleton et al., 1980; Amaral & Price, 1984; Barbas & De Olmos, 1990; Carmichael & Price, 1995; Hariri et al., 2000, 2003; Jacobson & Trojanowski, 1975; Morecraft et al., 1992; Nauta, 1962; Pandya et al., 1973; Porrino et al., 1981; Quirk et al., 2003; Van Hoesen, 1981) and the role of the PFC in regulating affect (Ochsner et al., 2002, 2004).

Non-exercise fMRI studies have identified increased activity in the DLPFC and mPFC during affect regulation (i.e., the up- or downregulation of pleasure/displeasure), which is closely coupled with the modulation of amygdala activity (Davidson, 2001, 2002; Jackson & Moghaddam, 2001). Interoceptive information processed by the amygdala has biological significance, however the PFC exerts regulatory control over the amygdala and modulates this significance by increasing or decreasing its activity (Le Doux, 1986, 2000; Ochsner et al., 2004; Whalen, 1998). In conjunction with the activity generated in several cortical and subcortical regions, the activity within the amygdala helps to facilitate the emergence of core affect. Ultimately, the PFC perceives and regulates affect, however, in the case of severe-intensity
exercise, the PFC enters a hypometabolic state of reduced activity and a relative decline in local oxygenation (Rooks et al., 2010). Presumably, physical deactivation limits the PFC’s ability to downregulate the amygdala; therefore, activation of the amygdala is increased through intensification of the interoceptive cues due to the increase in homeostatic perturbations caused by the exercise. Functionally, affective responses decline at a much faster rate than they would in cases where the PFC regulates amygdala activation. In fact, PFC hypometabolism is a common characteristic of clinical depression (Baxter et al., 1989; George et al., 1994; Koenigs & Grafman, 2009). A reduction in amygdala hyperactivity is a psychological effect of antidepressant drugs and cognitive–behavioral therapy. Thus, an increase in activity in the PFC attenuates the reactivity of the amygdala to threats (Furmark et al., 2002).

In addition to physiological responses, each domain of exercise intensity is characterized by a distinct pattern of affective responses. An affective response is defined by two bipolar dimensions, valence (pleasure-displeasure) and activation (high-low) (Russell, 1980). According to the DMT (Ekkekakis, 2003; Ekkekakis et al., 2005b), how an individual feels during exercise is influenced by the interplay of two factors, interoceptive information (e.g., afferent feedback from chemoreceptors and metaboreceptors) and cognitive factors (e.g., self-efficacy, experience with exercise, and motivation). The relative contribution of each differs across the intensity domains, and the physiological and psychological profiles of each domain reflect specific evolutionary adaptations that are beneficial to the survival of the human species.

In the context of exercise, the DMT may offer the most useful conceptualization of the mechanisms that underlie exertional fatigue. According to this theory, affective responses are the primary means by which the brain consciously monitors the status of the internal milieu. Affective responses during exercise are a function of two modes, top–down cortically mediated
cognitive factors (e.g., exercise self-efficacy and self-talk) and amygdala-mediated bottom-up interoceptive information. Each mode shares a common network of integration in the brain. The extent of each mode’s influence on changes in affective response systematically depends on exercise intensity and is directly related to the degree of homeostatic perturbation. Interoceptive contribution increases as a function of signal strength from sensory afferents in the periphery and is projected through the sensory thalamus and other areas. The stimulus (i.e., the degree of homeostatic perturbation) is interpreted, and this information is then sent to the amygdala, which assigns it a positive or negative affective quality (Ekkekakis & Acevedo, 2006).

At a relatively low intensity (i.e., moderate-intensity exercise below the VT), homeostatic perturbations are minimal, and cognitive factors account for most individual differences in affective responses. However, as exercise intensity increases and exceeds the VT, it is perceived as more challenging because the interoceptive cues (e.g., an elevated heart rate, increased core temperature, metabolite accumulation) become more salient. Above the VT, the cognitive and interoceptive factors exert approximately equal influence on the affective response; however, continued physical effort demands greater mobilization of cognitive resources. The increased allocation of cognitive resources limits the extent to which these resources can be devoted to other cognitive tasks. For example, during exercise above the VT, performance in cognitive tasks, such as the Stroop test, worsens significantly. Clearly, then, there is a limit to the capacity of the PFC to expend cognitive resources for the top–down regulation of increasingly powerful inputs from subcortical regions, such as the amygdala. Indeed, when exercise intensity exceeds the point at which the physiological steady state can no longer be maintained (i.e., the RCP) (Gaesser & Poole, 1996; Wasserman et al., 1973), severe metabolic perturbations (e.g., metabolite accumulation, fuel depletion, type II muscle fiber recruitment, heart rate acceleration,
and the VO$_2$ slow component) are relayed through intensified afferent signaling to the amygdala and are interpreted as threats to survival (Ekkekakis, 2003). At this intensity, the affective responses are driven primarily by the intensity of interoceptive projections into the amygdala; this causes hyperactivation and exceeds the limits of PFC top–down control. It follows that physical effort will cease when the displeasure associated with exercise becomes uncontrollable and overwhelming.

The variance in affective response that is accounted for by cognitive factors (e.g., self-efficacy) and individual differences in sensory modulation (e.g., intensity-tolerance and intensity-preference) also depends on exercise intensity. By definition, perturbations during moderate-intensity exercise are negotiable, and cognitive factors mostly drive positive affective responses. However, if the intensity is too high (i.e., severe-intensity exercise), interoceptive cues predominate and override cognitive processing, causing most individuals to report a large decline in affective valence, regardless of dispositional cognitive traits (Ekkekakis, 2005b).

Between individuals, affective responses are most variable when the relative influence of cognitive and interoceptive factors is changeable. This occurs when the intensity of the exercise presents an appreciable challenge (i.e., not too easy and not too difficult) with some level of perturbation. While these perturbations are not life threatening, they are nevertheless pervasive, and a measure of PFC attentional capacity is expended to determine whether the stimulus is good or bad (depending on dispositional traits). In short, cognitive factors determine a range of dispositional traits that are associated with affect regulation. For example, individuals with a preference for or tolerance of high-intensity exercise typically report deriving unwavering or increased pleasure from such exercise (Ekkekakis, 2003; Ekkekakis et al., 2005a). It seems likely that this relates either to a person’s capacity to cognitively downregulate interoceptive stimuli or
there is less bottom–up input from the amygdala (e.g., individual differences in amygdala reactivity). Conversely, it is likely that individuals with a low preference or tolerance for challenging exercise would report less positive or more negative affect during heavy exercise; presumably, this reflects reduced PFC mediation of the interoceptive cues.

**Hemispheric Laterality in Affective Regulation**

The PFC contains multiple subregions, and each hemisphere specializes in different functions. More broadly speaking, the PFC serves numerous executive functions responsible for processes involving response execution, memory retrieval, affective response evaluation and regulation, goal orientation, attentional focus, sensory interpretation, etc. In the context of affective processing, competing hypotheses explain hemispheric specialization. According to perception models, the right PFC is involved in the regulation of displeasure and avoidance, whereas the left PFC is involved in pleasure and approach (Coan et al., 2001; Cunningham et al., 2005; Reuter-Lorentz & Davidson, 1981). This implies that since the right hemisphere is primarily involved with perceptions of displeasure, it must also be involved in perceptions of fatigue, when using the definition of exertional physical fatigue by Hartman et al. (2019). However, other studies suggest that the right PFC is involved in both pleasure and displeasure (Leventhal & Tomarken, 1986; Silberman & Weingartner, 1986), while others link left PFC functioning to displeasure (Hagemann et al., 1998). Using the perception model of hemispheric specialization, a more direct physical manipulation of hemisphere function was tested by Terzian and Cecotto (1959). The researchers injected of sodium amytal into the right carotid artery, thus temporarily suppressing the brain activity in the right hemisphere, leading to acute depressive symptoms (including fatigue). A subsequent injection of the same barbiturate derivative into the left carotid artery temporarily suppressed brain activity in the left hemisphere, causing acute euphoria. The mechanisms of the depressive and euphoric symptoms were virtually impossible
to explain because the injections deactivated an entire brain hemisphere. This study, among other perception model studies, led researchers to question whether affective processing is a passive task or whether active, regulatory processes are more important.

If affective processing is an active task, it is assumed that the cognitive regulation of affect, to some degree, is constantly occurring, in addition to perceiving the affective state. According to cognitive regulation models, PFC hemispheric specialization is a function of the interaction between stimulus valence and the individual’s regulation goal (i.e., increase, decrease, or maintain the affective state). For example, when the participants viewed positively valanced images and were instructed to increase their feelings of pleasure (e.g., imagining themselves being a part of, and enjoying the scenario portrayed by the images), greater activation was shown to occur in the left DLPFC compared to the right (Li et al., 2009; Vanderhasselt et al., 2013). In contrast, when participants were instructed to increase their feelings of displeasure while viewing negatively valanced images (e.g., imagining the tragedy portrayed in the image involved a close family member), a greater activation was observed in the right DLPFC compared to the left (Feeser et al., 2014). However, other studies have demonstrated that actively decreasing feelings of displeasure while viewing negatively valanced images engages both the right and the left DLPFC, in addition to several other PFC regions (Ochsner et al., 2002; Ochsner & Gross, 2005). Similarly, actively decreasing feelings of displeasure while viewing negatively valanced images has been shown to involve both hemispheres (Davidson et al., 1990). It is likely that inconsistent findings for cerebral asymmetry can be attributed to individual differences in cognitive regulation ability that have not been taken into account, along with the type of regulation goals evaluated in the experiments (Davidson & Irwin, 1999). For example, affective valence can be upregulated (e.g., by intentionally increasing feelings of pleasure or displeasure),
downregulated (e.g., by intentionally decreasing feelings of pleasure or displeasure), or maintained; the associated processes likely involve both overlapping and distinct neural networks (Eippert et al., 2007; Giuliani et al., 2008; Li et al., 2018; Ochsner et al., 2002). In addition, language proficiency is associated with the ability to regulate emotional states (Eisenberg et al., 2005). A variety of dispositional traits are known to influence one’s emotional regulation style and ability (Gross & John, 2003).

The approach–avoidance motivational system is associated with emotional regulation but has a unique contribution to PFC asymmetry. Approach–avoidance behavior is defined as the motivational tendency to move toward or away from something (Lazarus, 1991). Asymmetric prefrontal activation is observed depending on which motivation is engaged, either to approach or avoid a stimulus (Davidson et al., 1990; Spielberg et al., 2008, 2011). Although affective responses and approach–avoidance motivation are two distinct concepts, they are related; in fact, it is difficult to isolate their independent effects from a methodological standpoint (Davidson, 1993). In general, a pleasant stimulus evokes the motivational tendency to approach, whereas an unpleasant stimulus induces a motivational tendency to avoid. One key to isolating the presumed affective and motivational functions of PFC asymmetry, would be knowing the causal functional significance to the observed asymmetry. One way to achieve this is the direct experimental manipulation of PFC activity. For example, using transcranial direct-current stimulation (tDCS), anode (positive electric charge) stimulation of the left DLPFC, and cathode (negative electric charge) stimulation of the right DLPFC can augment cognitive regulation of valenced stimuli. In a tDCS study by Feeser et al. (2014), participants viewed negative valanced images and were instructed to either downregulate feelings of displeasure or upregulate feelings of displeasure. When participants performed these tasks while receiving anodal stimulation of the right DLPFC,
negative affective states were attenuated compared to placebo/sham stimulation. However, when participants were asked to upregulate their displeasure, the anodal stimulation of the right DLPFC potentiated the negative affective state compared to placebo/sham (Feeser et al., 2014). The effect of stimulating the left DLPFC on cognitive regulatory goal was examined by Vander Hasselt et al. (2013). The authors found that anodal tDCS of the left DLPFC enhanced the ability to cognitively regulate both positive and negative valanced stimuli. While the effects of DLPFC stimulation may overlap in terms of how each hemisphere responds to a particular regulatory goal in moderating pleasure or displeasure, overall, both hemispheres appear to be involved in the regulation of displeasure.

**Cortical Hemodynamic Activity During Exercise**

Modern neuroimaging technologies facilitate investigation of the neurophysiological processes that underlie self-reported psychological states. While there is extensive psychological literature on the association between brain activity and cognitive performance, brain function during exercise remains a neglected area of research. This, in part, reflects the limitations of many imaging technologies; neuroimaging techniques are highly susceptible to motion-related artifacts (e.g., electroencephalogram, magnetoencephalography, and fMRI), are constrained by temporal resolution (e.g., PET and SPECT), or are confined to pre and post assessments (Ekkekakis, 2009a). Some of the more advanced fMRI software packages include motion tracking and stabilization methods that can significantly reduce the influence of motion-related artifacts. However, for anything beyond light-intensity exercise, fMRI cannot distinguish between global perfusion changes caused by a cardiovascular response and local neurovascular coupling caused by focal neural activity. Additionally, fMRI is not capable of continuous recording; it is only able to capture epochs of 1–2 seconds, separated by minutes or more.
To date, NIRS is the most viable neuroimaging device for observing brain states during exercise (Boone et al., 2016; Ekkekakis, 2009a; Perrey, 2012; Quaresima & Ferrari, 2016). The advantage of NIRS is its reduced sensitivity to motion-related artifacts; therefore, it is usable during high-intensity exercise (Ekkekakis, 2009a). Typically, the quality of NIRS data is preserved during most exercise modalities (e.g., running, cycling, and basketball) and during performance at most levels of intensity (Rooks et al., 2010). In addition, the temporal resolution of NIRS is high (up to 100 Hz), and it records continuously. Therefore, changes in the activity of specific brain regions can be compared in real time during physical exertion. A variety of NIRS preprocessing and filtering methods, when utilized, are able to partially account for the systemic physiological changes that occur during exercise (i.e., changes in heart rate, blood pressure, and ventilation), motion-related artifacts, and other sources of nonhemodynamic-related signal interference (Pinti et al., 2019; Scholkmann et al., 2014).

The mathematical principles and physics of NIRS have been extensively reviewed elsewhere (Cope et al., 1988; Devor et al., 2012; Ekkekakis, 2009; Ferrari & Quaresima, 2012; Jobsis, 1977; Leff et al., 2011; Pellicer & Bravo, 2011; Perrey, 2012; Quaresima & Ferrari, 2016; Scholkmann et al., 2014). NIRS detects changes in hemoglobin species (concentration of oxygenated hemoglobin [O$_2$Hb], deoxygenated hemoglobin [HHb], and total hemoglobin [THb]) that accompany neuronal activity and associated processes (i.e., metabolic processes of the neurons, astrocytes, and glial cells). According to the principle of neurovascular coupling, increased neural activity metabolizes more oxygen, while the extraction of this oxygen from the O$_2$Hb yields a greater concentration of HHb within the region and triggers neurometabolic demand for an increase in blood flow to supply more oxygen via O$_2$Hb (Buxton, 2002; Buxton & Frank, 1997; Raichle & Mintun, 2006; Wong et al., 1998). The initial effect of the neural activity
increases local HHb concentrations, while simultaneously reducing local O$_2$Hb concentrations. However, the change in hemoglobin concentration mediates the neurovascular response, which causes dilation of the endothelial cells proximal to the neural activity. Subsequently, localized blood flow and blood volume increase, thereby causing the concentration of O$_2$Hb to increase and that of HHb to decrease. NIRS is used to measure this localized neurovascular response. A change in global blood perfusion versus a localized hemodynamic change due to neurovascular coupling can be differentiated because NIRS is able to measure both hemoglobin species. It is difficult to differentiate between local and global changes by only examining the change in concentration for a single hemoglobin species. For example, changes in O$_2$Hb concentration could reflect cortical activation. At the same time, blood pressure and scalp vasodilation also demonstrate an increase in O$_2$Hb. Furthermore, changes in HHb may reflect cortical activation, but this also occurs in response to global ischemia. Likewise, changes in THb (an increase in both O$_2$Hb and HHb) occur in response to a global increase in blood perfusion. Therefore, when measured using NIRS, a local neurovascular process is indicated when there is an observed increase in O$_2$Hb, along with a decrease in HHb. A tissue oxygenation index (TOI) can be used to express changes in O$_2$Hb relative to changes in THb (O$_2$Hb·THb$^{-1}$). When applying this approach to data consolidation, in theory, a change in TOI represents a local change in brain activity (Al-Rawi & Kirkpatrick, 2006).

In the context of exercise, the assessment of PFC activity using NIRS is common. Pragmatically, the reduced interference of scalp hair is an advantage of evaluating the PFC region for achieving optimal signal transmission and reception. Neurologically, the PFC is hierarchically organized to regulate and control cortical (e.g., motor cortex [MC]) and subcortical regions (e.g., amygdala). While the MC is principally important in relation to muscle
movement, the PFC regulates and initiates most MC responses (Fuster et al., 1982; Goldman-Rakic, 1987; Lu et al., 1994; Quintana et al., 1989). In other words, the higher-order decision to engage in an action is commanded by the PFC and is therefore of greater relevance to understanding the genesis of movement. However, a major drawback of research into the effect of exercise on the brain is that distinctions are not usually made between changes in global cerebral perfusion and those in localized neurovascular coupling caused by neural activity (Buxton, 2002; Buxton & Frank, 1997; Hoshi & Tamura, 1993; Raichle & Mintun, 2006; Villringer, 1997; Wolf et al., 2011). It is well-known in cognitive neuroscience that functional differences exist within PFC subdivisions (Bianchi & MacDougall, 1922; Fuster et al., 1982; Fuster & Alexander, 1971; Miller & Cohen, 2001; Rolls, 2000). The activity patterns within different PFC regions are indicative of specific cognitive and behavioral processes. Brain functions are not isolated; most functions are mediated by brain region systems that work together (Rolls & Treves, 1997). Nonetheless, for a given function, within a complex brain network, the brain regions that contribute to the network can be determined according to functions that contribute to a given process or those that are detected during cognitive and emotional processes.

Exercise does not simply produce global changes in blood flow due to cardiovascular effects. In addition, the hemodynamic response differs depending on the brain region examined. For example, during exercise, the hemodynamic responses in the PFC, MC, and occipital cortex are significantly different, which suggests that NIRS detects region-specific changes in cortical activity rather than changes in cardiovascular activity caused by exercise (Jung et al., 2015). It follows that if NIRS detects region-specific changes during exercise, then NIRS is also capable of detecting localized activation differences. The implication is that, depending on where the
NIRS sensors are placed, the underlying brain region being measured will reflect hemodynamic changes specific to functional differences (possibly) related to changes in the psychological and behavioral phenomena associated with that area. Therefore, the observed dose–response relationship between regional PFC hemodynamic activity and exercise intensity is an indication that the dose–response relationship within specific functional brain regions relates to specific mental processes (i.e., pleasure–displeasure, appraisal, cognitive regulation, and associative/dissociative thoughts).

There are a few notable limitations to using NIRS. Firstly, the depth of measurement is confined to superficial layers of the cerebral cortex (i.e., a penetration depth of 1–2 cm under ideal conditions). Secondly, many cortical regions are difficult to assess using NIRS due to significant signal interference encountered by infrared light as it travels through scalp hair. Therefore, most cerebral NIRS researchers access the brain through the forehead (i.e., over the PFC) (Balconi & Molteni, 2016; Ekkekakis, 2009a; Ferrari & Quaresima, 2012; Rooks et al., 2010). However, techniques have been developed to mitigate the interference of scalp hair (Subudhi et al., 2009), and other cortical regions have been examined (e.g., MC areas).

The degree to which scalp blood flow influences NIRS cerebral hemodynamic measurement is open to debate (Byun et al., 2014; Ekkekakis, 2009a; Elwell et al., 1994; Miyazawa et al., 2013). Studies using radioactive tracers to track exercise-induced blood redistribution reported no changes in forehead blood volume after exercise (Froelich et al., 1988; Rowell, 1988; Sandler et al., 1984). However, radioactive tracer studies cannot measure blood redistribution during exercise; they can only do so before and after exercise. Considering that several characteristics of the microvasculature vary depending on the body region, the temporal response of forehead cutaneous tissue might be complete by the time tracers are imaged (Rowell,
1988). Using high-temporal resolution devices, such as Doppler ultrasound, the increase in scalp blood flux during exercise is significant. However, a significant change in Doppler data may not necessarily equate to a significant change in NIRS data since these devices measure different phenomena. Doppler measures blood (plasma, erythrocytes, leukocytes, and thrombocytes) flux within the cutaneous tissue down to a maximal depth of approximately 1 mm, whereas NIRS measures hemoglobin concentrations within any tissue down to a maximal depth of approximately 1–3 cm.

When measuring cortical hemodynamic activity with NIRS, the common assumption is that part of the signal is influenced by scalp blood flow (Auger et al., 2016; Balconi & Molteni, 2016; Boone et al., 2016; Ekkekakis, 2009a; Ferrari & Quaresima, 2012; Scholkmann et al., 2014; Smith & Ainslie, 2017; Takahashi et al., 2011). At rest, cortical hemodynamic activity represents 39–69% of the NIRS signal if the sensor has an optode separation distance of between 3.0 cm and 4.0 cm (Germon et al., 1994, 1998; Kohri et al., 2002). The other 20–40% of the signal artifact is partly due to non-hemoglobin chromophores (e.g., water, lipids, bone, and cerebral spinal fluid) and partly due to extra-cerebral hemoglobin contained within the subcutaneous scalp capillaries (Takahashi et al., 2011), superficial skull veins (Dehaes et al., 2011), and skull bone marrow (Firbank et al., 1998; Fukui et al., 2003). What is uncertain is whether the cortical hemodynamic contribution (i.e., 39–69%) to the NIRS signal holds constant across all intensities of exercise. In theory, NIRS-derived cortical hemodynamic activity could be amplified or masked due to disproportional changes in scalp blood flow. Even if a NIRS sensor has an adequate optode separation distance (i.e., of > 3 cm), the photons will always pass through the scalp and inevitably interact with the hemoglobin contained in the subcutaneous capillaries and extracerebral veins of the forehead. In theory, increased cutaneous blood flow is
accompanied by increased cutaneous venous volume, which potentially alters the oxyhemoglobin and deoxyhemoglobin concentrations. Another consideration that is unique to the exercise context is whether the concentration of water within the observed tissue remains constant, which is a principal assumption of NIRS. During exercise, blood plasma water concentration changes in two major ways that alters the relative concentration of hemoglobin: (1) hydrostatic and osmotic effects cause a portion of blood plasma water to perfuse into the interstitial compartments, thereby increasing the relative concentration of hemoglobin in the blood, and (2) the reduction in blood plasma volume due to sweating, thereby increasing the relative concentration of hemoglobin in the blood (Matcher & Cooper, 1994). It is not clear how much the NIRS signal would be altered by normal (i.e., during a standard incremental exercise test) changes in plasma blood volume. However, the change in blood plasma volume during exercise is notable and the magnitude of the effect does vary between individuals. For example, plasma volume changes (a maximum of 19% and 12%) were demonstrated to be greater in untrained than in trained cyclists, respectively, during incremental exercise (Sullivan et al., 1993).

Changes in water concentration not only affect the relative concentrations of hemoglobin that NIRS detects, but changes in blood water concentration violates a mathematical principle of NIRS, in which water in the blood is assumed to be constant (~70%). The absorption coefficients for water overlap with the absorption coefficients for $O_2Hb$ (~ 830 nm) within the “NIRS window.” In fact, the absorption coefficient for water at 830 nm is approximately half of the $O_2Hb$ absorption coefficient (i.e., ~50% of the raw $O_2Hb$ signal is water). However, this overlap between water and $O_2Hb$ is taken into account when calculating the $O_2Hb$ concentration using the modified Beer-Lambert Law (Cope & Delply, 1988; Delpy et al., 1988). Because NIRS
operates under the principle assumption that the water concentration is constant (~70% of blood plasma), the concentration of $O_2Hb$ is derived by essentially subtracting the absorption due to water (a fixed concentration of water) from the 830 nm absorption data (Boushel et al., 2001). In purely mathematical terms, a reduction in blood plasma water would yield a NIRS calculation with an inflated $O_2Hb$ concentration.

Several attempts have been made to reduce the influence of non-cortically derived hemodynamic activity on the NIRS signal. Multi-distance frequency-domain NIRS devices are relatively insensitive to superficial tissue layers owing to the considerable photon–hemoglobin interaction that occurs at the deepest penetration depth (i.e., the photon path apex) (Franceschini et al., 1998). There is general agreement that the minimum optode separation is 3.0 cm for adequate noise-to-signal artifacts; with anything less, the percentage of the signal that is derived from non-cortical hemodynamic activity becomes larger than the percentage represented by cortical hemodynamic activity (Gagnon et al., 2012; Germon et al., 1994, 1998). Therefore, at very short optode separation distances (e.g., < 1.0 cm), presumably the data would reflect only superficial non-cortically derived hemodynamic changes. Researchers have capitalized on this effect by developing the “short–long channel” technique, whereby the hemodynamic signal detected by the shorter optodes is regressed out from the signal of longer distance optodes (> 3.0 cm) (Cope et al., 1988; Gagnon et al., 2012). The use of multi-channel NIRS that simultaneously records short separation distances (e.g., 0.5–1.0 cm) and long separation distances (3.0–5.0 cm) facilitates the ability to obtain a known measurement of purely superficial non-cortical hemodynamic activity.

With NIRS, significant progress has been made in understanding the dose–response relationship between exercise intensity and global PFC hemodynamic activity. A meta-analysis
on PFC oxygenation during incremental exercise (Rooks et al., 2010) reported a clear dose–response relationship; cortical oxygenation increased from a “Low” intensity (< 30% of VO$_{2\text{max}}$) to a “Hard” intensity (> 60% of VO$_{2\text{max}}$ to below VO$_{2\text{max}}$), and then it began to decrease at a “Very Hard” intensity (equivalent to or higher than VO$_{2\text{max}}$). A consistent finding of this review was that cortical oxygenation typically decreased at specific metabolic landmarks (e.g., the RCP). The participants in these studies usually terminated the exercise test when PFC oxygenation was at its most pronounced decline relative to the peak or when the oxygenation dropped below the baseline level. Several reasons have been provided to explain the decline in PFC oxygenation. For example, a change in global brain perfusion, such as the reallocation of blood supply (Dietrich, 2003, 2006), a reduction in the cerebral blood pressure (Ogoh & Ainslie, 2009; Smith & Ainslie, 2017), the onset of cerebral ischemia (Noakes et al., 2001), and elevated arterial carbon dioxide concentration (Ogoh et al., 2005). Alternatively, from an evolutionary perceptive, the reason why the PFC enters a hypometabolic state near the limit of exercise tolerance is that the response is a reflexive protective mechanism whereby the autonomic subcortical brain regions involved in preserving hemostasis (possibly the amygdala) exerts an unstoppable inhibitory effect (bottom–up regulation) on the PFC, reducing the drive from the PFC to pre-motor cortex, and effectively terminating the exertion.

**Indirect Measure of Subcortical Activity: Affective Modulation of the Acoustic Startle Eyeblink**

In response to an intense and sudden auditory stimulus, humans rapidly produce several involuntary muscle movements (e.g., flinching), known as the *acoustic startle response* (Hunt, 1936; Hunt & Landis, 1936; Landis & Hunt, 1939, 1936). Characterized as an unconditioned reflex, the onset of the acoustic startle response usually takes place within 30–50 milliseconds (ms) of the startle stimulus (Jäncke et al., 1994). This response functions as a defensive reflex
and activates several autonomic functions to facilitate escape or protection—in other words, the initial stage of the “fight or flight” response (Lang, 1995; Leaton & Borszcz, 1985). Typically, only an intense startle stimulus elicits a whole body reaction. Landis and Hunt (1936) noted that the repeated presentation of a startle stimulus habituated the whole-body response over time, with the notable exception of the eyeblink component, which was more resistant to habituation. Since the early experiments conducted by Landis and Hunt (1936, 1937, 1939), the whole-body startle response has rarely been investigated, and the eyeblink response is now considered the “gold standard” for quantifying startle and is the most consistent and reliable component of the response (Berg & Balaban, 1999; Blumenthal et al., 2005; Dawson et al., 2008).

In the context of psychophysiology, the startle paradigm has been used to study a wide range of sensory, cognitive, and affective processes (Yeomans et al., 2002). Defining parameters include response amplitude (i.e., the speed of eyelid closure) and latency (i.e., the time taken from the stimulus to the blink onset), both of which are modified by intra- and inter-individual factors. For example, individual differences in startle amplitude are associated with affective reactivity (Blumenthal et al., 1995; Cook et al., 1991) and the presence of a clinical or neurological disorder (Grillon et al., 1994; Morris et al., 1991; Schlenker et al., 1995).

Acute modulation of startle eyeblink amplitude within individuals has been extensively studied in the context of affective science. When processing affective stimuli, eyeblink amplitude is modulated by content valence; specifically, the amplitude increases when an acoustic startle stimulus is presented while viewing unpleasant images, and it diminishes when viewing pleasant images (Balaban & Taussig, 1994; Bradley et al., 1996b, 1996a; Bradley & Lang, 2000; Corr et al., 1997; Lang et al., 1990; Vrana & Lang, 1990). The effect of affective modulation is most robust between images with polar opposite valence (i.e., pleasant vs. unpleasant content).
However, there are notably inconsistencies across studies that compared pleasant or unpleasant images with neutral images. Some studies find no difference in the ASER between neutral and pleasant images (Bradley et al., 1996a; Corr et al., 1997; Vrana & Lang, 1990), neutral and unpleasant images (Bradley et al., 1993, 1999, 2001; Corr et al., 1997; Vrana et al., 1988), and pleasant and unpleasant images (Balaban & Taussig, 1994; Bernat et al., 2006; Bradley et al., 1996b; Cuthbert et al., 1996).

Since “neutral” is not an affective state, the effect of "neutrally" valenced images may be trivial and therefore irrelevant in the context of affective responses. Conceptualizing the ASER as an index used to differentiate between affective states (e.g., pleasure–displeasure), is a more valuable method of evaluating the startle effect. Using this approach, an attenuated ASER modulated by pleasant affect indicates utility and a propensity to approach the stimulus, while a potentiated ASER modulated by unpleasant affect signifies danger and facilitates avoidance of the stimulus (Cabanac, 1979; Panksepp, 2005). The organism’s approach–avoidance motivation is underpinned by the affective state (Zajonc, 1980). Other theoretical positions have sought to distinguish approach–avoidance motivation from affect, which is portrayed either as a secondary phenomenon or a parallel process.

The controversy around these frameworks, and what the affect modulation of the ASER best represents, remains. However, there is broad consensus that the affect–startle effect is the result of the integration of exteroceptive (e.g., auditory) afferent neural pathways and efferent motor control pathways in the subcortical brain regions that are associated with the processing of affective information. For instance, prior to processing a visual stimulus in the visual cortex, the raw and rudimentary sensory input is sent to the thalamus for basic sensory gating. If the thalamus does not filter this information out, it is sent to the basolateral nucleus of the amygdala,
where its adaptive significance (or lack thereof) is processed and coded as positive or negative. The information is then relayed to the central nucleus of the amygdala, which produces an appropriate physiological response (e.g., pleasant–approach, unpleasant–avoid). The central nucleus also mediates several efferent motor pathways, including the eyelid muscles (Lang & Bradley, 2008, p. 54). By the time the stimulus information reaches the ventral striatum and the visual and prefrontal cortices, the stimulus has already been assigned “significance” by the pre-processed affective label from the subcortical regions.

The standard method in ASER studies to measure the muscle activity of the eyelid (e.g., orbicularis oculi) is using EMG (Blumenthal et al., 2005). With EMG, the ASER has an onset range of ~30–60 ms from the time the acoustic stimulus is delivered. This is followed by rapid contraction of the orbicularis oculi muscle, causing an increase in the eyelid muscle activity, which peaks just before closure. The orbicularis oculi muscle then relaxes, which causes the eyelid to reopen. The speed of eyelid closure corresponds directly with the strength of orbicularis oculi muscle activity, measured as the motor unit electrical activity using EMG. This method measures the frequency and strength (summation) of orbicularis oculi muscle action potential, which produces a peak waveform during peak contraction as a measure of startle eyeblink amplitude. A larger amplitude recruits a greater number of muscle fibers in the orbicularis oculi muscle, which elicits stronger contraction and a more rapid closure of the eyelid than that observed with smaller startle responses (Blumenthal et al., 2005).

Although EMG is widely accepted as a valid method of studying the affective modulation of startle, its use during exercise confers major limitations. For example, EMG is highly sensitive to movement artifacts, and, during exercise, excessive extraneous movements are practically unavoidable, especially during high-intensity exercise. In addition, facial movements, such as
grimacing or mouth/cheek movements due to labored breathing, significantly interfere with the EMG signal. Infrared reflectance oculography (IOG) is an alternative method of eyeblink measurement. An IOG device contains a small probe that is fitted with an infrared emitter and detector. Positioned at the participant’s eye level, the sensor emits infrared light and the detector monitors the amount of infrared light reflected from the eye back to the detector. During a blink, the eyelid movement disrupts the amount of infrared light reflected by the eye (i.e., less light is received by the detector), which is proportional to the degree of eyelid closure. Integrated over time, the degree of eyelid closure produces a waveform with a peak positive amplitude that corresponds to the peak velocity of the closing eyelid. Following eyelid closure, reopening of the eyelid produces a negative amplitude waveform that returns to baseline levels as the eyelid opens (Johns et al., 2007; Perez et al., 2011). The primary difference between IOG and EMG pertains to what each device physically measures. IOG tracks the actual lid closure itself, while EMG records the intensity of the motor signal sent to the muscle that closes the eyelid, regardless of the extent of actual lid closure. The responses measured by IOG and EMG are significantly correlated ($r = 0.58–0.81$) (Anders et al., 2004), although the eyeblink response latency is slightly delayed when measured with IOG compare to EMG ($\sim 60$ ms) (Lovelace et al., 2006).

The terminology used by human ASER EMG researchers identifies the startle response as a “blink,” which implies actual lid movement; however, movement of the eyelid is affected by the position of the eyeball. In other words, it relates to where the person is gazing or fixating. For instance, looking up or down while blinking produces different eyelid closure speeds. This would not be associated with a difference in the EMG signal, but it could possibly affect the IOG signal (Hillman et al., 2005).
Cortical Modulation: Transcranial Direct Current Stimulation

tDCS is a brain stimulation method that is used to noninvasively modulate local neuronal activity. Scalp electrodes (typically 20–35 cm²) are placed over a region of interest and emit a continuous low-level current (~ 9 V, 0.5–2.0 mA) that typically lasts from 10–30 minutes for a single session. The effect of the current on the brain tissue is polarity dependent. Specifically, anodal (positive charge) current depolarizes the neuronal membrane, thereby increasing cortical excitability, whereas cathodal (negative charge) current hyperpolarizes the neuronal membrane, thereby decreasing cortical excitability (Bindman et al., 1964; Nitsche & Paulus, 2000). In addition, anodal stimulation increases the concentration of cortical oxyhemoglobin proximal to the stimulating electrode when measured using NIRS (Merzagora et al., 2010; Zheng et al., 2011) and fMRI (Jang et al., 2009; Kesser et al., 2011). Temporally, the effect of tDCS is dependent on the size of the electrodes, location of the reference electrode (cranial or extracranial), and current density (Coffman et al., 2014). Individual characteristics, such as skull thickness, hair cover, superficial vein innervation, mental state, and drug use, can affect the efficacy of tDCS.

In the short term, a tDCS device can alter neuronal membrane potential by modulating the voltage-gated ion channels, namely the sodium and calcium channels of GABAergic (gamma aminobutyric acid) and glutaminergic neurons (Liebetanz et al., 2002; Nitsche et al., 2003, 2004; Stagg & Nitsche, 2011). Currently, the most studied brain regions in tDCS research are the cortical regions (Dedoncker et al., 2016; Dissanayaka et al., 2017; Holgado, Vadillo, et al., 2019; Machado et al., 2019). This is primarily because, with most montages, tDCS current rarely penetrates beyond the cortical layers (Nitsche et al., 2008). However, there is some evidence that tDCS current can penetrate deeply enough to affect cortical–subcortical connectivity with a specific montage (Weber et al., 2014). Some have also proposed that tDCS may directly
modulate specific subcortical regions (Chhatbar et al., 2018; Polania et al., 2012). At the cortical level, neurophysiological studies have demonstrated that the superficial cortical layers are less affected by anodal tDCS than the deeper layers (Chan et al., 1988; Yazdan-Shahmorad, Kipke, Lehmkuhle, 2011), an effect that is opposite to what is expected given that an electrical current diminishes in strength further away from its source. According to a modeling study, tDCS had a heterogenous effect across six layers of the cortex (Radman et al., 2009). Deep cortical layers IV and V contain nonsymmetric dendritic pyramidal cells, which tend to be larger in size and have a higher tissue density owing to the substantial dendritic overlap and increased interconnections, compared to the more superficial layers (Das et al., 2016). When combined, the effect of these morphological characteristics at layers IV and V results in a neural membrane with a relatively high sensitivity to subthreshold polarization. In contrast, the cells within superficial layers II/III are smaller, more symmetrical, and less numerous; consequently, the effect of a subthreshold electric field on the membrane is relatively small (Chan et al., 1988; Hern et al., 1962). Notably, the neurons within cortical layer IV comprise the bulk of the connection with the thalamic nuclei; likewise, layer V innervates the amygdala and several other basal ganglia nuclei (Amaral & Price, 1984; Krettek & Price, 1977; Sherman & Guillery, 1998). Therefore, tDCS appears to preferentially influence key layers of the cortical cytoarchitecture containing anatomical projections to the subcortical circuits.

Long-term tDCS interventions produce lasting changes in cortical plasticity (Jamil et al., 2017). tDCS plasticity is driven by the modulation of N-methyl-D-aspartate glutamate receptors (Liebetanz et al., 2002; Nitsche et al., 2003) and the modulation of certain polymorphisms of the brain-derived neurotropic factor gene, a major regulator of neuroplasticity (Fritsch et al., 2010). In addition, the effects of tDCS plasticity modify the cerebral regulation of dopamine,
acetylcholine, and serotonin (Kuo et al., 2008, 2014; Monte-Silva et al., 2009; Nitsche, Kuo, et al., 2009).

A typical acute stimulation session ranges from 10–30 minutes in duration. Once stimulation begins, the electrophysiological effects are almost immediate and can last up to several hours after the session (Bindman et al., 1964; Hunter et al., 2013; Nitsche et al., 2008; Stagg & Nitsche, 2011). The amount of electrical current that enters the brain is variable. Overall, studies on monkeys and humans have demonstrated that approximately 50% of the current emitted by a tDCS electrode enters the brain (Dymond et al., 1975; Rush & Driscoll, 1968), and fMRI studies have confirmed its neurophysiological effects (Antal et al., 2011; Jang et al., 2009; Keeser et al., 2011; Weber et al., 2014).

tDCS has been extensively investigated in numerous clinical and cognitive studies that tested sensorimotor and cognitive functions (Holgado, Vadillo, et al., 2019; Machado et al., 2019; Nitsche & Paulus, 2000; Priori et al., 1998; Schlaug & Renga, 2008; Steinberg et al., 2019). As an adjunct treatment in clinical neurological disorders, tDCS improves the symptoms of depression (Kalu et al., 2012; Nitsche, Boggio, et al., 2009), acute and chronic pain (Antal et al., 2008; Mori et al., 2010), Parkinson’s disease (Boggio et al., 2006; Fregni et al., 2006), Alzheimer’s disease (Bystad et al., 2016; Ferrucci et al., 2008), stroke (Lindenberg et al., 2010), and fatigue associated with multiple sclerosis (Chalah et al., 2017). Anodal tDCS of the DLPFC enhances working memory (Javadi & Walsh, 2012), improves response inhibition (Beeli et al., 2008), reduces food cravings (Goldman et al., 2011), and decreases pain perception induced by electrical shock (Boggio et al., 2008), as well as pain perception induced by noxious heat (Aslaksen et al., 2014). tDCS also enhances emotional control (Ironside et al., 2019) and the
neuropsychological effects of cognitive reappraisal, which has the result of either increasing or decreasing emotional responsiveness, depending on the regulatory goal (Feeser et al., 2014).

Studies have used tDCS in the context of exercise, both for its effects on psychological responses and performance measures. In the context of exercise, a meta-analysis of tDCS studies that stimulated M1 reported a small effect or no effect on performance (Holgado et al., 2019). Objective and subjective indices of exercise performance were also examined by the meta-analysis and overall tDCS (across all brain regions examined) yielded a small positive effect on performance. However, of the 24 studies included in the meta-analysis, only four focused on the PFC (most studies targeted M1). Of the studies that performed PFC stimulation, only two evaluated full-body exercise.

Holgado et al. (2019) examined cathodal and sham tDCS of the left DLPFC during a 20-minute self-paced cycling time trial in trained cyclists, with no difference in performance or ratings of perceived exertion (RPE). Lattari et al. (2018) assessed anodal and sham tDCS of the left DLPFC during cycling exercise at a 100% of VO$_{2\text{max}}$ until volitional termination. The authors reported that anodal stimulation significantly increased performance by 62.4 seconds, with no differences in the RPE. Another meta-analysis conducted by Machado et al. (2019) reviewed 22 studies examining the effect of tDCS on exercise performance. However, only seven of the 22 studies examined full-body aerobic exercise, of which only one study (Lattari et al., 2018) used tDCS on the PFC. The Lattari et al (2018) study reported that anodal tDCS over the left DLPFC significantly improved time to exhaustion (+62.4 s) compared to sham in a cycling test performed at 100% of VO$_{2\text{max}}$ until volitional termination.

Mechanistically, there are several reasons why targeting the PFC regions is more likely to produce greater exercise performance compared to stimulating M1. Firstly, the motor cortex is
regulated by the supplemental motor cortex which in turn is regulated by the PFC (Fuster et al., 1982; Goldman-Rakic, 1987; Lu et al., 1994; Quintana et al., 1989). Therefore, the decision to slow down, speed up, continue, or quit the exercise may be influenced by the PFC.

Since the PFC is involved in regulating emotional states exerting control over the activity of subcortical regions, specifically the amygdala, stimulation of the PFC would enhance its regulatory control over the amygdala. It is questionable to what degree emotional control would be achieved by stimulating the PFC, which may depend on an intentional regulatory goal (to increase/decrease pleasure or displeasure). While this has not been tested directly, it is thought that pharmacological interventions and cognitive-behavioral therapy increase the activity of the PFC while decreasing activity of the amygdala. If prefrontal cortical control diminishes the threat response, then increasing PFC activity should result in greater control (inhibition) of the amygdala (Furmark et al., 2002), especially during exercise when the PFC enters a hypometabolic state at high intensities. A study by Ironside et al. (2019) evaluated whether anodal tDCS of the DLPFC reduced the reactivity of the amygdala to threats while viewing affective images. Anodal tDCS stimulation of the DLPFC was shown to increase cortical activity, which, in turn, enhanced control of the response of the amygdala to threats (i.e., reduced amygdala activity) when assessed using fMRI. If tDCS enhances attentional control and decreases amygdala reactivity, this suggests the substantiation of a psychobiological mechanism, which could be used to provide evidence of DLPFC attenuation of fatigue during exhaustive exercise. Depending on the aim of the intervention or study, with tDCS, functional hypotheses can be mechanistically tested through the “activation” or “deactivation” of semi-localized brain regions.
CHAPTER 3. METHODS AND PROCEDURES

This chapter describes the equipment, measures, and methods used in the study.

Participants

No previous study has examined the effect of DLPFC stimulation on affective responses during heavy and severe exercise. In non-exercise contexts, tDCS studies stimulating the right or left DLPFC report “medium” effect sizes for modulating affective responses (Feese et al., 2014) and attenuating amygdala activity (Ironside et al., 2019). Simultaneous anode stimulation of both DLPFC hemispheres produce “large” effects on cognitive inhibition (Priori et al., 1998). In the exercise context, tDCS studies of double anodal tDCS over M1 yielded a "medium" effect size on perception of effort (Angius et al., 2016). Given the variability in the literature, we conservatively considered the smallest anticipated effect for our primary variables, in this case affective response modulation by tDCS. Therefore, a medium effect size ($f = 0.25$) (Cohen, 1988) for an analysis of variance comparing four dependent means (conditions), $\alpha = 0.05$ and $1 - \beta = 0.8$, correlated dependent variables ($r = 0.7$), and a violation of the assumption of sphericity ($\varepsilon = 0.7$), indicated that a sample size of 34 was required to yield sufficient statistical power.

Thirty-four participants were recruited from the undergraduate and graduate student body of Iowa State University. Participants were eligible to participate if (a) between 18-45 years old, (b) were not pregnant, (c) a native English speaker, (d) right-handed, (e) a non-smoker, (d) had no known skin disease on face or forehead, (f) no history of mental health problems, (g) no history of neurological problems, (h) no current prescription medications for the following conditions: depression, bipolar, anxiety, pain, cholesterol, blood pressure, attention deficit hyperactive disorder, type I or type II diabetes, (i) no pacemaker, (j) no intracranial electrodes, (k) no implanted defibrillators or prosthetics, (l) below “high-risk” as defined by the American
College of Sports Medicine (ACSM) risk stratification criteria. All participants read and signed an informed consent form before participating in the study. After completing the study, participants were provided a personalized fitness report and paid $200.00 (five sessions: $30 for each of the first four sessions and $80 for the fifth session) in compensation for their time. The study was approved by the Iowa State University Institutional Review Board on 11/21/2019, IRB # 19-547-00 (Appendix A).

Of the 34 participants enrolled in the study, four participants were unable to complete all five sessions due to the University’s decision to indefinitely halt in-person human subjects testing due to the Covid-19 global pandemic. Therefore, the final sample size for the dissertation is 30. The characteristics of the 30 participants is displayed in Table 1.

Self-report measures

Trait Assessment

*The Preference for and Tolerance of the Intensity of Exercise Questionnaire* (Appendix B). The Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q) (Ekkekakis et al., 2005a) was used to assess the trait variables for the preference and tolerance for high and low exercise intensities. The tolerance scale contains eight items, four items that assess high tolerance for intense exercise (e.g., “I always push through muscle soreness and fatigue when working out”) and four items that assess low exercise tolerance (e.g., “Feeling tired during exercise is my signal to slow down or stop”). The preference scale contains eight items, four items that that assess preference for high intensity (e.g., “I would rather have a short, intense workout than a long, low intensity workout”) and four items that assess preference for low intensity (e.g., “I’d rather go slow during my workout, even if that means taking more time”). Each item is accompanied by a five-point response scale ranging from 1 (“I totally disagree”) to 5 (“I totally agree”). Psychometric analyses of the PRETIE-Q conducted by Ekkekakis et al.
(2005a) reported alpha coefficients of internal consistency ranging between .81 and .85 for the preference scale and between .82 and .87 for the tolerance scale. In the present study, the alpha coefficients of internal consistency were .86 and .85 for the tolerance and preference scales, respectively. The PREITIE-Q was used to assess the influence of trait differences on the sense of exertional fatigue.

**Affective Responses**

*The Empirical Valence Scale* (Appendix C). Affective valence responses were assessed using the Empirical Valence Scale (EVS) (Lishner et al., 2008) presented on a touch screen. The EVS is a continuous, single item, bipolar rating scale used for the assessment of affective valence (pleasure-displeasure). The scale is presented similarly to a visual analogue scale, as a horizontal line, punctuated by 15 empirically spaced anchors, ranging from “most unpleasant imaginable” to “most pleasant imaginable.” While no numeric values are presented on the scale, when responses are scored, the scale is divided into equal integers between -100 to 100 to quantify the responses. Participants were provided with the following instructions (modified from Lishner, Cooter, & Zald, 2008):

“This scale assesses how you feel in the moment. During the exercise, you may feel pleasure or displeasure. Think of the middle of the scale as “neutral,” which would indicate that at the moment you do not feel any pleasure or displeasure. Think of the right side of the scale as “pleasure,” indicating that at the moment you feel pleasure, which can be anything from the “Most Pleasant Imaginable” to “Barely Pleasurable.” Think of the left side of the scale as “displeasure,” indicating that at the moment you feel displeasure, which can be anything from the “Most Unpleasant Imaginable” to “Barely Unpleasant. When rating how you feel, try to rate how pleasant or unpleasant you feel relative to other pleasant or unpleasant feelings of all kinds.”
**Felt Arousal Scale** (Appendix D). The affective dimension of perceived activation was measured using the Felt Arousal Scale (FAS) (Svebak & Murgatroyd, 1985) presented on a touch screen. The FAS is a 6-point, single-item rating scale ranging from one to six, with anchors at 1 (‘‘Low Arousal’’) and 6 (‘‘High Arousal’’). All participants were provided with the following standardized instructions:

“Estimate here how activated you actually feel. Do this by choosing the appropriate number. By ‘‘activation’’, this refers to how ‘‘worked-up’’ you feel. You might experience high activation in one of a variety of ways, for example as excitement or anxiety or anger. Low activation might also be experienced by you in one of a number of different ways, for example as relaxation or boredom or calmness.”

**Perceived Exertion**

**Rating of Perceived Exertion** (Appendix D). Whole-body perception of exertion was measured using the Rating of Perceived Exertion scale (RPE) (Borg, 1998) presented on a touch screen. The RPE is a 15-point single-item scale ranging from six to 20, with anchors ranging from ‘‘Very, very light’’ to ‘‘Very, very hard’’. All participants were provided with the following standardized instructions:

“During the exercise bout, we want you to pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, comibing all sensations and feelings of physical stress, effort, and fatigue. Don’t concern yourself with any one factor, such as leg pain, shortness of breath, or exercise intensity, but try to concentrate on your total, inner feeling of exertion. Try not to underestimate or overestimate your feeling of exertion; be as accurate as you can. How hard is the work rate? Please point to a number.”
Physical Activity Level

*The International Physical Activity Questionnaire, short version* (Appendix F). The International Physical Activity Questionnaire, short version (IPAQ-S7S) (Craig et al., 2003; Lee et al., 2011), was used to assess physical activity level. The IPAQ-S7S is a 7-item questionnaire that assesses minutes per week of moderate- and vigorous-intensity physical activity across four domains: work-related, transportation, housework, and leisure-time sport or exercise. In the present study, the IPAQ-S7S was used as the activity level variable for the customized incremental exercise test algorithm. Specifically, minutes per week of moderate and vigorous leisure-time sport or exercise were converted into a physical activity level rating according to Jamnick et al. (2016). Physical activity level was then used as a variable in computing the work-rate for the customized incremental exercise test.

Physiological Measures

Pulmonary Gas Exchange

*TrueMax 2400, metabolic analyzer.* Breath-by-breath oxygen consumption and carbon dioxide production were measured with an open-circuit computerized spirometry system (TrueMax 2400, ParvoMedics, Salt Lake City, UT). The system consists of a paramagnetic O\textsubscript{2} analyzer, an infrared CO\textsubscript{2} analyzer, and a pneumotachometer (3813, Hans Rudolph, Kansas City, MO) to measure ventilation. Participants breathed through a nasal and mouth facemask (7450 Series Silicone V2, Hans Rudolph, Kansas City, MO) equipped with an ultra-low resistance, T-shaped, two-way nonrebreathing valve (Hans Rudolph, Kansas City, MO). Plastic tubing connected the mask to the metabolic analyzer. The system was calibrated before each test according to manufacturer guidelines. Breath-by-breath gas exchange and respiratory data were analyzed offline using the WinBreak 3.7 software (Ekkekakis et al., 2008) (see Data Preprocessing).
Gas-exchange data were used to determine the power output corresponding to each participant’s VT, where which carbon dioxide (VCO₂) production blood begins to disproportionately increase above the oxygen consumption (VO₂), and RCP, where VO₂ and VCO₂ rises exponentially to VO₂max (Gaesser & Poole, 1996). These parameters were used to prescribe the relative intensities for each constant work-rate bout used in the study. Prescribing intensities based on the VT and RCP ensures that the exercise evokes an identical metabolic response across participants.

**Cortical Hemodynamics**

*OxiplexTS, near-infrared spectroscopy.* Absolute concentrations (μM·mL⁻¹) of oxygenated (O₂Hb), deoxygenated (HHb), and total (THb) hemoglobin in the right (between AF4-F4) and left (between AF3-F3) dorsolateral prefrontal cortex (DLPFC) was measured using an eight-channel frequency-domain near-infrared spectroscopy (NIRS) device (OxiplexTS, ISS, Champaign, IL). The OxiplexTS device emits two wavelengths of near-infrared light (690 nm and 830 nm) at optode separation distances of 2.0 cm, 2.5 cm, 3.0 cm, and 3.5 cm. The data sampling rate was set to 20 Hz.

To ensure consistency and accuracy for the location of each sensor, a BraiNet (Jordan NeuroSciences Inc., Redlands, CA) was used to guide sensor placement. The BraiNet is a template positioning cap based on the EEG 10-20 system. The participant’s cranial diameter was measured and fitted with the appropriate cap size. The NIRS sensors were positioned under the cap, between AF4-F4 (right DLPFC) and AF3-F3 (left DLPFC) (Fitzgerald et al., 2009) and secured to the head using dark stretchable wrapping. Concentrations of oxy- and de-oxyhemoglobin measured via NIRS were used to quantify the activity of the DLPFC (see Figure 2 for experimental set-up).
Heart Rate

Polar heart rate monitor. Heart rate was continuously recorded with a heart rate monitor (RS800, Polar Electro Oy, Finland) consisting of a stretchable chest band and a mounted wireless receiver. Electroconductivity gel was used to enhance signal detection. Validation studies have shown correlations with electrocardiographically measured heart rate typically in the .94–.99 (Engström et al., 2012; Plews et al., 2017; Weippert et al., 2010). Heart rate was used as a manipulation check for the exercise intensity.

Cutaneous Scalp Blood Flow

moorVMS-LDF, laser Doppler flux. Cutaneous scalp blood flow was quantified as an index of red blood cell flux (laser Doppler flux) and was continuously measured with two multifiber integrated laser Doppler flowmetry sensors (moorVMS-LDF; Moor Instruments, Wilmington, UK). Doppler sensors were positioned near the right and left NIRS sensors. Cutaneous scalp blood flow was measured in order to differentiate skin blood flow from cortical neurovascular coupling changes in the NIRS signal (see Figure 2 for experimental set-up).

Acoustic Startle Eye Blink Responses

SR-HLAB PEC, startle response system. The acoustic startle eyeblink response was elicited and measured using the SR-HLAB PEC startle response system (San Diego Instruments, Inc., San Diego, CA). Eyeblink data were collected at 1000 Hz using a photoelectric cell (PEC) probe. The probe contains an infrared emitter and detector. The PEC probe was mounted to a headset with a bendable arm which positioned the probe aimed toward the sclera of the left eye. The distance between the probe was as close as possible to the eye without touching the eyelashes during a blink.

To elicit a startle eyeblink response, the SRH-LAB was programmed to deliver an acoustic startle stimulus binaurally through headphones. The acoustic startle stimulus was a 50
ms burst (120 db) of white noise with an instantaneous rise-time. An orienting tone, “warning
tone” (55 db, single tone, 20 ms, instantaneous rise time) was presented two seconds before each
startle stimulus.

A study conducted by Carlsen et al. (2011) reported that the probability of obtaining
“valid” eyeblink data was 50% with a 105 db acoustic startle stimulus and 90% with 124 db
acoustic startle stimulus. Several human studies have used startle stimuli above 120 db (Brown et
al., 1951; Carlsen et al., 2004a, 2004b; Cressman et al., 2006; Maslovat et al., 2008, 2009; R. F.
Reynolds & Day, 2007; Siegmund et al., 2001; Valls-Solé et al., 1999) and even up to 150 db
(Valls-Solé et al., 1995). An earlier study by Cuthbert et al. (1996) found that affect modulation
of the ASER was maintained across different acoustic volumes, but louder stimuli yielded a
larger number of valid blinks. According to the Occupational Noise Exposure (U.S. Department
of Health and Human Services, Public Health Service, Centers for Disease Control and
Prevention, National Institute for Occupational Safety and Health (NIOSH), 1998), the total
daily exposure limit for 120 db sound is 9 s. For example, a startle stimulus of 120 db for 50 ms
(1/20th of a second) safely permits a daily exposure of 180 stimuli. In the current study, the
maximum number of startle probes (120 db for 50ms) delivered per session was 40. The ASER
was used to index the activity of the amygdala (see Figure 2 for experimental set-up).

Local Cutaneous Vasodilation

*moorVMS-HEAT*, *electrical heating*. Vasodilation of the forehead skin proximal to the NIRS
sensors was induced using two heaters (moorVMS-HEAT; Moor Instruments). The heaters
contain a small electric heating element designed to locally warm cutaneous tissue and a
thermocouple to monitor the skin surface temperature. Vasodilation of the forehead skin was
performed as an experimental test of the influence of skin blood flow on the NIRS signal (see
Figure 2 for experimental set-up).
Cortical Stimulation

*Neuroelectrics, transcranial direct current stimulation.* Electrical current (0.057 mA cm\(^{-2}\)) was delivered by a battery-driven transcranial direct current stimulation (tDCS) device (Neuroelectrics, Cambridge, MA). Direct current was transferred by a saline-soaked pair of surface sponge electrodes (25 cm\(^2\)). Anode electrodes were placed on the right DLPFC (between AF3-F3) and left DLPFC (between AF4-F4) and the extracephalic reference electrodes (35 cm\(^2\)) were placed over the right and left shoulder. For sham stimulation, 30 seconds of stimulation were applied (0.057 mA cm\(^{-2}\), ramp-up/ramp-down 20 s, on 10 s). tDCS was used to increase the neural activity of the DLPFC (see Figure 2 for experimental set-up).

**Procedures**

**Online Prescreening Survey**

A recruitment email was sent to Iowa State University students using a purchased email list and a mass email service provided by Iowa State University (ISU). Interested participants were instructed to complete a prescreening survey (Appendix G) by clicking on a web-link at the bottom of the email. The prescreening survey was created using Qualtrics (Qualtrics, Provo, Utah) with a University license. Upon completion of the survey, an automated algorithm scored the responses and an automated message informed participant as to whether they qualified or not. Eligible participants were asked to submit their availability for scheduling.

**Brief Experimental Overview**

The study involved five laboratory visits (90 minutes for the first visit and 60 minutes for visits 2-5). During the first session, participants completed several questionnaires, completed an experimental cutaneous heating protocol, completed a self-talk standardization procedure, and performed a maximal exercise test to volitional termination. During visits two through five, participants completed a single constant work-rate exercise bout (either at a heavy-intensity or
severe-intensity) while receiving tDCS or sham. The order of the conditions was randomized and counterbalanced across participants (see Figure 2 for experimental set-up).

**Session 1**

The purpose of the first session was to, a) obtain informed consent, b) complete the self-report questionnaires, c) conduct a local heating protocol, d) complete an incremental exercise test for VT and RCP determination, e) self-talk standardization, f) familiarization with responding to single-item measures during exercise, and g) familiarization with the gear and equipment.

Upon arriving at the laboratory for the first time, participants read and signed an informed consent form. Next, participants filled out the PRETIE-Q and IPAQ-S7S questionnaires. Each participant’s weight was measured with a scale (BF-626, Tanita, Tokyo, Japan) and height was measured with a wall-mounted stadiometer.

**Local Heating Protocol**

Before the incremental exercise test, a local heating protocol was performed to determine the influence of scalp blood flow on the cerebral NIRS signal. The protocol induced localized (proximal to the NIRS sensors) cutaneous vasodilation using heating. The temperature of the local heating units increased at a rate of 0.5 degrees Celsius every 5 seconds until 40 degrees Celsius, then the rate of change was reduced to 0.1 degrees Celsius every minute (Minson et al., 2001). The heating ended once the plateau phase of the local heating response was observed in the Doppler flux data. Adjustments to the heating rate and peak temperature were based on the participant’s verbal feedback related to the heating sensation. The maximum heating duration limit was 35 minutes (see Figure 2 for experimental set-up).

**Self-talk Standardization**

Whether by default or through intention, individuals differ in how they regulate their affective states. In response to a stimulus with innate or learned affective significance, cognitive
regulatory processes may be recruited intentionally or without conscious awareness to enhance, reduce, or maintain the affective response (Mauss et al., 2007). During exercise, individuals will likely engage in some form of cognitive regulation, whether deliberate or not, which will potentially influence responses on self-report and neuropsychological measures (see Chapter 2). Therefore, in order to control for this possible source of variation, participants were taught to use positive self-talk statements during the exercise. While, positive-self talk is a form of cognitive regulation, our objective was only the standardization of a regulatory goal across participants in an effort to minimize variability of undirected thoughts.

On the first day and after the exercise test was performed, participants completed several self-talk exercises in the self-talk workbook (Appendix H), designed in accordance with the guidelines established by Barwood et al. (2008) and Blanchfield et al. (2014). Participants identified the thoughts they experienced during the exercise. Negative statements were restructured into counteracting positive phrases directed toward motivating themselves (e.g., this is a challenge I’m going to meet, I have the mental tools to cope, head up, back straight, maintain my pedal cadence, drive forward, I’m doing my best, push through this, I can manage a bit longer, the better performance = more accurate personal fitness report). Positive statements, if used by the participants during the exercise were used as stand-alone positive self-talk statements or incorporated into the restructuring of negative statements (Barwood et al., 2008; Blanchfield et al., 2014). Each participant’s personal statements were displayed in front of the bike during their subsequent sessions. Participants were given the following instructions:

“Throughout the exercise, focus your thoughts and self-talk on the phrases you identified in the first session. As a reminder, the phrases are displayed in front of you. As we reviewed
earlier, during the exercise you will be asked to rate how you feel on the Empirical Valence Scale. After responding to the scale, you will be instructed to engage in positive self-talk, it is important that you do this by engaging in one or more of the phrases.”

The Custom Exercise Test Protocol
Participants were fitted with the heart rate monitor, Brainet, NIRS sensors, breathing face mask, PEC headset, headphones, Doppler sensors, and heating units. Participants sat on a recumbent cycle ergometer (Corival Recumbent, Lode BV, Groningen, Netherlands), received instruction for the EVS, FAS, and RPE and responded to each measure on a touch screen. Baseline data were recorded at rest for 5 minutes. At the end of the baseline period, participants responded to the EVS, FAS, and RPE. Physiological data were continuously recorded, and every minute participants responded to the EVS, FAS, and RPE in a randomized order presented on a touch screen. Participants were prompted every minute (via the touch screen) to engage in positive self-talk. The participants’ self-talk statements were displayed in front of them. Finally, participants were instructed that they would warm-up for 5 minutes, followed by a maximal exercise test, which they should continue until they are no longer able to.

Participants performed the warm-up at a power output corresponding to 40% of their estimated VO2max (Jamnick et al., 2016) a conservative estimation of moderate-intensity exercise (Jones & Poole, 2005, p. 304). After the warm-up, participants completed a customized incremental exercise test to volitional exhaustion on a computer-controlled, electronically braked recumbent cycle ergometer (Corival Recumbent, Lode BV, Groningen, Netherlands). The end of the test was defined by volitional termination or when cadence dropped by more than 10 rpm below average cadence for ten consecutive seconds or longer (Jamnick et al., 2016).

A customized incremental exercise test protocol was chosen for the study due to the several advantages offered by the test. First, the work-rates are not arbitrary nor broadly applied
to all participants. Instead, work-rates are determined on an individual basis relative to the individual’s fitness level and demographics. Second, customized work-rates minimize the variability in test duration between participants, which increases the validity of the outcome. The validity of the VO$_{2\text{max}}$ value obtained during an exercise test is in part related to test duration (Kirkeberg et al., 2011). For example, the fatigue processes associated with early volitional termination of a test (e.g., less than 5 minutes) is primarily the limitation of anaerobic metabolism and muscle power. Similarly, exceedingly long protocols (e.g., 14-20 minutes or longer) drive fatigue processes related to thermal-regulatory factors and cardiac drift (Howley et al., 1995). By definition, VO$_{2\text{max}}$ represents the limit of oxygen consumption for sustaining aerobic metabolism (Bassett & Howley, 2000; Burnley & Jones, 2007). Therefore, a valid test should minimize termination factors related to anaerobic metabolism, muscle power, thermal, and cardiac drift. The test-rest reliability for a VO$_{2\text{max}}$ achieved during customized protocols is superior to traditional protocols (Dicks et al., 2016; Jamnick et al., 2016). The best practice recommendation for test duration dictate that VO$_{2\text{max}}$ should be achieved within 10-12 minutes (Kirkeberg et al., 2011).

In the present study, the exercise test work-rates were based on previously published customized protocols (Dicks et al., 2016; Jamnick et al., 2016). Briefly, algorithms modeled by Jackson et al. (1990) used each participant’s demographic information (e.g., physical activity level, height, weight, age, and sex) to estimate his or her relative VO$_{2\text{max}}$ and the corresponding peak power output (W$_{\text{peak}}$) (Jackson et al., 1990). The estimated W$_{\text{peak}}$ values were used to compute a work-rate expected to cause exhaustion (volitional termination) after 10 minutes (Dicks et al., 2016; Jamnick et al., 2016; Pettitt et al., 2013).
**Acoustic Startle Stimulus Protocol During the Exercise**

A large fixation cross was positioned directly in front of the bike above the self-talk poster. During the exercise, participants were instructed to fixate their gaze on the self-talk statements when not responding to the EVS, FAS, and RPE. Gaze fixation has been shown to reduce eye movement during startle eyeblinks and increase the number of valid eyeblinks (Lovelace et al., 2006).

Participants were instructed to engage in positive self-talk as often as possible. However, it was especially emphasized to engage in positive self-talk immediately after responding to the EVS, FAS, and RPE scales. Every minute during the exercise (after responding to the EVS, FAS, and RPE), participants were prompted on the computer screen to focus on the self-talk statements and engage in positive self-talk. After 7-12 seconds, the orienting and acoustic startle stimulus pair were presented (Eippert et al., 2007).

To reduce predictability, the acoustic stimulus pair was randomly presented during the 7-12 second window. The next orienting tone and acoustic startle stimulus pair randomly occurred within the following 20-40 seconds. In other words, two orienting and startle stimulus pairs were presented during each minute of exercise until the end of the test. After the exercise, participants responded to a questionnaire asking questions about their use of self-talk during the exercise. For example, questions inquired about whether or not they actually engaged in positive self-talk, the positive self-talk phrases they used, how often, and how successful they believe they were in engaging in positive self-talk. Additional questions were asked related to whether they engaged in any negative self-talk and how often this occurred (Appendix I).
Session 2-5

**General Procedures for All Sessions**

The order of experimental conditions was randomized and counterbalanced across participants for sessions 2-5. At the beginning of each session, participants reviewed their positive self-talk phrases and were instructed to use positive self-talk during the exercise. Next, the researcher explained the procedures for the session. Participants were fitted with the same equipment used during the first session (excluding the heating units). Participants sat on the recumbent cycle ergometer and received instructions for the EVS, FAS, and RPE. Participants were told that the exercise session would consist of a short warm-up followed by an exercise session. Baseline data were recorded at rest for 5 minutes. The protocol for the orienting and startle stimuli, reappraisal prompts, and presentation of the EVS, FAS, and RPE scales were the same as in the first session. No vasodilation protocol was performed in sessions 2-5. To control for cardiac drift and other factors that may influence relative intensity over time, participants were monitored for oxygen consumption and heart-rate to assure that the exercise intensity would be maintained within the heavy (or severe) domain (see Figure 2 for experimental set-up). At the end of each session, participants completed the tDCS symptoms questionnaire (Appendix J), to assess whether participants could perceive a difference between the active vs sham tDCS conditions, and to ensure the participants’ safety. Upon completion of the study (end of fifth session), participants were compensated $200 and given a personalized fitness report.

**Differences Between Conditions A, B, C, D**

- Condition (A) “Heavy Sham”: Cycling exercise at a constant power output corresponding to $10\% > VT$ for 20 minutes. Sham tDCS. Participants were told they would perform up to 20 minutes of cycling at a fixed intensity “randomly selected by the researcher.” In
addition, participants were told that “you may find the exercise easy or hard, go until you can no longer continue or until I tell you to stop after 20 minutes.”

- **Condition (B) “Heavy Stim”:** Cycling exercise at a constant power output corresponding to $10\% > \text{VT}$ for 20 minutes. Double (bilateral) anode stimulation of the DLPFC. Participants were told they would perform up to 20 minutes of cycling at a fixed intensity “randomly selected by the researcher.” In addition, participants were told that “you may find the exercise easy or hard, go until you can no longer continue or until I tell you to stop after 20 minutes.”

- **Condition (C) “Severe Sham”:** Cycling exercise at a constant power output corresponding to $5\% < \text{RCP}$ until volitional termination. Sham tDCS. Participants were told they would perform up to 20 minutes of cycling at a fixed intensity “randomly selected by the researcher.” In addition, participants were told that “you may find the exercise easy or hard, go until you can no longer continue or until I tell you to stop after 20 minutes.”

- **Condition (D) “Severe Stim”:** Cycling exercise at a constant power output corresponding to $5\% < \text{RCP}$ until volitional termination. Double (bilateral) anode stimulation of the DLPFC. Participants were told they would perform up to 20 minutes of cycling at a fixed intensity “randomly selected by the researcher.” In addition, participants were told that “you may find the exercise easy or hard, go until you can no longer continue or until I tell you to stop after 20 minutes.”

**Data Preprocessing**

**Single-item Measures**

The EVS, FAS, and RPE data were treated as one-min epochs as well as epochs of one-tenth time segments ($t_{\text{LIM}} \times 10^{-1}$), to standardize the different $t_{\text{LIM}}$ (min) values across participants.
and conditions. The data were analyzed as slopes (change over time) and change scores (the change from warm-up to the end of the exercise) for each condition. In order to capture a more characteristic physiological response that is representative of each exercise-intensity domain, the data were analyzed starting from minute nine onward, due to the time required (~ 3 minutes) for a variety of physiological processes (e.g., VO₂ kinetics) to match the metabolic demand as exercise intensity increases (Jones & Burnley, 2009).

**Gas Exchange Data**

After the completion of the customized incremental exercise test and prior to the next session, two researchers independently analyzed the gas exchange data offline (WinBreak 3.7, Epistemic Mindworks, Ames, IA) for determination of the VT and RCP (Ekkekakis et al., 2008). The Winbreak software combines three methods for VT determination, V-slope (Beaver et al., 1986), ventilatory equivalents (Jones & Molitoris, 1984), excess CO₂ (Gaskill et al., 2001), and two methods for RCP determination, minute ventilation over CO₂ production and ventilatory equivalent of CO₂ over time (Beaver et al., 1986). Breath-by-breath data were averaged over 20 s epochs and data points 20 times smaller or larger than the average of their two adjacent points were classified as outliers and filtered out of the analysis (Ekkekakis, et al. 2008). Data were analyzed from minute nine onward.

**Eyeblink Recordings**

The raw waveform eyeblink data were exported by the SR-HLAB proprietary software for offline signal processing and response scoring. Eyeblink response amplitudes were examined using MatLab (R2019a, The Math Works, Natick, MA). Raw amplitudes were subtracted from the baseline activity (50 ms pretrial activity), to control for shifting baseline effects. Next, eyeblinks were manually scored as “valid” or “invalid” according to the criteria proposed by Berg and Balaban (1999) and Blumenthal et al. (2005). Eyeblinks were classified as invalid if the
waveform contained one or more of the following features; 1) an elevated (>100 a.u.) amplitude or a rising amplitude within 0-20 ms following the startle stimulus onset indicating spontaneous eye activity unrelated to startle stimuli, 2) a peak amplitude greater than or less than three standard deviations (SDs) from the session mean (within individuals), 3) a peak amplitude occurring beyond 150 ms from the startle stimulus onset, 4) no visible negative amplitude immediately following a positive amplitude (within the parameters described above) indicating that a typical blink sequence (i.e., eyelid opening following eyelid closing) did not occur.

After scoring, the percentage of valid eyeblinks for each participant session was calculated by dividing the number of valid eyeblinks by the total number of startle stimuli (i.e., 40) and converted into a percentage. Invalid eyeblinks were marked as missing values. A Missing Completely at Random (MCAR) missing-value analysis was performed for participant data sets with less than 100% viable eyeblinks. If the MCAR was not significant, missing values were replaced with Multiple Imputation using Estimation Maximization (Enders, 2010).

Within participants, the eyeblink amplitudes from each individual session were separately transformed into z-scores \( z\text{-score} = \frac{\text{raw blink} - \text{mean(raw blinks)}}{\text{SD(raw blinks)}} \). The z-score transformed eyeblink amplitudes were converted into slopes (change in z score amplitudes over time) for each exercise session, for every participant. \( R^2 \) values for each slope were calculated to determine how well the linear slope represented the data. Data were analyzed from minute nine onward.

**NIRS Preprocessing**

Absolute concentrations of O\(_2\)Hb, HbH, and THb were exported by the proprietary software that accompanies the OxiplexTS device for offline preprocessing. Signal preprocessing was performed using MatLab (R2019a, The Math Works, Natick, MA) following the procedures
recommended by Piniti et al. (2019). Specifically, the following steps were performed on the 
O$_2$Hb and HHb data;

1) Large movement-related artifacts (i.e., atypical signal inflections) were eliminated, and 
baseline shifts (i.e., instantaneous signal shifts) were corrected using the NIRS Analysis Package 
(NAP) (Fekete et al., 2011).

2) The data segments affected by the movement-related artifacts were reconstructed using a 
piecewise low-order polynomial interpolation.

3) A zero-lag Finite Impulse Response (FIR) bandpass filter was used to remove systemic 
physiological oscillations specific to exercise (i.e., 0.09 Hz – 0.01 Hz) (Pinti et al., 2019).

4) A denoising algorithm (Feuerstein et al., 2009) removed any additional noise (e.g., amplitude 
spikes) unrelated to the underlying hemodynamic signal.

5) For each time series representing the baseline, a linear regression was used to quantify the 
baseline (i.e., end value for the baseline regression). All data points were subtracted from 
baseline to be represented as change from baseline values.

6) For each time series representing the exercise, the data were represented as one-minute 
epochs.

7) For each epoch, the median value of each hemoglobin species was calculated.

8) For each time series, The Total Oxygen Index (TOI; O$_2$Hb·THb$^{-1}$) was calculated. Evidence 
suggests that examining the change in oxygenation indices is more indicative of neural activation 
than change in single hemoglobin species (Yoshitani et al., 2007).

9) Each time series was converted into the change in TOI from the exercise warm-up. The data 
points were converted into one-min epochs as well as epochs of one-tenth time segments ($t_{\text{LIM}}$ 
$\cdot 10^{-1}$), to standardize the duration of $t_{\text{LIM}}$ (min) differences between participants and conditions.
The data were analyzed as slopes (change over time) and change scores (the change from warm-up to the end of the exercise) for each condition. In order to capture a more characteristic physiological response that is representative of each exercise-intensity domain, the data were analyzed starting from minute nine onward (5 min warm-up plus 3 min), due to the time required (~ 3 minutes) for a variety of physiological processes (e.g., VO$_2$ kinetics) to match the metabolic demand as exercise intensity increases (Jones & Burnley, 2009).

**Statistical Assumptions and Missing Data**

For each variable, departures from normality were examined using the Shapiro-Wilks test, the skewness, and kurtosis of each distribution. Violations of normality were defined by 1) a significant Shapiro-Wilks statistic ($p < .05$), indicating the distribution significantly deviates from normal, and a skewness statistic outside the range of ± 2, suggesting the distribution is highly asymmetric, or 2) a significant Shapiro-Wilks statistic ($p < .05$), indicating that the distribution significantly deviates from normal, and a kurtosis statistic outside the range of ± 9, suggesting the distribution is excessively “tailed” (Schminder et al., 2010). In cases in which a violation of normality occurred, a two-step relative rank transformation was used according to Templeton (2011). Data points beyond ± 3 SD of the sample average were classified as outliers and were examined on a case-by-case basis as indicated in the results section. Violations of sphericity were examined via Mauchly’s Test of Sphericity and $F$ tests were Greenhouse-Geisser adjusted where necessary and any relevant follow-up tests for pairwise comparisons were Bonferroni-adjusted.

**Statistical Analyses**

For Hypothesis 1 regarding the effect of tDCS during heavy and severe exercise, a series of multivariate ANOVA with repeated-measures compared EVS, ASER, right TOI, and left TOI
between all four conditions (sham tDCS vs. active tDCS and heavy- vs. severe-intensity exercise).

For Hypothesis 2 regarding the effect of exercise intensity on EVS scores, DLPFC TOI, and the ASER, we focused on solely the heavy- and severe-intensity exercise conditions from the multivariate ANOVA with repeated-measures conducted for Hypothesis 1. Additionally, for Hypothesis 2, a series of bivariate correlational analyses were performed to examine the associations between EVS, ASER, right TOI, and left TOI. To assess changes in the strength of these relationships during severe-intensity exercise, bivariate correlations were computed between EVS, right TOI, and left TOI across time (10 segments). Correlations were examined between the ASER slope and the EVS slope in each condition.

For Hypothesis 3 regarding individual differences in EVS scores, DLPFC TOI, and the ASER, independent of tDCS, bivariate correlations were computed to examine an individual’s tolerance of high-intensity exercise and preference for high-intensity exercise (PRETIE-Q) and their associations with EVS, ASER, right TOI, and left TOI.
CHAPTER 4. RESULTS

Missing Data

Overall, 41.1% of the data from the ASER and 0.3% of the data from NIRS were missing. In the case of NIRS, the missing data were lost due to machine malfunctioning. In the case of the ASER, the missing data included the invalid blinks (i.e., a recorded eyeblink that did not meet the requisite criteria) or blinks that were not detected by the sensor (i.e., either a blink did not occur or the sensor may have shifted out of place). Missing data for the ASER were variable between conditions and across participants. For example, 18 participants had one or more exercise sessions with more than 75% of blinks missing. The missing data patterns of the ASER and NIRS (within participants and within conditions) were evaluated using Little’s Missing Completely At Random tests (MCR) (Little, 1988). In each case, the MCR statistic was not significant ($p > .05$), indicating that the missing data were missing completely at random.

The Expectation Maximization (EM) method was used to impute the missing data. Due to a technical malfunction with the Polar heart-rate monitor, two-thirds of all heart-rate data were lost. The magnitude of this data loss violates the assumptions of EM and therefore the heart-rate data were excluded from further analysis.

Manipulation Checks

Metabolic responses during each of the exercise-intensity conditions

The VO$_2$ response during the exercise conditions are presented in Table 2 relative to the parameter that defines the lower metabolic boundary of that domain (i.e., the VO$_2$ VT% for the heavy-intensity exercise, and the VO$_2$ RCP% for the severe-intensity exercise). In addition, the VT% in both domains were computed for an absolute comparison.
The targeted level of bodily perturbations and physiological drift, defined by the VT% during the final minute of exercise, was achieved in the heavy-intensity conditions (i.e., between 10% above VT to below RCP) and in the severe-intensity conditions (i.e., between 5% below RCP to above RCP). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the final minute of the VT% responses, was statistically significant for the exercise-intensity conditions \[F(1, 29) = 37.698, p < .001, \eta_p^2 = .565\] and not significant for the tDCS conditions \[F(1, 29) = 3.020, p = .093, \eta_p^2 = 0.094\] and there was no significant interaction \[F(1, 29) = 0.003, p = .955, \eta_p^2 = 0.000\]. Specifically, the VT% was significantly lower in the heavy-intensity sham tDCS \((M = 136.2\%, SD = 46.4\%)\) and active tDCS \((M = 129.6\%, SD = 41.9\%)\) conditions compared to the severe-intensity sham tDCS \((M = 165.7\%, SD = 44.1\%)\) and active tDCS \((M = 159.4\%, SD = 44.4\%)\) conditions. This suggests that the targeted exercise intensity manipulation for the heavy- and severe-intensity trials was successful and tDCS did not alter the VO\(_2\) response. Accordingly, the metabolic profiles (i.e., the level of bodily perturbations) matched the expected levels that are characteristic of heavy-and severe-intensity exercise.

The metabolic response during the warm-up exercise was consistent across conditions (Table 2). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the final minute of the warm-up VT% responses, was not statistically significant for the exercise-intensity conditions \[F(1, 29) = .865, p = .360, \eta_p^2 = .030\], and the tDCS conditions \[F(1, 29) = 1.409, p = .245, \eta_p^2 = .048\]. Additionally, the interaction was not significant, \(F(1, 29) = 344, p = .562, \eta_p^2 = .012\], which suggests that the physiological drift during the heavy-intensity exercises did not overlap with the metabolic response that was observed during the severe-intensity exercises. Overall, 90.0% \((n = 27)\) of participants completed the entire 20-min
duration in the heavy-intensity exercise sham tDCS, 93.3% \((n = 28)\) in the heavy-intensity exercise active tDCS, 36.7% \((n = 11)\) in the severe-intensity exercise sham tDCS, 33.3% \((n = 10)\) in the severe-intensity exercise active tDCS condition.

**Perceptions of Physiological Activation and Effort**

The RPE data are presented in Table 3. A 2 (exercise-intensity conditions) x 2 (tDCS conditions) repeated-measures ANOVA on the change in RPE ratings from the average of the warm-up to the final minute of exercise was statistically significant for the exercise-intensity conditions \([F(1, 29) = 42.599, p < .001, \eta_p^2 = .565]\) and not significant for the tDCS conditions \([F(1, 29) = 0.000, p = .990, \eta_p^2 = 0.000]\). Additionally, the interaction was not significant \([F(1, 29) = 0.139, p = .712, \eta_p^2 = 0.005]\).

The RPE response during the warm-up exercise was consistent across conditions. A 2 (exercise-intensity conditions) x 2 (tDCS conditions) repeated-measures ANOVA on the average RPE ratings during the warm-up was not statistically significant for the exercise-intensity conditions \([F(1, 29) = .005, p = .944, \eta_p^2 = .000]\) and not significant for the tDCS conditions \([F(1, 29) = .080, p = .779, \eta_p^2 = .003]\). Additionally, the interaction was not significant \([F(1, 29) = .079, p = .780, \eta_p^2 = .003]\).

The FAS data are presented in Table 4. A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the change in FAS ratings from the average ratings during the warm-up to the final minute of the exercise was statistically significant for the exercise-intensity conditions \([F(1, 29) = 28.711, p < .001, \eta_p^2 = .497]\) and not significant for the tDCS conditions \([F(1, 29) = 1.865, p = .183, \eta_p^2 = 0.060]\). Additionally, the interaction was not significant \([F(1, 29) = 0.725, p = .402, \eta_p^2 = 0.024]\).
The FAS response during the warm-up exercise was consistent across conditions. A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the average FAS ratings during warm-up was not statistically significant for the exercise-intensity conditions \[ F(1, 29) = .666, p = .421, \eta_p^2 = .022 \] and not significant the tDCS conditions \[ F(1, 29) = 2.789, p = .106, \eta_p^2 = .088 \]. Additionally, the interaction was not significant \[ F(1, 29) = .023, p = .880, \eta_p^2 = .001 \].

The EVS response during the warm-up exercise was consistent across conditions. A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the average EVS scores during the warm-up was not statistically significant for the exercise-intensity conditions \[ F(1, 29) = .914, p = .347, \eta_p^2 = .031 \], tDCS conditions \[ F(1, 29) = .017, p = .897, \eta_p^2 = .001 \] and their interaction \[ F(1, 29) = .867, p = .029, \eta_p^2 = .029 \] (Table 5).

For the heavy-intensity exercise conditions, nearly every participant \((n = 27)\) completed the full 20 minutes. The average \(t_{\text{LIM}}\) of the participants who quit early was 15.6 ± 2.6 min across the heavy-intensity conditions. For the severe-intensity exercise conditions, 11 participants completed the full time in the sham tDCS condition, and 10 participants completed the full time in the active tDCS condition (one participant completed the full sham tDCS condition, but not the full active tDCS condition). For the participants who did not complete both severe-intensity exercise conditions \((n = 19)\), the average \(t_{\text{LIM}}\) in the active tDCS condition was slightly longer \((M = 11.6, SD = 3.9)\) compared to the sham tDCS condition \((M = 11.3, SD = 4.6)\). However, a repeated measures ANOVA on the \(t_{\text{LIM}}\) of the severe-intensity exercise conditions revealed that the difference was not statistically significant \[ F(1, 29) = .160, p = .649, \eta_p^2 = .009 \].

The Relationship Between the Doppler Flux and the NIRS Signal at Rest
Gradual heating of the forehead skin increased the superficial capillary blood perfusion, as measured by the Doppler flux, without altering the NIRS recordings of the cortical hemodynamics (Figure 12). The duration of the cutaneous heating was contingent upon the Doppler flux response (i.e., a plateau in the flux curve) \((n = 28)\) or upon participant request due to discomfort \((n = 2)\). On average, the highest temperature achieved was \(41.8 \pm 0.9 \, ^\circ\text{C}\) and the average heating duration was \(27 \pm 3.8\) min. A repeated measures ANOVA for the 10 time-segments on the forehead skin temperature was significant 
\[
F(1.765, 51.190) = 74.350, \ p < .001, \ \eta^2_p = .719.
\]
A repeated measures ANOVA for the 10 time-segments on the forehead skin Doppler flux was also significant 
\[
F(1.526, 44.266) = 10.353, \ p = .001, \ \eta^2_p = .263.
\]
In contrast, a 2 (hemispheres) by 10 (time segments) repeated measures ANOVA on the DLPFC \(\Delta O_2\text{Hb}\) concentration was not significant for the hemispheres 
\[
F(1, 29) = .224, \ p = .639, \ \eta^2_p = .008,
\]
the time segments 
\[
F(2.083, 60.406) = 2.124, \ p = .126, \ \eta^2_p = .068,
\]
or their interaction 
\[
F(1.949, 56.519) = .370, \ p = .687, \ \eta^2_p = .013.
\]
Additionally, a 2 (hemispheres) by 10 (time segments) repeated measures ANOVA on the DLPFC \(\Delta \text{HHb}\) concentration was not significant for the hemispheres 
\[
F(1, 29) = .863, \ p = .361, \ \eta^2_p = .029,
\]
the time segments 
\[
F(2.296, 66.570) = 1.871, \ p = .156, \ \eta^2_p = .061,
\]
or their interaction 
\[
F(1.601, 46.420) = .954, \ p = .375, \ \eta^2_p = .032.
\]
Of the changes in the forehead skin temperature recordings, the left DLPFC \(\Delta O_2\text{Hb}\), the right DLPFC \(\Delta O_2\text{Hb}\), the left \(\Delta \text{HHb}\), and the right \(\Delta \text{HHb}\), only the forehead skin temperature recordings were significantly correlated with the Doppler flux recordings across time.

**Hypothesis 1**

As hypothesized, the rate of decline in affective responses (EVS) was greater during severe-intensity exercise compared to heavy-intensity exercise (Figure 3 & Table 5). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the slope of EVS scores \((\Delta \text{EVS} \cdot \text{min}^{-1})\) was statistically significant for the exercise-intENSITY conditions
\[ F(1, 29) = 31.440, p < .001, \eta_p^2 = .520 \]. While decline in EVS was somewhat larger in the sham tDCS conditions (Figure 3), the main effect of tDCS \[ F(1, 29) = .008, p = .927, \eta_p^2 = .000 \] and the interaction \[ F(1, 29) = 1.016, p = .322, \eta_p^2 = .034 \] were not significant. The average EVS scores were more positive during the heavy-intensity conditions compared to the severe-intensity exercise conditions. A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the average EVS scores was statistically significant for the exercise-intensity conditions \[ F(1, 29) = 46.727, p < .001, \eta_p^2 = .617 \]. Although the average EVS scores were somewhat more positive during the active tDCS conditions (Figure 3), the main effect of tDCS \[ F(1, 29) = 2.000, p = .168, \eta_p^2 = .065 \] and the interaction \[ F(1, 29) = .146, p = .706, \eta_p^2 = .005 \] were not significant.

As hypothesized, the activity of the DLPFC was reduced during severe-intensity exercise compared to heavy-intensity exercise, while active tDCS resulted in higher DLPFC activity compared to the sham tDCS conditions. Moreover, the activity of the right DLPFC during exercise decreased compared to the left DLPFC (Figure 4). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) by 2 (hemispheres) repeated-measures ANOVA on the average \( \Delta \text{TOI} \) percentages (throughout the exercise), was statistically significant for the exercise-intensity conditions \[ F(1, 29) = 10.702, p = .003, \eta_p^2 = .270 \], the tDCS conditions \[ F(1, 29) = 6.219, p = .019, \eta_p^2 = .177 \], and for the hemispheres \[ F(1, 29) = 9.663, p = .004, \eta_p^2 = .250 \]. All four interactions; exercise-intensity by tDCS \[ F(1, 29) = .151, p = .700, \eta_p^2 = .005 \], exercise-intensity by hemisphere \[ F(1, 29) = .055, p = .816, \eta_p^2 = .002 \], tDCS by hemisphere \[ F(1, 29) = .041, p = .841, \eta_p^2 = .001 \], and exercise-intensity by tDCS, by hemisphere \[ F(1, 29) = 1.140, p = .295, \eta_p^2 = .038 \], were not significant.
The decline in the activity (TOI) of the DLPFC was larger during severe-intensity exercise compared to heavy-intensity exercise, and this decline was larger in the right DLPFC compared to the left DLPFC (Figure 5). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the ΔTOI% slope was statistically significant for the exercise-intensity conditions \( [F(1, 29) = 4.965, p = .034, \eta^2_p = .146] \) and for the hemispheres \( [F(1, 29) = 10.714, p = .003, \eta^2_p = .270] \). The main effect of tDCS \( [F(1, 29) = .614, p = .440, \eta^2_p = .021] \) and all four interactions; exercise-intensity by tDCS \( [F(1, 29) = .966, p = .334, \eta^2_p = .032] \), exercise-intensity by hemisphere \( [F(1, 29) = .083, p = .775, \eta^2_p = .003] \), tDCS by hemisphere \( [F(1, 29) = .289, p = .595, \eta^2_p = .010] \), and exercise-intensity by tDCS, by hemisphere \( [F(1, 29) = .583, p = .451, \eta^2_p = .020] \) were not significant.

The ASER showed greater decline during severe-intensity exercise compared to heavy-intensity exercise and the decline was attenuated in the active tDCS conditions compared to the sham tDCS conditions, irrespective of intensity (Figure 6). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the ASER slopes was statistically significant for the exercise-intensity conditions \( [F(1, 29) = 9.984, p < .001, \eta^2_p = .256] \) and the tDCS conditions \( [F(1, 29) = 12.338, p = .001, \eta^2_p = .298] \). The interaction \( [F(1, 29) = 3.354, p = .077, \eta^2_p = .104] \) was not significant.

**Hypotheses 2 and 3**

At the end of the severe-intensity exercise conditions, the decline in affective responses (EVS) from the warm-up was greater compared to the end of the heavy-intensity exercise conditions (Table 5). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) repeated-measures ANOVA on the change in EVS scores (ΔEVS\text{Final}) was statistically significant for the exercise-intensity conditions \( [F(1, 29) = 48.254, p < .001, \eta^2_p = .625] \). However, the main effect
of tDCS \( [F(1, 29) = .525, p = .475, \eta_p^2 = .018] \) and the interaction \( [F(1, 29) = 2.598, p = .118, \eta_p^2 = .082] \) were not significant. For both severe-intensity exercise conditions, the slope of the EVS ratings over time was significantly correlated with \( \tau_LIM \) (sham tDCS: \( r = 0.54, p = 0.002 \); active tDCS: \( r = 0.60, p < .001 \))

DLPFC activity (TOI) was reduced to a larger degree from the warm-up to the end of exercise in the severe-intensity conditions compared to the heavy-intensity conditions, and this drop was larger in the right DLPFC compared to the left DLPFC (Figure 7). A 2 (exercise-intensity conditions) by 2 (tDCS conditions) by 2 (hemispheres) repeated-measures ANOVA on the \( \Delta \text{TOI} \) percentages at the change to the final minute of the exercise (\( \Delta \text{TOI} \%_{\text{Final}} \)) was statistically significant for the exercise-intensity conditions \( [F(1, 29) = 17.536 , p < .001, \eta_p^2 = .370] \) and for the hemispheres \( [F(1, 29) = 15.546, p < .001, \eta_p^2 = .349] \). The main effect of tDCS \( [F(1, 29) = 1.596, p = .217, \eta_p^2 = .052] \) and all four interactions; exercise-intensity by tDCS \( [F(1, 29) = .074, p = .787, \eta_p^2 = .003] \), exercise-intensity by hemisphere \( [F(1, 29) = .016, p = .900, \eta_p^2 = .001] \), tDCS by hemisphere \( [F(1, 29) = .030, p = .863, \eta_p^2 = .001] \), and exercise-intensity by tDCS by hemisphere \( [F(1, 29) = .009, p = .924, \eta_p^2 = .000] \) were not significant. Descriptively, the numbers of participants in each condition with a final left DLPFC TOI below baseline were as follows: (a) heavy-intensity sham tDCS (\( n = 3 \)), (b) heavy-intensity active tDCS (\( n = 4 \)), (c) severe-intensity sham tDCS (\( n = 14 \)), and (d) severe-intensity active tDCS (\( n = 13 \)). The numbers of participants in each condition with a final right DLPFC TOI below baseline were as follows: (a) heavy-intensity sham tDCS (\( n = 11 \)), (b) heavy-intensity active tDCS (\( n = 7 \)), (c) severe-intensity sham tDCS (\( n = 18 \)), and (d) severe-intensity active tDCS (\( n = 15 \)).

For each condition, bivariate correlations were computed at each time point during exercise (10 equal segments) between \( \Delta \text{EVS}_{\text{Final}} \) scores and \( \Delta \text{TOI}_{\text{Final}} \) percentages in the right and
left DLPFC (Figure 8). The relationship between affective responses (EVS) and DLPFC activity (TOI) was different depending on the exercise intensity and tDCS condition. During heavy-intensity exercise, the correlations between affective responses (EVS) and the right and left DLPFC activity (TOI) increased (a positive association) throughout the exercise, however none were statistically significant. In contrast, during severe-intensity exercise, the correlations between affective responses (EVS) and the right and left DLPFC activity (TOI) increased (a positive association) across time and became statistically significant at approximately 50% of t_LIM (although the probability values across the remainder of the exercise tended to fluctuate above and below \( p = .05 \)). The effect of active tDCS during severe-intensity exercise appeared to invert the associations (changing to negative correlations) between affective responses (EVS) and the right and left DLPFC activity (TOI). The negative correlations increased in strength throughout the exercise session and achieved statistical significance at approximately 50% of t_LIM.

When EVS scores and TOI percentages are averaged at each time point within each condition, significant associations are observed (Figure 8). However, when averaging the data across all time points (i.e., representing the entire exercise condition as an average) (Figure 9) or with a single change score (Figure 10), the relationships are not significant, although there is a trend in the same direction as the correlations per time-point. The correlations between the \( \Delta \text{EVS}_{\text{Final}} \) scores and the \( \Delta \text{TOI}_{\text{Final}} \) percentages in the right and left DLPFC are shown in Figure 10. A higher level of tolerance was associated with a greater activation of the right DLPFC during the heavy-intensity sham exercise (Figure 10 A). This association, between tolerance and the right DLPFC activity (TOI) during heavy-intensity exercise, was attenuated in the active tDCS condition (Figure 10 B). Finally, the correlations between the slopes of the \( \Delta \text{EVS} \) scores
and the slopes of the ASER responses in are displayed in Figure 11. The average tolerance score of the sample was 29.6 ± 4.9 (range 16-39 out of a possible range of 1-40).
CHAPTER 5. DISCUSSION

Overview of Findings and Implications

The objective of this dissertation was to test a theoretical framework for the neural basis of exertional physical fatigue. This theoretical framework proposes that the sense of exertional fatigue is a primordial negative affective response to substantial exercise-induced homeostatic perturbations. Therefore, its genesis and regulation are a function of the same brain networks involved in processing other types of affective responses. Specifically, the interaction between cortical (i.e., the DLPFC) and subcortical (i.e., the amygdala) regions. The primary objective of the present study was to test the main tenets of the proposed framework by examining associations between interoceptive perturbations (with VO₂ indicating metabolic strain), activity in the right and left DLPFC (ΔTOI%), the ASER (amplitudes), and affective responses (EVS scores) during cycling exercise. A secondary objective was to test the functional role of the DLPFC in regulating exertional fatigue. A third objective was to determine whether the trait of exercise intensity tolerance was associated with individual differences in the responses of the assessed variables.

It was hypothesized that active tDCS (anodal) would be most effective in modifying affective responses during heavy-intensity exercise because the intensity is challenging (i.e., it requires some degree of cognitive engagement) and within the range of intensity in which cognitive factors (e.g., cognitive regulation, self-efficacy) are theorized to exert a considerable influence on affective responses. Additionally, active tDCS was predicted to be least efficacious in modifying affective responses during severe-intensity exercise because affective responses at this level of intensity are primarily driven by subcortical interoceptive cues (i.e., pervasive homeostatic perturbations) and less by cognitive factors. The distinct metabolic profiles
associated with heavy- and severe-intensity exercise allowed for a direct comparison of the ways that cognitive and interoceptive factors contribute to the sense of exertional fatigue.

The second study hypothesis was that the interoceptive perturbations caused by exercise would be manageable (i.e., most participants would complete the entire duration of exercise) during heavy-intensity exercise, but there would still be substantial homeostatic perturbations, such that the development of exertional fatigue would be evident (i.e., a decline in valence would be accompanied by an increase in DLPFC activation). It was predicted that active tDCS applied to the right and left DLPFC would attenuate the decline in affective response compared to sham tDCS by modulating the activity in the DLPFC and, therefore, cognitive inhibition of the amygdala. The second study hypothesis anticipated that, during severe-intensity exercise, interoceptive perturbations would continue to intensify and reach a level that most participants would not be able to manage. It was anticipated that proximal to the termination of exercise, a direct association between the EVS score and oxygenation of the DLPFC, and an indirect association with the ASER, would be observed. The third hypothesis predicted that higher exercise intensity-tolerance scores would be associated with higher EVS scores, increased DLPFC TOI, and reduced ASER amplitudes compared to the lower tolerance scores recorded during heavy-intensity exercise.

The VO₂ response (percentage relative to the VT during heavy-intensity exercise and relative to the RCP during severe-intensity exercise) indicated that the manipulation of exercise intensity was achieved during heavy- and severe-intensity exercise, therefore eliciting the intended levels of perturbation (Table 2). Homeostatic perturbations during severe-intensity exercise were more pervasive; proximal to the tLim, an average VO₂ response was recorded for each participant (i.e., 112–117% of their RCP) (Table 2). While only two participants were
unable to complete the full time in the heavy-intensity exercise conditions, over two-thirds of the participants were unable to complete the 20-min time allotted in the severe-intensity exercise conditions. This is important because it suggests that the collected data (the EVS scores, DLPFC TOIs, and ASER amplitudes) reflected the full range of the response to exertional fatigue, from genesis to termination.

Overall, during heavy- and severe-intensity exercise, the EVS score decreased and the FAS score increased proportionately, with the largest change occurring in the final minute of exercising (Tables 4 and 5). In addition, the EVS slope was shown to correlate significantly with $t_{\text{lim}}$, which mirrors a previously reported finding (Hartman et al., 2019). The decline in valence, both in terms of the EVS slope and EVS average, was more rapid during severe-intensity compared to heavy-intensity exercise. As expected, active tDCS during severe-intensity exercise did not have a statistically significant effect on the EVS slope or EVS average. During heavy-intensity exercise, the EVS slope was slightly attenuated, and the EVS average was slightly more positive when active tDCS was used compared to sham tDCS. However, contrary to what was predicted, these differences were not statistically significant.

As hypothesized, the average DLPFC TOI changed depending on the exercise intensity and the application of active tDCS, and the magnitude of this change differed between the right and left hemispheres. Overall, there was a difference between sham and active tDCS for TOI across both exercise conditions. The TOI was reduced in the right and left DLPFC during severe-intensity compared to heavy-intensity exercise. The TOI response was consistently lower in the right DLPFC compared to the left DLPFC during both exercise conditions. This relative difference in TOI between the hemispheres was not altered by active tDCS. However, the
increased TOI observed in the right DLPFC during active tDSC was almost identical to the TOI observed in the left DLPFC during sham tDSC (Figure 4).

The ASER amplitude pattern was altered by the exercise intensity and the application of active tDSC. Overall, the ASER slope declined at a slower rate during heavy-intensity compared to severe-intensity exercise. Considering that a faster decline in affective response occurred during severe-intensity compared to heavy-intensity exercise, the affective modulation of the ASER was opposite to what was expected. Active tDSC increased the ASER slope in both exercise conditions, which was also unexpected. Notably, the EVS slope and EVS average during active tDSC and sham tDSC conditions did not differ significantly, whereas the slope of ASER during active tDSC and sham tDSC were significantly different. This unexpected pattern of the ASER may have been due to several limitations, which are addressed in the section entitled “Limitations and Future Directions.” Thus, evaluating the ASER in combination with the other variables and interactions may be more informative than interpreting the ASER patterns in isolation.

The second and third hypotheses predicted that several functional relationships would exist between the EVS scores, DLPFC TOI percentages, and the ASER slopes during the development of exertional fatigue. In conjunction with the decline in EVS scores, the decline in right and left DLPFC TOI until the final minute of exercise was greater during severe-intensity compared to heavy-intensity exercise. The drop in TOI was most prominent during severe-intensity exercise, when, on average, the right DLPFC TOI dropped below baseline, therefore leading to a hypometabolic state (Figure 7). The reduction in DLPFC TOI suggests a hypoactivation of the PFC networks that are involved in emotional regulation (Davidson, 2000; Davidson, 2001). One possible interpretation would be that the participant’s ability to regulate
their affective responses was poor; therefore low DLPFC activity would be reflected by the reduced utilization of cognitive resources (Gross & John, 2003). However, this explanation is unlikely given that the DLPFC dropped below baseline (i.e., a hypometabolic response), whereas it may be the case that the effect of poor emotional regulatory proficiency or low motivation would result in nominal changes relative to baseline rather than in a decline below baseline. Another possible explanation is that the PFC deactivated as a protective mechanism to prevent the body from exceeding an unsafe level of exertion (Ekkekakis, 2003; Hartman et al., 2019; Noakes et al., 2001). Cognitive regulation strategies (e.g., inhibition) and cognitive factors (e.g., mental toughness, self-efficacy) would have minimal or no impact on exercise performance if the physical substrate of these mental processes were essentially taken “offline.” Therefore, without optimal PFC functioning, the ability to inhibit displeasure would be significantly diminished. According to the proposed theoretical framework, cognitive inhibition of displeasure by the PFC is a process that attenuates exertional fatigue and allows a person to continue to persevere through a challenging exercise.

Individuals with higher levels of exercise intensity-tolerance showed greater activation of their right DLPFC during the heavy-intensity sham tDCS exercise compared to individuals with lower tolerance (Figure 10 A). The association between tolerance and right DLPFC activity (TOI) during heavy-intensity exercise was attenuated with active tDCS (Figure 10 B). In other words, tDCS might have reduced the difference in right DLPFC activity between individuals with lower tolerance and individuals with higher tolerance. Although this is speculative, it suggests that tDCS may be more beneficial to individuals with lower tolerance by increasing activity in their right DLPFC to levels that are comparable with those in individuals with higher tolerance during bouts of physical exertion. For example, implementing immersive audio-visual
simulation during exercise, compared to control, has been shown to reduce the difference in the DLPFC activity between individuals who score high on the preference PRETIE-Q metric compared to individuals who score low on the preference metric (Jones & Ekkekakis, 2019).

The relationship between EVS scores and the TOI of the right and left DLPFC varied across conditions; in addition, these associations varied as a function of time during exercise. During heavy-intensity exercise with sham tDCS, the correlations between EVS scores and the right and left DLPFC TOI increased over time (i.e., there was a stronger positive association); however, none of the correlations were statistically significant. On the other hand, during severe-intensity exercise with sham tDCS, statistically significant correlations were observed across several time points between the EVS scores and the right DLPFC TOI, but not the left DLPFC TOI (Figure 8). Notably, the EVS scores and the right DLPFC during severe-intensity exercise with sham tDCS were positively correlated, and the strength of association increased throughout the exercise, reaching statistical significance around the halfway point (~50% tLim) of the exercise. In other words, increased activation of the right DLPFC was associated with more pleasure or less displeasure. The strengthening of the relationship between the EVS scores and the right DLPFC TOI over time may have been a function of the increase in the severity of bodily perturbations caused by the exercise and concomitant intensification of pervasive interoceptive cues that occupied conscious awareness. The time point during severe-intensity exercise at which the correlation between the EVS scores and the DLPFC achieved statistical significance was likely to be the point during the exercise when, on average, the metabolic profile of the severe-intensity domain was achieved (Hill & Stevens, 2001), and when the participants began to experience greater strain from the increase in interoceptive perturbations.
In contrast to the direct associations observed between the EVS scores and DLPFC TOI across time during severe-intensity exercise with sham tDCS, during active tDCS, the associations were the opposite (Figure 8D). In other words, increased activation of the right DLPFC was associated with more displeasure or less pleasure. Notably, the strength of the inverse relationship increased throughout the exercise and reached statistical significance at approximately 50% tLIM, a mirror image of the correlational pattern observed with sham tDCS (Figure 8C). The change in the direction of this association between the sham and active tDCS during severe-intensity exercise could be due to the volatility of the correlations associated with the small sample size. According to the ANOVA results, the difference in EVS scores between severe-intensity exercise with sham tDCS and severe-intensity exercise with active tDCS was not statistically significant, but the change in DLPFC TOI was statistically significant. Alternatively, if the change in the direction of association between the EVS scores and the DLPFC TOI represents something meaningful, it is possible that the increase in DLPFC TOI induced by the tDCS was not large enough to reverse the effects of the hypometabolic state of the DLPFC. The DLPFC TOIs during both the sham and active tDCS severe-intensity exercise conditions were significantly smaller compared to the values observed during the heavy-intensity sham and active tDCS conditions (Figures 4 and 8). In addition, when a comparison was made between the hemispheres between the sham tDCS and active tDCS severe-intensity conditions, the effect of tDCS was not statistically significant, but this does not necessarily imply that the responses were identical. Underlying differences between the two conditions remained; the average TOI was greater under active tDCS conditions, so the effect of an increase in the TOI, while having no effect on the decline in EVS scores, could have resulted in an inverse correlation. The second and more speculative explanation for the inverted correlation is that tDCS increased TOI,
independently of any actual change in neural activation. This does not draw into question the principle of neurovascular coupling, which is widely supported by evidence (Buxton, 2002; Buxton & Frank, 1997; Hoshi & Tamura, 1993; Raichle & Mintun, 2006; Villringer, 1997; Wolf et al., 2011). However, whether assumptions of neurovascular coupling can be extrapolated to highly unnatural biological conditions, such as the application of a strong external electric field to the cortex, has not been thoroughly examined. A few studies have suggested that tDCS may independently change the hemodynamic response in parallel with modulating neural activity (Dutta, 2015; Moore & Cao, 2008; Stagg et al., 2013; Vernieri et al., 2010). Mechanistically, electric fields can increase blood flow in various types of biological tissue. For example, transdermal iontophoresis of non-vasoactive compounds (e.g., saline) increases cutaneous blood flow, an effect that is known as nonspecific vasodilation (Berliner, 1997; Grossman et al., 1995; Tartas et al., 2005). Additional research is required to identify whether tDCS directly modulates the hemodynamic response independently of neural modulation.

According to the proposed theoretical framework, exertional fatigue becomes increasingly pervasive in response to a significant elevation in interoceptive perturbations, which is consciously perceived as displeasure. The response of an individual to pervasive interoceptive stimuli can be to either immediately quit the exercise or begin to utilize additional cognitive resources and strategies (e.g., reappraisal, suppression, association, dissociation, imagery) to regulate his or her affective state, push through the discomfort, and continue to exercise, provided that the PFC does not enter a hypometabolic state. The latter explanation is more likely for two reasons. Firstly, based on significant increases in RPE and VO₂, there is no evidence to suggest that the participants intentionally tried to go easy during the exercises. Secondly, the participants in the present study had been taught how to use positive self-talk strategies during
exercise, and several steps were taken to remind and encourage them to use these strategies (refer to the self-talk protocol described in the “Methods” section). The purpose of positive self-talk was to encourage the participants to engage in cognitive regulation but also to control for the type of cognitive regulation strategies utilized across all participants and conditions. Therefore, if the participants attempted to regulate their affective responses, the consequence of this would be a direct increase in the coupling between their affective responses and DLPFC activation (Banks et al., 2007; Feeser et al., 2014; Ochsner et al., 2002).

In the present study, the active tDCS conditions were not shown to have a statistically significant effect on affective response. This could be owing to variability in the activity of the DLPFC between participants. If the DLPFC was functioning normally, its corresponding activity would increase in proportion to the cognitive resources utilized to regulate the affective response generated by the interoceptive cues associated with the bodily perturbations. As the perturbation increased over time, the negative affect would increase, along with the amount of cognitive resources required to regulate the negative affect (i.e., by corresponding to increased DLPFC activity). This functional coupling of the DLPFC and affective response was reflected in the increased strength of correlation between the EVS scores and the DLPFC, presumably when greater cognitive resources were utilized. However, it has been reported that if the DLPFC enters a hypometabolic state, which often occurs during high-intensity exercise (Ekkekakis, 2009a; Rooks et al., 2010), for reasons that are not fully understood (Dietrich 2003, 2006; Meeusen et al., 2016), several PFC processes (e.g., cognitive inhibition) become severely impaired (Arnsten, 2009; Del Giorno et al., 2010) and the ability to inhibit pervasive interoceptive cues becomes difficult (Etkin et al., 2015; Lindquist et al., 2012).
During heavy-intensity exercise, approximately one-third (sham tDCS) and one-fourth (active tDCS) of the participants were shown to have below-baseline TOI values in the right DLPFC at the end of the exercise. By contrast, during severe-intensity exercise, this was true of approximately half of the participants. It is possible that the number of participants who demonstrated a right DLPFC hypometabolic response was not affected by tDCS. If this was the case, this could have contributed to the non-significant effect of tDCS on the EVS scores. It is noteworthy that the change in EVS scores between active and sham tDCS during heavy-intensity exercise trended in the hypothesized direction. While not a statistically significant finding, the EVS scores increased by five points ($\eta^2_p = .065$) during heavy-intensity exercise with tDCS, compared to sham (Table 5). Therefore, tDCS could have impacted the EVS scores during heavy-intensity exercise but probably only for individuals who, as a result, sustained an above-baseline level of DLPFC activity. This warrants further investigation, especially since it cannot be stated with certainly what effect tDCS had on the hypometabolic state of the DLPFC during exercise, based on the results of the present study.

It has been proposed that below-average activation of the PFC is a neurological marker of depression (Baxter et al., 1989; Drevets et al., 1997; George et al., 1994). The degree of depressive symptoms has been shown to correlate inversely with PFC activation, including symptoms of fatigue (Galynker et al., 1998; George et al., 1994). Indeed, long-term treatment of mild and severe depression with tDCS increases PFC activity, the magnitude of which is directly associated with the reduction in depressive symptoms (Brunoni et al., 2011; Ferrucci et al., 2009; Fregni et al., 2006a). Nevertheless, there is a limit to the efficacy of tDCS in treating more severe forms of depression (e.g., treatment-resistant depression) (Meron et al., 2015), which suggests that PFC deactivation under some circumstances cannot be reversed using tDCS.
The findings of the present study provide evidence of hemispheric specialization in the DLPFC. During severe-intensity exercise with sham tDCS, the right DLPFC TOI, but not the left, was significantly correlated with the EVS scores. The results also indicated that, overall, individuals reported declines in the EVS scores (greater displeasure) throughout severe-intensity exercise. In other words, while, on average, participants reported declines in affective valence (Figure 3), those who experienced increased activation in their right DLPFC reported feeling better than those with lower activation levels in their right DLPFC (Figure 8C). This finding supports the notion of right hemispheric specialization in the regulation of displeasure (Feeser et al., 2014; Goldman et al., 2011; Ochsner & Gross, 2005; Okada et al., 2004).

A heating protocol was used to assess the influence of skin blood flow (i.e., in the forehead) on the measurement of oxy- and deoxyhemoglobin with NIRS. Temperature-dependent vasodilation did not appear to alter the measurement of either hemoglobin species. Both Doppler flux and forehead skin temperature significantly increased across time, while significant changes were not observed in oxy-and deoxyhemoglobin concentrations. Furthermore, across nearly every time point, skin temperature and Doppler flux were significantly correlated. A significant correlation was not observed between Doppler flux and oxy- and deoxyhemoglobin in either the right or left DLPFC at any time (Figure 12). The results of the heating protocol align with the findings of previous research (Auger et al., 2016; Ito et al., 2000). However, several studies have reported finding a significant effect of forehead skin blood flow on the NIRS signal (Davis et al., 2006; Kondo et al., 1998; Sorensen et al., 2012). Discrepancies in the findings might be due to the different types of NIRS instruments used, especially inter-optode distances (as explained in the literature review). A multi-distance frequency-domain NIRS instrument was used to measure the cerebral hemodynamics in the
present study, whereas a continuous-wave (CW) NIRS instrument was used in the studies by Davis et al. (2006), Kondo et al. (1998), and Sorensen et al. (2012).

Comparatively, CW NIRS machines are associated with more limitations compared to frequency-domain machines. CW machines can only measure relative changes in hemoglobin (not absolute concentrations) (Ekkekakis, 2009a); typically, they have less accuracy and reliability (Stienbrink et al., 2001), and, most importantly, they are more susceptible to noise induced by extracerebral changes (i.e., skin blood flow) (Gratton et al., 1997; Hemelt & Kang, 1999). Optode separation distance is another contributing factor. Sensors with an optode separation distance of < 3.0 cm have a shallow depth of measurement; therefore, are less likely to penetrate the cortex compared to an optode separation distance of > 3.0 cm (Germon et al., 1994, 1998; Kohri et al., 2002). In the present study, sensors with an optode separation distance of up to 3.5 cm were used. Ultimately, skin blood flow can influence the NIRS signal, but these effects are mitigated more effectively by some NIRS machines compared to others.

**Limitations**

The ASER data exhibited considerable noise, and the number of missing blinks (both invalid and undetected blinks) was higher compared to that reported in the non-exercise literature (Berg & Balaban, 1999; Blumenthal et al., 2005). However, the use of the ASER paradigm during exercise in the present study is a novel approach. The ASER paradigm has primarily been studied under resting conditions while performing passive tasks (e.g., viewing images on a screen while seated) (Blumenthal et al., 2005). Notwithstanding the problem of missing data in the present study, the main effects of the exercise intensity and the tDCS conditions were statistically significant. However, it is interesting that the direction of the ASER slopes was contrary to what was predicted. There could be several reasons for this. The “noise” in the eyblinks data tended to increase throughout the exercises. In other words, usually, there were
fewer valid eyeblinks toward the end of the exercise compared to the beginning. Based on the EVS scores, the participants generally reported more positive responses at the beginning of each exercise compared to the end. Therefore, if affect-modulated startle occurred, its trajectory may have been biased to some degree by the greater number of data points at the beginning of the exercise. Valid eyeblinks may have decreased over time due to the IOG sensor shifting during the exercise and thus moving slightly outside of the eye field. The effect of global peripheral physiological changes that occur during exercise, which could potentially have had a dampening effect on either the eyeblink itself, auditory processing/sensitivity, or the startle circuit, is another possible explanation for what might have impacted the eyeblinks. Evidence suggests that the ASER is directly modulated by cardiac baroreceptor afference (Schulz et al., 2009), which may alter the ASER in a way that is independent of affect modulation and the interoceptive modulation of affect. Another issue was that the eyeblink amplitudes were highly sensitive to the position and distance of the IOG sensor relative to the eye. While extensive effort was made to ensure that the placement of the sensor was consistent across conditions, even small deviations could have disturbed the signal. The rationale for analyzing the ASER data as the slope of z-score-converted amplitudes (z scores within each exercise session for every participant) was in an attempt to partially mitigate these limitations by creating a standard score that could be compared across conditions and between participants.

Another limitation of the present study was that the sample consisted of mostly young, physically active, and relatively fit individuals. This somewhat restricted the external validity of the findings, considering that the average American adult is hypoactive (Troiano et al., 2008; Tudor-Locke et al., 2010). Fitness and physical activity levels are known to influence affective responses (Ekkekakis & Lind, 2006) and the activation of the PFC during exercise (Rooks et al.,
In addition, the tolerance scores in the present study were somewhat higher than average when compared to the findings of other studies. Overall, the average tolerance score of the participants was between the 81st and 85th percentile according to norms presented by Ekkekakis et al. (2007).

A major limitation was that some participants completed the full severe-intensity exercise (approximately one-third of the sample) while others did not (approximately two-thirds of the sample). Participants with $t_{lim}$ less than 20 minutes presumably achieved a higher level of exertional fatigue compared to those who completed the full exercise. This result may influence the interpretation of psychophysiological responses in terms of the development of exertional fatigue compared to the response driving the cessation of exercise.

A fourth limitation, which was not a function of the study design but is nonetheless noteworthy, was the reduction in the sample size due to the Coronavirus Disease 2019 (COVID-19) global pandemic. While nearly all the participants were able to complete the study, four of them could not do so owing to the suspension of human-subjects research by the University. Therefore, from a statistical perspective, the study was slightly underpowered, which may have contributed to some of the unexpected findings.

Conclusion

Generally, the findings of this dissertation supported several tenets of the proposed theoretical framework of exertional physical fatigue. In the context of exertional fatigue, affective responses reflected the severity of homeostatic perturbations in the form of interoceptive processes mediated by cortical and subcortical pathways within a defined, hierarchically organized system. Exertional fatigue emerged at a defined threshold when the intensity of the interoceptive cues indicated ongoing non-steady state physiological processes. To an extent, exertional fatigue is regulated by PFC networks via top–down inhibitory projections to
subcortical networks, which includes regions such as the amygdala. While further work is needed on the genesis of exertional fatigue, its acute progression during exercise is coupled with activation of the PFC and its capacity to downregulate negative affect.

Certainly, the mechanisms and findings presented in this dissertation warrant further exploration and replication in future research. Specialization of the right PFC in cognitive inhibition of fatigue has potential in therapies that target modulation of PFC inhibitory control (top–down) or interoceptive sensitivity (bottom–up) networks. Future work should evaluate exertional fatigue in the broader context of the symptoms of fatigue associated with clinical disorders.
Figure 1. A neural basis of the sense of exertional fatigue
Raw interceptive stimuli enter the brain from the spine (Lamina I) & Vagal afference (projecting to the NTS)

Rudimentary processing pathways of the sub-cortical nuclei involved in regulating homeostasis, the relevance of stimuli in terms of its impact on homeostasis is encoded within these regions

Subcortical pathways involved with processing of the adaptational significance of stimuli

Affective qualities of stimulus emerge as the information from sub-cortical circuits project to the cortical regions

The perception of the stimulus as an affective state emerges within the cortical circuitry. Top-down regulation of the affective state is possible if sufficient cognitive resources are utilized.

Under normal conditions, PFC top-down regulation of the sub-cortical signaling readily inhibits the amygdala, hereby altering the intensity of the bottom-up signally and changing of the affective state (i.e., the sense of exertional fatigue).

Note. DLPFC: dorsolateral prefrontal cortex, involved deploying cognitive strategies, emotional regulation, goal oriented behaviors, working memory; mPFC: medial prefrontal cortex, appraising emotional states of self and others, emotional regulation, regulation of autonomic nervous system processes, decision making, direct projections with amygdala and other subcortical circuits; vACC: ventral anterior cingulate cortex, affective representations, reward anticipation, autonomic regulation; dACC: dorsal anterior cingulate cortex, reward based decision based on affective states; vACC: ventral anterior cingulate cortex, reward based decision making based on cognitive factors; AN: anterior group (thalamus); MD: mediodorsal nucleus (thalamus); LNG: lateral geniculate nucleus (thalamus), regulation of other sub-cortical regions, including the amygdala, and regulation of the cortex; VGN: ventral nuclear group (thalamus), somatosensory and motor information relay between the sub-cortical processing and the cortex; VPM: Ventral posteromedial nucleus (thalamus); PVN: Paraventricular nucleus (hypothalamus), cardiovascular, respiratory, and hormonal regulation during bouts of exertion; B: Basal amygdala, projects the adaptational significance of stimuli to the cortex; C: Central amygdala; modulates the autonomic nervous system including the startle response; L: Lateral amygdala, involved in modulating the affective reactivity of a stimulus; M: Medial amygdala, involved with motor, olfactory, and sexual function; PB; Parabrachial area, involved with cardiovascular, respiratory, and metabolic maintenance; PAG: Periaqueductal Gray, involved with processing nociception and core affect; VLM: ventrolateral medulla, regulation of cardio-respiratory functioning; NTS: nucleus of the solitary tract, coordination and relay of interoceptive information and homeostatic regulation.
Figure 2 A. Trial schematics of the initial visit

Note. PRETIE-Q: The Preference for and Tolerance of the Intensity of Exercise Questionnaire (Ekkekakis et al., 2005a); [(x)w·s⁻³]: the customized exercise test work-rate protocol (Dicks et al., 2016; Jamnick et al., 2016); tDCS: transcranial direct current stimulation; NIRS: near-infrared spectroscopy; EVS: Empirical Valence Scale (Lishner et al., 2008); FAS: Felt Arousal Scale (Svebak & Murgatroyd, 1985); RPE: Ratings of Perceived Exertion Scale (Borg, 1998); HR: Heart-rate; ASER: Acoustic Startle Eyeblink Response.
### Four Trials (completed by all participants)

**Order Counterbalanced**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Heavy Sham”</strong></td>
<td><strong>“Heavy Active”</strong></td>
<td><strong>“Severe Sham”</strong></td>
<td><strong>“Severe Active”</strong></td>
</tr>
</tbody>
</table>
| **Exercise Condition** | **tDCS Montage:** Anodal electrodes over AF3 & AF4, return electrodes over right and left shoulder  
**Current Density:** 0 mA·cm\(^2\) (sham)  
**Protocol:** Starting at WU onset, an acute 20 s current ramp-up, then a 20 s ramp-down | **tDCS Montage:** Anodal electrodes over AF3 & AF4, return electrodes over right and left shoulder  
**Current Density:** 0.057 mA·cm\(^2\) (active)  
**Protocol:** Starting at WU onset, an acute 20 s current ramp-up, then a constant current of 0.057 mA·cm\(^2\) until the end of the exercise | **tDCS Montage:** Anodal electrodes over AF3 & AF4, return electrodes over right and left shoulder  
**Current Density:** ~0 mA·cm\(^2\) (sham)  
**Protocol:** Starting at WU onset, an acute 20 s current ramp-up, then a 20 s ramp-down | **tDCS Montage:** Anodal electrodes over AF3 & AF4, return electrodes over right and left shoulder  
**Current Density:** 0.057 mA·cm\(^2\) (active)  
**Protocol:** Starting at WU onset, an acute 20 s current ramp-up, then a constant current of 0.057 mA·cm\(^2\) until the end of the exercise |
| **Regulation Control:** Positive self-talk  
**WU:** 5 min at cycling 60% VT w  
**CWR:** Cycling at 10% > VT w for 20 min (+ WU) or until volitional termination | **Regulation Control:** Positive self-talk  
**WU:** 5 min at cycling 60% VT w  
**CWR:** Cycling at 10% > VT w for 20 min (+ WU) or until volitional termination | **Regulation Control:** Positive self-talk  
**WU:** 5 min at cycling 60% VT w  
**CWR:** Cycling at 5% < RCP w for 20 min (+ WU) or until volitional termination | **Regulation Control:** Positive self-talk  
**WU:** 5 min at cycling 60% VT w  
**CWR:** Cycling at 5% < RCP w for 20 min (+ WU) or until volitional termination |

### During Exercise Measures

**Self-Report Measures**
- EVS (every min)  
- FAS (every min)  
- RPE (every other min)

**Physiological Measures**
- Pulmonary gas-exchange (breath-by-breath)  
- HR (10 Hz)  
- ASER (~every 20-40 s)  
- NIRS Cerebral hemodynamics (25 hz)

**Post-exercise Measures**
- tDCS symptoms questionnaire  
- Self-talk work-book review

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**B. Overall view of the experimental protocol for visits 2-5**

Note. Overall view of the experimental protocol during the heavy-intensity cycling exercise with sham transcranial direction current stimulation (tDCS) condition (Heavy Sham), the heavy-intensity cycling exercise with active tDCS over the left (AF3) and right (AF4) dorsolateral pre-frontal cortex (DLPFC) condition (Heavy Active), the severe-intensity cycling exercise with sham tDCS condition (Severe Sham), and the severe-intensity cycling exercise with active tDCS over the left and right DLPFC condition (Severe Active). All equipment used in visit one where used in visits 2-5 except for Doppler and the heating/temperature probe; VT: Ventilatory threshold; RCP: Respiratory compensation point; WU: cycling warm-up; w: watts; EVS: Empirical Valence Scale (Lishner et al., 2008); FAS: Felt Arousal Scale (Svebak & Murgatroyd, 1985); RPE: Ratings of Perceived Exertion Scale (Borg, 1998); ASER: Acoustic Startle Eyeblink Response; HR: Heart-rate.
C. Transcranial Direct Current Stimulation (tDCS) Electric Field Map

Note. A mathematical simulation of the electric field generated beneath the AF3 and AF4 anode electrodes. The return electrodes were placed on the right and left shoulder (not shown).
Figure 3. The Individual and Group Average Slopes of the Empirical Valence Scale (EVS) Scores During Each Experimental Condition

Note. Individual slopes of the Empirical Valence Scale (EVS) ratings (gray lines), group average EVS slopes (gray arrows), and group average EVS scores (black line) in the heavy-intensity exercise with sham tDCS (H-Sham) condition, the heavy-intensity exercise with active tDCS (H-Active) condition, the severe-intensity exercise with sham tDCS (S-Sham) condition, and the severe-intensity exercise with active tDCS (S-Active) condition; (A) H-Sham EVS $\mu = 2.9 \pm 18.5$, slope: $b = -0.8 \pm 1.1$; (B) H-Active EVS $\mu = 5.9 \pm 19.1$, slope: $b = -0.6 \pm 0.8$; (C) S-Sham EVS $\mu = -11.1 \pm 20.5$, slope: $b = -2.5 \pm 2.3$; (D) S-Active EVS $\mu = -9.2 \pm 20.6$, slope: $b = -2.7 \pm 2.6$. The unstandardized slope ($b$) is the absolute change of the EVS ratings over time (minutes) from three minutes after the warm-up to the end of the exercise. The $\mu$ is the group average $\pm$ SD for each condition. The Gray Lines terminate at volitional termination time ($t_{VOL}$) for each participant and the black lines terminate at the group average $t_{VOL}$ in each condition. The decline in the EVS slope in the severe-intensity conditions was significantly greater ($p < .001$) compared to the heavy-intensity exercise conditions.
Note. The heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition (H-Sham), the heavy-intensity exercise with active tDCS condition (H-Active), the severe-intensity exercise with sham tDCS condition (S-Sham), and the severe-intensity exercise with active tDCS condition (S-Active). The ΔTOI % represents the TOI change from the warm-up exercise baseline. Error bars represent the standard error. *Significantly lower ΔTOI% in the severe-intensity conditions compared to the heavy-intensity conditions ($p = .003$) and ΔTOI% in the right DLPFC was significantly lower compared to the left DLPFC across conditions ($p = .019$).
Individual slopes of $\Delta$TOI% (gray lines) and the group average slopes of $\Delta$TOI% (large gray arrow) in the heavy-intensity exercise with sham tDCS, heavy-intensity exercise with active tDCS, severe-intensity exercise with sham tDCS, and severe-intensity exercise with active tDCS conditions. Gray Lines terminate at the participant’s volitional termination time ($t_{\text{LIM}}$) and the large gray arrows terminate at the group average $t_{\text{LIM}}$ in each condition. Slopes represent the relative change (relative to the warm-up) in TOI% over time (minutes) calculated from three minutes post warm-up to the end of the exercise. Slopes were centered at minute nine (three minutes post warm-up). The $\Delta$TOI % represents the TOI change from the warm-up exercise baseline. The slope of $\Delta$TOI% decline was significantly greater in the severe-intensity exercise conditions compared to the heavy-intensity conditions ($p = .034$) and the slope of $\Delta$TOI% decline was significantly greater in the right DLPFC compared to the left DLPFC across conditions ($p = .003$).

Figure 5. Individual and Group Average Slopes of the Tissue Oxygenation Index Percentage ($\Delta$TOI%) in the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) During Each Experimental Condition
Figure 6. Individual and Group Average Slopes of the Acoustic Startle Eyeblink Response (ASER) During Each Experimental Condition

Note. Individual slopes of the ASER (gray lines) and the group average ASER slopes (large gray arrow) in the (A) heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition, (B) heavy-intensity exercise with active tDCS condition, (C) severe-intensity exercise with sham tDCS condition, and (D) severe-intensity exercise with active tDCS condition. Gray Lines terminate at the participant’s volitional termination time ($t_{\text{LIM}}$) and the large gray arrows terminate at the group average $t_{\text{LIM}}$ in each condition. Slopes represent the absolute change in the acoustic startle eyeblink response (ASER) amplitudes ($z$-scores) over time (minutes) starting from three minutes post warm-up to the end of the exercise. Slopes were centered at minute nine (three minutes post warm-up); A) H-Sham slope: $b = -0.0010 \pm 0.0695$; (B) H-Active slope: $b = 0.0070 \pm 0.0983$; (C) S-Sham: slope: $b = -0.2112 \pm 0.3087$; (D) S-Active: slope: $b = -0.0065 \pm 0.1403$. The unstandardized slope ($b$) is the change of the ASER $z$-scores (within-subjects, within-conditions) over time.
The heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition (H-Sham), the heavy-intensity exercise with active tDCS condition (H-Active), the severe-intensity exercise with sham tDCS condition (S-Sham), and the severe-intensity exercise with active tDCS condition (S-Active). The ΔTOI % represents the TOI change from the warm-up exercise baseline. Error bars represent the standard error. *Significantly greater decline in the final minute ΔTOI% in the severe-intensity conditions compared to the heavy-intensity conditions (p = .000) and the final minute decline in ΔTOI% in the right DLPFC was significantly greater compared to the left DLPFC across conditions (p < .001).

Figure 7. The Final Minute Change of the Tissue Oxygenation Index Change (ΔTOI %) in the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) During Each Experimental Condition

Note. The heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition (H-Sham), the heavy-intensity exercise with active tDCS condition (H-Active), the severe-intensity exercise with sham tDCS condition (S-Sham), and the severe-intensity exercise with active tDCS condition (S-Active). The ΔTOI % represents the TOI change from the warm-up exercise baseline. Error bars represent the standard error. *Significantly greater decline in the final minute ΔTOI% in the severe-intensity conditions compared to the heavy-intensity conditions (p = .000) and the final minute decline in ΔTOI% in the right DLPFC was significantly greater compared to the left DLPFC across conditions (p < .001).
Note. Data points were converted into epochs of one-tenth time segments to standardize the duration differences between participants and conditions. (A) heavy-intensity exercise with sham transcranial direct current stimulation (tDCS), (B) heavy-intensity exercise with active tDCS, (C) severe-intensity exercise with sham tDCS, and (D) severe-intensity exercise with active tDCS. The threshold for statistical significance (dashed-line) was set at the alpha level of $p < .05$.

Figure 8. Correlations Across Time Points (Segments) Between the Change in the Empirical Valence Scale ($\Delta$EVS) Scores and the Tissue Oxygenation Index ($\Delta$TOI%) in the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) During Each Experimental Condition
Figure 9. Correlations Between the Change in the Empirical Valence Scale Scores ($\Delta$EVS$_{\text{Final}}$) and the Tissue Oxygenation Index ($\Delta$TOI$_{\text{Final}}$) in the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) During the Final Minute of Exercise During Each Experimental Condition

Note. (A) heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition, (B) heavy-intensity exercise with active tDCS condition, (C) severe-intensity exercise with sham tDCS condition, and (D) severe-intensity exercise with active tDCS condition. Outliers (i.e., data points ± three standard deviations from the sample mean), are indicated with red arrows. The removal of the outlier data point in graph (C), changes the correlation between the $\Delta$EVS$_{\text{Final}}$ scores and the right DLPFC $\Delta$TOI$_{\text{Final}}$ to $r = 0.35, p = 0.06$. The removal of the outlier data point in graph (D), changes the correlation between $\Delta$EVS$_{\text{Final}}$ scores and the left DLPFC $\Delta$TOI$_{\text{Final}}$ to $r = 0.22, p = 0.24$. 

A. Left DLPFC $r = 0.33, p = 0.07$
   Right DLPFC $r = 0.30, p = 0.10$

B. Left DLPFC $r = 0.22, p = 0.23$
   Right DLPFC $r = 0.20, p = 0.28$

C. Left DLPFC $r = 0.20, p = 0.29$
   Right DLPFC $r = 0.07, p = 0.70$

D. Left DLPFC $r = 0.37, p = 0.04$
   Right DLPFC $r = -0.29, p = 0.11$
Figure 10. Correlations Between Tolerance Scores and the Change in the Tissue Oxygenation Index (ΔTOI% Final) in the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) During the Final Minute of Exercise During Each Experimental Condition

Note. (A) heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition, (B) heavy-intensity exercise with active tDCS condition, (C) severe-intensity exercise with sham tDCS condition, and (D) severe-intensity exercise with active tDCS condition. Outliers (i.e., data points ± three standard deviations from the sample mean), are indicated with red arrows. The removal of the outlier data point in graph (C), changes the correlation between tolerance scores and the right DLPFC ΔTOI% Final to \( r = 0.15, p = 0.36 \). The removal of the outlier data point in graph (D), changes the correlation between tolerance scores and the left DLPFC ΔTOI% Final to \( r = 0.08, p = 0.66 \).
Figure 11. Correlations Between the Slope of the Empirical Valence Scale (EVS) Scores and the Slope of the Acoustic Startle Eyeblink Response (ASER) During Each Experimental Condition

Note. (A) heavy-intensity exercise with sham transcranial direct current stimulation (tDCS) condition, (B) heavy-intensity exercise with active tDCS condition, (C) severe-intensity exercise with sham tDCS condition, and (D) severe-intensity exercise with active tDCS condition.
Note. Doppler flux correlations across time (segments) with the concentration change in oxygenated hemoglobin (O₂Hb) in the right and left dorsolateral prefrontal cortex (DLPFC), the concentration change in deoxygenated hemoglobin (HHb) of the right and left DLPFC, and the forehead skin temperature in the heating protocol. Data points were converted into epochs of one-tenth time segments to standardize the duration differences between participants and conditions. The threshold for statistical significance (dashed-line) was set at the alpha level of $p < .05$.

Figure 12. Correlations Across Time Points (Segments) Between the Change in Doppler Flux and the Forehead Skin Temperatures and the Right and Left Dorsolateral Prefrontal Cortex (DLPFC) Hemoglobin Concentrations During the Heating Protocol Experiment
Table 1

*Combined Participant Characteristics for Women (n = 12) and Men (n=18)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
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<tr>
<td>Age (years)</td>
<td>20.8 ± 3.2</td>
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<tr>
<td>Height (cm)</td>
<td>173.7 ± 10.5</td>
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<tr>
<td>Body Mass (kg)</td>
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<td>BMI (kg·m⁻²)</td>
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<tr>
<td>Body Fat (%)</td>
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<td>VO₂peak (ml·kg⁻¹·min⁻¹)</td>
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<tr>
<td>Weekly Moderate PA (min)</td>
<td>195.5 ± 242.2</td>
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<tr>
<td>Weekly Vigorous PA (min)</td>
<td>222.6 ± 160.0</td>
</tr>
<tr>
<td>Tolerance Score</td>
<td>29.6 ± 4.9</td>
</tr>
<tr>
<td>Time Point</td>
<td>Heavy-intensity Exercise</td>
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<tr>
<td>-----------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>tDCS Sham</td>
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<tr>
<td>Warm-up</td>
<td>81.5 ± 29.4</td>
</tr>
<tr>
<td>Final Minute of Exercise Trial</td>
<td>136.2 ± 46.4</td>
</tr>
</tbody>
</table>

*Note.* Data presented as means ± standard deviations (SD). Warm-up: the average oxygen uptake (VO$_2$) percentage during the 5-minute warm-up, Final Minute of Exercise Trial: the difference in VO$_2$ percentage between the final minute of the exercise trial and the average percentage during the 5-min warm-up; tDCS: transcranial direct current stimulation.
Table 3
*Ratings of Perceived Exertion (RPE) Responses in the Four Experimental Conditions*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Heavy-intensity Exercise</th>
<th>Severe-intensity Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tDCS Sham</td>
<td>tDCS Active</td>
</tr>
<tr>
<td>Warm-up (score)</td>
<td>7.6 ± 1.0</td>
<td>7.6 ± 0.8</td>
</tr>
<tr>
<td>Final Minute Change (Δscore)</td>
<td>5.3 ± 3.2</td>
<td>5.5 ± 2.6</td>
</tr>
</tbody>
</table>

Note. Data presented as means ± standard deviations, Warm-up Final Minute: the average RPE score during the 5-minute warm-up, Final Minute Change: the difference in RPE score between the final minute of the exercise trial and the average RPE score during the 5-min warm-up; tDCS: transcranial direct current stimulation. *Significantly larger change compared to heavy-intensity conditions p < .001.
### Table 4

**Felt Arousal Scale (FAS) Responses During Each Experimental Condition**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Heavy-intensity Exercise</th>
<th>Severe-intensity Exercise</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>tDCS Sham</td>
<td>tDCS Active</td>
</tr>
<tr>
<td>Warm-up (score)</td>
<td>2.0 ± 0.9</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>Final Minute Change (Δscore)</td>
<td>1.6 ± 1.8</td>
<td>1.7 ± 1.4</td>
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</tbody>
</table>

*Significantly larger change compared to the heavy-intensity conditions $p < .001$.*

**Note.** Data presented as means ± standard deviations, Warm-up; the average FAS score during the 5-minute warm-up, Final Minute Change; the difference in FAS score between the final minute of the exercise trial and the average score during the 5-min warm-up; tDCS: transcranial direct current stimulation.
Table 5

*Empirical Valence Scale (EVS) Responses During Each Experimental Condition*

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<th>Time Segment</th>
<th>Heavy-intensity Exercise</th>
<th>Severe-intensity Exercise</th>
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<tr>
<td></td>
<td>tDCS Sham</td>
<td>tDCS Active</td>
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<tr>
<td>Warm-up (score)</td>
<td>21.1 ± 16.8</td>
<td>20.3 ± 17.3</td>
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<tr>
<td>Slope (ΔEVS·min⁻¹)</td>
<td>-0.7 ± 1.1</td>
<td>-0.6 ± 0.7</td>
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<tr>
<td>Final Minute Change (Δscore)</td>
<td>-23.8 ± 22.9</td>
<td>-18.5 ± 18.6</td>
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*Note.* Data presented as means ± standard deviations (SD). Warm-up Final Minute; the average EVS score during the 5-minute warm-up; Slope: the change in EVS scores (range: -100-100) across time (minutes) from three minutes after the warm-up to the end of the exercise; Final Minute Change; the difference in EVS score between the final minute of the exercise trial and the average score during the 5-min warm-up; tDCS: transcranial direct current stimulation. *Significantly lower End Change (p < .001) and larger negative decline in slope (p < .001) compared to the heavy exercise conditions.*
REFERENCES


cerebral vasculature in diffuse optical imaging: A simulation study. *Biomedical Optics Express, 2*(3), 680. https://doi.org/10.1364/BOE.2.000680


APPENDIX A: INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL LETTER

Study 19-547-00 (IRB)

Study:
- Study: 19-547
- Committee: IRB #1
- Category: Kinesiology
- Title: Examining brain mechanisms during exercise
- Approved Date: November 21, 2019 for 12 months
- Initial Approval: November 21, 2019
- Status: Active
- Approver: Eklekakis, Panteleimon PhD
- Expiration: November 20, 2020

Notes:
We are currently developing a psycho-biological model of the feeling of fatigue during exhaustive exercise and wish to extend our progress with this study. The study expands upon the findings and methodologies of two previous studies conducted by the investigators (never for more...)

Study Site Contacts (4)

- Dolce, Catrina - Research Staff
- Garrett, Georgina - Research Staff
- Hartman, Mark - Research Staff
- True, Ryan - Research Staff

Reference xForms (1)

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<td>Modification Examining brain mechanisms during exercise</td>
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APPENDIX B: THE PREFERENCE FOR AND TOLERANCE OF THE INTENSITY OF EXERCISE QUESTIONNAIRE (PRETI-Q)

Please, read each of the following statements and then use the response scale below to indicate whether you agree or disagree with it. There are no right or wrong answers. Work quickly and mark the answer that best describes what you believe and how you feel. Make sure that you respond to all the questions.

1 = I totally disagree  2 = I disagree  3 = I neither agree nor disagree  4 = I agree  5 = I totally agree

1. Feeling tired during exercise is my signal to slow down or stop.  
2. I would rather work out at low intensity levels for a long duration than at high-intensity levels for a short duration.  
3. During exercise, if my muscles begin to burn excessively or if I find myself breathing very hard, it is time for me to ease off.  
4. I’d rather go slow during my workout, even if that means taking more time.  
5. While exercising, I try to keep going even after I feel exhausted.  
6. I would rather have a short, intense workout than a long, low-intensity workout.  
7. I block out the feeling of fatigue when exercising.  
8. When I exercise, I usually prefer a slow, steady pace.  
9. I’d rather slow down or stop when a workout starts to get too tough.  
10. Exercising at a low intensity does not appeal to me at all.  
11. Fatigue is the last thing that affects when I stop a workout; I have a goal and stop only when I reach it.  
12. While exercising, I prefer activities that are slow-paced and do not require much exertion.  
13. When my muscles start burning during exercise, I usually ease off some.  
14. The faster and harder the workout, the more pleasant I feel.  
15. I always push through muscle soreness and fatigue when working out.  
16. Low-intensity exercise is boring.
APPENDIX C: EMPIRICAL VALENCE SCALE (EVS)
APPENDIX D: FELT AROUSAL SCALE (FAS)

Please Rate Your Level Of Arousal

6   High Arousal

5

4

3

2

1   Low Arousal
APPENDIX E: RATINGS OF PERCEIVED EXERTION (RPE)

How hard do you feel the work is?

6   NO EXERTION AT ALL
7   EXTREMELY LIGHT
8
9   VERY LIGHT
10
11  LIGHT
12
13  SOMewhat HARD
14
15  HARD
16
17  VERY HARD
18
19  EXTREMELY HARD
20  MAXIMAL EXERTION
APPENDIX F: THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE-SHORT FORM (IPAQ-SF)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?
   
   ______ days per week
   
   □ No vigorous physical activities  → Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?
   
   ______ hours per day
   ______ minutes per day
   
   □ Don’t know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
   
   ______ days per week
   
   □ No moderate physical activities  → Skip to question 5
4. How much time did you usually spend doing moderate physical activities on one of those days?

   _____ hours per day
   _____ minutes per day

   [ ] Don't know/Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

   _____ days per week

   [ ] No walking → Skip to question 7

6. How much time did you usually spend walking on one of those days?

   _____ hours per day
   _____ minutes per day

   [ ] Don't know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?

   _____ hours per day
   _____ minutes per day

   [ ] Don't know/Not sure

This is the end of the questionnaire, thank you for participating.
APPENDIX G: PRESCREENING QUESTIONNAIRE

[welcome and information page before responding to survey questions]

Thank you for your interest in participating in this research study. The survey you are about to take asks questions pertaining to the study's eligibility criteria.

Below is a link to the *Informed Consent Document, which describes the study and what you will be asked to do. Please click on the link and read the informed consent.

Click HERE to read Informed Consent [insert link to informed consent document]

Brief description:
The study will require FIVE visits (1st visit= 90 minutes, visits 2-5 = 60 minutes each) to our lab which will involve exercising on a stationary bike. The purpose of this study is to assess brain activity during exercise. We are interested in the activation of certain brain regions at different exercise intensities. Using low levels of direct current (2 milliamps), brain regions can be stimulated non-invasively. We are interested in testing this technique during different types of exercise.

By starting this survey, you consent to this screening process. You will be asked about your age and medical conditions. Please respond as honest and as accurate as you can.

When you are ready to take the pre-screening survey click the arrow button below. When you are ready to take the pre-screening survey click the arrow button below.

[survey questions start]

Prescreen

1. Are you at least 18 years of age?
   ○ Yes
   ○ No

2. Are you currently pregnant?
   ○ Yes
   ○ No
   ○ I am not a female

3. Do you speak English as a second language?
   ○ Yes
   ○ No
[ACSM Risk Stratification Questions]

4. Do you have asthma, exercise-induced asthma, or any other lung disease?
   - Yes
   - No

5. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
   - Yes
   - No

6. Is your doctor currently prescribing drugs (for example, water pills) for blood pressure or heart condition?
   - Yes
   - No

7. Have you ever been diagnosed with cardiovascular disease, stroke, or cerebrovascular disease, or another vascular disease?
   - Yes
   - No

8. Have you ever been diagnosed with a renal disease, metabolic disease, or diabetes (Type I or Type II)?
   - Yes
   - No

9. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
   - Yes
   - No

10. Do you ever experience pain or discomfort in your chest, neck, jaw, or arms?
    - Yes
    - No

11. In the past month, have you had chest pain when you were not doing physical activity?
    - Yes
    - No

12. Do you lose your balance because of dizziness or do you ever lose consciousness?
    - Yes
    - No
13. Do you ever experience shortness of breath when lying down?
   ○ Yes
   ○ No

14. Do you experience shortness of breath at rest or with mild effort?
   ○ Yes
   ○ No

15. Do you ever experience ankle edema or swelling of the foot, ankle, or leg?
   ○ Yes
   ○ No

16. Do you ever experience a noticeably strong heart rate or a resting heart rate of over 100 beats per minute?
   ○ Yes
   ○ No

17. Do you ever experience an aching, crampy, tired, or sometimes burning pain in the leg that comes and goes?
   ○ Yes
   ○ No
18. Do you have a heart murmur?
   ☐ Yes
   ☐ No

19. Do you have unusual fatigue or shortness of breath with usual activities?
   ☐ Yes
   ☐ No

20. Please enter your age (years)
    _______________

21. Please select your sex
    ☐ Male
    ☐ Female

22. Please enter your weight (lbs)
    _______________ lbs

23. Please enter your height (inches)
    ________________ inches

24. Do you currently smoke cigarettes?
    ☐ Yes
    ☐ No

25. Has anyone in your immediate family been diagnosed with cardiovascular disease?
    ☐ Yes
    ☐ No

26. Do you participate in at least 30 minutes of moderate intensity (e.g., brisk walks), physical
activity on at least 3 days of the week for at least 3 months?
  ○ Yes
  ○ No

27. Have you ever been diagnosed with high cholesterol?
  ○ Yes
  ○ No

28. Have you ever been diagnosed with hypertension?
  ○ Yes
  ○ No

29. Has your doctor ever told you that your blood sugar is too high?
  ○ Yes
  ○ No

[Psychological health & additional health screening questions]

30. Do you have a history or currently have any mental health problems (anxiety, panic, PTSD, past trauma)?
  ○ Yes
  ○ No

31. Do you have a pacemaker?
  ○ Yes
  ○ No

32. Do you have intracranial electrodes?
  ○ Yes
  ○ No

33. Do you have a history of neurological problems such as concussions, epilepsy, or seizures?
  ○ Yes
  ○ No

34. Do you have a history of migraine headaches?
  ○ Yes
  ○ No

35. Are you currently prescribed medications for any of the following conditions: depression, bipolar, anxiety, pain, cholesterol, blood pressure, attention-deficit hyperactivity disorder (ADHD),
type I or type II diabetes?
- Yes
- No

36. Do you have any implanted defibrillators or any other prosthetic?
- Yes
- No

37. Do you currently have a known skin disease on face or forehead?
- Yes
- No

38. Which hand do you prefer to use when writing?
- Left
- No preference
- Right

39. Do you ever use your other hand for writing?
- Yes
- No

40. Which hand do you prefer to use when drawing?
- Left
- No preference
- Right

41. Do you ever use your other hand for drawing?
- Yes
- No

42. Which hand do you prefer to use when throwing?
- Left
- No preference
- Right

43. Do you ever use your other hand for throwing?
44. Which hand do you prefer to use when using scissors?
   - Left
   - No preference
   - Right

45. Do you ever use your other hand when using scissors?
   - Yes
   - No

46. Which hand do you prefer to use when using a toothbrush?
   - Left
   - No preference
   - Right

47. Do you ever use your other hand when using a toothbrush?
   - Yes
   - No

48. Which hand do you prefer to use when using a knife (without a fork)?
   - Left
   - No preference
   - Right

49. Do you ever use your other hand when using a knife (without a fork)?
   - Yes
   - No

50. Which hand do you prefer to use when using a spoon?
   - Left
   - No preference
   - Right

51. Do you ever use your other hand when using a spoon?
   - Yes
   - No

52. Which hand do you prefer to use when using a broom (upper hand)?
53. Do you ever use your other hand when using a broom (upper hand)?
   - Yes
   - No

54. Which hand do you prefer to use when holding a computer mouse?
   - Left
   - No preference
   - Right

55. Do you ever use your other hand when holding a computer mouse?
   - Yes
   - No

56. Which hand do you prefer to use when opening a box (holding the lid)?
57. Do you ever use your other hand when opening a box (holding the lid)?
   ○ Yes
   ○ No

58. Which foot do you prefer to kick with?
   ○ Left
   ○ No preference
   ○ Right

59. Which eye do you use when using only one?
   ○ Left
   ○ No preference
   ○ Right

[additional safety questions]

60. Have had surgery on your brain or skull or hospitalized for a brain injury or concussion?
   ○ Yes
   ○ No

61. Do you have/had brain aneurysm clips?
   ○ Yes
   ○ No

62. Do you have any implanted medical devices, clips, or systems (cochlear implants, implanted or external medication pumps, catheters with metallic components, pacemakers or defibrillators, neurostimulation systems, etc.)
   ○ Yes
   ○ No

63. Do you have a bullet, shrapnel, or other type of metallic fragment in your body?
   ○ Yes
   ○ No

64. Do you have any metallic or foreign objects in or near your eye or head (including dental work such as implants, braces, and fillings)?
   ○ Yes
   ○ No
65a. Do you have any tattoos on your neck or above?
   - Yes
   - No

65b. (if yes to 65a) Can confirm that the tattoo(s) on your neck or above does NOT contain a metallic pigment?
   - Yes
   - No

66. Has your medical provider ever informed you that should not receive Magnetic Resonance Imaging (MRI)?
   - Yes
   - No

67. Do you have a history of hearing problems such as hearing loss, reduced hearing acuity, recent otitis, injured eardrum, or tinnitus?
   - Yes
   - No

68. Are you sensitive to loud sounds or have been diagnosed with hyperacusis?
   - Yes
   - No

QUALIFIED:

NRLastName Thank you for your interest. You are eligible to participate. Please enter your last name in the text box below.

NRE-mail Please enter your e-mail address.

Please fill out your availability below for scheduling.

DISQUALIFIED:

Thank you for your interest. Unfortunately, it is unsafe for you to participate in this exercise study. Your responses to this survey are anonymous and will not be retained.

However, you may qualify for future studies. If you are interested in participating in future studies and would like us to contact you, please enter your e-mail address below:

________________________
APPENDIX H: SELF-TALK BOOKLET

Examining Brain Mechanisms During Exercise Study

POSITIVE SELF-TALK

Participant Training Booklet

What is self-talk?
Anytime we think about something, our thoughts will usually be in the form of dialogue, images, or feelings. When we think in terms of words, we are, in a sense, talking to ourselves (self-talk). We often engage in self-talk when making decisions, performing difficult tasks, and reflecting about what we are doing or feeling (e.g., “this workout feels great, I want to keep going”).

Positive Self-Talk

Positive self-talk uses motivational words and phrases to increase concentration, improve performance, and change our mindset. Positive self-talk typically focuses on words that increase energy, effort, and a positive attitude. Self-talk functions as a mediator between our behavior and our response (see EXAMPLE).

“Just focus on pushing a little bit harder each moment”
-Dr. Positive

Negative Self-Talk

Negative self-talk is when we are hyper critical and self-demeaning. Negative self-talk gets in the way our goals (e.g., performance) and is counterproductive (see EXAMPLE).

“I won’t be able to finish this exercise”
-Dr. Negative

EXAMPLE: Engaging in positive (+) responses increase performance while negative (-) responses impair performance.
Positive Self-Talk Toolbox: Example Phrases

INSTRUCTIONS: Below is a list of positive self-talk words and phrases commonly used by exercise scientists. Circle and record (BOX 1) 4-6 positive self-talk words or phrases that you believe could be beneficial to your performance. You may also create your own statements if you wish (BOX A).

Guidelines for creating positive self-talk statements:
- Keep your phrases short & specific
- Use the first person & present tense
- Construct positive phrases
- Say your phrases with meaning & attention
- Speak kindly to yourself

BOX 1
Self-talk statements selected:
#___
#___
#___
#___
#___

1) “I’m doing well”
2) “Fast”
3) “Quick”
4) “Do it”
5) “Go”
6) “Sprint”
7) “Drive forward”
8) “Hold onto it”
9) “Push”
10) “Go for it”
11) “I can do it”
12) “Let’s go”
13) “Power”
14) “Give 100%”
15) “Do your best”
16) “Strong”
17) “I can make it”
18) “I feel strong”
19) “Push through this”

BOX A CREATE YOUR OWN (Optional)

20) “Stay tough throughout the test.”
21) “Just hang in there a little longer”
22) “This is a challenge I’m going to meet”
23) “Head up, back straight, maintain my pedal cadence”
24) “Come on, it’s time to give it my all!”
25) “I’m doing my best”
26) “I can manage a bit longer”
27) “Better performance = more accurate fitness report”
28) “I’m earning $200 for this study!”
29) “I have the mental strength to do this”
30) “I can manage my energy until the end”
31) “I’ve done hard workouts before, so I can do this one too”
32) “I care, and I’ll be happier if I push myself”
33) “Of course it’s tough, but the rewards are worth it”
34) “I feel excited and ready”
35) “Keep my rhythm, I have more to give”
36) “Push a little bit harder each moment”
Reframing & Refocusing—Counteracting negative self-talk

Reframing

⇒ Uses positive self-talk to defend against negative thoughts
⇒ Transforms how we view things—changing weaknesses into strengths
⇒ Does not deny or downplay what we are experiencing or ignore the discomfort
⇒ Acknowledges what is happening and uses it to our best advantage (e.g., “I’m feeling anxious” --- “I feel excited and ready”)

Reframing Examples:

(negative statement) “I’ve worked too hard” and changed this to (positive statement) “I can manage my energy until the end”

“My legs are stiff, I feel tired” or “the heat is overwhelming, I’ll have to slow down” --- “This is a challenge I’m going to meet, I have the mental tools to cope”

“This exercise is really hard, I’ll never finish it.” --- “I’ve done hard workouts before, so I know if I’m persistent I can do this one too.”

“I’ll take it easy today and go hard next workout” --- “The next workout will be easier if I go hard now.”

“Who cares how well I do anyway?” --- “I care, and I’ll be happier if I push myself.”

“This hurts, I don’t know if it’s worth it.” --- “Of course it hurts, but the rewards are worth it.”

“I’m feeling anxious.” --- “I feel excited and ready”

“This sucks, I’m tired.” --- “Keep my rhythm, I know I have more to give”

“I won’t be able to finish this exercise.” --- “Just focus on pushing a little bit harder each moment”
Reframing the negative thoughts you experienced during the exercise

INSTRUCTIONS: Reflect upon the exercise test you just completed. Was it difficult? Were there times that were more difficult than others? What did you feel and what were your thoughts? Were any of your thoughts or feelings negative? If so, write down a few examples of the negative thoughts and/or feelings you experienced (in the “Negative Thoughts” box). Think of ways you could change those thoughts or feelings into positive self-talk (in the “Reframed Thoughts” box). Alternatively, you can use positive self-talk to distract from your negative thoughts or feelings.

A “cue” can be anything that reminds you to refocus during the exercise. For example, this could be focusing your attention/gaze on the positive self-talk words displayed on the TV screen in front of the bike (during the future exercise sessions in the study).

In addition to the positive self-talk statements you previously developed, the above statements will be displayed during your next exercise session.
APPENDIX I: SELF-TALK QUESTIONNAIRE

Self-Talk Post Assessment
1. Did you engage in positive self-talk during the exercise?
   YES  NO
2. Did you encounter any negative thoughts about the exercise?
   YES  NO
3. Did you use positive self-talk to restructure/counteract negative thoughts to motivate yourself?
   YES  NO
4. List any/all positive self-talk phrases that you used during the exercise:
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
5. How often did you use the above phrases (times per minute)?
   __________
6. Rate how consistent you were in using positive self-talk throughout the exercise (0 “never”, to 10 “every moment during the exercise”)
   0  1  2  3  4  5  6  7  8  9  10
7. Did using positive self-talk influence or change how you felt during the exercise?
   YES  NO
8. List and negative self-talk statements you had during the exercise:
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
9. During the exercise, how often did negative self-talk occur?
   __________________________
APPENDIX J: TDCS SYMPTOMS QUESTIONNAIRE

Participant Symptoms Report

1. Did you feel any sensation from the forehead sponges during your exercise session?  
   Yes  No

2. If you felt something, describe how it felt and how long you felt it.  
   It felt like  
   a(n)_____________________________________________________________  
   I felt this for

3. Do you think the sensation made you feel better in any way?  
   Yes  No

4. If you felt better, rate how much better you felt from 0 (not better at all) to 10 (best I’ve ever felt)  
   0  1  2  3  4  5  6  7  8  9  10

5. Did the sensation bother you in any way?  
   Yes  No

6. Was the sensation painful in any way?  
   Yes  No

7. If it was painful, rate the pain from 0 (not at all painful) to 10 (worst pain ever)  
   0  1  2  3  4  5  6  7  8  9  10