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Creation of a Virtual Interface for Stress-Trauma Investigations through Open World Navigation: An Exploration of Tolerability and Physiological Reactions

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Abstract

It is estimated that as many as 50% of people suffering from Whiplash -Associated Disorders (WAD) may experience chronic alterations of their activities of daily living as much as 1-year post injury. Despite their burden, there is little to evidence to suggest why some people may be more likely to acquire WAD or develop chronic symptomology. Additionally, the link between biomechanical forces at the time of impact and symptom development or recovery is poor. As a result, interest in alternative theories such as stress system reactivity have received interest in recent literature, but empirical methods to test them has been lacking. Thus, the purpose of this thesis was to explore the relationship between stress and trauma using a known stressor and a newly developed virtual reality (VR)-based car crash simulator to better understand the immediate reaction to being involved in a motor vehicle crash (MVC). In Chapter 2, we evaluated conditioned pain modulation (CPM) in reaction to the cold pressor task and measured associations with indices of sympathetic and hypothalamic-pituitary-adrenal function. It was found that only 30% of participants experienced inhibitory CPM. Within this group, there was a positive moderate correlation between CPM and the absolute change in skin conductance pre-to-post cold pressor task. In Chapter 3, we explored the initial tolerability to a novel VR-based car crash simulator in healthy subjects and also evaluated sense of presence and simulator sickness. The system was well tolerated by a majority of participants, and it appeared that the sense of presence and simulator sickness shared an inverse relationship. In Chapter 4, we evaluated the pain and stress response to our VR-based car crash simulator in the form of pain pressure detection thresholds, CPM, heart rate variability, and salivary cortisol. Over 40% of participants were more sensitive to pain following the simulation, and this may have been associated with an increase in parasympathetic nervous system activity and salivary cortisol. These results may help to explain some of the heterogeneity of WAD presentations after a MVC and signify that the pain/stress response to simulated trauma is variable.

Keywords

Conditioned pain modulation, whiplash-associated disorders, virtual reality, stress reactivity, pressure pain detection threshold, galvanic skin response, heart rate variability, pain

Summary for Lay Audience

While there has been much research over the last 20 years to understand car crashes, it remains unclear why some people develop neck pain and others do not. This collection of symptoms immediately after a car crash is referred to as Whiplash. Recent research has suggested that neck pain after a car crash could be due to high amounts of stress that are felt during a car crash. Unfortunately, until now there has been no way to test this theory. We recently created a new virtual reality based simulator that is designed to mimic the experience of being in a car crash without the physical injury. Thus, this research project was designed to examine how healthy people react to being involved in a virtual reality car crash.

The first project in this thesis was designed to look at how healthy people react to being stressed using a common way of generating stress. We did this by placing healthy people's hands into cold water and measuring their nervous system activity and their pain before and after. It appeared that some people become less sensitive to pain and that this was associated with the 'fight' aspect of the fight or flight response. For the second project in this thesis, we wanted to see if healthy people could tolerate exposure to a virtual reality car crash. We also measured how much they felt like they 'were actually there' and if they became sick or not. Most people were able to tolerate this virtual reality car crash and that as the feeling of 'being there' increased, sickness decreased. The third project in this thesis looked how healthy people responded to a virtual reality car crash in terms of their pain and nervous system activity. We surprisingly found that some people become more sensitive to pain after a virtual car crash and that this was associated with the 'flight' aspect of the fight or flight response. With this information, we may be able to start better understanding why some people get neck pain after a car crash and some people do not.

Co-Authorship Statement

This thesis contains three seminal chapters that are being prepared for publication that would not be possible without a team of collaborators. Michael Lukacs is the primary author of all included chapters in this thesis (Chapters 1 through 5), as he was responsible for designing the studies, recruitment of participants, data collection, analyzing the data, and producing the initial draft of each chapter. Chapters 2, 3, and 4 were all co-authored by Dr. Jamie Melling, Dr. James Dickey and Dr. David Walton who provided invaluable feedback regarding study design and feedback on each chapter. Chapter 3 was also co-authored by Mr. Mathias Babin who assisted in the creation of the simulator used in the study and provided feedback on the final manuscript. Lastly, the students within the MPT program at Western University aided with data collection and participant recruitment in Chapter 2.

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Table of Contents

List of Tables

List of Figures

List of Appendices

Chapter 1

1 Introduction

1.1 The Burden of Neck Pain

The experience of pain is one of the most complex, universal, and fundamental human experiences, which is also the most common reason why patients seek medical care.[1] It is generally accepted that the individual experience of pain is the result of some combination of biological, psychological and sociocultural factors.[2] Due to its multiple inputs, The International Association for the Study of Pain re-defined pain as, "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*."[3] Chronic pain is estimated to affect 18.9% of adults in Canada, with half having lived with chronic pain for over 10 years.[4] Specifically, neck pain (NP) (as of 2019) constituted the 12th leading cause of years lived with disability globally, while road injuries were the 7th leading cause of disability-adjusted life years.[5]

Recent concept mapping has suggested that the impact of NP extends far beyond the physical, with influences on performing activities of daily living, social participation and financial consequences.[6] People suffering from NP have also expressed that they have faced misunderstanding regarding their condition from their families and employers.[6] Unfortunately, despite its burden, the cause of NP is not always evident and thus makes treatment options for its sufferers challenging.[7,8] NP can arise from any structure in the neck including but not limited to muscles, ligaments, joints, and intervertebral discs.[9] As a result, most NP has been labelled as non-specific NP to reflect this problem and can generally be broadly sub-divided into two categories: traumatic and non-traumatic.[10] One of the most common causes of NP in a traumatic setting is exposure to a motor vehicle crash (MVC).[11]

1.2 Motor Vehicle Crashes and Whiplash-Associated Disorders

Exposure to either a rear-end or side-impact MVC can impart an acceleration-deceleration transfer of energy to the head and neck, which is known as a Whiplash mechanism of injury.[12] The term MVC is used instead of motor vehicle accident (MVA) to reflect that calling these events accidents undermines the experience of their sufferers.[13] In turn, Whiplash-Associated Disorders (WAD) refer to the range of symptoms that result after a MVC from an acceleration-deceleration mechanism of injury.[14] The symptoms of WAD can include but are not limited to: neck pain, loss of range of motion of the neck, neurological signs and even fracture of the cervical spine.[15] Due to the myriad of presentations, the Quebec Task Force classified patients with whiplash[16] as:

- Grade 0: No injury. No neck complaints. No physical signs
- Grade 1: Injuries for which there is a complaint of neck pain, or stiffness, or tenderness. No physical signs
- Grade 2: Injuries for which there is a neck complaint and physical sign such as loss of range of motion or point tenderness
- Grade 3: Injuries for which there is a neck complaint and neurological signs such as decreased sensation and/or weakness
- Grade 4: Injuries for which there is a neck complaint and cervical fracture

Interest in prognosis from whiplash injuries has seen great interest as half of affected adults have resolution of their symptoms (without intervention) while the remainder will experience either prolonged recovery or chronic symptomology.[11,17] Prior work has also shown that, amongst other factors, the experience of higher pain severity shortly after injury is a strong predictor of poor outcomes 6 to 12 months later.[18] Despite numerous studies elucidating various prognostic factors in the recovery of WAD, recovery rates have changed little in the last 30 years, and the mechanisms behind WAD remain elusive.[19,20]

1.3 Historical Models of WAD

Historical models of WAD have been explored from the basis of a pathoanatomical model of injury.[19] Cadaveric biomechanical studies demonstrated that in a rear-end MVC, the cervical spine experiences a reversed S- shaped curve leading to lower cervical spine hyperextension and upper cervical spine flexion.[21,22] Thus, it was postulated that this mechanism could result in increased shearing and tensile forces at individual cervical levels leading to injury of the soft tissues of the neck.[21,22] Most notably, the facet joints of the cervical spine have been implicated in NP due to their potential for nociception and their capsular strain during a whiplash event.[22–24] Cervical radiofrequency neurotomy of facet joints in patients with chronic WAD has been shown to improve pain and disability scores even 3 months following the procedure.[24] However, even in patients who received radiofrequency neurotomy of their facet joints, they still present with mild to moderate pain.[24]

In spite of biomechanical studies, traditional diagnostic imaging (e.g., plain films or magnetic resonance imaging) have been unable to consistently and accurately detect the presence of soft tissue lesions in patients with WAD.[25] Nevertheless, it has been suggested that 40 to 45% of patients with chronic WAD likely have a peripheral articular lesion responsible for their NP.[19] There also appears to be little association between crash parameters such as speed and direction of collision, or awareness of impending collision and recovery from development of WAD.[17,19,26] Further complicating WAD, is that there is little evidence to suggest why one individual may experience a lack of symptoms from a high force collision, while someone else may present with significant symptomology from a low-speed perturbation.[20] Due to the disparity between these findings, newer models for understanding WAD have been proposed.

1.4 New Integrated Models of WAD

To try and reconcile gaps in the literature and to help explain the heterogeneity of the clinical presentation of WAD, Walton and Elliot (2017) proposed an Integrated Model of WAD, drawing upon previous work in both the Fear-Avoidance Model of Pain as well as the Diathesis-Stress model of pain.[19] The Fear-Avoidance model of pain postulates that

when pain is experienced, there are two likely outcomes.[27] The first is one of recovery where the situation is seen as non-threatening, thereby the person is likely to stay engaged in functional activities that promote recovery. The second outcome is one of prolonged suffering, in which fear of pain leads to fear of movement which leads to a vicious cycle where pain can be catastrophized leading to the potential for further pain and suffering. The Diathesis-Stress model of pain on the other hand sought to give considerations to the interactions of individual predisposing factors in the reaction to trauma.[2]

Diatheses can be individual personal and contextual variables (e.g., psychological, genetic) that either lead to protection or vulnerability in the context of injury.[19] Walton and Elliot (2017) built upon these theories to present an integrated model of WAD that fully considers the interaction effects between psychological and neurobiological systems as well as their contributions from personal and environmental factors.[19] Also included in this model was the idea that the MVC acted as a unique catalyst that led to a cascade of both physiological and psychological responses to protect from injury.[19] These responses are thought to include an acute stress response to trauma, that has been postulated to be abnormal or maladaptive in those who develop chronic WAD.[19,28]

1.5 Stress Reactivity and Pain

A stressor can be defined as circumstances that threaten the physical and/or psychological state of the individual.[29,30] In response, the individual may experience distress which consists of a psychological appraisal of the situation and can include both the feelings of anxiety and/or feeling overwhelmed.[30] While the term distress expresses a negative connation, some degree of distress is considered advantageous in reaction to a stressor, as individuals who experience little distress may also be at risk of developing psychopathology.[19,31]Distress is a separate experience from that of eustress which has been typically been defined as ‘good stress’ and includes an optimal stress response to a stressor to a stressor that the individual has appraised as non-threatening (e.g., exercise).[32] The psychological appraisal of the situation at hand is assessed by the prefrontal cortex, hypothalamus, and amygdala which determine if the circumstance is threatening to the homeostasis of the body.[33]

Next, the body experiences two major physiological processes: the fast activation of the sympathetic nervous system (SNS) component of the autonomic nervous system (also known as the sympathetic-adreno-medullary (SAM) axis), and the slow activation of the hypothalamus-pituitary-adrenal (HPA) axis.[33–35] Activation of the SNS leads to an increase in heart rate, blood pressure, and perspiration, while activation of the HPA axis ultimately leads to the release of the stress hormone cortisol.[33,34] Cortisol aids the body in its ability to use glucose for fuel and is also a potent anti-inflammatory.[36] However, under chronic stress conditions, elevated cortisol levels can lead to its dysfunction causing increased systemic inflammation and pain.[36] Acute activation of these systems (SNS & HPA axis) can lead to stress-induced analgesia (SIA) to help protect the individual from harm, which is controlled by descending opioid and non-opioid brain circuits.[37,38]

If the stressor includes a noxious or painful stimulus, then activation of a similar yet unique system known as Diffuse Noxious Inhibitory Control (DNIC) can also occur simultaneously.[38] DNIC consists of a spinal-medullary-spinal pathway that can be activated for pain inhibition in response to a painful stimulus, more commonly referred to as 'pain inhibits pain'.[39] Interest in DNIC and stress reactivity in chronic WAD patients has been gaining interest in recent years, as both impaired DNIC[40] and stress reactivity[28,41] have been implicated in patients suffering from chronic WAD. Due to these findings, there has been a push to try and identify both physical and psychological factors that may be predictive in determining outcomes after whiplash injuries for the development of chronic pain.[42]

1.6 Pain and Stress Measurement as Biomarkers for Chronic Pain

Conditioned Pain Modulation (CPM) is one technique that has seen increasing use and is conceptualized as a means to evaluate the functioning of pain inhibitory pathways (i.e., DNIC).[43] CPM protocols typically consist of exposing participants to a testing stimulus before and after exposing them to a different noxious conditioning stimulus. The testing stimulus is commonly a measure of pain pressure detection threshold (PPDT)(e.g., mechanical or thermal) and the difference in threshold between the pre- and post-exposure to the conditioning stimulus is considered the CPM.[43,44] Assuming well-

functioning DNIC, pain thresholds normally increase (the system becomes less sensitive to the testing stimulus) following exposure to the conditioning stimulus, though negative CPM, considered dysfunctional DNIC, is a consistent feature of chronic pain presentations (e.g., fibromyalgia).[45] However, recent evidence has suggested that CPM may not be a universal finding, even among healthy individuals.[44,46]

Stress reactivity is also of interest in the context of WAD, as chronic WAD shares common psychological sequelae with those suffering from post-traumatic stress disorder (PTSD).[19,47] Stress reactivity can be captured using non-invasive measurement tools such as Galvanic Skin Response and Heart Rate Variability (HRV).[48,49] Galvanic Skin Response (GSR) has been shown to be one of the quickest non-invasive evaluative tools through which to evaluate a physiological stress.[50,51] GSR is a measure of a change in the electrical properties of the skin, where more sweat (moisture) reduces current resistance in reaction to a noxious stimulus due to activation of the SNS.[52] This happens on a millisecond scale and is completely outside of voluntary control, making it an attractive metric for stress research.[50,53] HRV is a physiological measure that has been used as a clinical proxy of autonomic tone (sympathetic: parasympathetic balance) in healthy and diseased states.[54,55] While there are many methods to measure HRV using standard ECG recordings, the time domain methods (e.g., root mean square of the successive differences (RMSSD) between normal heartbeats), are some of the simplest to perform, appear to be clinometrically robust, and can be captured in a 5 minute period.[55] HRV in particular has been shown to be decreased in subjects with chronic WAD in comparison to healthy controls.[56]

1.7 Opportunities for Innovative Technologies in Understanding WAD

Unfortunately, many of these newly proposed theories and/or models of WAD have remained firmly fixed in the theoretical phase as it isn't feasible or ethical to place subjects in live car crashes for scientific research.[57] Emerging technologies in the form of driving simulators could be a novel method through which the experience of a MVC can be replicated without the potential for tissue damage or excessive biomechanical forces.[57] To date, lab-based research involving driving simulators has been limited to exposure

therapy studies for treatments of patients suffering from PTSD or intervention to alter driving behaviour.[58,59] One promising technology in this domain is the use of virtual reality (VR). VR can be understood as technologies that produce a virtual environment via hardware or software that simulates real-world objects or events and allows the subject to interact with the virtual environment.[60,61] VR relies on interactivity and immersion to create a sense of presence, and interactivity to either replicate real world environments or imaginative settings.[62] Immersion in this context refers to the objective level of sensory feedback and/or fidelity that a of which a VR system is capable.[63]

In an interesting study simulating a MVC before the advent of VR, Castro and colleagues (2001) exposed healthy participants to what they termed a placebo car crash. This experimental setup was designed such that participants would experience sudden braking, and glass shattering to believe that they had been involved in a rear-end MVC without actual vehicle collision.[64] This study reported that up to 20% of participants can experience symptoms of WAD, even in reaction to a placebo car crash.[64] It could be argued however that this experimental setup was not as immersive as that of a VR-format in which the subject can be fully immersed in the experience. As such, exposure to a VR-based MVC may be able to allow subjects believe that they are participating in a MVC, such that the effects of low-speed MVC with low biomechanical forces can be directly observed. Additionally, the work of Castro and colleagues (2001) also relied on symptom self-report, and therefore it is unclear if there were any objective physiological findings present in those that experienced WAD-like symptoms.[64] Again, a VR-based MVC could be advantageous in simulating various MVC crash types (e.g., rear-end vs side-impact) with real-time physiological monitoring from both pain and stress measurement perspectives.

1.8 Overall Purpose

The overall purpose of this thesis was to explore CPM and measures of stress system reactivity in reaction to both a known stressor (e.g., cold pressor task) and a novel VR-based road collision simulator. We understood that this line of work would likely raise more questions than it would answer but were hopeful that it might help to illuminate why symptoms of WAD may persist in the absence of biomechanical forces that impart

tissue damage. It was also our hope that this work would fundamentally aid patients in understanding why they have their symptoms while others do not. Thus, the work of this thesis is presented in three separate but related main chapters.

The aim of Chapter 2 of this thesis was to identify meaningful CPM in a cohort of healthy young adults in reaction to the cold pressor task and to explore relationships with measurements of stress system reactivity (e.g., skin conductance and salivary cortisol). We envisioned this study as a comparator with other studies examining pain responses to different conditioning stimuli. This study was also designed to contribute to the growing body of literature in identifying meaningful CPM.

The aim of Chapter 3 was to explore the initial tolerability of participants using a novel virtual reality-based road collision simulator designed to mimic the experience of being the passenger in a car crash. This study was also designed to gather user feedback regarding sense of presence and simulator sickness to help refine the simulator for future use. Adverse events were also recorded to help refine the simulator for future study.

The aim of Chapter 4 of this thesis was to begin to examine the range of physiological reactions to a novel virtual reality-based road collision simulator. We explored CPM using the VR-based MVC as a conditioning stimulus with PPDT as our testing stimulus, again examining for meaningful CPM based on literature recommendations. We also explored any relationships with measurements of autonomic nervous system reactivity such as heart rate variability.

We envisioned this work as the start of a new research initiative designed to explore the experience of involvement in a MVC without the potential for tissue injury. By viewing a car crash as a catalyst towards the development of neck pain, we are hopeful that future work can continue to shed light on the heterogeneity of the condition that is WAD.

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Chapter 2

2 Exploring the Relationship between Conditioned Pain Modulation Efficacy and Stress System Reactivity in Healthy Adults in Reaction to the Cold Pressor Task

2.1 Introduction

Conditioned Pain Modulation (CPM) is a technique used to evaluate the functioning of pain inhibitory pathways in the human body.[1] CPM protocols consist of exposing participants to a testing stimulus before and after exposure to a noxious conditioning stimulus, which historically has been the Cold Pressor Task (CPT), though a variety of conditioning stimuli can be used. [1–3] Previous literature has demonstrated that the use of cold water immersion can be used for sessions up to three minutes in duration before self-reported pain becomes too intense.[4] The testing stimulus is commonly pain detection threshold and the difference in the testing stimulus threshold between the pre- and post-exposure is considered the metric for CPM.[1] Prior recommendations have suggested that CPM is best conceptualized as the absolute change or percentage change in the testing stimulus from pre-to-post exposure in order to compare results across studies and institutions.[4] In healthy adults, it is thought that CPM is typically positive (i.e., an increase in pain threshold) in nature, though prior work has found that negative/impaired CPM is a common feature of chronic pain syndromes.[5]

Complicating this matter is that some prior studies have identified non-responders in CPM research, with a paucity of evidence exploring the proportion of healthy participants without pain that also show reversed CPM under normal clinical conditions.[4] As such, there have been attempts to define what constitutes true meaningful change in CPM measurements, beyond simple measurement error. Previously, Kennedy and colleagues (2020) used a distribution-based statistical approach based on two standard errors of measurement (SEM) of the testing stimulus to classify participants as having experienced inhibition (i.e., increase in pain threshold), facilitation (i.e., decrease in pain threshold), and non-response (i.e., no appreciable change).[6] Despite this classification system, it is

unclear what individual factors may contribute to the experience of these responses, though higher state anxiety was associated with inhibitory CPM effect.[6]

Geva and Defrin (2018) also recently found a relationship between CPM and perceived stress in that those participants who experienced a perceived high stress response had reduced CPM.[7] However, these authors were unable to demonstrate a relationship between CPM and physiological measures of the stress response such as salivary cortisol or Galvanic Skin Response (GSR), nor did they explore meaningful CPM as it relates to these measurements. Salivary cortisol and GSR are promising measures of stress system reactivity as they provide estimates of sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis.[8]

In recent years, CPM has been highlighted as a potential biomarker for the development of chronic pain, although questions remain regarding its validity as a biomarker considering it is fully dependent on participant perception of and willingness to report pain.[4,9] Concurrently, a maladaptive or exaggerated stress response has been reported as a potentially important mechanism through which chronic pain following trauma is developed.[10,11] Inversely, it has also been suggested that people who experience a lack of a stress response or a blunted one, may also be at risk of developing pain and/or psychopathology following trauma.[12,13] As such, it appears that there may be a relationship between stress (exaggerated or blunted) and pain; however, the directionality of this relationship requires further investigation.[14] Thus, the purpose of this study was to explore the relationship between statistically meaningful CPM after exposure to a CPT and its associations with measures of stress system reactivity (i.e., salivary cortisol and GSR).

2.2 Methods

Study Design

This was a cross-sectional study with repeated measures design. Participants had their pain pressure detection threshold (PPDT), GSR, and cortisol measured before and after exposure to a CPT.

Participants

A convenience sample of participants was recruited from Western University between February 2019 and March 2020. Eligible participants were 18 years or older, without recent musculoskeletal injury for two weeks, and could read/write conversational English. Exclusion criteria were: infection, cardiovascular instability, cancer, Raynaud's phenomenon, cryoglobulinemia, stroke, multiple sclerosis, amyotrophic lateral sclerosis, and cervical radiculopathy. Participants were required to discriminate between thermal stimuli using hot/cold test tubes and light touch using a 200mg Von Frey filament on the neck as part of the screening protocol for eligibility. Recruitment was purposive to ensure equal representation of sexes given the clear sex bias in biomedical research.[15] This study was approved by the Health Sciences Research Ethics Review Board at Western University (London, ON, Canada) prior to commencement and all participants provided written informed consent and the rights of the subjects were protected.

Experimental Protocol

All participants were asked to refrain from consumption of food/ drink, analgesic medications, and any physical activity for the hour before testing. On the first testing day, participants completed a study-specific demographic questionnaire indicating their age and sex. Participants then sat in an isolated room for five minutes with consistent lighting, noise, and temperature.

PPDT

PPDT was evaluated using the protocol of Walton et al. (2011).[16] This protocol consists of testing PPDT at upper fibers of the trapezius muscle using a handheld digital algometer (Wagner FDX-25, Wagner Instruments, Greenwich CT, USA) on the participant's dominant side. Increasing force was applied to the angle of the upper trapezius and participants were instructed to verbalize 'there' when the sensation changed from pressure to pain. The rate of application was 5N/second and the rater was trained until they could perform this rate of application consistently. The value of the algometer at verbalization was recorded in kilograms of force (kgf). The process was repeated three

times with 30 seconds between testing, and the average of these three sessions was the baseline PPDT.

GSR

In order to evaluate peripheral sympathetic nervous system activity, participants had their GSR measured using ADInstruments PowerLab (PowerLab®, ADInstruments, Sydney, Australia) at a sampling rate of 1000 Hz using two finger cuffs on the participants non-dominant hand on the second and fourth fingers. GSR was measured in microsiemens (uS) zeroed to each participant prior to use to determine a relative change in skin conductance from their baseline resting state. Measurements relative to each subject's resting state were used to avoid any baseline variability in GSR which may have been influenced by circadian systems, to isolate the stress response to the stressor used in the present study.[17,18] GSR was recorded over a five-minute baseline period, during the experimental pain protocol, and two 5-minute periods during recovery (0 to 5 minutes, 5 to 10 minutes). Participants were also asked to minimize any movements of their non-dominant hand and fingers to minimize measurement errors.

Salivary Cortisol

With the GSR sensors still in place, a salivary sample was collected from each participant prior to the CPT using a small poly-cotton swab. Each participant rolled the swab around the inside of their mouth for about 30 seconds before returning it to a sterile salivette. The salivette was then sealed, and immediately transferred to a -30°C freezer for later off site analysis. Salivary cortisol (Cortisol (Saliva) ELISA, Alpco (Salem, NH, USA), cat no.11-CORHU-E01-SLV) was analyzed using typical industry standard approaches based on the specifications set by the manufacturer and all samples were run in duplicate, whereby the values were the average of the two duplicate samples.

Cold Pressor Task

Experimental pain was simulated with the CPT. Similar to the protocol of Kaunisto et al. (2013),[19] participants submerged their dominant hand up to the wrist into an ice-water bath (2-4 degrees centigrade) in a cooler with dimensions 16.5 cm x 12.4 cm x 13 cm.

The ice was separated from the participants hand with a mesh basket and temperature was monitored using a submersible digital thermometer. The water was mechanically agitated regularly and temperature was checked in several spots to ensure a consistent temperature. No pump was used as preliminary testing found interference with the GSR readings. Participants kept their hand submerged until they experienced an 8/10 on the Numeric Pain Rating Scale (NPRS) (0 = no pain to 10 = extreme pain) or until 90 seconds had elapsed, whichever came first. Kennedy et al. (2016) recently highlighted that a conditioning stimulus must not be overly painful, otherwise it may not be tolerated by all participants.[4] As such, an 8/10 on the NPRS was selected as a cut-off as it was deemed sufficiently noxious, but not overly painful such that the CPT could be tolerated by a majority of participants. Participants rated their pain every 10 seconds. Cold endurance time was recorded to the nearest 0.1 seconds using a digital stopwatch. Following the CPT, participants dried their hands and sat quietly for 30 seconds after which PPDT and salivary cortisol were re-evaluated. PPDT was re-measured by the same rater that performed the baseline test in a sequential manner. GSR measurement continued throughout both the CPT and during recovery for offline analysis.

Statistical Analysis

Descriptive statistics (mean, standard deviation) were calculated for participant demographics, PPDT, CPM, GSR, and salivary cortisol at baseline and after the CPT. For descriptive purposes, participants' cold endurance time was coded as either 1 (immersion = 90 seconds) or 2 (immersion < 90 seconds) and was reported as the frequency of participants to reach the full immersion time. The other metrics (PPDT, GSR, and salivary cortisol) were retained as ratio-level variables (microsiemens or ng/ml). Data were visualized via box-and-whisker plots and outliers were identified through visual and statistical tests of normality (Kolmogorov-Smirnov tests). PPDT values were logarithmically transformed for parametric statistics, as they were not normally distributed. Data are reported in their un-transformed state for comparison to the literature.

A one way repeated measures analysis of variance (rmANOVA)was used to detect any significant changes in mean 5-minute GSR intervals at each testing point compared to baseline testing, with a Bonferroni correction factor applied (T1 = 5 minute baseline, T2 = during CPT, T3 = 0 to 5 minutes after CPT, and T4 = 5 to 10 minutes after CPT). While GSR can be measured with parameters like amplitude or recovery time,[20] only average skin conductance was used due to the prolonged exposure of the CPT, which was not an acute startle event. A paired samples t-test was used to compare mean difference in cortisol and PPDT before and after the CPT. The difference between PPDT before and after the CPT was the CPM and was analyzed as both absolute change (CPM_{ABS} = Post - Pre immersion (in kgf)) and percent change ($CPM_{PERCENT}$ = ΔCPM_{ABS}/Pre immersion kgf x100) as per the recommendations of Kennedy et al. (2016).[4]

Meaningful CPM

Next, the recommendations of Kennedy et al. (2020) were used to explore meaningful CPM.[6] The reliability of the baseline PPDT was evaluated using an intraclass correlation coefficient ($ICC_{3,1}$). ICCs were interpreted as suggested by Shrout & Fleiss[21] where values less 0.4 were poor, between 0.4 and 0.59 was fair, between 0.60 and 0.75 was good, and greater than 0.75 was excellent. From this, the standard error measurement was calculated for the baseline PPDT ((SEM = pooled standard deviation of baseline PPDT (SDpooled)$\sqrt{}$(1-ICC)). Per the protocol of Kennedy et al. (2020) $\pm$ 2 SEM were used to group participants into three classification groups (inhibition = increase in threshold/decreased sensitivity, facilitation = decrease in threshold/increased sensitivity, and non-response).[6] Both the absolute and percentage change of $\pm$ 2 SEM were used to account for those participants who may have had a minor increase in absolute PPDT, but a large percentage change relative to their baseline measurement. Descriptive values of both the pain and stress metrics were also calculated for participants within these groups.

Associations between CPM Classification and Indicators of Stress

Pearson correlations were used to explore any initial relationships between CPM classification and the changes in salivary cortisol and GSR before and after the CPT as a measure of stress system reactivity. Strength of Pearson correlations were interpreted

using the recommendations of Mukaka (2012), whereby: <0.30 (negligible), 0.30 to 0.50 (low), 0.50 to 0.70 (moderate), 0.70 to 0.90 (high), >0.90 (very high).[22] Scatter plots were used to visually model the date for interpretation.

All statistical analyses were completed using IBM SPSS Statistics Version 27 and the p-value for statistical significance was set at 0.05.

Sample Size Calculation

For this study, no formal sample size was calculated due to the exploratory nature of the work, though a similar number of participants (n=50) were sought compared to other studies investigating meaningful CPM in healthy adults.[6]

2.3 Results

Descriptive Statistics

50 healthy participants (male = 25, female =25) were included in the study with a mean age of 24.5 + 3.3 years (18 to 35)(*Table 1*). No subjects reported their sex as different from their self-reported gender; thus, only sex is reported. 52% (26/50) of participants tolerated the full 90 seconds of the CPT used in the present study. Mean PPDT values across the full sample were not significantly different from baseline to after the CPT; see *Table 2* for a full description of values. The one-way repeated measures ANOVA revealed that there was a statistically significant main effect for testing time for mean 5-minute GSR (F=44.58, p=0.001), with post hoc pairwise comparisons indicating GSR was significantly elevated from baseline (6.08 $\pm$ 8.77 uS, 95%CI: 3.45 to 8.72 uS) at all subsequent time points (all p<0.001) during the CPT (15.25 $\pm$ 9.30 uS , 95%CI: 12.45 to 18.04 uS), for 0 to 5 minutes after (13.84 $\pm$ 8.51 uS , 95%CI: 11.28 to 16.40 uS), as well as 5 to 10 minutes after (14.07 $\pm$ 9.23 uS , 95%CI: 11.30 to 16.84 uS). See *Figure 1* for a visual description of GSR values across testing points. When analyzed across the entire sample, CPM_{ABS} was 0.24 $\pm$ 1.04 kgf (95% CI: -0.06 to 0.53kgf) while $CPM_{PERCENT}$ was 7.73 $\pm$ 21.00% (95% CI: 1.76 to 13.70%). Cortisol values were not statistically significantly different before and after the CPT *(Table 2)*.

Meaningful CPM

The reliability for baseline PPDT was ($ICC_{3,1}$), which was 0.97, indicating an excellent level of reliability based on the recommendations from Shrout & Fleiss.[21] Thus, for this study the SEM of PPDT was 0.39 kgf. Accordingly, participants who had greater than a +0.78 kgf (or +18.3% of baseline mean PPDT)) increase in PPDT were termed modulation, a decrease greater than -0.78 kgf (or -18.3% of baseline mean PPDT) were termed facilitation, and participants who experienced anything between were described as having experienced non-response. 15 participants (30%) experienced inhibition of their pain thresholds, 6 participants (12%) experienced facilitation, while the remainder had no significant change of their PPDT values (58%). See *Table 3* for a full description of PPDT and CPM values within these sub-groups (inhibition, facilitation, and non-response).

Associations with Indicators of Stress

When disaggregated by class, there was a moderate positive correlation ranging from r = 0.63 to 0.69 ($p<0.011$) between CPM (CPM_{ABS} or $CPM_{PERCENT}$) and the absolute change in GSR from baseline to immersion, or from baseline to the immediate 5 minutes after immersion, but only in the 15 participants who experienced inhibition of their PPDT values. See *Table 4* for a full description of the correlational matrix between CPM and stress measures in the inhibition group. Within the non-response group, there was a low negative correlation of r = -0.47 ($p=0.01$) between CPM_{ABS} and the absolute change in GSR from baseline to the immediate 5 minutes after immersion. There were no other statistically significant relationships within the non-response group. There was no significant relationship between CPM and any indices of SNS activity in the group that experienced facilitation. There were also no significant relationships between CPM and the change in salivary cortisol in any of the classes.

2.4 Discussion

The purpose of this study was to explore the associations between indicators of stress system reactivity (i.e., salivary cortisol, GSR) and meaningful CPM within healthy young adults in reaction to a standard experimental pain protocol using noxious cold (CPT). It

appeared that in reaction to the CPT, when analyzed as a group, there was no significant CPM effect, as PPDT values remained statistically unchanged. Salivary cortisol values also remained unchanged in reaction to the CPT. This was despite a statistically significant increase in GSR values at all timepoints compared to baseline, suggestive of an increase in sympathetic nervous system activity. When we evaluated for meaningful CPM in relation to $\pm$ 2 SEM, a majority of participants experienced no appreciable change of their PPDT (58%), while 30% of participants experienced the expected inhibition (i.e., increase in PPDT) of their pain sensitivity. Within this group of participants who experienced inhibition, there was a moderate positive association with the change in GSR, suggesting that pain modulation may be related to the magnitude of the stress response in reaction to the CPT in those who can suppress their pain experience.

Approximately half of the current study's participants were able to complete the full 90 seconds of submersion for the CPT. Previous work by Kaunisto et al. (2013) found that 24% of their sample could tolerate cold water immersion for the full 90 seconds, however this result may have been explained by the presence of chronic pain.[19] One criticism of using cold endurance in this manner is the presence of a ceiling effect. However, as there were a large amount of participants in the present study and previous investigations[19] that could not tolerate the full immersion time, 90 seconds of immersion may still be appropriate. Future work is required to establish an upper limit on CPT immersion time.

There is a growing body of evidence that PPDT inhibition in CPM protocols is not a universally experienced phenomenon even in healthy participants, and our results are in agreement with the literature. Locke et al. (2014) first evaluated CPM with respect to 1 SEM of their testing stimulus (PPDT), finding that 92% of participants experienced an inhibitory CPM effect in reaction to the CPT as a conditioning stimulus.[23] However, this analysis was only conducted on a pilot of 10 participants. In contrast, Vaegter et al. (2018) found that only 62% of participants (total sample = 26 participants) experienced pain inhibition using cold water immersion as a conditioning stimulus and mechanical PPDT as the test stimulus, using 1 SEM of the test stimulus to classify participants as

responders.[24] To help increase the confidence in true change, Kennedy and colleagues examined meaningful CPM in relation to ± 2 SEM of PPDT (to reflect a 95% confidence interval), finding that 59% of participants (total sample = 50 participants) experienced inhibitory CPM in reaction to a cold conditioning stimulus, while up to 6% of participants experienced facilitation of their PPDT across testing paradigms.[6]

As such, it appears that CPM responses can be categorized as inhibitory (i.e., increase in pain threshold), faciliatory (i.e., decrease in pain threshold), and non-response. Future work will be required to ascertain the individual characteristics of participants that lead to these responses, and to clarify which response could be predictive in the development of conditions like chronic pain. Interestingly, it appeared that the participants who experienced inhibitory CPM in our study, had a lower PPDT at pre-test compared with those in the faciliatory CPM cohort who experienced a higher base PPDT. This may reflect that those who are able to experience CPM and exhibit efficient diffuse noxious inhibitory control have a reserve that they are able to use when exposed to a noxious stimulus. Previous work conducted by Grouper et al. (2019) also suggests that those who are less sensitive to pain, experience less pain inhibition following a CPM protocol.[25] Larger samples will be required to investigate these CPM responses with respect to individual variability.

Our study suggests that there exists a relationship between pain modulation and sympathetic nervous system activity in participants who experienced inhibitory CPM, as the change in PPDT values were moderately positively correlated with the change in GSR values both during and after the CPT. This relationship was reversed in the participants who had a non-response of their CPM. This is somewhat unsurprising, as acute stress can lead to an increase in sympathetic nervous system activity,[26] which may lead to stress-induced analgesia.[27,28] The CPT as a physiological stressor has also been known to produce strong sympathetic nervous system activity.[26,29] These findings are in contrast to those of Geva and colleagues (2018), who found a reduction in CPM in participants who perceived themselves as having a high stress response.[7] However, we did not evaluate the appraisal of each participant to determine whether or not they were

cognitively experiencing high or low stress. As such, cognitive appraisal of the situation could partially explain the 12% of participants in the present study who experienced facilitatory CPM. Geva and colleagues (2014) also suggested that pain inhibition may only result when there is a perceived risk of injury, and when risk of injury is low, hyperalgesia could result.[30] In all likelihood, the relationship between inhibitory CPM and stress likely follows a curvilinear relationship compounded by the degree of physiological stress and cognitive appraisal of the stressor involved. Future work is also required to understand why a large percentage of subjects in both the present study and previous investigations experience non-response in terms of CPM. Despite previous work suggesting that individual factors (e.g., age, sex, attention, physical activity levels, and genetics) play a role in CPM,[31] it is unclear how they factor into identification of meaningful CPM.

Salivary cortisol levels of the participants in the study were elevated compared to normative values reported in the literature.[32] One explanation for this may be that as the cohort consisted of graduate level students, higher levels of stress and anxiety may have been present leading to elevated salivary cortisol levels. We were also unable to detect a relationship between CPM and the change in salivary cortisol as an indicator of the HPA axis. There are various explanations for these findings. On one hand, as cortisol has been known to peak 10 to 20 minutes after an acute stressor it may be that our study protocol measured cortisol too early to detect true change.[10,14] Additionally, we did not rigorously control for time of day for our data collection. To circumvent this issue, we examined for the relationship between the change in PPDT and salivary cortisol to evaluate the cortisol reactivity of each participant. Thus, we believe the first explanation to be the more plausible of the two. These findings taken together suggest that the SNS may be implicated in the pain inhibition response that in those experiencing inhibitory CPM after exposure to an acute stressor. It is also possible that since our CPT did not include a social-evaluative element, a smaller change in cortisol reactivity was demonstrated.[29]

Limitations

There are limitations that should be addressed in the present study. As subjects were aware of the impending pain from the CPT, it is possible that the expectation of pain impacted the salivary cortisol data collected. However, seeing as GSR values increased significantly after the CPT, we believe that this is unlikely. As mentioned earlier, we did not control for time of day which may have impacted the stress response of each participant. Future work will want to control the time of day where cortisol is collected to allow for more robust comparisons. Our also cohort consisted of university students who may have had similar psychosocial tendencies that influence the pain experience.[33]Accordingly, our results may not apply to people from different socioeconomic statuses or with poorer health literacy. Due to interference with our GSR measurement devices, a circulating pump was not used, and we accept that a warm envelope could have formed around each participant's hand during the CPT. However, as almost half the sample could not tolerate the full 90 seconds of the CPT, we believe that it was sufficiently painful to induce a CPM effect. As the present study is cross-sectional in nature, we were unable to explore any causal relationships between CPM and GSR. It should be noted that CPM protocols have been known to vary across different investigations, using different conditioning and testing stimuli.[4,34]As such, it is unclear if the results of our study would have varied had used a different CPM protocol. Sequential evaluation of the test stimulus has been suggested to be a better representation of CPM responses as it may be less prone to distraction than parallel designs.[35] However, future work is required to determine both the most appropriate conditioning stimuli as well as the timing of the test stimulus is CPM studies.

2.5 Conclusion

In conclusion, only 30% of healthy adults in our study experienced inhibition of their pain threshold in reaction to a CPT. This appeared to be associated with an increase in sympathetic nervous system activity, as measured by GSR, but was not associated with cortisol reactivity. Further work is required to examine for the presence of other individual variables which may contribute to the experiences of the various CPM responses (such as cognitive appraisal). Future research may also want to identify which

CPM responses may be useful as a biomarker for the development of chronic pain conditions.

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Table 1: Participant Characteristics. Data are presented as mean ± standard deviation. Range is provided in brackets where applicable.

	Males	Females	Total
Sample Size (n)	25	25	50
Age (years)	24.2 ± 3.9 (18-35)	24.8 ± 3.9 (21-30)	24.5 ± 3.2 (18-35)
Height (cm)	178.6 ± 7.2 (167.6-194.0)	166.3 ± 7.4 (149.9-177.8)	172.5 ± 9.5 (149.9-194.0)
Weight (kg)	78.8 ± 12.5 (57.0-104.5)	61.3 ± 8.3 (47.7-81.8)	70.1 ± 13.7 (47.7-104.5)

Table 2. Descriptive values for group PPDT, CPM, Salivary Cortisol, and GSR before and after CPT. Data are presented as mean ± standard deviation. A 95% CI is provided in brackets.

	Baseline	After CPT
PPDT (kgf)	4.31 + 2.03 (3.70 to 4.90)	4.57 + 2.20 (3.92 to 5.23)
GSR(uS)	6.13 ± 8.96 (3.50 to 8.76)	12.92 ± 9.46 (10.14 to 15.70)
Salivary Cortisol (ng/ml)	27.32 ± 11.32 (24.11 to 30.54)	28.17 ± 12.20 (24.71 to 31.64)

Note: PPDT: Pain pressure threshold; CPM: conditioned pain modulation; kgf: kilograms of force; GSR: Galvanic Skin Response; uS: microsiemens; ng/ml: nanogram per milliliter

Table 3. Descriptive values for PPDT and CPM within classification groups. Data are presented as mean ± standard deviation. A 95% CI is provided in brackets.

	Inhibition (n =15)	Facilitation (n=6)	Non-response (n = 29)
Baseline PPDT (kgf)	3.92 ±1.85 (2.90 to 4.95)	6.29 ± 2.90 (3.24 to 9.33)	4.09 ±1.75 (3.42 to 4.76)
Post PPDT (kgf)	5.34 ± 2.62 (3.89 to 6.80)	4.99 ± 2.54 (2.32 to 7.66)	4.03 ± 1.73 (3.37 to 4.69)
CPM_{ABS} (kgf)	1.42 ± 0.82 (0.97 to 1.87)	-1.29 ± 0.74 (-2.07 to -0.51)	-0.06 ± 0.34 (-0.19 to 0.07)
$CPM_{PERCENT}$ (kgf)	35.27 ± 6.79 (31.51 to 39.04)	-21.61 ± 8.03 (-30.04 to -13.18)	-0.44 ± 8.78 (-3.78 to 2.89)

Note: PPDT: Pain pressure threshold; CPM: conditioned pain modulation; kgf: kilograms of force.

Table 4. Correlational matrix between CPM and stress response measures within the Inhibition group.

	CPM_{ABS}	$CPM_{PERCENT}$	ΔGSR (during CPT)	ΔGSR (after CPT)	ΔSalivary Cortisol
CPM_{ABS}	-	0.43	0.65**	0.63*	0.20
$CPM_{PERCENT}$	-	-	0.69**	0.65*	0.34
ΔGSR (during CPT)			-	0.96**	0.44
ΔGSR (after CPT)				-	0.35
ΔSalivary Cortisol					-

Note: CPM: conditioned pain modulation; kgf: kilograms of force; GSR: Galvanic Skin Response; uS: microsiemens; ng/ml: nanogram per milliliter

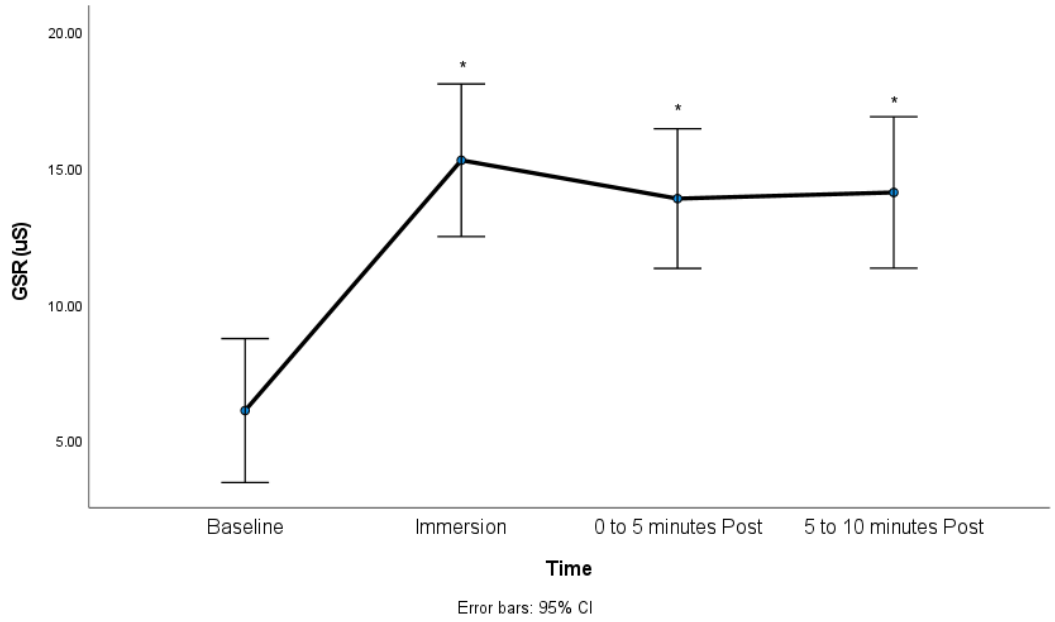

Figure 1. GSR values at each testing time point with 95% confidence intervals for entire sample of participants. * denotes significantly different from baseline values at p< 0.001.

Chapter 3

3 Initial Tolerability and Reactions to a Novel Virtual-Reality-Based Road Collision Simulator: An Exploratory Study

3.1 Introduction

Symptomology following a motor vehicle crash (MVC), has been a well-documented occurrence.[1,2] Of these various symptoms, whiplash-associated disorders (WAD) represent a common and burdensome problem from many different contexts including social and personal costs.[3] The symptoms of WAD can include but are not limited to: neck pain, loss of range of motion of the neck, neurological deficits, and even fracture of the cervical spine.[4] However, despite the persistent issues associated with WAD, consensus regarding its etiology is far less certain.[5,6] Many theories have proposed that the development of symptoms may be due to the biomechanical influences of the car crash, such as the speed or direction of impact.[5,7] Other competing theories have suggested that the development of WAD in some cases is not due to biomechanical influences, but rather psychosocial factors including maladaptive beliefs and/or an exaggerated stress response to trauma.[7,8] Unfortunately, many of these theories are difficult to investigate empirically as it is simply not ethical to place individuals in live car crashes nor has the manipulation of car crash parameters under controlled circumstances been feasible.[9]

Accordingly, Virtual Reality (VR) has emerged as a technology through which otherwise dangerous situations such as MVCs can be simulated without the risk of biomechanical injury causing tissue damage.[9] Recently, VR has been leveraged as a means to create pain distraction, improve neck range of motion, and to engage adolescents in physical activity through exergaming.[10–12] VR is usually achieved through the combination of a head-mounted display (HMD), head/limb tracking hardware, and a powerful computer to create an immersive three-dimensional environment.[13] The creation of an immersive three-dimensional virtual environment can help to create a sense of presence in said environment, which has been defined as the psychological sense of ‘being there’.[14]

Traditionally, the sense of presence is amplified by enhanced virtual interactivity, greater visual vividness, and multi-sensory input while it is diminished by feelings of simulator sickness and an awareness of the apparatus being used.[15,16]

We have created an immersive Virtual Reality (VR)-based road traffic collision simulator that also interfaces with a programmable 6 degrees of freedom robotic platform. While other such driving simulators exist, (to our knowledge) ours is the first where a virtual collision is the main intent.[17,18] Also, while previous research has demonstrated the effects of placebo car crashes in lab settings,[5] ours was specifically created to immerse participants in a scenario designed to imitate the settings of a real-world MVC and elicit feelings of presence. A VR environment that is designed to mimic emotional or stressful environments (i.e., MVC) may elicit greater feelings of presence, and thus may be more appropriate to explore the sensation of involvement in a MVC than traditional laboratory settings.[19] MVC's are considered to be a unique stressor in adult life, that can lead to feelings of sudden chaos and a fear of safety, all of which may act as a catalyst toward the development of WAD.[7] Thus, the purpose of this study was to explore the tolerability of using a VR road collision simulator, to gather user feedback for optimization, and to examine the development of any adverse events (i.e., reports of neck pain longer than 48 hours, vomiting, inability to tolerate VR, disorientation). Exploration of development of symptoms following exposure to the VR platform was also deemed relevant as previous research has highlighted the possibility of symptom development following exposure to a placebo car crash.[5]

3.2 Methods

This was a cross-sectional exploratory study with a pre-to-post design.

Participants

Healthy participants were recruited from the community via email and word of mouth at Western University between October 2020 and January 2021. Eligible participants were: 18 years or older, otherwise healthy with no recent (3 months) significant trauma or injury that required medical care and were able to read and understand conversational

English. Exclusion criteria were recent neck pain, headache, concussion, cardiovascular instability (e.g., heart disease, high or low blood pressure), were actively undergoing cancer treatment, neurological or systemic conditions that affect balance or postural control (e.g., Benign paroxysmal positional vertigo), migraines, visual pathology (e.g., saccades), technophobia, and claustrophobia. Subjects also had to pass a cervical dysfunction clearing test performed by one of the primary investigators (M.J.L). Secondary to the COVID-19 pandemic, participants also had to complete a standardized questionnaire examining their suitability to return to campus and also had to have their temperature checked and screened prior to participation. This study was approved by the Health Sciences Research Ethics Review Board at Western University (London, ON, Canada) prior to participation in the study and all participants provided written informed consent prior to participation.

The VISION System

The VISION (Virtual Interface for Stress-Trauma Interactions through Open World Navigation) system is comprised of a HTC Vive (HTC Corporation, Xindian City, Taipei) head mounted VR display (HMD), noise cancelling headphones, and a Mikrolar R3000 (Mikrolar Inc., Hampton, NH, USA) robotic platform. The virtual environment these hardware peripherals interface with depicts a simulated car ride through a city. The visuals of this simulation are delivered by the onboard screens of the HMD which also tracks the participant's head position via two fixed infra-red base stations, allowing the participant to examine 360 degrees of their surroundings from the passenger seat of the moving vehicle (Figure 2). To maintain a heightened sense of immersion, the simulation's audio is delivered by a set of noise-cancelling headphones such the volume of all external audio sources is reduced, further emphasizing the sounds of the virtual environment. Lastly, the simulation is designed such that the movements of the participant's virtual car are synchronized with a robotic platform which can be controlled along six programmable degrees of freedom: the x-,y-, and z-planes as well as yaw, pitch and roll (Figure 1). Prior to the collision, the robotic platform will simulate the feeling of acceleration and deceleration by modulating its yaw, pitch, and roll to match that of the virtual car. At the moment of impact, the VISION system also delivers a perturbation to

its occupants based upon the type of crash selected (rear-end, side-impact, or front-end). Instructions provided to the robot were designed to not accelerate beyond 1g for any of the crash scenarios; for reference the head and neck experiences 1 to 3 g of acceleration during sneezing.[20] On pilot testing we determined that for the rear crash scenario the peak accelerations at the head were no greater than 0.2 g. It should also be noted that the cervical spine regularly experiences such accelerations (1 g) in daily life without provoking symptoms.[5]

The VISION system is capable of 12 different crash scenarios, each of which can be altered via the following crash parameters: the type of crash encountered (rear-end, side-impact, or front-end), amplitude of perturbation (low or high), time of day (night or dusk), weather (rain or clear skies), seat position (front passenger, or right/left rear passenger), audio selection (no music or various musical selections), whether or not the glass of the car shatters upon impact, and whether or not the participant receives audio indication that a collision is to take place (e.g. lights and horn of colliding vehicle). For the purpose of this initial exploration of tolerability to the system, participants were exposed to a low speed rear-end collision at night under clear weather while they sat in the front right passenger seat with no music playing. The windshield glass of the virtual car was set to shatter and the participant received an audio indication that a crash was imminent via a simulated car horn played through the earphones. These parameters were selected as they were thought to be the least provocative in nature yet mirror those in rear-end MVCs, for which development of whiplash injuries has been reported to be the most common.[21,22]

Experimental Protocol

Prior to their visit with the research team, each participant completed a study-specific demographic questionnaire indicating their sex and age. Each subject also completed the state version of the State-Trait Anxiety Inventory-6 (STAI-6)[23] to assess general anxiety as well as the Fear of Pain Questionnaire–9 (FPQ-9)[24] to assess fear of pain. The FPQ-9 is a shortened version of the FPQ-III which has demonstrated good psychometric properties. The FPQ-9 consists of 9 items scored on a 5-point Likert-scale, with higher

summed scored indicating higher fear of pain.[24] The FPQ-9 also has three subscales which can be calculated: Fear of Severe Pain, Fear of Minor Pain, and Fear of Medical/Dental Pain.[24] The STAI-6 consists of 6 questions measured on a 1 to 4 Likert-scale and has been determined to provide similar results to that of the full 20-item STAI.[23] Each question is summed with higher scores signifying greater anxiety ranging from a minimum of 6 to a maximum of 24. For comparison to norms, the total score was divided by six, and multiplied by 20 to generate a pro-rated score from 20-80 as would be obtained from the full version.[25] STAI scores can be interpreted as 'no to low anxiety' (20-37), 'moderate anxiety' (38-44), and 'high anxiety' (45-80).[26]

For the hour before the study, each participant was advised to refrain from any eating, drinking, or physical activity. After having their cervical spines screened, and sitting quietly for five minutes, each subject sat in the VISION simulator during a non-crash route for five minutes to become acclimatized to being in a virtual reality simulation and to judge the immersion of the simulator. This non-crash route involved sitting in the front right passenger of a virtual car with it making four turns around a city block with no crash. Seat height of each participant was optimized to their respective height based on personal preference, the time of day was set to night, and no in-simulator music was playing. Each subject was allowed to survey their virtual environment as much as they wished during the virtual drive. Following the five minute acclimatization period during the non-crash route, subjects were given a minute of rest prior to the next simulation. This rest period consisted of removal of the VR-headset, but participant remained in the seated in the robotic platform. Immediately following the non-crash simulation, each participant was informed that the subsequent simulation would include a virtual car crash but were not told when or where (i.e., rear-end collision) it would transpire. Each participant was then exposed to the low-speed rear end collision through the VISION platform, that occurred after approximately 1 minute of simulated riding in the virtual car. During the crash the robot delivered a small anterior perturbation (<1 g) to the participant through the car seat to further the immersion of the simulation. Afterwards, the participants dismounted from the simulator, and were observed for five minutes to monitor for the presence of any immediate adverse events.

Sense of Presence and Simulator Sickness

After this period each participant completed the Presence Questionnaire (PQ),[27,28] and the Simulator Sickness Questionnaire (SSQ)[29] to gather initial feedback regarding the immersion of the VISION simulator and to capture any adverse reactions. The PQ has 24 items from 1 to 7 on a Likert scale designed to measure the degree to which a participant feels immersed or present in a virtual simulation. Each item from the Presence Questionnaire is summed with higher scores representing greater immersion.[27] The individual items from the PQ can also be summed to produce summary scores in the following categories: Realism, Possibility to act, Quality of interface, Possibility to examine, and self-evaluation of performance.[27] For the present study, questions 20 to 24 were pertinent to sounds and haptic and such were excluded from the study as they were deemed not immediately relevant before study commencement. The 19-item version of the PQ with a maximum score of 133 was selected over the original 32-item questionnaire due in part to its shortened length and good internal consistency.[27,28]

The SSQ is a 16-item survey with responses ranked from 0 to 3 points.[29] The 16 symptoms are placed into three categories (Oculomotor, Disorientation, and Nausea) with unique weights attached and summed to produce a total score, with higher scores indicating a greater degree of nausea with a maximum score of 235.62.[29,30] Total scores above 20 have been suggested to indicate 'sufficient discomfort'.[31] Each participant was instructed to follow-up with the research team should they develop any adverse events that lasted beyond 48 hours following the protocol.

Statistical Analysis

Descriptive statistics, including mean, standard deviation and range, were calculated for participant demographics, STAI (pre and post-simulation), SSQ and PQ scores (as well as their subscales). Data were visualized via box-and-whisker plots and outliers were identified through visual and statistical tests of normality. The majority of the measures were non-parametric in nature (Kolmogorov-Smirnov tests). Individual items from the PQ and SSQ were critically examined independently in order to determine the usability of the VISION platform and to ascertain areas for improvement. SSQ items were

recorded as a percentage of the total sample to understand incidence for each of the scores (i.e., none, slight, moderate and severe). As the PQ items do not have a descriptor for each part of the scale, individual items were examined descriptively (mean ± standard deviation). Adverse events were recorded throughout the protocol as incident counts of reported neck pain longer than 48 hours, immediate vomiting, inability to tolerate the simulator, and self-reported disorientation post-protocol. A Wilcoxon-signed rank test was used to examine differences in STAI-6 scores from before and after exposure to the simulator. Spearman's correlations were used to examine for relationships between SSQ, STAI-6, FPQ, and PQ scores. Strength of Spearman correlations were interpreted as: <0.30 (negligible), 0.30 to 0.50 (low), 0.50 to 0.70 (moderate), 0.70 to 0.90 (high), >0.90 (very high).[32] All analyses were conducted using IBM SPSS Version 27, and the level of significance was set at $p<0.05$.

Sample Size Calculation

As this research project was exploratory in nature, no formal sample size calculation was performed, though a small sample of as little as 20 participants has been suggested as appropriate for exploratory studies.[33] A sample of 25 participants was deemed to be sufficient in order to ascertain an initial impression of tolerance to the VISION simulator and to determine to areas of improvement while minimizing risk of exposure to this potentially provocative scenario.

3.3 Results

Participants

25 healthy participants (16 male, 9 female) with no recent (3 months) significant trauma or injury that required medical care participated in the study. The mean age of the group was 27.3 ± 4.1 years (*Table 5)*. All subjects successfully completed all aspects of the protocol and there were no verbal reports of nausea, inability to tolerate VR, and complete disorientation in response to the virtual simulation. There were no reports of neck pain immediately after the simulation. One subject did report neck pain on the day immediately after the virtual simulation but their symptoms only lasted one day. No medical follow-up was required. Total FPQ-9 scores were similar to those reported in

previous investigations into otherwise healthy participants.[34] STAI-6 scores prior to the simulation indicated 'high anxiety' prior to the simulation. There were no significant differences between STAI-6 scores from before (46.53 ± 6.05) and after (44.27 ± 5.14) the VISION simulator.

Simulator Sickness and Sense of Presence

Results for the Simulator Sickness Questionnaire and Presence Questionnaire and their subscales (mean ± standard deviation, range) are presented in *Table 6*. In terms of Simulator Sickness, the mean total score was 23.49 ± 21.98 (0.00 to 89.76) out of a possible 235.62 indicating sufficient discomfort. The majority of participants indicated none to slight for each item of the SSQ with twelve participants reporting moderate severity of a number of symptoms including nausea and fatigue, and only one participant indicating severe symptoms (eye strain) (*Table 7).* In terms of feelings of presence and immersion, the mean of the total PQ score was 91.04 ± 14.08 (54.00 to 112.00) out of a possible 133. Participants rated the ability to control events (mean 2.04 out of 7.0), environmental responsiveness (mean 3.4 out of 7.0) least favorably compared to the remainder of the PQ items (mean 5.0 out of 7.0; *Table 8*).

Correlation Analysis

A significant low negative correlation (r=-0.40 to -0.49) was observed between the Self-Evaluation subscale of the PQ and the SSQ total score, as well as its Nausea and Disorientation subscales. There was no significant correlation observed between the PQ and SSQ total scores. There was a significant low negative correlation (r=-0.41 to -0.48) between Post-simulation STAI-6 scores and SSQ total score, as well as its Nausea and Disorientation subscales. A full description of the correlation analyses is presented in *Table 9.*

3.4 Discussion

The purpose of this study was to explore initial user reactions to a novel virtual reality-based road collision simulator for empirical investigation into potential mechanisms of WAD. We also sought to screen for the presence of any adverse events in reaction to the

VISION simulator. Our study demonstrated that exposure to a VR-based MVC was well tolerated by a majority of participants, although one participant reported neck pain the following day, which did not last longer than 24 hours. There appeared to be a negative relationship between sense of presence and simulator sickness, specifically between the Self-evaluation subscale of the PQ and the SSQ total score as well as the Disorientation subscale of the SSQ. This relationship may indicate that as a participants sense of presence increases, they experience less feelings of simulator sickness.

One subject reported severe eye strain in reaction to the simulator; otherwise, the simulator was well tolerated across all other items of the SSQ. The mean SSQ score was 23.49 + 21.98, which based on previous research, indicates 'sufficient discomfort'.[31] However, SSQ score interpretation has faced some contention as the cutoff score of 20.0 has been criticized as too strict in the context of non-aviation VR simulations, nor is it recommended to interpret scores compared to the maximum possible score (235.62). [35] That being understood, as the majority of the items on the SSQ were rated as 'None' or 'Slight', we are reasonably confident that we can conclude that the VISION platform was tolerated well enough. There were no adverse events recorded in reaction to the simulator, allowing us to conclude that the use of VR-based road collision simulator can be safely used to simulate rear-end MVCs in a controlled fashion.

One of the 25 participants (4%) in the present study reported neck pain following exposure to the novel VR-based MVC. We are confident in saying that this was not due to the perturbation delivered by the VISION platform, as the peak accelerations were magnitudes lower than those encountered in daily life. The peak accelerations of the VISION platform were also lower than that of those reported by Fice et al. (2019) who simulated laboratory based rear-end collisions without VR with peak accelerations of 2.1g seemingly without incident.[36] However, this finding of neck pain stands in stark contrast to the findings of Castro et al. (2001), who found that approximately 20% of their sample developed whiplash like symptoms in exposure to a placebo car crash.[5] There could be multiple explanations for this finding. In our study, one explanation is that participants were aware that the VISION platform was a simulator, and in essence a video game compared to the real world objects were used to provide a placebo car crash

in the study by Castro et al. (2001).[5] However, as VR has been previously used successfully to treat posttraumatic stress disorder following a MVC,[18,37] it appears that VR is able to replicate near-real virtual representations of traumatic scenarios.[38] While the present study was not able to effectively confirm the development of WAD in reaction to a VR-based MVC, it also is not able to refute the theory either. Future work is needed to clarify the development of WAD-like symptoms from simulated collisions.

While our PQ total score (68.4%) was lower than the clinically acceptable amount for VR-based driving simulators for VR-based exposure therapy (80%), we believe that with further refinement PQ scores will improve which may lead to higher incidences of self-reported neck pain and/or other symptoms.[39] Another possible explanation for the discrepancy between our findings and that of Castro and colleagues is that the sample in our study was much more limited than Castro et al. (2001).[5] The psychological profile of our sample was limited to university students aged 18-35 and may not have included participants with a higher tendency for psychosomatic disorders who may be a higher risk for WAD-like symptoms from a simulated MVC without biomechanical potential for injury.[5]

As the VISION platform is a prototype for simulation of MVCs, visual fidelity of the VR may be partially to blame for the lower-than-desired presence scores. There were occasional visual ‘skipping’ or ‘lag’ episodes where the framerate of the virtual display would drop to an unrealistic level. These episodes may explain why subjects rated the responsiveness of the virtual environment lower on the PQ but are expected to improve as the framerate of the VISION platform is optimized. These issues may also partially explain the statistically unchanged STAI-6 scores from pre- to post- exposure. As higher levels of anxiety have been associated with increased presence,[40] it stands to reason that as the visuals and responsiveness of the VISION platform improve, STAI scores post exposure should also reflect greater anxiety. It should also be noted that this line of research was conducted during the COVID-19 pandemic, and as such there may have been influences on baseline levels of stress and/or anxiety that we could not control for.

There appeared to be an inverse relationship between both the sense of presence and simulator sickness as measured by the PQ and SSQ. This finding is in agreement with the findings of Weech and colleagues who conducted a scoping review in 2019, concluding that a majority of the available literature favors a negative relationship between the sense of presence and simulator sickness.[41] However, these authors did conclude that this relationship is likely mediated by several factors such as sex, personality type, and previous gaming experience (for which we did not control). Lastly, oculomotor dysfunction can be one finding of WAD, even in patients who do not report symptoms.[42] As simulator sickness has been characterized by a predominance of oculomotor symptoms,[41,43] it is unclear if simulator sickness is a prognostic indicator for those most likely to develop WAD. As such, further investigation will be required to explore how high SSQ scores in otherwise healthy people may relate to the development of WAD following exposure to a simulated MVC.

Limitations

The sample size of this exploratory study was small and as such its conclusions must be interpreted with caution. However, this study sought to seek initial responses to a novel virtual car collision simulator and sought to explore initial reactions and the presence of adverse events. As such, we believe we were successful in this endeavor and that the results of the study will help to inform larger study designs in order to answer additional questions. Another limitation with this work is that we did not control for multiple comparisons as the work was preliminary in nature. However, we feel that due to the exploratory nature of the research the results still hold merit and invite future investigation. As mentioned earlier, we also did not control for subjects with previous virtual reality experience nor did we control for participants who had been involved in previous car crashes. Both of these variables could influence the sense of presence and/or simulator sickness in response to the VISION platform. That being said, the results of our study are in agreement with previous literature highlighting a negative relationship between simulator sickness and presence.

Additionally, there were rare occurrences of the base stations losing track of the participant's head in 3-D space. As a result, the system had to be re-set in order to re-track the participant's location. These tracking errors may have led to lower feeling of presence during the simulation. Again, with further refinement, it is expected that that the incidence of these episodes should be greatly reduced. The framerate of the VISION system also requires optimization. Lower frame rates could partially explain feelings of simulator sickness. Participants were also made aware that a collision would occur which may have influenced their reaction to the simulator. Lastly, we only used a small sub-set of the VISION platform's settings. As such, it is unclear how the other settings (e.g., direction of impact, in-simulation music, awareness of impending collision) may impact stress, the sense of presence, and simulator sickness.

3.5 Conclusion

In conclusion, we have successfully created a virtual-reality based road collision simulator that is capable of simulating motor vehicle crashes under a controlled fashion for lab-based research. There were no adverse events, and all participants tolerated the VISION system well despite one participant reporting neck pain the following day. It appeared that the sense of presence may be negatively associated with simulator sickness. Sense of presence was not as high as we would have hoped, and opportunities for improvement include improvement of framerates to increase the responsiveness of the simulator, and better tracking of the HMD used in the simulator. Future research should examine the effects of combining simulator settings (e.g., front end collision with no audio warning) in order to explore adverse effects and the sense of presence.

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Table 5. Baseline Participant demographics. Data are presented as mean ± standard deviation with range in brackets.

	Total
Sample Size (%female)	25 (36%)
Age	27.3 ± 4.1 (18-35)
FPQ Total Score	18.88 ± 4.41 (10.00 to 27.00)
$FPQ_{Fear\ of\ Severe\ Pain}$	9.20 ± 2.43 (4.00 to 14.00)
$FPQ_{Fear\ of\ Minor\ Pain}$	4.64 ± 1.35 (3.00 to 8.00)
$FPQ_{Fear\ of\ Medical/Dental\ Pain}$	5.04 ± 1.76 (3.00 to 8.00)

Table 6. Simulator Sickness Questionnaire and Presence Questionnaire results post simulation including subscales. Data are presented as mean ± standard deviation with range in brackets.

	Total
SSQ_{nausea}	17.55 ± 19.80 (0.00 to 85.86)
$SSQ_{oculomotor}$	19.71 ± 19.08 (0.00 to 45.48)
$SSQ_{disorientation}$	22.27 ± 26.07 (0.00 to 97.44)
SSQ_{total}	22.59 ± 21.98 (0.00 to 89.76)
$PQ_{Realism}$	33.28 ± 6.69 (17.00 to 42.00)
$PQ_{Possibility\ to\ act}$	15.36 ± 4.48 (7.00 to 22.00)
$PQ_{Quality}$	16.48 ± 3.71 (6.00 to 21.00)
$PQ_{Possibility\ to\ examine}$	14.44 ± 2.97 (10.00 to 20.00)
$PQ_{Self\text{-}evaluation\ of\ performance}$	10.96 ± 2.37 (5.00 to 14.00)
PQ_{Total}	91.04 ± 14.08 (54.00 to 112.00)

Table 7. Simulator Sickness Questionnaire individual items analysis. Data are presented as percentages reported by total sample.

Symptoms	None	Slight	Moderate	Severe
General Discomfort	56%	40%	4%	-
Fatigue	76%	16%	8%	-
Headache	72%	28%	-	-
Eye Strain	56%	36%	4%	4%
Difficulty Focusing	60%	40%	-	-
Salivation Increase	92%	8%	-	-
Sweating	80%	20%	-	-
Nausea	68%	24%	8%	-
Difficulty Concentrating	60%	40%	-	-
Fullness of Head	80%	20%	-	-
Blurred Vision	84%	16%	-	-
Dizziness (Eyes open)	76%	20%	4%	-
Dizziness (Eyes closed)	92%	4%	4%	-
Vertigo	96%	4%	-	-
Stomach Awareness	76%	20%	4%	-
Burping	100%	-	-	-

Table 8. Presence Questionnaire individual items analysis. Data are presented as mean+ standard deviation. Each item was rated from 1 to 7, with higher scores representing increased immersion, but items 14, 17, and 18 are reversed.

PQ Item	Mean Score ± SD
1. How much were you able to control events?	2.04 ± 1.40
2. How responsive was the environment to actions that you initiated (or performed	3.40 ± 1.85
3. How natural did your interactions with the environment seem?	4.46 ± 1.23
4. How much did the visual aspects of the environment involve you?	4.32 ± 1.34
5. How natural was the mechanism which controlled movement through the environment?	4.60 ± 1.26
6. How compelling was your sense of objects moving through space?	5.04 ± 1.14
7. How much did your experiences in the virtual environment seem consistent with your real world experiences?	4.76 ± 1.16
8. Were you able to anticipate what would happen next in response to the actions that you performed?	4.00 ± 1.91
9. How completely were you able to actively survey or search the environment using vision?	5.92 ± 0.86
10. How compelling was your sense of moving around inside the virtual environment?	5.08 ± 1.08
11. How closely were you able to examine objects?	4.64 ± 1.38
12. How well could you examine objects from multiple viewpoints?	3.92 ± 1.58
13. How involved were you in the virtual environment experience?	5.20 ± 1.22
14. How much delay did you experience between your actions and expected outcomes?	5.42 ± 1.32
15. How quickly did you adjust to the virtual environment experience?	5.32 ± 1.49
16. How proficient in moving and interacting with the virtual environment did you feel at the end of the experience?	5.64 ± 1.19
17. How much did the visual display quality interfere or distract you from performing assigned tasks or required activities?	5.32 ± 1.46
18. How much did the control devices interfere with the performance of assigned tasks or with other activities?	6.21 ± 0.93
19. How well could you concentrate on the assigned tasks or required activities rather than on the mechanisms used to perform those tasks or activities?	5.88 ± 0.97

Table 9. Spearman correlations between STAI-6 (Pre & Post), FPQ, PQ, and SSQ (as well as their subscales).

	Pre STAI-6	*Post-STAI-6*	*FPQ-9*	$PQ_{Realism}$	$PQ_{Possibility\ to\ Act}$	$PQ_{Quality}$	$PQ_{Possibility\ to\ Examine}$	$PQ_{Self\text{-}Evaluation}$	PQ_{Total}	SSQ_{Nausea}	$SSQ_{oculo\ motor}$	$SSQ_{disorientation}$	SSQ_{total}
Pre STAI-6	-	0.35	0.10	0.02	-0.240	0.03	0.12	-0.24	-0.03	-0.18	-0.12	-0.09	-0.12
Post-STAI-6		-	0.13	0.06	-0.28	0.11	0.11	0.20	0.01	-0.48*	-0.37	-0.41*	-0.46
FPQ-9			-	-0.20	-0.35	-0.19	-0.19	-0.22	-0.34	-0.02	-0.18	0.00	-0.07
$PQ_{Realism}$				-	0.37	0.36	0.65**	0.63**	0.86**	-0.34	-0.22	-0.20	-0.27
$PQ_{Possibility\ to\ Act}$				-	-	-0.14	-0.01	0.32	0.45*	0.02	0.11	0.01	0.06
$PQ_{Quality}$				-	-	-	0.51**	0.18	0.58*	-0.13	-0.08	-0.01	-0.02
$PQ_{Possibility\ to\ Examine}$				-	-	-	-	0.31	0.60**	-0.12	-0.02	-0.06	-0.08
$PQ_{Self\text{-}Evaluation}$				-	-	-	-	-	0.60**	-0.49*	-0.32	-0.40*	-0.46*
PQ_{Total}				-	-	-	-	-	-	-0.34	-0.03	-0.1.6	-0.17
SSQ_{Nausea}				-	-	-	-	-	-	-	0.75**	0.68**	0.90**
$SSQ_{Oculomotor}$				-	-	-	-	-	-	-	-	0.69**	0.92**
$SSQ_{Disorientation}$				-	-	-	-	-	-	-	-	-	0.84**
SSQ_{Total}				-	-	-	-	-	-	-	-	-	-

STAI-6: State and Trait Anxiety Inventory – 6, *FPQ-9:* Fear of Pain Questionnaire -9, *PQ:* Presence Questionnaire, *SSQ:* Simulator Sickness Questionnaire

** Significance at p<0.05; **Significance at p<0.01*

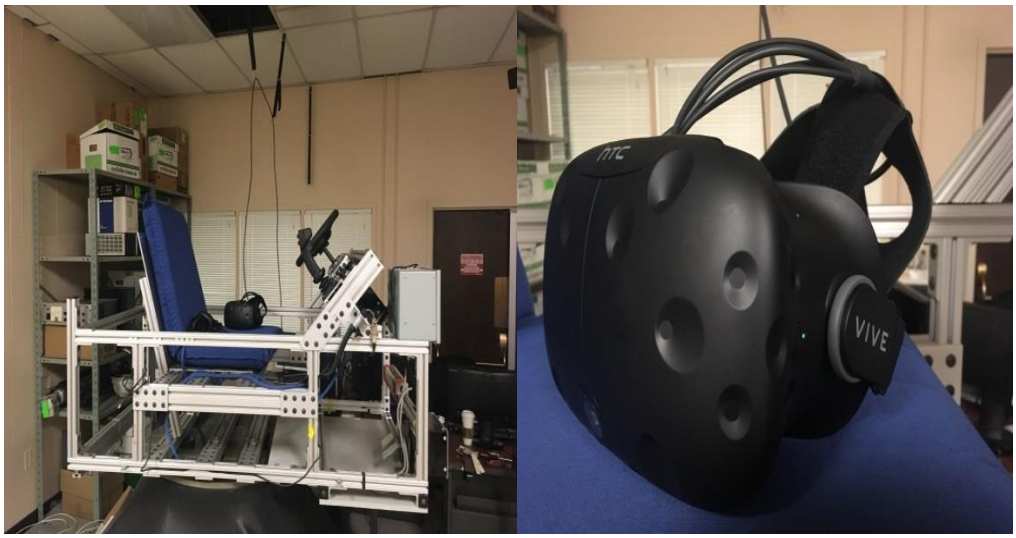

Figure 2. VISION Platform and HTC Vive VR Head Mounted Display

Figure 3. Virtual display of participant while using VISION platform

Chapter 4

4 Changes in Heart Rate Variability, Pressure Pain Threshold and Salivary Cortisol After Exposure to a Novel Virtual Reality-Based Motor Vehicle Crash

4.1 Introduction

The impact of whiplash-associated disorders (WAD) following a motor vehicle crash (MVC) are substantial, with both burden on the healthcare system and numerous personal costs.[1] The symptoms of WAD vary, but commonly include both physical symptoms (e.g., neck pain) and psychological symptoms (e.g., post-traumatic stress disorder), often co-occurring.[2] Despite its evident global burden, debate over the mechanisms for the development and maintenance of WAD has persisted, especially for the transition from acute to chronic symptomology.[3,4] Previous literature has suggested that direction and speed of impact do not correlate with poor recovery,[5] while other novel models of WAD have proposed that its development may be due to a dysregulated or maladaptive stress response to trauma.[3,6]

In this context, the stress/startle reaction is considered any physiological change that indicates an increased sympathetic: parasympathetic tonal balance. In practice, this could be a sudden increase in somatic neuromuscular activity, change in heart rate, heart rate variability (HRV), or increased endocrine activity to protect against potential injury.[7] Autonomic dysregulation (i.e., sympathetic nervous system dominance) has been suggested as a further clinical feature of WAD and other persistent conditions (e.g., Concussion), for which there is symptom overlap.[1,6,8] Endocrine abnormalities in the form of reduced cortisol reactivity have been implicated in patients with chronic WAD compared to healthy controls.[9] Cortisol is a glucocorticoid hormone that is released in reaction to a stressor that aids with the restoration of homeostasis.[10,11] Previous research has indicated a negative association between pain perception and cortisol levels, suggesting that increased pain sensitivity was found in participants with higher cortisol (Choi, 2012).[10] HRV has also emerged as an objective measure for psychological stress,

as it provides non-invasive indication of both sympathetic and parasympathetic control of the body.[12]

Autonomic dysregulation following a MVC has also been suggested to be related to pain inhibition.[6,13] Decreased pressure pain detection threshold (PPDT) (or higher sensitivity to pain) locally at the neck has been reported in patients with both acute and chronic WAD, as well as impaired ability to modulate pain in the presence of a noxious stimulus, a process known as Conditioned Pain Modulation (CPM).[13,14] Typically, a decrease in sensitivity to one pain stimulus (e.g. mechanical pressure) after exposure to a different 'conditioning' stimulus (e.g. noxious cold) is classified as having experienced inhibition, while an increased sensitivity indicates facilitation.[15] In other words, inhibition of PPDT represents an increase in pain threshold as measured by PPDT, while facilitation represents a decrease in PPDT. CPM is considered a quantifiable psychophysical test of nociceptive processing and has seen increasing use in pain research and practice owing to prior literature indicating that the nociceptive modulation is less effective, or perhaps even reversed (i.e., increased sensitivity to the testing stimulus after conditioning) in some chronic pain conditions.[16] However, it is also unclear of exactly when increased pain sensitivity arises after trauma (i.e., immediately after or delayed onset) as sensory hypersensitivity has typically been investigated up to five weeks post-injury.[17]

To date, the mechanisms of WAD have remained unclear, as previous longitudinal research has been forced to adopt an observational approach (as opposed to experimental) in order to understand what types of individuals develop conditions such as WAD.[3,18] As a result, innovative research design has been called for to better assess the role of proposed theoretical models.[3] Recently, we have developed a novel Virtual Reality (VR) and robot-based road collision simulator (see Chapter 3) designed to mimic the participant's perspective of being involved in a MVC, without the potential for tissue damage from biomechanical forces. As a result, we are now poised to measure the physiological effects of VR-based MVC in real-time on healthy participants. Thus, the purpose of this study was to explore aspects of the physiological response to a novel Virtual Reality-based road collision simulator, using quantitative sensory tests (PPDT) and indicators of stress system reactivity such as heart rate variability (HRV) and salivary

cortisol. We also aimed to explore the use of the novel VR MVC simulator as a conditioning stimulus to examine its effects in eliciting a CPM response and any associations between the change in stress reactivity metrics and CPM.

4.2 Methods

Study Design

This was an exploratory cross sectional study with a repeated measures design. Participants had baseline levels of PPDT, HRV, and salivary cortisol before and after exposure to VR-based MVC as described below. CPM was evaluated using a pre-to-post design for which the simulated collision was the conditioning stimulus.

Participants

A convenience sample of healthy adult participants was recruited via email and word of mouth at Western University between October 2020 and January 2021. Participants were eligible for participation if they were: 18 years or older, otherwise healthy with no recent (3 months) significant trauma or injury requiring medical care and could read and understand conversational English. Potential participants were excluded if they reported any pre-existing neck pain, headache, concussion, cardiovascular instability, active cancer treatment, neurological or systemic conditions that affect balance or postural control (e.g., Benign paroxysmal positional vertigo), migraines, visual pathology (e.g., saccades), technophobia, and claustrophobia. Secondary to the COVID-19 pandemic, participants also had to clear a standardized questionnaire examining suitability to return to campus and had their temperature screened prior to participation. This study was approved by the Health Sciences Research Ethics Review Board at Western University (London, ON, Canada) prior to participation in the study and all participants provided written informed consent prior to participation.

Experimental Protocol

Participants were asked to refrain from any strenuous physical activity and to avoid consumption of any food or drink (including caffeine) for the hour prior to data

collection. Participants completed a study-specific demographic questionnaire including details such as sex and gender identity. A three-lead set-up was used to capture the electrocardiogram (ECG) and the participants had the option of placing the electrodes (200 Foam Series, Cardinal Health) themselves using a figure for reference or the option of one of the primary investigators placing the electrode for them. After application of the sensors, participants sat quietly for five minutes in a comfortable chair in a climate-controlled windowless room while HRV was continuously captured by proprietary computer software. Conditions in the lab were maintained as consistently as possible across participants and testing days (lighting, temperature, noise, etc.). HRV_{5min} was evaluated, as five minute recordings are considered the minimum essential length of time for evaluation of HRV.[19] During data collection of HRV, participants were asked to avoid talking or moving and to breathe otherwise normally. HRV was measured simultaneously using ADInstruments PowerLab (PowerLab®, ADInstruments, Sydney, Australia) at a sampling rate of 1000 Hz, with real time digitized and filtered data stored on a laboratory laptop.

One saliva sample was collected near the end of the 5 minute rest period using a small poly-cotton swab that was rolled around inside the mouth for about 30 second before being sealed in a sterile salivette and immediately transferred to a -30°C freezer. Next, pressure pain detection threshold (PPDT) was tested at the angle of the upper trapezius following a previously published protocol.[20] In brief, the $1cm^2$ rubber tip of a digital algometer (FDX-25, Wagner Instruments, Greenwich CT) was pressed into the skin over top of the upper trapezius of the dominant side of the participant at a constant rate of 5N/s until they indicated that the sensation changed from pressure to pain. This was repeated three times, with a minimum 30 seconds between applications and the same rater conducted each test (MJL). The mean of the three trials (measured in kilograms of force (kgf)) was considered the PPDT.

Each participant was then assisted into the VISION (Virtual Interface for Stress-Trauma Interactions through Open World Navigation) platform. A thorough description of the VISION platform is in *Chapter 3* of this thesis. The VISION platform consists of a seat

affixed to a six degree of freedom robotic platform ((Mikrolar R3000 (Mikrolar Inc., Hampton, NH, USA)), a HTC Vive head mounted display (HTC Corporation, Xindian City, Taipei) with active noise cancelling headphones. During its use, subjects were first exposed to five minutes of driving in a virtual city as the passenger in the front seat of a virtual vehicle in an urban setting at dusk where they were able to view their environment as much as they wished but could not control the direction of speed of the vehicle. They were then given one minute of rest. The robotic platform was programmed to interface with the virtual reality headset such that movements of the virtual car were synchronized with the robot's movements to add a proprioceptive experience to the visual and audio stimuli of being in a car. Subsequently, each participant was informed that the next simulation would have a virtual car crash but were not told when or where it would take place. In brief, subjects were exposed to a virtual reality based rear end collision that delivered a perturbation at a peak acceleration of 0.2 g (measured at the head) that coincided with the visual and audio indications of a rear end collision in the simulator (i.e., a second car approached and collided from the rear while the participant vehicle was stopped at a traffic light). Audiovisual stimuli included shattering glass of the windshield, squealing tires, a simulated car horn just before and after the collision, and no music was playing on the virtual car radio.

Following exposure to the virtual collision, participants were assisted out of the VISION platform and the ECG leads were re-applied to their torso in the same fashion as the baseline measurements; the electrode placement remained unchanged. Participants sat quietly for 30 seconds prior to the re-evaluation of PPDT. PPDT was then measured immediately after exposure to the VISION platform serially in the same fashion as the pre-test for evaluation of any change. HRV was captured continuously throughout the post-exposure resting period for off-line analysis of recovery. At the 5-minute post-removal point, one more saliva sample was collected using the same poly-cotton swabs for post-exposure salivary cortisol. Each participant was also asked to return three to seven days later to recapture only the resting baseline PPDT and HRV. Salivary cortisol was not re-evaluated on the re-test day.

Statistical Analysis

Descriptive statistics including mean and standard deviation of the sample were calculated for each variable after normality was assessed using Kolmogorov-Smirnov tests. Outliers were removed and ratio level data were transformed if necessary, using logarithmic transformation. Data were presented in their un-transformed state to allow for easier comparison to the greater body of literature.

HRV was analyzed over the five minute baseline period prior to the CPT and two five minute bins after (post-exposure and resting-state retest three to seven days later). A variety of HRV indices were selected in order to evaluate those best poised for further investigation in future studies. HRV indices were reported in Time domain parameters including root mean square of successive NN interval differences (RMSSD) and the standard deviation of the RR intervals (SDRR). For the frequency domains, HRV was analyzed with a high frequency (HF) band from 0.15 to 0.45 Hz and a low frequency band from 0.04 to 0.15Hz. HF and LF were both measured in absolute (us^2) and normalized units (nu), as per the recommendations from the Task Force of The European Society of Cardiology.[21] The ratio of LF/HF was also calculated, whereby a higher ratio indicates sympathetic dominance, and a low ratio indicates parasympathetic dominance.[19]

Physiological Reactions to VISION Platform

For purpose 1 (normative reactions to the VISION platform), mean PPDT and HRV were compared across testing times (T1 = 5 minute pre-simulation, T2 = 0-5 minute post-simulation, and T3= 5 minutes retest 3 to 7 days later) using one way repeated measures analysis of variance (rmANOVA) with Bonferroni post-hoc to further explore significant main effects of time. Salivary cortisol (Cortisol (Saliva) ELISA, Alpco (Salem, NH, USA), cat no.11-CORHU-E01-SLV) was analyzed using industry standard approaches according to the manufacturer's specifications and all samples were run in duplicate. Salivary cortisol was evaluated using the absolute difference before and after the exposure to the VR-based MVC to account for individual variation and a paired t-test was used to detect for significant differences. A logarithmic transformation was applied to

HF_{ms} and LF_{ms}, as all other measurements were found to be normally distributed for parametric statistics.

CPM Response

For purpose 2, (CPM responses) CPM was recorded in both absolute ($\Delta CPM_{ABSOLUTE}$ = Post - Pre simulation (in kgf)) and percent (%) change (($\Delta CPM_{PERCENT}$ = $\Delta CPM_{ABSOLUTE}$/Baseline PPDT(kgf) x100)) terms, as per the recommendations of Kennedy et al., 2016.[16] Meaningful CPM was evaluated using a similar approach was used to the work of Locke et al. 2014 and Kennedy et al., 2020.[15,22] Next, the standard error of measurement (SEM) was calculated for PPDT ((SEM = pooled standard deviation of baseline PPDT (SDpooled)$\sqrt{}$(1-ICC)). Based on the work of Kennedy et al., 2020, CPM was examined in relation to $\pm$2 SEM of baseline PPDT to reflect a 95% confidence interval in order to determine true change.[15] This was then converted a percentage change based upon baseline mean PPDT. Both a percentage change and absolute change were included to reflect participants who may have experienced a small absolute difference, but large percent change compared to baseline testing.

Relationship between CPM and Stress System Reactivity

For purpose 3 (associations between CPM, change in HRV and salivary cortisol) Pearson/ Spearman correlations were used to explore the relationship between CPM, itself a metric of change, and change in the various HRV indices. Associations were explored with all HRV indices in order to target the ones best positioned for future studies. Strength of Pearson/Spearman correlations were interpreted using the recommendations of Mukaka (2012), whereby: <0.30 (negligible), 0.30 to 0.50 (low), 0.50 to 0.70 (moderate), 0.70 to 0.90 (high), >0.90 (very high).[23] Scatter plots were also used to both visually model and interpret the relationships of the data.

All statistical analyses were completed using IBM SPSS Statistics Version 27 and the p-value for statistical significance was set at 0.05.

Sample Size Calculation

As this work was hypothesis-generating rather than hypothesis-testing, no formal sample size calculation was performed.

4.3 Results

Descriptive Statistics

25 participants (16 males, 9 females) participated in the study and no participant in the study indicated their sex as different from their identified gender. As such, only male and female sexes are reported. The mean age was 27.3 $\pm$ 4.1 (18 to 35) years. Demographics of the study population are displayed in *Table 10.* There was no attrition, as all participants returned for re-evaluation of their baseline measurements on the second testing day.

Physiological Reactions to VISION Platform

In terms of the time domain measures of HRV, RMSSD was significantly increased ($p<0.002$) after exposure to the VISION platform from 39.80 $\pm$ 17.08 ms (95%CI: 32.75 to 46.85ms) to 48.63 + 19.40ms (95%CI: 40.44 to 56.82). For the frequency domains, absolute high frequency power was significantly increased ($p=0.004$) from 900.96 $\pm$ 766.95 ms^2 (95%CI: 33.22 to 47.68) to 1262.96 $\pm$ 853.38 ms^2 (95%CI: 893.93 to 1631.99 ms^2) after exposure to the VISION platform. Absolute low frequency power was also significant increased ($p=0.004$) after the VR-based MVC from 1534.42 $\pm$ 1251.07 ms^2 (95%CI: 993.41 to 2075.42 ms^2) to 2108.87 $\pm$ 1332.82 ms^2 (95%CI: 1558.71 to 2659.03 ms^2). All other HRV indices at each time point are displayed in *Table 11*. There were no significant differences in any HRV measurement upon retest approximately one week later compared to baseline. Baseline values of PPDT were 3.36 $\pm$ 1.14 kgf (95% CI: 2.89 to 5.80 kgf) with no significant differences in values immediately after the VR MVC, or three to seven days later upon re-test. See *Table 11* for a full description of PPDT values at these time points. Baseline levels of salivary cortisol were 31.57 $\pm$ 13. 95 ng/mL (95% CI: 24.39 to 38.74 ng/mL) with no significant differences after exposure to the VR-based MVC. Cortisol data were only available on 17 participants because of COVID-19 related interruptions during the study period.

CPM Response in reaction to VISION platform

When assessed as a group mean, $CPM_{ABSOLUTE}$ was found to be -0.24 $\pm$ 0.68 kgf (95% CI: -0.52 to 0.04 kgf) while $CPM_{PERCENT}$ was found to be -8.57% $\pm$ 22.40 % (95%CI: -17.82 to 0.68%) after exposure to the VISION platform. The reliability of PPDT in the present study was measured using intraclass correlation coefficient ($ICC_{3,1}$) and was 0.96. For this study, SEM of the baseline PPDT measurements was 0.23 kgf. Thus, it was determined that based on $\pm$2 SEM of PPDT any change in PPDT greater than + 0.47 kgf (or +13.9% of baseline mean PPDT) reflected inhibition, less than -0.47 kgf (or -13.9% of baseline mean PPDT) reflected facilitation, and in between these values reflected non-response. After classification based on meaningful change of CPM > $\pm$ 2 SEM, it appeared that 16% (4/25) of participants experienced inhibition of their pain threshold, 44% (11/25) experienced facilitation of their pain threshold, with the remainder experiencing no appreciable change. See *Table 12* for a description of CPM within these groups. Using the CPM classification criteria, 16% (4/25) of participants still had a noticeably decreased PPDT compared to their baseline measurements one week prior upon re-test.

Associations between CPM and Stress System Reactivity

There was a statistically significant negative low correlation (r= -0.41, p=0.046) between $CPM_{PERCENT}$ and ΔRMSSD before and after exposure to the VR-based MVC (*Figure 4*). There was also a statistically significant negative moderate correlation (r= -0.64, p<0.001) between the $\Delta HF(ms^2)$ and $CPM_{PERCENT}$ (*Figure 5)*. Taken together, it appeared that that a decrease in pain thresholds (facilitation) was associated with an increase in parasympathetic nervous system activity. See *Table 13* for a full description of the correlational matrix.

There was a moderate negative correlation between $CPM_{ABSOLUTE}$ and pre-post simulator change in salivary cortisol (r = -0.51, p = 0.035) (*Figure 6)*. The association was maintained for $CPM_{PERCENT}$ (r = -0.59, p= 0.03) (*Figure 7)* reflecting that a decrease in pain threshold (facilitation) was associated with increased cortisol levels.

4.4 Discussion

The purpose of this study was to explore the range of physiological reactions after exposure to a novel VR-based MVC. We also explored the use of such a simulator in determining its suitability as a potential CPM protocol. Our study demonstrated that when analyzed as a group, while there was no significant changes in PPDT, there was a statistically significant increase in HRV indices (RMSSD, absolute HF, absolute LF**)** suggestive of an increase in parasympathetic nervous system post-exposure to a VR-based MVC. This increase in parasympathetic nervous system activity appeared to be associated with greater sensitivity to mechanical pain (decreased pain thresholds). There was also a significant moderate negative association between CPM and change in salivary cortisol. When meaningful CPM was assessed as a change of PPDT greater than $\pm$ 2 SEM, it appeared that 44% of participants experienced actual facilitation (i.e., decrease) of their pain threshold in response to the VISION platform. Approximately one week later, up to 16% of participants continued to have a noticeably decreased PPDT measurement compared to their baseline levels.

We were unable to demonstrate any autonomic system dysregulation following exposure to the VR-based MVC in the present study as evidenced by the non-significant changes in LF/HF. Baseline RMSSD values were within reported normative values from the literature.[24] HRV indices were similar to those of baseline values post-exposure, however a statistically significant increase in parasympathetic nervous system activity was noted after exposure to the simulated collision. Previous investigations into the relationship between the autonomic nervous system and pain perception generally reflect that there is an increase in sympathetic nervous system activity associated with decreased pain sensitivity during an acute stressor – physical or mental.[13,25,26] Unfortunately, due to the wired configuration of the ECG we used, we were unable to measure the effects of the VISION platform at the time of the virtual collision as the leads had to be removed to allow the participant to enter the simulator.

We observed a low to moderate negative relationship between the percent change of CPM and change in HRV values measurement reflective of parasympathetic system activity after exposure to the VR-based MVC. Other studies have also investigated the

relationship between autonomic reactivity and CPM to various degrees, however most of these studies examine the relationship to resting HRV values. De Kooning et al., (2013) found no significant correlations between CPM values and HRV indices and concluded that autonomic reactivity and CPM appear to be unrelated.[13] However, these authors did not explore the change in HRV as it relates to CPM which may explain the dissonance in findings. Koenig and colleagues (2016) did find a negative relationship between self-reported pain and resting RMSSD values in healthy participants as opposed to chronic pain cohorts.[27] Similarly, Nahman-Averbuch and colleagues (2016) also reported a negative correlation existing between CPM and resting HRV (measured with RMSSD) adaptations in men, but not women using tonic heat as a conditioning stimulus.[28] Thus, there may be sex-related differences in the relationship between CPM and autonomic reactivity, however we were not sufficiently powered to explore this area. Sex-related differences in autonomic reactivity as it relates to CPM requires further investigations, especially given that WAD appears to affect a higher number of females than males.[29]

Nonetheless, our study is not the first to report increased parasympathetic nervous system activity during recovery after exposure to an acute stressor. Mezzacappa and colleagues (2001) reported that in reaction to a mental stressor, healthy participants experienced a compensatory increase in RMSSD activity during recovery (also known as vagal rebound) that they postulated might be needed to recover from stress.[30] Rat studies have also confirmed that exposure to repeated psychophysical stress leads to vagal rebound lasting beyond the duration of the stressor.[31] However, other authors have suggested that while initial vagal rebound may be protective, prolonged exposure to stress may eventually elicit a maladaptive phase of parasympathetic withdrawal and sympathetic dominance.[32] This speculation may also apply to individuals who are suffering from chronic WAD, as sympathetic dominance has been suggested to be a causal factor in the development of chronic pain.[6,33] Mezzacappa and colleagues (2001) also suggested that a lack of or impaired vagal rebound following a stressor may reflect a failure of the parasympathetic nervous system to react, potentially increasing the risk for illness.[30] Given the various psychosocial stressors that can arise after a MVC (i.e., insurers, lawyers, and medical services),[3] further research is needed to evaluate when and how parasympathetic recovery is altered following exposure to an MVC.

An interesting finding from this study was that there was a significant negative moderate association between CPM (absolute difference or percent change) and the change in salivary cortisol in reaction to the VR-based MVC. As a group, salivary cortisol was not significantly different after the VR-based MVC, but this may reflect that cortisol reactivity follows different patterns individually in reaction to a stressor. An explanation for the non-significant increase in salivary cortisol levels may be that we evaluated it too soon, as salivary cortisol levels have been known to peak after 10 to 20 minutes.[34] Other authors have also examined for the relationship between CPM and salivary cortisol in healthy subjects. Timmers and colleagues (2018) found a positive correlation ($r = 0.34$) between change in PPDT and salivary cortisol using the Maastricht Acute Stress Task (combination of cognitive and physical stress) as a stressor.[34] However, Hoegh and colleagues (2020) who also found a negative correlation between the change in salivary cortisol and PPDT using a cognitive Montreal Imaging Stress Test as a conditioning stimuli, whereby the change in cortisol could explain 19% of the variance in PPDT values.[35] While we did not evaluate the role of cortisol in predicting PPDT values, it appears that elevated cortisol immediately after a mental stressor may be associated with decreased ability to modulate pain.[35] Of course, due to mixed findings in the literature, it is likely that this relationship is dependent on the type of conditioning stimuli used. Larger studies will be required to investigate cortisol reactivity within meaningful CPM to further explore these relationships.

Baseline PPDT values were higher than in previous investigations, possibly representing that the participants in the current study experienced some degree of hyposensitivity, and the SEM of baseline PPDT in the present study was similar to previous descriptions of PPDT in healthy participants.[20,36] However, as baseline measurements of PPDT were the average of three measurements, we feel that regression to the mean cannot fully explain the change in PPDT values. Most interesting was that just over 40% of the participants included in this study had increased pain sensitivity of their trapezius muscles after exposure to the VISION platform. Thus, unlike a majority of CPM protocols, the protocol used in the present study did not encourage inhibition of pain thresholds, possibly indicating that it is likely not appropriate as a conditioning stimulus in CPM protocols.[16] However, there has also been debate over whether or not the conditioning stimulus in a

CPM protocol needs to be noxious in nature to produce modulation of pain thresholds.[37] For example, exposure to a mental conditioning stimulus (e.g., arithmetic counting) has also been shown to lead to pain inhibition.[25] Most recently, Kennedy and colleagues (2020) evaluated the role of a sham conditioning stimulus (tepid water) in eliciting a CPM response in healthy participants.[15] They also found that over 40% of their subjects experienced facilitation of their pain thresholds after exposure and concluded that expectation of pain may have contributed to this effect.[15] Thus, it appears that CPM (either inhibition or facilitation) is dependent on the type of conditioning stimuli used as well as the potential contribution of expectation of pain.

In the present study, we did not evaluate the role of expectation prior to exposure to the VR-based MVC, however each participant was informed prior to the exposure that a virtual collision would take place. A MVC is a traumatic stressor as evidenced by its own nomenclature reflecting the idea that these incidents are not merely accidents,[38,39] and as such subjects could have anticipated that some degree of pain was expected. Therefore, expectation of pain and/or injury following exposure could at the very least partially explain the facilitated PPDT findings, though we are unable to fully account for them due to the sample size of the study. However, this line of thinking is in agreement with the findings of Bostick and colleagues (2009) who reported that even among healthy Canadians without previous injury, there was widespread pessimism regarding recovery after a potential MVC.[40] As a MVC is a unique combination of physical and psychological stressors [3,41] it may very well be that the psychological exposure of being involved in a MVC (even a virtual one) can lead to an increase in pain sensitivity to the point that pain is perceived from relatively low biomechanical forces.[42] If such findings are valid, both patients suffering from WAD and the clinicians treating them may have a better understanding of why some patients acquire WAD and some do not. However, further research is required to properly explore these theories.

Limitations

This study is not without limitations. Most noticeably, the sample size for the study was a small convenience sample of participants. As such, we were unable to explore the

relationships between the various measures of HRV (as well vagal rebound) and meaningful CPM within subgroup analyses with sufficient statistical power. That being said, this initial study was conceived as the beginning of a larger body of work exploring the range of physiological reactions to VR-based MVC's without potential for tissue damage. We were also unable to capture HRV indices acutely during the virtual collision due to the physical constraints of our data capturing system and the physical space of the simulator. As such, we could not measure the effects of a virtual collision on HRV indices at the time of the collision and is an area for further improvement. While we did ask participants to refrain from any strenuous exercise or consuming any food or drink prior to study, we did not control for time of day which may have impacted the stress response of each participant. That said, most of the re-test data was conducted at a similar time of day to that of each participant's initial data collection. Salivary cortisol data was also only available on 17 participants due to study interruptions because of the COVID-19 pandemic.

Due to the shorter time frames used for analysis, we were unable to capture other HRV indices. However, we are confident that the periods of analysis that we used were sufficient in order to explore HRV in the time and frequency domains selected. We also did not control for the breathing rate of each participant during HRV measurement. However, during these periods of time participants were instructed to breathe normally, and as such we do not believe that this would have influenced our results greatly. Also, as participants had their HRV measured in a seated position, there may have been increased contribution to the absolute LF values from the parasympathetic nervous system and the baroreflex.[19] Thus, we may not have been able to accurately estimate sympathetic nervous system activity. Lastly, as this work was conducted on healthy participants, we were unable to make direct comparisons to patients with WAD, which is an important area for future investigation.

4.5 Conclusion

In conclusion, exposure to a VR-based MVC appears to have elicited an increase in pain sensitivity of the trapezius muscle in up to 44% of participants. In 16% of participants these effects persisted even up to three to seven days later upon re-test. It also appears

that a majority of participants experienced an increase in parasympathetic nervous system activity as measured by HRV after exposure reflecting vagal rebound which was associated with a decrease in pain thresholds. This line of work is envisioned as the first in exploring the range of physiological reactions to an otherwise safe and controllable MVC with little risk of actual tissue damage. Future work should examine the effects of exploring various simulator settings upon other physiological metrics as well as expanding the psychological profile of the participants exposed.

4.6 References

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Table 10. Participant demographics. Data are presented as mean ± standard deviation with range in brackets.

	Total
Sample Size (%female)	25 (36%)
Age (years)	27.3 ± 4.1 (18-35)
Height (m)	1.76 ± 0.09 (1.57 to 1.93)
Weight (kg)	76.23 ± 19.06 (32.00 to 111.40)

Table 11. HRV indices, PPT values, and salivary cortisol at baseline, post VR MVC, and upon retest. Data are presented as mean ± standard deviation with range in brackets.

	Baseline	Post VR MVC	Re-test (3 to 7 days)
RMSSD(ms)	39.80 ± 17.08 (11.26 to 86.75)	48.63 ± 19.40 (15.43 to 85.89)*	39.30 ± 16.36 (13.90 to 76.66)
SDRR(ms)	57.30 ± 22.53 (8.35 to 108.00)	64.47 ± 22.92 (16.51 to 103.60)	57.48 ± 18.36 (21.67 to 89.53)
HF(ms^2)	900.96 ± 766.95 (34.50 to 3615.00)	1262.96 ± 853.38 (55.26 to 3529.00)*	680.40 ± 511.32 (76.14 to 1834.00)
LF(ms^2)	1534.42 ± 1251.07 (165.20 to 4508.00)	2108.87 ± 1332.82 (345.10 to 5350.00)*	1557.37 ± 979.01 (180.10 to 3185.00)
HF(nu)	38.01 ± 19.76 (8.99 to 74.89)	38.99 ± 17.26 (5.91 to 70.41)	36.01 ± 17.38 (4.89 to 69.78)
LF(nu)	59.76 ± 22.79 (12.30 to 90.84)	57.20 ± 20.46 (23.41 to 95.19)	62.33 ± 20.49 (21.71 to 95.52)
LF/HF	2.35 ± 2.12 (0.16 to 9.30)	1.79 ± 1.30 (0.33 to 4.67)	2.53 ± 2.37 (0.31 to 9.82)
PPT(kgf)	3.36 ± 1.14 (1.31 to 5.80)	3.12 ± 1.43 (0.84 to 6.56)	3.12 ± 1.29 (1.28 to 5.55)
Salivary cortisol (ng/ml)	31.57 ± 13.95 (15.30 to 65.81)	31.16 ± 14.85 (12.13 to 65.06)	N/A

** Significance at $p<0.05$ compared to baseline*

Note: A logarithmic transformation was applied to HF(ms^2) and LF (ms^2) for statistical comparisons. RMSSD: root mean square of successive NN interval differences; SDRR: standard deviation of the RR intervals; HF(ms2):absolute high frequency; LF(ms2): absolute low frequency; HF(nu): normalized high frequency; LF(nu): normalized low frequency, LF/HF: frequency between low and high frequency power; PPT(kgf): Pain pressure threshold; VR: virtual reality; MVC: motor vehicle crash.

Table 12. CPM expressed in absolute and percent change terms for all participant, inhibitors, facilitators, and non-responders. Data are presented as mean ± standard deviation with range in brackets.

	$\Delta CPM_{ABSOLUTE}$ (kgf)	$\Delta CPM_{PERCENT}$(%)
All Participants (n =25)	-0.24 ± 0.68 (-1.30 to 1.15)	-8.57 ± 22.40 (-52.30 to 36.64)
PPT Inhibited (n=4)	0.76 ± 0.30 (0.48 to1.15)	24.21 ± 9.16 (15.76 to 36.64)
PPT Facilitated (n= 11)	-0.86 ± 0.26 (-1.30 to -0.50)	-28.30 ± 12.53 (-52.30 to -15.45)
PPT Non-Response (n=10)	0.04 ± 0.38 (-0.39 to 0.76)	0.02 ± 10.04 (-13.78 to 13. 10)

Note: PPT: Pain pressure threshold; CPM: conditioned pain modulation; kgf: kilograms of force.

Table 13. Correlational matrix between CPM and change in HRV indices and change in salivary cortisol

	CPM_{ABS}	$CPM_{PERCENT}$	$\Delta RMSSD$	$\Delta SDRR$	$\Delta HF(ms^2)$	$\Delta LF(ms^2)$	$\Delta HF(nu)$	$\Delta LF(nu)$	$\Delta LF/HF$	Δcortisol (ng/ml)
CPM_{ABS}	-	0.92**	-0.34	-0.32	-0.46*	-0.38	-0.11	0.11	0.08	-0.51*
$CPM_{PERCENT}$		-	-0.41*	-0.41*	-0.64**	-0.48*	-0.17	0.17	0.12	-0.59*
ΔRMSSD			-	0.77*	0.43*	0.00	0.34	-0.30	-0.28	0.10
ΔSDRR				-	0.29	0.05	-0.01	0.03	-0.06	0.34
$\Delta HF(ms^2)$				-	-	0.48*	0.48*	-0.56**	-0.66**	0.24
$\Delta LF(ms^2)$				-	-	-	0.44*	0.44*	0.42	-0.09
ΔHF(nu)				-	-	-	-	0.89**	-0.88**	0.06
ΔLF(nu)								-	0.92**	-0.25
ΔLF/HF									-	0.02
Δcortisol(ng/ml)										-

Note: CPM_{ABS}: absolute change in PPT values, $CPM_{PERCENT}$: percent change in PPT values, ΔRMSSD: change in root mean square of successive NN interval differences; ΔSDRR: change in standard deviation of the RR intervals; ΔHF(ms2): change in absolute high frequency; Δ LF(ms2): change in absolute low frequency; ΔHF(nu): change in normalized high frequency; ΔLF(nu):change in normalized low frequency, ΔLF/HF: change in frequency between low and high frequency power.

* Significance at p<0.05; **Significance at p<0.01

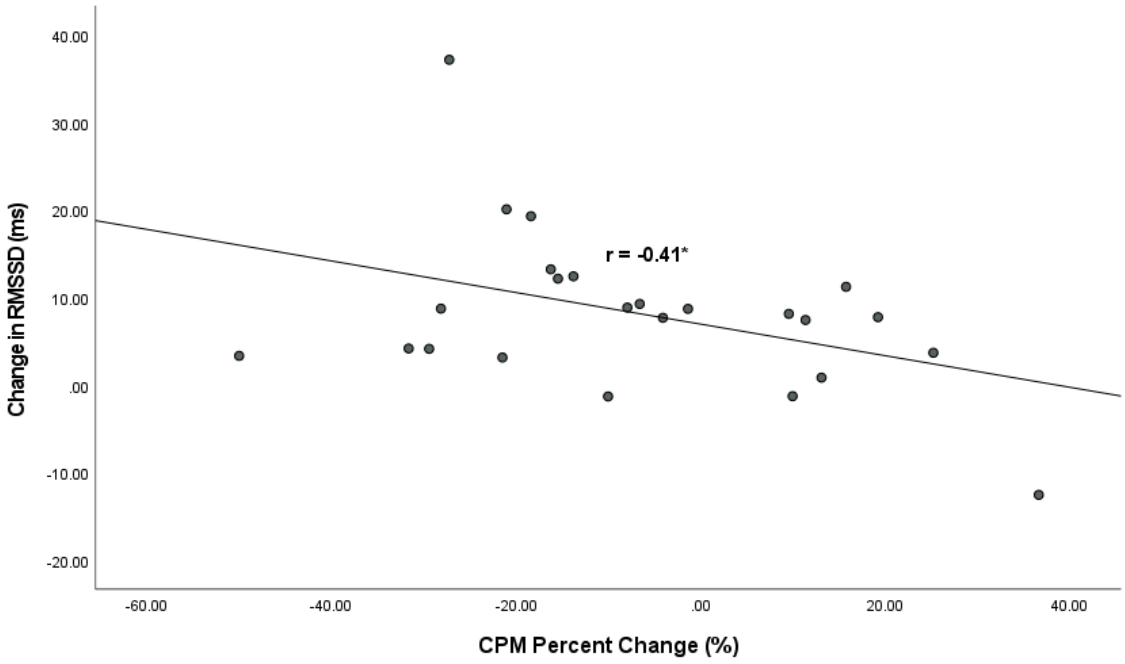

Figure 4. Relationship between Percent Change CPM and Change in RMSSD values before and after VR-based MVC. * Denotes significance at p<0.05.

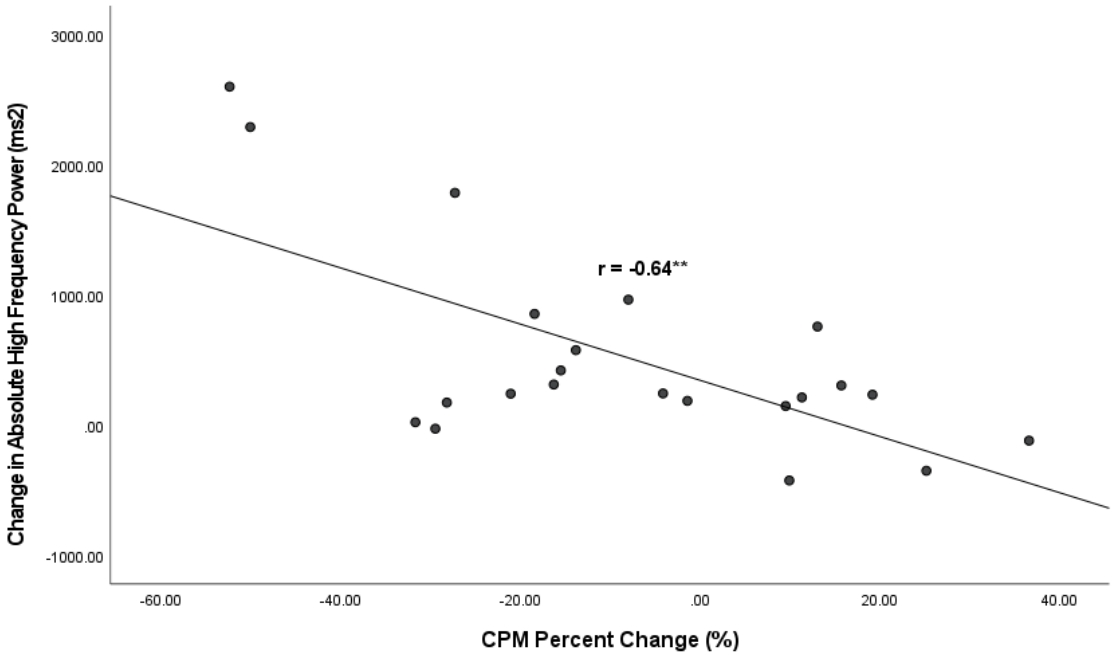

Figure 5. Relationship between Percent Change CPM and Change in Absolute High Frequency Power before and after VR-based MVC. * Denotes significance at p<0.01.

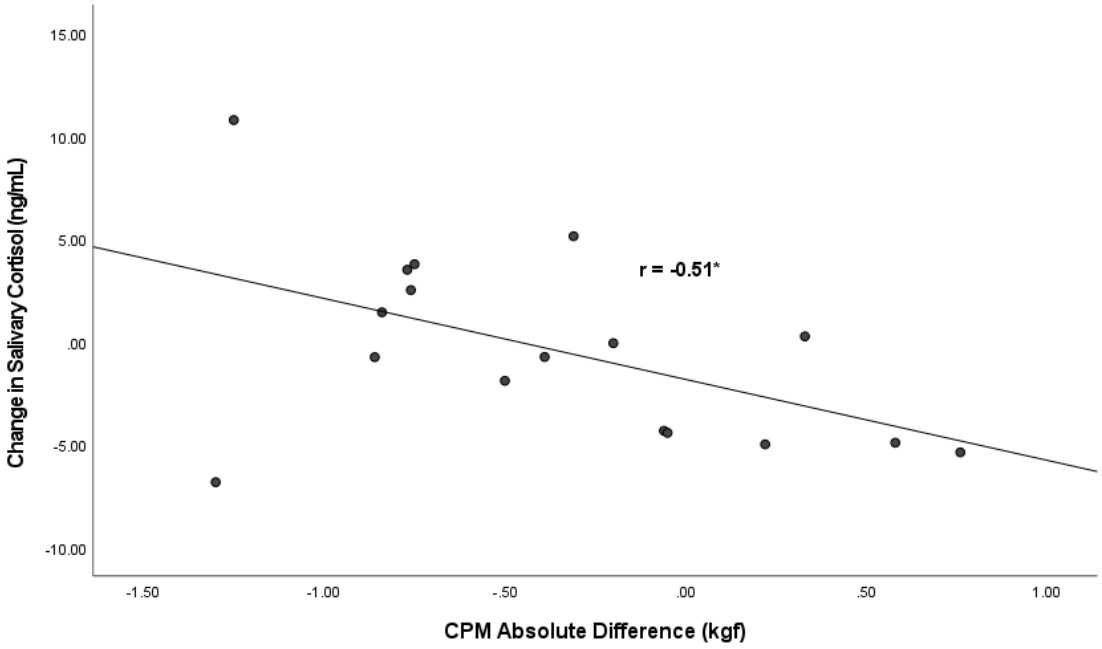

Figure 6. Relationship between Absolute Change CPM and Change in Salivary Cortisol before and after VR-based MVC. * Denotes significance at p<0.05.

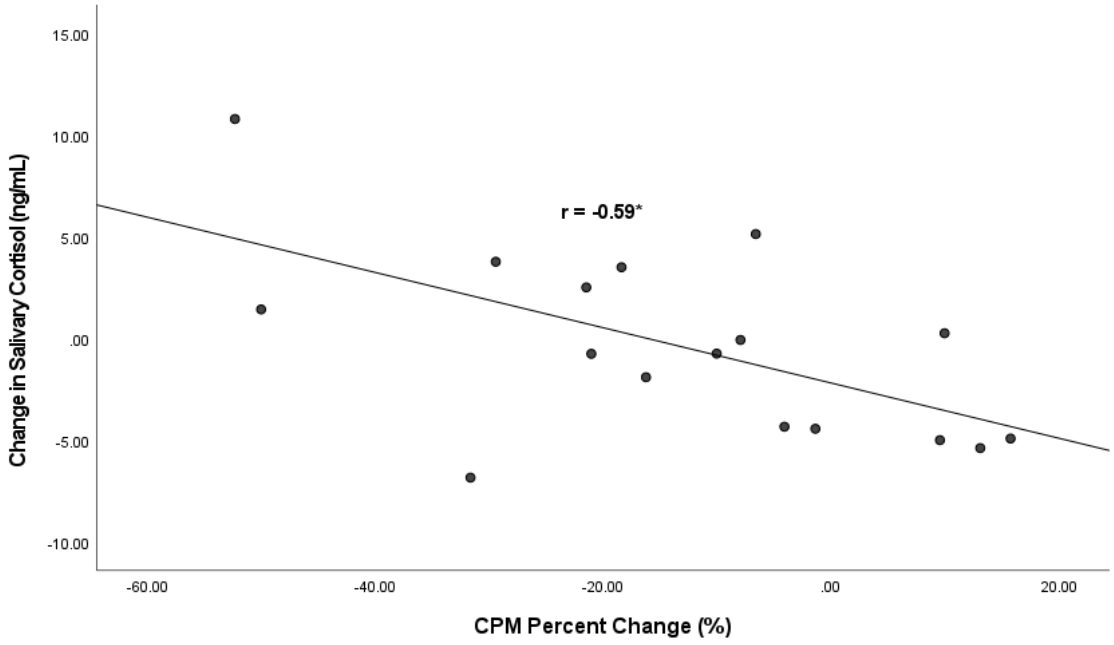

Figure 7. Relationship between Percent Change CPM and Change in Salivary Cortisol before and after VR-based MVC. * Denotes significance at p<0.05.

Chapter 5

5 Summary

While it appears that acute pain may confer survival value in reaction to trauma, chronic pain may be best thought of as a disease where its effects are multidimensional, with interactions between biology, psychology, and social factors.[1] This interplay between biological, psychological, and social factors in the context of Whiplash-Associated Disorders (WAD) may help to explain some of the heterogeneity in presentation.[2] In development of this thesis, we approached WAD using the Integrated Model as proposed by Walton and Elliot (2017), whereby the motor vehicle crash (MVC) acts as a stressor/catalyst towards the development of WAD based upon the pre-existing vulnerabilities or protections (biological, psychological, social) of the individual.[3] While we did not examine for pre-existing protections and vulnerabilities, we still performed this research under the idea that a MVC is a unique and complex stressor that interacts with each person uniquely. Thus, the purpose of this thesis was to explore the complex relationship between pain and stress using a novel virtual reality (VR)-based road collision simulator which has been designed to explore the experience of being involved in a car crash, with comparisons to a known stressor (i.e., the cold pressor task). We viewed this work as exploratory and likely the beginning of a new research directive aiming to provide new avenues for exploring live, simulated traumas and to aid in developing the types of measurements that can be used with them. This project was also conceived as a means by which to begin to question why and how different stress responses occur, and we hope that this knowledge will begin to shed light on competing theories to explain such responses in the context of WAD.

In Chapter 2, we sought to explore if meaningful CPM had relationships with both the sympathetic nervous system (SNS) and hypothalamus-pituitary-adrenal (HPA) axis reactivity in healthy adults following exposure to the cold pressor task. Healthy participants underwent evaluation of their pressure pain detection threshold (PPDT), conditioned pain modulation (CPM), galvanic skin response (GSR) and salivary cortisol both before and after a cold pressor test as a stressor (CPT). Meaningful CPM was evaluated based on change greater than or less than 2 Standard Error of Measurement

(SEM) of baseline PPDT to classify participants experiencing inhibition of pain, facilitation or non-response. When meaningful CPM was assessed, only 30% of participants experienced inhibitory CPM. Within this inhibitory CPM group, there was a moderate positive association between CPM and the absolute change in GSR as an index of SNS activity. In agreement with the literature, this work suggests that inhibitory CPM is not a universally experienced phenomenon and may be related to SNS activity. Future work may want to explore for various other individual factors that have been implicated in CPM using this meaningful CPM framework such as sex and age.

In Chapter 3, we sought to evaluate initial tolerability to a recently developed novel VR-based road collision simulator. This was done to gather user feedback for optimization, and to explore the development of any adverse events (i.e., reports of neck pain longer than 48 hours, nausea, inability to tolerate VR, and disorientation). Healthy participants had their state anxiety measured before exposure to a novel virtual reality-based rear-end collision simulator with a small perturbation (0.2 g) at the time of simulated impact. We also evaluated Simulator Sickness and Presence Questionnaires post-exposure. We observed that the VR-based MVC was well tolerated by a majority of participants while one participant (4%) reported neck pain the following day that did not last longer than 48 hours. There were no other adverse events found. There appeared to be an inverse relationship between items on the Presence Questionnaire and Simulator Sickness Questionnaire (greater sense of presence, less experience of sickness or nausea). It appeared that a VR-based MVC could be safely used with healthy participants to model MVCs, but future work is required to optimize the VR environment and to investigate the effects of various crash parameters (e.g., direction of impact).

In Chapter 4, we began quantification of the range of physiological responses to the novel VR-based road collision simulator. Healthy participants had their PPDT, heart rate variability (HRV), and salivary cortisol measured before and after exposure to a novel Virtual Reality (VR)-based rear end collision. Meaningful CPM was again determined based on baseline PPDT to classify participants as having experienced inhibition, facilitation, or non-response. There was an increase in HRV indices (root mean square of the successive differences (RMSSD) between normal heartbeats, absolute high

frequency), suggestive of an increase in parasympathetic nervous system activity after the virtual exposure, while PPDT values remained statistically unchanged based upon group means. When meaningful CPM was assessed, 44% of participants experienced facilitation of their pain threshold in following the VR-based MVC. There was a low to moderate negative association between the percent change in CPM and change in HRV (RMSSD, absolute high frequency) indicating decreased pain thresholds were associated with increased parasympathetic nervous system activity. There was also a negative moderate association between percent change CPM and change in salivary cortisol. It appeared that exposure to a VR-based MVC may increase pain sensitivity in some participants who are exposed, which may be related to increased cortisol reactivity or parasympathetic nervous system activity. Future work is recommended with larger samples for confirmation of these findings.

While exposure to a cold pressor task appeared to induce decreased pain sensitivity in some participants with an associated increase in sympathetic nervous system activity, these findings were not replicated in a VR-based MVC. Instead, it appeared that there was an increase in pain sensitivity associated with increased parasympathetic nervous system activity and cortisol reactivity in the absence of injury-inducing biomechanical forces. In reaction to a stressor, post-traumatic stress research has described that there can be up to six different fear responses (which mainly present as sympathetic uproar and parasympathetic shutdown), though the time spent in each is dependent on the cognitive appraisal of the situation at hand.[4] With the CPT, while participants are aware that the stressor will be painful, their perception of it its risks may be mitigated as they remain in control at all times during the immersion of their hand. In contrast, it could be that participants in our VR-based MVC experienced less locus of control, which in turn elicits a different stress response. Bolini and colleagues (2004) highlighted that in participants who had increased locus of control over a noise-cognitive paradigm, had a decreased cortisol response.[5] Thus, we speculate that one of the major differences in these stressors and their associated stress/pain responses is the role of expectation of injury, despite not having measured it in this thesis.

It is our hope that by continuing to identify the myriad of stress and startle responses to simulated trauma, we may be better able to help identify the characteristics of individuals who are more likely to develop WAD such that treatment options can be better tailored to their care. While nervous system activity was measured differently across the two stressor studies, it is possible that the results of both studies are communicating similar findings. In reaction to the cold pressor task, participants who became less sensitive to pain experienced an associated increase in sympathetic nervous system. Comparatively, in reaction to a VR-based MVC, participants who became more sensitive to pain had an association with increased parasympathetic nervous system activity. Although not definitive, it appears that activation of the sympathetic nervous system after a trauma (simulated or otherwise), may lead to inhibitory pain modulation while activation of the parasympathetic nervous system, (or the absence of sympathetic tone) can lead to facilitatory pain modulation or heightened pain sensitivity. While it remains unclear if these nervous system activity patterns remain heightened for days after exposure, our results suggest that different physiological responses to trauma may be helpful in explaining the presence of alteration in pain sensitivity immediately following a stressor (both noxious or non-noxious).

Taken together, our work suggests that the both the stress response and pain response to a given stressor is variable and appears to be based both on the individual's appraisal of the stressor as well as the stressor selected. By removing participants from the VR-based MVC, it is possible that we provided a conditioned safety stimulus, which has been known to inhibit conditioned analgesia.[4] In other words, the participant could have felt that they were immediately placed into a safe environment, thus leading to a recovery period of parasympathetic nervous system activity. Additionally, increases in SNS activity following the CPT could be explained by the presence of ongoing pain and or discomfort (even after its termination) signaling that 'danger' was still present. This thesis also suggests the possibility that some individuals who are exposed to a car crash may be at higher risk of pain and/or injury due to increased pain sensitivity resulting from the psychological experience of involvement in a MVC. In our society, a MVC may be considered a unique stressor due to its ability to create a fear of safety that is compounded

by the psychosocial impacts that present following the crash (i.e., litigation, ability to pay for services).[3,6]

5.1 Future Directions and Questions

As predicted, this thesis raises more questions regarding the relationship between pain and stress than it answers. These results have opened up discussion for identifying why some people develop WAD and others may not, but we recognize that future work is needed to continue to identify appropriate stress/pain responses to simulated trauma. This thesis presents the initial results and implications of the VISION project, and given the novelty of the VISION platform, we anticipate that there will be other future investigations into understanding WAD using controllable laboratory VR collisions.

In the context of exploring the relationship between stress system reactivity and pain, we decided to explore these associations using simple bivariate correlations. However, after having performed this work we acknowledge that the relationship between stress and pain is likely a curvilinear relationship, and as such, future work will want to examine stress and pain from this perspective. Recently, Lee and colleagues (2021) investigated the role of blood-based protein/hormone biomarkers in the prediction of recovery following acute musculoskeletal trauma using a cluster analysis, as opposed to simple bivariate relationships.[7] They found that in people with persistent disability there were also moderate to high levels of serum brain derived neurotrophic factor and transforming growth factor-beta 1. As such, the relationships between measurements of stress system reactivity (heart rate variability, salivary cortisol, galvanic skin response) and pain could be explored using such cluster analysis in future research to help predict recovery from trauma.

While we chose to examine the immediate pain and stress response to controlled stressors, other research teams have spent great time trying to predict recovery from trauma. These investigations have appeared to consistently highlight three unique trajectory pathways: those very likely to recover, likely to recovery, and not likely to recover.[8,9] At the same time, our work adds to the growing body of literature suggesting that Conditioned Pain Modulation (CPM) also consists of three unique responses, namely

inhibition, facilitation, and non-response.[10,11] At this point, it is unclear if these three CPM responses align with trajectories predicting recovery. As interest in CPM as a biomarker for chronic pain continues to increase,[12] future work may want to identify if these CPM responses can aid in identification of those likely to recover from trauma or not. Additionally, those investigating exercise-induced analgesia may want to evaluate meaningful CPM, as inefficient CPM and impaired exercise-induced analgesia have been linked in patients with other chronic conditions such as knee osteoarthritis.[13]

One of the most surprising findings of this thesis was that that over 40% of healthy participants who were exposed to a virtual rear-end MVC exhibited increased mechanical pain sensitivity of their upper fibers of trapezius immediately post-collision. This finding is of particular interest as it may help to shed light on those participants who present with neck pain from low-speed collisions. It may be that the acquisition of neck pain following a MVC is due to a combination of the psychological exposure of the experience as well as any biomechanical forces imparted during said collision. As this finding was not replicated in all subjects, it is suggestive that there are different responses to being involved in a MVC which may help to explain the heterogeneity of WAD.[3] Increased pain sensitivity may also have implications in the areas of recent imaging studies which have found fatty muscle infiltrate of the cervical musculature in chronic WAD patients.[14,15] It may very well be that an immediate increase in pain sensitivity, compounded by the presence of biomechanical forces and/or other psychological stressors leads to a learned disuse of the neck musculature causing fatty muscle infiltration.[15] Future work will want to examine increased pain sensitivity shortly after the time of injury to prevent these secondary sequelae from occurring.

Lastly, this thesis only examined the effects of a rear-end VR-based MVC upon healthy participants. The VISION platform is capable of manipulation of collision type (e.g., rear-end vs front end) as well as other variables such as audiovisual knowledge of an impending collision. Future studies may want to manipulate these variables to gain further insight into the various pain and stress responses that may present in addition to examining how WAD patients may react to these stimuli. In the current study, we informed participants that a rear-end collision would occur, but did not say exactly when

it would happen. Future studies could attempt to manipulate the participants knowledge of the impending MVC to evaluate differential responses. For example, informing participants that a car crash would occur but not saying which type versus telling them exactly when the collision may take place would be of particular interest with respect to locus of control. Finally, to ensure that the simulator is adequately representing a MVC, qualitative inquiry with MVC survivors would be helpful to understand the experience of being involved in a MVC. Methodological approaches such as Qualitative Description, have been reported appropriate when specific descriptions of a phenomenon are desired and allow for a flexible yet simplistic approach to understanding such experiences, especially when there is a lack of information on a given topic.[16,17] Qualitative inquiries would be helpful in continuing to understand why MVC's and WAD affect different people differently and continue to shed light on this condition that continues to plague its sufferers.

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Appendices

Appendix A: Ethics Approval for VISION Pt. I

Western Research

Date: 10 December 2018

To: Dr. Dave Walton

Project ID: 111280

Study Title: Quantification of the stress response and change in pain modulation in reaction to the cold pressor task in healthy adults

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 18December2018

Date Approval Issued: 10/Dec/2018 09:21

REB Approval Expiry Date: 10/Dec/2019

Dear Dr. Dave Walton

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Initial Contact E-mail	Email Script	19/Nov/2018	1.0
LETTER OF INFORMATION AND CONSENT-VISION Pt1 V6.0	Written Consent/Assent	29/Nov/2018	6.0
VISION - Recruitment E-mail 2.0	Recruitment Materials	19/Nov/2018	2.0
VISION Pt. I - Bio Data Collection Form - V2	Other Data Collection Instruments	19/Nov/2018	2.0
VISION Pt.1 - Initial Data Collection Package 3.0	Paper Survey	17/Nov/2018	3.0
VISION Pt.1 - Protocol v3.0	Protocol	29/Nov/2018	3.0

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geogehgan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Ethics Approval for VISION Pt. II

Western Research

Date: 20 February 2020

To: Dr. Dave Walton

Project ID: 114681

Study Title: Quantifying the normal stress response(s) and change in conditioned pain modulation following a novel virtual road collision simulation

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 10March2020

Date Approval Issued: 20/Feb/2020 09:23

REB Approval Expiry Date: 20/Feb/2021

Dear Dr. Dave Walton

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Initial Contact E-mail -1.0.docx	Email Script	18/Dec/2019	1.0
LETTER OF INFORMATION AND CONSENT-VISION Pt2 V3.0	Written Consent/Assent	19/Feb/2020	3.0
VISION - Pt. 2- Protocol v.1.0	Protocol	18/Dec/2019	1.0
VISION 2.0 - Recruitment E-mail 1.0	Recruitment Materials	18/Dec/2019	1.0
VISION Pt. II - Bio Data Collection Form - V1	Other Data Collection Instruments	18/Dec/2019	1.0
VISION Pt.2 - Initial Data Collection Package 2.0	Paper Survey	12/Feb/2020	2.0
VISION Pt.2 - Post Immersion Data Collection Package 1.0	Paper Survey	13/Dec/2019	1.0

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Transdisciplinary Bone and Joint Training Award Budget	Study budget	18/Feb/2020	1.0

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geogehgan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix C: VISION Pt. I Letter of Information and Consent

Quantification of the stress response(s) and changes in conditioned pain modulation in reaction to the cold pressor task

LETTER OF INFORMATION AND CONSENT

Principal Investigator
Dr. David Walton PT PhD
Western University
Elborn College
London, ON

Funding: Faculty Scholar Award & Chronic Pain Network Grant

Dear Sir/Madam,

Thank you for your time in reviewing this letter of information and for considering participation in our study. Please be sure you've read this letter in its entirety and have had any questions answered to your satisfaction before consenting to participate.

Invitation to Participate

You are being invited to participate in a study examining how pain can change following an acute stressful event. You are being invited because you have indicated that you are otherwise healthy and have had no recent trauma or injury affecting your muscles, joints, bones or ligaments in the previous 2 weeks. Furthermore, you are at least 18 years of age and are able to read and understand conversational English.

In order to be eligible to participate, you must not have any of the following conditions. Please tell the research coordinator if any of these apply to you.

1. Significant health conditions including infection or a history of cardiovascular instability (e.g., heart disease, high or low blood pressure)
2. Actively undergoing cancer treatment
3. Any health condition that affects your reaction to cold, including conditions such as Raynaud's phenomenon or cryoglobulinemia
4. Any health condition that impairs your ability to feel touch or temperature, including stroke, multiple sclerosis, amyotrophic lateral sclerosis, or nerve pinch in your neck.

What the purpose of this study?

We are evaluating how your sensitivity to pressure can be altered by a stressful event, and why that might occur. We will ask you to dip your hand into cold water (a task known as the Cold Pressor Task), which considerable prior research has used as a low risk and reliable way to create stress. We will also be examining the effects of some of your

personal attributes like your biological sex or gender orientation on your pain sensitivity. The results of this study will help us better understand the connections between pain and stress.

How long will you be in the study?

This study will occur over two 1-hour sessions separated by about one week (2 hours total commitment).

What are the study procedures?
If you agree to participate, the study will be conducted in the Pain and Quality of Life Integrative Research Lab (P.I.R.L.) located in Elborn College, Western University in London, ON. Prior to your visit you are asked to avoid eating, drinking sugary or caffeinated drinks or participating in vigorous activity for the hour prior. On each visit, the following procedures will occur:

1. You will be asked to complete a few questionnaires. These will start by asking things about you: your age, height, weight, sex at birth, time you awoke that day, and the quality of sleep you had the previous night. You will also be asked to complete the Gender and Pain Expectation Scale that will ask you questions about how well different traits describe you and your beliefs about your sensitivity to pain compared to other people like you. Finally, you will be asked 6 short questions about your current level of anxiety.
2. Next, the researchers will place recording electrodes on your chest to measure your heart rate, and on two finger tips of your non-dominant hand to measure your skin's reaction to stress. You will have the option of placing the electrodes yourself according to a diagram or having the researchers do it for you. A standard inflatable blood pressure cuff will be wrapped around your upper arm. Then you will be invited to sit comfortably for 5 minutes while the researchers record data coming from the different sensors. At the end of the 5 minutes you will be asked to provide a small sample of saliva by placing a sterile cotton swab under your tongue for about 10 seconds before sealing it in a tube. It is important to note that none of the data we are collecting can be used for diagnostic purposes, however if your blood pressure should be very high, we will let you know and suggest some options you may wish to explore. Finally, your sensitivity to pressure will be tested by one of the researchers who will apply pressure using a battery-powered device with a small rubber tip with slowly increasing force until you indicate the sensation is painful.
3. Next, you will be asked to submerge your dominant hand into a container of cold water (approximately 3-4 degrees Celsius) up to the wrist. During this time the researchers will continue to collect the information from the sensors connected to you. You will also be asked to rate your current pain on a scale of 0 (no pain) to 10 (extreme pain) every 10 seconds. You are encouraged to keep your hand in the water for up to 90 seconds but may remove your hand at any point if you should choose to do so.

4. After your hand has been removed from the water and dried, the researchers will retest your pain sensitivity with the same rubber-tipped device. You will also be asked to provide one more saliva sample. You will then be asked to sit comfortably for another 5-minute period while heart rate, skin reactivity, and blood pressure are collected. During this time you will be asked to complete the 6 anxiety questions one more time.

You will be asked to come back to the PIRL for the exact same testing protocol approximately 1 week later.

What are the risks and benefits of participating?

There are no immediate direct benefits for participation in this study. However, we believe the information obtained will help us and others studying pain to better understand the various influences on the experience.

The perceived risks of participation are minimal. The most evident risk is a momentary increase in pain and/or stiffness as a result of keeping your hand in the cold water for 1 minute, but this should resolve after you start moving it once more. Additionally, as this is a pain provocation test, you will experience cold pain while your hand is submerged. The cold-water, while uncomfortable, is non-damaging in nature. There is little to minimal risk of frostbite and you are in complete control of all aspects of this test. You may remove your hand at any point if you choose. However, in the event that frostbite occurs, your hand will be immediately removed from the cold water, dried, and you will be taken to the closest Emergency Department (University Hospital) for medical management. Again, the risk of this is extremely minimal. Finally, you are likely to experience some increased heart rate, blood pressure, or sweating due to the cold-water immersion of your hand. Again, you are in complete control of the study and may remove your hand from the cold water at any point. Also, the researchers will be monitoring your heart rate during the study and if it should get too high (above 80% of your age-adjusted maximum) they will stop the study. It is possible that you will see a bit of bruising around the area of the pressure pain test.

All data will be secured, but there is a chance of a privacy breach, in which case you will be immediately informed.

In addition, there is a small chance that you may experience some irritation or a potential allergy to the gel used for the heart rate monitoring. If you are aware of any skin sensitivities to gel or adhesives, please let the researchers know ahead of time. If you do begin to experience itch or redness under any of the recording electrodes, the study will be stopped and medical management, if needed, will be offered.

Finally, you will be asked to rate your own stress, anxiety and fear as part of this study. For some, providing personal information regarding your own anxieties and fears can be a difficult experience. Once again, you are in complete control and may choose to not provide this information.

Please note that medical treatment in the event of study related injury would be provided at no additional cost.

Reminders and Responsibilities

Participants will be required to refrain from eating, drinking sugary or caffeinated drinks, or engaging in vigorous physical activity (e.g., going to the gym) for the hour prior to each data collection period described above. In addition, please do not smoke or chew gum prior to your lab visit.

How will participants' information be kept confidential?

All information will be kept confidential to the best of our ability. Your data will be stored separately from any information that could connect you to it. A unique 4-digit ID number will be generated for you and will be attached to your results in the study. The primary investigator at Western University, Dr. David Walton and PhD Student Michael Lukacs, will collect all of the data provided and analyze it as a de-identified group. All data will be stored on the secure, password protected and firewalled server of Western University. Identifying information will be retained for 7 years after study completion as per institutional policy. Western University's REB will have access to participant's data to ensure that it is following the proper laws and regulations. Outside of these acknowledged groups, your specific information (i.e., name) will not be shared with anyone without your express written consent to do so. Note: Only group averages will ever be published and you will not be identified. Data will be retained for a period of 7 years before they are destroyed. You are free to request the removal of your data from the study up until this point.

Will I be compensated for my participation?

There is no direct financial compensation for participation in this study. However, those who incur costs beyond their usual daily routines (e.g., having to drive and park at Elborn College for this study) will have those costs reimbursed.

What are the Rights of Participants?

Participation in this study is completely voluntary. You may choose to not participate, withdraw from the study at any point in time without penalty and without any explanation required. If you choose not to participate or to leave the study at any time it will have no effect on your academic standing or your relationship with Western University or the researchers. Additionally, if you withdraw, you may request to have your data withdrawn from the study. Participation in this study does not prevent you from participating in any other research studies at the present time or future. If you are participating in another research study, we ask that you please inform of us of your participation. You do not waive any legal rights by signing the consent form.

What if I want more information?

You may contact the lead researcher, Dr. David Walton at Western University (London, Canada) if you require any further clarification. His contact information can be found on the first page of this document. If you have any questions regarding your rights as a participant in this research study or the conduct of the study, you may contact the Office of the Research Ethics at (519) 661-3036 or by e-mail at ethics@uwo.ca.

In addition, if you wish to receive a summarized copy of the results of this study, you may leave your email address on a separate sheet. This sheet will be held by the lead researcher, and the email address will only be used to provide the summarized results, after which the list will be destroyed.

We thank you in advance for considering participation in this study.

This letter is yours to keep for future reference.

Sincerely,

Dr. David Walton PT PhD
Michael Lukacs PT, PhD Student
Mohamad Fakhereddin, PhD Student
Maryam Ghodrati, PhD Student
Walter Siqueira, DDS, PhD
Sandro Cestra, MPT Student
Henry Tan, MPT Student
Carmen Fung, MPT Student
Harleen Nijjar, MPT Student
Julian Quaglia, MPT Student
Jaipaul Dhaliwal, MPT Student

If any part of this study causes you stress or anxiety that you find difficult to deal with, please feel free to contact us directly. The lead researcher is Dr. David Walton.

You may also find the following resources helpful for dealing with stress:

1. **Supportive Family Member or Friend**

2. **Your Family Doctor or Other Healthcare Provider**

3. **Psychological Services (in your neighborhood hospital, university, or clinic)**

4. **Telephone Support Lines (London and District Distress Centre; available 24 hours/day)**

Distress Line	519-667-6711
Crisis Response Line	519-433-2023

5. **Telehealth Ontario (available 24 hours/day)**

   1-866-797-0000

If your blood pressure should be abnormally high, or outside of normal range, you will receive a written note on the day of testing, and it will be suggested that you should consult your family doctor.

Consent Form

Quantification of the stress response(s) and changes in conditioned pain modulation in reaction to the cold pressor task

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

_____

Participant name (print)

_____ _____

Participant signature Date

_____ _____

Person obtaining consent (print) Date

_____

Signature of person obtaining consent

Appendix D: VISION Pt. II Letter of Information and Consent

Quantifying the normal stress response(s) and change in conditioned pain modulation following a novel virtual road collision simulation
LETTER OF INFORMATION AND CONSENT

Principal Investigator

Dr. David Walton PT PhD
Western University
Elborn College
London, ON

Funding: Bone and Joint Institute Transdisciplinary Award

Dear Sir/Madam,

Thank you for your time in reviewing this letter of information and for considering participation in our study. Please be sure you've read this letter in its entirety and have had any questions answered to your satisfaction before consenting to participate.

Invitation to Participate

You are being invited to participate in a study examining how healthy people react to being exposed to a virtual reality car crash. You are being invited because you have indicated that you are otherwise healthy and have had no recent trauma or injury affecting your muscles, joints, bones or ligaments in the previous 3 months . Furthermore, you are at least 18 years of age and are able to read and understand conversational English.

In order to be eligible to participate, you must not have any of the following conditions. Please tell the research coordinator if any of these apply to you.

1. Significant health conditions including infection or a history of cardiovascular instability (e.g., heart disease, high or low blood pressure)
2. Actively undergoing cancer treatment
3. Any health condition that impairs your ability to feel touch, including stroke, multiple sclerosis, amyotrophic lateral sclerosis, or nerve pinch in your neck.
4. An inability to have your cervical neck tested for dysfunction
5. Neurological or systemic conditions that affect balance or postural control, and vestibular conditions that would affect ability to use virtual reality such as Vertigo or Benign paroxysmal positional vertigo (BPPV) (i.e. a disorder of the inner ear affecting balance)
6. Have a history of migraines
7. Visual pathology such as eye saccades (i.e. rapid eye movements) or other visual or movement-related disturbances
8. Technophobia or fear of technology
9. Claustrophobia or any fear of enclosed spaces

What the purpose of this study?

Until now, it has been impossible to examine the range of stress responses for those involved in a car crash, especially at the time of the crash. We have successfully developed a new virtual reality-based road collision simulator that is designed to simulate the experience of being in a car crash without any of the biomechanical trauma. Thus, the purpose of this study is to examine how healthy people react to being part of a virtual car crash. We hope that the results of this study will help us better understand the connections between pain and stress. This study is conducted as part of the PhD work for PhD candidate Michael Lukacs.

How long will you be in the study?

This study will occur over two sessions separated by about one week, with the first one lasting just over an hour, and the second lasting only 20 minutes (roughly 2 hours total commitment).

What are the study procedures?

If you agree to participate, the study will be conducted in the Robot Biomechanics lab located in 030 1R16 in the Arts and Humanities Building, Western University in London, ON. Prior to your visit you are asked to avoid eating, drinking sugary or caffeinated drinks or participating in vigorous activity for the hour prior. As part of the screening process, your neck will be screened for dysfunction. You will be asked to rotate your head from side to side to ensure that you have full, pain-free range of motion of your cervical spine. You will then be asked to side-bend and rotate your head while a small amount of pressure is applied to the top of the head. Any production of symptoms would warrant exclusion from the study. On your visit, the following procedures will occur:

5. You will be asked to complete a few questionnaires. These will start by asking things about you: your age, height, weight, sex at birth, time you awoke that day, and the quality of sleep you had the previous night. You will also be asked 6 short questions about your current level of anxiety. Finally, you will be asked a series of 9 questions regarding your fear of pain.

6. Next, the researchers will place recording electrodes on your chest to measure your heart rate, and on two fingertips of your non-dominant hand to measure your skin’s reaction to stress. You will have the option of placing the electrodes yourself according to a diagram or having the researchers do it for you. Then you will be invited to sit comfortably for 5 minutes while the researchers record data coming from the different sensors. During these 5 minutes, you will be asked to refrain from using any electronic devices. At the end of the 5 minutes you will be asked to provide a small sample of saliva by placing a sterile cotton swab under your tongue for about 10 seconds before sealing it in a tube. It is important to note that none of the data we are collecting can be used for diagnostic purposes.

Finally, your sensitivity to pressure will be tested by one of the researchers who will apply pressure using a battery-powered device with a small rubber tip into your trapezius muscle with slowly increasing force until you indicate the sensation is painful.

7. Next, you will be asked to sit in a car seat attached to a robot that is designed to mimic the movements of a car during driving. You will also be asked to wear a virtual reality helmet which will display the visuals of the simulation. In this simulation you will experience the role of being a passenger in a car. In addition, we will ask you to wear noise-cancelling headphones such that you are further immersed in the simulation. The movements of the robotic platform are synchronized with the visuals of the VR helmet in order to increase the immersiveness of the simulation. For example, as you view the car turning a corner, the robot will also turn accordingly. In order to see how you tolerate being exposed to virtual reality, you will be exposed to a driving route with no crash for 5 minutes in duration. You will be given 1 minute of rest. During this rest period, you will be asked to refrain from using electronic devices.

8. You will again be asked to be exposed to a virtual driving route, but this time there will be a virtual car crash. During this crash, the platform you are sitting on will exert a small force against you to increase your immersion of feeling like you are in a car crash. The platform you are sitting on cannot accelerate beyond 1g, which is the equivalent of you sneezing. At any point you are free to quit the simulation should you choose. This route is only expected to take 1 minute in length.

9. Immediately after the virtual car crash, the researchers will retest your pain sensitivity with the same rubber-tipped device. You will then be asked to sit comfortably for another 10-minute period while heart rate, and skin reactivity are continuously measured. At 5 minutes post, one more saliva sample will be collected using the same poly-cotton swabs. The researchers will re-evaluate your pain sensitivity every 3 minutes following. At the end of the 10 minutes, the researchers will ask you 6 questions to evaluate your anxiety, and 2 questionnaires regarding both the immersiveness of the virtual simulation and the extent to which you experienced nausea or not.

You are invited to come back for a second visit 3 to 7 days later to have your pain sensitivity, heart rate, and skin sensitivity re-evaluated under the same environmental conditions for evaluation of their test-retest reliability following the virtual car crash exposure. This is an optional study visit and your initial data will still be used even if you do not return. This second testing session does not include a virtual car crash and is expected to take 10-15 minutes.

What are the risks and benefits of participating?

There are no immediate direct benefits for participation in this study. However, we believe the information obtained will help us and others studying pain to better understand the various influences of stress on the development of pain following injury/trauma.

The perceived risks of participation are minimal. The most evident risk is a momentary increase the stiffness of the muscles of your neck, but this should resolve after you start moving it once more. You are also likely to experience some increased heart rate, blood pressure, or sweating due to stressful nature of the car crash simulation. Again, you are in complete control of the study and may quit the study at any time, should you choose to do so. Also, the researchers will be monitoring your heart rate during the study and if it should get too high (above 80% of your age-adjusted maximum) they will stop the study. It is also possible that you will see a bit of bruising around the area of the pressure pain test. Due to the nature of virtual reality, there is a very small risk that you may experience some nausea after experiencing the simulation. From previous work in our lab examining virtual reality and neck movement, nausea following exposure to virtual reality did not last longer than 24 hours.

As we are examining the hypothesis that neck pain may be due to stress, it is possible that some people may experience pain and/or stiffness of the neck following exposure to the simulation. We expect these symptoms to be short-lived (i.e., not lasting more than 1-2 days). We are confident that the magnitude of force that you will be exposed to in the simulator is not great enough to cause damage to the tissues of the neck. However, in the event that you should experience neck pain and/or stiffness that persist greater than 1-2 days, we would ask you to follow up with your family physician for medical management. We will also send your family physician a letter outlining the nature of the study and the simulation that you were exposed to.

All data will be secured, but there is a chance of a privacy breach, in which case you will be immediately informed.

In addition, there is a small chance that you may experience some irritation or a potential allergy to the gel used for the heart rate monitoring. If you are aware of any skin sensitivities to gel or adhesives, please let the researchers know ahead of time. If you do begin to experience itch or redness under any of the recording electrodes, the study will be stopped and medical management, if needed, will be offered.

Finally, you will be asked to rate your own stress, anxiety and fear as part of this study. For some, providing personal information regarding your own anxieties and fears can be a difficult experience. Once again, you are in complete control and may choose to not provide this information.

Please note that medical treatment in the event of study related injury would be provided at no additional cost.

Reminders and Responsibilities

Participants will be required to refrain from eating, drinking sugary or caffeinated drinks, or engaging in vigorous physical activity (e.g., going to the gym) for the hour prior to each data collection period described above. In addition, please do not smoke or chew gum prior to your lab visit.

How will participants' information be kept confidential?

All information will be kept confidential to the best of our ability. Your data will be stored separately from any information that could connect you to it. A unique 4-digit ID number will be generated for you and will be attached to your results in the study. The primary investigator at Western University, Dr. David Walton and PhD Student Michael Lukacs, will collect all of the data provided and analyze it as a de-identified group. All data will be stored on the secure, password protected and firewalled server of Western University. Identifying information such as your full name, age, email address, sex and gender will be retained for 7 years after study completion as per institutional policy. Western University's REB will have access to participant's data to ensure that it is following the proper laws and regulations. Outside of these acknowledged groups, your specific information (i.e., name) will not be shared with anyone without your express written consent to do so. Note: Only group averages will ever be published and you will not be identified. Data will be retained for a period of 7 years before they are destroyed. You are free to request the removal of your data from the study up until this point.

Will I be compensated for my participation?

There is no direct financial compensation for participation in this study. However, those who incur costs beyond their usual daily routines (e.g., having to drive and park at Western University for this study) will have those costs reimbursed.

What are the Rights of Participants?

Participation in this study is completely voluntary. You may choose to not participate, withdraw from the study at any point in time without penalty and without any explanation required. If you choose not to participate or to leave the study at any time it will have no effect on your academic standing or your relationship with Western University or the researchers. Additionally, if you withdraw, you may request to have your data withdrawn from the study. Participation in this study does not prevent you from participating in any other research studies at the present time or future. If you are participating in another research study, we ask that you please inform of us of your participation. You do not waive any legal rights by signing the consent form.

What if I want more information?

You may contact the lead researcher, Dr. David Walton at Western University (London, Canada) if you require any further clarification. His contact information can be found on the first page of this document. If you have any questions regarding your rights as a

participant in this research study or the conduct of the study, you may contact the Office of the Research Ethics at (519) 661-3036 or by e-mail at ethics@uwo.ca.

In addition, if you wish to receive a summarized copy of the results of this study, you may leave your email address on a separate sheet. This sheet will be held by the lead researcher, and the email address will only be used to provide the summarized results, after which the list will be destroyed.

We thank you in advance for considering participation in this study.

This letter is yours to keep for future reference.

Sincerely,

Dr. David Walton PT, PhD
Dr. James Dickey PhD
Michael Lukacs PT, PhD(c)

If any part of this study causes you stress or anxiety that you find difficult to deal with, please feel free to contact us directly. The lead researcher is Dr. David Walton. In addition, if you do have neck pain, headache, and/or nausea persisting for more than 1-2 days please do not hesitate to contact us.

You may also find the following resources helpful for dealing with stress:

10. **Supportive Family Member or Friend**

11. **Your Family Doctor or Other Healthcare Provider**

12. **Psychological Services (in your neighborhood hospital, university, or clinic)**

13. **Telephone Support Lines (London and District Distress Centre; available 24 hours/day)**

Distress Line	519-667-6711
Crisis Response Line	519-433-2023

14. **Telehealth Ontario (available 24 hours/day)**

1-866-797-0000

Consent Form

Quantification of the stress response(s) and changes in conditioned pain modulation in reaction to the cold pressor task

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

_____

Participant name (print)

_____ _____

Participant signature Date

_____ _____

Person obtaining consent (print) Date

_____

Signature of person obtaining consent

Appendix E: State-Trait Anxiety Inventory-6 (STAI-6)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very Much
1. I feel calm…….	**1**	**2**	**3**	**4**
2. I am tense…….	**1**	**2**	**3**	**4**
3. I feel upset……	**1**	**2**	**3**	**4**
4. I am relaxed…….	**1**	**2**	**3**	**4**
5. I feel content…….	**1**	**2**	**3**	**4**
6. I am worried…….	**1**	**2**	**3**	**4**

Appendix F: Fear of Pain Questionnaire (FPQ-9)

The items listed below describe painful experiences. Please look at each item and think about how FEARFUL you are of experiencing the PAIN associated with each item. If you have never experienced the PAIN of a particular item, please answer on the basis of how FEARFUL you expect you would be if you had such an experience. Circle one number for each item below to rate your FEAR OF PAIN in relation to each event.

	Not at all	Somewhat	Moderately	Very Much	Extreme
1.Breaking your arm	**1**	**2**	**3**	**4**	**5**
2.Having a foot doctor remove a wart from your foot with a sharp instrument	**1**	**2**	**3**	**4**	**5**
3.Getting a papercut on your finger	**1**	**2**	**3**	**4**	**5**
4.Receiving an injection in your mouth	**1**	**2**	**3**	**4**	**5**
5.Getting strong soap in both your eyes while bathing or showering	**1**	**2**	**3**	**4**	**5**
6.Having someone slam a heavy car door on your hand	**1**	**2**	**3**	**4**	**5**
7.Gulping a hot drink before it has cooled	**1**	**2**	**3**	**4**	**5**
8.Receiving an injection in your hip/buttocks	**1**	**2**	**3**	**4**	**5**
9.Falling down a flight of concrete stairs	**1**	**2**	**3**	**4**	**5**

Appendix G:Presence Questionnaire

Characterize your experience in the environment, by marking an "X" in the appropriate box of the 7-point scale, in accordance with the question content and descriptive labels. Please consider the entire scale when making your responses, as the intermediate levels may apply. Answer the questions independently in the order that they appear. Do not skip questions or return to a previous question to change your answer.

WITH REGARD TO THE EXPERIENCED ENVIRONMENT

1. How much were you able to control events?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL SOMEWHAT COMPLETELY

2. How responsive was the environment to actions that you initiated (or performed)?

|_____|_____|_____|_____|_____|_____|_____|

NOT MODERATELY COMPLETELY

RESPONSIVE RESPONSIVE RESPONSIVE

3. How natural did your interactions with the environment seem?

|_____|_____|_____|_____|_____|_____|_____|

EXTREMELY BORDERLINE COMPLETELY

ARTIFICAL NATURAL

4. How much did the visual aspects of the environment involve you?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL SOMEWHAT COMPLETELY

5. How natural was the mechanism which controlled movement through the environment?

|_____|_____|_____|_____|_____|_____|_____|

EXTREMELY BORDERLINE COMPLETELY

ARTIFICIAL NATURAL

6. How compelling was your sense of objects moving through space?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL MODERATELY VERY

COMPELLING COMPELLING

7. How much did your experiences in the virtual environment seem consistent with your real world experiences?

|_____|_____|_____|_____|_____|_____|_____|

NOT CONSISTENT | MODERATELY CONSISTENT | VERY CONSISTENT

8. Were you able to anticipate what would happen next in response to the actions that you performed?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL | SOMEWHAT | COMPLETELY

9. How completely were you able to actively survey or search the environment using vision? |_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL | SOMEWHAT | COMPLETELY

10. How compelling was your sense of moving around inside the virtual environment?
|_____|_____|_____|_____|_____|_____|_____|

NOT COMPELLING | MODERATELY COMPELLING | VERY COMPELLING

11. How closely were you able to examine objects?
|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL | PRETTY CLOSELY | VERY CLOSELY

12. How well could you examine objects from multiple viewpoints?
|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL | SOMEWHAT | EXTENSIVELY

13. How involved were you in the virtual environment experience?
|_____|_____|_____|_____|_____|_____|_____|

NOT INVOLVED | MILDLY INVOLVED | COMPLETELY ENGROSSED

14. How much delay did you experience between your actions and expected outcomes?

|_____|_____|_____|_____|_____|_____|_____|

NO DELAYS MODERATE DELAYS LONG DELAYS

15. How quickly did you adjust to the virtual environment experience?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL SLOWLY LESS THAN ONE MINUTE

16. How proficient in moving and interacting with the virtual environment did you feel at the end of the experience?

|_____|_____|_____|_____|_____|_____|_____|

NOT PROFICIENT REASONABLY PROFICIENT VERY PROFICIENT

17. How much did the visual display quality interfere or distract you from performing assigned tasks or required activities?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL INTERFERED SOMEWHAT PREVENTED TASK PERFORMANCE

18. How much did the control devices interfere with the performance of assigned tasks or with other activities?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL INTERFERED SOMEWHAT INTERFERED GREATLY

19. How well could you concentrate on the assigned tasks or required activities rather than on the mechanisms used to perform those tasks or activities?

|_____|_____|_____|_____|_____|_____|_____|

NOT AT ALL SOMEWHAT COMPLETELY

Appendix H: Simulator Sickness Questionnaire

Instructions: Circle how much each symptom is affecting you right now.

1. General Discomfort	None	Slight	Moderate	Severe
2. Fatigue	None	Slight	Moderate	Severe
3. Headache	None	Slight	Moderate	Severe
4. Eye Strain	None	Slight	Moderate	Severe
5. Difficulty Focusing	None	Slight	Moderate	Severe
6. Salivation Increasing	None	Slight	Moderate	Severe
7. Sweating	None	Slight	Moderate	Severe
8. Nausea	None	Slight	Moderate	Severe
9. Difficulty Concentrating	None	Slight	Moderate	Severe
10. Fullness of the Head	None	Slight	Moderate	Severe
11. Blurred Vision	None	Slight	Moderate	Severe
12. Dizziness With Eyes Open	None	Slight	Moderate	Severe
13. Dizziness With Eyes Closed	None	Slight	Moderate	Severe
14. Vertigo	None	Slight	Moderate	Severe
15. Stomach Awareness	None	Slight	Moderate	Severe
16. Burping	None	Slight	Moderate	Severe

*Vertigo is experienced as a loss of orientation with respect to vertical upright

**Stomach awareness is usually used to indicate a feeling of discomfort which is just short of nausea

Curriculum Vitae

Name: Michael Lukacs

Post-secondary Education and Degrees:

Western University
London, Ontario, Canada
2015-2017 MPT

Western University
London, Ontario, Canada
2011-2015 B.Sc. Kinesiology (Hons. Spec)

Honours and Awards:

Transdisciplinary Bone and Joint Training Award – CMHR
August 2020
- Value ($5000)

CMHR Trainee Award
August 2020
- Value ($250)

Ontario Graduate Scholarship
May 2020 – April 2021
- Value ($15000)

Transdisciplinary Bone and Joint Training Award – CMHR
August 2019
- Value ($9750)

CMHR Trainee Award
June 2019
- Value ($500)

CMHR Trainee Award
June 2018
- Value ($400)

HRS Grad Conference – 1st Year PhD Category- 1st Place
February 2018
- Value ($100)

Western Graduate Research Scholarship
September 2017- Present
- Variable Value (approx. $12000/year)

Graduated Undergraduate Degree with Distinction
June 2015

Dean's Honours List
June 2012-2015

UWO In-Course Scholarship
November 2013
- Value ($700)

Western Scholarship of Excellence
September 2011
- Value ($2000)

Governor General's Bronze Medal
June 2011

Related Work Experience:

Registered Physiotherapist, Ontario Workers Network
November 2020 – Present
London Health Sciences Centre – Victoria Hospital
- Worked in conjunction with Sports Medicine Physicians as part of the Occupational Health Assessment Program to help facilitate return to work
- Performed Specialty Assessments in tandem with Neurosurgeons as part of the Back and Neck Specialty clinic with a focus on patients with chronic presentations and possible surgical candidates

Other Related Experience:

4th Year Independent Study Supervisor September 2019 – May 2020
Western University, London ON
- Supervised 4th year Health Sciences student for an independent study regarding the test-retest reliability of Conditioned Pain Modulation
- Student responsibilities included: participant recruitment, data collection, data analysis and production of final paper

MPT Student Research Project Supervisor September 2018-July 2019
- Supervised 2nd year MPT students at Western University for a study regarding the test-retest reliability of Conditioned Pain Modulation
- Responsible for providing direction to students, directing roles and responsibilities towards the production of a final paper and research poster

MPT Student Research Project Supervisor September 2018-July 2019
- Supervised 2nd year MPT students at Western University for a study regarding the effects of neck neuromuscular training on 40-yard running times
- Responsible for providing direction to students, directing roles and responsibilities towards the production of a final paper and research poster

Volunteer Assistant Strength and Conditioning Coach September 2011- August 2017
Michael Kirkley Training Center, London ON
- Attained a wide spectrum of knowledge relating to the training of the human body with athletes of various backgrounds
- Developed a deep passion for strength and conditioning as it relates to the head/neck and its relation to concussion prevention

Professional and Administrative Experience:

HRS Graduate Research Judge February 2021

Western University, London ON

- Performed evaluation for both PhD oral and poster presentations for students from the Faculties of Health & Rehabilitation Sciences, Health Information Science, Physical Therapy, Occupational Therapy, Communication Sciences, Kinesiology, and Nursing

PT 9630: Research Judge July 2020

Western University, London ON

- Reviewed and critically appraised poster presentations for students enrolled in the Master of Clinical Science programs for manual therapy

PT 9590: Research Judge July 2019

Western University, London ON

- Helped appraise and critique 2nd year MPT research project poster presentations

Contributor to Entry to Practice Essentials (EPE) March 2019 - May 2019

- Created database of multiple-choice questions and clinical vignettes in order to help prepare users for the Physiotherapy Competency Exam (PCE)

Ontario Physiotherapy Association Member September 2017-August 2018

London, ON

- Treasurer – accountable for allocation of funds, resource management, and event planning

Contributor to "The Humerus" October 2015-2016

Western University, London ON

- Frequent collaborator in student-led newsletter designed to highlight the Physical Therapy community at Western University

Co-Founder of Integrating Research Into Students (IRIS) September 2015-Present

- Launched student-led research initiative in 2015
- Hosted seminars consisting of speakers from leaders in the research areas of neurological and orthopedic populations
- Now in third year since launch in the MPT program

SPT Student Representative September 2015-August 2017

- Sat in on and contributed to meetings dedicated to the running of the MPT program at Western University
- Spoke on behalf of the student body and advocated for their place in the MPT program

Publications:

Published Papers

- Docter S, **Lukacs MJ**, Fathalla Z, Khan MC, Jennings M, Liu SH, Dong S, Getgood A, Bryant DM. Inconsistencies in Methodological Framework Throughout Published Studies in Top Orthopaedic Journals: A Systematic Review. JBJS. (June 2021)[Percent Contribution 20%- Major Contributing Author
- Docter S, Fathalla Z, **Lukacs MJ**, Khan MC, Jennings M, Liu SH, Dong S, Getgood A, Bryant DM. Interpreting Patient-Reported Outcome Measures in

Orthopaedic Surgery: A Systematic Review. JBJS. 2021 Jan 20;103(2):185-90. [Percent Contribution 20%- Major Contributing Author]

- Churchill L, **Lukacs MJ**, Pinto R, Macdonald SJ, Giffin JR, Laliberte Rudman D, Bryant D. A qualitative dominant mixed methods exploration of novel educational material for patients considering total knee arthroplasty. Disability and Rehabilitation. 2020 Nov 18:1-8 [Percent Contribution 30%- Major Contributing Author]
- Schulz JM, Birmingham TB, Atkinson HF, Woehrle E, Primeau CA, **Lukacs MJ**, Al-Khazraji BK, Khan MC, Zomar BO, Petrella RJ, Beier F. Are we missing the target? Are we aiming too low? What are the aerobic exercise prescriptions and their effects on markers of cardiovascular health and systemic inflammation in patients with knee osteoarthritis? A systematic review and meta-analysis. British journal of sports medicine. 2020 Jul 1;54(13):771-5. [Percent Contribution 15% – Major contributing author]
- **Lukacs M**, Salim S. Exploring immersive technologies: the potential for innovation in whiplash research. Health Science Inquiry. 2018 Jun 1;9(1):69-70. [Percent Contribution 70% - Main Contributing Author]
- Salim S, **Lukacs M**. A call for interdisciplinary collaboration between video game designers and health care professionals to fight obesity. Health Science Inquiry. 2018 Jun 1;9(1):43-44. [Percent Contribution 30% - Major Contributing Author]
- Lee JY, Guy SD, **Lukacs MJ**, Letwin ZA, Fakhereddin MF, Al-Nasri IJ, Salim S. Management of fibromyalgia syndrome. University of Western Ontario Medical Journal. 2018 Apr 24;87(1):34-7. [Percent Contribution 30% – Major contributing author]

Lectures/Presentations:

Lecturer, Clinics I (2 hours)
March 2020
Western University, London ON

- Educated first year Master of Physical Therapy students on the assessment and treatment of generalized mechanical neck pain and cervical arthrosis

Lecturer, Neuroscience for Physical Therapists (2 hours)
October 2019
Western University, London ON

- Educated 1st year MPT students regarding principles surrounding motor units and motor control considerations
- Aided in construction of midterm examination material

Lecturer, Clinics II (2 hours)
October 2019
Western University, London ON

- Taught 2nd year MPT students management of Whiplash-Associated Disorders from a biopsychosocial perspective and consideration of relevant pain science
- Aided in construction of midterm examination material

Lecturer, Foundations of Physical Therapy (2 hours) September-December 2019
Western University, London ON

- Educated 1st year MPT students regarding the use of resistance training in physical rehabilitation
- Provided content for midterm examinations practical lab scenarios

Guest Lecturer: Professional Consolidation (1 hour) June 2019
Western University, London ON

- Detailed studying strategies for attempting the clinical component of the Physiotherapy Competency Exam
- Provided insight into the licensing process of becoming a physiotherapist

Presenter, Bone and Joint Institute Biennial Research Retreat (10 minutes) May 2019
Western University, London ON

- Outline current progress of a virtual reality-based road collision simulator and highlighted next steps for lines of inquiry

Lecturer, Clinics I (2 hours) April 2019
Western University, London ON

- Educated first year Master of Physical Therapy students on the symptomology, diagnosis, and treatment of Whiplash-Associated Disorders integrating the most up-to-date research

Lecturer, Clinics I (1 hour) March 2019
Western University, London ON

- Instructed first year students on the differential diagnosis for medial, lateral, and posterior knee pain with an emphasis on evidence-based practice

Lecturer, Neuroscience for Physical Therapists (2 hours) October 2018
Western University, London ON

- Instructed first year students on clinical implications for when ascending information from motor and sensory systems goes does not function normally
- Aided in construction of midterm examination material

Guest Lecturer: Professional Consolidation (1 hour) June 2018
Western University, London ON

- Lectured 2nd year physiotherapy students' expectations for first year of clinical practice following graduation
- Provided insight into the licensing process of becoming a physiotherapist