Individual Variability and Sex Differences in Conditioned Pain Modulation and the Impact of Resilience, and Conditioning Stimulus Pain Unpleasantness and Salience

by

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Institute of Medical Science
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Abstract

This thesis determined how individual variability in conditioned pain modulation (CPM) relates to sex and resilience (personal attributes), and pain unpleasantness and salience (attributes of conditioning stimuli (CS)). Healthy participants (51 females, 55 males) underwent CPM testing with painful heat test stimuli (TS) and CS. The CS reduced TS pain ratings in half of participants (CPM subgroup) but had no effect or increased TS pain in the others (no-CPM subgroup). A whole group regression model explained CPM after accounting for all variables. In the CPM subgroup model, CPM correlated with CS pain unpleasantness. Correlation analyses showed that in the 1) CPM subgroup: CPM correlated with CS pain unpleasantness in males, 2) no-CPM subgroup: CPM and resilience were negatively correlated in males; CPM and CS pain unpleasantness were correlated in females, 3) whole group: CPM correlated with CS salience and pain unpleasantness. Therefore, personal attributes and CS attributes contribute to CPM.

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Statement of Contributions

I designed this research project with Dr. Karen D. Davis, who assisted and mentored me at all steps. Together we decided on my research topic, and she guided me through formulating my research questions. I analyzed psychophysical data that were collected by Natalie R. Osborne, Joshua C. Cheng, Junseok A. Kim, Rachael L. Bosma, Kasey S. Hemington, and Anton Rogachov. Throughout the project, further insights for data analyses and interpretations were provided by Lee B. Kisler, Camille Fauchon, and Geoff Pope. Program committee members, Lucia Gagliese and Massieh Moayedi, provided on-going guidance throughout the project. I wrote the first draft of the associated paper. All data collectors as well as Karen D. Davis assisted with editing and revisions of the paper. This thesis was edited by Karen D. Davis, with advice from Lucia Gagliese and Massieh Moayedi.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
CBT	Cognitive Behavioural Therapy
CPM	Conditioned Pain Modulation
CPT	Cold Pressor Test
CS	Conditioning Stimulus
CSQ	Coping Strategies Questionnaire
DMN	Default Mode Network
DNIC	Diffuse Noxious Inhibitory Controls
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
FPS-R	Faces Pain Scale-Revised
GABA	Gamma Aminobutyric Acid
HPLP	Health Promoting Lifestyle Profile
IASP	International Association for the Study of Pain
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISI	Interstimulus Interval

MAPS	Multidimensional Affect and Pain Survey
MPD	Myofascial Pain Dysfunction
MPQ	McGill Pain Questionnaire
NMDA	N-Methyl-D-Aspartic Acid
NRS	Numerical Rating Scale
OFC	Orbitofrontal Cortex
PAG	Periaqueductal Gray
PCS	Pain Catastrophizing Scale
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PPT	Pressure Pain Threshold
PTSD	Posttraumatic Stress Disorder
QST	Quantitative Sensory Testing
RVM	Rostral Ventromedial Medulla
SD	Standard Deviation
SRD	Subnucleus Reticularis Dorsalis
TMD	Temporomandibular Disorder
TPJ	Temporoparietal Junction
TS	Test Stimulus
TS1	First Test Stimulus

TS2	Second Test Stimulus
TS3	Third Test Stimulus
VAS	Visual Analogue Scale
VNS	Verbal Numerical Scale
VRS	Verbal Rating Scale
WDR	Wide Dynamic Range

Chapter 1

Introduction

This thesis includes material from the following paper in PAIN, comprising parts of the methods, results, and discussion sections of that paper:

Firouzian S, Osborne NR, Cheng JC, Kim JA, Bosma RL, Hemington KS, Rogachov A, and Davis KD. (2020). Individual variability and sex differences in conditioned pain modulation and the impact of resilience, and conditioning stimulus pain unpleasantness and salience. *PAIN* – 2020 Mar 5. doi: 10.1097/j.pain.0000000000001863. [online ahead of print]

Pain is an enormous personal and societal hardship, with 1 in 5 Canadians suffering from chronic pain conditions that are often longstanding and severe (Schopflocher et al., 2011). Pain is also a subjective experience that varies from individual to individual. A one-size-fits-all approach to pain management may be failing in part due to this individual variability in the pain experience, thus pointing to the need for more personalized pain treatments (Davis, 2019). Pain research often involves group comparisons. Therefore, in this thesis, pain was studied on an individual level as well as at the whole group level.

Studying acute experimental pain in healthy individuals can provide insight into the individual variability of pain so as to better characterize these individuals and can also shed light on factors that could potentially serve as risk factors for developing future pain. In those with chronic pain, an understanding of acute experimental pain sensitivity can be useful to determine who would benefit most from certain pain treatments. Of note, however, studying acute experimental pain in healthy individuals cannot necessarily be generalized to chronic pain populations.

Pain is a multidimensional experience with sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions that together impact motor systems for pain behaviour to prevent future injury (Melzack & Casey, 1968). There has been a historical emphasis on the sensory dimension of pain; however, emphasis on only one dimension addresses only part of the pain experience.

There are both personal attributes and attributes of noxious stimuli that can play a role in the pain experience. Personal attributes can be positive or negative, such as resilience and depression,

respectively. Although the literature largely focuses on negative attributes, positive ones may be equally important.

The pain experience can be thought of as arising from the interplay between the pronociceptive and antinociceptive systems (Yarnitsky et al., 2014). This thesis focused on the phenomenon of conditioned pain modulation (CPM). CPM can manifest variability across individuals, ranging from pain inhibition to pain facilitation (Kennedy et al., 2016; Tansley et al., 2019). This variability can have predictive value, such as for predicting the risk in developing future pain (Granovsky & Yarnitsky, 2013), and thus studying this variability can be useful. Therefore, this thesis aimed to characterize this variability and examine the factors that contribute to CPM. These factors included personal attributes (sex and resilience) and CS attributes (pain unpleasantness and salience).

Chapter 2
Literature Review

2.1 Pain: Definition and Experimental Testing

According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (https://www.iasp-pain.org). Recently, IASP has proposed a new definition of pain, which was open to the public for commenting. This new proposal defines pain as "an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury" (https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=9218). Both definitions frame pain as an "experience", which emphasizes that pain is subjective, and as such, there may not always be an identifiable pathophysiological source.

Pain includes both sensory and affective dimensions, which will be the main focus of this thesis (Melzack & Casey, 1968). These dimensions reflect pain intensity and unpleasantness, respectively (see section 2.4), and can be assessed using quantitative sensory testing (QST). QST can vary from lab to lab, but in general consists of a battery of standardized tests, some of which are part of the protocol established by the German Research Network on Neuropathic Pain (Rolke et al., 2006). These tests are designed to evaluate many somatosensory modalities, including experimental pain measurements that can be used to assess and quantify pain sensitivity to different stimulus modalities such as thermal, mechanical, electrical, ischemic, and chemical stimulations (Yarnitsky & Granot, 2006). QST has been used to assess pain in healthy individuals and to profile sensory abnormalities in people with chronic pain. Understanding these profiles can help identify the underlying mechanisms of chronic pain, that then may be used to determine whether particular subtypes/phenotypes will be responsive to a particular treatment. QST experiments can include assessments of sensory/pain threshold and suprathreshold responses, as well as measures of pain facilitation/augmentation and pain inhibition/modulation. Pain facilitation can be probed by temporal summation of pain (TSP) that assesses the increase in pain perception towards a regularly repeated nociceptive stimulus of constant magnitude (Arendt-Nielsen et al., 1994), which is thought to reflect central sensitization. The integrity of the endogenous pain modulatory system can be probed by CPM, which assesses the reduction in

pain perception towards a painful test stimulus (TS) applied to one part of the body due to a painful conditioning stimulus (CS) applied to another part of the body (see section 2.2) (Yarnitsky et al., 2015). Examples of these tests include thermal detection (cool/warm) and pain thresholds (cold/hot), mechanical detection and pain thresholds to von Frey filaments, vibration detection threshold, and pressure pain thresholds. QST has exhibited good inter-observer and test-retest reliability (Geber et al., 2011).

The German QST protocol allows data from one individual to be compared to group responses (from a large cohort) via z-transformed data (Maier et al., 2010; Rolke et al., 2006). The z-transformed data can be used to identify individual deviations from the normative or reference group. For instance, based on the z-scores of data from healthy individuals, those with chronic pain can be identified as having either loss or gain of function. The occurrence of loss or gain of function in different sensory modalities can vary within each disease between people. This variability can also be found in combinations of loss or gain of function in different sensory modalities. QST can provide insight into the function and mechanisms of nociception (Haanpaa et al., 2011; Pfau et al., 2012; Rolke et al., 2006), including the functioning of primary afferents such as the Aß-, Aδ-, and C-fibres in both healthy controls and those with chronic pain (Dougherty et al., 2007; LaMotte et al., 1983; Meyer & Campbell, 1981; Pfau et al., 2012). Underlying mechanisms can also be studied by combining QST with other methodological modalities, such as electrophysiology in animals and microneurography in humans. By combining these two methods in animal studies, for example, primary afferents can also be probed specifically for channels that they contain, such as transient receptor potential channel subtypes (Ran et al., 2016). QST can also reveal whether there may be different and/or altered underlying mechanisms between various sensory abnormalities, such as differences between primary and secondary hyperalgesia (Raja et al., 1984). It should be noted, however, that altered QST responses may not always indicate a change in only the sensitivity of these underlying mechanisms (e.g., primary afferent sensitivity), and could be a result of multiple contributing factors.

2.2 Conditioned Pain Modulation

Modulation of pain can be excitatory or inhibitory. As introduced in section 2.1, CPM is intended to probe the integrity of the endogenous pain modulation system (Yarnitsky, 2010). The

CPM phenomenon is known colloquially as “pain inhibits pain” or “counter-irritation”. Previously, CPM testing was thought to produce pain inhibition under normal conditions, but it is now recognized that CPM can evoke faciliatory as well as inhibitory effects in healthy individuals.

2.2.1 Neuroscience of Conditioned Pain Modulation and its Relation to Diffuse Noxious Inhibitory Controls

The phenomenon known as CPM in humans is thought to be analogous to the neurophysiological effect called diffuse noxious inhibitory controls (DNIC) that was discovered and characterized in animals (Le Bars et al., 1979a, 1979b; Pud et al., 2009). While these initial studies were conducted in rats (Le Bars et al., 1979a, 1979b), DNIC has also been demonstrated in other species, including cats (Morton et al., 1988; Morton et al., 1987) and monkeys (Brennan et al., 1989; Gerhart et al., 1981). A depiction of descending pain modulation mechanisms is shown in Figure 2-1.

In the pioneering work by Le Bars and colleagues, activity in rat convergent dorsal horn neurons (i.e., wide dynamic range (WDR) neurons)—which receive inputs from both low and high threshold afferents—was attenuated when simultaneous noxious stimuli were applied to body regions of the rat outside of these neurons’ receptive fields (Le Bars et al., 1979a, 1979b). WDR neurons respond to both innocuous and noxious stimuli (Calvino & Grilo, 2006). This DNIC phenomenon is thought to be mediated through a spinobulbospinal loop, whereby neurons in the spinal and medullary dorsal horns are activated by Aδ-fibre and C-fibre afferents responding to a noxious CS (Le Bars & Willer, 2002; Nir & Yarnitsky, 2015). Activation of these neurons results in neuronal signals being sent superiorly via the ventrolateral funiculi to the subnucleus reticularis dorsalis (SRD) (Le Bars & Willer, 2002; Nir & Yarnitsky, 2015), which is located in the caudal medulla between the trigeminal subnucleus caudalis and nucleus of the solitary tract (Le Bars & Willer, 2002; Villanueva et al., 1996). The SRD lies within the reticular formation. In rats and monkeys, SRD neurons are primarily or exclusively activated by noxious stimulation applied to any area of the body surface (Villanueva et al., 1996). From the SRD, inhibitory neural signals are sent inferiorly to WDR neurons in the dorsal horn—initially activated by a TS—via the dorsolateral funiculus ipsilateral to these WDR neurons (Villanueva et al., 1986). The DNIC effect has not only been observed in spinal dorsal horn neurons, but also in the medullary dorsal horn (i.e., trigeminal subnucleus caudalis) neurons that subserve orofacial

sensations (Dickenson et al., 1980; Villanueva et al., 1984). Both a TS and CS can activate the spinothalamic tract (an anterolateral system) for non-orofacial nociceptive neural signals, and the trigeminal lemniscus for orofacial nociceptive neural signals (Purves et al., 2001). These pathways can carry nociceptive/thermal information in the form of neural impulses resulting from the TS and CS applications. Thus, DNIC activated by the CS can inhibit neural activity conveyed by the spinothalamic tract or trigeminal lemniscus resulting from a TS applied to either the body or face, respectively (Le Bars et al., 1979a, 1979b; Purves et al., 2001). Specifically, the CS can inhibit the second order WDR neurons that are initially activated by primary afferents responding to the TS.

The SRD plays an important role in DNIC mechanisms. Lesions of the SRD in rats reduced the DNIC effect, suggesting that this brainstem region may be an important relay region—if not the sole region—underlying DNIC (Bouhassira et al., 1992; Villanueva et al., 1996). Furthermore, it was found that naloxone—an opioid antagonist—applied in the SRD can block DNIC, which suggests an opiate-dependent role of the SRD in DNIC (Patel & Dickenson, 2019). In rats with muscle inflammation, DNIC was induced by noxious heat to the tail (de Resende et al., 2011). In these animals, naloxone injected into the SRD but not the RVM prevented DNIC, which further supports the role of opioids in the SRD. There is also evidence that the SRD plays a role in pain facilitation, and not just inhibition (Lima & Almeida, 2002). The SRD projects to the thalamus in rats—specifically the ventromedial thalamus (Monconduit et al., 2002; Villanueva et al., 1996), and receives afferents from the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), hypothalamus, amygdala, orbital cortex, insula, and both the somatosensory and motor cortices (McMahon et al., 2013).

Another lesion study investigated three structures in the rat: PAG, cuneiformis nucleus, and parabrachial nucleus (Bouhassira et al., 1990); how the PAG plays a role in descending modulation through non-DNIC mechanisms is discussed below. However, lesions of these areas in rats had no effect on DNIC recorded in convergent neurons of the trigeminal subnucleus caudalis. It was therefore concluded that these mesencephalic structures may not have a direct role in the loop that underlies the proposed DNIC mechanism, supporting a role in non-DNIC mechanisms. However, rats that received electrical stimulation to the PAG did not exhibit responses to noxious stimulation, nor did they require chemical anesthetics to endure surgery (Reynolds, 1969), which suggests that the PAG could play a role in both DNIC and non-DNIC

mechanisms. Moreover, the rat infralimbic region has been shown to modulate DNIC activation (Patel & Dickenson, 2019).

The rat RVM, which is known to be involved in descending pain modulation, consists of three cell types. These cells are classified based on the activity evoked by a noxious stimulus that is typically applied to the rat tail to evoke a tail flick response: ON-cells fire before the withdrawal response evoked by a noxious heat stimulus; OFF-cells stop firing before the withdrawal from the noxious stimulus; and NEUTRAL-cells do not show consistent firing with respect to a nociceptive withdrawal response (Fields & Heinricher, 1985). While ON-cells fire maximally when noxious stimulation is strong enough to induce a withdrawal reflex, OFF-cells can be activated by morphine application that inhibits tail flick (Cheng et al., 1986; Fields & Heinricher, 1985; Fields et al., 1983). Thus, OFF-cells are involved in antinociception associated with opiate-mediated activity within the RVM (Heinricher et al., 1994). For instance, μ-opioid receptor agonists administered into the RVM can activate RVM OFF-cells and inhibit ON-cells (Heinricher et al., 1994). On the other hand, ON-cells are suppressed by morphine administration (Cheng et al., 1986). The tail flick threshold is higher with OFF-cell activity and ON-cell inactivity, and lower with OFF-cell inactivity and ON-cell activity (Heinricher et al., 1989). Therefore, nociceptive behaviour associated with an increase in ON-cell activity could also be a result of reduced OFF-cell activity, that is, removal of descending inhibition (Fields et al., 1991). While the RVM projects to different brainstem and spinal cord regions, its major descending projections are to the spinal and medullary dorsal horns. Aside from its role in overall descending pain modulation, there is also evidence that the RVM plays a role specifically in DNIC-mediated pain modulation (Hernandez et al., 1994). For instance, the activity of RVM ON-cells and tail flick responses to noxious heat applied to the tail were reduced during simultaneous noxious stimulation of other body regions in the rat.

Neurotransmitters play a role in descending pain modulation. Excitatory monoamines, including noradrenaline (NA) and 5-hydroxytryptamine (5-HT), known as serotonin, can modulate nociception and pain through inhibitory and facilitatory mechanisms (Bannister & Dickenson, 2016, 2017). NA neurons in the locus coeruleus of the dorsolateral pontine tegmentum project to the spinal dorsal horn. 5-HT neurons in the RVM also project to the spinal dorsal horn (Bannister & Dickenson, 2016; Moore, 1981). 5-HT and NA are both known to be involved in descending pain modulation, playing a pro-nociceptive or antinociceptive role based on the receptors upon

which they act (Bannister & Dickenson, 2017; Ossipov et al., 2014). For instance in the rat brain, a_2-adrenergic receptors are thought to mediate antinociception whereas the a_1-adrenergic receptors are thought to mediate nociception (Bannister & Dickenson, 2016, 2017; Holden et al., 1999). Activation of RVM ON-cells can be mediated by the a_1 receptors while inhibition of the ON-cells can be mediated by the a_2 receptors (Fields et al., 1991). Furthermore, pain inhibition is thought to be mediated by certain subtypes of the 5-HT_1 and 5-HT_2 receptors (Millan, 2002). Many 5-HT-containing neurons in the RVM are OFF-cells, and thus the release of 5-HT can excite other OFF-cells and inhibit ON-cells (Fields et al., 1991). While there is also the PAG as a source of 5-HT release into the RVM, this release of 5-HT is not necessarily required for antinociception. Neurotensin containing neurons projecting from the PAG to the RVM can also play a role in antinociception. The antinociceptive effects of NA and 5-HT can also involve one class of neurotransmitters mediating the pain-modulating effects of the other class.

In addition to excitatory neurotransmitters in the RVM, there are also inhibitory neurotransmitters, including gamma aminobutyric acid (GABA) neurons (Millhorn et al., 1988). Blocking $GABA_A$ receptors in the RVM can have antinociceptive effects (Drower & Hammond, 1988; Heinricher & Kaplan, 1991). GABAergic neurons in the RVM project to RVM OFF-cells (Fields et al., 1991). The activity of both GABA and opioids collectively suggest that opioid neurons projecting from the PAG can inhibit GABAergic neurons—with ON-cell characteristics—that then disinhibit OFF-cells (Fields et al., 1991; McMahon et al., 2013). In the ventrolateral PAG, glutamatergic neuronal activation and GABAergic neuronal inhibition together can play a role in antinociception and the reverse can play a role in nociception (Samineni et al., 2017).

Hormones are also involved in descending pain modulatory pathways. For instance, fMRI revealed that male rats with intact testosterone functionality had stronger PAG connectivity with the prelimbic cortex, anterior cingulate cortex (ACC), and insula compared to females and to males lacking testosterone (Da Silva et al., 2018). The importance of testosterone in descending pain modulatory pathways has also been shown with fMRI in human females taking oral contraceptives (Vincent et al., 2013). In oral contraceptive users, positive correlations were found between greater RVM activity and greater testosterone levels, but in non-users, correlations were found between amygdala/PAG regions and testosterone levels. In a subgroup

of these participants who had low testosterone levels due to the pill consumption, RVM activity was reduced compared to non-users.

Aside from the roles of these neurotransmitters and hormones in descending pain modulation, neurotransmitters and hormones also play a role specifically in DNIC-mediated and CPM-mediated pain modulation. Naloxone inhibits DNIC in rats (Itomi et al., 2016; Kraus et al., 1981; Le Bars et al., 1981b), and naloxone and naltrexone inhibit CPM in humans (King et al., 2013; Willer et al., 1990). In line with this, in healthy human participants, opioids (delivered through a patch) can potentiate CPM compared to placebo administration (Arendt-Nielsen et al., 2012), but GABA agonists do not have this potentiating effect (Kunz et al., 2006). However, this idea is likely too simplistic. For example, there are studies showing that morphine—an opioid agonist—can inhibit DNIC (Duggan et al., 1980; Le Bars et al., 1981a; Soja & Sinclair, 1983; Villanueva & Le Bars, 1986), and there is evidence that GABA agonists but not naloxone injected in the RVM can prevent DNIC (Gear et al., 1999a). Similarly, human males with chronic pain who are given opioid analgesics exhibited reduced CPM compared to those given non-opioid analgesics (Ram et al., 2008). It should be noted that opioidergic signalling in pain-modulating brain regions like the PAG and the RVM may not be specific to descending pain modulation, and could also be involved in placebo analgesia, for example (Eippert et al., 2009). This can be a result of convergence on the same neural regions. Similar to opioids, NA and 5-HT are involved in DNIC (Bannister & Dickenson, 2017). For instance, DNIC in rats were restored after spinal nerve ligation by blocking 5-HT_3-mediated descending facilitation and increasing NA modulation (Bannister et al., 2015), or by blocking the reuptake of 5-HT to the point that 5-HT binds to inhibitory 5-HT receptors like 5-HT_7 (Bannister & Dickenson, 2017; Bannister et al., 2017). The action of neurotransmitters in reward-related brain regions can also impact DNIC (Gear et al., 1999a). Both dopamine antagonists and naloxone injected into the nucleus accumbens, for instance, both can block DNIC. In healthy humans, administration of a dopamine agonist—apomorphine—increased CPM more than placebo administration (Treister et al., 2013), which supports the role of dopamine in CPM-like mechanisms. Hormones are also a factor in DNIC and can contribute to sex differences. Testosterone, for example, significantly increases DNIC in rats (Da Silva et al., 2018). A lack of testosterone could result in the recruitment of reward and emotion brain circuitries during DNIC.

The neuroscience of CPM (the human phenomenon) has been studied in parallel to DNIC-mediated descending pain modulation. Lesion studies provide evidence for the role of the brainstem in CPM (De Broucker et al., 1990; Roby-Brami et al., 1987). For example, CPM was absent in people with Wallenberg syndrome—which affects the brainstem—when the CS was applied to the affected side but not the unaffected side (De Broucker et al., 1990), and in people with spinal cord transections that also impact connectivity with the brainstem (Roby-Brami et al., 1987).

Overall, there is a lack of converging evidence for specific CPM-related brain activity, because of divergent findings across studies. Brain imaging with fMRI—while offering limited temporal resolution—in healthy individuals and those with chronic pain has provided insight into the neuroscience of CPM. In the orofacial system of healthy adults who exhibited reduced pain during a CPM paradigm, brainstem fMRI responses were reduced in the trigeminal subnucleus caudalis, SRD, and dorsolateral pons in the parabrachial nucleus (Youssef et al., 2016b). In terms of cortical fMRI responses, increased pain during CPM can be associated with greater signal intensity increases during the TS applied with the CS compared to without the CS (Youssef et al., 2016a). These increases were found in the mid-cingulate cortex and dorsolateral prefrontal cortex (PFC), and there was increased functional connectivity between these regions and the SRD. Given the role of the SRD in DNIC reviewed above, this suggests that CPM and DNIC are not necessarily the same. In another fMRI study of healthy individuals, CS-induced modulation resulted in activation of the lateral orbitofrontal cortex (OFC) throughout CS application, which correlated with pain inhibition (Piche et al., 2009). Another fMRI study reported a positive correlation between pain reduction during CS application and increase in functional coupling between the subgenual ACC and brain regions involved in descending pain modulation: PAG, amygdala, hypothalamus, and medulla (Sprenger et al., 2011). In healthy females who underwent CPM during fMRI, TS-evoked activity within the posterior insula and secondary somatosensory cortex changed with CS application, and this activity correlated with an individual's CPM (Bogdanov et al., 2015). Thus, some participants exhibited a decrease in TS pain intensity (CPM), which was associated with reduced TS-evoked activity in the posterior insula and secondary somatosensory cortex during the CS; others exhibited an increase in TS pain intensity (lack of CPM), which was associated with increased TS-evoked activity in the same two regions during the CS. In those participants who exhibited CPM, brain activity during the CS application

increased in the subgenual ACC, rostral ACC, and lateral OFC; but activity was reduced during the CS in these regions for participants with a lack of CPM.

Studies using electroencephalography (EEG) also provide insight into CPM brain mechanisms. In healthy males undergoing a CPM paradigm, EEG nociceptive-evoked potentials (N2-P2 waveforms) had potential sources in the OFC, amygdala, and parahippocampal gyrus with increase in activation at 250-300ms and 400-450ms after evoking CPM (Moont et al., 2011). In an EEG study of healthy individuals, both somatosensory-evoked potentials and intensity ratings of noxious and innocuous electrical stimulation of the sural nerve were attenuated by a CPT serving as the CS (Rustamov et al., 2016). This suggests that somatosensory-evoked potentials due to Aß-fibre activity (reflecting innocuous electrical stimulation) can be inhibited via CPM. PAG abnormalities may be related to dysfunctional CPM (Harper et al., 2018). For instance, people with fibromyalgia who lack CPM exhibited reduced gray matter volume in the PAG (Harper et al., 2018). Connections between the PAG and both the insula and ACC were associated with greater CPM in both healthy individuals and those with chronic pain. In healthy individuals, however, PAG connectivity with the locus coeruleus was associated with greater CPM. While in healthy individuals PAG connectivity with the pons/RVM was associated with pain inhibition, this connectivity was associated with pain facilitation in those with fibromyalgia.

In contrast to DNIC, CPM may be independent of descending modulation, and instead rely on cerebral mechanisms (Nir & Yarnitsky, 2015; Piche et al., 2014). For instance, in healthy participants who underwent a CPM paradigm involving modulation of the RIII reflex (a nociceptive withdrawal reflex induced by electrical stimulation of the sural nerve) with hand immersion in cold water, both μ-opioid receptor availability and EEG were monitored (Piche et al., 2014). While there was no evidence of modulation of the RIII reflex and its associated pain ratings, greater μ-opioid receptor availability in the amygdala was associated with reduced somatosensory-evoked potentials that reflected reduced activity in the ACC.

To summarize, descending pain modulation can be faciliatory or inhibitory. Modulation can arise due to 1) the segmental and hetero-segmental stimulus application conducted in DNIC and CPM paradigms; or 2) the PAG-RVM system that does not necessarily require stimulation at two distinct body regions. The phenomenon of DNIC is by definition an inhibitory effect in animals evoked by a noxious stimulus applied to a body region outside the receptive fields of convergent

(WDR) neurons (Le Bars et al., 1979a, 1979b). The inciting stimulus that causes DNIC can be considered to be a noxious CS that initiates neural signals activating dorsal horn neurons, which then activate both higher brain centers and the brainstem (Le Bars & Willer, 2009). Brainstem mechanisms activate DNICs, which inhibit the noxious test stimulus (TS) response of the convergent neurons applied within the same (homosegmental) or different (hetero-segmental) spinal segment as the CS. This DNIC mechanism is different from other descending modulatory mechanisms, such as the PAG-RVM system, which typically does not involve diffuse noxious stimulation for antinociception to occur. In the PAG-RVM system, the PAG controls nociceptive transmission at the spinal dorsal horn via the RVM (Fields & Heinricher, 1985). Together, the PAG and RVM form a system that can play a pronociceptive or antinociceptive role as determined by the complex interaction between different neurons and neurotransmitters discussed in this section (McMahon et al., 2013). Cerebral areas like the amygdala and hypothalamus can activate the PAG-RVM system to produce pronociceptive responses. Therefore, while the PAG-RVM system can be involved in descending modulation of pain, the SRD can be involved in the segmental and hetero-segmental mechanisms of DNIC (McMahon et al., 2013; Wilder-Smith et al., 2004). Nevertheless, the SRD can interact with the descending pain modulatory system that functions independently of these segmental mechanisms (Bannister & Dickenson, 2017). Figure 2-1 depicts descending pain modulation mechanisms, including specifically the mechanism of DNIC.

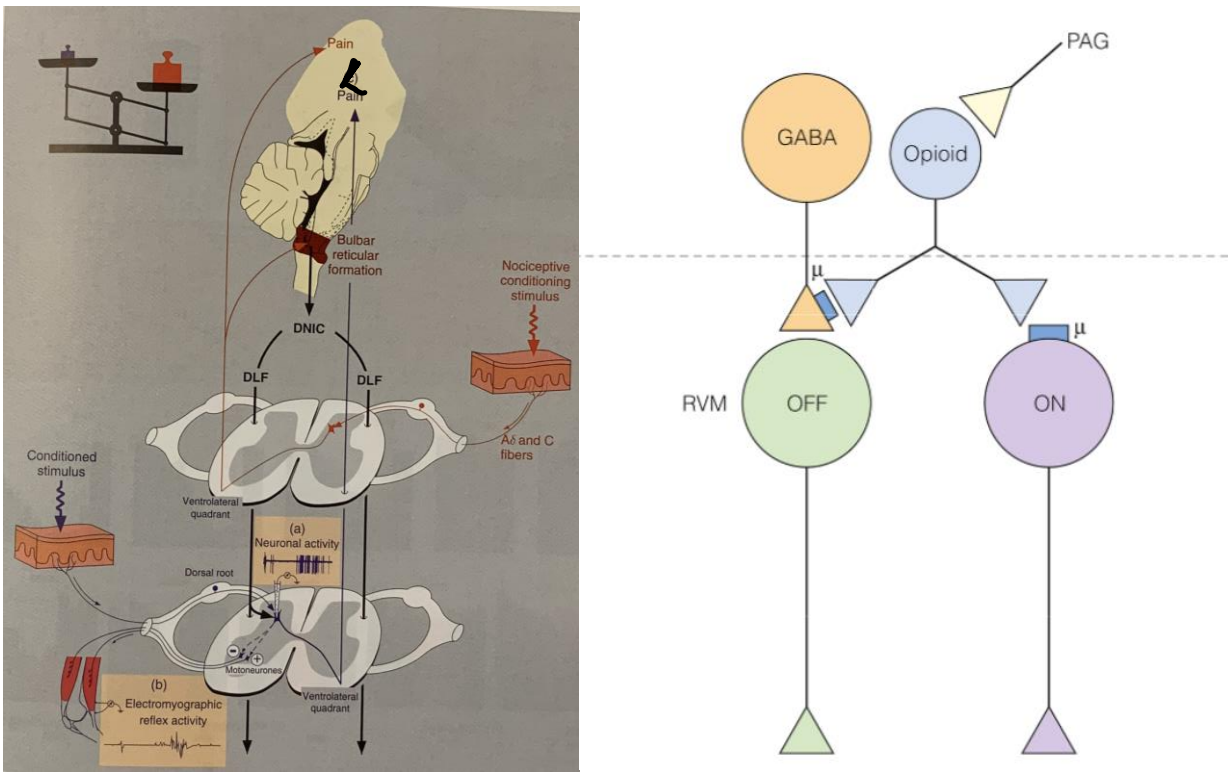

Figure 2-1. A depiction of descending pain modulation mechanisms, including the specific example of DNIC The left panel depicts the mechanism of DNIC based on data in rat studies. The conditioned (not conditioning) stimulus in this panel refers to the TS, which activates convergent (WDR) neurons in the spinal dorsal horn. The CS activates spinal dorsal horn neurons by means of Aδ- and C-fibre afferents, which can then activate supraspinal structures like the SRD. This results in inhibition of the WDR neurons via the dorsolateral funiculi, which are represented here by "DLF". The right panel depicts the mechanism of descending pain modulation via the PAG-RVM system. Opioid neurons in the PAG can inhibit both RVM ON-cells and GABAergic neurons that project to RVM OFF-cells, which is a projection that can disinhibit OFF-cells. Based upon the net activity of the RVM ON- and OFF-cells, nociception or antinociception may occur. It is the activity of OFF-cells that inhibits nociceptive neural signals at the spinal dorsal horn. Left panel: Le Bars et al. (2009); right panel: McMahon et al. (2013).

2.2.2 Methodology to Test Conditioned Pain Modulation

The literature on CPM is riddled with inconsistencies in terminology and methodology used to assess the phenomenon. Across labs that assess CPM in humans, different terminology has been used, including DNIC, DNIC-like effect, heterotopic noxious conditioning stimulation, and endogenous analgesia (Pud et al., 2009). In this thesis, I use the term "CPM" to refer to any studies in humans that report pain to test the effect of a CS applied to one body region on the pain evoked by a TS delivered to a different body region.

While there are recommendations on CPM methodology (see below), different CPM paradigms are used across labs, often because of practical issues like equipment availability, the type of participants (healthy or suffering from chronic pain), and in the case of chronic pain, the location of pain. The methodology used to evaluate CPM across studies can differ in terms of the body regions that are stimulated (e.g., hand/arm/leg/foot), whether the TS and CS are applied to the same or different spinal segments (i.e., homosegmental or heterosegmental), the timing of TS and CS stimulations (parallel or sequential), duration of stimulation, a fixed stimulus intensity for the TS and CS versus a variable stimulus intensity to fix the pain intensity evoked by the TS and CS, interstimulus interval (ISI), number of trials, and method of TS pain evaluation (i.e., pain thresholds or pain ratings to suprathreshold stimulation) (Pud et al., 2009; Yarnitsky, 2015). Finally, the quantification of CPM can be made based on the percent change or absolute difference in TS pain rating (or threshold) before versus after/during the CS.

A task force led by David Yarnitsky published recommendations on how to evaluate CPM and report the findings (Yarnitsky et al., 2015). The panel recommended: 1) the use of mechanical and thermal stimuli for the TS (which would require more than one CPM test session); 2) that the intensity of the TS be fixed at a level that evokes pain rated 40 out of 100 (Pain40), which can be determined either by ascending intensity until Pain40 is reported by the participant, or by a fixed temperature from a predetermined Pain40; 3) that CPM be repeated twice with at least a 10 minute ISI; 4) that the CS be at an intensity to evoke mild to moderate pain (pain intensity rating greater than 20/100); and 5) that for the calculation of CPM responses, the difference between the TS with and without the CS should be calculated such that negative values always reflect pain inhibition (decrease in TS pain), and positive values always reflect pain facilitation

(increase in TS pain). Ideally, these calculations should be presented both in absolute and percent changes.

The most potent and reliable CS used in a CPM paradigm is a noxious cold stimulus, typically in the form of a water bath applied to an extremity, termed the cold pressor test (CPT) (Damien et al., 2018; Kennedy et al., 2016; Pud et al., 2009). Although a water bath is commonly used as the CS (Yarnitsky, 2015), there are studies that used a contact thermode for both the CS and TS (Defrin et al., 2010; Geva & Defrin, 2018; Geva et al., 2014, 2017; Granovsky et al., 2016; Kashi et al., 2018; Levy et al., 2018). Use of such thermal devices has been adopted by some labs because of practical issues (e.g., convenience of bedside testing in chronic pain populations). Although the upper extremity may have been the most common site for CS application (Pud et al., 2009), there are now many studies that have applied the CS to the lower extremity (Arendt-Nielsen et al., 2008; Bogdanov et al., 2015; Graven-Nielsen et al., 1998; Graven-Nielsen et al., 2017; King et al., 2013; King et al., 2009; Kisler et al., 2018; Kisler et al., 2019; Lautenbacher & Rollman, 1997; McPhee & Graven-Nielsen, 2019; Nahman-Averbuch et al., 2013a; Piche et al., 2009; Pielsticker et al., 2005; Riley et al., 2010; Song et al., 2006; Sprenger et al., 2011; Torta et al., 2015; Vaegter et al., 2017; Youssef et al., 2016a, 2016b). Compared to the CS modalities, there is a greater variety of TS modalities, including thermal, mechanical, electrical, and chemical stimulations (Pud et al., 2009). As is the case with CPM paradigms with two thermodes, pressure has also been used for both the TS and CS, such as pressure to the thumbnail (Schoen et al., 2016) and cuff pressure (Graven-Nielsen et al., 2017; Petersen et al., 2016; Rathleff et al., 2016; Vaegter & Graven-Nielsen, 2016). Most studies use pressure pain threshold (PPT) (Damien et al., 2018; Kennedy et al., 2016) and contact heat pain for the TS (Damien et al., 2018). A CPM paradigm with a tonic TS may produce a larger CPM effect than a phasic TS (Lie et al., 2017). CPM can also be tested using viscerosomatic inhibition, whereby pain behaviour can be reduced by experimentally induced visceral pain, such as gastric distention produced by a balloon placed near the stomach (Bouhassira et al., 1994).

Due to the individual variability in pain sensitivity, it can be beneficial to use TS and CS that are perceptually matched for pain intensity across participants (Mackey et al., 2017). Pain ratings or thresholds measured during CPM are subjective; however, objective measures (although not the standard) have also been used to measure antinociception, including the flexion reflex termed RIII (Bouhassira et al., 1994; France & Suchowiecki, 1999; Piche et al., 2009; Rustamov et al.,

2016; Sandrini et al., 2006; Serrao et al., 2004; Willer et al., 1989) and somatosensory-evoked potentials with EEG (Fujii et al., 2006; Haefeli et al., 2014; Kakigi, 1994; Moont et al., 2011; Oono et al., 2008; Piche et al., 2014; Quante et al., 2008; Reinert et al., 2000; Rustamov et al., 2016; Torta et al., 2015). However, subjective and objective measures of antinociception may not differ (Pud et al., 2009). This is further supported by comparable test-retest reliabilities for subjective pain ratings and the RIII (Jurth et al., 2014).

Despite the variable methodology used across labs, CPM can have good inter-session reliability (Granovsky et al., 2016; Kennedy et al., 2016). In one study, test-retest reliability was determined using different stimulus modalities for the TS (electrical, heat, pressure delivered from either a handheld or computer cuff pressure algometry), and the CS (CPT or cuff pressure) (Imai et al., 2016). The CPM magnitude was more reliable when cuff pressure algometry TS and CS combination or handheld pressure algometry TS and CPT CS combination were used. Moreover, all combinations induced CPM except combinations with electrical/heat TS and cuff pressure algometry as the CS. Therefore, inter-session reliability may depend on the modality of the CS—the CPT being the superior modality—and intra-session reliability of CPM may be better than this inter-session reliability (Lewis et al., 2012a).

The duration of CPM effects after the end of a CS is clinically important to understand the duration of pain inhibition in relation to the integrity of the endogenous pain modulation system. However, the effects vary across studies based on how long the inhibitory effects last after the removal of the CS, from a short amount of time to as long as 60 minutes (Bouhassira et al., 1990; Bouhassira et al., 1994; De Broucker et al., 1990; Fujii et al., 2006; Pantaleo et al., 1988; Tuveson et al., 2006; Willer et al., 1989). An important consideration is the dynamic changes in CPM over time as the overall CPM effect can wane, and this waning may be different between those with chronic pain and healthy controls (Nahman-Averbuch et al., 2013a). For instance when CPM paradigms were repeated, CPM decreased in people with migraines but not in healthy individuals (Nahman-Averbuch et al., 2013a). Furthermore compared to healthy individuals, those with polyneuropathy demonstrate increase in CPM with time (Nahman-Averbuch et al., 2011).

Although some have proposed that CPM is driven by distraction, the mechanisms underlying CPM are thought to be different than pain inhibition that arises from distraction (Kakigi, 1994;

Lautenbacher et al., 2007; Moont et al., 2010). This is supported by the finding that TS pain was reduced more by simultaneous distraction and CPM (potential additive effect) than CPM alone, and also by the finding that some participants could exhibit CPM but not distraction when the two were assessed separately (Moont et al., 2010). Further evidence that CPM and distraction function through different mechanisms is that distraction does not further enhance pain inhibition that is induced by CPM alone (Staud et al., 2003). There are other nonpainful attributes of the CS that could interfere with the interpretation of CPM responses. One study specifically examined multiple potential types of pain inhibition strategies: mildly painful CS, nonpainful CS, distraction task, and nonpainful stress task (Quiton & Greenspan, 2007). Both the distracting and painful CS protocols reduced TS pain ratings, but interestingly, the effect of distraction on pain reduction was larger in males than females. Moreover, regression analysis revealed that perceived distraction and stress of the CS predicted CPM magnitude. In terms of the stress task, greater stress was associated with greater CPM in males while the opposite trend was true for females. This finding indicates that the nonpainful attributes of the CS can impact CPM differently across the sexes.

It is also important to separate CPM from a more general effect of stimulus habituation. Interestingly, healthy subjects but not people with migraine, can habituate to a CS but not to the TS, possibly because the CS had a longer duration than the TS (Nahman-Averbuch et al., 2013a). When healthy female subjects underwent CPM with fMRI, brain activations were found for early and later times of a sustained CS in the precuneus and posterior insula, respectively (Bogdanov et al., 2015). This suggests different brain responses to the early and later time points of CS applications, perhaps reflecting differences in pain perception throughout its stimulation, as a decrease in CS pain ratings was also observed. Moreover, early and sustained CS brain activity correlated differently with brain activity during the CPM paradigm. Early CS brain activity in regions like the PFC, ACC, OFC, insula, striatum, and lingual/fusiform gyrus correlated with activity in the posterior insula and secondary somatosensory cortex. Sustained CS brain activity in brain regions like the cerebellum, putamen, and insula correlated with activity in the posterior insula and secondary somatosensory cortex. In a study that aimed to determine whether CPM is confounded by habituation, painful electrical stimulations were applied to healthy individuals both at constant intensities and variable intensities (Eitner et al., 2018). Stimulation by constant intensity caused habituation of electrical pain (i.e., pain reduction). However, reduction in

electrical pain due to CPM was much greater than this habituation, suggesting that CPM can function from a different mechanism than habituation.

2.2.3 The Clinical Value of Conditioned Pain Modulation for Chronic Pain

The CPM effect can differ between healthy individuals and those with pain: the latter often exhibit reduced CPM (Granovsky & Yarnitsky, 2013; Lewis et al., 2012b; Yarnitsky, 2010, 2015). CPM can even vary amongst people with chronic pain (Vaegter & Graven-Nielsen, 2016). A meta-analysis reported a large effect size of reduced CPM across many chronic pain conditions, with the effect being greater in younger people and in females (Lewis et al., 2012b). Chronic pain conditions associated with reduced CPM include fibromyalgia (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997; Potvin & Marchand, 2016), irritable bowel syndrome (IBS) (Chang, 2005; King et al., 2009; Song et al., 2006), headache (Buchgreitz et al., 2008; Pielsticker et al., 2005; Sandrini et al., 2006), temporomandibular disorder (King et al., 2009; Maixner et al., 1995), osteoarthritis (Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012; Kosek & Ordeberg, 2000; Quante et al., 2008), whiplash (Daenen et al., 2013), low back pain (McPhee & Graven-Nielsen, 2019), and painful neuropathy-related conditions (Nahman-Averbuch et al., 2011; Yarnitsky et al., 2012). Based on studies in pain-free individuals about to undergo surgery (see below), lower CPM can be a risk factor for developing chronic pain.

In painful neuropathy, the CPM effect can depend on whether the TS and CS are applied to a region of the body where the participant is experiencing pain (Granovsky, 2013). It has been reported that lower CPM, reflecting pain facilitation, occurs when both the TS and CS are applied to unaffected body regions, or when ongoing chronic pain is used as the TS and the CS is applied to an unaffected body region. Greater CPM, reflecting pain inhibition, occurs when the TS is applied to an affected body region (e.g., allodynia present at that site) and the CS is applied to an unaffected body region, or vice versa. It is unclear whether the duration of pain experienced as a result of the chronic pain condition is associated with reduced CPM (Petersen et al., 2019). Various clinical features of chronic pain have been investigated and correlated with CPM, which can give insight on the concurrent validity of CPM so as to understand which features it can predict (Fernandes et al., 2019). The clinical pain feature that was most frequently correlated with CPM was the pain intensity of the clinical pain condition. Studies that reported significant correlations between CPM and clinical pain intensity found that higher clinical pain intensity

was associated with lower CPM. Moreover, these correlations were stronger if both thermal TS and CS were used.

The CPM test has the potential value to predict treatment outcome for chronic pain (Granovsky & Yarnitsky, 2013). For instance, in people with painful diabetic neuropathy, those with lower pre-treatment CPM reported more pain relief from duloxetine treatment compared to those with higher pre-treatment CPM (Yarnitsky et al., 2012). Those with lower pre-treatment CPM also experienced improvements in CPM along with their pain relief. Duloxetine is a 5-HT and NA reuptake inhibitor (Wong et al., 1993), which can improve descending pain modulation (Iyengar et al., 2004). In line with this idea, there are also studies showing improvements in CPM with pain relief after hip (Kosek & Ordeberg, 2000) and knee surgeries (Graven-Nielsen et al., 2012; Vaegter et al., 2017). These results suggest that a poorly functioning pain modulatory system has the capacity to change and improve, whereas an already functioning system cannot be further enhanced. Thus, for an individual with chronic pain and a functioning pain modulatory system, other mechanisms may be contributing to the chronic pain state such as an enhanced pain sensing system and inflammation. It could be that CPM may only be predictive of pain treatments that function along the lines of CPM-related mechanism, such as those involving 5-HT and NA neurotransmitters. This is supported by the fact that CPM was not predictive of pregabalin—a GABA agonist—treatment efficacy for chronic pancreatitis (Olesen et al., 2013).

The CPM test also has potential predictive value for the risk of developing future pain (Granovsky, 2013; Yarnitsky, 2010). However, it might not be as common in preclinical settings, because the reliability may not be as high as clinicians would like. In one example, lower CPM at the pre-operative state in pain-free individuals undergoing thoracotomy was associated with more intense chronic post-operative pain (Yarnitsky et al., 2008). Similarly, lower pre-operative CPM was associated with chronic post-operative pain in individuals undergoing elective major abdominal surgery (Wilder-Smith et al., 2010). Individuals with lower pre-operative CPM also experienced post-operative mechanical hyperalgesia (Wilder-Smith et al., 2010), similar to females undergoing elective caesarean sections who also exhibited lower pre-operative CPM (Landau et al., 2010). In a more recent study, stronger CPM measured prior to total knee arthroplasty was associated with post-operative pain improvement (Vaegter et al., 2017), but this was not the case 12 months after surgery for individuals with a combination of lower CPM and higher TSP (Petersen et al., 2016). In another recent study that investigated biomarkers of central

neuropathic pain after spinal cord injury, CPM was one tested measure, both at and above the injury level (Gruener et al., 2019). Individuals who developed central pain exhibited early (1.5 months post-injury) reduced at-level CPM than those who did not develop pain. At-level CPM also predicted the severity of the pain 24 months after injury. These studies collectively provide strong support for increased risk of chronic pain due to lower CPM; therefore, lower CPM can be a risk factor for chronic pain.

In sum, there are three key reasons to measure CPM, which pertain to its clinical value. First, CPM can characterize individuals with chronic pain, who typically demonstrate reduced CPM compared to healthy individuals. Second, CPM can be measured prior to surgery in pain-free individuals to predict the risk of future pain. Third, pre-treatment CPM can predict the efficacy of pain treatments.

2.3 Personal and Psychological Attributes and their Relation to Pain

2.3.1 Resilience

2.3.1.1 The Personal Attribute of Resilience

Resilience has been defined as a successful adaption in response to adversity (American Psychological Association, 2014; Feder et al., 2009; Huey & Weisz, 1997; Pietrzak & Southwick, 2011; Reich et al., 2010), trauma, tragedy, threats, and stress (American Psychological Association, 2014). Commonly, it is referred to as the ability to bounce back in response to adversity (Hemington et al., 2018; Padesky & Mooney, 2012; Southwick et al., 2014). Resilience can be thought of including both recovery from adversity and adapting to aversive circumstances, because it can also be defined as the amount of stress an individual can tolerate while still having the ability to pursue meaningful life aims (Reich et al., 2010). Stress and adversity can be measured on a continuum, and so individuals may exhibit variability in the extent to which they are affected by and respond to these stressors and adversities (Pietrzak & Southwick, 2011). Thus, resilience is likely not a binary attribute, but lies on a spectrum (Southwick et al., 2014). However, these definitions of resilience do not encompass the biological, psychological, social, and cultural factors that play a role in the response to adversity. The most recent definition of resilience encompasses both physiological and psychological stress responses in psychobiological allostasis (Feder et al., 2009). This definition is included in

version 3.33 of the user's guide of the Resilience Scale (see section 2.3.1.2) (Wagnild, 2009; Wagnild & Young, 1993). In a review of definitions for resilience, two core concepts were identified as being common to all: experiencing adversity and achieving positive adaptation (Fletcher & Sarkar, 2013).

There is an issue of whether resilience is a state or a trait. Some suggest that resilience is not a trait because an individual's level of resilience can vary based on environmental risk factors outside of genetic control (Rutter, 2007). Furthermore, resilience can be viewed as malleable. For instance, people with post-traumatic stress disorder (PTSD) receiving pharmacotherapy experienced a 25% or greater increase in their resilience after their intervention (Connor & Davidson, 2003). Resilience can also be thought of as a process or an outcome (Padesky & Mooney, 2012; Southwick et al., 2014). However, resilience has shown test-retest reliability as long as 4 months (Bartone, 2007; Friborg et al., 2003; Windle et al., 2011), supporting on the concept that it can be a trait as well, because of its stability throughout multiple measures. Studies that view resilience as a trait aim to identify physical and psychological characteristics that allow individuals to overcome adversity (Jacelon, 1997).

There are two aspects to resilience: recovery and sustainability (Reich et al., 2010). Recovery is the ability to bounce back from challenges and recover to normal trajectories (Masten, 2001), returning to functioning as it was prior to the challenge (Bonanno, 2004). Sustainability is the idea of continuing to move forward in the face of challenges (Reich et al., 2010). Thus, resilience includes the ability to achieve and maintain a stable equilibrium with good psychological and physical functioning despite stressors (Bonanno, 2004). From a psychological perspective, healthy individuals with higher levels of resilience experience protective effects from the direct and indirect impacts of traumatic stress in developing PTSD, compared to those with lower levels of resilience (Lee et al., 2014). Psychological resilience can be understood from a physiological perspective as well. For example, positive emotions experienced by resilient, healthy young adults contribute to faster recovery from cardiovascular reactivity induced by a negative, emotionally arousing task (Tugade & Fredrickson, 2004).

Positive and negative personal characteristics may not always be strongly related through a direct relationship, and thus the presence of one may not signify the absence of the other. Therefore, although studies have historically focused on negative personal characteristics, we can also study

positive traits. A study by our group in healthy adults found that resilience explained a significant portion of variance in a multiple linear regression model of relative pain unpleasantness that did account for negative personal characteristics, like depression and anxiety (Hemington et al., 2017). In females with osteoarthritis, negative personal characteristics but not positive ones predicted weekly increase in negative social interactions (Smith & Zautra, 2008). Similarly, positive personal characteristics but not negative ones predicted weekly increase in positive social interactions. Moreover, the presence of positive affect may not always be directly related to negative affect, and instead be confounded by high pain and stress levels (Zautra et al., 2005). In a sample of healthy older adults, even when neuroticism was controlled, only those with low resilience (and not high resilience) exhibited an inverse relationship between daily positive and negative emotions that differed between high-stress and low-stress days (Ong et al., 2006). Similarly, when controlling for neuroticism, experiencing positive emotions removed the association between the experience of stress in one day and negative emotions the following day. Thus, resilience can be independently related to outcome measures of pain, evident from these studies that controlled for negative personal characteristics. Collectively, these studies also suggest that resilience has predictive value in pain research.

The Resilience Scale (Wagnild & Young, 1993) measures the Resilience Core, which consists of a set of five characteristics (see section 2.3.1.2): purpose, perseverance, equanimity, self-reliance, and existential aloneness or authenticity. The Resilience Scale was designed to measure resilience as a trait. These five themes were originally identified in older females who had successfully adjusted to a recent major loss, and this adjustment was reflected by social involvement, morale, and self-report (Wagnild & Young, 1990). Purpose refers to the meaning of one's life and can be the most important characteristic as it forms the foundation for the other four characteristics. Perseverance refers to not giving up. Equanimity refers to balance and harmony in life, which can be achieved by understanding that not all bad events turn into catastrophes. Self-reliance refers to the understanding of one's own capabilities and limitations. Finally, existential aloneness refers to learning how to live with oneself. Therefore, resilience can be viewed as a collection of positive personality characteristics. Resilience is also viewed as a personality profile that includes high optimism, high extraversion, high openness to experience, and low neuroticism (Waugh et al., 2008).

There are sex differences in resilience, although most of the data derive from indirect measures of resilience (e.g., measures of positive personality traits, but not resilience *per se*). Females are more likely to use coping strategies than males (Tamres et al., 2002), and this may be a result of resilience being more effective in females (Fallon et al., 2019). Sex differences in epigenetics can also contribute to sex differences in resilience to mental health disorders (Jessen & Auger, 2011; Kigar & Auger, 2013), because epigenetic differences can produce sex differences in vulnerability. Sex differences in resilience towards such mental health disorders can also be a result of sex differences in the response to stress exposure at different developmental periods (Hodes & Epperson, 2019). In veterans, males had higher resilience scores than females, although this was no longer the case when trauma type (based on the traumatic events experienced) was controlled (Portnoy et al., 2018). Similarly, heritability of resilience as a trait can be greater in males compared to females (Boardman et al., 2008). Males can have a lower risk for chronic pain compared to females that can be related to sex differences in gene expression (Smith et al., 2019). It could be that genetic factors are a risk factor for males whereas environmental factors are a risk factor for females (Newsome et al., 2016).

2.3.1.2 Measuring Resilience

There are several scales that can be used to measure resilience (Windle et al., 2011), but this thesis will focus on the Resilience Scale (Wagnild & Young, 1993). This scale was the first tool designed to directly measure resilience as a trait. The scale comes in two forms, initially 50 items and now 25 items in length, which assesses the five characteristics of resilience (see 2.3.1.1). The 25-item scale used for this thesis provides a total score that can range from 25 (lowest resilience) to 175 (highest resilience). Each item involves a 7-point Likert scale. Factor analysis of the Resilience Scale found that the scale has two major encompassing factors: acceptance of self and life, and personal competence (Wagnild & Young, 1993). Wagnild and Young describe resilience as a positive personality characteristic that improves adaptation.

The Resilience Scale was first tested on a sample of 810 middle- and older-aged adults (Wagnild & Young, 1993). The data arising from this led to designating levels of resilience: moderately-high to high resilience (scores >145), moderately-low to moderate resilience (scores 121-145), and low resilience (scores 120 and under). Levels of resilience were used by our group for a study of healthy adults (Hemington et al., 2017). In this study, scores below 116 were classified

as low, scores between 116 and 130 were classified as the low end, scores between 131 and 145 were classified as moderate, scores between 146 and 160 were classified as high moderate, and scores above 160 were classified as high. These groupings can be observed in the following figure.

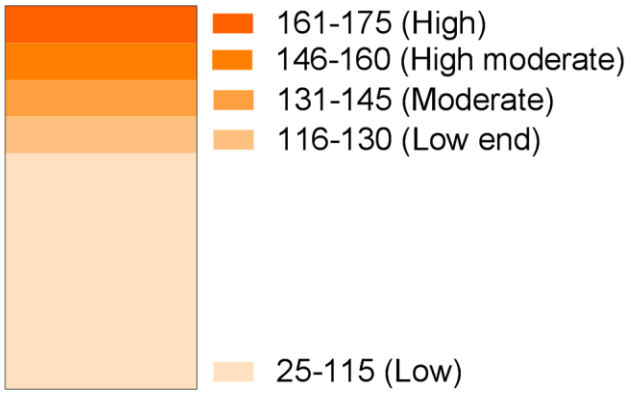

Figure 2-2. Resilience Scale scores The scores are divided based on different levels of resilience. This figure was inspired by data presented by Wagnild and Young (1993) and Hemington et al. (2017).

The Resilience Scale has strong internal consistency, and construct validity (Wagnild & Young, 1993). For internal consistency, studies of different samples of individuals exhibited Cronbach's alpha coefficients that exceeded 0.80. In terms of the two factors encompassed by the Resilience Scale—acceptance of self and life, and personal competence—internal consistency was higher for personal competence than acceptance. For construct validity, scores from the Resilience Scale were positively correlated with scales measuring morale (Lawton, 1975) and life satisfaction (Neugarten et al., 1961). Strong correlations were found between the Resilience Scale and other scales, including Personal Competence, Acceptance of Self and Life, Health Promoting Lifestyle Profile (HPLP) (Walker et al., 1987), and Self-Actualizing (Jones & Crandall, 1986). For instance, the Resilience Scale had high correlations with the following three domains of the HPLP: self-actualization, interpersonal support, and stress management.

2.3.1.3 Resilience in Relation to Pain

Resilience has been studied in the pain field, however more so in chronic pain conditions than in acute experimental pain. In a study of females with rheumatoid arthritis or osteoarthritis, two factors were investigated: vulnerability (consisting of negative personal characteristics) and resilience (consisting of positive personal characteristics) (Smith & Zautra, 2008). Vulnerability predicted increased negative social interactions and negative affect, and resilience predicted increased positive interactions and positive affect. Another study consisted of people mostly with chronic lower back pain and osteoarthritis of the hip or knee (Ong et al., 2010). For these individuals, hierarchical linear models showed that resilience (measured using the Ego-Resiliency Scale) predicted lower pain catastrophizing, such that those with higher resilience reported lower pain catastrophizing compared to those with lower resilience. Moreover, the relationship between resilience and pain catastrophizing was mediated by positive emotions. In another study, individuals experiencing chronic spinal pain who had higher resilience (measured using the Spanish Resilience Scale) reported greater levels of pain acceptance and active coping (Ramirez-Maestre et al., 2012). Moreover, those with higher resilience experienced lower levels of anxiety and depression. Those with chronic pain have been classified as resilient and non-resilient on the basis of pain severity, interference, and emotional burden (Karoly & Ruehlman, 2006). In terms of pain coping, resilient subjects used more ignoring, positive self-talk, and task persistence compared to the non-resilient subjects. In terms of pain attitudes and beliefs, resilient subjects experienced higher control perceptions and lower levels of disability belief, medical

cure belief, and fear caused by pain. Resilient subjects also experienced lower catastrophizing, and non-resilient subjects were more likely to receive pain treatment. In a more recent study, older adults with low back pain were tested for physical function, pain intensity, disability, back-related physical functioning, depression, quality of life, and resilience (Bartley et al., 2019). Composite domains of functioning measures were created, resulting in psychological, health, and social domains. Subjects were then clustered based on their level in each domain. Those with higher resilience experienced lower levels of disability, higher quality of life, higher psychological functioning, and better functional performance compared to those with lower resilience. In another recent study of older adults with chronic low back pain, resilience (measured using the Pain Resilience Scale) was found to moderate the relationship between fear-avoidance and functional performance and movement-evoked pain (Palit et al., 2019). That is, higher fear-avoidance was related to lower functional performance and greater movement-evoked pain, but only for subjects with low pain resilience and not in those with high resilience.

Although resilience has been studied more extensively in chronic pain, knowledge of the relationship between resilience and acute experimental pain sensitivity under healthy conditions can help explain how resilience contributes to chronic pain. For instance, as was the case with CPM (see section 2.2.3), resilience may be another behavioural measure in the pain-free state that may predict the risk for chronic pain. A study from our group found resilience to be negatively correlated with relative pain unpleasantness, defined as the ratio of pain unpleasantness to pain intensity in response to a noxious heat stimulus, in healthy people (Hemington et al., 2017). This relationship was more prominent in individuals with higher anxiety. In an fMRI study by our group, resilience was assessed in people with chronic pain from ankylosing spondylitis and in healthy adults (Hemington et al., 2018). In healthy adults, resilience was negatively correlated with functional connectivity between nodes of the default mode network (DMN), a network is known to be active when individuals mind wander away from pain (Kucyi & Davis, 2015). However, in those experiencing high chronic pain, resilience was positively correlated with connectivity between nodes of the DMN (Hemington et al., 2018). In a different study with healthy female adults, both resilience and purpose in life were associated with habituation to cold and heat pain (Smith et al., 2009). Of note, sense of purpose is reflected by resilience; thus, this overlap in results can serve as construct validity for resilience, because both resilience and purpose in life were associated with habituation.

Therefore, we can study resilience in healthy individuals as well as in those with chronic pain to understand how the two groups can experience resilience differently.

There are also examples that study positive characteristics associated with resilience—without referring to resilience *per se*—in relation to chronic pain and acute pain. In a study of middle- to older aged adult females with osteoarthritis and/or fibromyalgia, positive emotions were considered a source of resilience, such that individuals who experienced them more were expected to be more resilient (Zautra et al., 2005). In this study, higher weekly and average self-report measures of positive affect led to lower negative affect (e.g., distressed, upset), both through a direct relationship and through an interaction with high pain and stress (presence of positive affect was associated with lower negative affect on high pain and stress days). Hierarchical models also revealed that higher overall positive affect predicted lower pain levels in the coming weeks. In a different study of older adults with knee osteoarthritis, greater dispositional optimism was associated with lower TSP, and this relationship was mediated by pain catastrophizing (Goodin et al., 2013a). Similarly, in healthy younger adults, optimism lowered pain intensity during a CPT, which was mediated by situational pain catastrophizing (Hanssen et al., 2013). In another study, both experimental and clinical pain were investigated in those with myofascial pain dysfunction (MPD) (Harkins et al., 1989). Subjects high in extraversion experienced lower affective inhibition (inhibition of expressed suffering) compared to those low in extraversion. Subjects who had low neuroticism reported lower affective ratings for both experimental and clinical pain compared to those high in neuroticism. Compared to these highly neurotic individuals, the low neurotic subjects also reported lower ratings for emotions related to suffering. Therefore, resilience can also be measured indirectly through these various positive factors, which are encompassed by resilience. These factors, however, can be used to supplement direct measures of resilience that specifically evaluate the attribute of resilience.

2.3.2 Understanding Pain Catastrophizing

2.3.2.1 The Personal Attribute of Pain Catastrophizing and Related Pain Studies

Many studies provided the foundation for catastrophic thinking associated with pain prior to the development of the Pain Catastrophizing Scale (PCS, see section 2.3.2.2) questionnaire (Sullivan

et al., 1995). In a study of participants who underwent dental work, for instance, some subjects coped with the pain and stress, while others catastrophized by exaggerating their fear (Chaves & Brown, 1987). In another study, students reported their pain experience after an experimental CPT (Spanos et al., 1979). Those who reported worry, fear, and inability to shift attention away from the pain of the cold water were classified as catastrophizers; these individuals also reported the highest pain to CPT. Consistent with these studies, pain catastrophizing has been defined as an exaggerated negative mental set during actual or anticipated pain (Sullivan et al., 2001).

Catastrophizing is associated with pain and illness behaviour, which include help-seeking or preoccupation with managing pain symptoms (Sullivan et al., 2001). For instance, individuals with sickle cell disease who had high engagement in negative thinking, such as catastrophizing, had more frequent and longer hospitalizations over a nine month period (Gil et al., 1992), and had more frequent contact with health care professionals (Gil et al., 1993). In another example, females who had undergone breast cancer surgery and who exhibited high catastrophizing reported greater analgesic use and higher pain intensity, compared to females with low catastrophizing (Jacobsen & Butler, 1996). In adolescents, those who were classified as high catastrophizers experienced higher levels of pain intensity for five types of pain, and took over-the-counter medications more often than low catastrophizers (Bedard et al., 1997). PCS scores are associated with higher pain intensity, perceived disability, and higher psychological distress in those with chronic pain (Severeijns et al., 2001). The PCS can also be used to predict future pain as demonstrated by a study of individuals undergoing knee arthroplasty, where pre-surgical PCS was the only measure that predicted poor post-surgical pain outcomes (Riddle et al., 2010).

Sex differences in pain catastrophizing have been reported. Females score higher on the PCS overall, and in the rumination and helplessness subscales compared to males (Osman et al., 2000; Osman et al., 1997). Catastrophizing may mediate sex differences in pain (see section 2.3.3 for review of sex differences), that is, catastrophizing contributes to different pain experiences between females and males for both healthy individuals and people with pain (Sullivan et al., 2001). Pain catastrophizing plays a mediating role in other relationships. For instance, it can mediate the relationship between positive traits and pain perception (Pulvers & Hood, 2013). In healthy young adults, greater optimism was associated with lower pain intensity during a CPT, and this relationship was mediated by situational pain catastrophizing measured by the PCS

(Hanssen et al., 2013). In older adults with knee osteoarthritis, pain catastrophizing mediated the relationship between greater dispositional optimism and lower TSP (Goodin et al., 2013a).

Overall, since high pain catastrophizing is associated with pain severity and poor pain relief, it is a valuable factor to consider in the study of pain (Petersen et al., 2019). This value is further supported by the fact that a lack of negative personal characteristics does not provide the same information as the presence of positive characteristics (see section 2.3.1.1). Of particular interest to this thesis is the relationship between resilience and pain catastrophizing, and whether there is divergent validity for this relationship. Vulnerability in pain adaptation (e.g., pain catastrophizing) mostly reflects emotional functioning while resilience in pain adaptation mostly reflects coping (e.g., pain acceptance) (Sturgeon & Zautra, 2013). Therefore, while pain catastrophizing and resilience can be related, they do not lie on the same spectrum. In fact, as reviewed in section 2.3.1.1, the relationship between resilience and pain catastrophizing is not necessarily direct and can be mediated by positive emotions (Ong et al., 2010).

2.3.2.2 Measuring Pain Catastrophizing

The PCS questionnaire measures pain catastrophizing (Sullivan et al., 1995). This is a 13-item scale with total scores ranging from 0 to 52. The items in this scale are derived from definitions of catastrophizing as well as the catastrophizing subscale from the Coping Strategies Questionnaire (CSQ) (Rosenstiel & Keefe, 1983). Participants reflect on painful experiences and indicate the level at which they experienced a thought or feeling listed in the questionnaire (Sullivan et al., 1995). Factor analyses of the PCS revealed three dimensions (Osman et al., 2000; Osman et al., 1997; Sullivan et al., 1995): rumination, magnification, and helplessness. The PCS is a valid and reliable scale with adequate to excellent internal consistency (Osman et al., 2000; Sullivan et al., 1995). A total PCS score of 30 represents a clinically relevant level of catastrophizing (Sullivan et al., 1995).

2.3.3 Sex Differences in Pain

Sex differences in pain is of interest for both the public and researchers, yet there is a persisting issue of excluding females from pain studies (Mogil & Chanda, 2005). Part of this discussion is the appropriate terminology, particularly the difference between the terms sex and gender. Sex differences are biological, and thus sex differences reflect biological differences. Gender, on the

other hand, is a social construct, and thus gender differences reflect social phenomena (Greenspan et al., 2007). In this thesis, I focus on sex differences and thus any terminology used to distinguish between participants is intended to identify them on the basis of sex.

The prevalence of clinical pain within each sex differs (Unruh, 1996). For instance, in headache and migraine pain, females had higher prevalence rates for chronic tension headache, migraine, post-lumbar puncture headache, and chronic post-traumatic headache (Unruh, 1996); whereas males had a higher prevalence of episodic and chronic cluster headaches, and headaches associated with sexual activity. Females also experience more severe headaches, including greater frequency and longer durations. There are also higher prevalence rates of facial/oral pain, musculoskeletal pain, and abdominal pain for females than males. Other highly prevalent chronic pain conditions occur more often in females, including chronic fatigue syndrome, fibromyalgia, interstitial cystitis, and temporomandibular disorder (TMD) (Mogil, 2012). In one population study, widespread pain was assessed in various anatomical regions: the head, arms, legs, neck, shoulders, upper back, anterior chest, abdomen, lower back, and anterior pelvis (Gerdle et al., 2008). In each region, females had higher prevalence rates of pain compared to males. The severity of clinical pain can also be higher in females than males, including in lower/upper back or neck pain (Fillingim et al., 2003), osteoarthritis (Keefe et al., 2000), inflammatory arthritis (Barnabe et al., 2012), and IBS (Tang et al., 2012). Therefore, females experience greater clinical pain than males.

There are also sex differences in experimental pain. Sex differences in CPM will be discussed in section 2.5.1. In healthy individuals, males have higher pressure and electrical pain threshold (PPT) and tolerance than females (Riley et al., 1998; Walker & Carmody, 1998). Healthy females report higher suprathreshold (i.e., above pain threshold) pressure pain ratings compared to males, and show greater pupil dilations at high pressures (Ellermeier & Westphal, 1995). Most studies generally support a lack of sex differences in ischemic pain for healthy individuals (Fillingim et al., 2009), with some evidence to suggest that healthy males have higher pain threshold and pain tolerance compared to females (Girdler et al., 2005). From a review, 81% of studies showed that healthy females had lower heat pain thresholds and 94% of studies found lower heat pain tolerance in females (Fillingim et al., 2009). When both contact heat pain threshold and tolerance as well as CPT threshold and tolerance were measured, males experienced greater tolerance compared to females in both modalities (Tousignant-Laflamme et

al., 2008). Evidence from our group shows that females exhibit greater heat pain habituation than males (Hashmi & Davis, 2009, 2010). In experimental visceral pain, healthy females have lower esophageal pain thresholds compared to males, as determined by esophageal balloon distention (Nguyen et al., 1995).

Hormonal differences between females and males play a role in the sex differences for pain, particularly the hormonal cycles of females (Mogil, 2012). Females' response to experimentally induced pain can vary across the menstrual cycle (Sherman & LeResche, 2006). However, there is inconsistency in the literature regarding the phases of the menstrual cycle associated with pain, which can be a result of inconsistent tracking of the phases and different stimulus modalities across studies. For instance, for electrical stimulation, pain thresholds can be higher during the luteal phase; but for a variety of other stimulus modalities, the follicular phase can be associated with higher pain thresholds compared to later phases (Riley et al., 1999).

Animals also show sex differences to experimental pain (Martin et al., 2019). For example, male mice, but not female mice, exhibited context-dependent pain hypersensitivity, which was also observed in human males. The sex of the experimenter may also impact pain (Sorge et al., 2014). In particular, decreases in mouse pain behaviour were associated with the presence of a male experimenter or male-associated olfactory stimuli. Therefore, both clinical and experimental studies suggest that females have greater pain sensitivity than males.

The prevalence of back pain, headache, and TMD can increase with pubertal development (i.e., age) for girls but not boys (LeResche et al., 2005). Pain is also known to be associated with comorbidities, including anxiety and depression (Von Korff et al., 1988). Females with chronic pain experience more comorbidities compared to males and are more likely to experience anxiety and depression (Greenspan et al., 2007; Tang et al., 2012), thus supporting their disparate pain experiences compared to males. There are also sex differences in pain coping strategies (Unruh et al., 1999). It was found that females mostly used problem solving, behavioural distraction, positive self-statements, and palliative behaviours. Males mostly used cognitive/behavioural distraction and problem solving. Therefore, multiple factors can contribute to sex differences in pain, including pubertal development, comorbidities, and coping strategies.

In addition to the sex differences in the experience of pain, there are also sex differences in opioid-based pharmacokinetics. For instance, females receiving pentazocine (a kappa-opioid

analgesic) before oral surgery showed greater analgesia compared to males (Gordon et al., 1995). Similarly, females given nalbuphine (another kappa-opioid analgesic) for post-operative dental surgery pain showed greater analgesia compared to males (Gear et al., 1999b). Generally, females are thought to be more sensitive to dosage and type of opioid analgesic (Paller et al., 2009), and the optimal analgesic dose for females may be less than the highest safe dose (Gear et al., 1999b). Unlike these examples, a study of experimentally induced electrical pain found that only males and not females had significant analgesic response towards ibuprofen (Walker & Carmody, 1998).

2.4 Attributes of Painful Stimuli

2.4.1 Pain Intensity and Measurement

Historically, the level of pain (i.e., pain intensity) has been measured in terms of categories: none, mild, moderate, and severe (Collins et al., 1997) and typically refers to the sensory dimension of pain (i.e., its intensity). Pain intensity scales that are used to measure clinical pain can be evaluated on the basis of five criteria (Jensen et al., 1986): ease of administration and scoring, rates of correct response, number of response categories, sensitivity for detecting treatment effects, and strength of relationship between the scale and a combined measure of pain. Although these criteria are geared towards optimizing a rating scale for clinical pain, they also have value in optimizing scales for experimental pain in healthy participants. A scale that can be used for both clinical and experimental measurements would be advantageous as this would allow for translation capabilities. There are many scales that can be used specifically to evaluate the intensity of clinical pain, which are embedded into multidimensional pain assessment tools such as the McGill Pain Questionnaire (MPQ) (Melzack, 1975) and the Brief Pain Inventory (Cleeland, 1989). For this thesis, we tested healthy individuals, and thus these clinical pain measurement tools were not used and will not be further discussed.

Unidimensional scales that are commonly used to assess clinical and experimental pain in adults include the visual analogue scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS). The VAS usually consists of a 10-cm line with anchor labels on both ends (Jensen et al., 1986; Price et al., 1983). These anchors can be words showing a response continuum from “no pain” to “worst pain imaginable”. The participant reports their pain intensity rating by marking the line at the level that matches their pain perception. The pain rating is quantified as the

distance from the “no pain” end to the marked point (Jensen et al., 1986). The NRS is a numerical scale that starts at 0 and goes to a defined end point (typically 10 or 100) (Downie et al., 1978; Jensen et al., 1986). The number on the lower extreme of the scale can represent “no pain” and the upper extreme can represent “worst pain imaginable”. The participant can report their pain intensity rating verbally—in the form of a verbal numerical rating scale (vNRS)—or mark it on a visually presented scale with gradations, such as by intervals of 1 in the case of the 0-10 NRS (Downie et al., 1978; Herr et al., 2004). The 0-100 NRS may be more suitable than the 0-10 NRS, because participants may be more likely to give a full rating than a decimal rating. For instance, they may choose 55 on the 0-100 NRS, but round up to 6 or down to 5 on the 0-10 scale. The VRS is a list of adjectives that describe pain levels, and each descriptor is given a numerical score such that the least intense descriptor is given a score of 0 (Jensen et al., 1986).

The VAS is known to be internally consistent, reliable, and valid for measuring not only pain intensity, but also pain affect (Price et al., 1983). Indeed, it is suggested that the VAS is comparatively more sensitive than the VRS, but similarly sensitive to the NRS (Breivik et al., 2000). Although debatable, it is suggested that on a 100mm VAS, ratings above the 30mm mark may correspond to at least a moderate level of pain (Collins et al., 1997), with the ratings changing to severe pain at the 75mm mark (Hawker et al., 2011). Due to its measurement properties, the VAS is known to be superior among the different scales (Price et al., 2012). As reviewed here, these properties include high test-retest reliability, repeatability, internal consistency, sensitivity, it can measure multiple dimensions of pain, and it is simple and easy to use.

The ability of the NRS to detect small changes in pain may be greater than the VRS (Bolton & Wilkinson, 1998; Downie et al., 1978; Ferreira-Valente et al., 2011; Williamson & Hoggart, 2005) and the VAS (Bolton & Wilkinson, 1998; Ferreira-Valente et al., 2011; Williamson & Hoggart, 2005). However, the sensitivity of the NRS for detecting changes in painful stimuli could be similar to the VAS (Breivik et al., 2000; Herr et al., 2004). A 101-point NRS may not be necessary to precisely assess pain intensity (Jensen et al., 1994). For instance, subjects often treated the NRS101 as much shorter by rating in multiples of 5 or 10, suggesting that a shorter scale can provide a similar level of precision as the longer scale for detecting even small changes in pain. Like the VAS, the NRS is also a valid scale (Herr et al., 2004; Jensen et al., 1986). In

particular for testing young adults, the NRS had the best internal consistency compared to the VAS and VRS (Herr et al., 2004).

Since the VRS consists of verbal descriptors of pain (Jensen et al., 1986), the number of descriptors is an important consideration for the precision of the scale (Bryce et al., 2007). Increasing the number of descriptors does not necessarily result in a more sensitive and valid scale (Jensen et al., 1986). In a study evaluating the VAS, NRS, and VRS along with other scales, the VRS was deemed the overall best choice, because it was ranked the best for scale completion and sensitivity in detecting changes in painful stimuli (Herr et al., 2004). Compared to the VAS, the VRS may have better test-retest reliability (Lund et al., 2005). Overall, the VRS is considered a valid and reliable scale as well (Bryce et al., 2007).

In this thesis, pain intensity ratings were reported using a 0-100 vNRS, mostly due to practical issues. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) suggests the NRS over the VAS and VRS (Dworkin et al., 2005). The VAS can be associated with more missing and incomplete data compared to the NRS, because the NRS may be less abstract (e.g., it has clear gradations for pain intensity levels). The VAS can therefore be harder to use with older participants. For older adults who are cognitively intact and can self-report, the NRS is recommended, because these participants typically prefer this method of reporting pain intensity (Hadjistavropoulos et al., 2007). The vNRS has the good psychometric properties of the NRS, with the added benefit of being completed verbally, which can be preferred by older adults and even younger adults. Although age may not be a direct contributor to the failure of properly using the VAS, conditions associated with aging like cognitive and psychomotor impairments can render the VAS less ideal (Herr et al., 2004). While impairments may not always impact participants' abilities to use different pain intensity scales, the test-retest reliability of the scales can be weaker for older adults with cognitive impairments than those without impairments (Taylor et al., 2005). However, the NRS has been validated for use by participants with cognitive impairments (Herr, 2011). In older adults who underwent surgical operations and reported pain thereafter, the VAS produced high rates of data that could not be scored and had low face validity, whereas the NRS had high face validity for both younger and older adults (Gagliese et al., 2005). In fact, the VAS may not be sensitive enough to detect age differences in post-operative pain, but verbal ratings—such as the vNRS used for the study presented in this thesis—are better able to capture age differences (Gagliese & Katz, 2003).

Specifically, for the study presented in this thesis, the vNRS makes it easier to quickly report multiple ratings (see section 4.4.2), whereas the act of moving a dial for the VAS or using pen and paper could be ineffective. Furthermore, future work with older lifespans would still be feasible with our choice.

2.4.2 Pain Unpleasantness and Measurement

Pain has both sensory and affective dimensions (Melzack & Casey, 1968). Pain unpleasantness is encompassed in this affective dimension (Gracely, 1992). A new definition of pain was proposed in a 2016 paper: "pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components (Williams & Craig, 2016). The term "distressing" emphasizes the aversive quality of pain. That pain intensity and unpleasantness can be rated differently provides evidence that multiple dimensions of pain can be assessed (Price, 2000; Price et al., 1987). Studies have tried to distinguish between these two dimensions. In those with back pain, complaints of back pain were able to be grouped into different distinguishable patterns, the major one being emotional discomfort (Leavitt et al., 1978). In a study with healthy participants, subjects immersed their hand in a water bath of 47ºC and underwent hypnotic suggestions towards pain unpleasantness in a first experiment, and towards pain intensity in a following experiment (Rainville et al., 2005). In the first experiment, hypnosis modulated pain unpleasantness but not pain intensity. In the second experiment, hypnosis modulated both pain unpleasantness and intensity (Rainville et al., 2005), suggesting that changes in pain intensity may lead to changes in pain unpleasantness (Price, 2000). Thus, modulating pain intensity can involve a different mechanism than modulating pain unpleasantness. Similarly, changing mood via pleasant/unpleasant odors (Villemure et al., 2003) and visual stimuli (Loggia et al., 2008) can modulate perceived unpleasantness of a hot water bath, but not pain intensity in healthy participants. In a MPD group, individuals high in neuroticism—a negative personality trait—experienced greater pain unpleasantness for clinical and experimental pain, compared to those low in neuroticism (Harkins et al., 1989). However, there were no differences in pain intensity between low and high neuroticism, suggesting that personality can also play a role in the distinction between pain intensity and unpleasantness. Thus, neuroticism can modulate pain intensity and unpleasantness by different mechanisms. Consequently, although pain intensity and unpleasantness are often correlated, these can be dissociated with different experimental manipulations and conditions. Therefore, measuring both

intensity and unpleasantness is important to capture an accurate picture of the complete pain experience.

There are many studies, reviewed in this section, that investigated pain unpleasantness in both acute and chronic pain conditions. As reviewed in section 2.3.1.3 on resilience studied by our group, relative pain unpleasantness negatively related with resilience in healthy adults, and this relationship was more prominent for individuals with high anxiety (Hemington et al., 2017). In another study with healthy participants, those high in trait anxiety described an electric shock as very unpleasant and disturbing, and while not very different, those low in trait anxiety described it as between unpleasant and very unpleasant (Weisenberg et al., 1984). In a chronic pain group, anxiety and frustration were important predictors of clinical pain unpleasantness in multiple linear regression models (Wade et al., 1990). In healthy individuals, decreasing the expectation of avoiding pain—by signaling the onset of noxious heat stimulation—resulted in lowered pain unpleasantness (Price et al., 1980). In another study with healthy individuals, the pain intensity and unpleasantness of noxious heat decreased when participants' attentions were manipulated by drawing them towards a non-noxious visual stimulus (Miron et al., 1989). In a study of TMD, pain sensitive individuals reported their current facial pain to be more intense and unpleasant than pain tolerant individuals (Fillingim et al., 1996). In a submaximal effort tourniquet procedure, those with TMD reported greater ischemic arm unpleasantness compared to healthy individuals (Maixner et al., 1995). However, in a study comparing those with fibromyalgia and healthy individuals, surprisingly the chronic pain group exhibited lower relative pain unpleasantness towards noxious pressure stimuli than healthy controls (Petzke et al., 2005). It was thus suggested that chronic pain from fibromyalgia may reduce relative unpleasantness associated with evoked experimental pain. In children undergoing surgery, logistic regressions showed that pain unpleasantness predicted the transition from acute to more severe chronic post-surgical pain (Page et al., 2013). For instance, children who reported higher pain unpleasantness two weeks after their surgery were more likely to report moderate/severe chronic post-surgical pain six and 12 months after surgery.

There are many studies that have investigated the neural correlates of pain unpleasantness. In healthy humans undergoing fMRI, the effect of the induction of depressed mood on the pain unpleasantness of noxious heat was investigated (Berna et al., 2010). In those who reported the largest increase in pain unpleasantness, there was greater activation of the inferior frontal gyrus

and amygdala. In a positron-emission tomography (PET) study of the effects of hypnotic suggestion on pain unpleasantness, activity in the primary motor cortex, ACC, and the rostral insula related to pain unpleasantness changes (Rainville et al., 1997).

The studies reviewed above used different methods to measure pain unpleasantness in healthy individuals and those with chronic pain. In our group, for instance, pain unpleasantness was rated using a vNRS of 0 to 100 whereby 0 represented “not unpleasant at all” and 100 represented “most unpleasant imaginable” (Hemington et al., 2017). A vNRS was similarly used by others (Page et al., 2013; Rainville et al., 2005; Rainville et al., 1992). Pain unpleasantness has also been assessed using a VAS (Berna et al., 2010; Harkins et al., 1989; Quiton & Greenspan, 2007; Villemure et al., 2003; Vincent et al., 2013; Wade et al., 1990). In other studies, pain unpleasantness was reported using verbal word descriptors (Fillingim et al., 1996; Maixner et al., 1995; Miron et al., 1989; Petzke et al., 2005; Weisenberg et al., 1984).

2.4.3 Salience and Measurement

A clear definition of salience is somewhat elusive, often described in terms of how it arises or the behaviour that it evokes (e.g., draws your attention). For instance, salience is a property typically related to the contrast of feature dimensions associated with stimuli (Yantis, 2008). Thus, stimuli that are unique in those feature dimensions will have high contrast and stand out relative to other stimuli with features that are similar to the surrounding stimuli (Itti & Koch, 2001; Knudsen, 2007; Yantis, 2008). Within the context of these concepts, salience can be thought of as the ability that a stimulus has to stand out from surrounding stimuli in the neighbouring environment (Legrain et al., 2011). In this sense, the salience of a stimulus can depend on its relationship to other stimuli (Fecteau & Munoz, 2006). There are physical features that render an object more salient compared to others in the surrounding, including colour, orientation, size, motion, depth cues, and surface properties (Fecteau & Munoz, 2006; Wolfe, 1992). Other factors that can contribute to stimulus salience include stimulus intensity, novelty, sharpness of onset, and deviance (Legrain et al., 2011). New events may be salient due to their novelty, or because they do not align with recent or past experiences, such as past contexts and memories. When salient stimuli occur (e.g., sudden sound), they can have instinctive or biologically important value (Knudsen, 2007).

A salience detection system serves a role in all sensory systems, including the nociceptive system, so as to detect and orient attention in a selective manner towards important sensory events (Legrain et al., 2011). Factors that increase stimulus salience can also enhance the magnitude of neural responses evoked by nociceptive stimuli. Bottom-up selection of sensory stimuli includes the capture of attention by salient stimuli (i.e., stimulus-driven selection) to give them stronger neural representation, and top-down selection directed by cognitive goals can influence this bottom-up selection (Legrain et al., 2009). Thus, even if a painful stimulus is salient, an individual may not necessarily pay attention to it.

Many studies provide insight on salience in pain through studies of brain activity. In a study of healthy participants, nociceptive lasers evoked different EEG responses, which were thought to be determined by stimulus saliency and not necessarily pain perception (Iannetti et al., 2008). Thus, since a perceptually more intense noxious stimulus is more salient than a weaker laser, correlation between EEG response magnitudes and pain intensity may be confounded by and/or an indirect result of stimulus saliency. Thus, the repeated stimuli likely led to reduced amplitude of the EEG signal, because repeated stimuli were less salient, even though they were identical in intensity. In an event-related fMRI study, visual, auditory, and tactile stimuli were presented to healthy individuals (Downar et al., 2000). When features of these sensory stimuli were manipulated, regardless of the stimulus modality, a multimodal "salience network" of right-lateralized brain regions were activated that included the temporoparietal junction (TPJ), inferior frontal gyrus, insula, and the left cingulate and supplementary motor areas. The right TPJ also responds to novel stimuli across visual, auditory, and tactile modalities (Downar et al., 2002). Both the left and right TPJ can also respond to changes in auditory and visual stimuli that are behaviourally or context-relevant (Downar et al., 2001). While this potential "salience network" can activate at the onset or offset of nonpainful electrical stimulation of the median nerve, it activated for the entire duration of painful stimulation (Downar et al., 2003). The thalamus and putamen also responded throughout the duration of painful but not nonpainful stimulation. Another fMRI study in heathy individuals found that the posterior parietal operculum preferentially responded to painful heat but not acoustic stimulation of different intensities (Horing et al., 2019). This suggests at least one brain region that can respond specifically to pain and not salience. Studies with resting state fMRI continue to expand our understanding of the "salience network".

2.5 Personal, Psychological, and Stimulus Attributes in Conditioned Pain Modulation

2.5.1 Variability in Conditioned Pain Modulation

Studies of sex differences in CPM have not been conclusive as to whether there are sex differences in CPM (Hermans et al., 2016). While there is some evidence for a lack of sex differences in CPM, numerous studies did find such sex differences in healthy individuals (Hermans et al., 2016; Popescu et al., 2010). For the most part, these studies found that CPM was stronger in males compared to females. Based on a review of pain-free adults, studies that collected pain reports found greater CPM in males than females (Popescu et al., 2010). However, the opposite was true when pain thresholds and the RIII were collected, although this was no longer the case when the studies were weighted on the basis of the number of participants in each study. Sex alone can significantly predict CPM in a regression model, except when PCS is added to the model (Weissman-Fogel et al., 2008). Different CPM methodologies show sex differences in CPM. For instance, a CPT increased PPT in males more than females (Arendt-Nielsen et al., 2008), and hypertonic saline injection increased the PPT in males but not in females (Arendt-Nielsen et al., 2008; Goodin et al., 2013b). A study investigating different determinants of endogenous analgesia tested CPM using contact heat as the TS and a water bath of varying temperatures as the CS (Granot et al., 2008). A sex effect was found, with greater pain inhibition in males than females. Influencing CPM by means of expectations that indicate whether the CS will decrease or increase pain can affect females but not males (Bjorkedal & Flaten, 2012). CPM has also been found to be greater for healthy females during the ovulatory phase compared to the menstrual and luteal phases (Tousignant-Laflamme & Marchand, 2009). A final example also demonstrates sex differences in the temporal characteristics of CPM. In healthy adults, PPTs were evaluated before, during, and after hypertonic saline injections (Ge et al., 2004). CPM lasted longer in males than in females.

Age also plays a role in CPM, with studies supporting stronger CPM in healthy young adults compared to older adults generally above the age of 40 (Hackett et al., 2019; Hermans et al., 2016). Even when pain inhibition is observed in older adults, the magnitude of this inhibition can be lower compared to younger adults (Washington et al., 2000). As was the case with sex, many different CPM paradigms have found this age effect. In one study, CPM was tested in both younger and older adults using a series of thermal pulses as the TS (i.e., TSP) and the CPT as the

concurrent CS (Edwards et al., 2003). While younger adults experienced some pain inhibition, older adults experienced pain facilitation with increases in thermal pain instead of decreases. Pain facilitation in older adults, but inhibition in younger adults, was also observed in another study in which thermal pain ratings were measured both with and without foot immersion in a cold water bath (Riley et al., 2010). In another study that assessed thermal pain thresholds before and during a CPT, an increase in thermal thresholds was found up to middle age, and thereafter remained low in old age (Lariviere et al., 2007). Therefore, CPM gradually decreased with age. Nevertheless, there are also studies that did not find as great of an age effect in CPM. For instance, CPM was not observed in either a middle-age group nor older-age group in some studies (Grashorn et al., 2013; Riley et al., 2014). CPM in older adults may depend on the CPM paradigm, based on whether a parallel or sequential method is used (Hackett et al., 2019).

Although CPM is typically thought to result in reduced pain, there exists a tremendous amount of inter-subject variability in the effects of a remote CS on TS pain—ranging from increased pain (facilitation), to no change in pain, to decreased pain (inhibition) (Kennedy et al., 2016), and this has been observed in numerous studies. Therefore, CPM can be understood as variable and can be exhibited as pain inhibition or pain facilitation. This is in contrast to DNIC studied in animals, which reflects only antinociception. Here, I will summarize some methods that were used to highlight variability in response to different CPM paradigms. In a study consisting of both people with Parkinson's disease and healthy controls, CPM was deemed to be efficient if the resulting CPM score was negative, reflecting pain inhibition (Granovsky et al., 2013). Using these definitions, both those with the disease and healthy controls exhibited variable CPM responses, from negative to positive. In another study comparing people with fibromyalgia and healthy individuals, pressure pain served as both the TS and CS (Harper et al., 2018). In this case, CPM was defined as inhibitory if the calculated CPM value was negative, and facilitatory if the calculated CPM value was positive. In fact, when it comes to those with fibromyalgia, pain facilitation is more common compared to healthy controls (Potvin & Marchand, 2016). In a migraine study, both healthy individuals and migraineurs exhibited a wide range of CPM responses, and pain inhibition was defined as a negative calculated CPM score (Kisler et al., 2018). Even when the entire spectrum of CPM responses is not explicitly highlighted, a wide range of CPM values from pain inhibition to pain facilitation can be observed (Nir et al., 2011). Another study grouped both healthy controls and those with chronic low back pain based on

whether they exhibited inhibitory CPM effect, no effect, or facilitatory CPM effect so as to characterize pronociceptive and antinociceptive CPM effects in both groups (Rabey et al., 2015). Despite these examples, of note is that if threshold measures are used (i.e., PPT) as the TS, then positive CPM calculations would reflect pain inhibition instead of pain facilitation (Klyne et al., 2018). Finally, there are also examples whereby a two-standard deviation band method was used to group healthy participants into subgroups of CPM efficacies (Youssef et al., 2016a, 2016b). In this case, participants were placed into a CPM group if their TS pain intensity ratings during a CS decreased by more than two standard deviations from their TS pain prior to CS application. All other participants were placed into a no-CPM group. Although the method of CPM grouping in this thesis was different from this, I adopted the terminology of "CPM" and "no-CPM" subgroups. Variability in CPM can impact the overall CPM measured for the whole group. For example in a study of healthy females, no overall CPM effect was found due to variability at the individual level, because some participants exhibited decrease in pain and others exhibited increase in pain (Bogdanov et al., 2015).

2.5.2 Psychological Factors in Conditioned Pain Modulation

There are multiple psychological factors that can influence CPM. Pain catastrophizing has been associated with CPM, but with conflicting findings (Hermans et al., 2016). Many studies of healthy individuals have found a negative correlation between CPM and PCS, such that greater pain catastrophizing was associated with lower CPM (Goodin et al., 2013b; Goodin et al., 2009; Traxler et al., 2019; Weissman-Fogel et al., 2008). A meta-analysis of healthy individuals and those with chronic pain showed that the negative association between CPM and pain catastrophizing may depend on the modality of the TS, particularly if it is electrical (Nahman-Averbuch et al., 2016). Furthermore, the negative association was also reflected in healthy individuals between PCS and brain activity in regions related to top-down pain control during moderate pain stimulation (Seminowicz & Davis, 2006). However in other studies, positive correlations were found between pain catastrophizing and CPM, such that greater pain inhibition was associated with greater pain catastrophizing (Granot et al., 2008). Naltrexone-mediated inhibition of endogenous opioids can reduce CPM for healthy individuals with lower pain catastrophizing but not those with higher pain catastrophizing, which suggests a moderating role for pain catastrophizing (King et al., 2013).

As reviewed in section 2.3.1.3, resilience is studied more often in chronic pain than acute experimental pain. Resilience has not been studied directly in relation to CPM, and only one study investigated indirect relationships in those with knee osteoarthritis (Thompson et al., 2018). In this study, the association between optimism and clinical knee pain severity was mediated by CPM, suggesting that greater optimism is associated with greater CPM, which is associated with less pain severity. Optimism can be defined as expectation for positive outcomes and can be one of the positive traits associated with resilience. Furthermore, a moderation model showed that optimism moderates the association between resilience and CPM such that greater resilience was associated with greater CPM only in individuals with low optimism. While resilience has not been well studied directly in relation to CPM, the relationship between CPM and positive factors encompassed by resilience have been studied directly. Optimism is one such example that has been well studied in relation to CPM, directly. Some studies have found no relationship between the two in both healthy individuals and those with chronic pain (Nahman-Averbuch et al., 2016; Traxler et al., 2019). However, one study did find that in healthy individuals, greater dispositional optimism was associated with greater CPM when accounting for other factors like sex, ethnicity, pain catastrophizing and depression (Goodin et al., 2013b). The reverse association between dispositional optimism and CPM has also been found (Hinkle & Quiton, 2019).

There are also other psychological factors, beyond pain catastrophizing and positive factors, that have been studied in relation to CPM (Nahman-Averbuch et al., 2016). They will be reviewed here in brief as they were not considered in further analyses in this thesis. These factors have been previously studied; a meta-analysis found that CPM was negatively related to trait and state anxiety (when a pressure TS was used) and positively related to depression (when a heat TS was used) (Nahman-Averbuch et al., 2016). In one study that evaluated state and trait anxiety in healthy individuals, no correlations were found between these measures and CPM (Granot et al., 2008). Depression has also been studied in relation to CPM (Goesling et al., 2013). In one study consisting of those with fibromyalgia, major depressive disorder, and healthy individuals, CPM was lower for the fibromyalgia group than healthy individuals (Normand et al., 2011). However, CPM efficacy was similar between the depression group and healthy individuals. Evidence also suggests that pain-free high stress responders experience reduced CPM when exposed to stress (Geva & Defrin, 2018; Geva et al., 2014). Harm avoidant personalities are also relevant,

whereby greater harm avoidance can be associated with lower CPM (Nahman-Averbuch et al., 2016).

2.5.3 Stimuli in Conditioned Pain Modulation and its Efficacy

As reviewed in section 2.2.2 on the methodology for CPM, there are two stimuli used in the CPM paradigm, the TS and CS. Studies show that attributes of the TS and CS can impact CPM, and these examples will be reviewed here. It has been noted that various parameters of both the TS and CS, including modality, intensity, and body area can influence CPM efficacy (Tansley et al., 2019).

The modalities used in CPM paradigms can influence the CPM response. In a study of healthy participants, CPM was compared across different paradigms that used the same CS (contact heat) applied to the hand and different modalities of TS: heat pain threshold, PPT, heat pain ratings, pressure pain ratings, mechanical TSP, and thermal TSP (Nahman-Averbuch et al., 2013b). Only PPT and thermal TSP modalities resulted in CPM. Greater CPM occurred when greater TS pain intensities were used, but only in the CPM paradigms with heat pain threshold, and thermal and mechanical TSP. CPM can also depend on the site of stimulus application (Defrin et al., 2010). In healthy humans, different CPM responses have been observed across studies that used different body sites for stimulation (Pielsticker et al., 2005; Pud et al., 2009). While homotopic and heterotopic stimulation within a CPM paradigm can both result in pain inhibition (Pud et al., 2005), evidence suggests that only heterotopic and not homotopic stimulation may result in pain inhibition (Graven-Nielsen et al., 1998). The magnitude of CPM resulting from heterotopic stimulation can depend on the location order of the TS and CS applications (Haefeli et al., 2014). In one study that investigated DNIC in rats, pain inhibition was observed from the impact of hindpaw immersion in hot water on tail flick from radiant heat (Morgan et al., 1994). However, pain facilitation was observed from the impact of tail immersion in hot water on hindpaw flick from radiant heat.

The relationship between CS pain or CS intensity and CPM has been well studied, but results have been inconsistent (Pud et al., 2009). Some studies in healthy individuals reported that CPM is positively correlated with CS pain (Baad-Hansen et al., 2005; Graven-Nielsen et al., 1998; Sprenger et al., 2011). However, other studies have reported either a negative relationship (Bogdanov et al., 2015) or no relationship (Lewis et al., 2012a; Pud et al., 2005; Serrao et al.,

2004; Youssef et al., 2016b) between CPM and CS pain. In a study of healthy participants, contact heat pain ratings were reduced by water immersion that was perceived as moderately and intensely painful, but not with water that was perceived as mildly painful (Nir et al., 2011). Moreover, CPM was greater when the CS was perceived as both moderately and intensely painful than when perceived as mildly painful. Nevertheless, the conditioning pain was not associated with CPM, even though CS intensity was positively associated with it. The influence of CS pain on CPM can also depend on sex. For instance, a hierarchical regression model showed that CS pain predicted CPM magnitude in healthy males but not females (Treister et al., 2010). As briefly introduced here, CS intensity can also play a role in CPM. The interaction between CS intensity and duration can influence CPM such that both high CS intensity and long duration can result in greater CPM for females (Razavi et al., 2014). In another study, while there was no relationship between CS pain intensity ratings and CPM, there was an association between the intensity of the CS and CPM (Granot et al., 2008). In this study and many others, higher CS intensities resulted in greater pain inhibition (Bouhassira et al., 1994; Tanaka et al., 2015; Willer et al., 1989).

Despite the aforementioned studies, there is also evidence to suggest that even a nonpainful CS can induce CPM. For instance, both gastric and rectal distensions can produce nonpainful stimulations that inhibit the RIII reflex in healthy individuals (Bouhassira et al., 1994; Bouhassira et al., 1998). Moreover in healthy participants and those with headaches, both painful and nonpainful thermal CS can induce increases in electrical pain thresholds (Kunz et al., 2006; Lautenbacher & Rollman, 1997; Pielsticker et al., 2005). In another study with healthy subjects, a nonpainful CS reduced pain intensity ratings of a painful TS, and a painful CS reduced pain intensity ratings of a nonpainful TS (Lautenbacher et al., 2002). In DNIC studies with rodents, it has been shown that even the intensity of the TS can influence whether pain inhibition or pain facilitation occurs (Tansley et al., 2019). In this case, lower TS intensities resulted in pain facilitatory behaviour and greater TS intensities resulted in pain inhibitory behaviour.

Chapter 3
Rationale, Aims, Hypotheses

3.1 Rationale

Although the variability in CPM has been well-explored, less is known about how this variability relates to both personal and stimulus attributes in healthy individuals. As reviewed above, many different factors play a role in CPM, which justifies incorporating both elements in this thesis so as to better understand CPM. In the case of personal attributes, this thesis included sex and resilience. Sex differences in CPM have been observed in studies (see section 2.5.1), with the majority suggesting that males exhibit stronger CPM than females (Hermans et al., 2016). Resilience is studied more in chronic pain conditions than in acute experimental pain. Since resilience reflects a collection of positive personality characteristics (Wagnild & Young, 1990), it emphasizes the role of positive factors in the pain experience. Thus, despite the emphasis in previous studies on negative personal attributes, positive attributes can also be important to study. The CS is well-studied in relation to CPM; however, as reviewed above (see section 2.5.3), the focus has mainly been on CS pain and CS intensity. CS pain refers to the perception of pain evoked by the CS, whereas CS intensity refers to the absolute stimulus intensity of the CS. Consequently, this study investigated other attributes of the CS: pain unpleasantness and salience. Therefore, given the existing literature, the focus of this thesis was to understand CPM variability in relation to both personal attributes of sex and resilience, as well as CS attributes of pain unpleasantness and salience.

3.2 Aims

The aims were as follows.

1) To assess the distribution of CPM effects across healthy individuals.

2) To determine the relationship between CPM and

    a. Resilience as a personal attribute, and

    b. Pain unpleasantness and salience as CS attributes.

3) To determine whether females and males exhibit different or similar relationships between CPM and personal/CS attributes.

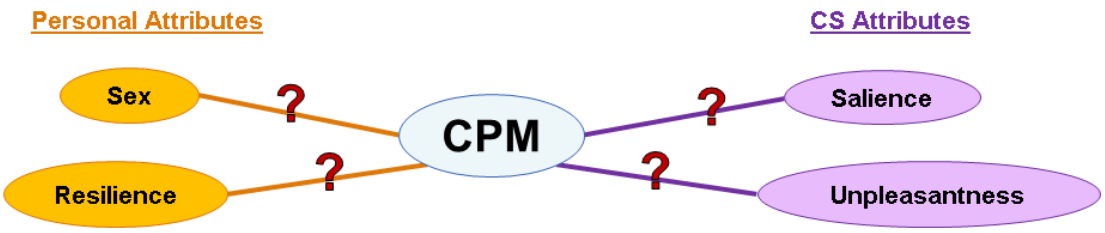

Figure 3-1. Visual depiction of thesis aims Sex and resilience are personal attributes of interest. Pain unpleasantness and salience are CS attributes of interest.

3.3 Hypotheses

The hypotheses were as follows.

1) Healthy individuals will exhibit CPM effects that range from pain inhibition to facilitation.

2) There is a positive relationship between CPM and resilience.

3) There are positive relationships between both CPM and CS pain unpleasantness and salience.

4) The relationships in 2) and 3) above will be more prominent in males compared to females.

Chapter 4
Methods

4.1 Overview

The study presented in this thesis is based on psychophysical data and self-report questionnaire data collected at Toronto Western Hospital. Healthy participants were recruited from hospital advertisements to collect data as part of a battery of psychophysical tests for previous and ongoing studies of acute and chronic pain. This data was collected by Natalie R. Osborne, Joshua C. Cheng, Junseok A. Kim, Rachael L. Bosma, Kasey S. Hemington, and Anton Rogachov. To begin the experimental session, participants were seated in a comfortable office chair at a desk inside a quiet testing room, and they completed a demographics form.

4.2 Participants and Recruitment

Data was collected from 155 healthy participants (81 females, 74 males) who provided written consent to take part in all study procedures, which was previously approved by the University Health Network research ethics board. All recruited participants were right-handed, because brain imaging data were also collected for other studies, and thus this decision was made to control for brain lateralization. Prior to testing day, participants were asked to refrain from drinking caffeinated beverages (as they are stimulants) up to one hour before the experimental session, and alcoholic beverages (as they are depressants) up to eight hours before the experimental session. While one hour may appear short for caffeine, a study of experimental pain in healthy adults showed that administering caffeine one hour before the study reduced pain ratings only briefly towards the beginning of the trial, compared to placebo administration (Myers et al., 1997). The use of tobacco or cannabis was not specifically documented. The list of exclusion criteria was as follows: 1) history of chronic pain defined as pain that lasts longer than three months; 2) current ongoing pain; 3) psychiatric or neurological disorders; 4) Beck Depression Inventory (BDI) scores greater than 13, indicating a score above the minimal range for self-reported depression (Beck et al., 1996); 5) ongoing use of medication, excluding birth control; 6) major chronic health conditions or diseases (self-reported); and 7) aged 40 years or older due to general reduction in CPM in older adults (Hermans et al., 2016).

In total, 106 participants (51 female, 55 male) were included in the study, thus excluding 49 participants (30 female, 19 male) from the initial recruitment. The reasons for excluding these 49 participants were as follows: four were excluded due to incomplete CPM data, one was excluded due to an undefined calculated CPM value resulting from a first test stimulus (TS1) pain rating equal to 0 (see section 4.4.3 on CPM calculation), 11 were excluded due to having BDI scores greater than 13, 19 participants aged 40 years and older were excluded, three were excluded due to both BDI score and age, 10 were excluded due to TS1 pain ratings less than 40 out of 100 to control for possible CPM floor effects (Kisler et al., 2018; Kisler et al., 2019; Nir & Yarnitsky, 2015), and one was excluded when they later informed the lab of a new autism diagnosis.

4.3 Questionnaires

The BDI (Beck, 1979) was used to measure self-reported depression. This is a 21-item scale with total scores ranging from 0 to 63. It was used only as part of the exclusion criteria and not in any further analyses. Higher scores indicate greater self-reported depression.

The Resilience Scale (Wagnild & Young, 1993) was used to measure resilience in all participants. This is a 25-item scale with total scores ranging from 25 to 175. Higher scores indicate greater trait resilience.

The PCS was used to measure pain catastrophizing (Sullivan et al., 1995). It is a 13-item scale with total scores ranging from 0 to 52. Higher scores indicate greater pain catastrophizing.

4.4 Evaluation of Conditioned Pain Modulation

All testing involved thermal stimuli delivered to either one or both volar forearms using 30x30mm contact thermodes (QSense device, Medoc Ltd, Ramat Yishai, Israel). The thermodes were applied about 15cm above the wrist.

The CPM testing was one part of an approximately 2-hour QST/questionnaire session. Participants were informed that they would be undergoing psychophysical testing of different modalities and filling out questionnaires. Brain imaging was also conducted on these participants, but this data was not used in this thesis. Participants were provided a remuneration of $75 for the entire experimental session of approximately 3.5 hours that included QST and brain imaging.

4.4.1 Determination of Pain50

First, a familiarization paradigm was used to determine Pain50, defined as the thermode temperature to evoke a heat pain intensity rating of 50 on a vNRS of 0 to 100, with 0 being “no pain” and 100 being “worst pain imaginable”. A thermode was applied to the left volar forearm and participants were instructed to verbally rate their pain towards a series of pre-determined thermal stimuli. These stimuli were applied in the following order: 44°C, 45°C, 43°C, 46°C, 42°C, and 47°C if the participant appeared comfortable and had not yet reported a pain rating greater than 75 out of 100. Each stimulus was delivered from a baseline thermode temperature of 35°C to the target temperature, at a ramp up rate of 2°C/s. Each target temperature was held for 6s, and participants rated their pain intensity towards the stimulus after 3s had elapsed from this time. After the 6s passed, the thermode temperature returned to the baseline temperature at a ramp down rate of 1°C/s. The ISI between the pre-determined temperatures was 15s. This Pain50 temperature was used for both the TS and CS thermodes, thus resulting in perceptually-matched stimuli.

4.4.2 Determination of Conditioned Pain Modulation

After determining Pain50, the CPM paradigm was conducted. One thermode was used to deliver the TS to the right volar forearm, and another thermode was used to deliver the CS to the left volar forearm. Each thermode delivered stimuli from a baseline temperature of 35°C to the target temperature of Pain50 as determined from familiarization for each participant.

The complete CPM paradigm is depicted in Figure 4-1.

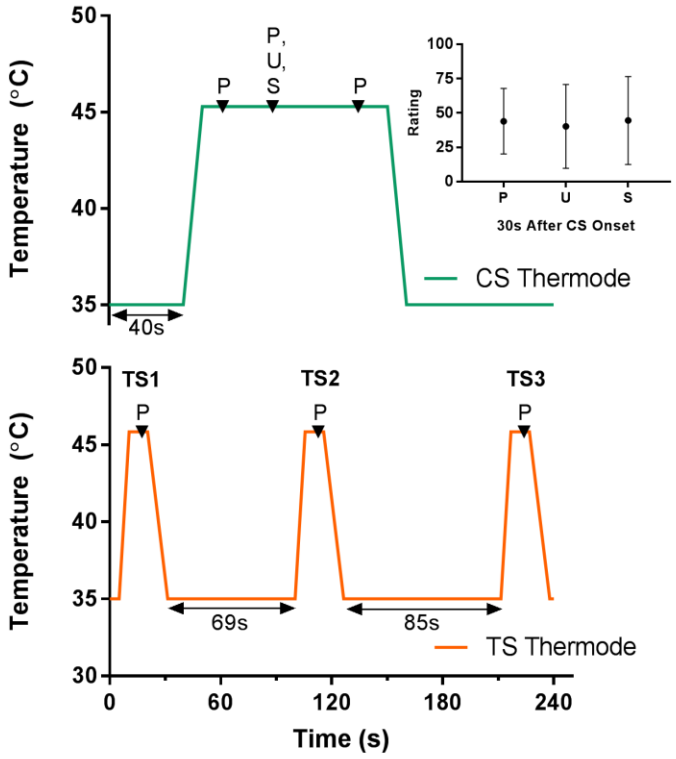

Figure 4-1. Complete CPM paradigm Three TS were delivered (orange line) and participants verbally rated their pain (P) each time. One long CS was delivered (green line) and participants verbally rated their pain (P) three times, at 10s, 30s, and 60s after CS onset. At 30s after CS onset, participants also verbally rated pain unpleasantness (U) and salience (S) towards the CS. The inset in the upper right of the figure shows the three CS measures collected after 30s of CS onset.

After a 5s delay from the beginning of the paradigm, TS1 was delivered. The TS thermode temperature increased from baseline (35°C) to the target temperature (Pain50) at a ramp up rate of 2°C/s, remained at target for 10s, and then returned to baseline at a ramp down rate of 1°C/s. The participant verbally rated their pain towards TS1 at 7s after the TS thermode reached the target temperature, using the 0-100 vNRS. The TS thermode then remained at baseline for 69s, after which the second TS (TS2) was delivered in the same manner as TS1. The participant verbally rated their pain towards TS2 also at 7s after the TS thermode reached the target temperature. The TS thermode then remained at baseline for another 85s, after which the third TS (TS3) was delivered in the same manner as TS1 and TS2. The participant verbally rated their pain towards TS3 again at 7s after the TS thermode reached the target temperature.

The CS was delivered after a 40s delay from the beginning of the paradigm. The CS thermode temperature increased from baseline (35°C) to the target temperature (Pain50) at a ramp up rate of 1°C/s, remained at target for 100s, and then returned to baseline at a ramp down rate of 1°C/s. The participant verbally rated their pain towards the CS at 10s, 30s, and 60s after the CS thermode reached the target temperature, using the 0-100 vNRS. Collecting three pain ratings towards the long CS allowed us to identify any changes in CS pain throughout the paradigm, which could suggest potential habituation. At 30s after CS onset, participants also verbally rated pain unpleasantness and salience towards the CS, after rating pain. Pain unpleasantness was defined as how bothersome the stimulus was. There were two examples of pain unpleasantness given to participants. One example described pain unpleasantness to be similar to how much one likes or dislikes music, while pain intensity was described to be similar to the volume of music (Hemington et al., 2017; Price & Harkins, 1987). Another example described a massage as being pleasant but painful, whereas other types of painful experiences could be unpleasant. Pain unpleasantness was verbally rated using a 0-100 vNRS, with 0 being “not unpleasant at all” and 100 being “most unpleasant imaginable”. Salience was described as the ability of the stimulus to capture attention. Since the definition of salience is often complex and can vary (see section 2.4.3), the following is the direct script line used to explain salience: “by salience, I mean the ability of the stimulus to capture your attention”. The example given to participants described the room being lit for some time as having little salience, whereas flashing lights would have more salience. Salience was verbally rated using a 0-100 vNRS, with 0 being “not salient at all” and 100 being “extremely salient”.

4.4.3 Conditioned Pain Modulation Calculation

In this thesis, the CPM effect refers to the full spectrum of possible CPM responses, ranging from pain inhibition to pain facilitation (from negative to positive, as determined from suprathreshold testing—see methods above). This effect refers to the individual responses of CPM magnitudes determined by subtracting TS2 pain ratings from TS1 pain ratings, which is different from an overall inhibitory CPM effect determined by checking whether TS2 pain ratings are significantly lower than TS1 pain ratings (see section 4.5) and how TS3 pain ratings compares to this TS1 pain. The CPM effect percent change was defined as the percent change in TS pain intensity induced by the CS. The following formula was used:

CPM Effect Percent Change = [(TS2 Pain – TS1 Pain)/TS1 Pain] x 100%.

Therefore, negative scores indicate pain inhibition, positive scores indicate pain facilitation, and zero indicates no effect. Although TS3 pain is not included in this formula for measuring the CPM magnitude, it was compared to TS1 pain to assess TS pain after CS application and control for any habituation effects.

4.5 Statistical Analyses

Statistical analyses were performed with:

1) R (version 3.4.3, https://www.r-project.org),

2) GraphPad Prism (version 7.03, https://www.graphpad.com), and

3) Microsoft Excel 2010 (office.microsoft.com/excel).

Shapiro-Wilk normality tests were conducted to determine whether the distribution of the data were amenable to parametric tests, or whether non-parametric tests were required for two-tailed tests of statistical comparisons. To evaluate the overall inhibitory CPM effect with respect to changes in TS pain intensity ratings, statistical comparisons were made using Wilcoxon tests between TS2 pain and TS1 pain, and between TS3 pain and TS1 pain. This was done for the whole group and subgroups (see section 5.2 for subgroups), to characterize each separately. A Friedman test (and associated post hoc Dunn’s test) or repeated measures analysis of variance (ANOVA) (and associated post hoc Tukey test) were used to compare the three CS pain intensity

ratings to identify any changes in CS pain (e.g., CS adaptation). This was done for all subjects, females only, and males only. Assessing CS adaptation was of interest, because as described in section 2.5.3, the relationship between CS pain and CPM is well studied; thus, it was important to determine if CS pain changed throughout the duration of the CS application. A Friedman test was also used to evaluate differences between all three TS pain intensity ratings at the whole group level to assess TS adaptation. This was of interest, because it was important to determine whether a reduction in TS pain occurred over time that could serve as an alternative explanation to an overall inhibitory effect. Moreover, the difference between TS3 and TS1 pain intensity ratings was correlated with the difference between CS60 and CS10 pain intensity ratings for the whole group to further assess adaptation. Spearman correlation was used based on results of Shapiro-Wilk tests that suggested non-normally distributed data.

Three multiple linear regression models were created in R, one for the whole group and for each subgroup. Each model contained the CPM effect percent change as the response variable, and the predictors were sex, resilience, CS pain unpleasantness, CS salience, and an interaction between resilience and sex. Variance inflation factors were calculated for each predictor to rule out multi-collinearity (less than 5). The variance inflation factor is a ratio of the variance of the model with all predictors to the variance of the model with one predictor alone, and researchers have commonly used 10 as a threshold for the rule of thumb (O'brien, 2007).

To further explore the predictors and CPM, the variables of interest (i.e., predictors from the regression models) were correlated. Shapiro-Wilk normality tests were used to determine whether it would be appropriate to conduct Pearson or Spearman correlations. Pearson correlations were used when all variables in the correlation were normally distributed, and Spearman correlations were used when all variables in the correlation were not normally distributed. Fisher's r-to-z transformations were conducted to compare correlations between pairs of female and male correlations.

Chapter 5
Results

5.1 Conditioned Pain Modulation Effect and Subgroups

For the whole group, the mean ± standard deviation (SD) measures for the CPM effect raw and percent change were -5.3 ± 18.8 and -8.3 ± 34.9%, respectively. Both of these measures were more negative in the CPM subgroup than in the no-CPM subgroup ($P < 0.001$). Only the CPM effect percent change was used in this thesis for analyses and discussion. The raw change is not further used because only the percent change was normally distributed. Thus, the CPM effect will always refer to the CPM effect percent change. The skewness and kurtosis of the data were, respectively: -0.0528 and 3.89. The CPM effect ranged from -100% to +112.5%, suggesting large inter-subject variability as shown in Figure 5-1. From this large range, we were able to subdivide the participants based on their CPM response, thus creating two subgroups: a CPM subgroup with 53 participants (26 female, 27 male) exhibiting pain inhibition, and a no-CPM subgroup with 53 participants (25 female, 28 male) exhibiting pain facilitation or no change in pain. The whole group refers to both subgroups combined. This cut-off point was chosen, because as reviewed in section 2.5.1, many studies used the direction of change in TS pain (increase or decrease) as a means of defining inhibitory and facilitatory CPM.

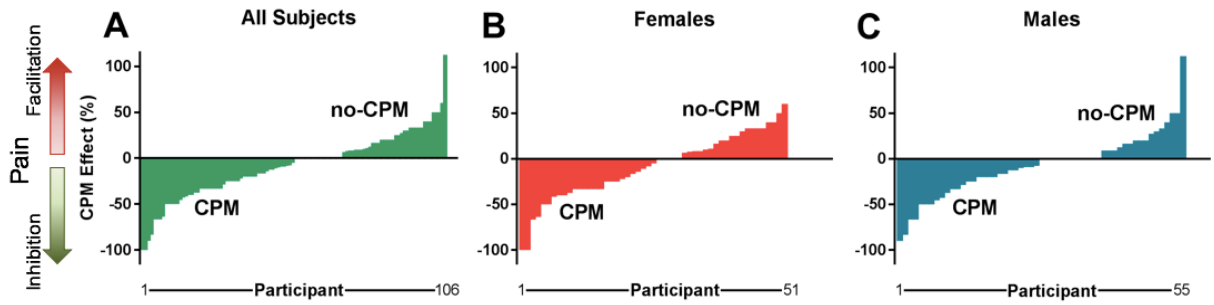

Figure 5-1. Distributions of the CPM effect percent change The distributions are shown for (A) all 106 participants, (B) females only (n = 51), and (C) males only (n = 55). In each case, CPM and no-CPM subgroups were identified as labeled on each graph. The CPM subgroup includes participants with pain inhibition, and the no-CPM subgroup includes participants with pain facilitation or no effect.

5.2 Demographics and Descriptive Statistics

Of note, this study had a large sample size (106 participants). Since many experimenters collected the data for this study, the sex of the experimenter was investigated to ensure that it did not present as a confound in the variability of CPM. The experimenter female-male ratio did not differ between the CPM and no-CPM subgroups ($P = 0.581$); therefore, it is unlikely that the sex of the experimenter contributed to the large inter-subject variability in CPM magnitudes. Table 5-1 displays the demographic data (sex and age) and descriptive statistics for all 106 participants, and for both the CPM and no-CPM subgroups. There were no sex ($P = 0.85$) or age ($P = 0.69$) differences between these subgroups. The mean ± SD age of all participants together was 26.8 ± 5.3 years. For the whole group, the mean ± SD measures for resilience and PCS were 145.1 ± 15.6 and 12.2 ± 8.5, respectively. These measures did not significantly differ between the CPM and no-CPM subgroups. The whole group measures for the TS pain intensity ratings were as follows (mean ± SD): 53.1 ± 10.2 for TS1, 47.9 ± 18.2 for TS2, and 52.0 ± 18.7 for TS3. The TS1 pain intensity ratings did not significantly differ between the CPM and no-CPM subgroups ($P = 0.053$); however, both TS2 and TS3 pain were significantly higher in the no-CPM subgroup than in the CPM subgroup (both $P < 0.001$). The whole group measures (mean ± SD) for CS pain intensity ratings were 60.3 ± 17.7 at 10s after CS onset, 43.9 ± 23.8 at 30s after CS onset, and 42.6 ± 26.3 at 60s after CS onset. CS pain ratings at 30s and 60s after CS onset were both significantly higher in the no-CPM subgroup than in the CPM subgroup (both $P < 0.01$). The other CS attributes measured at 30s after CS onset were (mean ± SD) 40.2 ± 30.5 for CS unpleasantness and 44.5 ± 32.0 for CS salience. Both CS unpleasantness ($P < 0.01$) and CS salience ($P < 0.001$) ratings were significantly higher in the no-CPM subgroup than in the CPM subgroup. Finally, the whole group measures (mean ± SD) was 45.84 ± 2.02ºC for the TS thermode temperature, and 45.29 ± 1.97 ºC for the CS thermode temperature. Both of these measures were significantly higher in the no-CPM subgroup than in CPM subgroup (both $P < 0.0001$).

Table 5-1. Demographic information and descriptive statistics of participants by CPM subgrouping Data for all 106 participants, and for the subgroups are shown. The CPM subgroup only includes participants with pain inhibition, and the no-CPM subgroup only includes participants with pain facilitation or no effect. The p-values refer to statistical comparisons between the CPM and no-CPM subgroups. Values shown include mean ± SD. *Significant at α = 0.05 level based on Mann-Whitney U test. †Significant at α = 0.05 level based on unpaired *T*-test.

Variable	Whole Group	CPM Subgroup	no-CPM Subgroup	*P*-Value (CPM vs no CPM)
N (F, M)	106 (51, 55)	53 (26, 27)	53 (25, 28)	0.85
Age (Years)	26.8 ± 5.3	26.4 ± 4.5	27.3 ± 6.0	0.69
Resilience	145.1 ± 15.6	145.7 ± 14.7	144.6 ± 16.6	0.81
PCS	12.2 ± 8.5	12.5 ± 8.9	11.8 ± 8.1	0.83
CPM Effect (raw change)	-5.3 ± 18.8	-19.6 ± 14.5	9.1 ± 9.4	<0.001*
CPM Effect (percent change)	-8.3 ± 34.9	-35.2 ± 23.3	18.6 ± 21.1	<0.001*
TS1 Pain Intensity	53.1 ± 10.2	55.0 ± 10.5	51.3 ± 9.6	0.053
TS2 Pain Intensity	47.9 ± 18.2	35.4 ± 14.2	60.4 ± 12.3	<0.001*
TS3 Pain Intensity	52.0 ± 18.7	42.7 ± 17.3	61.4 ± 15.2	<0.001*
CS Pain Intensity (10s after CS onset)	60.3 ± 17.7	61.9 ± 17.3	58.7 ± 18.0	0.34
CS Pain Intensity (30s after CS onset)	43.9 ± 23.8	37.9 ± 24.6	49.9 ± 21.6	<0.01†
CS Pain Intensity (60s after CS onset)	42.6 ± 26.3	35.9 ± 26.9	49.2 ± 24.1	<0.01*
CS Unpleasantness (30s after CS onset)	40.2 ± 30.5	31.3 ± 29.0	49.2 ± 29.6	<0.01*
CS Salience (30s after CS onset)	44.5 ± 32.0	33.5 ± 30.3	55.5 ± 30.0	<0.001*
TS Thermode (ºC)	45.84 ± 2.02	45.04 ± 2.15	46.65 ± 1.52	<0.0001*
CS Thermode (ºC)	45.29 ± 1.97	44.65 ± 2.11	45.92 ± 1.60	<0.0001*

The same information in Table 5-1 can be found in Table 5-2 below, which displays the data by sex. Based on sex, only PCS was significantly different between females and males, with females scoring higher (P = 0.022). Considering that clinically relevant PCS score is 30, the table indicates that there were high pain catastrophizing scores for both healthy females and males.

Table 5-2. Demographic information and descriptive statistics of participants by sex

Data for all 106 participants, and for females and males are shown. The p-values refer to statistical comparisons between females and males. Values shown include mean ± SD. *Significant at $\alpha = 0.05$ level based on Mann-Whitney U test.

Variable	Whole Group	Females	Males	*P*-Value (Females vs. Males)
Age (Years)	26.8 ± 5.3	26.4 ± 5.0	27.3 ± 5.5	0.31
Resilience	145.1 ± 15.6	143.6 ± 17.7	146.5 ± 13.5	0.68
PCS	12.2 ± 8.5	14.0 ± 8.0	10.5 ± 8.6	0.022*
CPM Effect (raw change)	-5.3 ± 18.8	-5.5 ± 20.0	-5.0 ± 17.9	0.93
CPM Effect (percent change)	-8.3 ± 34.9	-8.8 ± 35.6	-7.7 ± 34.6	0.87
TS1 Pain Intensity	53.1 ± 10.2	53.6 ± 10.2	52.7 ± 10.2	0.66
TS2 Pain Intensity	47.9 ± 18.2	48.0 ± 19.1	47.7 ± 17.6	0.93
TS3 Pain Intensity	52.0 ± 18.7	53.3 ± 18.5	50.9 ± 19.1	0.30
CS Pain Intensity (10s after CS onset)	60.3 ± 17.7	61.4 ± 17.8	59.3 ± 17.6	0.53
CS Pain Intensity (30s after CS onset)	43.9 ± 23.8	47.5 ± 23.9	40.6 ± 23.6	0.14
CS Pain Intensity (60s after CS onset)	42.6 ± 26.3	46.2 ± 25.4	39.3 ± 26.9	0.15
CS Unpleasantness (30s after CS onset)	40.2 ± 30.5	45.3 ± 32.4	35.5 ± 28.1	0.13
CS Salience (30s after CS onset)	44.5 ± 32.0	48.9 ± 33.8	40.4 ± 30.0	0.20
TS Thermode (ºC)	45.84 ± 2.02	46.05 ± 2.12	45.65 ± 1.93	0.19
CS Thermode (ºC)	45.29 ± 1.97	45.59 ± 1.94	45.01 ± 1.97	0.075

5.3 Changes in the Test Stimulus Pain Intensity Ratings

For the whole group, there was a significant reduction in TS pain during the CS with TS2 pain intensity ratings significantly lower than TS1 pain ratings ($P < 0.01$), while TS3 pain ratings were not significantly different from TS1 pain ratings ($P = 0.71$). Thus, there was an overall inhibitory CPM effect (Figure 5-2A). For the CPM subgroup, there was a significant reduction in TS pain with both TS2 and TS3 pain intensity ratings significantly lower than TS1 pain ratings ($P < 0.001$). For the no-CPM subgroup, there was a significant increase in TS pain with both TS2 and TS3 pain intensity ratings significantly higher than TS1 pain ratings ($P < 0.001$). These differences are depicted in Figure 5-2. The individual data in the figure also show individual variability, with some participants exhibiting an increase in TS pain and others showing a decrease in pain. Results of the Friedman test and post hoc analysis that assessed TS pain adaptation by comparing all three TS pain ratings showed that TS3 pain ratings were significantly higher than TS2 pain ratings at the whole group level ($P = 0.0047$). Thus, there was no consistent pattern of reduction in TS pain over time.

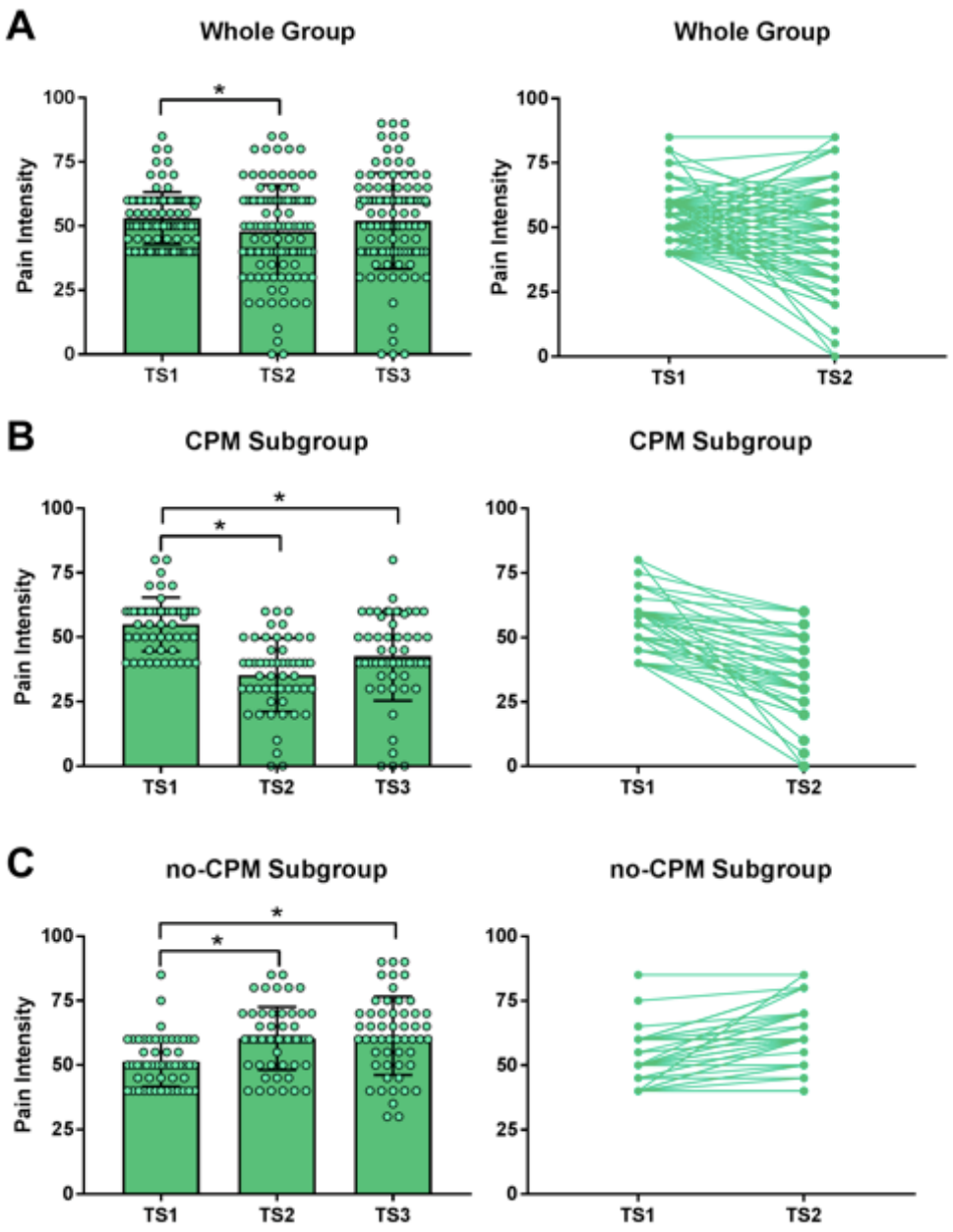

Figure 5-2. The change in TS pain intensity ratings due to the CS (A) In the whole group, only TS2 pain ratings were significantly lower than TS1 pain ratings. (B) In the CPM subgroup, both TS2 and TS3 pain ratings were significantly lower than TS1 pain ratings. (C) In the no-CPM subgroup, both TS2 and TS3 pain ratings were significantly higher than TS1 pain ratings. The right panels show changes in TS pain ratings before (TS1) to during (TS2) the CS. The CPM subgroup includes participants with pain inhibition, and the no-CPM subgroup includes participants with pain facilitation or no effect. *Significant at $\alpha = 0.05$ level based on Wilcoxon tests.

5.4 Changes in Conditioning Stimulus Pain Throughout its Application

In the whole group (Figure 5-3A), both CS pain intensity ratings at 30s and 60s after CS onset were significantly lower than CS pain at 10s (both $P < 0.0001$). This was also the case for females ($P < 0.001$; Figure 5-3B) and males ($P < 0.0001$; Figure 5-3C). The individual points in Figure 5-3 show that females and males exhibited both increases and decreases in CS pain throughout the CS application. The change in TS and CS pain ratings were correlated at the whole group level ($rho = 0.37$, $P = 0.0001$).

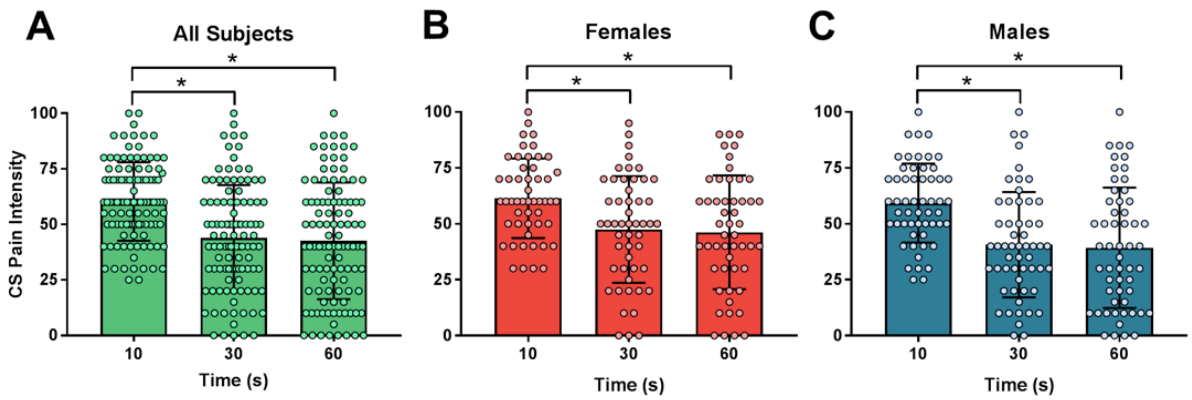

Figure 5-3. The CS pain intensity ratings reduced over time CS pain intensity at 30s and 60s after CS onset were both significantly lower than at 10s for all subjects (A), females only (B), and males only (C). *Significant at $\alpha = 0.05$ based on Friedman and Dunn's post hoc tests, or ANOVA and post hoc Tukey test.

5.5 Regression Models

We created regression models to understand the role of both personal and CS attributes on the CPM effect. As a recap, the multiple linear regression models consisted of the CPM effect percent change as the response variable, and the predictors were sex, resilience, CS pain unpleasantness and salience, and an interaction between sex and resilience. For the whole group, the regression model shown in Table 5-3 explained 17.9% of the variance ($R^2 = 0.179$, adjusted $R^2 = 0.138$) in the CPM effect ($F = 4.35$, $P < 0.01$). For the CPM subgroup regression model shown in Table 5-4, CS unpleasantness was positively associated with the CPM effect ($\beta = 0.65$, $P = 0.027$). Although this model was not overall significant ($F = 1.48$, $P = 0.21$), it explained 13.6% of the variance ($R^2 = 0.136$, adjusted $R^2 = 0.0443$) in the CPM effect. For the no-CPM subgroup regression model shown in Table 5-5, although it was also not overall significant ($F = 1.71$, $P = 0.15$), it explained 15.4% of the variance ($R^2 = 0.154$, adjusted $R^2 = 0.0638$) in the CPM effect.

Table 5-3. Multiple linear regression model of factors that explain the CPM effect in the whole group

B denotes the unstandardized variable coefficient, and β denotes the standardized variable coefficient.

Predictor	B (Unstandardized)	Standard Error	β (Standardized)	t	P
Female Sex	2.04	61.4	0.029	0.033	0.97
Resilience	-0.15	0.26	-0.065	-0.55	0.58
CS Pain Unpleasantness	0.26	0.23	0.23	1.13	0.26
CS Salience	0.23	0.22	0.21	1.049	0.30
Interaction: Resilience x Female Sex	0.027	0.42	0.058	0.065	0.95

Table 5-4. Multiple linear regression model of factors that explain the CPM effect in the CPM subgroup, which only includes participants with pain inhibition

B denotes the unstandardized variable coefficient, and β denotes the standardized variable coefficient. *Significant at α = 0.05 level.

Predictor	B (Unstandardized)	Standard Error	β (Standardized)	t	P
Female Sex	8.010	63.63	0.17	0.13	0.90
Resilience	0.19	0.29	0.12	0.67	0.51
CS Pain Unpleasantness	0.53	0.23	0.65	2.29	0.027*
CS Salience	-0.33	0.22	-0.44	-1.52	0.14
Interaction: Resilience x Female Sex	-0.016	0.43	-0.052	-0.037	0.97

Table 5-5. Multiple linear regression model of factors that explain the CPM effect in the no-CPM subgroup, which only includes participants with pain facilitation or no effect

B denotes the unstandardized variable coefficient, and β denotes the standardized variable coefficient.

Predictor	B (Unstandardized)	Standard Error	β (Standardized)	t	P
Female Sex	79.61	53.81	1.90	1.48	0.15
Resilience	0.030	0.22	0.023	0.13	0.90
CS Pain Unpleasantness	0.14	0.21	0.20	0.70	0.49
CS Salience	0.064	0.20	0.091	0.31	0.76
Interaction: Resilience x Female Sex	-0.55	0.37	-1.94	-1.48	0.15

5.6 Relationship between Conditioned Pain Modulation Effect and Resilience

We conducted correlation analyses to understand how resilience, a personal attribute, relates to the CPM effect. As discussed in the literature review (see section 2.3.1.1), we can study both positive and negative personal characteristics. To show that resilience and pain catastrophizing are different concepts in our dataset, the two were correlated. While the two are correlated (rho = -0.2743, P = 0.0044), the association was negative. However, it should be noted that the resilience scores in our sample do not represent the full extent of the possible scores in the resilience scale: the lower end of the scale were not represented. Therefore, strong conclusions cannot be drawn to suggest that resilience and pain catastrophizing are similar or different concepts. Participant resilience ranged from 83-175. Correlations for the whole group did not show any significant relationships between the CPM effect and resilience neither for all subjects, nor females only and males only. These results are shown in Figure 5-4, where the lines are shown to highlight the trend. The two CPM subgroups (CPM and no-CPM subgroups) also did not reveal any significant relationships between the CPM effect and resilience for all subjects. However, further dividing these two subgroups based on sex, resulting in four subgroups, revealed a significant negative relationship between the CPM effect and resilience in the no-CPM subgroup for males (rho = -0.40, P = 0.036). The other subgroups did not exhibit significant relationships: CPM subgroup for females, CPM subgroup for males, and no-CPM subgroup for females. Based on the Fisher z-transformations, there was a significant difference between the correlations in the female CPM and male no-CPM subgroups (P = 0.043).

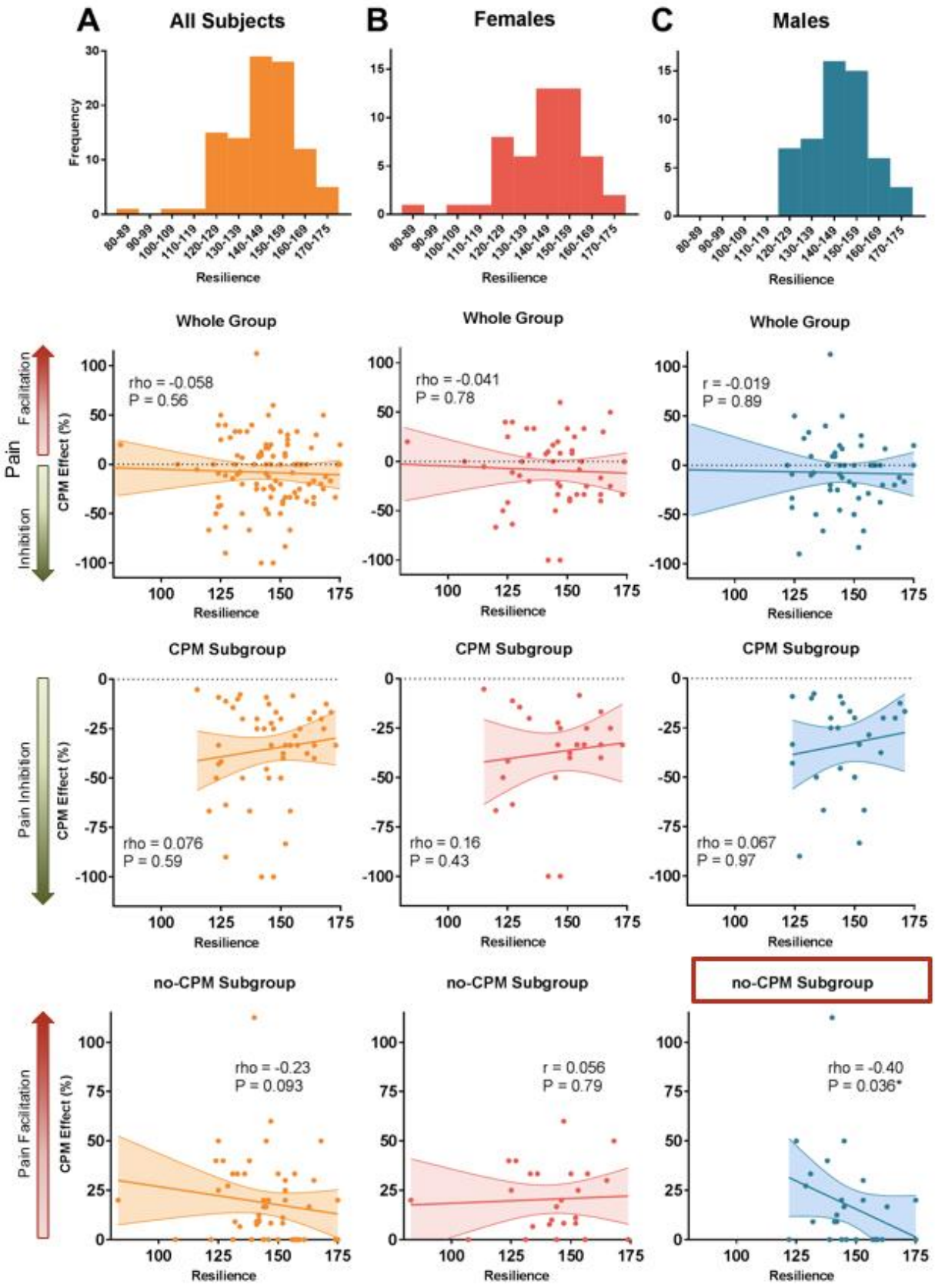
A
All Subjects
B
Females
C
Males
Frequency
Resilience
Whole Group
rho = -0.058
P = 0.56
rho = -0.041
P = 0.78
r = -0.019
P = 0.89
Pain
Facilitation
Inhibition
CPM Effect (%)
CPM Subgroup
rho = 0.076
P = 0.59
rho = 0.16
P = 0.43
rho = 0.067
P = 0.97
Pain Inhibition
no-CPM Subgroup
rho = -0.23
P = 0.093
r = 0.056
P = 0.79
rho = -0.40
P = 0.036*
Pain Facilitation

Figure 5-4. Relationship between resilience and the CPM effect Resilience data are shown for three groups of participants: (A) all subjects, (B) females only, and (C) males only. The distribution of resilience scores are shown by the histograms in the first row. The relationships between individual resilience scores and the CPM effect for the whole group, and for the CPM and no-CPM subgroups are shown in the second, third and fourth rows, respectively. A significant negative correlation (indicated by the red box) between the CPM effect and resilience was found in the male no-CPM subgroup ($P = 0.036$). The CPM subgroup includes participants with pain inhibition, and the no-CPM subgroup includes participants with pain facilitation or no change in pain. *Significant at $\alpha = 0.05$ level.

5.7 Relationship between Conditioned Pain Modulation Effect and Characteristics of the Conditioning Stimulus

We conducted correlation analyses to understand how CS pain unpleasantness and salience—CS attributes in this thesis—relate to the CPM effect. Both CS pain unpleasantness and salience ratings ranged widely from 0 to 100. For CS unpleasantness, correlations for the whole group showed significant positive relationships between the CPM effect and CS unpleasantness for all subjects (rho = 0.38, $P < 0.001$), females only (rho = 0.39, $P < 0.01$), and males only (rho = 0.40, $P < 0.01$). These results are shown in Figure 5-5, where the lines are shown to highlight trends. From the two CPM subgroups (CPM and no-CPM subgroups) for CS unpleasantness, a borderline significant positive relationship (rho = 0.27, $P = 0.049$) was found between the CPM effect and CS unpleasantness only in the CPM subgroup for all subjects. However, further dividing the two subgroups based on sex to create four subgroups revealed significant positive relationships between the CPM effect and CS unpleasantness in the CPM subgroup for males (rho = 0.40, $P = 0.038$) and in the no-CPM subgroup for females ($r = 0.45$, $P = 0.025$). The other subgroups did not exhibit significant relationships: CPM subgroup for females and no-CPM subgroup for males.

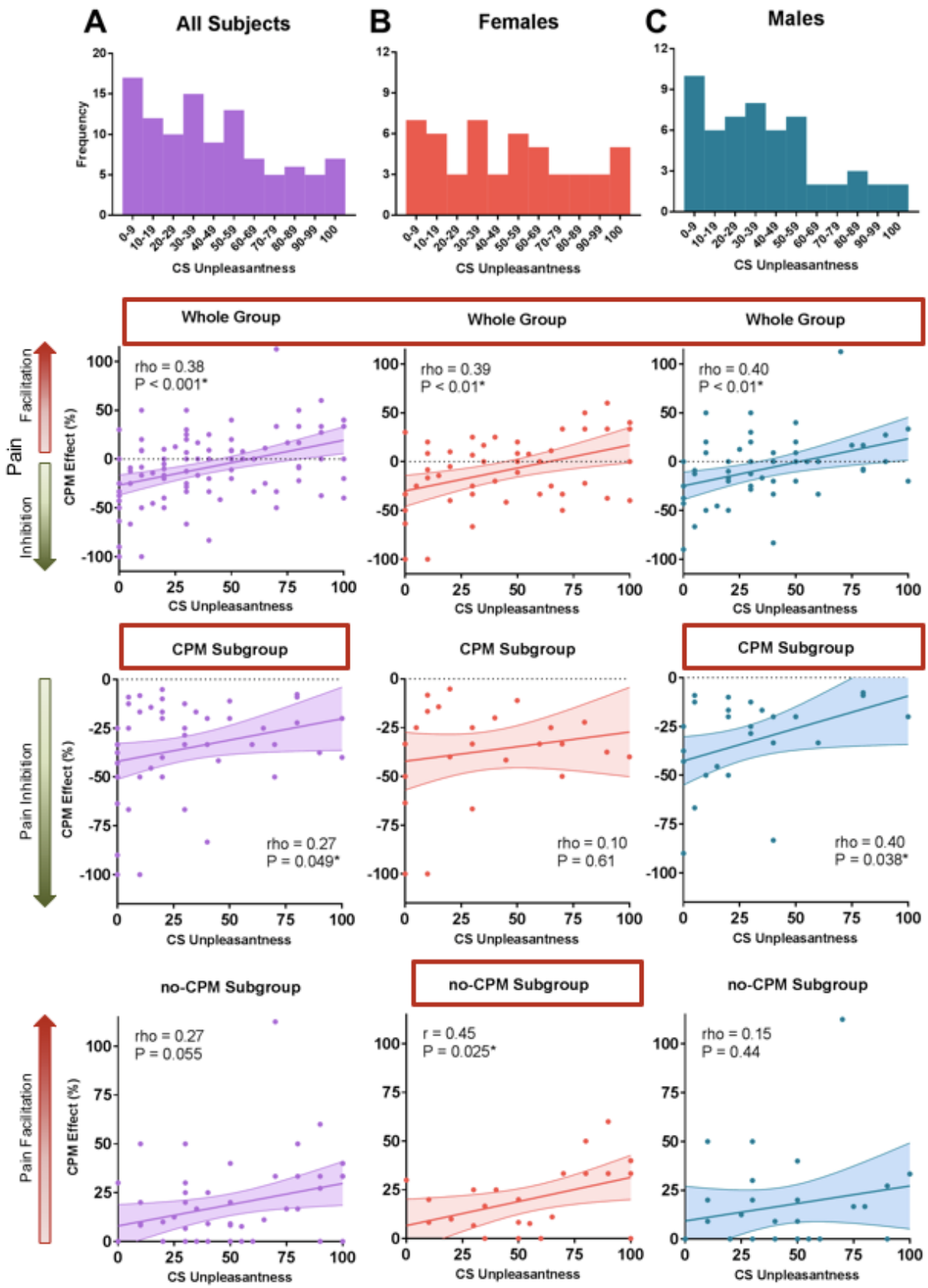
A
All Subjects
B
Females
C
Males
Frequency
CS Unpleasantness
Whole Group
rho = 0.38
P < 0.001*
rho = 0.39
P < 0.01*
rho = 0.40
P < 0.01*
Pain
Facilitation
Inhibition
CPM Effect (%)
CPM Subgroup
rho = 0.27
P = 0.049*
rho = 0.10
P = 0.61
rho = 0.40
P = 0.038*
Pain Inhibition
no-CPM Subgroup
rho = 0.27
P = 0.055
r = 0.45
P = 0.025*
rho = 0.15
P = 0.44
Pain Facilitation

Figure 5-5. Relationship between CS unpleasantness and the CPM effect CS unpleasantness data are shown for three groups of participants: (A) all subjects, (B) females only, and (C) males only. The distribution of CS unpleasantness ratings are shown by the histograms in the first row. The relationships between individual CS unpleasantness ratings and the CPM effect for the whole group, and for the CPM and no-CPM subgroups are shown in the second, third and fourth rows, respectively. Significant correlations (indicated by the red boxes) were found between the CPM effect and pain unpleasantness in all subjects for the whole group ($P < 0.001$), and a borderline significant correlation was found in all subjects for the CPM subgroup ($P = 0.049$). Significant correlations were also found between the CPM effect and pain unpleasantness in the female whole group ($P < 0.01$) and female no-CPM subgroup ($P = 0.025$), as well as in the male whole group ($P < 0.01$) and male CPM subgroup ($P = 0.038$). The CPM subgroup includes participants with pain inhibition, and the no-CPM subgroup includes participants with pain facilitation or no change in pain. *Significant at $\alpha = 0.05$ level.

For CS salience, correlations for the whole group exhibited significant positive relationships between the CPM effect and CS salience for all subjects (rho = 0.38, $P < 0.001$), females only (rho = 0.41, $P < 0.01$), and males only (rho = 0.37, $P < 0.01$). These results are shown in Figure 5-6. From the two CPM subgroups (CPM and no-CPM subgroups) for CS salience, a borderline significant positive relationship (rho = 0.28, $P = 0.045$) was found between the CPM effect and CS salience only in the no-CPM subgroup for all subjects. However, further dividing the two subgroups based on sex to create the four subgroups also revealed a borderline significant positive relationship between the CPM effect and CS salience in the no-CPM subgroup for females (rho = 0.40, $P = 0.048$). The other subgroups did not exhibit significant relationships: CPM subgroup for females, CPM subgroup for males, and no-CPM subgroup for males.

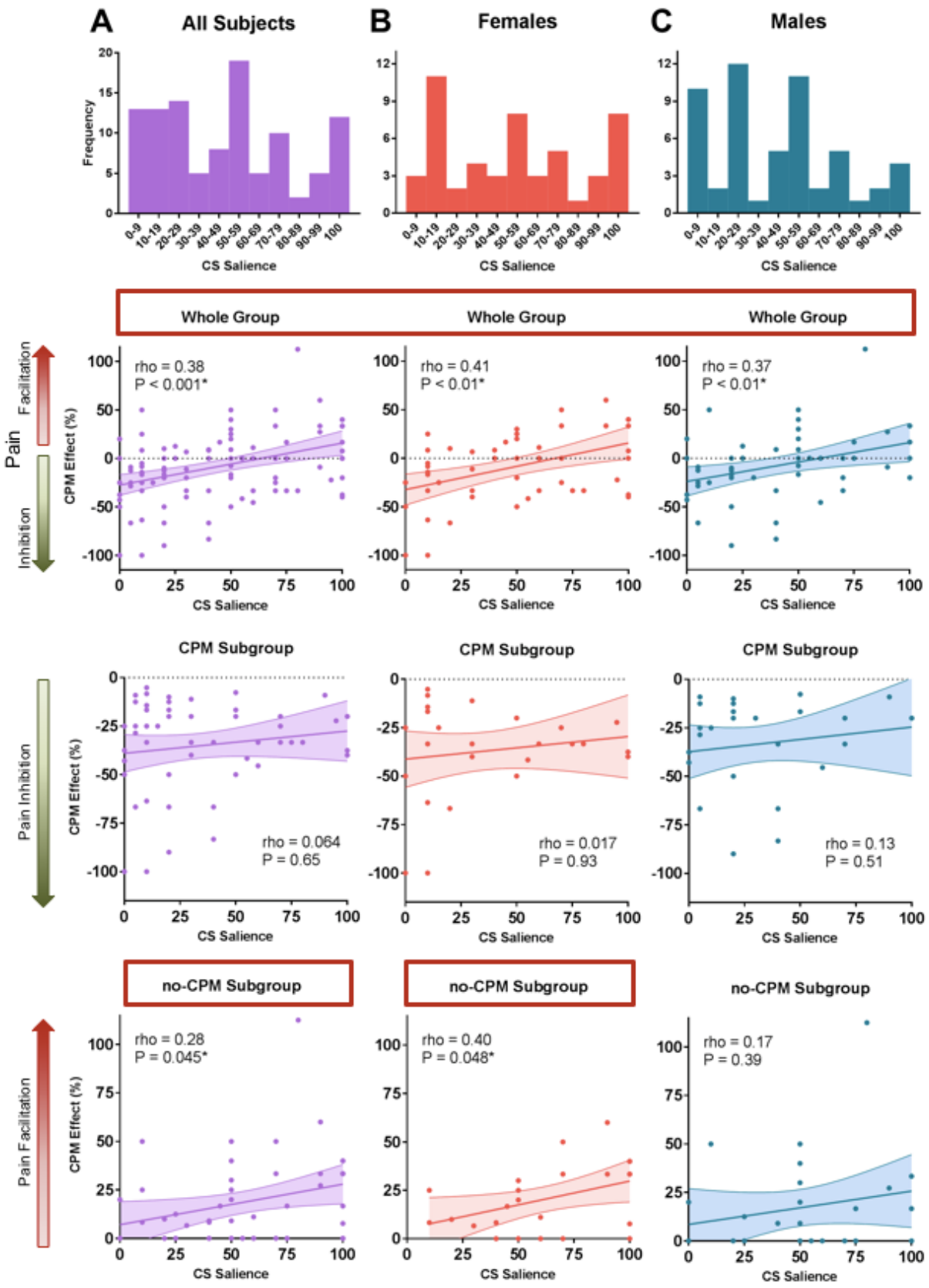
A
All Subjects
B
Females
C
Males
Frequency
CS Salience
Whole Group
Whole Group
Whole Group
Pain
Facilitation
Inhibition
CPM Effect (%)
rho = 0.38
P < 0.001*
rho = 0.41
P < 0.01*
rho = 0.37
P < 0.01*
CPM Subgroup
CPM Subgroup
CPM Subgroup
Pain Inhibition
rho = 0.064
P = 0.65
rho = 0.017
P = 0.93
rho = 0.13
P = 0.51
no-CPM Subgroup
no-CPM Subgroup
no-CPM Subgroup
Pain Facilitation
rho = 0.28
P = 0.045*
rho = 0.40
P = 0.048*
rho = 0.17
P = 0.39

Figure 5-6. Relationship between CS salience and the CPM effect CS salience data are shown for three groups of participants: (A) all subjects, (B) females only, and (C) males only. The distribution of CS salience ratings are shown by the histograms in the first row. The relationships between individual CS salience ratings and the CPM effect for the whole group, and for the CPM and no-CPM subgroups are shown in the second, third and fourth rows, respectively. Significant correlations (indicated by the red boxes) were found between the CPM effect and salience in all subjects for the whole group ($P < 0.001$), and a borderline significant correlation was found in all subjects for the no-CPM subgroup ($P = 0.045$). Significant correlations were also found between the CPM effect and salience in the female whole group ($P < 0.01$), and a borderline significant correlation was found in the female no-CPM subgroup ($P = 0.048$). There was also a significant correlation between the CPM effect and salience in the male whole group ($P < 0.01$). The CPM subgroup includes participants with pain inhibition, and the no-CPM subgroup includes participants with pain facilitation or no change in pain. *Significant at $\alpha = 0.05$ level.

Figure 5-7 shows a summary of the correlations.

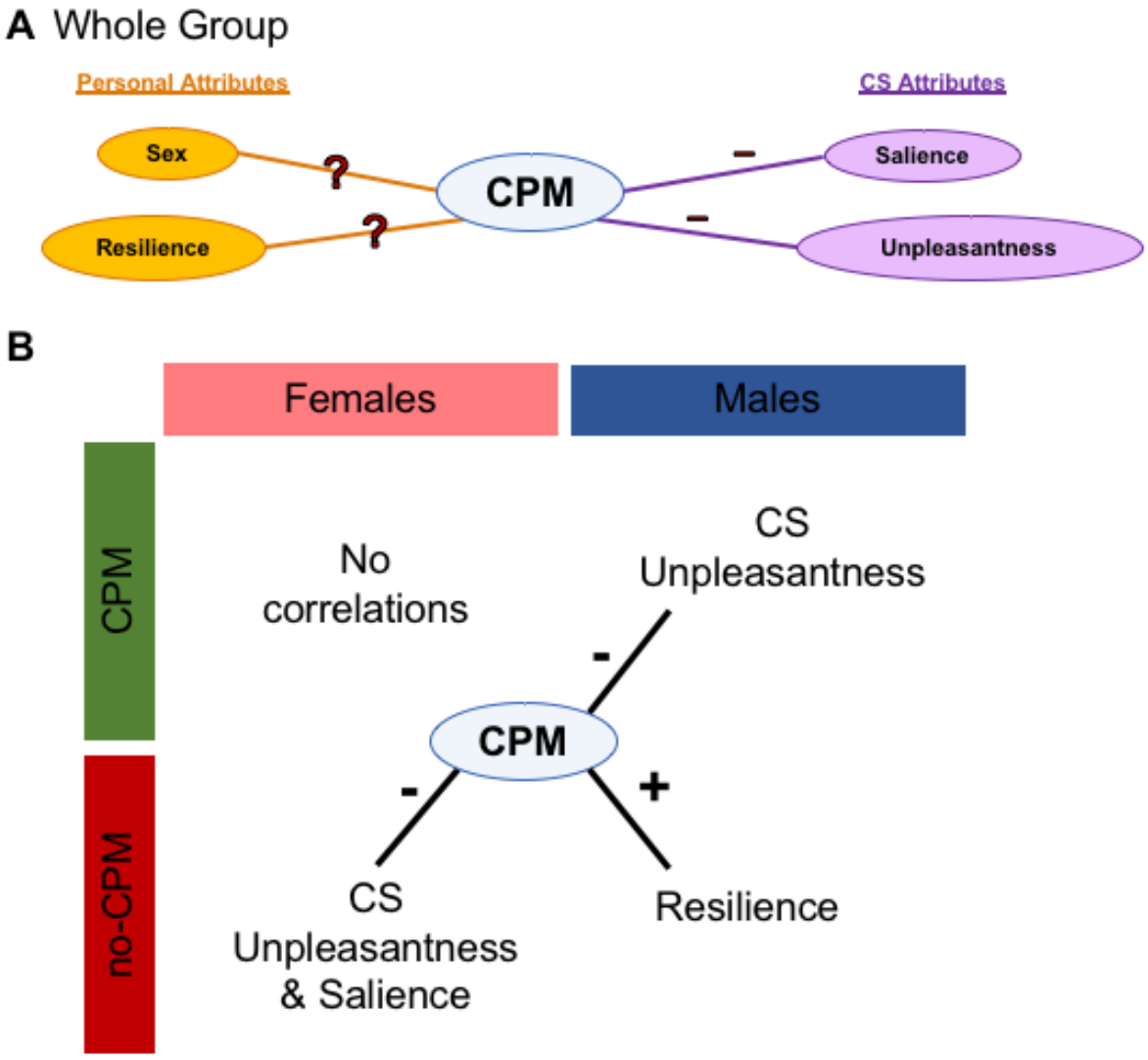

Figure 5-7. Summary of findings (A) In the whole group, sex and resilience did not directly impact the CPM effect. Lower CS unpleasantness and salience, however, were directly associated with greater CPM. (B) In the CPM subgroup, lower CS unpleasantness was associated with greater CPM for males. In the no-CPM subgroup, lower CS unpleasantness was associated with lower pain facilitation in females, lower CS salience had a positive trend with lower pain facilitation in females, and higher resilience was associated with lower pain facilitation in males.

Chapter 6
Discussion

6.1 Summary of Findings

In this thesis, CPM varied widely for individuals across a large cohort of healthy young adults, and personal attributes (sex and resilience) and CS attributes (pain unpleasantness and salience) contributed to the CPM effect. The impact of these attributes on the CPM effect also varied largely across individuals. The key findings were: 1) There was an overall inhibitory CPM effect, but half of the participants exhibited pain facilitation or no effect; 2) A regression model of data from all subjects revealed that sex, resilience, CS pain unpleasantness and CS salience together explained some of the variance in the CPM effect; 3) A regression model in the CPM subgroup showed that lower CS unpleasantness was associated with stronger CPM. Additional correlation analyses to investigate how the variables influenced the CPM effect revealed that a) for the whole group, lower CS unpleasantness and CS salience were associated with stronger CPM; b) For the CPM subgroup, lower CS unpleasantness was associated with stronger CPM in males; c) For the no-CPM subgroup, higher resilience was associated with decreased pain facilitation in males, lower CS unpleasantness was associated with decreased pain facilitation in females, and lower CS salience had a positive trend with decreased pain facilitation in females. An overview of the main findings of the study is shown in Figure 8 in section 5.7.

6.2 Revisiting the Hypotheses

As a recap of the hypotheses presented in section 3.3, it was hypothesized that 1) healthy individuals will experience a range of CPM responses that encompass pain inhibition to pain facilitation, 2) CPM and resilience are positively related, and 3) CPM and CS unpleasantness as well as CPM and CS salience are also both positively related. Evidence is clearly presented in support of the first hypothesis since all subjects, females, and males exhibited both pain inhibition, no effect, and pain facilitation with respect to their CPM responses. For the second hypothesis, no relationships were found between the CPM effect and resilience in the whole group. However, for males with no-CPM, a negative correlation was found between their CPM effect and resilience such that higher resilience was associated with decreased pain facilitation. While the correlation was negative, intuitively this is can be reasoned because higher resilience can be viewed as protective against pain facilitation. Finally, for the third hypothesis, positive

relationships were found between the CPM effect and both CS unpleasantness and salience in the whole group. This was also the case for CS unpleasantness in the CPM and no-CPM subgroups in males and females, respectively. Moreover, in the CPM subgroup regression model, CS unpleasantness was a significant predictor exhibiting a positive association with the CPM effect. Intuitively, these relationships can also be reasoned because unpleasantness and salience associated with pain can be viewed as risk factors towards weaker CPM.

6.3 Understanding the Variability in Conditioned Pain Modulation

The variability in CPM magnitudes was clearly exhibited across all participants, as well as separately for females and males. As reviewed in section 2.5.1 that discusses the numerous studies that exhibited a range of CPM responses (from pain inhibition to pain facilitation), CPM is known to be variable (Kennedy et al., 2016). However, the factors that impact this individual variability have not been studied extensively. Although the study focused on the sensory-discriminative and affective-motivational dimensions of pain, there is also the cognitive-evaluative dimension to consider in relation to the results. Thus, in terms of this cognitive-evaluative dimension, it could be that higher order processes, such as recalling past memories (pain-related or otherwise), contribute to the variability of CPM. Certain memories may contribute to pain inhibition while others may not. This is supported by the moderate pain catastrophizing scores in this study, which could indicate that the participants may have memories of past painful experiences. There is also the context that one can consider as another cognitive factor. Being in a calm/relaxing context versus a stress-provoking one likely has different effects on how the CPM paradigm is perceived and thus responded to. Stress can influence the magnitude of CPM (Quiton & Greenspan, 2007). If such higher order processing can influence CPM variability, then it can also influence the relationships between the CPM effect and personal and stimulus attributes. The advantage of studying the entire spectrum of CPM responses is that it allows for not only the pain inhibitory side of CPM to be studied, but also the pain facilitation side. This is more reflective of the population, as the variability reviewed in section 2.5.1 shows that pain facilitation in CPM is not only reserved for individuals with chronic pain, because healthy individuals can also experience facilitatory CPM. The large sample size (n = 106) supports this variability and the results found from this study.

There is also the discussion of why CPM variability may be observed in healthy individuals that currently lack chronic pain. Reduced CPM may be an indicator of a risk for developing future pain, such as after a healthy individual undergoes surgical operation (Granovsky & Yarnitsky, 2013). Individual variability in CPM may also arise due to the amount of pain evoked by the CS. Since greater CS pain intensity can result in stronger CPM (Nir et al., 2011), lower CS pain likely diminishes pain inhibition for some individuals. This is relevant for the participants in this thesis, because as shown in section 5.4, CS pain intensity ratings reduced over the course of the 100s CS application. This reduction was similarly observed for all subjects, females only, and males only. Despite this similarity, it has been previously shown by our lab that females experience greater heat pain habituation compared to males (Hashmi & Davis, 2009, 2010). It has also been previously shown that healthy individuals can habituate towards a CS (Bogdanov et al., 2015; Nahman-Averbuch et al., 2013a).

Despite the supporting evidence for the idea that higher CS pain is associated with stronger CPM, the results presented in this thesis show some contradiction. Significantly higher pain ratings were reported towards both the CS at 30s and 60s after CS onset in the no-CPM subgroup than the CPM subgroup (see Table 5-1). While the effect size may not be as great as previous studies investigating the relationship between CS pain and CPM, our effect size is still large (Cohen's $d = 0.52$). This result suggests that higher CS pain may actually result in lower CPM. Moreover, this inconsistency suggests that reductions in CS pain intensity ratings over the CS application may not have resulted in the anticipated effect that lower CS pain reduces CPM. The relationship between CS pain and CPM remains unclear and inconsistent (Pud et al., 2009). One concern associated with a CS that is perceived as very painful is that it may result in distraction by drawing attention away from the TS. The ramp rate of the TS that is concurrent with the CS can also distract the participant, compared to a stable temperature that is held without ramps. However, evidence suggest that the modulating effect of the CS is independent of distraction (Lautenbacher et al., 2007; Moont et al., 2010).

Variability in CPM may also arise due to TS pain intensity ratings, as the CPM and no-CPM subgroups exhibited differences in these ratings as well. As shown in Figure 5-2, while the CPM subgroup exhibited reduced TS pain during and beyond the CS, the no-CPM subgroup exhibited enhanced TS pain during and beyond the CS, despite the fact that these were both calibrated to individual subjects' Pain50. Moreover, Table 5-1 shows that the no-CPM subgroup reported

significantly higher TS2 and TS3 pain ratings than the CPM subgroup. Therefore, changes in TS pain intensity ratings may also characterize the CPM and no-CPM subgroups. Of note, since TS pain ratings can characterize these subgroups, it is possible that the entire CPM paradigm is not necessary to study CPM variability. However, only TS2 and TS3 pain ratings differentiated the subgroups, but not TS1 pain ratings. Further studies would help to identify whether individuals with stronger CPM are likely to experience pain habituation and those with weaker CPM are likely to experience pain sensitization.

As described in section 4.4.1, both the TS and CS thermodes were set to evoke Pain50, a pain intensity rating of 50/100. As discussed above, the TS and CS pain ratings were not similar between the CPM and no-CPM subgroups, and thus this goal of percept-matching may not have been fulfilled (this will be discussed in the limitations, in section 6.5). Of note, the no-CPM subgroup may have required higher TS and CS thermode temperatures to reach the Pain50 level, because both thermode temperatures were significantly higher in the no-CPM subgroup than in the CPM subgroup.

6.4 The Role of Different Conditioning Stimulus Attributes in Conditioned Pain Modulation

Since the relationship between CS pain and CPM is unclear, it is useful to also study other attributes of the CS. Therefore, in this thesis, instead of only examining CS pain intensity, we aimed to also examine CS unpleasantness and salience, as these attributes may have greater affect and attentional load on individuals. These CS attributes exhibited the opposite relationship with the CPM effect than the aforementioned relationships between CPM and CS pain/intensity. Specifically, for the whole group, greater CS pain unpleasantness and salience were associated with lower CPM (greater pain facilitation). Thus, the unpleasant and salient nature of a CS may diminish CPM and even prevent it, perhaps due to the individual being in an overall negative state of arousal. Exploring these other aspects of the CS could therefore help to better understand the role of the modulating stimulus in CPM. Thus, these findings also have implications in the consideration of setting up a CPM paradigm to collect multiple measures of the CS. In a CPM paradigm, although a cold water bath can be the most potent and reliable CS (Damien et al., 2018), using two thermodes—as was the case for this thesis—can arguably be more easily utilized for bedside testing. Since our two thermodes method does not require the bulky and

practical issues associated with a water bath, nor the longer inter-test times in waiting for a limb to return to room temperature, it would be convenient for future clinical studies.

6.4.1 The Role of Sex and Conditioned Pain Modulation Efficacy in the Relationship between Conditioning Stimulus Attributes and Conditioned Pain Modulation

While the whole group provided information on the relationship between CS attributes and the CPM effect, further insight was provided on these relationships by accounting for sex and CPM efficacy. CS pain unpleasantness appeared to be important for both females and males in relation to their CPM effect. That is, 1) for females with no-CPM, lower CS unpleasantness was associated with decreased pain facilitation, and 2) for males with CPM, lower CS unpleasantness was associated with stronger CPM. Therefore, it is important to note the value of incorporating sex in the correlations, despite it not playing a significant role in the regression models. Ruling out sex on the basis of insignificant results from the regression models would not have revealed the correlational relationships that account for individual differences (sex and CPM variability). Of note, although the results of the Fisher's r-to-z transformations showed a significant difference only for the CPM effect-resilience relationship between the female CPM and male no-CPM subgroups, this does not necessarily preclude other sex differences. Our correlations are still significant in some groups but not others, despite these correlations not being significantly different from each other. In terms of CS salience in females with no-CPM, lower CS salience had only a positive trend with reduced pain facilitation (borderline significant positive association). Therefore, the role of salience at the subgroup level is not as clear as in the whole group. For salience, bottom-up selection allows for identifying salient stimuli, and top-down selection can influence this via attentional set and load (Legrain et al., 2009). Thus, the method of self-report used for this study did not allow the two types of selections to be disentangled, and perhaps one type may be more relevant for understanding the role of sex and CPM efficacy in the relationship between the CPM effect and CS salience.

Considering the extant literature that CPM is stronger in males compared to females (Hermans et al., 2016), it is interesting that both females and males (in the no-CPM and CPM subgroups, respectively) exhibited a relationship between their respective CPM effects and CS unpleasantness. This could be explained by the fact that sex differences were not found in neither the CPM responses nor the CS unpleasantness ratings (see Table 5-2). However, for CS salience,

there was a positive trend between CS salience and the CPM effect in only females with no-CPM. Thus, in contrast to the existing literature, lower CS salience had a positive trend with reduced pain facilitation in females rather than in males. Further studies and analyses can shed light on sex differences in CPM and the relationship of these differences with other stimulus attributes.

6.5 The Role of Resilience in Conditioned Pain Modulation

Resilience can be viewed as having both trait and state qualities. This study measured resilience as a trait. However, resilience could also have some state-like aspects, for example due to varying adversity as described in this section. Furthermore, it is possible that resilience is modified by prior pain experiences. Another way to understand the trait/state qualities of resilience is that some amount of underlying resilience could emerge after an adverse experience. This activated resilience could then be primed for future adverse experiences, including those related to pain.

The role of resilience in CPM is complex, as supported by the findings in this thesis. Resilience did not play a significant role in any of the regression models or whole group correlations. It was negatively related to the CPM effect only for males with no-CPM. Furthermore, the correlation in this male no-CPM subgroup was significantly different from the correlation in the female CPM subgroup, as determined by Fisher's r-to-z transformations. Thus, higher resilience may have protected against further pain amplification for males. Resilience encompasses a collection of positive personality characteristics (Wagnild & Young, 1993) (see section 2.3.1.1), thus it emphasizes the role of positive factors in the pain experience. This collection of characteristics could signify that certain personal traits encompassed by resilience may directly relate with CPM more strongly than the larger encompassing characteristic of resilience. These resilience-related characteristics are still valuable in understanding pain. For instance, in one study of females undergoing primary breast cancer surgery, psychological robustness—encompassing low psychological vulnerability and high psychological resilience—served as a predictor of postsurgical pain chronicity (Bruce et al., 2014). In those with knee osteoarthritis, optimism moderated the association between resilience and CPM, such that greater resilience was associated with stronger CPM only in individuals with low optimism (Thompson et al., 2018). Similarly, the role of resilience in CPM may be indirect for healthy individuals. Nevertheless, it

may be important to understand resilience in healthy individuals first in order to then understand its role in chronic pain. Yet, resilience is not as well studied in acute experimental pain as it is in chronic pain.

6.6 Personalized Pain Therapy

Resilience is becoming more recognized in predicting health outcomes in adults (Hemington et al., 2017). Many of the positive factors encompassed by resilience are targets for pain treatment, such as positive emotions (Ong et al., 2015). Trait resilience may be associated with experiencing positive emotions during challenges like severe pain and may help draw on resources to overcome and recover from such challenges. Thus, addressing positive emotions as part of pain interventions can be valuable, especially because those with chronic pain—such as in fibromyalgia—experience deficits in positive affect and in the ability to sustain that during painful periods (Finan et al., 2009; Ong et al., 2015). Modifications to cognitive behavioural therapy (CBT) can be used to help individuals build positive qualities so as to build resilience (Padesky & Mooney, 2012). These modifications involve four steps to resilience: searching for strengths, constructing a personal model of resilience for each individual, applying the model to difficult areas of life that are in need of resilience, and practicing resilience. Similarly, acceptance and commitment therapy has shown to promote resilience towards pain such that the outcome of the therapy can be pain reduction (Udell et al., 2018). The findings presented in this thesis suggest that understanding individual relationships between the CPM effect and resilience may help to select the most optimal treatments by identifying individuals who would benefit most from targeting positive traits like resilience. For instance, there are examples in the literature whereby behavioural measures (like CPM) were used to identify individuals who were more likely to benefit from improvements to their pain inhibition (Yarnitsky et al., 2012). If certain individuals are more likely to benefit from improvements to pain inhibition, then they may be suitable candidates for developing positive qualities like resilience.

Similarly, there is also value in understanding the role of pain unpleasantness in the CPM effect, so as to identify individuals who would also benefit most from improvements in pain inhibition. Although we measured pain unpleasantness as it relates to the CS, the overall affective dimension of pain may be a therapeutic target to reduce perceived pain unpleasantness (Hemington et al., 2017). Meditation is one method of altering pain unpleasantness, which was

investigated in a study with both novice and long-term meditation practitioners (Perlman et al., 2010). Both groups of individuals received noxious thermal stimulation during two different types of meditation, focused attention and open monitoring. During open monitoring meditation, long-term meditators experienced reduced pain unpleasantness compared to novices. As reviewed in section 2.4.2, hypnosis can also be used to alter unpleasantness. For instance in healthy participants, hypnotic suggestions towards pain unpleasantness of a water bath successfully modulated pain unpleasantness (Rainville et al., 2005). Furthermore, odor (Villemure et al., 2003) and visual stimuli (Loggia et al., 2008) can also modulate pain unpleasantness. CBT can also reduce pain unpleasantness, without impacting pain intensity (Salomons et al., 2014). Therefore, an understanding of specific individual relationships between the CPM effect and various pain-relevant attributes, like unpleasantness and salience, may provide insight into which individuals could benefit most from these interventions.

6.7 Limitations

There are some limitations to consider for this study.

1) This study only included healthy individuals. Therefore, the results may not be generalizable to chronic pain populations. It is important to note that the results presented in this thesis can serve as a starting point for understanding healthy individuals prior to them developing chronic pain. This can be valuable because in order to understand chronic pain and the transition from an acute or subacute pain state to a chronic one, researchers and clinicians may need to first characterize pain-free individuals. This may then help to understand the risk factors that increase the chance for developing pain down the line.

2) As reviewed in section 2.3.1.1, resilience is a collection of positive personality factors. In this thesis, resilience was measured using only the Resilience Scale (Wagnild & Young, 1993), and no other positive factors like perseverance and determination were measured. Therefore, although resilience encompasses multiple positive traits, measuring these other factors separately may have added value in understanding acute experimental pain, and the specificity and sensitivity to pain.

3) For the CPM paradigm used in this thesis, pain unpleasantness and salience were reported towards the CS. This may have served as a distraction, taking attention away from reporting

pain towards the TS that was concurrent with the CS. Nevertheless, pain inhibition was observed for the whole group and for the CPM subgroup. Perhaps this pain inhibitory effect may have been greater or smaller without reporting CS unpleasantness and salience. Compared to other studies that have presented a spectrum of CPM magnitudes, this thesis includes a large sample size.

4) As part of the familiarization paradigm, the aim was to determine the temperature to evoke a pain intensity rating of 50/100 (i.e., Pain50). However, Pain50 determined during familiarization included pain ratings ranging from 40/100 to 60/100, thus providing room for some variability in the percept-matched thermode temperatures.

5) The thermode temperatures were aimed to produce a perceptually-matched pain intensity rating of Pain50 across all participants. Although this was incorporated in the familiarization part of the methods, Table 5-1 shows that CS pain at 30s and 60s after CS onset were significantly higher in the no-CPM subgroup than the CPM subgroup. Thus, although the aim was to achieve percept-matched pain intensity ratings across all participants by setting the thermodes to Pain50, differences in CS pain ratings were still found when the CPM and no-CPM subgroups were compared.

6) Since changes in the TS and CS pain ratings were correlated at the whole group level, the overall inhibitory CPM effect presented in this thesis could at least partially be due to adaptation. Nevertheless, TS pain ratings did not overall reduce over time as supported by the results of the Friedman test that was conducted to assess TS pain adaptation.

7) Since hormones can play a role in the pain experience, grouping females who take oral contraceptives and those who do not could present a confound. Therefore, future studies could consider subgroups of females and compare these subgroups. Also to be considered is the menstrual cycle by studying subgroups of females who are at different stages of their cycle.

6.8 Conclusions

In conclusion, variability was found in CPM. Personal characteristics—sex and resilience—and characteristics of the CS—pain unpleasantness and salience—can impact the CPM effect, and

the variability in CPM can also play a role in this. The findings in this thesis can be useful in selecting appropriate current and future pain therapies that target resilience, pain unpleasantness, and salience as part of pain management.

6.9 Future Directions

Only psychophysical data were analyzed for this thesis. Therefore, one possible future direction would be to investigate the neural correlates of the behavioural measures from this study. Our group, for instance, investigated brain connectivity and its relationship with resilience in both healthy individuals and those with chronic pain (Hemington et al., 2018). Furthermore, only data from healthy individuals were used in this thesis. Therefore, these relationships can also be studied in different chronic pain populations and compared with healthy individuals. The behavioural measures collected and analyzed for this study can also be studied longitudinally to understand their dynamics. For instance, a lack of significant correlation at the time of data collection may not be reflective of correlations based on data collected at a different time point. Similarly, these behavioural data can be analyzed before and after surgical operations, to identify predictors of the risk in developing future pain. The data can also be analyzed before and after pain treatment in those with chronic pain, to determine baseline factors that can be used to identify individuals who would benefit most from pain treatment.

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