Investigating Mindfulness and Clinical hypnosis for Pain-Related Conditions Using Heart Rate Variability as a Marker of Vagal Heart Rate Modulation: Report of Three Randomized Trials

A Dissertation Submitted to the Faculty of Graduate Studies in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

Graduate Program in Clinical Psychology

York University

Toronto, Ontario

April 2021

Abstract

Chronic and post-surgical pain conditions are highly prevalent and often treated sub-optimally. Clinical pain is understood to originate from inflammatory and neurological dysfunction, and research literature has amassed to shed light on stress-related sympathetic nervous system hyper-activity as a critical component of the etiology and maintenance of pain. Conversely, the role of the parasympathetic vagus nerve has been less studied, and appears to hold promise as a therapeutic pathway that can be leveraged through administration of behavioral medicine treatments. The present dissertation employed heart rate variability as a measure of vagal heart rate modulation in three randomized, controlled trials to investigate responses to mindfulness meditation and clinical hypnosis, in individuals with chronic and post-surgical pain. The overall pattern of results indicate that both mindfulness and hypnosis-based treatments have beneficial effects on vagal heart rate modulation in individuals with chronic and post-surgical pain, respectively. Future research is needed to determine the extent to which these effects may translate to clinical pain outcomes.

Acknowledgement

I would like to extend my deepest appreciation to my supervisor, Dr. Joel Katz, for his guidance, mentorship, and generosity throughout my years at York University. His uncanny ability to encourage precision and attention-to-detail in my work, while also embracing curiosity and humor, were crucial parts of our relationship that I continue to treasure. I am proud to be able to say I had his tutelage during my formative years as a scientist-practitioner. I would like to warmly thank my committee member, Dr. Aliza Weinrib. Her commitment to the research and practice of clinical health psychology is contagious and provided fertile ground for my personal and professional growth throughout my doctoral degree. I am also honored to have had Dr. Hance Clarke and Dr. Paul Ritvo as advisors; I was inspired by their willingness to put me in positions to succeed. I also want to thank Dr. Sam Fashler for warmly extending me guidance and support throughout graduate school. I am very fortunate to have had the opportunity to learn from and work with these five incredible people.

I want to extend thanks, appreciation, and love to my mother and father. Each of them had their own way of supporting my triumphs, and being supportive in ways that deserve boundless gratitude. I am also thankful to have had my best friend, Ansaar Mohamed, for being an endless source of laughter, joy, and perspective throughout these hard-working years.

Finally, I want to thank all of the people I worked with at York University, including student volunteers that assisted in my research projects, my Clinical Psychology program cohort, and all of the faculty, staff, and fellow graduate students in the Department of Psychology and School of Kinesiology and Health Science that facilitated my process of professional and personal growth. I have grown considerably over my York University career and feel that I am becoming the person I have always wanted to become in ways that continue to inspire me.

TABLE OF CONTENTS

Chapter I. General Introduction & Background

Pain is a natural and purposeful stressor. Sensations of pain are a sensory-discriminative means of perceiving potential physical harm and actual injury or disease states in one's body that incorporate cognitive, emotional, motivational, and social information (Auvray, Myin, & Spence, 2010; Williams & Craig, 2016). The experience of pain usually triggers a stress reaction, commonly known as the sympathetic "fight-or-flight" response, which serves to energize the body to act vigilantly and quickly to mitigate damage. After the painful stimuli subside, one's physiological state is expected to return to baseline through parasympathetic recovery processes that also initiate healing from injury (Berntson, Quigley, & Lozano, 2007; Butler & Moseley, 2003). Although sympathetic responses and parasympathetic recovery processes are vital to the adaptive short-term response to pain, when persistent pain is the product of serious injuries, major surgeries, or underlying diseases, the relationship between pain and stress becomes maladaptive. Psychophysiological research in the last decade has consistently shown that people with chronic pain disorders have significantly lower heart rate variability (HRV) than people without chronic pain, a negative indicator of the body's capacity to regulate stress and pain (Barakat et al., 2012; Tracy et al., 2016). To stimulate advances in pain management, investigators have called for research on behavioral medicine treatments that can enhance HRV for the purposes of pain and stress relief.

The present dissertation reports a series of randomized trials that examined HRV during and after providing behavioral medicine treatments to people with chronic and post-surgical pain. In the literature review, pain is defined, and the pathophysiology of pain disorders is described. The following sections provide an overview of the comorbidity of pain disorders and psychopathologies, the relationship between psychopathologies and HRV, and the interactions between acute and chronic pain and the autonomic nervous system. The dissertation culminates

in three studies that investigated the following behavioral medicine treatments for their effects on HRV in people with chronic and post-surgical pain: (1) audio-instructed mindful breathing, (2) smart-phone assisted mindful breathing, and a peri-operative clinical hypnosis intervention.

Pain: Definition, Etiology, and Pathophysiology

Definition of Pain. According to the International Association for the Study of Pain (IASP), pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Other investigators have suggested revision to IASP's definition emphasizing the importance of emotional, cognitive, and social components of pain (Williams & Craig, 2016). These definitions wisely orient us to the fact that pain is not simply a product of linear sensory signaling systems from the periphery to the brain. Rather, it is imperative to understand pain as a dynamic interaction of ascending and descending inputs within the peripheral and central nervous systems, respectively (Melzack & Katz, 2013). Accordingly, a multitude of biopsychosocial factors have facilitatory or inhibitory effects on subjective pain perception. Knowledge of the modulating role of psychosocial factors has clarified the etiology of pain that is present without detectable physical damage or medical illness (Beecher, 1946; van Wilgen & Keizer, 2012). Understanding the multi-dimensional nature of pain helps explain why pain disorders present such a complex clinical challenge.

Pain has many properties and is generally classified into nociceptive, inflammatory, and neuropathic categories (Woolf, 2010). Nociceptive pain is an early-detection protective system that warns of bodily contact with noxious or damaging stimuli so that action can be taken to reduce contact with these stimuli and preserve bodily integrity. In cases of bodily damage, pain is in part a product of inflammation; an immune system biochemical process that repairs damage to tissues and nerves and heightens pain sensitivity at the location of the damage (Linley, Rose,

Ooi, & Gamper, 2010). Most inflammatory pain is adaptive as it acts to prevent further damage by discouraging physical contact and movement of damaged areas such as sprained muscles and joints or wounds from surgical procedures, enabling them to heal through the body's regenerative mechanisms with minimal strain (Butler & Moseley, 2003; Kidd & Urban, 2001). Neuropathic pain is a maladaptive product of malfunctions in the neural frameworks that govern pain processing. Although pain neuropathies may originate from tissue damage or inflammation, neuropathic pain can also develop and persist entirely due to diseases of the central and peripheral nervous systems in the absence of detectable physiological damage (Moulin et al., 2014).

The Biopsychosocial Determinants of Pain. Pain is generally caused by two types of stimuli: (1) physical stimuli in contact externally to the body and processed by peripheral and central neural pathways and perceived to be harmful or damaging, or (2) by internal somatic conditions of bones, tissues, and nerves that are in the process of healing or in a state of disrepair or dysfunction (Melzack & Katz, 2013; Moseley & Butler, 2015; Woolf, 2010). An integrated system of neural pathways in the periphery, spinal cord, and brain integrates sensory-discriminative and affective-motivational inputs to produce pain. This requires the synthesis of information related to the location, intensity, duration, and haptic quality of the pain, as well as the individual's cognitive-emotional state and history (Melzack & Katz, 2013; Moseley & Butler, 2015; Woolf, 2010). During an acute painful event, nociceptors transduce the energy signaled by a noxious stimulus into nerve impulses which are propagated along primary afferent neurons with cell bodies in the dorsal root ganglion (DRG) of the spinal cord. From there, the impulses are transmitted through the contralateral spinothalamic tract to the thalamus, which relays the nociceptive information to multiple brain regions (Butler & Moseley, 2013).

In the case of tissue damage, immune cells initiate inflammation and release biochemical mediators, including the neurotrophin nerve growth factor, the cytokine Tumour necrosis factor (TNF) Fα, the interleukins IL-1ß and IL-6, and prostaglandin E2 (Linley et al., 2010) that bind to nociceptors at the site of injury in the periphery. Increased blood circulation to the damaged area causes expansion of surrounding tissue leading to mechanical pressure on nerve cells. The purpose of this inflammatory response is to protect tissue from infection and to initiate healing, with one byproduct being the sensitization of peripheral nociceptors and DRG cell bodies (Sommer & Kress, 2004). Whether or not neural inputs are perceived to be painful is determined by patterns of activity in brain regions including the thalamus, primary and secondary somatosensory cortices, basal ganglia, insula, anterior cingulate cortex (ACC), amygdala, prefrontal cortex, and cerebellum (Apkarian et al. 2005).

According to the neuromatrix theory, pain is represented in the brain as an individual-specific neural firing pattern that assigns an anatomical reference to pain within a neurologically rendered and continuous virtual body map termed the "body-self neuromatrix" (Melzack, 2001). This genetically determined architecture of the neuromatrix arises from the dynamic functional connectivity between the thalamus, limbic system, and cortex, and thereby able to synthesize and be shaped by sensory-motor, emotional, and cognitive inputs throughout the lifespan. This framework accounts for the fact that pain influences cognitive-emotional processes and can also be influenced by them (Turk & Monarch, 2002). Neuroscientific research supports the role of emotion-related brain regions, the insula and the ACC, in modulating the affective-motivational components of pain (Ostrowsky et al., 2002; Rainville et al, 1997). Accordingly, pain elicits emotional arousal and hinders cognitive function (Bushnell, Čeko, & Low, 2013). Conversely, pain can be amplified by distressing emotional states (Wiech & Tracey, 2009) or empathy

towards another individual in pain (Lamm, Decety, & Singer, 2011; Ochsner et al., 2008), whereas positive emotions can alleviate pain (Zautra, Johnson, & Davis, 2005). Moreover, when pain is attended to with mindfulness and acceptance (Day et al., 2014), both pain intensity and unpleasantness can be reduced (Perlman et al., 2010; Zeidan et al., 2012). In the pathophysiology of pain, an individual's personal history with pain and related diseases (Katz & Seltzer, 2009), anxiety and mood disorders (Asmundson & Katz, 2009; Bair, Robinson, Katon, & Kroenke, 2003), and trauma (Otis, Keane, & Kerns, 2003) are leading risk factors for the development of chronic pain disorders. This body of evidence aligns with neuroimaging research that has observed changes to emotion-related neural circuitry (Hashmi et al., 2013) and deficits in reward pathways in the brain (Garland et al., 2013; Navratilova et al., 2016) to accompany the development of chronic pain. The extensive evidence of the relationship between pain and various forms of emotional distress points to a critical role of stress physiology in the onset and persistence of chronic pain.

Pain Disorders: Definition and Etiology. When pain persists due to illness or past the expected period of healing from an injury or surgery, repeated noxious stimulation of sensory nerves over time causes changes in how pain signals are processed, leading to a sensitized, pathophysiological state of the nervous system that heightens the perception of pain. Chronic pain is usually diagnosed when pain has been experienced nearly everyday for more than 12 weeks (Treede et al, 2015). Injury-induced acute pain may transition to chronic pain if the injury fails to heal or the pain is poorly treated, as the continuous nerve discharge through pain processing pathways becomes entrenched via neuroplastic changes (Melzack & Katz, 2013; Treede et al, 2015). Neural dysfunction in nociceptive pathways may occur at the peripheral location of tissue damage or centrally within the spinal cord and brain. According to IASP,

peripheral sensitization refers to increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields. Central sensitization reflects increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input (Treede et al, 2008; Woolf, 2010). Chronic pain is not only characterized by neuroplastic changes in nociceptive pathways; systemic changes can also be observed in immune, endocrine, and autonomic stress responses (Chapman, Tuckett, & Song, 2008). The relationship between pain disorders and autonomic stress dysregulation is evidenced in many of the aforementioned causal and correlated risk factors for chronic pain, including forms of anxious, depressive, and traumatic distress (Asmundson & Katz, 2009; Häuser, 2013; Katz & Seltzer, 2009; McLean, Clauw, Abelson, & al., 2005).

The causal role of physiological stress dysregulation in pain pathologies is not easily discernible given how closely linked pain and stress are on a temporal scale. Experimental (Kuehl et al, 2010; Rivat et al., 2010) and prospective studies (Slade et al., 2007) have found evidence for the relationship between psychological distress and lowered pain thresholds. Anticipatory anxiety about pain is associated with higher pain sensitivities (Hirsh, George, Bialosky, & Robinson, 2008). These findings suggest that the pre-existing substrates of stress in the nervous system may contribute to alterations in ascending and descending pain processing pathways. One possibility is that if persistent and excessive stress responses have made the nervous system highly reactive and sensitive to perceptions of threat, then pain signals may be amplified and more readily processed in the CNS. This hypothesis is aligned with a body of research showing that a prior history of anxiety, physical and psychological trauma, and depression are significantly predictive of onset of chronic pain later in life (Häuser, 2013; McClean, Clauw, Abelson et al, 2005; Nahit et al., 2003). A common thread between these

predispositions and chronic pain is that they are both associated with a compromised autonomic nervous system (ANS) responsible for regulating the stress response (Brosschot, Gerin, & Thayer, 2006; Kemp & Quintana, 2013). To bridge the gap between pain disorders and stress dysregulation, the next sections will provide an overview of how chronic pain is associated with various forms of psychopathology and a dysregulated ANS.

Comorbidity of Chronic Pain and Psychopathologies

Chronic pain is frequently associated with diagnosable psychopathology, including mood, anxiety, and post-traumatic stress disorders (PTSD) (Asmundson & Katz, 2009; Dersh, Polatin, & Gatchel, 2002). In terms of mood disorders, the development of depression as a consequence of chronic pain is understandable when considering that it can often mean living with perpetually aversive and emotionally draining pain symptoms, impairment and disability, secondary losses that occur across various domains (e.g. work and social relationships), and perceived lack of support from the medical system (Fishbain et al., 1997), all of which can adversely impact mood. A similar negative trajectory of mental illness may also partly explain the high rates of co-occurrence of chronic pain and anxiety disorders due to the perpetuation of anxiety symptoms such as excessive worry, avoidance of activities perceived as painful, and irritability due to the experience of pain. In a large scale study by the World Health Organization, Gureje et al. (2008) assessed 5,438 patients from 15 primary care sites and 14 countries. Of the 22% of patients who reported persistent pain for 6 months or longer, there was a 4-fold increase in associated depressive or anxiety disorders. However, this does not suggest an exclusively linear relationship in which chronic pain necessarily leads to the development of psychopathologies. The pattern of relationships between chronic pain and associated psychopathologies has also shown that predisposing psychological symptoms or disorders related to mood, anxiety, or trauma elevate the risk of developing chronic pain later in life (Häuser,

2013; McClean, Clauw, Abelson et al, 2005; Nahit et al., 2003). This evidence falls in line with the diathesis-stress model (Turk, 2002), which incorporates pre-existing maladaptive characteristics and coping tendencies with respect to stressors, including anxiety sensitivity, catastrophizing, learned helplessness, fear-avoidant tendencies, and poor self-efficacy. In the aftermath of traumatic injuries, pre-existing psychopathologies and/or characteristics can cause maladjustments such as fear of pain/re-injury, escape and avoidance behavior, and pain disability that are considered vulnerability factors for the transition from acute to chronic pain (Asmundson & Katz, 2009; Häuser, 2013; Katz & Seltzer, 2009; McLean et al., 2005).

Since the early 2000's, there has been increasing interest in the co-occurrence and common pathogenic mechanisms of chronic pain and PTSD (Asmundson, Coons, Taylor, & Katz, 2002; Sharp & Harvey, 2001). In this line of research, evidence-based explanatory models have been developed to explain the pattern of relations between comorbid chronic pain and PTSD. They include models that propose that chronic pain and trauma symptoms both maintain each other, and that pre-existing biological and psychological vulnerabilities cause maladjustments in coping with both pain and traumatic experiences rendering them more likely to progress to the syndromal stage. The Combined Shared Vulnerability and Mutual Maintenance Model combines both of these considerations (Katz, Page, Fashler, Rosenbloom & Asmundson, 2014; Rosenbloom, Khan, McCartney, & Katz, 2013). Biological vulnerabilities include an over-responsive startle reflex, sensitive hypothalamic-pituitary-adrenal axis, and concurrent disease or injury. Following a traumatic injury, stress-related factors including pain as a repetitive/intrusive stressor, fear of pain, pain catastrophizing, and poor self-efficacy may interact with posttraumatic stress symptoms such as re-experiencing, hyper-arousal, avoidance, and emotional numbing in a manner that reciprocally maintains both chronic pain and PTSD

(Turk, 2002). These potential links between pre-existing psychopathologies and chronic pain development reflect the need for ways to assess stress dysregulation of the nervous system to stimulate better understandings of predisposing, perpetuating, and protective factors for chronic pain.

Pain and Stress Regulation via the Autonomic Nervous System

Stress arousal and recovery processes are partly regulated by the ANS via two branches working synergistically upon target muscles and organs according to functional demands. The sympathetic nervous system (SNS) mobilizes the organism to react quickly in the presence of stressors. To facilitate this reaction, SNS activation diverts blood flow from the gastrointestinal tract towards the lungs and skeletal muscles for energy and vigor (Jänig & McLachlan, 2013). In the aftermath of stressful circumstances, the restorative parasympathetic nervous system (PNS) facilitates rest and recovery functions such as digestion, relaxation, tissue regeneration, and anti-inflammatory processes (Robertson, Low, & Polinsky, 2011).

Sympathetic stress responses that accompany instances of pain serve to invigorate the body to mitigate and prevent further pain. Invigorating functions such as the elevation of heart rate and blood pressure are adaptive as they promote blood circulation to muscles, tissues, glands, and organs to support energizing and protective-withdrawal functions needed to alleviate and prevent further pain. Fear-driven stress arousal, colloquially referred to as the "fight or flight" response, can sometimes produce a temporary reduction in pain sensitivity which serves a functional purpose so that pain does not impede the individual in confronting or escaping the threatening circumstances (Butler & Finn, 2009; Ford & Finn, 2008). This is known as stress-induced analgesia and it is mediated by descending inhibitory pain pathways from cerebral structures to the dorsal horn of the spinal cord (Bodnar, Kelly, Brutus, & Glusman, 1980). Once

pain and its source have been dealt with, recovery functions such as energy conservation and tissue regeneration are needed to recover to baseline and heal from any injuries.

Neural structures involved in pain processing and ANS-based stress regulation display functional connectivity in neuroimaging studies (Benarroch, 2001; Bruehl & Chung, 2004), reflecting close coupling between the two processes. As ANS regulation of stress arousal and recovery is implicated both during and after painful events, it is clinically relevant to investigate ANS indices in relation to pain disorders. This has led to investigations of the affective-motivational component of pain with the use of autonomic variables, such as heart rate and heart rate variability (Loggia, Juneau, & Bushnell, 2011; Möltner, Hölzl, & Strian, 1990).

Vagus Nerve Function and Pain Modulation. Given its role in cardiac stress recovery (Grossman & Taylor, 2007) and anti-inflammatory processes (Tracey, 2002) the vagus nerve serves as an important mediating structure for examining the relationship between pain and stress. The continuous and dynamic interplay between the SNS and PNS is salient in resting cardiac function by way of vagal-mediated respiratory sinus arrhythmia (RSA; Figure 1) (Neff et al., 2003). The biological basis for rhythmic cardio-respiratory synchrony is to calibrate cardiac output during inhalation and exhalation so that pulmonary gas exchange and blood circulation is optimized to decrease or accelerate according to the amount of oxygen available during these respiratory phases (Berntson et al., 2007; Yasuma & Hayano, 2004).

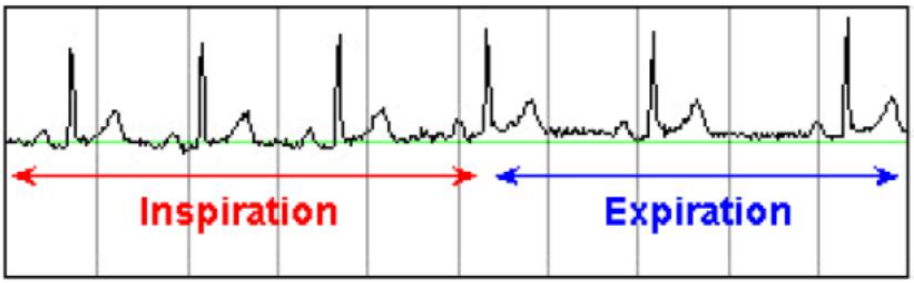


Figure 1. Respiratory Sinus Arrhythmia observed on an electrocardiograph. Image retrieved from the web ("Arrhythmia Reference Guide," 2015).

Heart Rate Variability Relations to Stress and Pain. At resting state, exhalation stimulates the ventral branch of the vagus nerve to slightly lower the heart rate (HR) by vagal-cholinergic inhibition of the sinoatrial (SA) node. Conversely, inhalation temporarily suppresses ventral vagal activity to enable SNS-mediated adrenergic activity on the SA node which slightly accelerates the HR. The ensuing heart rate variability (HRV) can be visualized on a resting electrocardiogram displaying slightly longer and shorter heartbeat intervals during exhalation and inhalation, respectively. Measures of HRV can be analyzed using the differences between successive heartbeat intervals and computing the variances in time-domain indices or summarizing the power in the high-frequency bandwidth using a Fourier transformation (Allen, Chambers, & Towers, 2007; Camm et al., 1996). The advantage in measuring HRV is that samples can be obtained in two ways: (1) HRV at resting state is an indirect estimate of parasympathetic activity (or vagal activity) used to index a variety of trait-like clinical characteristics (e.g. emotion dysregulation in psychological disorders), (2) HRV during experimental conditions assesses parasympathetic (vagal) withdrawal and recovery functioning as well as the relaxation response (Beauchaine, 2015; Beauchaine & Thayer, 2015; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). Elevated or increased HRV is considered a marker of robust ventral vagus function, and inferred as a positive indicator of an individual's stress regulatory capacity, adaptability, and recovery in response to intrinsic or extrinsic demands (McCraty & Shaffer, 2015; Shaffer, McCraty, & Zerr, 2014; Thayer et al., 2012).

A temporary reduction in ventral vagus nerve function is typically seen under stressful circumstances when the ANS reverts to a sustained period of sympathetic activity. In this case, differences in the time intervals between heartbeats are smaller, and the lower HRV metrics observed during this period reflect reduced vagal activity (Laborde et al, 2017). For example,

lower HRV is observed under conditions of anxiety (Jönsson, 2007) and worry (Brosschot, Van Dijk, & Thayer, 2007), increased mental workload (Nickel & Nachreiner, 2003), and post-traumatic distress (Minassian et al., 2014). This withdrawal of vagal activity is accompanied by increased activity of sympathetic nerve fibers on the SA node of the heart, with its excitatory impulses raising cardiac output to meet stressful demands. In the instance of an acute painful event, it is adaptive for the body to adjust the relative autonomic balance to a sympathetically-aroused state (e.g. elevated HR, lower HRV) to garner the physiological resources needed to act and prevent serious injury.

Once the pain has subsided, prolonged sympathetic arousal is unnecessary, and a gradual shift to parasympathetic recovery and resting state is expected (e.g. baseline HR, increased HRV). Nevertheless, the removal of stressful stimuli in the environment does not always coincide with a return to resting state. Physiological stress inevitably arises through worry, rumination, and distressing emotions such as fear, anxiety, and anger. These "perseverative stressors" are frequently related to past or anticipated stressors, and can linger at an unconscious level, creating a physiological undertone of stress arousal and allostatic load that leads to a gradual and sustained withdrawal of vagal cardiac control, quantified by reduced HRV (Ottaviani et al., 2016). Chronically lower HRV is a sign that the ANS is "sympathetically dominant", with persistent and excessive activation of the stress response that is less amenable to vagal-mediated parasympathetic recovery (Brosschot et al., 2006; Ottaviani et al., 2016). A series of research studies have established associations between lower HRV and a higher incidence of psychiatric (Beauchaine & Thayer, 2015) and medical conditions (Thayer et al, 2012).

Whereas pain is a common psychophysical stressor, chronic pain is a psychophysiological disorder. Evidence for acute and clinical pain's relationships to HRV have been observed in multiple studies. Firstly, HRV decreases amidst the experience of acute pain, as corroborated in many experimental studies (Bendixen, Terkelsen, Baad-Hansen, Cairns, & Svensson, 2012; Koenig, Jarczok, Ellis, Hillecke, & Thayer, 2014; Koenig, Jarczok, Ellis, et al., 2015; Pollatos, Füstös, & Critchley, 2012). In clinical settings, researchers have begun to examine the validity of HRV as a psychophysiological correlate of acute pain. The analgesia-nociception index is based on HRV as a continuous measure of parasympathetic tone under general anesthesia, and has been proposed as a parameter to assess the effectiveness of intraoperative and postoperative analgesia (Boselli, Bouvet, et al., 2013; Boselli, Daniela-Ionescu, et al., 2013; Ledowski et al., 2013; Turan et al., 2016). The utility of concurrent HRV assessment under conditions of resting state, experimental stress and pain induction, and self-regulatory psychological exercises (e.g. meditation, hypnosis) has opened possibilities to use HRV as a marker of pathophysiology and treatment progress. However, understanding the relationship between HRV and pain pathologies requires examining the patterns of ANS dysregulation observed in stress-related psychopathologies at a broader level.

Heart Rate Variability as a Marker of Stress-Related Psychopathology

The HRV literature provides evidence for the relationship between reduced parasympathetic activity and psychopathologies such as depressive and anxiety disorders. Vagal cardiac control (i.e. resting state HRV) assessment has revealed that individuals with major depressive disorder (MDD) exhibit lower HRV in comparison to controls. Additionally, individuals with comorbid MDD and generalized anxiety disorder (GAD) show even lower baseline HRV levels (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012). In terms of

anxiety disorders, a pattern of inflexible HRV has been observed in individuals with GAD, who tend to exhibit lower HRV with little change even across experimental stressor and relaxation conditions compared to controls (Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996). In a recent study, Pittig et al. (2013) compared HRV in individuals with panic disorder, social anxiety, obsessive-compulsive disorder, and GAD during a resting state and a meditative relaxation task. All conditions were associated with significantly lower HRV relative to controls at baseline and during the relaxation period, supporting the notion of chronically reduced and inflexible parasympathetic functioning in people with anxiety-related conditions (Pittig, Arch, Lam, & Craske, 2013). Another study measured resting HRV in patients of various psychiatric disorders (schizophrenia, bipolar disorder, PTSD, and MDD) and found all to exhibit significantly lower HRV measures compared to healthy controls, but no group HRV differences were observed between the psychiatric conditions (Moon, Lee, Kim, & Hwang, 2013). This pattern of low and inflexible HRV suggests a shared pathogenic mechanism of ANS-based stress dysregulation in psychopathologies.

Heart Rate Variability as a Stress Biomarker of Illnesses. Individual differences in magnitude of stress reactivity are considered to contribute to a range of chronic illnesses. In addition to magnitude, duration of stress reactivity also compromises ANS function. If the SNS remains active well past the expected response period an individual is dealing with a stressor, then the extended stress arousal can lead to detrimental effects (Berntson et al., 2004; Verkuil, Brosschot, de Beurs, & Thayer, 2009). The basis for these effects lies in the ability of human beings to psychologically represent past or anticipated stressors (e.g. rumination or worry), which elicit stress responses of varying magnitude and duration. Brosschot and colleagues (2006 & 2010) have proposed the 'perseverative cognition' hypothesis to explain the contribution of

psychological stress to the development of chronic disease. In the term 'perseverative cognitions' (PC), 'perseverative' refers to repetition, and the concept encapsulates anticipatory worry about a stressful event (future-oriented), and/or rumination after undergoing a stressful experience (past-oriented). Thus, a PC is defined as a thought process unit containing information about a stressor that either has occurred in the past, expected in the future, or is imagined. An individual prone to PCs experiences chronic activation of stress responses that would normally be activated amidst a stressful situation (e.g. running away from a predator), including elevated HR and reduced HRV (Brosschot et al., 2006; Brosschot et al., 2010; Verkuil et al., 2009). This has been supported by both short and long-term ambulatory monitoring studies investigating the cardiac stress response to worry and rumination (Brosschot & Thayer, 2003; Brosschot et al., 2007; Glynn, Christenfeld, & Gerin, 2002; Pieper, Brosschot, van der Leeden, & Thayer, 2007, 2010; Verkuil et al., 2009).

Distressing emotions typically have a more persistent, long-term cardiac activation effect. Naturally, parasympathetic activity is subdued in times of psychological stress in favor of sympathetic activity to generate physical and mental energy expenditure. However, there appears to be a cost associated with this if individuals who experience PCs remain in a stress arousal state as this impairs the capacity of the ANS to initiate parasympathetic recovery processes. According to the perseverative cognitions hypothesis, inefficient parasympathetic functioning and sympathetic overactivity leads to the depletion of physiological resources and leave the individual vulnerable to developing chronic illnesses such as hypertension, cardiac disease, and chronic pain (Brosschot et al., 2006; Brosschot et al., 2010; Verkuil et al., 2009).

Heart Rate Variability as a Clinical Biomarker of Chronic Pain

To understand the relationships between pain-related stress and HRV, it is necessary to consider some of the pain-related functions of the vagus nerve. More than 80% of vagal nerve fibers are afferent, and relay sensory information from the head, ears, neck, thorax, and abdomen

to the nucleus of the solitary tract (NTS) in the brain stem. Descending noxious inhibitory control pathways are also partly relayed by the NTS (Millan, 2002). Afferent vagal inputs at the NTS project to the amygdala, hypothalamus, and limbic systems, which comprise the neural circuity associated with emotional learning and responsivity (LeDoux, 2000). This neural connectivity illustrates a role for the vagus nerve in modulating the affective-motivational response to noxious visceral stimuli (De Couck, Nijs, & Gidron, 2014). Research has shown that compromised vagal nerve function is associated with inefficient integration of sensory information, leading to greater nociceptive processing and ineffective descending inhibitory pain modulation. Some evidence in support of this comes from animal models showing that a vagotomy not only reduces short-term HRV (Altimiras, Aissaoui, & Tort, 1995) but also leads to increases in the severity and duration of pain (Weissman-Fogel et al, 2008) and diminishes the anti-nociceptive effect of morphine (Randich et al, 1991). In clinical research, a large cross-sectional study of hospital patients has found individuals exhibiting significantly low resting state HRV to endorse higher pain-related disability and more frequent analgesic intake (Koenig, Jarczok, Fischer, & Thayer, 2015). Additionally, mean HRV was significantly higher in individuals reporting analgesic use that resulted in pain relief compared to ineffective analgesic use. These studies suggest that the experience of pain and analgesic drug effectiveness are linked to the stress regulatory capacity of the ANS.

One mechanism by which vagal activity may influence the experience of pain is through its effect on inflammation and the HPA axis more generally. The vagus nerve plays a major role in the cholinergic, anti-inflammatory neural circuit. Afferent vagal fibers sense peripheral inflammation through IL-1β receptors and transmit action potentials to the brain stem (e.g. NTS and area postrema). This in turn leads to efferent vagal-mediated release of acetylcholine which

stimulates the release of anti-inflammatory glucocorticoids in the periphery (Koopman et al., 2011) and inhibits pro-inflammatory cytokine production (e.g. IL-6) (Huston & Tracey, 2011). Additionally, vagus nerve activity stimulates the HPA-axis release of cortisol which inhibits pro-inflammatory cell production (Thayer, 2009). This is supported by cross-sectional (Haensel, Mills, Nelesen, Ziegler, & Dimsdale, 2008; Tateishi et al., 2007) and prospective (Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014) studies revealing an inverse relationship between HRV and levels of inflammatory markers, suggesting that parasympathetic (vagal) activity contributes to the inhibition of systemic inflammation. Conversely, elevated sympathetic activity increases muscle tension, oxidative stress, and leads to impaired local microcirculation, all of which may trigger or contribute to muscle inflammation, nociception, and pain (De Couck et al., 2014). Furthermore, sympathetic-mediated release of peripheral norepinephrine is known to aggravate pain in inflamed or injured tissue (Devor & Seltzer, 1999; Pertovaara, 2013). This pattern of evidence supports the hypothesis that sympathetic over-excitation and reduced vagus nerve activity reflects a potential mechanism by which acute pain may become chronic.

Two systematic meta-analytic reviews have found evidence of decreased HRV (with moderate-to-large effect sizes) in individuals with chronic pain in comparison to pain-free, matched controls (Koenig et al, 2016; Tracy et al., 2016). These include chronic low back pain (Kalezic et al, 2007), musculoskeletal pain (Hallman, Ekman, & Lyskov, 2014; Hallman & Lyskov, 2012), fibromyalgia (Cohen et al., 2001; Del Paso et al, 2010; Doğru et al., 2009; Furlan et al., 2005; Mostoufi et al, 2012; Raj et al, 2000), complex regional pain syndrome (Terkelson et al, 2012), phantom limb pain (de la Rosa, 2013), irritable bowel syndrome (Heitkemper et al., 1998; Mazur et al., 2007; Pellissier, Dantzer, Canini, Mathieu, & Bonaz, 2010), migraine (Elmenshawy & Sakr, 2009), tension headache (Gass & Glaros, 2013), and temporomandibular

disorder (Eze-Nliam, Quartana, Quain, & Smith, 2011; Maixner et al., 2011). Investigators have theorized that this persistently low vagal-mediated HRV may correspond to the disruption in descending pain modulation within the spinal cord dorsal horn underlying central sensitization (Koenig et al., 2016a; Koenig et al., 2016b; Tracy et al., 2016). Accordingly, they have proposed a hypothesis for the relationship between lower HRV and chronic pain in that greater sympathetic activity due to the continuous experience of pain gradually impairs efferent vagal control of the HR, signaling the impairment of parasympathetic recovery functions (Koenig et al, 2016; Tracy et al., 2016). Consequently, the transition from acute to chronic pain may be amplified by a sympathetically dominant state marked by over-reactive and persistent stress responses that deprive an individual of adaptive capacities to respond to and recover from pain. This converges with the literature on psychopathological risk factors of chronic pain, including forms of anxious, depressive, and traumatic distress, all known to be associated with reduced HRV and indicative of PNS dysregulation. Thus, the interaction of pain and stress within a nervous system with parasympathetic dysregulation may pose greater risks for chronic pain because of diminished capacities for stress recovery and somatic regenerative functions in the aftermath of bodily injuries and illnesses. Altogether, the evidence suggests that monitoring HRV may help to better understand the role of ANS dysregulation in the development, maintenance, and treatment of chronic pain disorders.

Increasing HRV to Treat Pain Disorders. Several well-known psychophysiological theories have emphasized the importance of increasing HRV to establish well-being as it signals the restoration and promotion of vital vagus nerve activity on relaxation and immune function (Laborde et al., 2017; McCraty & Shaffer, 2015; Shaffer et al., 2014). This has led to the development of a range of interventions based on vagal nerve stimulation (VNS) applied as a

treatment for pain disorders (Chakravarthy et al, 2015; Kirchner et al, 2001). The vagus nerve can be stimulated electrically with an implantable device (De Ferrari et al., 2010), transcutaneously (Busch et al., 2013) by stimulation of the auricular branch of the vagus nerve ("Arnold's nerve") (Asher et al., 2010), through administration of acetylcholine or its derivatives (Tracey & Huston, 2014), and practice of deep breathing (Del Pozo et al, 2004; Lehrer et al., 2003), clinical hypnosis (Aubert et al, 2009), and meditative practices (Azam et al, 2016; Krygier et al., 2013). Deep brain stimulation of the pain modulating region, periaqueductal grey, has been shown to increase the high-frequency (parasympathetic) component of HRV, corresponding to decreased pain ratings in chronic neuropathic pain patients (Perieria et al., 2010). Transcutaneous VNS has demonstrated increases in mechanical and pressure pain thresholds and a reduction in mechanical pain sensitivity in 48 healthy volunteers (Busch et al., 2013). VNS has also been shown to decrease pain perception in patients with treatment-resistant depression (Borckardt, Kozel, Anderson, Walker, & George, 2005). These findings reflect the promise of using HRV as a marker of effective stress regulation in the context of treatments for chronic and post-surgical pain. Accordingly, studies have shown that practice of self-regulation techniques to increase HRV by individuals with chronic pain is associated with reduced pain and disability (Berry et al., 2014; Soer et al, 2014). Given the comorbidity and relationship between pain, psychological distress, and psychological disorders, behavioral medicine treatments that target vagal nerve activation may prove beneficial by positively impacting stress-related ANS dysregulation.

The Need for Behavioral Medicine Treatments of Pain Disorders

Chronic pain affects approximately 1 in 5 people worldwide, with one-third of sufferers reporting severe pain (Breivik, Eisenberg, & O'Brien, 2013; Goldberg & McGee, 2011; Schopflocher, Taenzer, & Jovey, 2011). This is accompanied by substantial financial burdens to sufferers and to the healthcare system at large. In the US, approximately 22% of family

physician appointments involve pain symptoms (Centers for Disease & Prevention, 2015). Pharmacological treatments are the first-line approach to pain, and the total annual cost of prescription pain medications has been estimated to be up to $17.8 billion (Ma, Chan, & Carruthers, 2014). In the medical system, the prevalence of long-term, high dose opioid use for pain is a key factor in the current "opioid public health crisis", but this has led to disproportionate restrictions by doctors in prescribing opioids (Kolodny et al., 2015). Patients lacking resources to cope with chronic pain may be reliant on more than the maximum recommended dose of 90 mg of morphine-equivalent opioid medication per day, with increased risks of side effects, addiction, and overdose (Busse et al., 2017). In the perioperative setting, opioid use after surgery for acute pain is part of standard care. Patients undergoing major surgeries who do not receive adequate pain care are at risk of developing chronic post-surgical pain, with incidences in the range of 10-50% (Katz & Seltzer, 2009). These patients are also at risk of ramping up to high opioid doses with subsequent difficulties weaning back down. Patients who are refused or discouraged from using opioids are left with few alternative options. The gold standard treatment for chronic pain is comprehensive care (Gatchel, McGeary, McGeary, & Lippe, 2014) involving interdisciplinary pain specialists, including pain physicians, pain psychologists, and physiotherapists. However, comprehensive pain treatment clinics are scarce and overburdened with high caseloads and long wait times (Fashler et al., 2016).

There is now a growing emphasis on mind–body techniques to manage pain, with many chronic pain patients turning to psychological and alternative treatments for coping and relief strategies.

Summary of Literature Review

Both sympathetic and parasympathetic nervous systems are involved in the activation and recovery processes of pain and stress. The activity of these systems becomes dysregulated in individuals with acute and chronic pain as well as psychiatric symptoms, representing a potential shared pathogenic mechanism and target of treatment. The disruption in autonomic balance, specifically with regards to parasympathetic dysregulation, can be measured through the assessment of heart rate variability (HRV), that is, the beat-to-beat variability between consecutive heart beats amidst respiratory cycles. Consequently, the scientific and clinical communities have called for the design and study of behavioral medicine treatments that target the dysregulation of parasympathetic functioning to aid in the process of pain and stress relief.

Aims of the Dissertation

The main aim of the present dissertation is to evaluate behavioral pain interventions using HRV as a biomarker of pain and stress regulation. Study I assesses the effects of audio-instructed mindful breathing compared to audio lecture of mindfulness on HRV in individuals with and without self-reported tension-migraine headache conditions. Study II examines the effects of a smartphone app-assisted mindful breathing exercise compared to mindful breathing without an app on HRV in individuals with clinically significant symptoms of chronic pain and/or depression and anxiety as well as those who do not meet these criteria. Study III examines the effectiveness of a perioperative clinical hypnosis intervention compared to treatment-as-usual on HRV in participants undergoing surgery for cancer.

Chapter II. Study I – The effects of mindfulness meditation on heart rate variability in a randomized trial with students with and without self-reported tension-migraine headaches

Introduction

Tension and migraine headache conditions are neurovascular disorders that lead to severe pain and disability, and can be resistant to pharmacological treatment (Leandri, Luzzani, Cruccu, & Gottlieb, 2001; Leone et al., 2010). Recent estimates indicate migraine and tension-type headache conditions have a lifetime prevalence of 18–22% (Vos et al., 2012), and headache disorders are the 3rd ranked cause of disability worldwide (Steiner et al., 2015). Etiological research indicates that stress-related dysregulation of the autonomic nervous system (ANS) is a contributing factor to headache condition onset and maintenance (Elmenshawy & Sakr, 2009; Koenig, Williams, Kemp, & Thayer, 2016). Mindfulness meditation is a stress regulation practice that has demonstrated effectiveness for a wide range of chronic health conditions (Eisendrath et al., 2014; Murphy, Mermelstein, Edwards, & Gidycz, 2012; Ospina et al., 2008; Parswani, Sharma, & Iyengar, 2013) for treatment outcomes assessed by means of physiological markers (Chiesa & Serretti, 2010; Nyklíček, Mommersteeg, Van Beugen, Ramakers, & Van Boxtel, 2013). The purpose of the current study was to assess the effects of mindfulness meditation on the ANS in individuals reporting tension and migraine headache pain.

Heart rate variability (HRV) measures variations in beat-to-beat heart rate (HR), and indexes the activity of sympathetic (decreased HRV) and vagal parasympathetic (increased HRV) subsystems in the ANS (Allen et al., 2007; Beauchaine, 2015). Reduced HRV values have been observed in several chronic pain (Koenig, Jarczok, Ellis, et al., 2015; Tracy et al., 2016) and psychiatric (Kemp et al., 2012; Lyonfields et al., 1995; Pittig et al., 2013) conditions. These measures are considered to be indicative of impaired vagal activity, thereby reflecting poor capacity to regulate stress recovery. In the acute context, exposures to cognitive stressors

naturally lead to sympatho-excitatory elevations as seen in elevated HR, where cardiac vagal control, i.e. HRV, is expected to temporarily decrease, and once the stressor is diminished, resting cardiac vagal control is expected to be reinstated (Boonnithi & Phongsuphap, 2011; Porges, 1995). In general, a healthy and responsive ANS adapts to stressor demands when stress is present, and serves a restorative function with parasympathetic (vagal) activation to return to ANS balance after stressful periods conclude (Thayer et al., 2012). For example, it is adaptive to have sympathetic reactivity (HR elevation) to unintentionally placing one's hand on a hot stove as this generates the arousal level that triggers one to attenuate the acute pain and physical threat by quickly removing their hand. In the aftermath of the hand being removed from the pain stimulus, a vagal-mediated recovery to resting levels (baseline HR) is adaptive and situationally appropriate given the pain and threat has subsided. Low resting HRV signals usually indicate a nervous system that does not respond to stress in this manner, and instead is inflexible Additionally, it is useful to measure HRV during stress and recovery periods to examine possible deficiencies in parasympathetic regulation, as prolonged post-stress HRV reduction and delay in returning to resting cardiac vagal control can indicate a perpetuating risk factor of psychological and physical pathologies (Blascovich & Katkin, 1993; Brosschot et al., 2006; Verkuil, Brosschot, Gebhardt, & Thayer, 2010).

Several studies have found evidence of sympathetic hyperactivity and vagal hypoactivity in individuals with tension and migraine headaches (Elmenshawy & Sakr, 2009; Gass & Glaros, 2013; Grosu, Odobescu, Moldovanu, & Rotaru, 2013; Matei et al., 2015). However, despite evidence that individuals with headache conditions have greater sensitivity (Holm, Lamberty, McSherry, & Davis, 1997) and impaired recovery (Huss, Derefinko, Milich, Farzam, & Baumann, 2009) in relation to stressors, few studies have assessed HRV in these individuals in

response to and after stressful laboratory stimuli. HRV data on headache sufferers' capacity for stress recovery is necessary to inform the design of headache pain prevention and management interventions.

Associations between decreased HRV and headache conditions suggest increasing vagal-mediated HRV is a potential target of therapeutic intervention. Stress is considered a trigger of headache episodes (Hashizume et al., 2008; Nash & Thebarge, 2006; Wöber, Holzhammer, Zeitlhofer, Wessely, & Wöber-Bingöl, 2006) and stress reduction is central to the psychological-behavioural management of headaches (Cathcart & Pritchard, 2008; Nash & Thebarge, 2006; Schramm et al., 2015). Psychophysiology studies have found that in the aftermath of experimental stressors, individuals with headache conditions report significantly higher subjective stress sensitivity (Rojahn & Gerhards, 1986; Stronks et al., 1999), and exhibit significantly delayed cardiovascular recovery (Holm et al., 1997). Koenig et al. (2015) conducted a systematic review and meta-analysis and found several studies reporting sympathetic hyperactivity associated with migraines and tension-type headaches. Seven studies (n = 122) were included in the meta-analysis, and significantly decreased time and frequency-domain metrics of HRV (representing a medium effect size) were found to be associated with headache disorders while controlling for respiration rate, a confounding variable in HRV analyses. As a measure of cardiac vagal control, HRV is based on the natural cardio-respiratory interaction known as respiratory sinus arrhythmia; synchronized increases and decreases in HR during cycles of inhalation and exhalation, respectively (Allen et al., 2007; Porges & Byrne, 1992; Yasuma & Hayano, 2004). It is well documented that paced and relaxed breathing increases HRV (Bernardi et al., 2000; Peng et al., 2004; Perakakis, Taylor, Martinez-Nieto, Revithi, & Vila, 2009), and recently, breath-focused techniques such as mindfulness meditation have

demonstrated effectiveness in elevating HRV (Azam et al., 2015; Burg, Wolf, & Michalak, 2012; Krygier et al., 2013; Lumma, Kok, & Singer, 2015). The purpose of this study was to determine the effectiveness of a post-stress mindfulness meditation condition in increasing HRV in individuals with tension and migraine headache pain.

Mindfulness practices elicit nonreactive awareness and acceptance of present sensory, emotional, and cognitive experiences (Kabat-Zinn, Lipworth, & Burney, 1985). Brief and sustained mindfulness meditation practice is known to have beneficial physiological effects on autonomic indices of blood pressure (Palta et al., 2012), HR (Delizonna, Williams, & Langer, 2009), and HRV (Azam et al., 2015; Burg and Wolf, 2012; Krygier et al., 2013; Lumma et al., 2015). Breath-focused mindfulness meditation primarily instructs one to complete their breathing cycles while being aware of breathing sensations, and non-judgmentally noticing other sensory, cognitive, and emotional experiences arising in the present moment. Recent evidence shows this practice can promote respiratory sinus arrhythmia, the term for restful and healthy synchronization of HR and breathing rates reflected in increased HRV (Appelhans & Luecken, 2006; Berntron & Cacioppo, 2004). These findings reflect the potential of mindfulness-based interventions in increasing HRV and reducing the stress-related physiological response in individuals suffering from headaches. Accordingly, several studies have demonstrated the effectiveness of mindfulness-based interventions in helping to manage headache pain and pain-related cognitive stressors. Wells et al. (2014) conducted a randomized-control trial (RCT) comparing 8 weeks of mindfulness-based stress reduction (MBSR) delivered to episodic migraineurs ($n = 19$) vs. usual care ($n = 9$). Results indicated fewer and less severe migraines per month and significant between-group reductions on the Migraine Disability Assessment ($p < 0.05$) and Headache Impact Test ($p < 0.05$) for MBSR participants (Wells et al., 2014). In a

similar study, Day et al. (2014) evaluated mindfulness- based cognitive therapy (MBCT) by comparing headache participants classified as treatment responders (≥ 50% improvement in pain intensity and/or pain interference) and non-responders (> 50% improvement). They found 14 treatment responders among the 21 intervention participants, with large effect size differences (between responders and non- responders) for pre-to post-treatment change in standardized measures of pain acceptance and catastrophizing (Day, Thorn, & Rubin, 2014), reflecting the importance of targeting cognitive stress factors in the treatment of headache patients.

Objectives

The present study assessed HRV in participants with tension and migraine headache pain and headache-free controls using a 3-phase experiment consisting of baseline, stress, and random allocation to one of two post-stress conditions. The stress phase involved performing a pattern-recognition task covertly providing falsified real-time performance feedback to elicit cardiac elevation (Azam et al., 2015). Ratings were obtained after the stress phase with regards to the degree of subjective stress experienced during the task. The post-stress conditions were either audio-guided "mindfulness of breathing" instructions or an audio description of mindfulness meditation (each 10 min in duration).

The following hypotheses were tested:

1) A greater proportion of headache group participants would report moderate-high subjective stress after the stress task compared to headache-free controls.

2) Significant increases in HRV would be observed during the post-stress mindfulness meditation exposure for both groups.

3) Significantly lower HRV would be observed in the headache group, compared to the headache-free group, in the post-stress control condition.

Methods

This study was conducted at York University, a large public institution based in Toronto, Canada. Participants were undergraduate students of all years of study and majors. Recruitment was facilitated through an online system of research participation that grants course credits.

Participants. Online pre-screens selected for individuals self-reporting recurrent migraines or headaches. To recruit control participants, pre-screens selected for individuals not reporting recurrent migraines or headaches. Exclusion criteria for the study were current self-reported diagnoses of any anxiety disorder, major depressive disorder, and/or cardiovascular disease (hypertension, coronary artery disease, and arrhythmias). These conditions are known to involve ANS dysfunction (Chalmers, Quintana, Abbott, & Kemp, 2014; Haensel et al., 2008; Kemp et al., 2012; Miu, Heilman, & Miclea, 2009) and can interfere with accurate HRV data. There were no risks associated with participation in this study.

Sample size estimation. Based on data from a previous study (Azam et al., 2015), the present study was designed recruit a total sample size of 80 participants (40 participants per group), so that it would be powered (0.80-0.90) to detect an effect size between medium to large.

Materials.

Heart rate variability data collection & analyses. ECG recordings were collected using an ADInstruments (ADI) PowerLab 4-channel data acquisition system (Colorado Springs, United States) at a 1000 Hz sample rate. PowerLab utilizes 3 adhesive electrodes: one applied to the left side of the chest, one underneath the right collarbone and a ground electrode on the ankle. An ADI respiratory belt-transducer was acquired to obtain respiratory measures. The belt was fastened across the participant's midsection and acquired respiration rate data (Allen et al., 2007). Approximately halfway through the study, the belt's sensors malfunctioned and respiration data could not be collected for n = 53 (66.25%) of participants.

Measures.

Heart rate variability & respiration. Lab Chart Pro software by ADI processes data collected from the ADI PowerLab system and was used to process ECG recordings and calculate frequency-based HRV metrics (Allen et al., 2007). All ECG recordings underwent manual editing to identify and interpolate ectopic beats, according to Force (1996) recommendations. Frequency-based metrics (derived with a Fast Fourier Transformation) were used as they represent respiratory-based modulation of the ANS (Force, 1996). The primary three spectral components are in a spectrum calculated for ECG recordings of 2–5 min. They are very low frequency (VLF; 0.003–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF; 0.15–0.4 Hz). Greater power in the HF band is considered to reflect respiratory sinus arrhythmia as it reflects HR variation attributed to cardiac vagal control (Allen et al., 2007; Force, 1996). Thus, the power of the HF HRV bandwidth was used in the primary analyses. Additionally, a ratio of low-frequency to high-frequency power was also analyzed and is reported in Table 2 to provide a marker of sympatho-vagal balance in all participants. A higher LF-HF ratio is considered to reflect "sympathetic dominance", whereas values closer to 0 reflect sympatho-vagal balance (Eckberg, 1997). Respiration was calculated as breaths per minute. Two individuals separately inspected the ECG files to derive HRV values.

Procedure. The study procedure was approved by the Human Participants Review Subcommittee (research ethics board) at York University. Upon signing up for their appointment, participants were notified by email to refrain from consuming caffeinated beverages or exercise 24 h prior to their experiment. All participants provided informed consent upon arriving at the laboratory for the 90-minute experiment. After obtaining electronic informed consent, all participants completed computer-based self-report questionnaires.

Participants were then connected to the ECG system for the experimental session. All participants were first measured during a baseline rest phase, followed by a stress-induction phase, and a post-stress phase consisting of one of two conditions: mindfulness meditation instruction (MMP) or mindfulness meditation description (MMD). Participants were assigned at random (using a randomization schedule: www.randomization.com) to the post-stress phase condition (MMP or MMD) immediately after the stress-induction phase. Participants were not made aware of the purpose of the stress-induction phase or the post-stress phase conditions until the end of the experimental session when they were debriefed.

During the baseline rest phase, participants were asked to remain seated in a relaxed upright position for 5 min while thinking freely with their eyes closed. They were asked to keep their eyes closed, remain silent, and not make any sudden movements.

The stress-induction phase involved completing a computer-based Pattern-Recognition Task (PRT) designed to elicit a stress response (Azam et al., 2015). Participants were asked to study 4 alphanumeric characters presented at the top of the screen for 9 s and determine a pattern that fits the characters (Fig. 1). After 9 s, a 5th character was presented with the text "True or False?" in the middle of the screen. Participants were instructed to respond with the following keys as quickly as possible, "True" (← key) if they believed the 5th character followed the pattern or "False" (→ key) if it did not. Immediately after the response, "Right Answer" or "Wrong Answer" was presented at the bottom left or bottom right of the screen, respectively for 3 s. Numbers indicating total "Correct [x]" (bottom right) and "Incorrect [y]" (bottom left) answers were totaled to the current trial and remained on the screen for the entire task.

The alphanumeric characters were designed to appear to the participants as if they followed a simple or complex pattern, but none of the problems followed a specific pattern (see

Appendix A for characters used; Azam et al., 2015). The "Right Answer" and "Wrong Answer" presentation was created with a pre-determined random order so that each would be presented 11 times throughout the 22 trials. Participants were told that the PRT assessed cognitive capacity which is a "marker" of intelligence and the average score of the task is 80–85% correct answers with an average response time of 1 s.

After task completion, a stress manipulation check was performed by asking participants to rate their stress level while completing the PRT from the following options: "not stressed at all", "a little stressed", "moderately stressed", "highly stressed" or "extremely stressed".

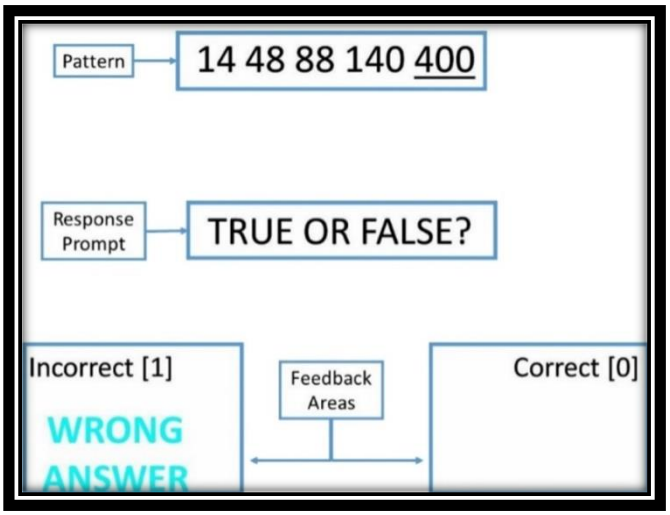


Figure 1. Pattern recognition task.

In the post-stress phase MMP condition participants were asked to remain seated in a relaxed and upright manner with eyes closed. A 10-minute audio recording was played featuring mindfulness instructions which emphasized bringing attention to sensations while breathing and re-focusing on breathing sensations once there was awareness of thoughts, feelings, bodily sensations, and/or external stimuli (Ritvo et al., 2013; Azam et al., 2015). The instructions were recorded by a clinical psychologist who is an experienced MM instructor.

In the post-stress MMD condition, participants were seated identically as in the MMP condition (including eyes closed). They were played 10-minute audio description of historical and scientific information about mindfulness meditation by the same clinical psychologist (Azam et al., 2015). During this recording, there were no instructions on practicing mindfulness of breathing.

After the experiment, participants were debriefed. They were informed that the PRT involved unsolvable problem sets. Participants were also told that feedback was prearranged for all participants to receive 50% and their score was not indicative of their intelligence. Participants were informed that the sole purpose of the PRT was for stress induction.

Statistical analyses. All data was examined for normality prior to statistical testing. First, the demographic data for the headache and headache-free groups were compared using independent *t*-tests and Chi-square tests of likelihood. Sympatho-vagal balance (LF-HF HRV) was examined using a 2 × 2 × 3 mixed ANOVA with Group (headache vs. headache-free) and Condition (MMP vs. MMD) as the between-subjects factors, and Phase (baseline, stress, post-stress) as the within-subjects factor. For Hypothesis 1, stress ratings were analyzed using a 2 × 2 (Group vs. stress ratings) Chi-square test of independence, and followed up by inspecting standardized residuals within cells. For hypotheses 2 and 3, HF-HRV was analyzed using a 2 × 2 × 3 mixed ANOVA with Group (headache vs. headache-free) and Condition (MMP vs. MMD) as the between-subjects factors, and Phase (baseline, stress, post-stress) as the within-subjects factor. Significant interaction effects were followed up with simple effects analysis and pairwise comparisons using a Bonferroni Type I error rate correction (alpha = 0.008).

Results

Data preparation. High-frequency HRV (HF-HRV) data was positively skewed (5.99) and was log transformed to reduce skewness to acceptable levels (0.277). The post-stress task stress ratings were collapsed into two categories; "none-to-mild" and "moderate-to-severe".

Participants & grouping. Eighty participants were recruited for the study (24 male, 56 female). Thirty-nine participants indicated they experienced migraine and/or tension-type headaches (8 male, 31 female). Three participants were excluded in the headache group and two participants were excluded in the headache-free group for not completing the experimental protocol or having signal noise in their ECG recordings (Fig. 2).

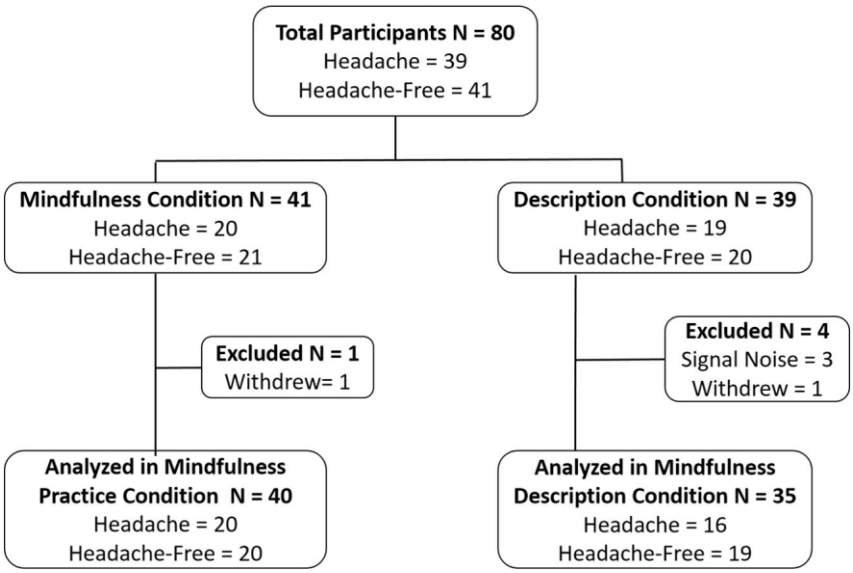


Figure 2. Flow of participants through the study.

The headache group comprised 39 participants who self-reported having migraines and/or tension-type headaches. The headache group was ~ 80.0% (n = 31) female, with a mean age of 19.54 (SD = 2.09). The headache-free group comprised 41 participants who did not endorse having headaches. The headache-free group was 61.0% (n = 25) female, with a mean age of 19.78 (SD = 1.90) (Table 1).

Groups did not significantly differ on age, gender distribution, educational status, and frequency of weekly exercise (Table 1).

Table 1
Demographic data according to groups.

Measure	Headache (n=39)	Headache-free (n=41)	Tests of significance
Age (years) (SD)	19.54 (2.09)	19.78 (1.90)	$t(78) = 0.72$, $p = 0.59$
Gender n (%)			$\chi2(1) = 3.26$, $p = 0.07$
Male	8 (20.51)	16 (39.02)	
Female	31 (79.49)	25 (60.98)	
Education n (%)			$\chi2(5) = 7.28$, $p = 0.20$
First year	20 (51.28)	21 (51.22)	
Second year	14 (35.90)	8 (19.51)	
Third year	3 (7.69)	3 (7.32)	
Fourth year	0 (0.00)	4 (9.76)	
Fifth year	2 (5.13)	4 (9.76)	
Sixth year/graduated	0 (0.00)	1 (2.44)	
Weekly exercise n (%)			$\chi2(2) = 1.96$, $p = 0.38$
Often	12 (30.77)	15 (36.59)	
Sometimes	21 (53.85)	16 (39.02)	
Rarely/never	6 (15.38)	10 (24.39)	

Note. SD = standard deviation.

Table 2 presents data on the characteristics of headaches and migraines in the headache group participants. Average numeric pain scale ratings for headaches was in the moderate-to-severe range (≥ 4/10) in ~ 88.0% (n = 34) of participants, and worst pain reached severe levels (> 7/10) in 74.0% (n = 29). 70.59% of participants had been having recurring tension or migraine headaches for over 1 year.

Table 2
Characteristics of tension & migraine headache group participants.

Characteristic	Frequency (%)
Average NRS pain score	
Mild (< 4/10)	4 (11.76)
Moderate (4-≤ 7/10)	22 (64.71)
Severe (> 7/10)	8 (23.53)
Worst pain	
Mild (< 4/10)	2 (5.88)
Moderate (4-≤ 7/10)	7 (20.59)
Severe (> 7/10)	25 (73.53)

Interference with schoolwork	
Mild (< 4/10)	2 (5.88)
Moderate (4–≤ 7/10)	24 (70.59)
Severe (> 7/10)	8 (23.53)
Interference with everyday activity	
Mild (< 4/10)	2 (5.88)
Moderate (4–≤ 7/10)	24 (70.59)
Severe (> 7/10)	8 (23.53)
History of headaches/migraines	
> 1 year	24 (70.59)
3–6 months	3 (8.82)
6–12 months	5 (14.71)
< 3 months	2 (5.88)
Duration of headaches/migraines	
1 day–7 days	15 (44.12)
3 h–24 h	6 (17.64)
1–3 h	6 (17.64)
30–60 min	6 (17.64)
< 30 min	1 (2.94)
Medication	
Excedrin	1 (2.94)
Flexeril	1 (2.94)
Nabumetone	1 (2.94)
Topiramate	1 (2.94)
Tylenol	3 (8.82)

Note. Headache information was available for n = 34 headache group participants. NRS; numeric rating scale.

Complete respiration data was available for n = 24 (61.54%) of headache group participants. According to a 2-way ANOVA (Phase × Condition), there was no significant main effect of phase, or interaction of phase and condition, for headache group participants, indicating no differences in respiration rate.

Sympatho-vagal balance. Mixed ANOVA with LF-HF (Table 3) indicated a significant main effect of Phase $F(2, 70) = 5.53$, $p < 0.01$, $\eta p^2 = 0.14$. Follow up pairwise comparisons revealed mean LF-HF for all participants was significantly higher during the post-stress phase (comprised of both MMP and MMD conditions) in comparison to baseline ($p = 0.011$) and stress ($p < 0.005$). The ANOVA did not indicate a statistically significant three-way interaction (Phase

× Condition × Group), or significant two-way interactions of Phase × Condition and Phase × Group. Consequently, LF-HF differences according to headache group or MMP and MMD conditions could not be explored.

Table 3
Means and SD of HRV during post-stress phases according to Condition and Group.

	Headache Group (n=36)			
	MMP (n=20)		MMD (n=16)	
Phase	**HF-HRV**	**LF-HF**	**HF-HRV**	**LF-HF**
Baseline	6.49 (1.17)	1.71 (0.45)	6.07 (0.76)	0.99 (0.50)
Stress	6.24 (0.84)	1.02 (0.38)	5.77 (0.80)	0.94 (0.42)
Post-stress	7.02* (0.97)	1.83 (0.67)	5.72 (0.66)	2.64 (0.60)
	Headache-free (n=39)			
	MMP (n=20)		MMD (n=19)	
Phase	**HF-HRV**	**LF-HF**	**HF-HRV**	**LF-HF**
Baseline	6.66 (1.10)	1.67 (0.45)	6.20 (0.74)	0.79 (0.46)
Stress	6.29 (0.93)	1.80 (0.38)	6.02 (0.72)	1.11 (0.39)
Post-stress	6.84* (1.03)	1.51 (0.62)	6.19 (0.71)	2.65 (0.60)

Note. MMP = mindfulness meditation practice; MMD = mindfulness meditation description; HF-HRV = high frequency HRV; LF-HF = ratio of low-frequency to high-frequency power; standard deviations in brackets. Bonferroni-adjusted ($p < 0.008$) pairwise comparisons were conducted with stress phase for the HF-HRV data (log-transformed).
* $p < 0.001$: Post-stress HF-HRV is significantly higher than Stress HF-HRV

Hypothesis 1: Self-reported stress ratings in groups after pattern-recognition task.

A significant Chi-square test of independence was found between Group and stress ratings, $\chi^2(1, n = 80) = 12.03$, $p < 0.001$. Within the headache-free group, twenty participants (48.9%) provided a rating of "none-to-mild" stress, and twenty-one reported "moderate-to-extreme" stress. Among the headache group, five participants provided a rating of "none-to-mild" (12.8%) while thirty-four (87.2%) reported "moderate-to-extreme". The largest standardized residual was associated with the headache group for "none-to-mild" stress rating—its observed count (34)

significantly deviated from its expected count (12.2), with a standard residual of − 2.1. This indicates that the headache group was less likely to report "none-to-mild" stress, and more frequently reported "moderate-to-severe" stress after the Pattern Recognition Task.

Heart rate variability results. The ANOVA revealed a significant main effect of Phase, $F(3, 213) = 14.54$, $p < 0.001$, $\eta p^2 = 0.17$, a significant Phase × Condition interaction, $F(3, 213) = 11.03$, $p < 0.001$, $\eta p^2 = 0.14$, and a significant three-way Group × Phase × Condition interaction, $F(3, 213) = 3.08$, $p = 0.05$, $\eta p^2 = 0.04$. All other main effects and interaction effects were not significant (all $p < 0.05$). Groups did not differ on HF-HRV at baseline, $F(1, 71)=0.42$, $p = 0.52$, $\eta p^2 = 0.006$, and stress phases, $F(1, 71)= 0.58$, $p = 0.45$, $\eta p^2 = 0.008$, according to simple effects tests.

The significant main effect of Phase was followed up with a pairwise comparison showing that, as expected, mean HF-HRV of all participants was lower during the stress phase (M = 6.08, SEM = 0.10) compared to baseline (M = 6.35, SEM = 0.11) ($p < 0.005$).

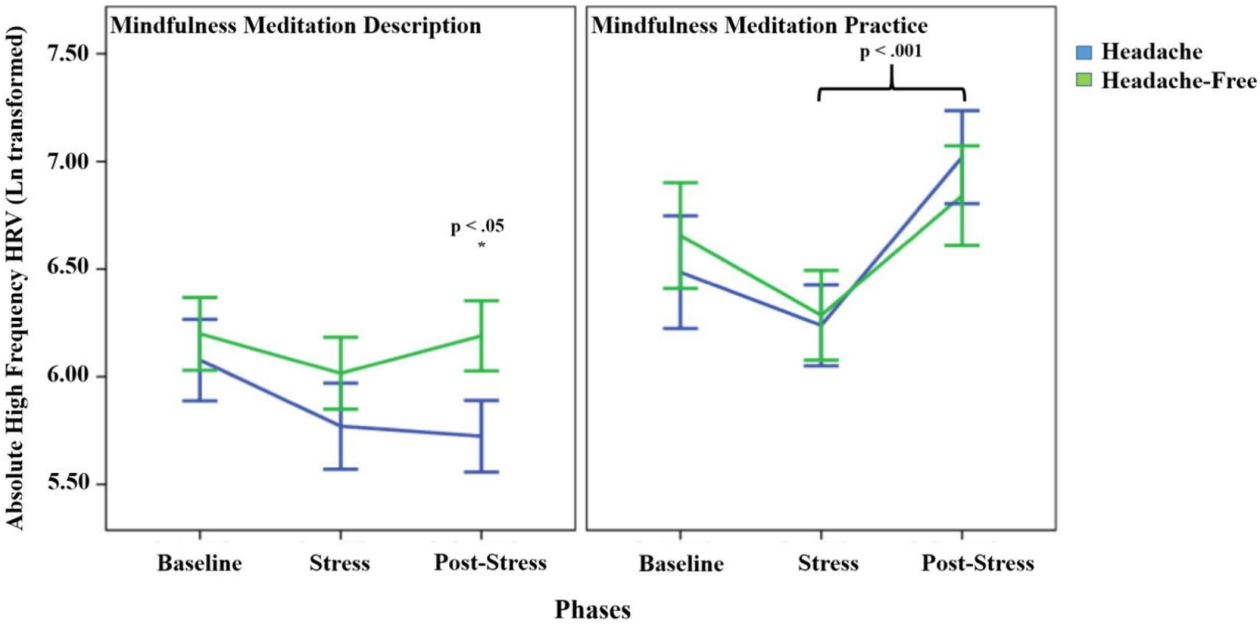


Figure 3. Log-transformed mean high frequency heart rate variability (ms^2) in headache and headache-free groups during the three phases of the experiment: baseline rest, stress, and post-

stress MMP or MMD. Left plot displays estimated marginal means for participants randomized to the mindfulness description condition, N = 40 (headache = 20; headache-free = 20); Right plot displays means for participants randomized to mindfulness instruction condition N = 35 (headache = 16; headache-free = 19). Bars represent standard errors.

Hypothesis 2. Increased HRV during mindfulness after stress. Hypothesis 2 was evaluated by analyzing the Group × Condition × Phase interaction effect. The multivariate simple effect of Phase within the MMP condition was significant for headache ($\wedge = 0.65$, $F(2, 70) = 18.48$, $p < 0.001$, $\eta p^2 = 0.35$) and headache-free ($\wedge = 0.81$, $F(2, 70) = 8.02$, $p = 0.001$, $\eta p^2 = 0.19$) groups. For the headache group in the MMP condition, HF-HRV increased significantly from stress ($M = 6.24$, SEM = 0.21) to MMP ($M = 7.02$, SEM = 0.20) ($p < 0.001$). Similarly, the headache-free group exhibited a significant HF-HRV increase from stress ($M = 6.29$, SEM = 0.19) to MMP ($M = 6.84$, SEM = 0.20) ($p < 0.001$).

In addition, the simple effect of Condition for headache group in the post-stress phase was significant ($F(1, 71) = 19.71$, $p < 0.001$, $\eta p^2 = 0.22$), indicating that the headache group in the MMP condition exhibited greater HF-HRV compared to the headache group in the MMD condition (Table 3). The simple effect of Condition for headache-free group was significant at the post-stress phase ($F(1, 71) = 5.45$, $p < 0.05$, $\eta p^2 = 0.07$), indicating the headache-free group exhibited greater HF-HRV during MMP compared to MMD.

Hypothesis 3. Lower HRV in headache group during post-stress MMD. Hypothesis 3 evaluated the Group × Phase interaction for the two conditions with simple effects tests. During post-stress MMD, the headache group exhibited significantly lower HF-HRV ($M = 5.74$, SEM = 0.22) than the headache-free group ($M = 6.19$, SEM = 0.20) ($p < 0.05$). In contrast, HF-HRV in headache and headache-free groups did not significantly differ during post-stress MMP. In addition, pairwise comparisons indicated the headache group exhibited significantly lower HRV

in the post-stress MMD condition (M = 5.72, SEM = 0.22) relative to their baseline HF-HRV (M = 6.08, SEM = 0.24) ($p < 0.05$; Bonferroni-adjusted).

Discussion

The present study assessed HRV during baseline and stress conditions, and during a post-stress condition where headache-affected and headache-free participants were exposed to audiotaped mindfulness instructions versus descriptions of mindfulness meditation with the same vocal features. As predicted, all participants responded to the mindfulness instructions with significant HRV elevations, reflecting effective parasympathetic regulation after stress exposure. Headache participants, but not the headache-free controls, exhibited significantly lower post-stress HRV while listening to the meditation description in comparison to their baseline, indicating they not only failed to recover from the stress condition, but their HRV continued to decline relative to baseline in this control condition. Lastly, the headache group was significantly more likely to report moderate-to-high stress levels after stressor task exposure.

Stress ratings in headache group. The relationship between stress and headache conditions has multiple components. According to Nash and Thebarge (2006), the physiological arousal resulting from cognitive stress can: 1) contribute to the onset of headaches in a person with a pre-existing headache vulnerability, 2) accelerate the progression of headache disorders, and 3) precipitate or worsen individual headache episodes. The recurrent pain experience and enduring emotional distress can both precipitate and sustain difficult lifestyle circumstances for the headache sufferer. In this respect, the present study's results that headache group participants more frequently report moderate-to-severe stress, after a brief stress induction, is consistent with prior research (Cathcart and Pritchard, 2008; Hashizume et al., 2008; Holm et al., 1997; Nash and Thebarge, 2006; Schramm et al., 2014; Stronks et al., 1999; Wöber et al., 2006). In a study of pain and cognitive stressors (Hassinger, Semenchuk, & O'Brien, 1999), n = 26 migraine

sufferers and n = 26 migraine-free controls were subjected to a cold pressor task and a mental arithmetic-based stress induction and found the migraineurs reported significantly higher levels of pain in response to the cold pressor ($p < 0.05$), and a significantly higher frequency of wishful thinking and self-criticism in response to the mental arithmetic stressor ($p < 0.05$). This suggests inherent sensitivities to demanding and aversive stressors for headache sufferers, leaving them more vulnerable to the onset and worsening of headache episodes (Nash and Thebarge, 2006). Extending this research trajectory, we found prolonged HRV reductions in headache sufferers during a post-stress phase while listening to a meditation description, suggesting that their perceived stress contributed to dysregulation in parasympathetic stress recovery. Conversely, the headache group responded to mindfulness instruction with effective parasympathetic stress recovery as evidenced by HRV elevations, suggesting that mental and physical relaxation associated with mindfulness practice aided their acute stress coping (Nyklíček et al., 2013; Tang et al., 2009).

Increased HRV during post-stress mindfulness meditation. Increased vagal-mediated HRV has been observed in individuals displaying psychological resilience (Lagos et al., 2008; Segerstrom & Nes, 2007), and during states of mindful meditation (Azam et al., 2015; Burg et al., 2012). Neuroimaging studies support HRV as an index of vagal activity resulting from prefrontal inhibitory control of attention regulation processes (Berntson & Cacioppo, 1999; Thayer et al., 2012). The current study's mindfulness instruction condition guided participants to focus attention on breathing sensations, achieving two important stress regulating functions: 1) it generated a relaxation effect via awareness and regulation of breathing, 2) it shifted attention away from the elevated arousal and cognitive features of the previously elicited stress response. The increased HRV of both headache and headache-free groups to the mindfulness condition is

consistent with previous research (Azam et al., 2015; Krygier et al., 2013; Lumma et al., 2015), and suggests mindfulness practice can help headache sufferers alleviate stress vulnerabilities by preventing, or mitigating, their contribution to the onset of headache episodes. It is worth highlighting here that in our previous study, control participants exhibited significantly elevated HRV during the two consecutive 5-minute phases of the post-stress mindfulness instruction ($p < 0.001$), but a maladaptive perfectionist subsample did not exhibit an HRV response to mindfulness instruction (Azam et al., 2015). We speculated that cognitive factors associated with maladaptive perfectionism (e.g. harsh self-evaluation, attention bias to failure) hindered the perfectionists from engaging in mindfulness practice and prevented parasympathetic stress recovery. Current study results indicate headache-affected individuals are not limited by such cognitive factors, and mindfulness-based interventions could be beneficial as adjuncts, or alternatives, to pharmacological treatment. This is particularly important given previous evidence of ANS dysregulation in headache disorders (Elmenshawy and Sakr, 2009; Koenig et al., 2015; Matei et al., 2015), and the present study's results showing significantly lower HRV for the headache group participants randomized to the control MMD condition.

Lower HRV in headache group during post-stress mindfulness description. Cardiac vagal control is a marker of ANS regulation (Gass and Glaros, 2013) and a contributing factor to headache disorders (Koenig et al., 2015; Matei et al., 2015). Thus, assessment of HRV patterns in response to cognitive stress protocols is clinically relevant. A systematic review and meta-analysis on HRV in headache patients indicated significant associations between sympathetic hyperactivity and migraine/tension-type headaches (Koenig et al., 2015). Specifically, seven studies (n = 122 subjects) reported that vagal-mediated HRV (assessed at baseline) was significantly lower in individuals with headache disorders (i.e. migraines and tension-type

headaches) (Koenig et al., 2015). The current study extends this area of research by reporting on post-stress HRV for headache-affected individuals, indicating significant declines in HRV in those randomized to the control MMD condition. Furthermore, the headache group in the MMD condition exhibited significantly lower HRV compared to their baseline. By contrast, the HRV of headache-free participants in the MMD condition recovered to baseline levels (Fig. 3). This is suggestive of parasympathetic dysregulation in headache-affected individuals and indicates their stress vulnerabilities in the absence of specific stress reduction practices. More research is warranted on HRV patterns in relation to headache disorders, especially as vascular complications in headache sufferers precipitate elevated risks for cardiovascular disorders (Grosu et al., 2013; Koenig et al., 2015).

Sympatho-vagal balance. The finding of increased LF-HF in the post-stress phase in all participants indicates a shift to "sympathetic dominance" (Eckberg, 1997) in this phase compared to baseline and stress. Interpretation of these data must be made with caution, as the mean LF-HF was higher during the MMD condition for both headache and headache-free groups (Table 3), in comparison to the MMP condition, suggesting that the greater sympathetic activity may mostly be attributable to the control resting (MMD) condition. It is important to note here that the effects of the MMP condition on LF-HF could not be tested as the mixed ANOVA model failed to reach statistical significance with respect to interactions. Follow up studies sufficiently powered to detect medium to large effect sizes in LF-HF measures and other markers of sympathetic tone are needed in the headache patient population given their documented cardiovascular complications (Ebinger, Kruse, Just, & Rating, 2006; Grosu et al., 2013).

Limitations & strengths. This study was limited by the use of a newly designed pattern recognition task (Azam et al., 2015) which requires further validation as a stress-induction task

for varying populations. This task was used in the previous study to elicit stress in maladaptive perfectionists, and in the present study, as a nonspecific stressor. Future research with HRV assessment protocols should consider using stress inductions more relevant to a pain condition with stronger ecological validity. Furthermore, our findings must be conservatively interpreted as they are only generalizable to undergraduate populations. Recruitment through a credit system predicated on research participation indicates reliance on a convenience sample. On this note, future studies focusing on headache sufferers should consider differentiating or stratifying for migraine vs. tension headache, younger vs. older participants, and older vs. recently diagnosed headache conditions.

The current study extends prior research on ANS dysfunction and headache conditions by investigating patterns of HRV in response to stress and mindfulness instruction conditions where previous studies have focused on baseline indicators. The use of an identically structured control condition featuring audio descriptions of mindfulness added methodological rigor in differentiating mindfulness from simple post-stress recovery effects and revealed further links between headache conditions and parasympathetic dysregulation.

Conclusion

The effects of mindfulness meditation on HRV in individuals with tension and migraine headaches were found to be largely consistent with study expectations. Both headache and headache-free participants randomized to the mindfulness practice exhibited HRV increases indicative of parasympathetic regulation. Additionally, results revealed that headache participants' HRV continued to decline in the post-stress control condition, indicating failures in parasympathetic recovery. Overall, this study indicates that brief mindfulness practices, and mindfulness-based interventions, can promote post-stress recovery in headache-affected

populations. It is hoped that future studies will look to further demonstrate the contribution of parasympathetic dysregulation to the onset and maintenance of headache disorders.

Acknowledgements

This dissertation study is based on the previously published article listed below:

Azam, M. A., Katz, J., Mohabir, V., & Ritvo, P. (2016). Individuals with tension and migraine headaches exhibit increased heart rate variability during post-stress mindfulness meditation practice but a decrease during a post-stress control condition–a randomized, controlled experiment. International Journal of Psychophysiology, 110, 66-74.

The dissertation author was a co-investigator on the study, contributing to conception and design of the study, data collection, data analyses and interpretation, drafting of the published manuscript, and critical revisions of the article for final publishing. JK and PR were senior investigators on the study, and contributed to conception and design of the study, data interpretation, and drafting and revisions of the published manuscript. VM was a research assistant on the study, and contributed to data collection and analyses, and drafting of the manuscript. All authors provided permission for inclusion of this article in the dissertation.

Chapter III. Study II – Comparison of mindful breathing and smartphone-assisted mindful breathing effects on heart rate variability in a randomized, controlled trial in students with clinically-relevant chronic pain, depression, and anxiety symptoms

Introduction

Mindfulness meditation (MM) is an element of the Buddhist traditions first introduced as a clinical intervention in western medicine by Jon Kabat-Zinn (1982). Over the past 35 years, the practice has received significant interest in clinical and health psychology, and more recently, neuro- and psychophysiology. A family of meditative practices based on mindfulness are commonly used as psychological approaches to mental illness and chronic pain management. Mindful breathing is central to the mindfulness practices, and places an emphasis on paying nonjudmental attention to one's cognitive, emotional, and physical experiences while reorienting focus on breathing sensations to cultivate emotionally regulated and progressively relaxed states (Kabat-Zinn, 2003). Mindfulness-based treatments have been shown to be effective in reducing symptoms of depression, anxiety, and chronic pain (Chiesa & Serretti, 2011; Hofmann, Sawyer, Witt, & Oh, 2010).

One proposed mechanism for the benefits accrued by mindfulness meditation is respiratory-based vagal stimulation (Gerritsen & Band, 2018), with its emphasis on slow, abdominal breathing, extended exhalations, and instruction to refocus attention on breathing sensations. In its clinical application, mindful breathing practice instructs bringing awareness to breathing sensations and observing repetitive thinking, distressing emotions, and somatic symptoms (e.g. pain) with nonjudgment and acceptance (Brown & Ryan, 2003; 2017). According to psychophysiological perspectives, the clinical efficacy of mindfulness can be examined in the degree to which it activates the parasympathetic response, inferred by increases in HRV amidst meditation practice (Burg et al., 2012; Krygier et al., 2013). However, individuals with pain, depression, and anxiety disorders typically begin with a 'lower baseline'

of HRV than those without, given their shared pathogenic mechanism of a dysregulated autonomic nervous system (ANS) (Brosschot et al., 2006; Thayer et al., 2012). The impact of a compromised parasympathetic response on the practice of mindful breathing in clinical populations warrants close examination given the increased use of mindfulness interventions in clinical care.

A key clinical characteristic of individuals with pain, depression, and anxiety disorders is found at the cognitive level. Rigid and inflexible types of mind-wandering, such as worry and rumination, are typically seen in individuals with psychiatric illnesses (Killingsworth & Gilbert, 2010) (Robison, Gath, & Unsworth, 2017) as well as chronic pain (Kucyi et al., 2014). These cognitive stressors lead to prolonged physiological stress activation linked to health risks (Brosschot et al., 2006; Ottaviani et al., 2016). Mindfulness meditation attempts to counteract unhealthy mind-wandering by instilling present-oriented attention that is more conducive to appropriately rested and relaxed states in the absence of stressful demands (Sood & Jones, 2013). Importantly, as the removal of stressful stimuli in the environment does not always coincide with a return to resting state, a rationale for mindful stress-reduction practices becomes salient. Physiological stress inevitably arises through worry, rumination, and distressing emotions such as fear, anxiety, and anger. Patterns of worry and rumination are defined as "perseverative stressors", as they are frequently related to past or anticipated stressors (Brosschot et al., 2006). Perseverative stress and can linger at a level below awareness, creating a physiological undertone of stress arousal and allostatic load that leads to a gradual and sustained withdrawal of cardiac vagal control, quantifiable by low heart rate variability (HRV) (Ottaviani et al., 2016). Chronically lower HRV is a sign that the ANS is "sympathetically dominant", with persistent and excessive activation of the stress response that is less amenable to vagal-mediated

parasympathetic recovery (Brosschot et al., 2006; Ottaviani et al., 2016). Mindfulness practice may be a key method to target this pathophysiological mechanism considered to underpin the development and maintainance of chronic pain, depression, and anxiety conditions (Thayer et al., 2012; Thayer et al., 1996). Mindful breathing can enhance cardiac vagal control through fostering a relaxed physiological state, as multiple studies have shown even brief mindfulness practice after stress significantly increases HRV (Azam et al., 2015; Azam et al., 2016). This augmentation of cardiac vagal control effect may have stress-relieving benefits for individuals with depressive-anxious symptoms (Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). Furthermore, reductions in self-reported pain have been demonstrated in individuals practicing HRV-based biofeedback (Sowder, Gevirtz, Shapiro, & Ebert, 2010), and it has been theorized that increased vagal activation is connected to several analgesic mechanisms such as lowered systemic inflammation and inhibited pain-processing brain regions (De Couck et al., 2014). Thus, the treatment potential of respiratory-based vagal stimulation may have clinical utility given the strong research evidence associating lower HRV and psychiatric (Beauchaine & Thayer, 2015) and pain conditions (Thayer et al., 2012).

A potentially impeding factor for clinical populations in practicing mindful breathing are the demand characteristics of the silent, inwardly focused exercise that may naturally make them more saliently aware of their symptoms of depression (e.g. rumination), anxiety (worry), and pain (sensations). Relatedly, a qualitative study revealed participant-reported experiential challenges to mindfulness meditation practice that must be addressed in clinical treatment contexts, including the fact that meditation is a difficult skill to learn and practice, and participants encounter difficult thoughts and feelings amidst practice (Lomas, Cartwright, Edginton, & Ridge, 2015). This is all the more relevant to naïve meditators with pain,

depression, and anxiety symptoms, making for a potentially more challenging experience that could discourage further mindfulness meditation practice.

Supportive training tools, such as smart-phone apps, are widely used to receive audio guidance on mindfulness meditation, and evidence is emerging for their immediate and long-term effects on altering mood states (Athanas et al., 2019). However, few studies have investigated the clinical utility and physiological changes related to meditation-based smart-phone apps (Mani, Kavanagh, Hides, & Stoyanov, 2015). Furthermore, audio instructions may not be readily applicable in participants with clinical symptoms who are vulnerable to symptom-related mind-wandering amidst meditation practice. In one study, a computer-based mindful breathing exercise provided random audio-tones during the practice to prompt healthy participants to re-orient attention to breathing sensations after pressing a button on the keyboard to indicate whether they had been paying attention to breathing or other experiences at the time of the tone (Burg et al., 2012). The results showed higher instances of breath-attention were correlated with increased HRV during the practice, suggesting a positive relaxation effect of the mindful breathing exercise. This paradigm could be effectively applied for clinical populations who may initially struggle to practice mindful breathing, such as those with chronic pain and severe anxious-depressive symptoms. Although multiple studies have shown mindfulness meditation leads to HRV increases (Azam et al., 2015; Burg et al., 2012), there are no known studies that have investigated the effects of a smart-phone based mindful breathing exercise on HRV in individuals with chronic pain and severe depressive-anxious symptoms. One study provided naïve meditators training in the mindfulness technique of thought distancing using a smartphone app or traditional mindfulness practice without an app. They found significantly greater mindfulness, pleasantness, and lower percieived difficulty associated with the

smartphone app-based mindfulness practice compared to the non-app conditions (Chittaro & Vianello, 2014). More investigations are needed to determine in what ways smartphone apps can be employed as an effective medium of delivering mindfulness training to vulnerable populations who are naïve to meditation.

A recent systematic review of mindfulness-related apps found over 500 apps in the marketplace, but only 23 were designed to provide mindfulness training and largely focused on providing audiovisual guidance, timers, and reminders to practice (Mani et al., 2015). The review revealed that only one randomized-controlled trial for a mindfulness app was underway at the time (Howells, Ivtzan, & Eiroa-Orosa, 2016), and that generally, there is limited evidence available for the efficacy of apps in increasing mindfulness (Mani et al., 2015). Furthermore, the literature on existing mobile applications marketed for chronic pain reveals that with few exceptions (2017) they rarely adhere to scientific guidelines and that healthcare professionals are rarely involved in their development (2014; Joshi et al., 2016; Rosser & Eccleston, 2011; Wallace & Dhingra, 2014).

The aim of this study was to overcome some of the aforementioned limitations by designing an app with input from clinical researchers and empirically testing the application's effectiveness in a sample of young adults with chronic pain, anxiety, and depression. In order to cultivate mindfulness, a mobile-based Mindfulness Meditation App (MMA) was developed based on Burg, Wolf and Michalak's (2012) Mindful Breathing Exercise (MBE) which "assesses the participants' ability to mindfully stay in contact with the bodily sense of the breath during an exercise aligned with breathing meditation" (Burg et al., 2012). In lieu of verbal meditation instructions amidst practice, the task provides audio tones at random intervals to which participants respond by pressing keys to indicate "breath" (if they were attending to their

breathing at the sound of the tone) or "other" (if they were attending to an experience other than the breath at the sound of the tone). This simplified task may be more suitable to beginner meditators, and particularly those with various psychiatric and pain symptoms that make meditation practice more difficult (Lomas et al., 2015). In a previous pilot study of the MMA (unpublished), participants with chronic pain and severe depression-anxiety symptoms randomized to the 12-minute MMA task exhibited significant reductions in mood states of anxiety, anger, and overall distress.

Objectives

The present study evaluated the psychophysiological effects of mindful breathing with a smart-phone based Mindfulness Meditation App (MMA+) compared to mindful breathing without an app (MMA-) for individuals with clinically significant symptoms of major depression and/or anxiety, or chronic pain. Specifically, the study examined parasympathetic activity using HRV (primary outcome) in participants who self-reported clinically significant symptoms of chronic pain (CP), depression and/or anxiety (DA), as well as participants (SC) who did not meet criteria for either (sub-criteria; SC). The study also assessed depressed and anxious mood and subjective distress before and after stress-induction and meditation, as well as state mindfulness and mind-wandering after the meditation conditions. All study groups were randomized to a mindfulness meditation app (MMA+) condition or a mindfulness meditation condition without the app (MMA-) after a brief stress-induction procedure.

The following hypotheses were tested:

Primary outcome

Hypothesis 1a. HF-HRV during mindfulness meditation (MM) will be significantly higher in the CP and DA groups receiving MMA+ compared to those receiving MMA-, respectively, as it is expected that the aid of "breath focus" audio prompts provided by the MMA+ condition will

foster relatively greater respiration-based vagal stimulation in these groups. HRV during the MM phase is not expected to differ between MMA+ and MMA- conditions in SC participants, as SC participants are deemed to have less symptom-related interference in practicing mindful breathing.

Hypothesis 1b. HRV will significantly increase from the stress to MM phases in CP and DA participants receiving MMA+, with greater effect sizes compared to corresponding groups in MMA-, respectively, demonstrating the expected effects of the MMA in enhancing vagal HR modulation. HRV is not expected to differ in SC participants receiving MMA+ and MMA- conditions, as past studies have already shown medium-to-large effect size HRV increases in these populations during post-stress mindfulness meditation (Azam et al., 2015; 2016).

Secondary outcomes

Hypothesis 2a. CP and DA participants recieving MMA+ will demonstrate lower and significantly reduced depressed and anxious mood symptoms after the MM task, with greater effect sizes compared to CP and DA participants receiving MMA-, reflecting the potential for MMA+ to enhance the emotion regulation effects of MM for clinical populations.

Hypothesis 2b. CP and DA participants receiving MMA+ will demonstrate lower and significantly reduced subjective distress after the MM task, with greater effect sizes compared to CP and DA participants in the MMA- conditions, reflecting the greater potential for MMA+ to facilitate the stress regulation effects of MM for clinical populations.

Hypothesis 3. CP and DA participants receiving MMA+ will report significantly higher levels of state mindfulness, due to "breath focus" audio prompts, relative to participants receiving MMA-. State mindfulness is not expected to differ in SC participants as a result of MM conditions.

Hypothesis 4. CP and DA participants receiving MMA+ will report significantly lower levels of mind-wandering given the aid of "breath focus" prompts, compared to corresponding participants receiving MMA-. There will be no significant difference among SC participants according to MM conditions.

Methods

Design

This randomized, controlled trial (RCT) study was designed according to the 2010 CONSORT statement (CONSORT E-HEALTH checklist) (Eysenbach G, Group, & CONSORT-EHEALTH:, 2011), reviewed and approved by the York University research ethics board (Human Participants Review Committee protocol # e2017 - 303), and registered with ClinicalTrials.gov (NCT03296007) prior to the recruitment of the first participant (09/22/2017). This study planned to enrol approximately 180 male and female participants from the York Undergraduate Research Participant Pool, based on voluntary participation, and classified into 3 groups of ~60 participants each (and randomized into MMA+ or MMA-) based on their pre-screening questionnaires: chronic pain (n=30 MMA+ and n=30 MMA-), depressive-anxious (n=30 MMA+ and n=30 MMA-), and condition-free participants (n=30 MMA+ and n=30 MMA-) (Figure 3).

Sample size estimation

Sample size estimate for a repeated measures ANOVA with 3 groups (CP, DA, CF), 2 conditions (MMA+, MMA-), and 3 phases (baseline, stress induction, MM) indicated that a total of 141 participants were needed to detect small-to-medium effect size (f=0.15) HRV changes with a Type I error rate (alpha) of 0.05, a power of 0.95, and a 0.50 correlation between repeated measures (G*Power). The small-to-medium effect size corresponds to previously published studies of HRV increases during brief mindfulness practice (Azam et al., 2015; Azam et al.,

2016). Recruitment of >180 participants was planned to allow for an attrition rate of ~20% due to withdrawals, drop-outs, technical failures, and missing data. Based on pre-screening and recruitment numbers in our past pilot study (Latman et al, unpublished) we found the percentage of participants reporting diagnosed chronic pain, or severe depression or anxiety symptoms, to be 27%, 33%, and 41%, respectively. Accordingly, the combined number of students expected to be pre-screened to net 60 participants per group was approximately N=550.

Inclusion and exclusion criteria

Participants were eligible for the study if they were enrolled in a course at York University that provided course participation credit via study enrollment through the Department of Psychology's Undergraduate Research Participant Pool website. On the recruitment website as well as on the consent form, we explained that the study may require use of a smartphone-based task. Participants with self-reported cardiac conditions (e.g. cardiac arrhythmias, coronary artery disease, pacemaker) were excluded as they contravene the interpretation of vagal-mediated HRV (Laborde et al, 2017). Participants in this study had no prior relationship with the researchers, including no participation in classes by faculty members on the research team.

Procedure

Group classification and randomization. Upon signing up for the study online, participants were instructed to arrive to the Human Pain Mechanisms Lab at York University, where the study procedures where explained, and informed consent was obtained from all participants. Participants completed pre-screening questionnaires for chronic pain, depression, or anxiety symptoms. A research assistant scored the questionnaire once completed, verifying whether the participant reported having a chronic pain condition (>3 months duration of pain on the Brief Pain Inventory) (Treede et al. 2015), and if so, they were classified in the chronic pain group. If they did not report a pain condition but met criteria for "severe" depression symptoms (≥21 on

the Centre for Epidemiological Studies Depression Scale) (Lewinsohn, Seeley, Roberts, & Allen, 1997) or anxiety symptoms (≥36 on the Beck Anxiety Inventory) (Leyfer, Ruberg, & Woodruff-Borden, 2006), they were classified into the depressive-anxious group. Participants who did not meet criteria for chronic pain or severe depressive-anxious symptoms were classified into the sub-criteria group.

A three-block randomization schedule (chronic pain, depression-anxiety, condition-free) with two treatment arm allocations (MMA+, MMA-) was created by the study co-investigator (Koopman et al.) using a randomization sequence generator (Dallal, 2007). The randomization schedule used a 1:1 ratio with blocks of 10. Treatment allocation was determined by study coordinators and staff members after participants completed their pre-screening questionnaires to determine their group classification (Figure 1). Study research assistants reviewed pre-screening questionnaires and assign the grouped participants to their corresponding treatment arm using a randomization schedule column concealed in a computer spreadsheet using the 'highlight black' function. Upon entering participants into the spreadsheet, research assistants un-highlighted the next available cell in the corresponding column to reveal their treatment assignment.

Experimental Session. Participants underwent a 3-phase (baseline, stress induction, MM) assessment during which electrocardiogram and respiration rate data as collected for later HRV analysis (Figure 1). A mobile cardiogram system by MindWare (Ohio, US) was used, requiring placement of 3 adhesive electrodes on the right clavicle and left and right hipbones, and a respiratory belt secured around the participant's waist.

Rest phase. The first phase comprised a 5-minute baseline period during which participants rested quietly with their eyes closed, and were instructed not to speak or make sudden movements.

Stress-induction phase. Following the baseline phase, a 5-minute stress-induction procedure was performed whereby the participant engaged in a set of mental arithmetic tasks, with the instruction to work as quickly as possible for maximal performance. The task involved a series of word problems and questions requiring mathematical operations such as addition, subtraction, division, fractions, and percentage calculations. Mental arithmetic was chosen as a stressor task due to its superior properties in eliciting sympathetic responses compared to other laboratory-based stressors (Fechir et al., 2008).

Post-stress meditation phase. After the stress induction phase, a post-stress mindfulness meditation phase involved either the MMA+ or MMA- task according to the randomization schedule.

After completing the pre-study set of questionnaires, participants were randomized to either the smartphone-based MMA+ or a mindful breathing practice without use of a mobile app (MMA-). Mindful breathing instructions involved paying attention to breathing sensations while seated with eyes closed for 12 minutes, and reorienting attention back to breathing as soon as they became aware of mind-wandering (Kabat-Zinn, 2003). Research assistants remained in the room during the intervention phase, for both intervention conditions, to address technical or practical issues with the interventions. There were no adverse events expected during the study, and participants were free to withdraw their participation at any time during the study with no penalty to their research credit or any other costs.

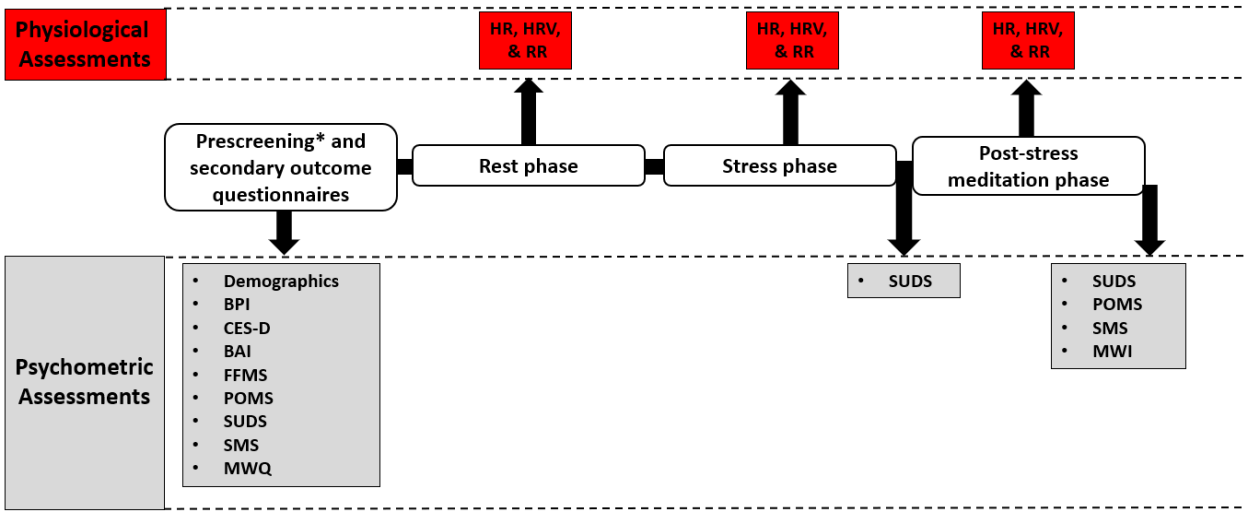


Figure 1. Study procedures. Physiological assessments in red boxes, questionnaire assessments in grey boxes. HR= heart rate; HRV = heart rate variability; RR = respiration rate; BPI = Brief Pain Inventory; CES-D = Center for Epidemiology-Depression Subscale; BAI = Beck Depression Inventory; FFMQ = Five Factor Mindfulness Questionnaire; POMS = Profile of Mood States; SMS = State Mindfulness Scale; MWQ = Mind-Wandering Questionnaire ; SUDS = Subjective Units of Distress Scale. *Participants were randomized to MM conditions after pre-screening and group classification was determined.

The Intervention Arm: Mindfulness meditation with the app

The MMA was developed using JavaScript and installed on an IPhone 4s (Figure 2). Since the application was designed with young adults in mind, the leading thought was to keep the intervention brief, and the design simple and easy to use. Participants were asked to hover their thumbs over two buttons, "Breath" and "Other", presented on a white screen for the duration of the task (Figure 1). The MMA is a 12-minute breath awareness task that involved a total of 24 silent periods of six different durations (5 seconds, 15 seconds, 25 seconds, 35 seconds, 45 seconds and 55 seconds) randomly presented four times each and followed by the presentation of a one-second tone. Instructions for the task included:

(1) Keep your eyes closed for the duration of the 12-minute task,

(2) During the silent periods of the task, practice mindful breathing by paying attention to your breathing sensations, including: (a) the feeling of the air passing through your nostrils, (b) the movement of your in-and-out breath at your chest and torso, (c) the sound of the air as you breathe in and out, (d) the temperature (coolness or warmth) of the in-and-out breath. Return

your attention to your breath when you have noticed your attention has been elsewhere or once the audio tone has sounded.

At the sound of the tone, press 'breath' if, in that moment, you were attending to your breath, or 'other' if you were attending to other experiences.

(4) Practice mindful breathing until the sound of the next tone.

Participants were provided a one-minute practice session with the MMA prior to the intervention session. Immediately after the practice session, participants used the MMA in conjunction with the practice of mindful breathing with the above instructions for 12 minutes in a seated and eyes closed position.

A prototype was first tested internally and feedback was gathered from the research team and pilot participants to ensure a smooth user experience without technical bugs. Feedback influenced decisions regarding the number of tones and interval between tones played, the size of the "breath" and "other" buttons, and the addition of a one-minute trial period prior to commencing the 12-minute meditation task.

Figure 2. The Mindfulness Meditation App (MMA+ condition).

The Control Arm: Mindfulness meditation with no app

Participants in the MMA- condition engaged in mindful breathing (instructions below) without use of the MMA for 12 minutes in a seated position with eyes closed.

(1) Keep your eyes closed for the duration of the 12-minute task,

(2) Practice mindful breathing by paying attention to your breathing sensations, including: (a) the feeling of the air passing through your nostrils, (b) the movement of your in-and-out breath at your chest and torso, (c) the sound of the air as you breathe in and out, (d) the temperature (coolness or warmth) of the in-and-out breath. Return your attention to your breath when you have noticed your attention has been elsewhere.

Measures

Physiological measures.

Heart Rate Variability (HRV). There are several metrics that quantify HRV, the majority of which are either time-based or frequency-based. With the beat-to-beat interval series (also referred to as the R-R series), one can estimate the square root of the mean of squared successive differences between interbeat intervals, which has been found to be strongly correlated with respiration-based HR changes (RMSSD) (Allen et al., 2007). It is important to note that both the IBI and SDNN are subject to increases with longer ECG recordings (influenced by slower, long range fluctuations in HR independent of respiration-induced beat-to-beat changes). Thus, the Task Force (Camm et al., 1996) has recommended 2-5 minutes as a minimum standardized length of HRV assessment in clinical and psychophysiological research. Using the frequency domain measure, one can examine the extent to which the HR varies within specific frequency ranges. The Fourier transform method deconstructs the time domain representation of the R-R series and computes a measure of 'power' in several frequency bands in units of milliseconds squared (ms^2). These bands include ultra-low frequency (< 0.003 Hz), very low frequency (0.0033 – 0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF; 0.15–0.4 Hz). Typically, the frequency band of interest for the purposes of HRV interpretation is the HF band, as this is where the respiratory-linked beat-to-beat changes are reflected (Allen et al., 2007; Quintana & Heathers, 2014). While this is not intended to be an exhaustive account of HRV metrics, the aforementioned measures are the most commonly used in studies of vagal influence on cardiac chronotropy. Based on the recommendations by the two international committees (Berntson et al., 1997; Camm et al., 1996), the present study focused on the high-frequency HRV as the primary measure to interpret changes in vagal-mediated HRV across different conditions.

Electrocardiogram (ECG) recordings were collected using MindWare Impedance Cardiograph acquisition system (Ohio, United States), and used to analyze HF-HRV as the

primary HRV measure. The MindWare system uses 3 adhesive electrodes applied to the right collarbone (-) and the lower left and right ribs (+ and ground), or alternatively the wrists (+ and -) and ankle (ground) if necessary. MindWare BioLab and HRV software was used to calculate time and frequency-based HRV metrics. Participants were measured during phases of: 1) Rest in a seated position with eyes closed (5 minutes), 2) a stress-induction task requiring rapid completion of arithmetic problems (5 minutes), and 3) meditation conditions of MMA+ or MMA-. Two individuals separately inspected the ECG files to derive HRV values.

Heart rate and Respiration Rate. Heart rate data was obtained through the ECG signal recorded by the MindWare system, and calculated using BioLab and HRV software. A MindWare respiratory belt (below the ribcage) was used to monitor respiration rate during rest, stress-induction, and meditation. Respiration rate was also computed with BioLab and HRV software. Respiration is a potential confounding variable for HRV interpretation, recommended for use as a covariate in HRV analyses if it is found to differ between study groups or conditions (Laborde et al., 2017).

Pre-screening questionnaires for group classification. The following psychometric questionnaires were administered to participants to determine group classification:

Brief Pain Inventory (BPI) – Short Form. The BPI is a 16-item, self-report questionnaire that measures pain intensity and pain interference. The test has good internal consistency (a=0.85) and high test-retest reliability (C. S. Cleeland & Ryan, 1994).

Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a screening test for depressive symptoms with good sensitivity and specificity, and high internal consistency (Lewinsohn et al., 1997). The CES-D has been found acceptable and reliable in adolescent and young adult populations (Radloff, 1991).

Beck Anxiety Inventory (BAI). The BAI is a 21-question multiple-choice self-report questionnaire that is used for measuring anxiety severity. Internal consistency (Cronbach's alpha) ranges from .92 to .94 for adults and test-retest (one week interval) reliability is .75 (Leyfer et al., 2006).

Secondary outcomes. Participants were asked to complete the following psychometric questionnaires for exploratory analyses:

Profile of Mood States (POMS-SF). The POMS-SF is a 37-item questionnaire designed to assess global distress as well as six mood states: Fatigue, Vigor-Activity, Tension-Anxiety, Depression, Anger-Hostility, and Confusion-Bewilderment. Participants are asked to indicate the degree to which they have experienced different mood states in the past week. The scale has good internal consistency (α=.91) and test-retest reliability (r=.74). The POMS has been validated for use in adolescents and adults (Terry, Lane, & Fogarty, 2003). Higher total scores represent greater total mood disturbance (Curran, Andrykowski, & Studts, 1995).

State Mindfulness Scale (SMS). The SMS is a state measure of mindfulness designed to reflect a conceptual model of mindfulness consistent with Buddhist scholarship (Analayo, 2004; Bodhi, 1993). Its items query the objects of mindful attention (i.e. physical sensations and mental events) and the qualities of mindfulness as a meta-cognitive state (i.e. how a person attends). The scale is designed to be administered after formal practice of mindfulness and has been tested for acceptable internal consistency (α=0.90 – 0.95) and test-retest reliability (r=0.65).

Subjective Units of Distress Scale (SUDS). The SUDS is a means of rating the severity of current distress (or anxiety), allowing for the monitoring of changes over time, where 0 is feeling perfectly relaxed and 100 is the worst anxiety and stress imaginable (Benjamin et al., 2010). Participants were asked to provide 0-100 SUDS ratings at baseline, post-stress-induction, and

after the meditation phases. The SUDS ratings were used for manipulation checks with respect to the mental arithmetic stressor and to monitor changes in stress as a result of the MM conditions.

Mind-Wandering Inventory (MWI). The MWI is a 5-point likert-based questionnaire developed by the authors with items retroactively assessing the frequency of different types of mind-wandering events the respondent experienced during the mindful breathing exercise. The MWI was used in a previous pilot study (manuscript in preparation) and statistical analyses of its psychometric properties is underway (Azam, Latman, & Katz, 2019).

Trait measures. Participants were also asked to complete the following psychometric questionnaires to understand key mindfulness-related characteristics of study groups:

The Five-Factor Mindfulness Scale (FFMS). The FFMS is a 39-item Likert-based scale that assesses five aspects of mindfulness: non -reactivity to inner experience, acting with awareness, describing, non-judging of inner experience, and observing. Research has demonstrated the FFMS to be valid in community and student samples with an internal consistency of alpha > 0.90 (Baer et al., 2008).

Mind-Wandering Questionnaire (MWQ). The MWQ is a 5-item scale that assesses the frequency of mind-wandering events. The MWQ has demonstrated high internal consistency (alpha = 0.85) and convergent validity with other measures of mind-wandering and task-unrelated thought (Mrazek et al, 2013).

Statistical Analyses

The present study specified two co-primary hypotheses based on published recommendations for HRV analyses (Laborde et al., 2017; Quintana & Heathers, 2014). Generally, within-subject designs and analyses are preferred considering the high inter-individual variations observed in HRV measures. Results were analyzed using a planned comparisons approach (Roger, 1995) to

test the proposed hypotheses. Planned comparisons were conducted using ANOVAs, corrected by Bonferroni method, and interpreted using significance values and effect sizes (Cohen, 2013). Intention-to-treat methodology was the guiding principle of analyses. A complete case analysis approach was used in anticipation of missing or unusable data.

Secondary analyses of depressed mood, tense-anxious mood, and subjective distress were conducted using three-way repeated measures ANOVA (group: CP, DA, SC; time: pre-rest, post-stress, post-meditation; condition: MMA+, MMA-) and state mindfulness and mind-wandering were analyzed using a two-way ANOVA (group: CP, DA, SC; condition: MMA+, MMA-). Significant main effects and interactions were followed up with simple main effects and Bonferroni-corrected post hoc tests of planned comparisons (significant p-value = 0.05 divided number of comparisons within hypothesis test). Demographic and clinical variables, as well as heart rate and respiration rate were analyzed with ANOVA followed by post-hoc comparisons and Chi-square tests for manipulation checks and to detect confounding group and condition differences. Baseline HRV measures were analyzed by examining the two-way interaction of group and phase using simple effects tests of group at the rest phase.

Primary outcome.

Hypothesis 1a: Higher HRV in CP and DA receiving MMA+. To test the hypothesis of higher HRV during the MM phase in CP and DA groups receiving MMA+ vs MMA-, 3-way ANOVA was conducted with group (CP, DA, SC), condition (MMA+ and MMA-), and phase (rest, stress, MM), followed by planned comparisons for hypothesized differences. Specifically, this involved examining the simple simple main effect of MMA+ and MMA- conditions for each group during the MM phase.

Hypothesis 1b: Greater HRV increases from stress to MM for CP and DA receiving MMA+. To test the hypothesis that HRV would increase from stress to MM for participants receiving MMA+ vs MMA- in groups CP and DA, but not SC, a 3-way ANOVA was examined with a planned comparisons approach, specifically examining the simple simple main effect of phase comparing stress to MM for MMA+ and MMA- conditions in each group.

Secondary outcomes.

Hypothesis 2a: Lower and greater reduction in depressed and anxious mood in MMA+ for CP and DA. To analyze pre-post changes in depressed and anxious mood, 2 three-way ANOVAs were conducted using group (CP, DA, SC), time (baseline, post-MM) and condition (MMA-, MMA+) as factors and POMS Depression and POMS Tension-Anxiety subscales as the dependent variables, respectively. Planned comparisons were conducted examining (1) the simple simple main effect of time (baseline vs post-MM) for MMA+ and MMA- conditions in each group, and (2) the simple simple main effect of condition (MMA+ vs MMA-) at post-MM for each group.

Hypothesis 2b: Lower and greater reduction in subjective distress in MMA+ compared to MMA- in DA and CP. Subjective distress ratings were analyzed by three-way ANOVA using group (CP, DA, SC), time (baseline, post-stress, post-MM), and condition (MMA-, MMA+) as factors and subjective distress (SUDS) as the dependent variable. Planned comparisons were conducted examining (1) the simple simple main effect of time (post-stress vs post-MM) for MMA+ and MMA- conditions in each group, and (2) the simple simple main effect of condition (MMA+ vs MMA-) at post-MM for each group.

Hypothesis 3: Higher state mindfulness in MMA+ in CP and DA. To analyze differences in state mindfulness, a two-way ANOVA with group (CP, DA, SC) and condition (MMA-, MMA+)

as factors was conducted. Planned comparisons examined the simple main effect of condition (MMA+ vs MMA-) in each group.

Hypothesis 4: Lower mind-wandering in MMA+ for CP and DA. To analyze differences in mind-wandering, a two-way ANOVA with group (CP, DA, SC) and condition (MMA-, MMA+) as factors was conducted. Planned comparisons examined the simple main effect of condition (MMA+ vs MMA-) in each group.

Results

Data preparation

HF-HRV data was log-transformed to reduce skewness (0.57) to acceptable levels (0.24), based on published recommendations (Laborde et al., 2017).

Participants & grouping

After prescreening and enrolment (Figure 3), N=213 participants were classified into study groups of chronic pain (CP; n=58), depressed-anxious (DA; n=64) and sub-criteria (SC; n=91). Groups did not differ on age, gender distribution, and educational status (Table 1).

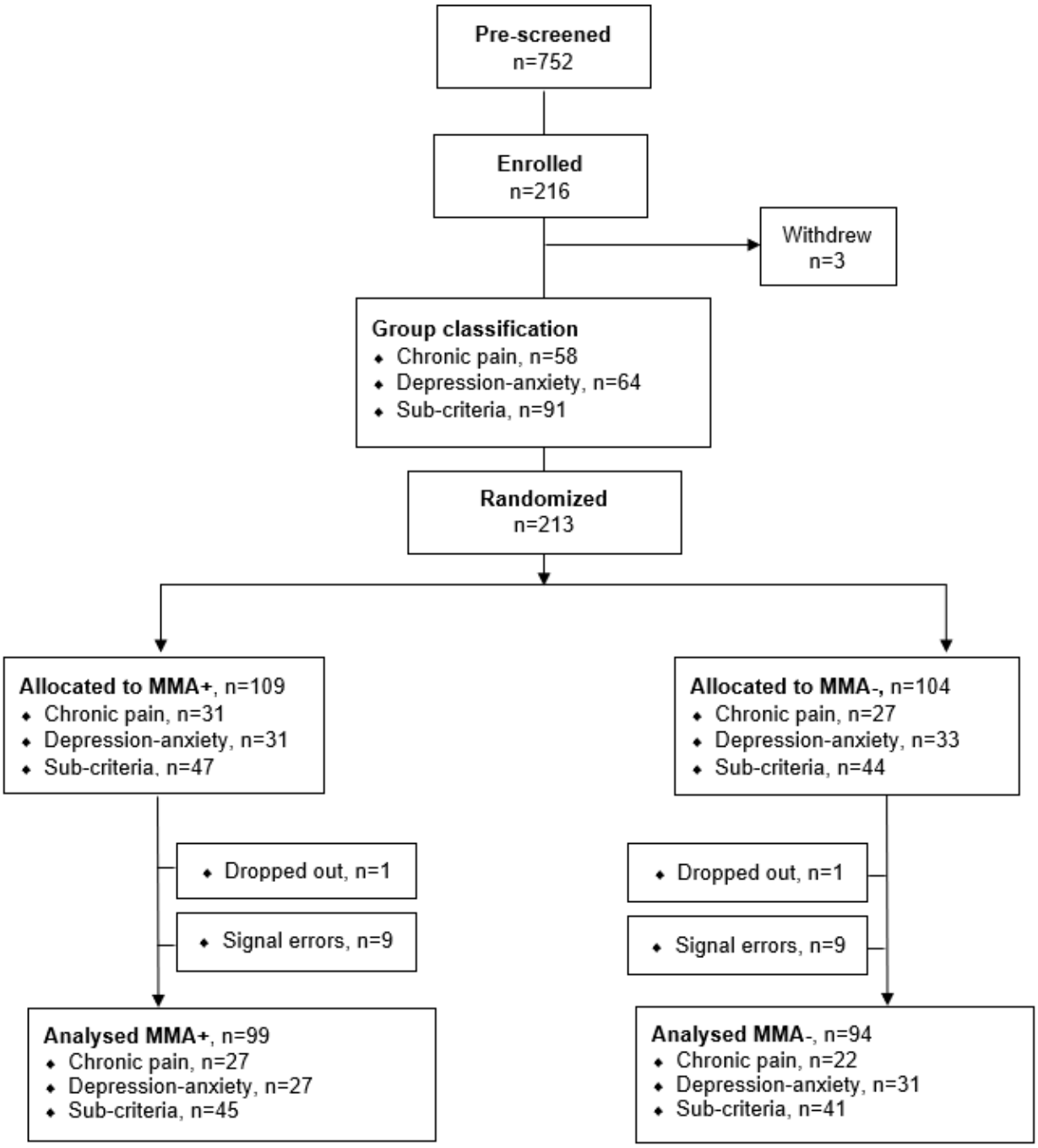


Figure 3. Consolidated Standards of Reporting Trials (2010) flow diagram showing participant flow for enrolment, group classification, randomization to intervention, and analyses. MMA-: mindful breathing practice without using the Mindfulness Meditation App; MMA+: mindful breathing practice using the Mindfulness Meditation App.

Table 1. Demographic data of study groups.

		Groups		Tests
Measure	**Chronic Pain (n=49)**	**Depressive-Anxious (n=58)**	**Sub-Criteria (n=86)**	
Age (yrs) (SD)	20.58 (3.5)	19.95 (2.78)	20.92 (4.94)	$F(2,191)=1.02$, $p=0.36$
Sex, n %				$\chi^2(4)=0.86$, $p=0.93$

Female	35 (72.0)	41 (71.2)	60 (69.8)	
Male	14 (28.0)	16 (27.1)	25 (29.1)	
Non-Binary	0 (0.0)	1 (1.7)	1 (1.1)	
Education, n (%)				$\chi^2(6)=6.64$, $p=0.35$
High School	43 (88.0)	48 (83.1)	68 (79.1)	
College	5 (10)	3 (5.1)	6 (7.0)	
Bachelor's	1 (2)	7 (11.9)	11 (12.8)	
Master's	0	0	1 (1.2)	
Ethnic Group, n (%)				$\chi^2(24)=27.83$, $p=0.27$
African	5 (10.0)	6 (10.2)	6 (7.0)	
Caribbean	7 (14.0)	7 (11.9)	11 (12.8)	
Chinese	2 (4.0)	4 (6.8)	2 (2.3)	
Indigenous	1 (2.0)	1 (2.0)	0	
Korean	0	3 (5.1)	3 (3.5)	
Latin American	2 (4.0)	0	0	
Mixed	5 (10.0)	8 (15.3)	9 (10.4)	
South Asian	9 (18.0)	10 (16.9)	26 (30.2)	
Southeast Asian	3 (6.0)	5 (8.5)	5 (5.8)	
West Asian	12 (26.0)	8 (13.6)	11 (12.8)	
White	3 (6.0)	6 (10.2)	13 (15.1)	

Group clinical characteristics and traits

Lifetime prevalence of a mood disorder diagnosis was 18.0% in CP, 33.9% in DA, and 14.0% in SC groups [$\chi^2(4) = 9.02$, $p = 0.06$]; DA group was more likely to report a mood disorder diagnosis. Lifetime prevalence of an anxiety disorder diagnosis was 26.5% in CP, 31.0% in DA, and 7.1% in SC groups [$\chi^2(4) = 9.02$, $p = 0.06$]; DA group was most likely, and SC group was least likely, to report an anxiety disorder diagnosis. Types of pain diagnoses in the CP group included migraine/tension headaches (54.0%), chronic back pain (28.0%), chronic joint pain (14.0%), and neuropathic pain (6.0%).

CP group reported significantly higher average pain intensity (past 24 hours) and current pain intensity than DA and SC groups ($p < 0.01$) (Table 2). Fifty-two percent of CP group participants reported mild-to-moderate current pain intensity compared to 27.7% and 21.0% of DA and SC groups, respectively. DA and CP groups reported significantly higher depression symptoms than SC group ($p < 0.001$). Eighty-one percent of DA group participants reported severe depressive symptoms compared to 54.0% in the CP group and 0% in the SC group. DA

group's current depressed mood was significantly higher than CP group's ($p < 0.001$), and both were higher than SC group ($p < 0.001$). Both the CP and DA groups reported significantly higher anxiety symptoms and current anxious mood than the SC group ($p < 0.001$).

CP and DA groups had significantly lower trait mindfulness than SC group, with lower subscales of observing, acting with awareness, and nonjudgment skills. Relatedly, CP and DA groups were significantly higher on trait mind-wandering ($p < 0.001$) relative to SC group.

Table 2. Clinical characteristics of study groups.

Characteristic	CP (n=49)	DA (n=58)	SC (n=85)	Between Group Tests
Average pain intensity[1], M (SD)	3.82 (2.44)	1.31 (1.99)	1.13 (1.54)	$F(2,191) = 33.92$, $p < 0.001$ CP > DA & SC ($p < 0.001$)
Current pain intensity[1], M (SD)	1.50 (2.12)	0.71 (1.43)	0.49 (1.56)	$F(2,191) = 7.1$, $p = 0.001$
No pain at all (0/10), n (%)	24 (48.0)	43 (72.9)	68 (79.1)	CP > DA & SC ($p < 0.01$)
Mild (1—3/10), n (%)	17 (34.0)	10 (17.5)	15 (17.5)	
Moderate (4—7/10), n (%)	9 (18.0)	6 (10.2)	3 (3.5)	
Severe (>7/10), n (%)	0	0	0	
Depression symptoms[2], M (SD)	24.76 (12.48)	27.40 (9.64)	10.74 (5.10)	$F(2,191) = 73.46$, $p < 0.001$
Range of scores	3—54	4—59	1—21	DA & CP > SC ($p < 0.001$)
Depression symptom severity[2], n (%)				$\chi^2(2)=105.54$, $p <0.001$
Symptom score >21	27 (54.0)	48 (81.4)	0	
Symptom score ≤21	23 (46.0)	11 (18.6)	86 (100)	
Current depressed mood[3], M (SD)	5.24 (6.36)	8.49 (6.93)	1.29 (1.97)	$F(2,191) = 34.88$, $p <$ 0.001 DA > CP > SC ($p \leq 0.001$)
Anxiety symptoms[4], M (SD)	22.46 (13.34)	24.12 (11.29)	9.41 (7.76)	$F(2,191) = 42.65$, $p < 0.001$
Range of scores				DA & CP > SC ($p < 0.001$)
Anxiety symptom severity, n (%)				$\chi^2(2)=15.85$, $p <0.001$
Symptom score >36	42 (84.0)	49 (83.1)	0	
Symptom score ≤36	8 (16.0)	10 (16.9)	86 (100)	
Current anxious mood[3], M (SD)	8.98 (6.24)	9.12 (5.43)	3.31 (3.31)	F(2,191)=33.43, $p < 0.001$ DA & CP > SC ($p < 0.001$)
Lifetime psychiatric diagnoses[5], n (%)				
None	33 (66.0)	34 (57.6)	70 (81.40)	$\chi2(2) = 10.04$, p = 0.01
Mood disorders	9 (18.0)	20 (33.9)	12 (14.0)	$\chi2(2) = 8.75$, p = 0.01
Anxiety disorders	13 (26.0)	18 (30.5)	6 (7.0)	$\chi2(2) = 14.76$, p = 0.001
Post-traumatic stress disorder	3 (6.0)	2 (3.4)	0	$\chi2(2) = 4.79$, p = 0.09
Substance use disorder	0	0	2 (2.3)	$\chi2(2) = 2.56$, p = 0.28
Attention-deficit disorder	2 (4.0)	6 (10.20)	4 (4.65)	$\chi2(2) = 1.75$, p = 0.10
Mindfulness skills total[6]	119.54 (14.00)	114.93 (16.36)	128.93 (16.19)	SC > CP & DA ($p < 0.001$)
Observe	23.24 (5.88)	23.19 (5.56)	23.69 (6.64)	p = ns
Describe	25.72 (3.46)	24.72 (4.21)	26.06 (3.41)	p = ns
Acting with awareness	23.70 (5.92)	21.36 (7.14)	28.74 (4.94)	SC > CP > DA ($p < 0.05$)
Nonjudging	23.86 (5.30)	21.71 (6.83)	28.63 (6.32)	SC > CP & DA ($p < 0.001$)
Nonreactivity	23.02 (5.14)	23.64 (3.83)	21.81 (4.83)	p = ns
Mind-wandering[7]	21.14 (4.38)	22.09 (4.47)	17.60 (4.81)	SC < CP & DA ($p < 0.001$)

Notes. [1] Brief Pain Inventory; [2] Center for Epidemiological Studies Scale II—Depression Subscale; [3] Profile of Mood States—Short Form; [4] Beck Anxiety Inventory; [5] Data is based on participant self-reported diagnoses (past or current); [6] Five-factor Inventory of Mindfulness Skills; [7] Mind-wandering Questionnaire. CP =Chronic Pain; DA=Depressive-Anxious; SC=Sub-criteria.

Analyses of experimental and confounding variables

Study groups did not differ on consumption of caffeinated beverages (Table 3), and all participants denied smoking cigarettes two hours prior to the experiment time. The SC group was significantly more likely to have exercised in the previous 24 hours relative to the CP and DA groups, and a follow-up Chi-square test revealed this did not differ within the SC group between the MMA+ and MMA- conditions. Previous experience with mindfulness meditation was reported by 38.8% of CP, 34.5% of DA, and 24.7% of SC group participants [$\chi^2(6) = 7.11$, $p = 0.31$].

Table 3. Self-reported experimental confounders among study groups.

	CP (n=50)	DA (n=59)	SC (n=86)	Between-Groups Tests
Consumed caffeinated beverage in the last 2 hours, n (%)	3 (6.0)	4 (6.8)	3 (4.4)	$\chi^2(2) = 0.88$, $p = 0.64$
Engaged in moderate or vigorous physical exercise in the last 24 hours, n (%)	0	2 (3.4)	12 (14.0)	$\chi^2(2) = 11.06$, $p < 0.01$ SC more likely to have reported exercise (expected count: 6.2) *followed up with Chi-square in SC between conditions, p =0.38
Consumed an alcoholic beverage in the last 24 hours, n (%)	2 (4.0)	3 (5.10)	2 (2.30)	$\chi^2(2) = 0.80$, $p = 0.67$
Medication use, n (%)				$\chi^2(9) = 0.07$, $p = 0.90$
Analgesic	4 (8.2)	1 (1.7)	8 (9.4)	
Amphetamine	1 (2.0)	1 (2.0)	0	
Anti-asthmatic	1 (2.0)	0	0	
Antidepressants	2 (4.0)	6 (10.3)	5 (5.9)	
Antihistamine	0	1 (1.7)	1 (1.2)	
Antipsychotic	0	0	1 (1.2)	
Anxiolytic	0	1 (1.7)	2 (2.1)	
Insulin	0	1 (1.7)	0	
Medical marijuana	0	1 (1.7)	2 (2.1)	
Nonsteroidal anti-inflammatory	5 (10.1)	3 (5.1)	5 (5.9)	

Note. Analgesics include Tylenol. Amphetamine includes Vyvanse. Anti-asthmatic includes Salbutamol. Anxiolytics include benzodiazepine. Nonsteroidal anti-inflammatory includes Advil and Aspirin. CP =Chronic Pain; DA=Depressive-Anxious; CF=Sub-criteria.

Heart rate. A three-way repeated measures ANOVA with group (CP, DA, SC), condition (MAA+, MMA-), and phase (rest, stress, meditation), with heart rate as dependent

variable, revealed a main effect of phase [$F(2, 188) = 6.22$, $p < 0.005$, $\eta_p^2 = 0.06$]. As expected, heart rate was lower during meditation compared to rest ($p = 0.01$) and stress ($p = 0.001$) phases. The Group and Condition main effects were not significant ($p > 0.05$), nor were any of the two-way or the three-way interaction effects (all $p > 0.05$). (Table 4).

Respiration rate. A three-way group (CP, DA, SC), by condition (MAA+, MMA-), by phase (rest, stress, meditation) ANOVA, with respiration rate as dependent variable, revealed a main effect of phase [$F(2,188) = 34.06$, $p < 0.001$, $\eta_p^2 = 0.27$). Respiration rate during stress was higher than rest ($p < 0.001$) phase. Respiration rate during meditation was lower than rest ($p = 0.001$) and stress ($p < 0.001$), as expected (Table 4). The Group and Condition main effects were not significant ($p > 0.05$), nor were any of the two-way or the three-way interaction effects (all $p > 0.05$). Thus, inclusion of respiration rate as a covariate in the primary HRV analyses was not deemed necessary.

Table 4. Means and standard deviations of heart rate and respiration rate in study groups according to phases and conditions

	Rest		Stress		MM	
	HR	**RR**	**HR**	**RR**	**HR**	**RR**
All participants (N=193)	81.22 (11.13)	14.82 (4.45)	81.67 (10.63)	17.03 (4.70)[a]	80.46 (10.47)[a, b]	13.78 (3.88)[a, b]
Chronic Pain						
MMA+ (n=27)	80.79 (10.71)	16.71 (4.28)	80.27 (9.79)	16.99 (5.18)	79.45 (9.85)	14.36 (4.50)
MMA- (n=22)	79.23 (9.02)	15.41 (5.31)	81.10 (9.42)	18.12 (5.34)	79.24 (8.88)	14.08 (3.88)
Depressive-Anxious						
MMA+ (n=27)	85.83 (12.58)	14.23 (3.43)	85.50 (11.57)	16.67 (4.28)	84.44 (12.35)	14.35 (3.11)
MMA- (n=31)	80.31 (10.27)	15.30 (5.05)	80.78 (9.95)	17.33 (4.05)	80.45 (9.76)	13.28 (3.82)
Sub-Criteria						
MMA+ (n=45)	80.30 (12.04)	14.09 (4.50)	80.78 (12.27)	16.96 (4.63)	79.66 (11.01)	13.36 (3.86)
MMA- (n=41)	81.41 (11.06)	14.21 (3.80)	81.93 (9.83)	16.44 (4.92)	80.10 (10.40)	13.73 (4.14)

Note. HR=Heart rate; RR=Respiration rate. [a]Within-subject change from rest ($p \leq 0.01$). [b]Within-subject change from stress ($p \leq 0.001$).

Primary results

Three-way ANOVA indicated a significant main effect of phase [$F(2, 374) = 29.32$, $p < 0.001$, $\eta_p^2 = 0.14$], and significant group x phase [$F(4, 374)=4.70$, $p =0.001$, $\eta_p^2=0.05$], condition

x phase [$F(2, 374) = 7.05$, $p = 0.001$, $\eta_p^2 = 0.04$] interaction effects, but the group [$F(2, 374)=2.48$, $p = 0.09$], condition [$F(2, 374) = 1.67$, $p = 0.20$], group x condition [$F(2, 187) = 0.04$, $p = 0.96$] and the three-way interaction [$F(4, 374) = 2.20$, $p = 0.07$] effects were not significant.

Baseline HRV. The two-way interaction of group x phase was significant, [$F(2, 374)=4.70$, $p = 0.001$, $\eta_p^2 = 0.05$]. The simple interaction effect of group was significant at rest phase [$F(2, 187) = 6.50$, $p = 0.002$, $\eta_p^2 = 0.07$]. As expected, HF-HRV was higher in SC (M = 6.48, SD = 1.16) than CP (M = 5.92, SD = 0.88, $p < 0.01$, $d = 0.52$) and DA (M = 5.95, SD = 0.94, $p < 0.01$, $d = 0.49$) groups.

Hypothesis 1a: Higher HRV in CP and DA receiving MMA+. The simple simple main effect of condition during the MM phase was significant for the CP group [$F(1, 374) = 4.72$, $p = 0.01$], but not the DA [$F(1, 374) = 2.80$, $p = 0.10$] or SC [$F(1, 374) = 0.23$, $p = 0.63$] groups.

Analyses of planned comparisons. The planned comparison indicated HF-HRV was significantly higher in the MMA- condition compared to the MMA+ for CP ($p = 0.001$, $d = 0.67$), contrary to the hypothesis (Table 6).

Hypothesis 1b: Greater HRV increases from stress to MM for CP and DA receiving MMA+. The simple simple main effect of phase in the MMA+ condition was significant for the SC group [$F(2, 374) = 5.75$, $p < 0.005$, $\eta_p^2 = 0.06$], but not the CP [$F(2, 374) = 1.76$, $p = 0.18$] or DA [$F(2, 374) = 1.13$, $p = 0.33$] groups.

Analyses of planned comparisons. Planned comparisons indicated HF-HRV significantly increased from the stress to MM phase in SC group receiving MMA+ ($p < 0.001$, $d = 0.25$). In contrast, the simple simple main effect of phase in the MMA- condition was significant for the CP [$F(2, 374) = 27.16$, $p < 0.001$, $\eta_p^2 = 0.23$], DA [$F(2, 374 = 15.53$, $p < 0.001$, $\eta_p^2 = 0.14$], and SC [$F(2, 374) = 3.24$, $p < 0.001$, $\eta_p^2 = 0.14$] groups. Planned comparisons indicated HF-HRV

increased significantly from the stress to MM phase in the MMA- condition for CP ($p < 0.001$, $d = 0.41$), DA ($p < 0.001$, $d = 0.35$), and SC ($p < 0.001$, $d = 0.21$) groups.

Table 6. Means and standard deviations of log-transformed high-frequency heart rate variability in study groups and conditions

	Rest	Stress	MM
All participants (n=193)			
MMA+ (n=99)	6.20 (1.10)	6.07 (1.06)	6.38 (0.97)
MMA- (n=94)	6.15 (1.03)	6.29 (0.93)	6.67 (0.98)
Total (N=193)	6.17 (1.06)	6.18 (1.00)	6.52 (0.99)
Chronic Pain			
MMA+ (n=27)	5.94 (1.00)	5.94 (0.95)	6.27 (0.71)
MMA- (n=22)	5.91 (0.77)	6.40 (1.10)	6.92 (0.98)[c]
Total (n=50)	5.92 (0.87)[a]	6.15 (1.03)	6.56 (0.91)
Depressive-Anxious			
MMA+ (n=27)	5.99 (1.08)	5.96 (0.99)	6.15 (1.11)
MMA- (n=32)	5.94 (0.82)	6.19 (0.79)	6.59 (0.84)[c]
Total (n=59)	5.95 (0.94)[a]	6.07 (0.89)	6.38 (0.99)
Sub-Criteria			
MMA+ (n=45)	6.44 (1.14)	6.17 (1.16)	6.55 (0.99)[b]
MMA- (n=41)	6.53 (1.20)	6.36 (0.91)	6.65 (1.07)[c]
Total (n=86)	6.48 (1.16)[a]	6.27 (1.05)	6.60 (1.02)

Note. [a]$p < 0.001$ for SC vs. CP & DA at rest; ; [b]$p < 0.005$ for SC of stress vs. MM in MMA+; [c]$p \leq 0.001$ for CP, DA, & SC of stress vs. MM in MMA-. [d]$p < 0.001$ for MMA+ vs. MMA- in CP. All comparisons were planned and Bonferroni-corrected.

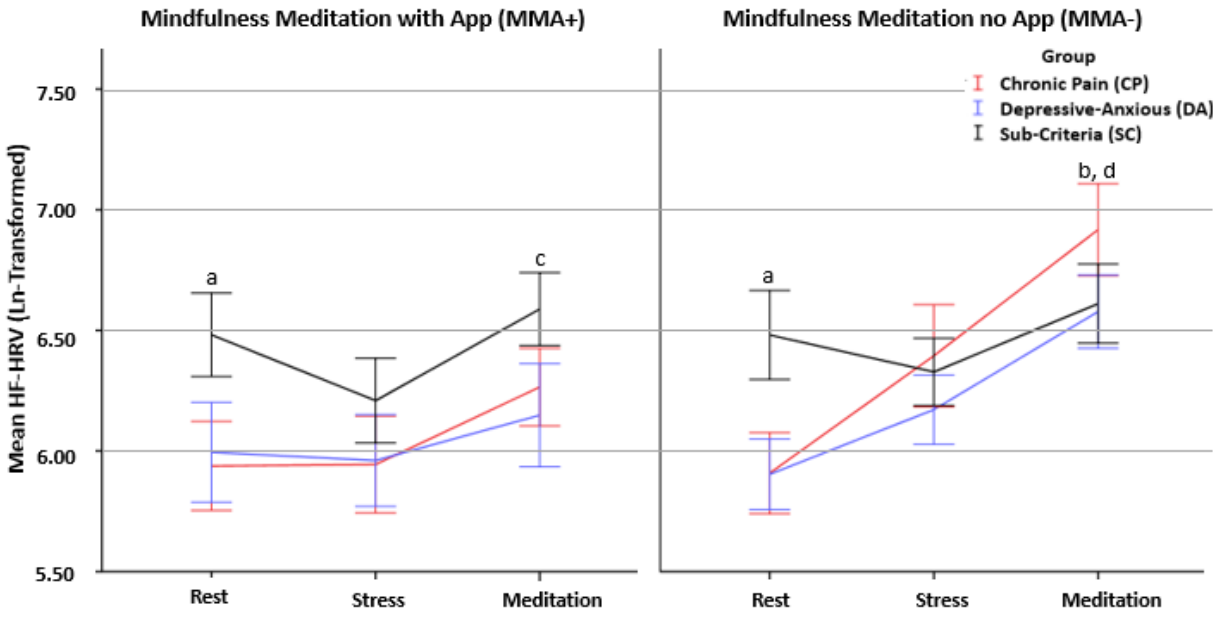


Figure 4. Mean plots of high-frequency heart rate variability (HF-HRV; Ln-transformed) in study groups and conditions across experimental phases. Error bars represents standard errors. a: $p < 0.01$ for SC vs. CP and SC vs. DA at rest; b: $p < 0.01$ for stress vs. MM in MMA- for SC, CP, and DA groups; c: $p < 0.005$ for stress vs. MM in MMA+ for SC group; d: $p < 0.001$ for MMA+ vs. MMA- in CP.

Secondary results

Hypothesis 2a: Lower and greater reduction in depressed and anxious mood in MMA+ compared to MMA- for CP and DA. Three-way repeated measures ANOVA of POMS-Depression (Figure 5) indicated a significant main effect of time [$F(1, 186) = 113.64$, $p < 0.001$, $\eta_p^2 = 0.38$] and group [$F(2, 186) = 29.04$, $p < 0.001$, $\eta_p^2 = 0.24$], and significant interactions of Group x Time [$F(2, 186) = 22.26$, $p<0.001$, $\eta_p^2 = 0.19$], and Condition x Time [$F(1, 186) = 8.23$, $p = 0.005$, $\eta_p^2 = 0.04$]. Neither the main effect of time nor the three-way interaction was significant (both $p > 0.05$).

Analyses of planned comparisons. The simple Group x Time interaction effect showed a significant group effect at baseline [$F(2, 186) = 31.29$, $p < 0.001$, $\eta_p^2 = 0.25$]. As expected, depressed mood was significantly higher in DA than CP ($p < 0.005$), and both were higher relative to SC (both $p < 0.001$) (Table 7). To note, the simple effect of condition at post-MM was not significant for any groups (all $p > 0.05$), indicating there were no differences in post-MM depressed mood according to MMA+ or MMA- conditions for any groups. The simple Time x Condition interaction effect shows that the simple effect of time on MMA+ condition was significant for CP [$F(1, 186) = 5.63$, $p = 0.01$] and DA [$F(1, 186) = 27.29$, $p < 0.001$], but not SC group [$F(1, 186) = 2.43$, $p = 0.12$]. Depressed mood was significantly reduced in CP ($p < 0.01$, $d = 0.35$) and DA ($p < 0.001$, $d = 0.48$) groups receiving MMA+. Similarly, simple effect of time on MMA- was significant for CP [$F(1, 186]=31.67$, $p<0.001$] and DA ($F(1, 186) = 89.31$, $p < 0.001$), but not SC [$F(1, 186) = 1.18$, $p = 0.18$) group. Depressed mood was significantly reduced in CP ($p < 0.001$, $d = 0.52$) and DA ($p < 0.001$, $d = 0.76$) groups receiving MMA-.

Three-way ANOVA of POMS-tension anxiety (Figure 6), indicated significant main effects of group [$F(2, 186) = 31.27$, $p< 0.001$, $\eta_p^2 = 0.25$], time [$F(1, 186) = 159.55$, $p < 0.001$, $\eta_p^2=0.46$], , and significant interactions of group x time [$F(2, 186) = 31.27$, $p < 0.001$, $\eta_p^2 =$

0.25], and time and condition [$F(1, 186) = 3.93$, $p < 0.05$, $\eta_p^2 = 0.02$]. Other main effects or three-way interaction were not significant (all $p > 0.05$).

Analyses of planned comparisons. Analysis of the Group x Time interaction showed that the simple effect of group was significant at baseline [$F(2, 186) = 31.29$, $p < 0.001$, $\eta_p^2 = 0.25$]. As expected, CP and DA groups reported significantly higher POMS tension-Anxiety scores than SC (both $p < 0.001$) at baseline. Simple effect of condition at post-MM was significant for DA group only [$F(1, 186) = 7.15$, $p < 0.01$, $\eta_p^2 = 0.04$], indicating, contrary to expectations, DA group in the MMA- condition had lower post-MM POMS Tension-Anxiety scores relative to MMA+ ($p < 0.01$). By contrast, simple effect of condition at post-MM was not significant for CP or SC group ($p > 0.05$). Simple effect of time on MMA+ condition was significant for CP [$F(2, 186) = 16.15$, $p < 0.001$, $\eta_p^2 = 0.08$], DA [$F(2, 186) = 31.45$, $p < 0.001$, $\eta_p^2 = 0.15$], and SC [$F(2, 186) = 9.07$, $p < 0.005$, $\eta_p^2 = 0.05$] groups. POMS Tension-Anxiety scores were significantly reduced in CP ($p < 0.001$, $d = 0.51$), DA ($p < 0.001$, $d = 0.69$), and SC ($p < 0.001$, $d = 0.52$) groups receiving MMA+. Similarly, simple effect of time on MMA- condition was significant for CP [$F(2, 186) = 45.90$, $p < 0.001$, $\eta_p^2 = 0.20$], DA [$F(2, 186) = 65.68$, $p < 0.001$, $\eta_p^2 = 0.26$], and SC [$F(2, 186) = 9.06$, $p < 0.005$, $\eta_p^2 = 0.05$] groups. POMS Tension-Anxiety scores were significantly reduced in CP ($p < 0.001$, $d = 0.52$), DA ($p < 0.001$, $d = 1.36$), and SC ($p < 0.001$, $d = 0.37$) groups receiving MMA- (Table 7).

Table 7. Means and standard deviations for the POMS Depression and Tension-anxiety subscales shown for the three groups in the MMA+ and MMA- conditions

POMS Depression	MMA+	MMA-	Total
All Participants			
Baseline	3.63 (4.93)	5.19 (6.97)	4.43 (5.97)
Post-Meditation	1.62 (3.46)	1.64 (3.23)	1.63 (3.23)
Chronic Pain			
Baseline	3.91 (4.64)	6.19 (7.52)	5.12 (6.37)
Post-Meditation	2.00 (2.79)[c]	1.90 (3.29)[c]	1.96 (3.03)

Depressive-Anxious			
Baseline	7.33 (6.04)	9.35 (7.65)	8.41 (6.97)[b]
Post-Meditation	3.44 (5.29)[c]	2.77 (3.95)[c]	3.09 (4.59)
Sub-Criteria			
Baseline	1.20 (2.16)	1.41 (1.77)	1.31 (1.98)[a]
Post-Meditation	0.30 (1.00)	0.61 (1.26)	0.45 (1.14)
POMS Tension-Anxiety			
All Participants			
Baseline	6.04 (5.21)	6.86 (5.95)	6.46 (5.60)
Post-Meditation	2.95 (3.79)	2.56 (3.16)	2.75 (3.48)
Chronic Pain			
Baseline	7.83 (5.52)	9.73 (6.67)	8.84 (6.23)
Post-Meditation	4.26 (4.21)[c]	4.08 (3.80)[c]	4.16 (3.96)
Depressive-Anxious			
Baseline	9.41 (4.83)	8.74 (3.35)	9.05 (5.45)
Post-Meditation	4.81 (4.56)[c]	2.55 (3.35)[c, d]	3.60 (4.08)
Sub-Criteria			
Baseline	3.05 (3.33)	3.61 (3.35)	3.32 (3.33)[a]
Post-Meditation	1.11 (1.71)[c]	1.61 (2.08)[c]	1.35 (1.91)

Note. Maximum POMS-Depression score is 28. Maximum POMS-Tension Anxiety score is 24. [a]$p < 0.001$ for SC vs. CP and SC vs. DA at baseline; [b]$p < 0.005$ for DA vs. CP at baseline; [c]$p < 0.01$ for baseline vs. post-meditation. [d]$p < 0.01$ for MMA+ vs. MMA- at post-meditation. All comparisons were planned and Bonferroni-corrected.

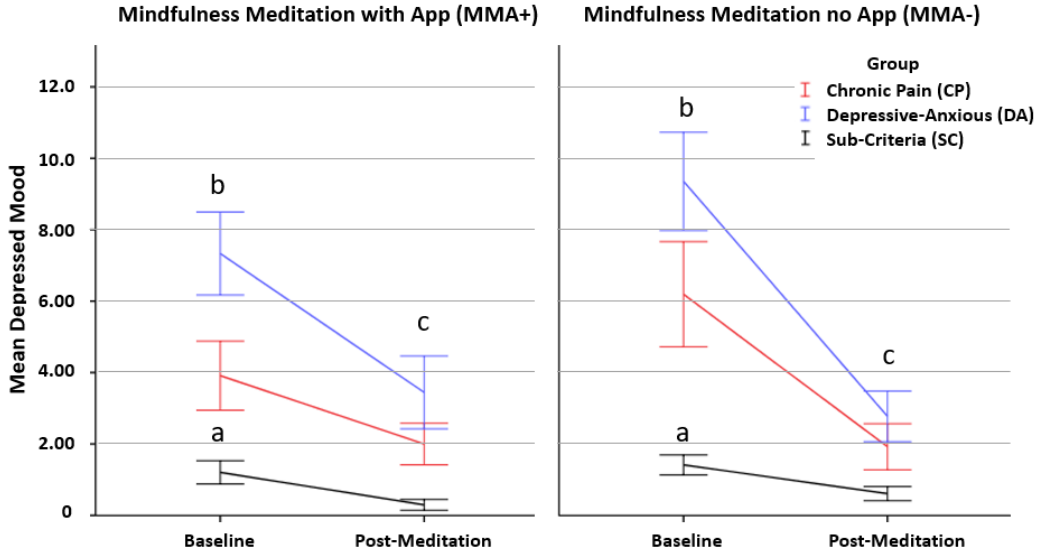


Figure 5. Mean plots of depressed mood (Profile of Mood States) in study groups and conditions across experimental phases. Error bars represents standard errors. Maximum score possible on POMS-Depression subscale is 28. [a]$p < 0.001$ for SC vs. CP & SC vs. DA at baseline; [b]$p < 0.005$ for DA vs. CP at baseline; [c]$p < 0.01$ for baseline vs. post-meditation.

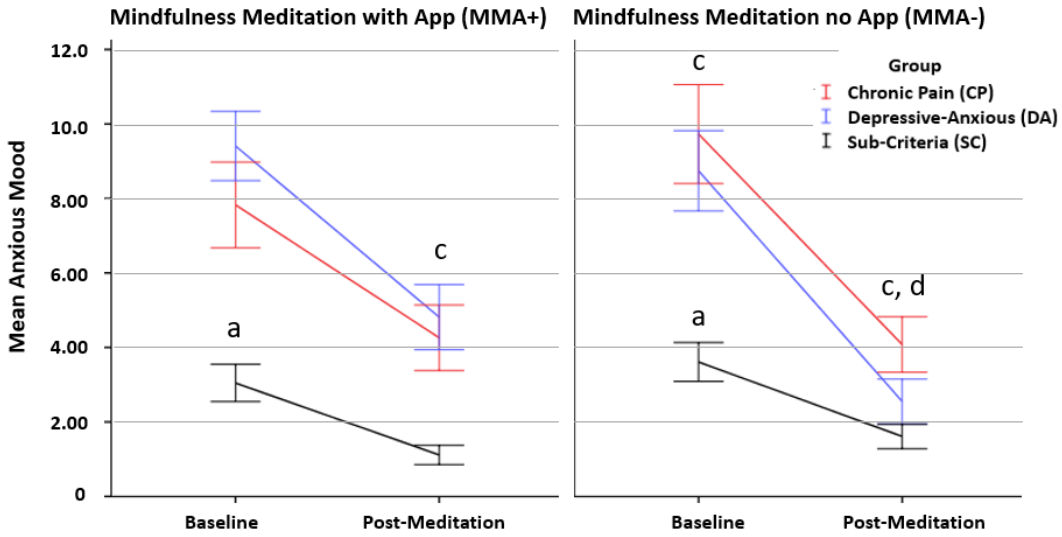


Figure 6. Mean plots of anxious mood (Profile of Mood States) in study groups and conditions across experimental phases. Error bars represents standard errors. Maximum score possible on POMS-Tension Anxiety subscale is 24. [a]$p < 0.001$ for SC vs. CP & SC vs. DA at baseline; [c]$p < 0.01$ for baseline vs. post-meditation. [d]$p < 0.01$ for MMA+ vs. MMA- at post-meditation.

Hypothesis 2b: Lower and greater reduction in subjective distress in MMA+ compared to MMA- in DA and CP. For the three-way repeated measures ANOVA with subjective distress, the sphericity assumption was violated (Mauchly's W = 0.96, $p < 0.05$) and so a MANOVA approach was taken. The MANOVA indicated a significant main effect of time [$F(2, 182) = 118.60$, $p < 0.001$, $\eta_p^2 = 0.57$] and group [$F(2, 183) = 23.18$, $p < 0.001$ $\eta_p^2 = 0.20$], but no significant interactions ($p > 0.05$).

Analyses of planned comparisons. According to the simple effect of group at rest phase, SC group reported significantly higher subjective distress than CP and DA groups at rest ($p < 0.001$). Simple effect of condition at post-MM was significant for DA group only [$F(1, 183) = 4.13$, $p < 0.005$, $\eta_p^2 = 0.02$], indicating that, contrary to expectations, DA participants in the MMA- condition reported significantly lower subjective distress compared to MMA+ ($p < 0.005$, $d = 0.54$). Simple effect of time for MMA+ condition was significant for CP [$F(2, 364) = 11.15$, $p < 0.001$, $\eta_p^2 = 0.11$], DA [$F(2, 364) = 18.05$, $p < 0.001$, $\eta_p^2 = 0.17$], and SC [$F(2, 364) = 16.76$,

$p < 0.001$, $\eta_p^2 = 0.16$] groups. Planned comparisons indicated subjective distress was significantly reduced from post-stress to post-MM in CP ($p < 0.001$, $d = 0.53$), DA ($p < 0.001$, $d = 0.67$), and SC ($p < 0.001$, $d = 0.52$) groups receiving MMA+. Comparably, simple effect of time for MMA- condition was significant for CP [$F(2, 364) = 16{,}34$, $p < 0.001$, $\eta_p^2 = 0.15$], DA [$F(2, 364) = 34.66$, $p < 0.001$, $\eta_p^2 = 0.28$], and SC [$F(2, 364) = 30.10$, $p < 0.001$, $\eta_p^2 = 0.25$] groups. Planned comparisons indicated subjective distress was significantly reduced from post-stress to post-MM in CP ($p < 0.001$, $d = 0.53$), DA ($p < 0.001$, $d = 0.81$), and SC ($p < 0.001$, $d = 0.68$) groups receiving MMA- (Table 8).

Table 8. Means and standard deviations of subjective distress in study groups and conditions

	MMA+	MMA-	Total
All Participants			
Baseline	49.53 (27.50)	51.27 (27.03)	50.99 (26.67)
Post-Stress	46.32 (27.58)	46.03 (27.58)	46.54 (27.52)
Post-Meditation	27.13 (24.96)	22.97 (23.15)	25.06 (24.04)
Chronic Pain			
Baseline	56.00 (24.07)	57.35 (27.15)	56.71 (25.94)
Post-Stress	53.61 (24.27)	52.56 (28.25)	53.10 (26.50)
Post-Meditation	34.39 (26.94)[b]	31.54 (28.25)[b]	32.88 (27.39)
Depressive-Anxious			
Baseline	64.81 (23.46)	58.77 (21.91)	62.83 (21.13)
Post-Stress	60.19 (21.00)	52.09 (23.48)	56.76 (21.50)
Post-Meditation	38.52 (24.84)[b]	25.63 (22.75)[b, c]	32.07 (24.25)
Sub-Criteria			
Baseline	36.77 (25.90)	41.73 (27.31)	39.20 (26.29)[a]
Post-Stress	46.32 (27.58)	37.21 (28.64)	35.40 (28.11)
Post-Meditation	27.13 (24.96)[b]	14.72 (16.48)[b]	15.44 (17.82)

Note. Measures obtained from Subjective Units of Distress Scale. Maximum score possible is 100. [a]Within-subject change ($p<0.001$). [a]$p < 0.001$ for SC vs. CP & SC vs. DA at baseline. [b]$p < 0.001$ for post-stress vs. post-meditation. [c]$p < 0.005$ for MMA+ vs. MMA- at post-MM.

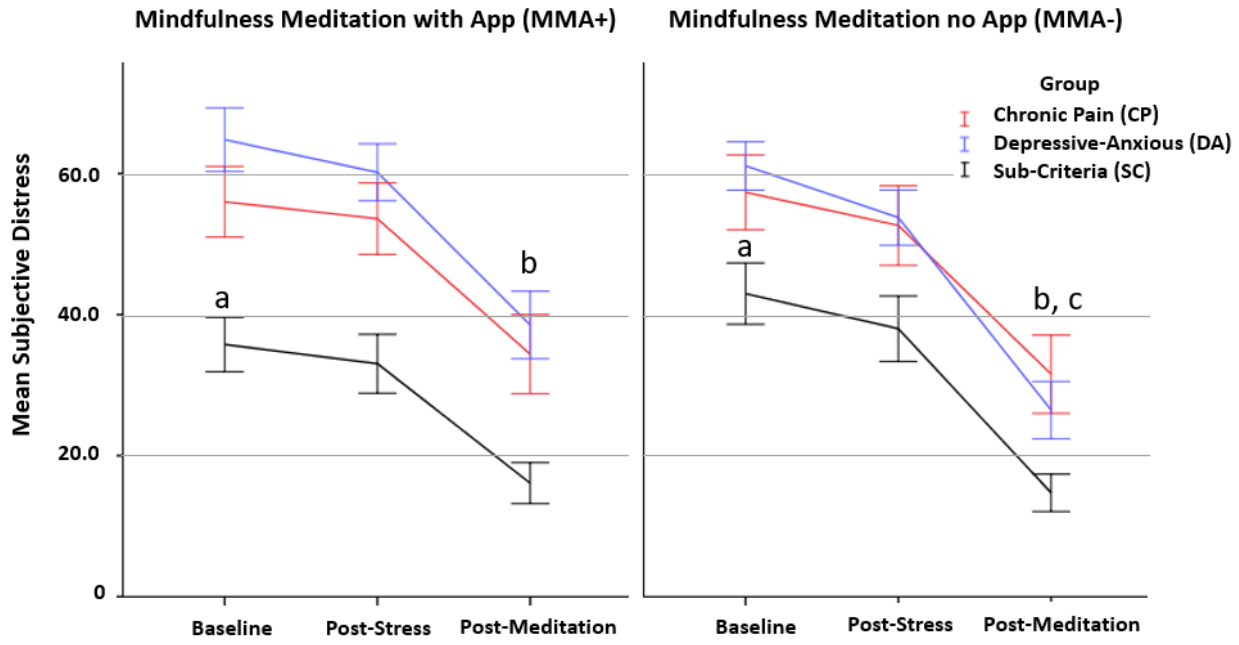


Figure 7. Mean plots of subjective distress (Subjective Units of Distress Scale) in study groups and conditions across experimental phases. Error bars represents standard errors. Maximum score is possible 100. [a]$p < 0.001$ for SC vs. CP & SC vs. DA at baseline. [b]$p < 0.001$ for post-stress vs. post-meditation. [c]$p < 0.005$ for MMA+ vs. MMA- at post-MM.

Hypothesis 3: Higher state mindfulness in MMA+ in CP and DA. Two-way ANOVA did not reveal a significant main effect of Group [$F(2, 186) = 0.55$, $p = 0.58$]. The main effect of Condition was marginally significant [$F(1, 186) = 3.81$, $p = 0.05$], and group x condition interaction effect was not significant ($p = 0.35$).

Analyses of planned comparisons. With regards to planned comparisons of the effect of condition on groups, the simple effect of condition was not significant for any groups (all $p > 0.05$); state mindfulness did not significantly differ according to conditions for any groups (Table 9).

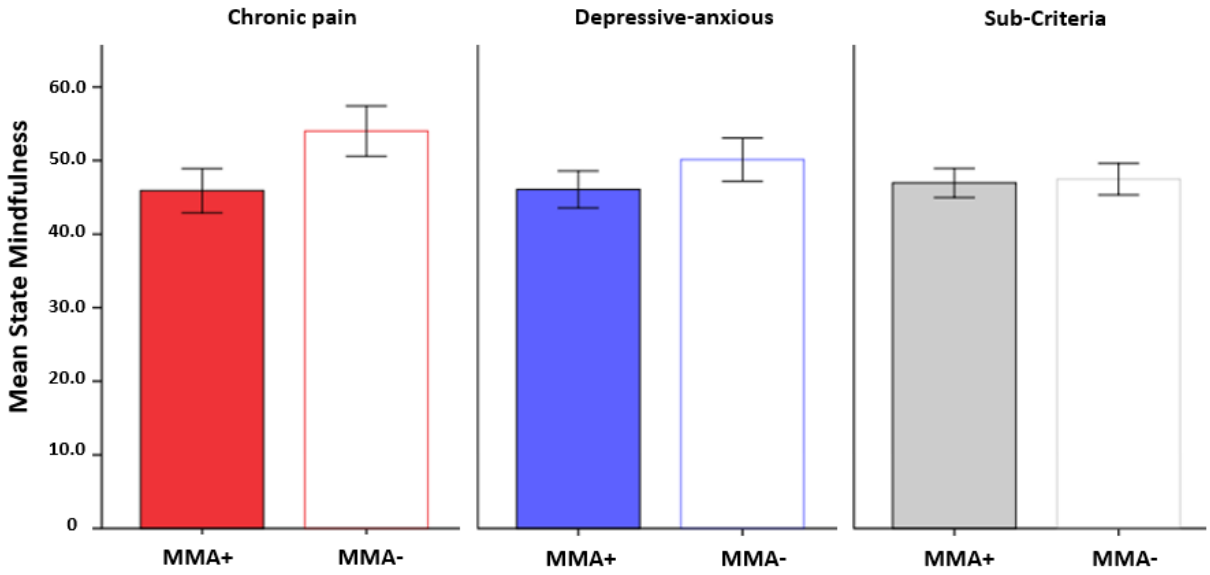


Figure 7. Mean plots of state mindfulness (State Mindfulness Scale) in study groups and conditions across experimental phases. Error bars represents standard errors.

Hypothesis 4: Lower mind-wandering in MMA+ for CP and DA. Two-way ANOVA revealed a significant main effect of group [$F(2, 186) = 3.96$, $p < 0.05$, $\eta_p^2 = 0.04$], but not condition [$F(1, 186) = 1.37$, $p = 0.24$] or the group x condition interaction [$F(2, 186) = 0.76$, $p = 0.47$]. Analysis of the main effect of group showed that the DA group (M = 60.87, SD = 18.39) reported significantly ($p < 0.01$, $d = 0.46$) higher mind-wandering than SC (M = 52.31, SD = 19.29) (Table 9). The simple effect of condition was not significant for any group (all $p > 0.05$).

Table 9. Means and standard deviations of depressed and anxious mood in study groups and conditions

	State Mindfulness			Mind-Wandering		
Group / Condition:	**MMA+**	**MMA-**	**Total**	**MMA+**	**MMA-**	**Total**
All Participants	46.45 (13.33)	50.05 (15.64)	48.25 (14.49)	57.79 (18.14)	59.29 (20.72)	58.54 (19.43)
Chronic Pain	45.91 (14.48)	54.00 (17.45)	50.20 (16.47)	58.26 (17.40)	62.58 (18.94)	60.55 (18.17)
Depressive-Anxious	46.07 (13.05)	50.13 (16.33)	48.24 (14.91)	60.93 (19.40)	64.94 (18.62)	63.07 (18.93)[a]
Sub-Criteria	46.95 (13.17)	47.49 (13.63)	48.29 (14.63)	55.61 (17.84)	52.93 (21.99)	54.32 (19.88)

Note. State mindfulness measures obtained from the State Mindfulness Scale. Mind-wandering obtained from the Mind-wandering inventory. Both questionnaires administered immediately after the meditation tasks. [a]p<0.01 for comparison of DA and SC.

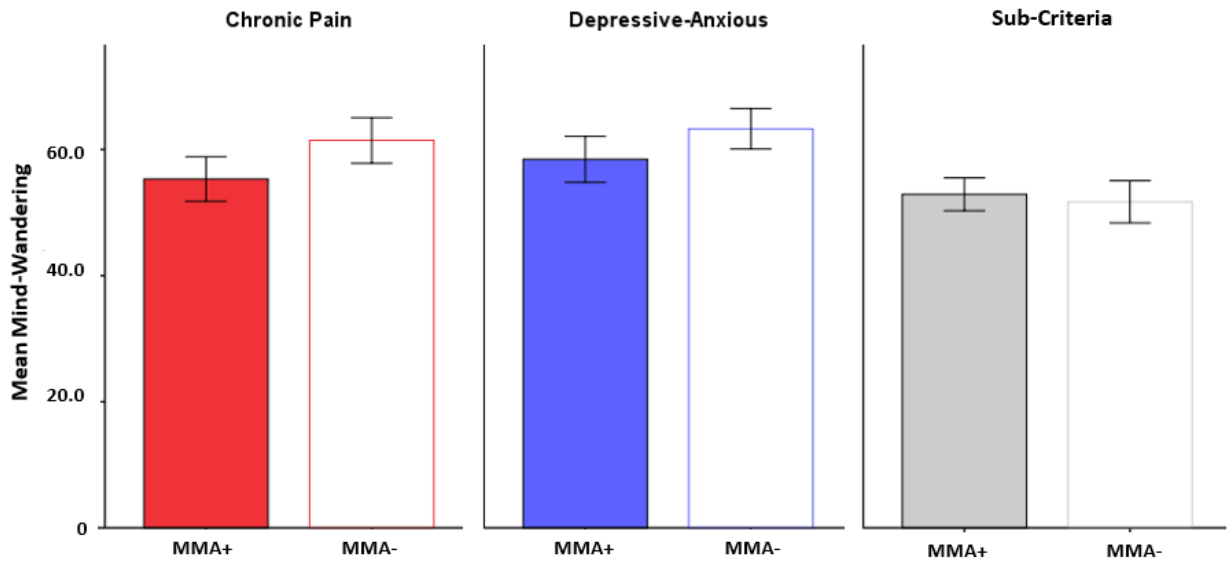


Figure 8. Mean plots of mind-wandering (Mind-Wandering Inventory) in study groups and conditions across experimental phases. Error bars represents standard errors.

Discussion

Mindfulness meditation has been shown to be of benefit to clinical populations, and cardiac vagal modulation has been proposed as a theoretical basis to explain these findings (Gerritsen & Band, 2018). Previous evidence has suggested breath focus prompts, such as the ones provided by the MMA, can increase HRV during MM (Burg et al., 2012), and thereby may render the benefits of vagal HR modulation to novice meditators with clinical symptoms of pain, mood, and anxiety. Results from the present study provide support for MM in promoting vagal HR modulation and psychological well-being. A comparison of the results associated with MMA+ and MMA- conditions among study groups are discussed below.

Comparison of MMA+ and MMA- effects on HRV

During MM, HRV was significantly higher during MMA- than MMA+ for the CP group, whereas a significant HRV difference between MMA- and MMA+ was not observed for DA and SC groups. This finding demonstrates that mindfulness can play a role in improving the dysfunction of vagal HR modulation seen in a wide array of chronic pain disorders (Tracy et al.,

2016). Multiple mechanisms have been proposed to explain how mindful breathing may provide vagal-mediated benefits to individuals with chronic pain, including modulation of activity in pain processing brain regions (Zeidan et al., 2015), and activation of anti-inflammatory functions of the vagus nerve (Thayer, 2009). It is important that future studies continue to explore mechanistic accounts of how MM-induced vagal HR modulation may be of benefit to people with chronic pain to inform best clinical practice recommendations. Furthermore, the superior effect of MMA- compared to MMA+ for the CP group expands upon findings from Study I. In Study I, HRV was measured during rest, stress, and post-stress mindfulness meditation practice or listening to a mindfulness audio lecture in students with tension-migraine headache conditions. During the post-stress conditions, the headache group exhibited significantly higher HRV when receiving a post-stress mindfulness meditation condition compared to listening to an audio lecture on mindfulness (Azam et al., 2016). The present study's CP group was comprised of students with various chronic pain conditions in addition to tension headaches/migraines, suggesting that the post-stress effect of MM in augmenting vagal HR modulation can be generalized to other chronic pain conditions. It is important to note that the MMA- condition in the present study was similar to the MM condition in Study I. However, the relatively lower HRV associated with the MMA+ condition suggests that the usefulness of the MMA in promoting vagal HR modulation may be limited, as discussed below.

Comparison of phasic changes from stress to MM revealed significant HRV increases for the SC group receiving MMA+, but this was not the case for the CP and DA groups. By comparison, HRV increased significantly from stress to MM phase in the MMA- condition for CP, DA, and SC groups. The increase in HRV from stress-to post-stress in the MMA+ condition for the SC group is consistent with previous studies that have shown similar medium effect size

increases associated with post-stress mindfulness meditation practice for healthy control participants (Azam et al, 2015; 2016). Additionally, previous research has also found a positive correlation between breath awareness and HRV during a computer-based mindful breathing practice that provided breath awareness prompts (Burg, Wolf, & Michalak, 2012). In the present study, the purpose of the MMA+ was to increase breath awareness by providing randomly timed breath awareness prompts during MM practice. As CP and DA groups did not exhibit significant HRV increases when receiving MMA+, this indicates that the MMA is not effective at increasing breath awareness in ways that could promote vagal HR modulation in people scoring at or above thresholds typically seen in clinical samples. It is possible that the audio tones served as a distraction, and were perhaps even perceived as reminders of "errors" (i.e. not attending to one's breath) during the mindful breathing exercise. As such, the audio tones and anticipation of further reminders may have contributed to an inability to maintain focus on breathing throughout the task, and thereby hindered the expected HRV effects of MM. Furthermore, the audio tones may have served as a demand characteristic to "perform" the task. It is possible that these performance cues prompted performance anxiety, manifesting in negative self-evaluative thoughts in CP and DA groups, and ultimately disrupting the process of mindfully attending to breathing. The perceived performative aspects of the MMA+ condition may explain why the SC group, being relatively free from the influence of mood, anxiety, and pain symptoms, showed increased HRV when receiving MMA+ whereas the clinically distressed groups, CP and DA, did not.

By contrast, it is promising that all groups exhibited significant, medium-to-large HRV increases when receiving MMA-, suggesting post-stress MM is effective at promoting vagal HR modulation for both clinical and non-clinical populations. In a prior study with a similar design,

maladaptive perfectionists, who also had depression and anxiety symptoms, did not exhibit a significant HRV elevation during post-stress MM (Azam et al, 2015) in contrast to healthy controls. It is important to highlight key differences between the study by Azam et al. (2015) and the present study that might explain the divergent findings. These differences include: 1) the nature of the stress-induction (pattern recognition task versus mental arithmetic), 2) type of MM practice (audio guided versus self-guided), and 3) the subgroup, maladaptive perfectionists, being more challenged to practice MM after a performance-based stressor compared to the CP and DA groups in this study. Furthermore, the present study's finding is particularly noteworthy given the expected significantly lower resting HRV of CP and DA relative to the SC group. Resting state HRV is a measure of cardiac vagal control, and low values suggest inflexibility and "sympathetic dominance" of the ANS, commonly seen in psychiatric (Kemp et al., 2012; Pittig et al., 2013) and chronic pain conditions (Tracy et al., 2016). Thus, these findings add to existing literature by demonstrating that people who report clinically relevant symptoms, despite being meditation-naïve, can employ MM to regulate acute distress and promote stress recovery with respect to their ANS. Further studies may consider exploring the effects of cumulative MM practice on HRV in clinical populations to determine the extent of MM experience needed to effectively ameliorate the ANS dysfunction that accompanies these conditions.

Comparison of MMA+ and MMA- effects on depressed and anxious mood and subjective distress

The effects of mindfulness meditation on state depressed and anxious mood have been examined in previous studies (Johnson, Gur, David, & Currier, 2015; Zeidan, Johnson, Gordon, & Goolkasian, 2010), but no known study has measured immediate mood changes after a brief, post-stress MM task in individuals with chronic pain and severe depression-anxiety symptoms.

In one study, a single 25-minute session of mindfulness meditation reduced POMS tension-anxiety scores significantly in meditation-naïve students who had not been screened for clinical symptoms (Johnson et al., 2015). Zeidan et al. (2010) compared mindfulness meditation to a sham mindfulness condition and found the meditation intervention was more effective than sham mindfulness at reducing POMS tension-anxiety and depressed mood in meditation-naïve students not screened for clinical symptoms. These findings provided the impetus explore if similar state mood and anxiety effects could be achieved in clinically symptomatic students using the MMA+. In the present study, POMS depressed mood was significantly reduced by post-MM in CP and DA groups receiving MMA+ with small effect sizes, and MMA- with medium effect sizes. For POMS anxious mood, the DA group in the MMA- condition scored lower at post-MM than MMA+. Furthermore, both MM conditions showed medium-to-large effect size reductions in anxious mood for all groups. Mood and anxiety disorders are widely recognized as stress-related conditions in the mental health domain (Hammen, 2005; Sawatzky et al., 2012; Shin & Liberzon, 2010). Linkages between chronic pain and the negative sequalae of stress, mood, and anxiety are well established in the clinical literature (Sachs-Ericsson, Cromer, Hernandez, & Kendall-Tackett, 2009). Mindful breathing is slow-paced and emphasizes awareness of the full breathing cycle, which tends to elicit a calm, relaxing effect that has been shown to have mood and anxiety regulating effects (Abbott et al., 2014; Kelly, 2008). Current study findings add to existing literature by showing that depressed and anxious mood can be significantly reduced in individuals with chronic pain and severe depression-anxiety symptoms with only 12 minutes of MM practice.

Both MM conditions achieved medium-to-large effect size reductions in subjective distress (from post-stress to post-MM) for all groups. These results are consistent with the

significant stress to MM reductions found across all groups and conditions in heart rate and respiration rate, two commonly used sympathetic stress markers. Interestingly, subjective distress in the DA group was lower at post-MM in MMA- compared to MMA+, and showed a greater effect size reduction from post-stress to post-MM in the MMA- condition. This seems to fit the pattern of results seen in the HRV data, in which DA group receiving MMA- showed significant HRV increases from stress to MM, indicative of effective stress recovery. As discussed above, the MMA's breath attention audio tones may have been perceived as a distraction by the DA group, hindering the potential stress-relieving effects of MM.

Comparison of MMA+ and MMA- effects on state mindfulness and mind-wandering

There were no differences found in state mindfulness and mind-wandering due to MM conditions. The MMA+ was expected to foster breath awareness, and thereby, greater mindful awareness of experiences amidst MM practice (e.g. mental events, sensations). It is possible that greater experience with MM, and practice using the MMA, is needed to attain the expected increases in state mindfulness. It was hypothesized that the MMA's breath awareness prompts would reduce mind-wandering by increasing awareness of the breath and instructing refocusing on breathing when noticing mind-wandering events, but mind-wandering frequency was not significantly different than during mindful breathing without the app. The higher level of mind-wandering of the DA relative to SC group is consistent with their pre-existing differences, as seen in higher trait mind-wandering (MWQ) and lower mindfulness skills (KIMS subscales of nonjudgment and acting with awareness). It is hoped that current results stimulate further refinement of MM-based clinical tools to effectively provide training in mindful breathing to increase subjective mindfulness and reduce mind-wandering.

Limitations. The present study has limitations. Firstly, there is the lack of blinding of research assistants with respect to group screening and treatment allocation procedures. Research assistants were required to remain in the room to address technical or practical issues with the intervention, negating the possibility of blinding research assistants to treatment. However, both MMA+ and MMA- conditions entailed app-guided or self-guided mindful breathing practice with no active involvement of research assistants, thus, risk of bias in intervention delivery was low. Another limitation is that the use of the MMA+ condition presented a demand characteristic requiring participants to report "breath" or "other" responses. Any accidental responses by participants that did not correspond to their attentional states (e.g. pressing "breath" when the intention was to press "other") cannot be corrected during the MMA task. While this introduces the possibility of some distraction to participants, the button pressing errors were expected to be randomly distributed among study groups using the app, rendering the risk of interfering with the results to be low. Additionally, participants were only provided one session of the MMA task, which is a limited duration of exposure that prevents examination of dose-response effects. We hope in future longitudinal studies to test repeated practice with the app and its effects on HRV, pain, mood, and other outcomes. In terms of study groups, classification criteria did not exclude individuals who reported mild-to-moderate levels of depressive-anxiety symptoms, or clinically-relevant pain for less than 3 months, instead classifying these participants as sub-criteria. Stricter classification criteria for a sub-criteria subgroup may be necessary to isolate the impact of distressing emotional and pain symptoms on HRV in the context of MM practice. With regards to study outcomes, it must be noted that the mind-wandering inventory is awaiting psychometric validation and will undergo factor analyses based upon the data gathered in this and other studies. Furthermore, while this study focused on the high-frequency measure of HRV, there are

other validated measures of frequency (low-frequency) and time domain (e.g. root mean squared of successive differences) metrics that warrant examination in future studies of mindfulness interventions. One procedural limitation is that the MMA- condition is not structurally identical to the MMA+ condition as it did not include the use of a smartphone app during the practice of mindful breathing. To preserve task similarity, future studies may consider employing different forms of a 'control app', such as one that provides participants with random audio tones using the parameters as in the MMA+ but not tied to any response requirement (i.e. button presses) as they practice mindful breathing. Lastly, the study was based on undergraduate student populations, limiting generalizability until future studies are conducted with community populations and individuals being seen in clinical settings.

Conclusion

This RCT adds to the burgeoning evidence-basis for the effectiveness of mindfulness-based treatments for individuals with clinically-relevant depressive-anxious and chronic pain symptoms. The findings also support the increasing relevance of HRV measures in assessment and treatment of psychological and health conditions, as well as the growing use of HRV as a biomarker and biofeedback tool within clinical and health psychology. However, it is important to note that designing an interactive smartphone app to train symptomatic and meditation-naïve individuals in mindful breathing is a novel and complex undertaking. It is hoped this study's attempt at developing and testing an interactive mindful breathing app represents a step on the iterative development pathway to build scalable digital tools for teaching mindfulness to clinical populations.

Acknowledgements

This dissertation study is based in part on the previously published protocol listed below:

Azam, M. A., Latman, V. V., & Katz, J. (2019). Effects of a 12-Minute Smartphone-Based Mindful Breathing Task on Heart Rate Variability for Students With Clinically Relevant Chronic Pain, Depression, and Anxiety: Protocol for a Randomized Controlled Trial. JMIR Research Protocols, 8(12), e14119.

The dissertation author was a co-investigator on the study, contributing to conception and design of the study, drafting of the published manuscript, and critical revisions of the article for final publishing. JK was a senior investigator on the study, and contributed to conception and design of the study, and drafting and revisions of the published manuscript. VL was a collaborator on the study, and contributed to conception and design of the study, and to drafting of the manuscript. All authors provided permission for inclusion of this article in the dissertation.

Chapter IV. Study III - The effects of perioperative clinical hypnosis on heart rate variability in a randomized clinical trial with patients undergoing oncology surgeries

Introduction

Hypnosis is one of the oldest treatment approaches for the management of pain; however, the application of hypnosis in clinical pain care has ebbed and flowed over time (Jensen, 2009). In the 18th century, pre-surgical hypnosis was frequently used as a stand-alone procedure to induce anesthesia and sedation, prior to the advent of chemical anesthesia. Over the past twenty years, there has been a new wave of scientific investigation into the efficacy of hypnosis for managing acute and chronic pain. As a result of this body of evidence for the efficacy of clinical hypnosis, the American Psychological Association has recommended that clinical hypnosis be included as part of standard care for pain relief, unless an individual indicates a strong aversion to it (APA, 2004; Wobst, 2007).

Hypnosis is a psychological technique that induces a temporary state of consciousness characterized by increased inner focus and deep relaxation, with enhanced receptivity to suggestions to alter subconscious physiological functions and symptoms such as pain, blood pressure, and gut motility (Elkins, 2016). It must be noted that this definition constitutes a state theory of hypnosis, whereas non-state theories have also been proposed to explain phenomena associated with hypnosis (e.g. socio-cognitive theory) (Lynn, Kirsch, & Hallquist, 2008). In the provision of clinical hypnosis to patients undergoing surgeries, suggestions for positive expectations, increased coping abilities, and induction of pleasurable experiences (i.e. relaxation) are used to influence post-surgical outcomes (Wobst, 2007), such as post-surgical pain intensity. Meta-analytic studies have reported that surgical patients who received adjunct hypnosis treatment had better outcomes (e.g., less pain intensity, better mood, and less medication use) than 89% of patients who received treatment as usual, as evidenced by large effect sizes across

1624 patients from randomized and non-randomized controlled trials (Montgomery, DuHamel, & Redd, 2000). A more recent meta-analysis demonstrated small to medium effects in favor of hypnosis on various post-surgical outcomes (e.g., pain intensity, emotional distress, medication consumption, and post-surgical recovery), across 2597 patients in randomized controlled trials (Tefikow et al., 2013). Given these promising findings, investigators have called for studies to evaluate hypnosis with clinically relevant biomarkers that can yield further insight into hypnosis' health benefits for post-surgical recovery.

Recent evidence suggests hypnosis can influence the body through the autonomic nervous system (ANS), a network of sympathetic and parasympathetic nerves connecting the brain to the organs of the body to control stress and recovery-related functions, respectively (Aubert et al., 2009). Parasympathetic nervous system (PNS) functions, which are mediated by vagal nerve activity, are critical for maintaining key body functions, including the control of inflammation. Studies have shown that the activity of the PNS is subdued in the aftermath of major surgery (Aubert et al., 2009; Grote et al., 2019; Williamson et al., 2010), a period characterized by heightened inflammatory activity due to surgery-related tissue or nerve injuries (Marsch et al., 1994; Williamson et al., 2010). Prolonged weakening of PNS may leave the body vulnerable to the adverse effects of excess inflammation, including sepsis and post-surgical pain (Searle & Simpson, 2010). To date, there is little known about the extent of PNS dysfunction post-surgery, as few studies have investigated post-surgical PNS functioning.

PNS function can be measured by heart rate variability (HRV), a clinical biomarker of vagal HR modulation is inversely associated with acute pain (Koenig et al., 2014) and persistent pain disorders (Koenig, Falvay, et al., 2016; Tracy et al., 2016). Moreover, high levels of inflammation are inversely related to HRV (Tateishi et al., 2007). These relationships are

explained by a vagal anti-inflammatory reflex (Martelli, McKinley, & McAllen, 2014; Oke & Tracey, 2009), which is triggered by the detection of cytokines and tumor necrosis factor reagents to initiate a cascade of cholinergic processes to inhibit inflammation (Tracey, 2009). Putatively, a robust PNS and vagal anti-inflammatory reflex is signified by elevated HRV, whereas diminished HRV levels would signal a dysfunctional PNS. Overall, meta-analyses have found evidence of decreased HRV with respect to a wide array of chronic pain populations, which strongly indicates that PNS dysfunction is a general pathogenic marker for the onset and maintenance of chronic pain (Koenig, Falvay, et al., 2016; Tracy et al., 2016).

Clinical hypnosis may exert a positive influence on vagal HR modulation (Debeneditis, Cigada, Bianchi, Signorini, & Cerutti, 1994; Sakakibara, Takeuchi, & Hayano, 1994) and ameliorate sympathetic stress activity (Hippel, Hole, & Kaschka, 2001). To date, no known study has investigated the effects of peri-operative clinical hypnosis on post-surgical HRV. There is emerging evidence that adjunct treatments that help promote or restore vagal HR modulation would be effective within the peri-operative context. A longitudinal study of patients undergoing orthopedic surgery found HRV was significantly decreased in the first four days post-surgery, during both daytime and nighttime (Grote et al., 2019). All patients received orthopedic rehabilitation treatment approximately 1-month after surgery, for roughly 2 weeks. During the rehabilitation period, all patient's showed gradual increases in HRV (i.e. returning to pre-surgery levels or beyond), which were sustained up to 1-year later. More importantly, they found that patients with lower pre-operative HRV values took a longer period of time for their HRV to return to pre-surgery levels, relative to patients with higher pre-surgery HRV values (Grote et al., 2019). These findings highlight the importance of studying the effectiveness of adjunct treatments in the peri-operative context that can foster greater vagal HR modulation prior to

surgery and during post-surgical recovery to increase patient's vagal-inflammatory resistance and enable them to cope with surgery more effectively.

Objectives

This study aimed to examine the effects of a perioperative clinical hypnosis intervention on cardiac vagal activity using HRV assessments. This includes measures during rest and guided relaxation using hypnotic induction at pre-surgery and 1-month post-surgery. The following hypotheses were tested:

Hypothesis 1a. Participants randomized to the clinical hypnosis treatment group will demonstrate greater HRV during rest and relaxation at the 1-month post-surgery assessment compared to the treatment-as-usual group, reflecting the protective effects of the clinical hypnosis intervention on vagal HR modulation.

Hypothesis 1b. Treatment-as-usual group will exhibit decreased HF-HRV during rest and relaxation at 1-month post-surgery assessment compared to their corresponding pre-surgery assessment, exhibiting expected impairments in vagal HR modulation post-surgery. By contrast, clinical hypnosis group will not exhibit significant HF-HRV reduction relative to pre-surgery assessment.

Methods

Study Design

This is a secondary outcome study of a single-center, stratified, randomized-controlled, parallel-group trial conducted at the Toronto General Hospital's Transitional Pain Service (TPS; Toronto, Canada) (Katz et al., 2015). This study was designed according to the 2010 CONSORT statement (CONSORT E-HEALTH checklist) (Eysenbach G et al., 2011), reviewed and approved by the University Health Network Research Ethics Board (certificate #: 17-5441) as well as the Human Participants Review Committee at York University (certificate #: e2019-031),

and registered with ClinicalTrials.gov (registration #: NCT03730350) prior to recruitment of any participants.

Participants. Eligible participants were all adults aged 18 years or older, scheduled for a surgical oncology procedure (e.g. thoracic, gastrointestinal, gynecologic, urologic, head and neck, breast cancer, etc.) at the Toronto General Hospital. Exclusion criteria included patients with limited comprehension of English who would not be able to understand the verbal instructions for clinical hypnosis, cognitive deficits due to dementia or other causes that would limit comprehension, or a serious history of mental illness (e.g. schizophrenia, dissociative identity disorder, PTSD with dissociation).

Sample size estimation. The sample size (N=92) estimate was based on a power analysis of daily morphine equivalents in milligrams, post-surgery, which was the primary outcome of the RCT. Primary RCT results will be presented in a subsequent manuscript.

Randomization

Random sequence generation. A study co-investigator (JK) with no clinical involvement in the trial created a computer-generated randomization schedule on Randomization.com (www.randomization.com), stratified by patient's current and/or past use of opioid medications or lack thereof (opioid-experienced versus opioid naïve) with a 1:1 allocation using random block sizes of ten to ensure close balance of the numbers of each group at any time during the trial. Participants were randomly assigned following blocked randomization procedures to one of two intervention arms, clinical hypnosis or treatment-as-usual.

Allocation concealment. To ensure that the person randomizing participants to treatment condition would not be aware of the next treatment allocation, a study coordinator inserted colored cards containing the intervention assignment details inside sealed, opaque envelopes that were consecutively numbered with participant study ID numbers. The allocation sequence was

concealed from the coordinator obtaining informed consent from participants as well as the outcome assessors, and the envelopes were opened and read only after participants had completed all pre-surgery assessments and it was time to allocate to intervention. Randomization took place at the end of the pre-surgery assessment, when the outcome assessor and/or clinician opened the next consecutively numbered sealed envelope corresponding to the participant's study ID.

Interventions

Clinical hypnosis intervention. Participants randomized to the clinical hypnosis arm of the study received standard perioperative care along with an adjunct perioperative clinical hypnosis intervention. One in-person session of clinical hypnosis was provided approximately 1-2 weeks prior to the day of surgery, and one in-person session of clinical hypnosis was provided in-hospital 1-3 days after the day of surgery (Table 2). The scripts for all hypnosis sessions were developed by the TPS pain psychologist and study co-investigator (Dr. Aliza Weinrib), based on the clinical literature (Elkins, 2016) and manualized for use in this study. The TPS psychologist and psychology trainees trained and certified in clinical hypnosis provided the hypnosis intervention.

Pre-surgery hypnosis. The pre-surgery clinical hypnosis session was 20-25 minutes in duration, and was aimed at preparing the participant for surgery by reducing anxiety and introducing relaxation and self-soothing strategies to be used after surgery for adaptive pain coping. Prior to the session, the clinician provided information on clinical hypnosis, including the use of hypnosis in the medical context and an overview of the pre-surgery hypnosis session. Furthermore, the participant was asked to think of a "special place" of comfort and relief, real or imagined, to incorporate into the session. The pre-surgery hypnosis session included the following steps: (1) hypnotic induction with slow, deep breathing; (2) hypnotic deepening using

progressive relaxation with suggestions of warmth; (3) suggestions of mental imagery and pleasurable sensory experiences in a "special place" of participant's choosing; (4) suggestions of positive imagery for participant's experiences leading up to, during, and after surgery; (5) suggestions for participant to engage in self-hypnosis before surgery and during surgical recovery; and (6) alerting with counting. While providing hypnosis, the clinician observed the participant and adapted delivery of instructions according to observed bodily cues of relaxation (e.g. facial muscles relaxing, slow breathing rhythm). Participants were given the option to lie prone on a hospital bed, or be seated, for the duration of the session. Participants were asked to keep their eyes closed for the majority of the session, to limit visual distractions and enhance inner focus. Sessions were provided in a private room with doors closed to reduce distracting noise. Participants were also provided with a recording of the pre-surgery hypnosis script to use at home, with instructions that they listen to it on the two days prior to their surgery day.

Post-surgery hypnosis. Following surgery, a clinician from the TPS pain psychology team visited the participant in hospital on post-operative day one or whenever the patient was ready to be seen prior to hospital discharge in order to guide them through a clinical hypnosis session, 10-15 minutes in duration, targeted at increasing comfort and pain relief. For this session, participants were given the option to incorporate their chosen "special place" of comfort and relaxation, or to be guided in a hypnosis session of having a "trip to the beach". In addition, participants were given the option to be alerted and re-awakened at the end of this session or be left to drift off to sleep if desired. The post-surgery hypnosis session included the following steps: (1) hypnotic induction with slow, deep breathing; (2) suggestions for minimizing impact of hospital room noise, hypnotic deepening using progressive relaxation with suggestions of warmth; (4) suggestions of mental imagery and pleasurable sensory experiences in a "special

place" of participant's choosing, or for a "trip to the beach"; (5) suggestions for sensory substitution, reduction of pain intensity, and reduction of pain unpleasantness; (5) suggestions for participant to engage in self-hypnosis; and (6) alerting with counting, or leaving participant to drift off to sleep.

Audio hypnosis tracks developed by the TPS psychologist were provided for independent use after surgery, with daily practice recommended. These audio tracks were accessible on the study's private YouTube webpage. If participants were not able to use a personal device to access audio hypnosis tracks during their post-surgical recovery, they were provided an MP3 audio player to use for the duration of their hospital stay. Each of these tracks was 20-25 minutes in duration, and aimed at promoting pain relief, reducing distress and anxiety, and facilitating sleep. Each track contained two endings which the participant could choose between - one to alert and awaken the patient at the end of the track to continue with their day, and one that did not alert the patient and facilitated drifting off to sleep if so desired. Patients were provided with daily tracking logs to track how frequently they practiced hypnosis before and after surgery.

Treatment-as-usual. Participants randomized to the treatment-as-usual arm of the study received standard perioperative care. Participants in this study arm were offered to undergo a session of in-person hypnosis at their one-month assessment, after all of the physiological and questionnaire measures had been completed. Hypnosis audio tracks were made available to participants randomized to the treatment-as-usual arm at their one-month appointment after completion of all assessments.

Blinding. Study personnel, including coordinators, outcome assessors, and clinicians providing the hypnosis interventions, were not blinded to treatment assignment in order to facilitate practical logistics of conducting the study. Coordinators corresponded with participants

to schedule post-surgery assessments, at which time they provided them with relevant questionnaires based on the intervention arm to which they had been randomized, and, in the case of the treatment-as-usual participants, to offer them an in-person session of clinical hypnosis at the one-month assessment. Clinicians were required to be aware of the intervention arm to which participants had been allocated to determine whether to provide a pre-surgery hypnosis session after the pre-surgery assessment was completed. In some cases, clinicians who provided the clinical hypnosis served the dual role as outcome assessors conducting the physiological assessments. Steps were taken to minimize potential bias in outcome assessors, such as randomizing to intervention arms (i.e. opening sealed envelopes) only after pre-surgery assessments were completed. Finally, participants were not blinded to study intervention, partly due to the lack of adequate "sham" or placebo hypnosis procedures to serve as appropriate controls for clinical hypnosis (Kendrick, 2012).

Outcomes

Heart rate variability (primary outcome). Electrocardiogram (ECG) recordings were collected using MindWare Impedance Cardiograph acquisition system (Ohio, United States), and used to analyze HRV; the beat-to-beat variation in either heart rate or the inter-beat intervals used to index parasympathetic nervous system activity. Using the MindWare equipment, we applied 3 adhesive electrodes to the right collarbone (-) and the lower left and right ribs (+ and ground), or alternatively the wrists (+ and -) and ankle (ground), to participants. MindWare BioLab and HRV software were used to calculate high-frequency HRV (HF-HRV) that is widely used to indirectly estimate vagal HR modulation (Laborde, et al, 2017). Patients were measured during phases of: 1) Rest in a seated position with eyes close (5 minutes), and 2) guided relaxation using features of hypnotic induction, including deep breathing and relaxing

suggestions (e.g. warmth, heaviness throughout body) (10 minutes). Two individuals separately inspected the ECG files to derive HRV values.

Preliminary analyses of respiration rate. A MindWare respiratory belt (placed below the ribcage) was used to monitor respiration rate during rest and relaxation. Respiration is a potential confounding variable for HRV interpretation, and it is recommended for use as a covariate in HRV analyses if it is found to differ between study groups (Laborde et al, 2017).

Secondary outcomes.

Heart rate. Heart rate (HR) is a measure of the number of times the heart muscle contracts per minute. HR is an autonomic measure of cardiac output, generally used to index states of psychological stress or relaxation, as well as a pathogenic marker (in the case of elevated HR). The present study assessed HR during rest and relaxation using the MindWare ECG recording.

Subjective relaxation. Subjective relaxation was measured using an 11-point numerical scale specifically developed for this study with the question; "On a scale with 10 being the most relaxed you can feel, and 0 being not at all relaxed, how would you rate yourself at this moment?". These ratings were obtained prior to and after the 5-minute rest phase, and 10-minute relaxation phase.

Pain now. The Brief Pain Inventory (BPI-SF) is one of the most widely used scales for measuring pain in patients with a variety of chronic pain problems. The BPI-SF is a 16-item, self-report questionnaire that consists of a body diagram that patients use to mark the location of their pain, a question about pain treatments and medications, and one concerning the percentage of relief obtained. The BPI-SF uses an 11-point NRS (0-10) with end points labeled "no pain" and "pain as bad as you can imagine" to measure the intensity/severity of "now" (present) pain. Pain now was used in assessments pre- and post-surgical pain in this study. The BPI has been

used extensively in a variety of pain conditions and has been shown to have excellent psychometric properties, including validity and reliability in patients with cancer and chronic nonmalignant pain (Cleeland, 1989; Tan, Jensen, Thornby, & Shanti, 2004).

Statistical analyses

Linear mixed models (LMM) were chosen for analyses to enable an intention-to-treat analysis approach (Chakraborty & Gu, 2009). We used IBM's SPSS Statistics (version 23) to perform a LMM analysis of the effects of treatment group (treatment-as-usual, clinical hypnosis) and assessment (pre-surgery rest, pre-surgery relaxation, 1-month post-surgery rest, 1-month post-surgery relaxation) on HF-HRV. Subject ID was used as a grouping variable for level 2 (i.e. person-level variables) to account for nesting of level 1 units (HF-HRV) within person. As fixed effects, we entered intercept, group, assessment, and the interaction term of group by assessment into the model. Assessment was included as a repeated factor nested within subject and modeled with a first order autoregressive (AR1) covariance-variance matrix. A random intercept nested within subject was also included in the model to account for idiosyncratic variation due to individual differences in HF-HRV. Significant interactions were examined by simple effects tests and Bonferroni-corrected comparisons. *P*-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question. Satterthwaite estimations were used for the degree of freedom denominators, as the SPSS MIXED procedure produces non-integer values that vary from analysis to analysis. Respiration rate was analyzed using LMM analysis following the same structure as the above LMM analysis with HF-HRV as the dependent variable to determine whether to include respiration rate as a covariate in the HRV analysis as differences in respiration rate present potential confounding influences on HRV and vagal activity interpretation (Laborde et al., 2017). Similarly, LMMs for secondary outcomes were also conducted separately for HR, "pain now",

and subjective relaxation rating variables, with unstructured variance-covariance matrices. Effect sizes (Cohen's d) were calculated using observed means and standard deviations. Baseline characteristics (e.g. age, gender, pre-operative pain, pre-operative "pain now") were analyzed by ANOVA and Chi-square tests of likelihood.

Results

Participants flow

After pre-screening and enrolment (Figure 1), N=92 participants were randomized into one of two treatment groups: clinical hypnosis (n=45), and treatment-as-usual (n=47). Nine participants were excluded prior to randomization, and one patient's surgery was cancelled after randomization (Figure 1). All patients in the clinical hypnosis group received a pre-operative hypnosis session at their pre-surgery assessment appointment, and 38 of these patients received post-operative hypnosis. Twenty-nine and 30 patients returned for the 1-month post-surgery assessment appointment in the clinical hypnosis and treatment-as-usual groups, respectively.

Recruitment

Recruitment commenced on November 6th, 2018 and was completed on November 1st, 2019 after the number of target participants randomized (N=92) was reached. Participant attrition rate according to this study's primary outcome of HRV was 35.56% in clinical hypnosis and 36.17% in treatment-as-usual. Reasons for dropouts in the clinical hypnosis group included: personal reasons (n=2), death (n=1), unable to schedule follow-up visit (n=5), lost to follow-up (n=8), and developed cardiac complications (n=1). Reasons for dropouts in the treatment-as-usual group included: surgery cancelled (n=1), personal reasons (n=1), unable to schedule follow-up visit (n=1), and lost to follow-up (n=13). Consistent with the intention-to-treat analytic principles, our LMM approach included all available participant data and preserved missing repeated measures data from a listwise deletion (Kristjanssen et al., 2007). Statistics on number

of days between study group's pre-surgery assessment visit, surgery day, inpatient visits, and 1-month assessment visit are summarized in Table 2.

Data preparation

Two ECG recordings of participants in the treatment-as-usual group could not be analyzed due to insufficient signal. High frequency HRV (HF-HRV) data was log-transformed to reduce skewness (0.60) to acceptable levels (0.27), based on published recommendations (Laborde et al., 2017). Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality.

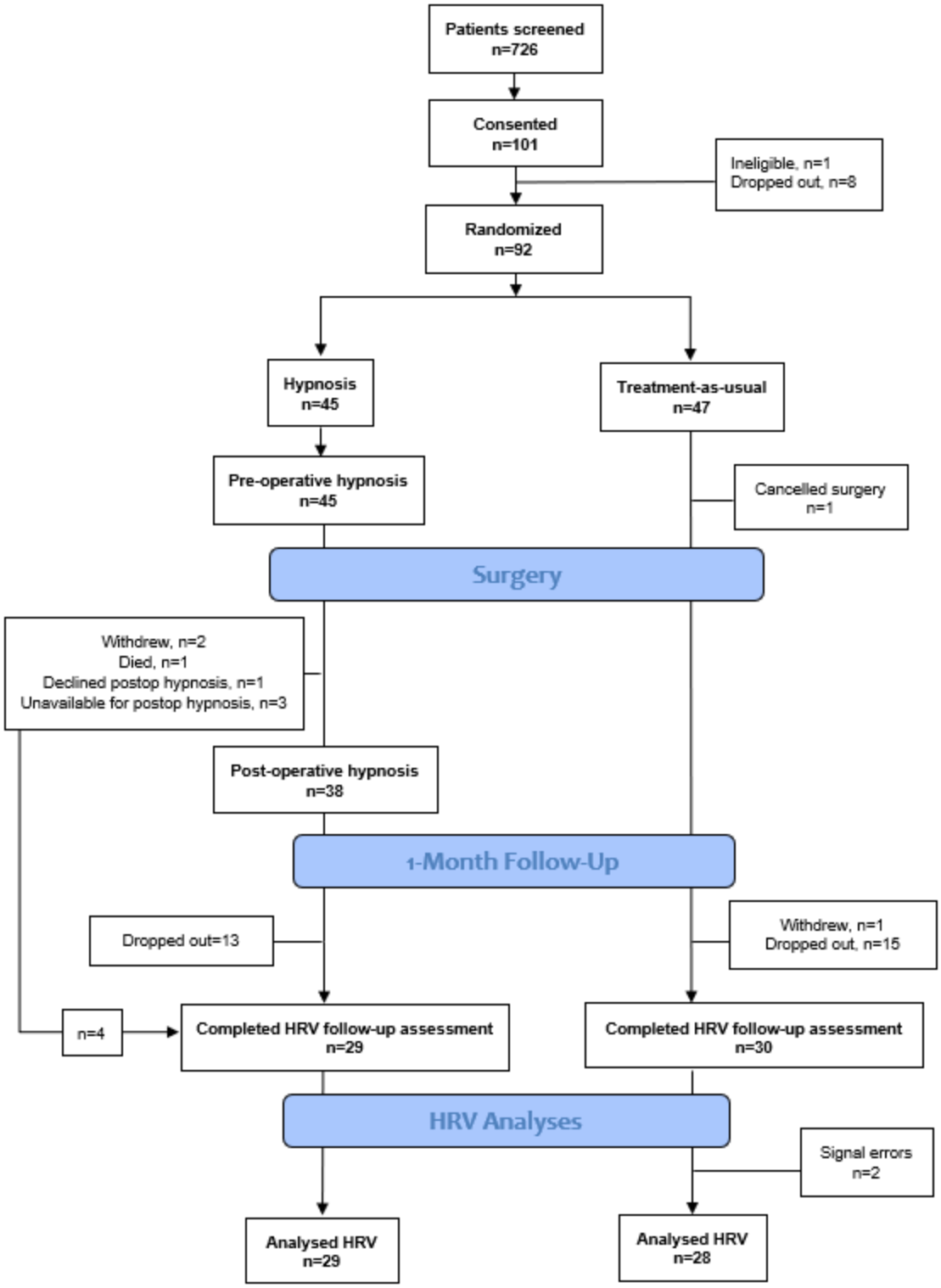


Figure 1. Consolidated Standards of Reporting Trials (2010) flow diagram showing participant flow for enrolment, group classification, randomization to intervention, and analyses. HRV: heart rate variability. All randomized cases were included in linear mixed model analyses, according to an intention-to-treat approach.

Table 1
Demographic and clinical characteristics of study groups

	Group	
Measure	**Treatment-as-Usual**	**Clinical Hypnosis**
Age in years, M (SD)	55.75 (9.7)	55.93 (12.03)
Gender, n %		
Female	16 (57.1)	15 (51.7)
Male	12 (42.9)	14 (48.3)
Surgery type, n		
Head & neck	4	3
Liver surgery	4	3
Kidney surgery	1	3
Hysterectomy	5	5
Breast surgery	4	2
Thoracic	3	3
Urologic	3	4
Major Abdominal	3	4
Laparoscopic Abdominal	1	2
Pre-Op Chronic Pain		
Yes	16 (57.1)	14 (48.3)
No	12 (42.9)	15 (51.7)
Pre-Op Pain "Now"		
Mean	1.68 (2.29)	1.00
Median	1	0
Range	0-8	0-7
Pre-Op Chronic Pain Condition		
Cancer	2	1
Neuropathic	3	2
Headache	2	2
Orofacial	1	0
Visceral	0	1
Musculoskeletal	13	12
Deep Vein Thrombosis	0	1
Pre-Op Pain Meds		
Yes	15 (53.6)	11 (37.9)
No	13 (46.4)	18 (62.1)
Class of Pre-Op Pain Meds		
Tramadol	0	1
Acetaminophen	9	8
Ibuprofen	4	3
Gabapentin	2	1
Pregabalin	2	1
Topical agents	1	0
Pre-Op Mental Health History		
Yes	1	1
No	27	28
Pre-Op Mental Health Meds		
SSRI	3	1
SNRI	1	0
Anxiolytics	1	0
Stimulants	1	0

Groups did not significantly differ on age, gender distribution, and types of surgeries undergone, as well as pre-existing chronic pain conditions, "pain now" ratings, and prescription pain medications prior to surgery (Table 1).

Table 2 Summary of days between key study timepoints.	Treatment-as-Usual	Clinical Hypnosis
Pre-surgery assessment and surgery, M (SD)		
Mean # of days between	13.69 (20.12)	8.93 (12.12)
Median # of days between	7	6
Range of # of days between	1-101	1-63
Surgery day and inpatient visit, M (SD)		
Mean # of days between	1.69 (1.11)	1.62 (0.94)
Median # of days between	1	1
Range of # of days between	0-4	1-5
Surgery day and follow-up visit, M (SD)		
Mean # of days between	30.55 (7.09)	31.69 (6.72)
Median # of days between	31	31
Range of # of days between	16-45	21-48
Inpatient and follow-up visit, M (SD)		
Mean # of days between	28.96 (7.34)	29.79 (6.92)
Median # of days between	30	28
Range of # of days between	13-43	20-47

LMM analysis examining respiration rate did not show significant effects of Group, Assessment, or the Group x Assessment interaction (Table 3). Following recommendations by Houtveen et al. (2007), HRV analyses were conducted without including respiration rate as covariate.

Table 3. Observed means and standard deviations of heart rate and respiration rate in study groups

	Heart rate			Respiration rate		
Pre-Surgery	**Clinical hypnosis**	**Treatment-as-usual**	**Total**	**Clinical hypnosis**	**Treatment-as-usual**	**Total**
Rest	72.06 (11.29)	69.08 (11.18)	70.62 (11.24)	13.14 (4.03)	12.98 (4.62)	13.06 (4.28)
Relaxation	67.68 (10.62)	71.26 (11.61)	69.50 (11.09)	13.50 (2.66)	13.10 (3.92)	13.31 (3.30)
1-Month						
Rest	77.07 (10.31)	75.70 (11.40)	76.41 (10.77)	13.70 (5.13)	14.29 (4.39)	13.98 (4.75)
Relaxation	75.50 (10.71)	75.69 (11.16)	75.59 (10.83)	13.59 (3.34)	14.18 (4.12)	13.87 (3.71)

Note.

Primary Outcomes

LMM analysis with Group and Assessment revealed a significant main effect of Assessment [$F(3, 165.77) = 10.32$, $p < 0.001$] that indicated HF-HRV differed across

assessments overall. Main effect of group was not significant [$F(1, 86.31) = 1.81$, $p = 0.18$]. In addition, a significant Group by Assessment interaction effect [$F(3, 165.77) = 6.58$, $p < 0.001$], indicated that HF-HRV change across assessments differed according to treatment group. The interaction effect was examined by simple effects tests using Bonferroni-corrected comparisons regarding Hypotheses 1a and 1b below. Variance estimates for the random intercept indicated that there was significant variation in the intercept (Wald Z = 4.97, $p < 0.001$). HRV data is summarized in Table 3.

Hypothesis 1a. Higher HRV in Clinical Hypnosis Group. The simple effect of Group was significant for 1-month rest, $F(1, 171.43) = 5.82$, $p < 0.05$, $d = 0.73$ and 1-month relaxation, $F(1, 170.61 = 7.20$, $p < 0.01$, $d = 0.73$ indicating that at these assessment times, HF-HRV was higher in the clinical hypnosis group than treatment-as-usual group (Table 4; Figure 2b).

Hypothesis 1b. Decreased HRV in Treatment-as-Usual Group. The simple effect of Assessment was significant for the treatment-as-usual group, $F(3,150.70) = 15.67$, $p < 0.001$, but not the clinical hypnosis group, $F(3, 147.60) = 1.05$, $p = 0.37$, indicating that in the treatment as usual group, 1-month rest ($d = 0.60$, $p < 0.001$) and 1-month relaxation ($d = 0.48$, $p < 0.001$) HF-HRV were lower than the corresponding pre-surgery rest and relaxation values (Table 4; Figure 2b).

Table 4. Observed means and standard deviations of log-transformed high-frequency heart rate variability in study groups

Pre-Surgery	Treatment-as-usual	Clinical hypnosis	Total
Rest	4.74 (1.36)	4.92 (1.29)	4.83 (1.32)
Relaxation	4.79 (1.25)	4.86 (1.53)	4.82 (1.39)
1-Month Post-Surgery			
Rest	3.62 (1.29)[a]	4.63 (1.47)[b]	4.13 (1.46)
Relaxation	3.85 (1.49)[a]	4.95 (1.54)[b]	4.41 (1.60)

Notes. [a]Within-person change compared to pre-surgery measures ($p > 0.001$). [b]Between-group difference ($p > 0.01$).

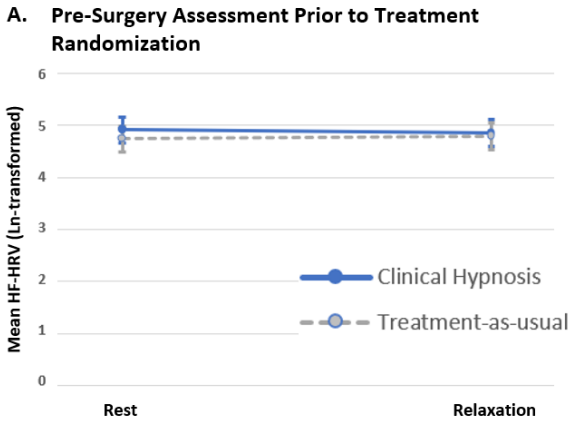


Figure 2A. Plot is based on observed means and standard errors. HF-HRV=High-frequency heart-rate variability (power as m^2). Pre-operative assessment, mean number of days before surgery = 11.17 (SD=16.82).

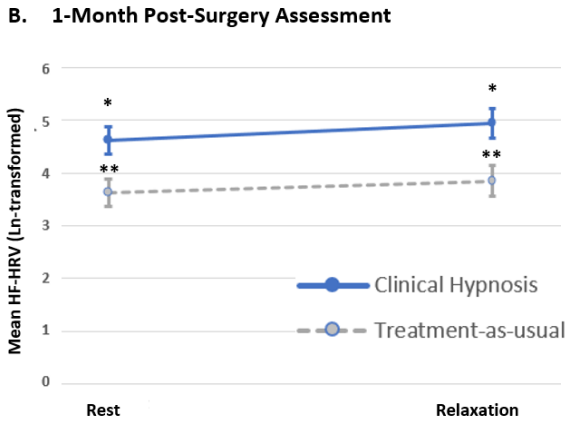


Figure 2B. Plot is based on observed means and standard errors. 1-month post-surgery assessment, mean number of days post-surgery = 31.19 (SD=6.94)
* p<0.01; group differences
** p<0.001; within-group change from pre- to post-surgery

Secondary Outcomes

Heart rate. LMM analysis with Group and Assessment revealed a significant main effect of Assessment [$F(3, 69.47) = 9.87$, $p < 0.001$]. Pre-surgery relaxation heart rate was lower than pre-surgery rest heart rate ($p < 0.01$, $d = 0.06$) in all participants. One-month rest and relaxation heart rate were significantly higher than the corresponding values for pre-surgery rest and relaxation heart rate (all $p < 0.005$, all $d > 0.37$). Group and interaction effects were not significant.

Subjective relaxation ratings. LMM analysis with Group and Assessment indicated a significant main effect of Assessment [$F(5, 54.27) = 69.74$, $p < 0.001$]. Post-relax relaxation ratings at pre-surgery (M = 8.61, SD = 1.88) and 1-month (M = 8.66, SD = 1.12) were significantly higher than corresponding pre-surgery pre-rest (M = 6.31, SD = 1.85) and post-rest (M = 7.25, SD = 1.90) ratings, and 1-month pre-rest (M = 6.27, SD = 1.88) and post-rest (M =

7.49, SD = 1.77) ratings in all participants (all $p < 0.005$, $d > 0.60$). The main effect of Group and the interaction effect were not significant.

Pain now ratings. LMM analysis with Group (treatment-as-usual, clinical hypnosis) and Assessment (pre-surgery, 1-week post-surgery, 1-month post-surgery) indicated a significant main effect of Assessment [$F(2,74.69) = 30.79$, $p < 0.001$]. "Pain now" ratings at 1-week (M = 2.93, SD = 2.44) and 1-month (M = 2.20, SD = 2.42) post-surgery were significantly higher than pre-surgery (M = 1.30, SD = 2.14) ($p \leq 0.001$, $d = 0.28$-0.50), and 1-month ratings were significantly lower than 1-week ratings ($p < 0.005$, $d = 0.21$). The main effect of Group and the interaction effect were not significant.

Discussion

Hypnosis-based interventions are theorized to promote cardiac vagal activity, which may be beneficial to post-surgical recovery when patients are vulnerable to prolonged inflammation and post-surgical pain. The present study examined the effects of perioperative clinical hypnosis on HRV at 1-month post-surgery, to understand its longer term effects on parasympathetic activity. Results from the present study showed that HRV was significantly higher in the clinical hypnosis group compared to the treatment-as-usual group at the 1-month rest and relaxation assessments. Moreover, as hypothesized, HRV significantly decreased from pre-surgical to post-surgical rest and relaxation assessments in the treatment-as-usual group but not the clinical hypnosis group. There were no significant treatment effects associated with mean heart rate, subjective relaxation, and "pain now" ratings.

Effects of clinical hypnosis on 1-month post-surgical HRV. The central implication of the present findings is the demonstrated potential for peri-operative clinical hypnosis to impart a protective effect on PNS functioning. The results suggest that clinical hypnosis prevents the deleterious effects of surgery on HRV, by helping to preserve pre-operative levels of PNS

functioning, in contrast to the treatment-as-usual group who display an expected course of HRV reduction in the absence of clinical hypnosis. Future studies are needed to better understand the acute effect of hypnosis on vagal HR modulation, specifically studies featuring assessment of HRV during peri-operative clinical hypnosis sessions, and during the first several post-operative days after patients receive peri-operative hypnosis sessions. Further investigations may also include measurement of other downstream effects of vagal activity, such as pro-inflammatory cytokines. Although previous studies have shown that HRV increases during hypnosis practice (Aubert et al., 2009; Yüksel, Ozcan, & Dane, 2013), other studies have not found this effect (Kekecs, Szekely, & Varga, 2016; Ray et al., 2000), so there may be specific components of hypnosis practice that are integral to vagal activation. Moreover, there are no other studies that have measured HRV during pre- and post-surgical hypnosis, so it is unclear to what extent any HRV changes during peri-operative hypnosis have an impact on long-term post-surgical HRV.

Study results suggest major surgery results in persistent withdrawal of vagal HR modulation activity up to 1-month post-surgery in participants assigned to the treatment as usual group but not the clinical hypnosis group. This finding corroborates and adds to previous literature reporting significant HRV reductions in patients in the immediate days and weeks following major surgery (Aubert et al., 2009; Dericioglu, Demirci, Cataltepe, Akalan, & Saygi, 2013; Grote et al., 2019; Williamson et al., 2010). Major surgery comprises acutely stressful procedures in which pain is elicited due to tissue damage, inflammation, and central sensitization (Searle & Simpson, 2010) all of which can have deleterious effects on vagal-mediated HRV (De Couck et al., 2014). Hence, promoting vagal HR modulation in patients before and after planned surgeries may be a feasible adjunct to improving postoperative outcomes. Theoretically, preserved PNS functioning can augment post-surgical recovery via the vagal anti-inflammatory

reflex (Martelli et al., 2014), and thereby inhibit inflammatory activity that characterizes persistent post-surgical pain.

The present results from the treatment as usual group show that some degree of diminishment in PNS activity occurred at the one-month time point. Adequate post-surgery recovery and healing is likely marked by a gradual restoration of PNS functioning. There is a dearth of data on post-surgical HRV to help understand the process of restoration of PNS functioning. For example, we do not know whether HRV decreased in the days after surgery in the clinical hypnosis group. It is important to establish the trajectory of HRV recovery after surgery. Grote et al's (2019) longitudinal study provides 3 relevant findings that may shed light on this issue: 1) HRV was reduced in all post-surgical patients during post-operative days 2-4, 2) gradual HRV increases were observed during 2 weeks of rehabilitation initiated 1-month post-surgery, and 3) during rehabilitation, HRV was quicker to return to pre-surgery levels for patients with higher pre-surgical HRV values. The authors concluded that restoration of PNS functioning after surgery is a gradual process that can be augmented by vagal HR modulation rehabilitation practices and is more efficient for those with robust PNS functioning prior to surgery. To the extent that Grote et al.'s findings can be generalized to the post-surgical PNS restoration process, peri-operative clinical hypnosis may offer a promising adjunct to augment PNS restoration. It is possible that peri-operative hypnosis positively alters a patient's trajectory in terms of coping with the aftermath of surgery by entraining them with a vagal-activating practice before and after surgery, as discussed below. Future similar RCT studies may yield more insight into the ebb and flow of sympathetic and vagal HR modulation post-surgery via ambulatory HRV monitoring during daytime and nighttime to yield greater insight into the process of PNS restoration post-surgery.

One of the more puzzling results of the present study is that, in contrast to the HRV findings, we did not observe a similar group by assessment interaction revealing a treatment effect for subjective relaxation and pain ratings, discussed below. This makes it somewhat challenging to interpret the HRV results, because the clinical hypnosis intervention was not only designed to impact post-surgical HRV, but to leverage its theoretical PNS benefits to enhance post-surgical relaxation and pain relief. However, resting state HRV is a general marker of the responsiveness and flexibility of the ANS (Quintana & Heathers, 2014), and is not necessarily a direct indicator of a person's state relaxation and current pain levels. In addition, HRV during relaxation assesses the capacity to increase cardiac vagal control (McCraty & Shaffer, 2015), and similarly, may not be readily associated with downstream, self-reported variables such as state relaxation and pain. Moreover, measurement of HRV during a relaxation task after a brief pain or stress-induction procedure, as recommended in the literature (Laborde et al., 2017), may have greater validity as a measure of cardiac vagal recovery that could be associated with one's ability to regulate current pain or stress. We chose not to employ pain or stress-induction procedures due to ethical considerations (i.e. reducing patient burden). Furthermore, it is possible that the effects of hypnosis on physiological parameters, whether they be HRV, blood pressure, or gut motility, are not directly accessible to psychological introspection and self-report. Relatedly, an RCT of hypnosis to treat mild hypertension found a significant treatment effect of reduced blood pressure up to one-year later, but found no association between blood pressure and self-reported anxiety or personality factors in the treatment group at follow-up study timepoints (Gay, 2007). Similarly, several studies have examined the possible role of psychological factors in mediating the treatment effect of hypnosis on irritable bowel syndrome (Camilleri & Choi, 1997; Lea et al., 2003; Whitehead & Palsson, 1998). These studies have not found evidence for a direct

relationship between psychological factors, such as anxiety and depression, and their physiological outcomes (e.g. gut rectal sensitivity).

The short and long-term impact of peri-operative clinical hypnosis on HRV may be understood by considering two of its commonly proposed mechanisms: (1) reduction of state emotional distress and (2) instilling of long-term positive expectancies (Montgomery et al., 2000). Patients guided in stress-relieving practices and primed with positive expectations via hypnosis may be better equipped to have a gradual and efficient restoration of PNS functioning post-surgery. In the current study, emotional distress was targeted by inducing a relaxation response through deep breathing and imagery-based suggestions during both pre- and post-surgery hypnosis sessions. These hypnosis sessions aimed to reduce pain and induce relaxation through dissociation and imaginal superimposition of pleasurable sensations onto body parts (Montgomery et al., 2000). Both relaxation and top-down pain regulation are characterized by reduced sympathetic and increased parasympathetic control of the ANS, reflected in higher HRV (Thayer & Lane, 2000).

Positive response expectancies for post-surgical recovery were targeted in both sessions through suggestions of positive imagery of experiences leading up to, during, and after surgery, as well as suggestions for continued self-hypnosis practices to further its benefits. Furthermore, post-hypnotic suggestions included the expectation that positive changes in pain and comfort level that patients experienced during hypnosis sessions would endure, and be achievable, well into the future. These functionally adaptive processes may be reflected in a sympatho-vagal shift towards restored vagal HR modulation in the weeks and months after surgery.

Effects of clinical hypnosis on subjective relaxation. It is noteworthy that HRV was not significantly increased by the relaxation task during assessments, in which patients were

provided audio guidance of a 10-minute practice including deep breathing and relaxing suggestions (e.g. warmth, heaviness throughout body). These instructions were also used by clinicians during the hypnotic induction stage of the pre- and post-surgery clinical hypnosis sessions provided to the clinical hypnosis group. Interestingly, 1-month relaxation HRV appears to trend upward from corresponding rest HRV values in the clinical hypnosis group, however, a significant HRV increase was not detected. Perhaps there is an underlying dose effect, and a duration of more than 10 minutes of relaxation is needed to capture a significant HRV increase associated with relaxation in the clinical hypnosis group. Alternatively, if pre-surgical clinical hypnosis helps preserve HRV, one possibility is that it might not be predominantly attributed to the relaxation effect of the hypnotic induction states. As such, the latter and deeper stages of hypnotic dissociation and positive expectancy suggestions may play an integral role in promoting vagal HR modulation. By contrast, subjective relaxation ratings showed a pattern of significant increases from pre-rest, post-rest, to post-relaxation similarly across both pre-surgical and 1-month post-surgical assessments. Having received perioperative clinical hypnosis was not associated with reporting higher subjective relaxation values at 1-month post-surgery. While higher HRV would be expected to be positively associated with subjective relaxation, this could largely depend on idiosyncratic variations in interoception (i.e. ability to accurately monitor one's internal bodily states). Furthermore, it may be that longer and deeper states of hypnosis (i.e. dissociation) may need to be reached for the dynamics of subjective and physiologically relaxed states to coalesce.

Patients were encouraged to maintain a self-hypnosis practice by using audio recordings (accessible via a YouTube channel) before and after surgery. Self-hypnosis practice may have contributed to a cumulative restorative effect on vagal-mediated HRV in the clinical hypnosis

group, explaining the differences observed at 1-month. Tracking logs proved to be an unfeasible method to gather self-hypnosis practice data from patients, as too few patients returned their logs at the 1-month follow-up to enable meaningful analyses of these data. Future studies should consider using more feasible procedures (e.g. phone or web-based surveys) to monitor self-hypnosis practices to examine the relationship between frequency of self-hypnosis practice and post-surgical HRV.

Effects of clinical hypnosis on heart rate and pain. Secondary analyses of physiological data revealed that all patients exhibited significantly elevated HR during rest and relaxation assessments at 1-month post-surgery. HR significantly influences HRV due to both physiological and mathematical reasons. Current results indicate that net ANS activity shifted towards greater sympathetic activity for all patients post-surgically. One contributing factor to explain this would be the significantly higher post-surgical pain ratings at one-month, as pain and sympathetic activity are interconnected functions (De Couck et al., 2014). Pain is generally associated with "sympathetically dominant" states (e.g. high HR, lower HRV), making the preservation of parasympathetic tone vital to stress and pain regulation during post-surgery. Another potential reason for the HR elevations may be that they signal the relative decline in fitness level of patients, due to the physical deconditioning that accompanies the post-surgical recovery period, when patients are engaging in less physical activity.

Limitations and future directions

The current study has limitations. Firstly, this study was not conducted as a double-blind study, to enable facilitation of the study by coordinators scheduling patients, and for outcome assessors who also served as clinicians providing the clinical hypnosis intervention to patients. To keep risk of bias as low as possible, treatment allocation concealment was used so it was

unknown to study staff which patients would be randomized to clinical hypnosis or treatment-as-usual arms until pre-surgical assessments had been completed. Furthermore, this study lacked an active control condition. The lack of adequate "sham" or placebo hypnosis procedures to enable appropriate controls for clinical hypnosis (Kendrick, 2012) poses challenges in designing active control conditions in hypnosis research. We decided against employing sham or placebo control conditions for ethical reasons. In the future, a suitable control intervention may be providing peri-operative sessions of relaxation (e.g. deep breathing) to serve to compare with the HRV effects observed with clinical hypnosis in the present study. It may also be prudent to control for non-specific therapeutic factors in the treatment-as-usual group, for example, by providing attention from a caring professional with the same allotted time and schedule as pre- and post-surgery clinical hypnosis sessions. Additionally, future studies may consider administering measures of hypnotic suggestibility to patients to better understand likelihood of response to hypnosis, and thereby stratify patients to study arms accordingly. The current study did not assess suggestibility to minimize patient burden. It is possible that patients who expected the most benefit self-selected into the study, whereas those with low expectations declined to participate. This possibility limits the generalizability of the findings for surgery populations. However, it is worth mentioning that a paper comprised of three studies on the relationship between hypnosis and HRV found no evidence that "high or low hypnotic susceptibility" impacts HRV responses to hypnosis (Ray et al., 2000). In terms of study outcomes, this study only focused on the high frequency measure of HRV, as this metric has garnered the most robust evidence in terms of an association with incidences of chronic pain (Tracy, et al., 2016). Future studies may consider examining other validated HRV metrics (e.g. low frequency, root mean squared of successive differences) to yield further insights. Another limitation of our approach is

that we did not address the multidimensional nature of pain (Melzack & Wall, 1983), particularly from an affective perspective. That is, future researchers may wish to assess affective pain, in order to establish an understanding of whether constructs such as pain unpleasantness may mediate the relationship between clinical hypnosis and post-surgical HRV.

Conclusion

Patients who received a peri-operative clinical hypnosis intervention focused on post-surgical pain relief showed preserved and significantly higher HRV values in comparison to treatment-as-usual patients who showed significantly reduced HRV values at 1-month post-surgery. This finding suggests clinical hypnosis interventions may be a useful adjunct to peri-operative pain management by providing protective effects on parasympathetic functioning up to 1 month after surgery. More research is needed to further elucidate the relationship between clinical hypnosis, post-surgical pain and HRV.

Chapter V. General Discussion

Pain conditions are complex and common health problems, with negative implications for individual quality of life and the healthcare system. Clinical pain can originate from inflammatory and neurological dysfunction, and emerging evidence indicates that stress-related ANS dysfunction is a critical component of the etiology and maintenance of pain. Enhancing vagal HR modulation, through behavioral medicine treatments, may offer a therapeutic pathway that targets multiple etiologic factors in pain.

Summary of Dissertation's Major Findings

The present dissertation employed HRV as a measure of vagal HR modulation in three RCTs to investigate responses to behavioral medicine treatments, mindfulness meditation and clinical hypnosis, in individuals with chronic and post-surgical pain. In Study I, undergraduate students with tension and migraine headaches and headache-free students exhibited significantly higher HRV during a mindfulness meditation practice condition compared to listening to an audio description of mindfulness. HRV significantly increased from a stress-induction phase to the mindfulness meditation practice condition, with no difference between headache and headache-free groups. Moreover, the headache participants in the meditation description condition had significantly lower HRV than their headache-free counterparts. These findings indicated potential for mindfulness interventions in inducing positive HRV responses in a chronic pain population, while highlighting possible dysfunctions in their cardiac vagal recovery in the absence of intervention. Study II involved comparing the HRV effects of an MMA+ condition, a smartphone app-based mindful breathing task, with an MMA- condition of mindful breathing practice without the app, after a brief stress-induction procedure. The effect of the app condition during the MM phase was significant for the chronic pain group, but not the depressed-anxious or sub-criteria groups. Planned comparisons showed, contrary to the hypothesis, that

HRV was significantly higher in the MMA- condition compared to the MMA+ for the chronic pain group. Furthermore, in the MMA+ condition, only the sub-criteria group showed significant stress-to-MM HRV increases, whereas all three groups showed significant HRV increases in the MMA- condition. These findings demonstrated the vagal HR modulating potential of mindfulness interventions for chronic pain and psychologically distressed populations and revealed possible hindering effects of features of the MMA (i.e. distracting breath-focus audio prompts). Study III examined HRV prior to oncological surgery and at one-month post-surgery in participants who received a peri-operative clinical hypnosis intervention for pain relief versus treatment-as-usual. One month after surgery, HRV was significantly higher in the clinical hypnosis group during rest and relaxation than the treatment-as-usual group. By contrast, rest and relaxation HRV significantly decreased from pre- to one-month post-surgery for the treatment-as-usual but not the CH group. These results suggest that peri-operative clinical hypnosis prevents the deleterious effects of surgery on HRV by preserving pre-operative vagal HR modulation. The treatment-as-usual group display an expected decrease in HRV in the absence of clinical hypnosis.

Comparison and Contextualization of Dissertation Study Findings

Mindfulness interventions and post-stress vagal HR modulation. As Study I and II employed mindfulness interventions, namely audio-guided, app-guided, and self-guided mindful breathing, it is relevant to compare and contextualize these study findings. The superior effect of MMA- for the chronic pain group in Study 2 extends findings from Study I that focused only on students with tension-migraine pain conditions. Study II's chronic pain group was comprised of students with tension-migraine headaches, chronic back and joint pain, and neuropathic pain conditions, and so the significant HRV increase associated with the MMA- condition suggests that the post-stress effect of MM in increasing cardiac vagal control can be generalized across

chronic pain conditions. The overall pattern of HRV results across both studies indicates that audio-guided and self-guided mindfulness interventions are effective in increasing HRV in chronic pain and depressed-anxious populations. App-guided mindful breathing, although evidently effective in increasing HRV for a sub-criteria group, appeared to hinder the expected HRV effects of mindful breathing in the symptomatic groups. As the MMA represents an initial step in designing an interactive smartphone app to entrain mindful breathing, it likely requires further refinements in its design to facilitate the theoretical benefits of mindful breathing on HRV. Taken together, results for these two studies show promising evidence that mindfulness interventions can promote vagal HR modulation for stress recovery in individuals with pain and stress-related conditions.

These findings fit amply into the context of research on behavioral medicine treatments featuring HRV assessment. In particular, it is important to highlight the central instruction of mindfulness meditation practice, that being the emphasis on taking full and slow breaths with attention to breathing sensations. Sufficient evidence has amassed that deliberately slow and deep breathing practice increases HRV indices of cardiac vagal control (Critchley et al., 2015; Larsen, Tzeng, Sin, & Galletly, 2010; Mortola, Marghescu, & Siegrist-Johnstone, 2015; Pal & Velkumary, 2004; Tavares et al., 2017) and lowers stress markers such as: heart rate, blood pressure and salivary cortisol (Lee et al., 2003; Perciavalle et al., 2017; Pramanik et al., 2009). Furthermore, HRV has been shown to increase in response to many forms of contemplative practice, lending credence to the hypothesis of cardiac vagal recovery through breath and attention regulation (Gerritsen & Band, 2018). Indeed, different forms of meditation (e.g., body scan, Acem meditation, Zen meditation) and mind-body exercises such as yoga practiced by healthy participants are all associated with increased or elevated levels of HRV relative to

comparison groups (Ditto, Eclache, & Goldman, 2006; Markil, Whitehurst, Jacobs, & Zoeller, 2012; Melville, Chang, Colagiuri, Marshall, & Cheema, 2012; Nesvold et al., 2012; Phongsuphap, Pongsupap, Chandanamattha, & Lursinsap, 2008; Tang et al., 2009; Telles et al., 2013; Wu & Lo, 2008). Few of these studies included stress-induction procedures or recruitment of individuals with chronic pain and severe symptoms of depression and anxiety. Study I and Study II from the present dissertation demonstrate these effects using a novel experimental paradigm of rest, stress-induction, and post-stress mindful breathing, showing that HRV can be increased acutely in individuals with chronic pain and severe depression-anxiety symptoms, in addition to non-symptomatic individuals.

Effects of mindfulness and clinical hypnosis interventions on pain and vagal HR modulation. Both mindfulness and clinical hypnosis interventions were demonstrated to be of benefit to vagal HR modulation in the present dissertation, however, it is worth discussing the implications of their different approaches to treating clinical pain. Garland et al. (2020) recently published a systematic review and meta-analysis examining the benefits of mind-body therapies for patients treated with opioids for acute, procedural, and chronic pain conditions. They found that the mindfulness-based intervention studies focused on treatment of non-cancer pain (e.g. low back pain), whereas most of the interventions based on hypnosis, including relaxation, imagery, and suggestion-based interventions, focused on treating acute, procedural, and cancer-related pain. Moreover, the authors highlighted how mindfulness and hypnosis-based interventions have different mechanisms with respect to how they impact pain. In this regard, they articulated that mindfulness training increases acceptance and decreases catastrophizing of pain, while facilitating a shift from affective to sensory processing of pain sensations through cognitive reappraisal. On the other hand, hypnosis techniques aim to reduce pain through dissociation or

imaginal superimposition of relaxation and pleasurable sensations on to painful body parts (Garland et al., 2020). Despite these differing mechanistic accounts, neurophysiological research has found evidence that both hypnosis and mindfulness help alleviate pain via corticothalamic modulation of ascending nociceptive input (Del Casale et al., 2015; Zeidan et al., 2011). More research is needed to disentangle the mechanisms by which hypnosis and mindfulness relieve pain, so that targeted interventions can be designed and optimized according to pain populations and types of pain condition (e.g. postsurgical versus chronic pain).

It must be noted that the focus of the present dissertation studies was not primarily on pain outcomes, but rather the primary focus was to determine whether these behavioral interventions could enhance vagal HR modulation, which is connected to several analgesic functions (e.g. relaxation, anti-inflammation, inhibition of pain processing brain regions) (De Couck et al., 2014) but is typically diminished in individuals with pain conditions (Koenig, Falvay, et al., 2016; Tracy et al., 2016). In students with self-reported pain, studies I and II showed HRV can be increased acutely with a mindfulness intervention, whereas with post-surgical pain patients, Study III showed a longitudinal protective effect on HRV associated with clinical hypnosis. Additional studies are needed to determine the extent to which these HRV effects translate to an effect on clinical pain outcomes, whether in lowering pain intensity, or specifically in the case of the post-surgical patients, being protective against the development of persistent post-surgical pain. It is plausible that both mindfulness and clinical hypnosis are governed by dose-response curves when it comes to their effects on pain. In other words, some consistent amount of practice over a period of time may be needed for vagal HR modulation to be ameliorated to the extent that it yields analgesic benefits reflected in self-reported pain ratings. For instance, in Study III, although there was no treatment effect on pain intensity at

one-month, additional follow-up assessments (e.g. three-months or six-months post-surgery) would be needed for reassessment of HRV and post-surgical pain. This could help to test the extent to which the trajectory of the clinical hypnosis group was positively altered (in terms of their preserved HRV levels), if in fact it revealed differences with respect to post-surgical pain outcomes (e.g. pain intensity, incidence of pain) at these timepoints relative to the treatment-as-usual group.

Mindfulness and hypnosis feature instructions that recruit several different cognitive functions. The mindfulness interventions in Studies I and II instructed sustained and refocusing of attention on breathing sensations, and open monitoring of private experiences, as described in the mindfulness literature (Brown & Ryan, 2003; Kabat‐Zinn, 2003). The clinical hypnosis treatment in Study III featured deep breathing and guided imagery involving active imagination of visual and somatic perceptions and sensations, also consistent with clinical literature (American Psychological Association, 2004; Elkins, 2016). Arguably, the primary overlap between the two interventions is on regulating attention to slow and deep breathing patterns. In mindfulness meditation, sustaining and refocusing attention to slow breathing is a central aim in practice, whereas clinical hypnosis uses deep breathing and breath awareness to induce and maintain a relaxed state throughout practice. This overlap may help explain the similar augmenting effects of mindfulness and clinical hypnosis on HRV in the present dissertation, as well as in the literature (Aubert et al., 2009; Azam et al., 2015; Debeneditis et al., 1994; Krygier et al., 2013). As discussed previously, much of the beneficial effects of several contemplative practices are considered to arise from respiration-based vagal stimulation (Gerritsen & Band, 2018). Gerritson and Band have proposed that the primary mediator of the effects of contemplative practices (featuring breathing regulation) on mental and physical health is the

vagus nerve. Specifically, the styles of respiration shown to elicit respiration-based vagal stimulation are controlled breathing techniques that slow and deepen respiration, extend expiration (Garcia, Koschnitzky, Dashevskiy, & Ramirez, 2013), and potentially exercises that emphasize diaphragmatic breathing. They highlight how this form of breathing regulation directly stimulates the vagus nerve, "top-down" from the executive network, through an efferent pathway. This phasic increase in efferent vagal activity increases HRV, lowers heart rate and blood pressure, inhibits the SNS and indirectly the hypothalamic-pituitary adrenal axis, and potentially activates the cholinergic anti-inflammatory pathway, resulting in a decrease of acute stress (Gerritsen & Band, 2018). Conversely, an indirect "bottom-up" pathway is considered to use afferent vagus nerve pathways that continuously signal respiratory patterns upwards to characterize a state of relaxation and low-threat to the central nervous system. Consequently, this further activates efferent vagal activity, increasing vagal tone and producing the associated physiological changes (e.g., lowering heart rate, blood pressure, increasing HRV); creating a "relaxation loop" (Gerritsen & Band, 2018). Further research is needed to validate the respiration-based vagal stimulation model for its clinical applications.

Breathing regulation is likely one of several components that helps to explain the HRV effects of mindfulness and clinical hypnosis found in the present dissertation. In terms of other components, it would be important to evaluate how mindful breathing alters the way individuals with pain conditions pay attention to their pain sensations amidst practice, and whether this is associated with HRV changes. Theoretically, bringing mindful attention to pain sensations in ways that promote acceptance and negate catastrophic thoughts would ultimately enhance stress regulation, reflected in increased HRV. This approach may be efficacious for chronic pain conditions in which pain can be exacerbated through negative cognitive schemas and

hypervigilance about pain (Dersh et al., 2002). In clinical hypnosis, rather than paying attention to pain differently, the aim is to alter perception by "replacing" pain sensations with imagery of relaxing and pleasurable sensations. From a stress-regulation perspective, this approach would be potent for acute pain conditions or procedural pain, such as post-surgical pain, where nociceptive peripheral or visceral afference during noxious stimulation are the cause of suffering. Taken together, mindfulness and clinical hypnosis practices both appear to be multi-modal interventions, with breathing regulation as an overlapping component, and with apparent benefits for vagal HR modulation. Additional studies are needed elucidate the unique and overlapping mechanisms of mindfulness and clinical hypnosis for their impacts on pain and vagal HR modulation.

PNS dysfunction in the absence of behavioral medicine interventions. An interesting parallel between Study I and Study III is worth considering for implications of stress-induced PNS dysfunction in the absence of behavioral medicine treatments. Within an acute experimental protocol, Study I revealed that tension-migraine headache students had significantly lower HRV (i.e. diminished PNS functioning) than their headache-free counterparts in the absence of a mindfulness intervention (only listening to a mindfulness audio description) after a brief stress-induction. Study II employed longitudinal HRV assessment, in which the "stressor" was major surgery. One-month after surgery, the treatment-as-usual group (which did not receive any intervention) showed significantly reduced HRV relative to baseline, and lower relative to their counterpart who received a clinical hypnosis intervention. Taken together, vulnerable populations that were exposed to stressors and did not receive a mindfulness or hypnosis intervention exhibited impaired cardiac vagal control afterwards, in both acute and long-term time scales. It has been hypothesized that diminished vagal activity, if left unaddressed, can

become entrenched and leave individuals vulnerable to the effects of "sympathetically dominant" states, contributing to the onset and maintenance of pain disorders (Koenig, Falvay, et al., 2016; Tracy et al., 2016). This highlights the important role behavioral medicine interventions, mindfulness and clinical hypnosis, can play in promoting stress recovery and preventing the deleterious effects of stressors on ANS health.

Conclusion: Significance and Future Imperatives for Research

It is hoped that the findings of the current dissertation will encourage future research to better understand the relationship between HRV and pain outcomes in clinical pain populations. This may include studies with various pain outcomes, such as: (1) affective measures of pain (e.g. pain unpleasantness), (2) behavioral measures of pain (e.g. mechanical and temperate pain thresholds), and dose and duration of opioid analgesic use. Future studies should also attempt to increase the dosage of treatments provided (e.g. brief versus multi-week mindfulness or hypnosis training) and vary delivery formats (e.g. delivered in-person by practitioners versus audio or internet recordings). Moreover, additional physiologic variables of stress (e.g. salivary cortisol, pro-inflammatory cytokines, blood pressure, galvanic skin response, etc.) should be included to further elucidate the neurobiological mechanisms implicated in the relationship between pain and stress. Importantly, studies should use double-blind or active placebo-controlled designs wherever possible to minimize risk of bias. Overall, these suggestions for future research would address questions and topics raised by the current dissertation and have important implications for the study and design of behavioral medicine interventions for acute and chronic pain.

References

Abbott, R. A., Whear, R., Rodgers, L. R., Bethel, A., Coon, J. T., Kuyken, W., . . . Dickens, C. (2014). Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *Journal of psychosomatic research, 76*(5), 341-351.

Allen, J. J. B., Chambers, A. S., & Towers, D. N. (2007). The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. *Biological psychology, 74*(2), 243-262.

Altimiras, J., Aissaoui, A., & Tort, L. (1995). Is the short-term modulation of heart rate in teleost fish physiologically significant? Assessment by spectral analysis techniques. *Brazilian journal of medical and biological research= Revista brasileira de pesquisas medicas e biologicas, 28*(11-12), 1197-1206.

American Psychological Association, D., Society of Psychological Hypnosis. (2004). Hypnosis for the Relief and Control of Pain. Retrieved from http://www.apa.org/research/action/hypnosis.aspx

Apkarian, A. V., Bushnell, M. C., Treede, R.-D., & Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European journal of pain, 9*(4), 463-484.

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of general psychology, 10*(3), 229-240.

Arrhythmia Reference Guide. (2015). Retrieved from http://www.practicalclinicalskills.com/ekg-reference-guide.aspx

Asher, G. N., Jonas, D. E., Coeytaux, R. R., Reilly, A. C., Loh, Y. L., Motsinger-Reif, A. A., & Winham, S. J. (2010). Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials. *The Journal of Alternative and Complementary Medicine, 16*(10), 1097-1108.

Asmundson, G. J. G., Coons, M. J., Taylor, S., & Katz, J. (2002). PTSD and the experience of pain: research and clinical implications of shared vulnerability and mutual maintenance models. *The Canadian Journal of Psychiatry, 47*(10), 930-937.

Asmundson, G. J. G., & Katz, J. (2009). Understanding the co‐occurrence of anxiety disorders and chronic pain: state‐of‐the‐art. *Depression and anxiety, 26*(10), 888-901.

Athanas, A. J., McCorrison, J. M., Smalley, S., Price, J., Grady, J., Campistron, J., & Schork, N. J. (2019). Association Between Improvement in Baseline Mood and Long-Term Use of a Mindfulness and Meditation App: Observational Study. *JMIR mental health, 6*(5), e12617.

Aubert, A. E., Verheyden, B., Beckers, F., Tack, J., & Vandenberghe, J. (2009). Cardiac autonomic regulation under hypnosis assessed by heart rate variability: spectral analysis and fractal complexity. *Neuropsychobiology, 60*(2), 104-112.

Auvray, M., Myin, E., & Spence, C. (2010). The sensory-discriminative and affective-motivational aspects of pain. *Neuroscience & Biobehavioral Reviews, 34*(2), 214-223.

Azam, M. A., Katz, J., Fashler, S. R., Changoor, T., Azargive, S., & Ritvo, P. (2015). Heart rate variability is enhanced in controls but not maladaptive perfectionists during brief mindfulness meditation following stress-induction: A stratified-randomized trial. *International Journal of Psychophysiology, 98*(1), 27-34.

Azam, M. A., Katz, J., Mohabir, V., & Ritvo, P. (2016). Individuals with tension and migraine headaches exhibit increased heart rate variability during post-stress mindfulness meditation practice but a decrease during a post-stress control condition–A randomized, controlled experiment. *International Journal of Psychophysiology, 110*, 66-74.

Baer, R. A., Smith, G. T., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., . . . Williams, J. M. G. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment, 15*(3), 329-342.

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Archives of internal medicine, 163*(20), 2433-2445.

Barakat, A., Vogelzangs, N., Licht, C. M. M., Geenen, R., MacFarlane, G. J., de Geus, E. J. C., . . . Dekker, J. (2012). Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain. *Arthritis care & research, 64*(8), 1209-1216.

Beauchaine, T. P. (2015). Respiratory sinus arrhythmia: A transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current opinion in psychology, 3*, 43-47.

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology, 98*(2), 338-350.

Beecher, H. K. (1946). Pain in men wounded in battle. *Annals of surgery, 123*(1), 96.

Benarroch, E. E. (2001). Pain-autonomic interactions: a selective review. *Clinical Autonomic Research, 11*(6), 343-349.

Bendixen, K. H., Terkelsen, A. J., Baad-Hansen, L., Cairns, B. E., & Svensson, P. (2012). Experimental stressors alter hypertonic saline-evoked masseter muscle pain and autonomic response. *Journal of orofacial pain, 26*(3).

Benjamin, C. L., O'Neil, K. A., Crawley, S. A., Beidas, R. S., Coles, M., & Kendall, P. C. (2010). Patterns and predictors of subjective units of distress in anxious youth. *Behavioural and cognitive psychotherapy, 38*(4), 497-504.

Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., & Sleight, P. (2000). Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. *Journal of the American College of Cardiology, 35*(6), 1462-1469.

Berntson, G. G., & Cacioppo, J. T. (1999). Heart rate variability: a neuroscientific perspective for further studies. *Cardiac Electrophysiology Review, 3*(4), 279-282.

Berntson, G. G., & Cacioppo, J. T. (2004). Heart rate variability: Stress and psychiatric conditions. *Dynamic electrocardiography*, 57-64.

Berntson, G. G., Quigley, K. S., & Lozano, D. (2007). Cardiovascular Psychophysiology. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of Psychophysiology* (3rd ed.). New York, USA: Cambridge.

Berntson, G. G., Thomas Bigger Jr, J., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., . . . Stone, P. H. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623-648.

Berry, M. E., Chapple, I. T., Ginsberg, J. P., Gleichauf, K. J., Meyer, J. A., & Nagpal, M. L. (2014). Non-pharmacological intervention for chronic pain in veterans: a pilot study of heart rate variability biofeedback. *Global Advances in Health and Medicine, 3*(2), 28-33.

Blascovich, J. J., & Katkin, E. S. (1993). APA science Vols. Cardiovascular reactivity to psychological stress & disease. American Psychological Association. In.

Bodnar, R. J., Kelly, D. D., Brutus, M., & Glusman, M. (1980). Stress-induced analgesia: neural and hormonal determinants. *Neuroscience & Biobehavioral Reviews, 4*(1), 87-100.

Boonnithi, S., & Phongsuphap, S. (2011, 2011). *Comparison of heart rate variability measures for mental stress detection*.

Borckardt, J. J., Kozel, F. A., Anderson, B., Walker, A., & George, M. S. (2005). Vagus nerve stimulation affects pain perception in depressed adults. *Pain Research and Management, 10*(1), 9-14.

Boselli, E., Bouvet, L., Bégou, G., Dabouz, R., Davidson, J., Deloste, J. Y., . . . Allaouchiche, B. (2013). Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. *British journal of anaesthesia, 112*(4), 715-721.

Boselli, E., Daniela-Ionescu, M., Bégou, G., Bouvet, L., Dabouz, R., Magnin, C., & Allaouchiche, B. (2013). Prospective observational study of the non-invasive assessment of immediate postoperative pain using the analgesia/nociception index (ANI). *British journal of anaesthesia, 111*(3), 453-459.

Breivik, H., Eisenberg, E., & O'Brien, T. (2013). The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health, 13*(1), 1229. doi:ttp://doi.org/10.1186/1471-2458-13-1229

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. *Journal of psychosomatic research, 60*(2), 113-124.

Brosschot, J. F., & Thayer, J. F. (2003). Heart rate response is longer after negative emotions than after positive emotions. *International Journal of Psychophysiology, 50*(3), 181-187.

Brosschot, J. F., Van Dijk, E., & Thayer, J. F. (2007). Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. *International Journal of Psychophysiology, 63*(1), 39-47.

Brosschot, J. F., Verkuil, B., & Thayer, J. F. (2010). Conscious and unconscious perseverative cognition: is a large part of prolonged physiological activity due to unconscious stress? *Journal of psychosomatic research, 69*(4), 407-416.

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *Journal of personality and social psychology, 84*(4), 822.

Bruehl, S., & Chung, O. Y. (2004). Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neuroscience & Biobehavioral Reviews, 28*(4), 395-414.

Burg, J. M., Wolf, O. T., & Michalak, J. (2012). Mindfulness as self-regulated attention. *Swiss Journal of Psychology*.

Busch, V., Zeman, F., Heckel, A., Menne, F., Ellrich, J., & Eichhammer, P. (2013). The effect of transcutaneous vagus nerve stimulation on pain perception–an experimental study. *Brain stimulation, 6*(2), 202-209.

Bushnell, M. C., Čeko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature reviews. Neuroscience, 14*(7), 502-511. doi:10.1038/nrn3516

Busse, J. W., Craigie, S., Juurlink, D. N., Buckley, D. N., Wang, L., Couban, R. J., . . . Guyatt, G. H. (2017). Guideline for opioid therapy and chronic noncancer pain. *CMAJ, 189*(18), E659-E666. doi:10.1503/cmaj.170363

Butler, D. S., & Moseley, G. (2003). Response Systems - The Sympathetic and Parasympathetic Nervous Systems. In *Explain Pain* (pp. 84-85). Adelaide, South Australia: Noigroup Publications.

Butler, D. S., & Moseley, G. L. (2013). *Explain Pain 2nd Edn*: Noigroup Publications.

Butler, R. K., & Finn, D. P. (2009). Stress-induced analgesia. *Progress in neurobiology, 88*(3), 184-202.

Camilleri, M., & Choi, M. G. (1997). Irritable bowel syndrome. *Alimentary pharmacology & therapeutics, 11*(1), 3-15.

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., . . . Kleiger, R. E. (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation, 93*(5), 1043-1065.

Cathcart, S., & Pritchard, D. (2008). Daily stress and pain sensitivity in chronic tension‐type headache sufferers. *Stress and Health: Journal of the International Society for the Investigation of Stress, 24*(2), 123-127.

Centers for Disease, C., & Prevention. (2015). Ambulatory health care data. *Atlanta, GA: Author. Retrieved from http://www. cdc. gov/nchs/ahcd. htm*.

Chakravarthy, K., Chaudhry, H., Williams, K., & Christo, P. J. (2015). Review of the uses of vagal nerve stimulation in chronic pain management. *Current pain and headache reports, 19*(12), 54.

Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Frontiers in psychiatry, 5*, 80.

Chapman, C. R., Tuckett, R. P., & Song, C. W. (2008). Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. *The Journal of Pain, 9*(2), 122-145.

Chiesa, A., & Serretti, A. (2010). A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychological medicine, 40*(8), 1239.

Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *The Journal of Alternative and Complementary Medicine, 17*(1), 83-93.

Chittaro, L., & Vianello, A. (2014). Computer-supported mindfulness: Evaluation of a mobile thought distancing application on naive meditators. *International Journal of Human-Computer Studies, 72*(3), 337-348.

Cleeland, C. (1989). *Measurement of pain by subjective report.* . New York: Raven Press.

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Annals, Academy of Medicine, Singapore*.

Cohen, H., Neumann, L., Alhosshle, A., Kotler, M., Abu-Shakra, M., & Buskila, D. (2001). Abnormal sympathovagal balance in men with fibromyalgia. *The Journal of Rheumatology, 28*(3), 581-589.

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*: Routledge.

Critchley, H. D., Nicotra, A., Chiesa, P. A., Nagai, Y., Gray, M. A., Minati, L., & Bernardi, L. (2015). Slow breathing and hypoxic challenge: cardiorespiratory consequences and their central neural substrates. *PloS one, 10*(5), e0127082.

Curran, S. L., Andrykowski, M. A., & Studts, J. L. (1995). Short form of the profile of mood states (POMS-SF): psychometric information. *Psychological assessment, 7*(1), 80.

Dalla, G. E. (2008). *Randomization.com*.
Dallal, J. (2007). Randomization.com. Retrieved from www.randomization.com
Day, M. A., Jensen, M. P., Ehde, D. M., & Thorn, B. E. (2014). Toward a theoretical model for mindfulness-based pain management. *The Journal of Pain, 15*(7), 691-703.
Day, M. A., Thorn, B. E., & Rubin, N. J. (2014). Mindfulness-based cognitive therapy for the treatment of headache pain: A mixed-methods analysis comparing treatment responders and treatment non-responders. *Complementary therapies in medicine, 22*(2), 278-285.
De Couck, M., Nijs, J., & Gidron, Y. (2014). You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. *The Clinical journal of pain, 30*(12), 1099-1105.
De Ferrari, G. M., Crijns, H. J. G. M., Borggrefe, M., Milasinovic, G., Smid, J., Zabel, M., . . . Kuschyk, J. (2010). Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *European heart journal, 32*(7), 847-855.
de la Rosa PhD, F. J. B. (2013). Heart rate variability and phantom pain in male amputees: Application of linear and nonlinear methods. *Journal of rehabilitation research and development, 50*(3), 449.
de la Vega, R., & Miró, J. (2014). mHealth: a strategic field without a solid scientific soul. a systematic review of pain-related apps. *PloS one, 9*(7), e101312.
Debeneditis, G., Cigada, M., Bianchi, A., Signorini, M. G., & Cerutti, S. (1994). Autonomic changes during hypnosis: a heart rate variability power spectrum analysis as a marker of sympatho-vagal balance. *International Journal of Clinical and Experimental Hypnosis, 42*(2), 140-152.
Del Casale, A., Ferracuti, S., Rapinesi, C., De Rossi, P., Angeletti, G., Sani, G., . . . Girardi, P. (2015). Hypnosis and pain perception: An Activation Likelihood Estimation (ALE) meta-analysis of functional neuroimaging studies. *Journal of Physiology-Paris, 109*(4-6), 165-172.
Del Paso, G. A. R., Garrido, S., Pulgar, Á., Martín-Vázquez, M., & Duschek, S. (2010). Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *PSYCHOSOMATIC MEDICINE, 72*(5), 462-470.
Del Pozo, J. M., Gevirtz, R. N., Scher, B., & Guarneri, E. (2004). Biofeedback treatment increases heart rate variability in patients with known coronary artery disease. *American heart journal, 147*(3), 545.
Delizonna, L. L., Williams, R. P., & Langer, E. J. (2009). The effect of mindfulness on heart rate control. *Journal of Adult Development, 16*(2), 61-65.
Dericioglu, N., Demirci, M., Cataltepe, O., Akalan, N., & Saygi, S. (2013). Heart rate variability remains reduced and sympathetic tone elevated after temporal lobe epilepsy surgery. *Seizure, 22*(9), 713-718.
Dersh, J., Polatin, P. B., & Gatchel, R. J. (2002). Chronic pain and psychopathology: research findings and theoretical considerations. *PSYCHOSOMATIC MEDICINE, 64*(5), 773-786.
Devor, M., & Seltzer, Z. (1999). Pathophysiology of damaged nerves in relation to chronic pain. In P. D. Wall & R. Melzack (Eds.), *The Textbook of Pain*. Churchill Livingstone, Edinburgh.
Ditto, B., Eclache, M., & Goldman, N. (2006). Short-term autonomic and cardiovascular effects of mindfulness body scan meditation. *Annals of behavioral medicine, 32*(3), 227-234.
Doğru, M. T., Aydın, G., Tosun, A., Keleş, I., Güneri, M., Arslan, A., . . . Orkun, S. (2009). Correlations between autonomic dysfunction and circadian changes and arrhythmia

prevalence in women with fibromyalgia syndrome. *Anatolian Journal of Cardiology/Anadolu Kardiyoloji Dergisi, 9*(2).
Ebinger, F., Kruse, M., Just, U., & Rating, D. (2006). Cardiorespiratory regulation in migraine. Results in children and adolescents and review of the literature. *Cephalalgia, 26*(3), 295-309.
Eckberg, D. L. (1997). Sympathovagal balance: a critical appraisal. *Circulation, 96*(9), 3224-3232.
Eisendrath, S. J., Gillung, E. P., Delucchi, K. L., Chartier, M., Mathalon, D. H., Sullivan, J. C., . . . Feldman, M. D. (2014). Mindfulness-based cognitive therapy (MBCT) versus the health-enhancement program (HEP) for adults with treatment-resistant depression: a randomized control trial study protocol. *BMC complementary and alternative medicine, 14*(1), 95.
Elkins, G. (2016). *Handbook of medical and psychological hypnosis: Foundations, applications, and professional issues*: Springer Publishing Company.
Elmenshawy, E., & Sakr, S. (2009). Autonomic dysfunction in migraine; what do we need to know. *Egypt J Neurol Psychiat Neurosurg, 46*(2), 489-496.
Eysenbach G, Group, C.-E., & CONSORT-EHEALTH:. (2011). Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. *J Med Internet Res, 13*(4), e126.
Eze-Nliam, C. M., Quartana, P. J., Quain, A. M., & Smith, M. T. (2011). Nocturnal Heart Rate Variability Is Lower in Temporomandibular Disorder Patients Tvhan in Healthy, Pain-free Individuals. *Journal of orofacial pain, 25*(3).
Fashler, S. R., Cooper, L. K., Oosenbrug, E. D., Burns, L. C., Razavi, S., Goldberg, L., & Katz, J. (2016). Systematic Review of Multidisciplinary Chronic Pain Treatment Facilities. *Pain Research and Management, 2016*, 1–19. doi:http://doi.org/10.1155/2016/5960987
Fechir, M., Schlereth, T., Purat, T., Kritzmann, S., Geber, C., Eberle, T., . . . Birklein, F. (2008). Patterns of sympathetic responses induced by different stress tasks. *The open neurology journal, 2*, 25.
Fishbain, D. A., Cutler, R., Rosomoff, H. L., & Rosomoff, R. S. (1997). Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *The Clinical journal of pain, 13*(2), 116-137.
Ford, G. K., & Finn, D. P. (2008). Clinical correlates of stress-induced analgesia: evidence from pharmacological studies. *Pain, 140*(1), 3-7.
Furlan, R., Colombo, S., Perego, F., Atzeni, F., Diana, A., Barbic, F., . . . Sarzi-Puttini, P. (2005). Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *The Journal of Rheumatology, 32*(9), 1787-1793.
Garcia, A. J., Koschnitzky, J. E., Dashevskiy, T., & Ramirez, J.-M. (2013). Cardiorespiratory coupling in health and disease. *Autonomic Neuroscience, 175*(1-2), 26-37.
Garland, E. L., Brintz, C. E., Hanley, A. W., Roseen, E. J., Atchley, R. M., Gaylord, S. A., . . . Keefe, F. J. (2020). Mind-body therapies for opioid-treated pain: a systematic review and meta-analysis. *JAMA internal medicine, 180*(1), 91-105.
Garland, E. L., Froeliger, B., Zeidan, F., Partin, K., & Howard, M. O. (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: cognitive, affective, and neuropsychopharmacologic pathways. *Neuroscience & Biobehavioral Reviews, 37*(10), 2597-2607.

Gass, J. J., & Glaros, A. G. (2013). Autonomic dysregulation in headache patients. *Applied psychophysiology and biofeedback, 38*(4), 257-263.
Gatchel, R. J., McGeary, D. D., McGeary, C. A., & Lippe, B. (2014). Interdisciplinary chronic pain management: past, present, and future. *American Psychologist, 69*(2), 119.
Gay, M.-C. (2007). Effectiveness of hypnosis in reducing mild essential hypertension: A one-year follow-up. *Intl. Journal of Clinical and Experimental Hypnosis, 55*(1), 67-83.
Gerritsen, R. J. S., & Band, G. P. H. (2018). Breath of life: The respiratory vagal stimulation model of contemplative activity. *Frontiers in human neuroscience, 12*, 397.
Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: Cardiovascular consequences of emotional states. *PSYCHOSOMATIC MEDICINE, 64*(5), 714-726.
Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health, 11*(770). doi:http://doi.org/10.1186/1471-2458-11-770
Grossman, P., & Taylor, E. W. (2007). Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological psychology, 74*(2), 263-285.
Grosu, O., Odobescu, S., Moldovanu, I., & Rotaru, L. (2013). Cardiovascular activity in migraine patients: Influence of age and headache chronification. *The Journal of Headache and Pain, 14*(S1), P139.
Grote, V., Levnajić, Z., Puff, H., Ohland, T., Goswami, N., Frühwirth, M., & Moser, M. (2019). Dynamics of vagal activity due to surgery and subsequent rehabilitation. *Frontiers in Neuroscience, 13*.
Gureje, O., Von Korff, M., Kola, L., Demyttenaere, K., He, Y., Posada-Villa, J., . . . De Girolamo, G. (2008). The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. *PAIN®, 135*(1-2), 82-91.
Haensel, A., Mills, P. J., Nelesen, R. A., Ziegler, M. G., & Dimsdale, J. E. (2008). The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. *Psychoneuroendocrinology, 33*(10), 1305-1312.
Hallman, D. M., Ekman, A. H., & Lyskov, E. (2014). Changes in physical activity and heart rate variability in chronic neck–shoulder pain: monitoring during work and leisure time. *International archives of occupational and environmental health, 87*(7), 735-744.
Hallman, D. M., & Lyskov, E. (2012). Autonomic regulation, physical activity and perceived stress in subjects with musculoskeletal pain: 24-hour ambulatory monitoring. *International Journal of Psychophysiology, 86*(3), 276-282.
Hammen, C. (2005). Stress and depression. *Annu. Rev. Clin. Psychol., 1*, 293-319.
Harrison, A. M., Scott, W., Johns, L. C., Morris, E. M. J., & McCracken, L. M. (2017). Are we speaking the same language? Finding theoretical coherence and precision in "mindfulness-based mechanisms" in chronic pain. *Pain Medicine, 18*(11), 2138-2151.
Hashizume, M., Yamada, U., Sato, A., Hayashi, K., Amano, Y., Makino, M., . . . Tsuboi, K. (2008). Stress and psychological factors before a migraine attack: a time-based analysis. *BioPsychoSocial medicine, 2*(1), 1-6.
Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., . . . Apkarian, A. V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain, 136*(9), 2751-2768.

Hassinger, H. J., Semenchuk, E. M., & O'Brien, W. H. (1999). Appraisal and coping responses to pain and stress in migraine headache sufferers. *Journal of behavioral medicine, 22*(4), 327-340.

Häuser, W., Galek, A., Erbslöh-Möller, B., Köllner, V., Kühn-Becker, H., Langhorst, J., . . . Glaesmer, H. (2013). Posttraumatic stress disorder in fibromyalgia syndrome: Prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. *Pain, 154*(8), 1216-1223.

Heitkemper, M., Burr, R. L., Jarrett, M., Hertig, V., Lustyk, M. K., & Bond, E. F. (1998). Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. *Digestive diseases and sciences, 43*(9), 2093-2098.

Hirsh, A. T., George, S. Z., Bialosky, J. E., & Robinson, M. E. (2008). Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *The Journal of Pain, 9*(9), 806-812.

Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of consulting and clinical psychology, 78*(2), 169.

Holm, J. E., Lamberty, K., McSherry, W. C., & Davis, P. A. (1997). The stress response in headache sufferers: physiological and psychological reactivity. *Headache: The journal of head and face pain, 37*(4), 221-227.

Howells, A., Ivtzan, I., & Eiroa-Orosa, F. J. (2016). Putting the 'app'in happiness: a randomised controlled trial of a smartphone-based mindfulness intervention to enhance wellbeing. *Journal of Happiness Studies, 17*(1), 163-185.

Huss, D., Derefinko, K., Milich, R., Farzam, F., & Baumann, R. (2009). Examining the stress response and recovery among children with migraine. *Journal of pediatric psychology, 34*(7), 707-715.

Huston, J. M., & Tracey, K. J. (2011). The pulse of inflammation: heart rate variability, the cholinergic anti‐inflammatory pathway and implications for therapy. *Journal of internal medicine, 269*(1), 45-53.

Jänig, W., & McLachlan, E. M. (2013). Neurobiology of the autonomic nervous system. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System Oxford*, 21-34.

Jarczok, M. N., Koenig, J., Mauss, D., Fischer, J. E., & Thayer, J. F. (2014). Lower heart rate variability predicts increased level of C‐reactive protein 4 years later in healthy, nonsmoking adults. *Journal of internal medicine, 276*(6), 667-671.

Jensen, M. P. (2009). Hypnosis for chronic pain management: a new hope. *Pain, 146*(3), 235-237. doi:10.1016/j.pain.2009.06.027

Johnson, S., Gur, R. M., David, Z., & Currier, E. (2015). One-session mindfulness meditation: a randomized controlled study of effects on cognition and mood. *Mindfulness, 6*(1), 88-98.

Jönsson, P. (2007). Respiratory sinus arrhythmia as a function of state anxiety in healthy individuals. *International Journal of Psychophysiology, 63*(1), 48-54.

Joshi, C., Jang, J. K., Luke, K., Ji, X., Miller, S. A., Klenner, A., . . . Gaeta, A. L. (2016). Thermally controlled comb generation and soliton modelocking in microresonators. *Optics letters, 41*(11), 2565-2568.

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General hospital psychiatry, 4*(1), 33-47.

Kabat-Zinn, J., Lipworth, L., & Burney, R. (1985). The clinical use of mindfulness meditation for the self-regulation of chronic pain. *Journal of behavioral medicine, 8*(2), 163-190.

Kabat‐Zinn, J. (2003). Mindfulness‐based interventions in context: past, present, and future. *Clinical psychology: Science and practice, 10*(2), 144-156.

Kalezic, N., Åsell, M., Kerschbaumer, H., & Lyskov, E. (2007). Physiological reactivity to functional tests in patients with chronic low back pain. *Journal of Musculoskeletal Pain, 15*(1), 29-40.

Katz, Weinrib, A., Fashler, S. R., Katznelzon, R., Shah, B. R., Ladak, S. S., & … Clarke, H. (2015). The Toronto General Hospital Transitional Pain Service: Development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. *Journal of pain research, 8*(695–702). doi:http://doi.org/10.2147/JPR.S91924

Katz, J., Pagé, M. G., Fashler, S., Rosenbloom, B. N., & Asmundson, G. J. G. (2014). Chronic pain and the anxiety disorders: Epidemiology, mechanisms and models of comorbidity, and treatment. In *Mental health and pain* (pp. 119-155): Springer.

Katz, J., & Seltzer, Z. (2009). Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert review of neurotherapeutics, 9*(5), 723-744.

Kekecs, Z., Szekely, A., & Varga, K. (2016). Alterations in electrodermal activity and cardiac parasympathetic tone during hypnosis. *Psychophysiology, 53*(2), 268-277.

Kelly, B. D. (2008). Meditation, mindfulness and mental health. *Irish journal of psychological medicine, 25*(1), 3-4.

Kemp, A. H., & Quintana, D. S. (2013). The relationship between mental and physical health: insights from the study of heart rate variability. *International Journal of Psychophysiology, 89*(3), 288-296.

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PloS one, 7*(2), e30777.

Kidd, B. L., & Urban, L. A. (2001). Mechanisms of inflammatory pain. *British journal of anaesthesia, 87*(1), 3-11.

Killingsworth, M. A., & Gilbert, D. T. (2010). A wandering mind is an unhappy mind. *Science, 330*(6006), 932-932.

Kirchner, A., Birklein, F., Stefan, H., & Handwerker, H. O. (2001). Vagus nerve stimulation-a new option for the treatment of chronic pain syndromes? *Schmerz (Berlin, Germany), 15*(4), 272-277.

Koenig, J., Falvay, D., Clamor, A., Wagner, J., Jarczok, M. N., Ellis, R. J., . . . Thayer, J. F. (2016). Pneumogastric (Vagus) Nerve Activity Indexed by Heart Rate Variability in Chronic Pain Patients Compared to Healthy Controls: A Systematic Review and Meta-Analysis. In.

Koenig, J., Jarczok, M. N., Ellis, R. J., Hillecke, T. K., & Thayer, J. F. (2014). Heart rate variability and experimentally induced pain in healthy adults: a systematic review. *European journal of pain, 18*(3), 301-314.

Koenig, J., Jarczok, M. N., Ellis, R. J., Warth, M., Hillecke, T. K., & Thayer, J. F. (2015). Lowered Parasympathetic Activity in Apparently Healthy Subjects with Self‐Reported Symptoms of Pain: Preliminary Results from a Pilot Study. *Pain practice, 15*(4), 314-318.

Koenig, J., Jarczok, M. N., Fischer, J. E., & Thayer, J. F. (2015). The association of (effective and ineffective) analgesic intake, pain interference and heart rate variability in a cross-sectional occupational sample. *Pain Medicine, 16*(12), 2261-2270.

Koenig, J., Loerbroks, A., Jarczok, M. N., Fischer, J. E., & Thayer, J. F. (2016). Chronic pain and heart rate variability in a cross-sectional occupational sample: Evidence for impaired vagal control. *The Clinical journal of pain, 32*(3), 218-225.

Koenig, J., Williams, D. P., Kemp, A. H., & Thayer, J. F. (2016). Vagally mediated heart rate variability in headache patients—a systematic review and meta-analysis. *Cephalalgia, 36*(3), 265-278.

Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., & Alexander, G. C. (2015). The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health, 36*, 559-574. doi:10.1146/annurev-publhealth-031914-122957

Koopman, F. A., Stoof, S. P., Straub, R. H., van Maanen, M. A., Vervoordeldonk, M. J., & Tak, P. P. (2011). Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. *Molecular Medicine, 17*(9-10), 937.

Krygier, J. R., Heathers, J. A. J., Shahrestani, S., Abbott, M., Gross, J. J., & Kemp, A. H. (2013). Mindfulness meditation, well-being, and heart rate variability: a preliminary investigation into the impact of intensive Vipassana meditation. *International Journal of Psychophysiology, 89*(3), 305-313.

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *Journal of Neuroscience, 34*(11), 3969-3975.

Kuehl, L. K., Michaux, G. P., Richter, S., Schächinger, H., & Anton, F. (2010). Increased basal mechanical pain sensitivity but decreased perceptual wind-up in a human model of relative hypocortisolism. *Pain, 149*(3), 539-546.

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research–Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Frontiers in psychology, 8*.

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Front Psychol, 8*, 213. doi:10.3389/fpsyg.2017.00213

Lagos, L., Vaschillo, E., Vaschillo, B., Lehrer, P., Bates, M., & Pandina, R. (2008). Heart rate variability biofeedback as a strategy for dealing with competitive anxiety: A case study. *Biofeedback, 36*(3), 109.

Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage, 54*(3), 2492-2502.

Larsen, P. D., Tzeng, Y. C., Sin, P. Y. W., & Galletly, D. C. (2010). Respiratory sinus arrhythmia in conscious humans during spontaneous respiration. *Respiratory physiology & neurobiology, 174*(1-2), 111-118.

Lea, R., Houghton, L. A., Calvert, E. L., Larder, S., Gonsalkorale, W. M., Whelan, V., . . . Miller, V. (2003). Gut‐focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. *Alimentary pharmacology & therapeutics, 17*(5), 635-642.

Leandri, M., Luzzani, M., Cruccu, G., & Gottlieb, A. (2001). Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia, 21*(7), 744-746.
LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual review of neuroscience, 23*(1), 155-184.
Ledowski, T., Tiong, W. S., Lee, C., Wong, B., Fiori, T., & Parker, N. (2013). Analgesia nociception index: evaluation as a new parameter for acute postoperative pain. *British journal of anaesthesia, 111*(4), 627-629.
Lee, J. S., Lee, M. S., Lee, J. Y., Cornélissen, G., Otsuka, K., & Halberg, F. (2003). Effects of diaphragmatic breathing on ambulatory blood pressure and heart rate. *Biomedicine & pharmacotherapy, 57*, 87-91.
Lehrer, P. M., Vaschillo, E., Vaschillo, B., Lu, S.-E., Eckberg, D. L., Edelberg, R., . . . Tahvanainen, K. U. O. (2003). Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. *PSYCHOSOMATIC MEDICINE, 65*(5), 796-805.
Leone, M., Franzini, A., Cecchini, A. P., Mea, E., Peccarisi, C., Tullo, V., . . . Bussone, G. (2010). Drug-resistant primary headache patients undergoing surgical therapies: how should we assess outcomes? *Neurological Sciences, 31*(1), 93-94.
Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., & Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and aging, 12*(2), 277.
Leyfer, O. T., Ruberg, J. L., & Woodruff-Borden, J. (2006). Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders. *Journal of anxiety disorders, 20*(4), 444-458.
Linley, J. E., Rose, K., Ooi, L., & Gamper, N. (2010). Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflügers Archiv-European Journal of Physiology, 459*(5), 657-669.
Loggia, M. L., Juneau, M., & Bushnell, M. C. (2011). Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. *PAIN®, 152*(3), 592-598.
Lomas, T., Cartwright, T., Edginton, T., & Ridge, D. (2015). A qualitative analysis of experiential challenges associated with meditation practice. *Mindfulness, 6*(4), 848-860.
Lumma, A.-L., Kok, B. E., & Singer, T. (2015). Is meditation always relaxing? Investigating heart rate, heart rate variability, experienced effort and likeability during training of three types of meditation. *International Journal of Psychophysiology, 97*(1), 38-45.
Lynn, S. J., Kirsch, I., & Hallquist, M. N. (2008). Social cognitive theories of hypnosis.
Lyonfields, J. D., Borkovec, T. D., & Thayer, J. F. (1995). Vagal tone in generalized anxiety disorder and the effects of aversive imagery and worrisome thinking. *Behavior Therapy, 26*(3), 457-466.
MA, A., V, L., & J, K. (2019). Development of the mind-wandering inventory to assess people with clinically significant depression, anxiety, and chronic pain after mindfulness practice [version 1; not peer reviewed]. *F1000Research, 8*(209). doi:https://doi.org/10.7490/f1000research.1116452.1
Ma, V. Y., Chan, L., & Carruthers, K. J. (2014). Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. *Archives of physical medicine and rehabilitation, 95*(5), 986-995.

Maixner, W., Greenspan, J. D., Dubner, R., Bair, E., Mulkey, F., Miller, V., . . . Diatchenko, L. (2011). Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *The Journal of Pain, 12*(11), T75-T91.

Mani, M., Kavanagh, D. J., Hides, L., & Stoyanov, S. R. (2015). Review and evaluation of mindfulness-based iPhone apps. *JMIR mHealth and uHealth, 3*(3).

Markil, N., Whitehurst, M., Jacobs, P. L., & Zoeller, R. F. (2012). Yoga Nidra relaxation increases heart rate variability and is unaffected by a prior bout of Hatha yoga. *The Journal of Alternative and Complementary Medicine, 18*(10), 953-958.

Marsch, S. C. U., Skarvan, K., Schaefer, H. G., Naegeli, B., Paganoni, R., Castelli, I., & Scheidegger, D. (1994). Prolonged decrease in heart rate variability after elective hip arthroplasty. *British journal of anaesthesia, 72*(6), 643-649.

Martelli, D., McKinley, M. J., & McAllen, R. M. (2014). The cholinergic anti-inflammatory pathway: a critical review. *Autonomic Neuroscience, 182*, 65-69.

Matei, D., Constantinescu, V., Corciova, C., Ignat, B., Matei, R., & Popescu, C. D. (2015). Autonomic impairment in patients with migraine. *Eur Rev Med Pharmacol Sci, 19*(20), 3922-3927.

Mazur, M., Furgala, A., Jablonski, K., Madroszkiewicz, D., Ciecko-Michalska, I., Bugajski, A., & Thor, P. J. (2007). Dysfunction of the autonomic nervous system activity is responsible for gastric myoelectric disturbances in the irritable bowel syndrome patients. *Journal of physiology and pharmacology, 58*, 131.

McCraty, R., & Shaffer, F. (2015). Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Global Advances in Health and Medicine, 4*(1), 46-61.

McLean, S., Clauw, D., Abelson, J., & al., e. (2005). The development of persistent pain and psychological morbidity after motor vehicle collision: Integrating the potential role of stress response systems into a biopsychosocial model. *PSYCHOSOMATIC MEDICINE, 67*(5), 783-790.

Melville, G. W., Chang, D., Colagiuri, B., Marshall, P. W., & Cheema, B. S. (2012). Fifteen minutes of chair-based yoga postures or guided meditation performed in the office can elicit a relaxation response. *Evidence-Based Complementary and Alternative Medicine, 2012*.

Melzack, R. (2001). Pain and the neuromatrix in the brain. *Journal of dental education, 65*(12), 1378-1382.

Melzack, R., & Katz, J. (2013). Pain. *Wiley Interdiscip Rev Cogn Sci, 4*(1), 1-15. doi:10.1002/wcs.1201

Millan, M. J. (2002). Descending control of pain. *Progress in neurobiology, 66*(6), 355-474.

Minassian, A., Geyer, M. A., Baker, D. G., Nievergelt, C. M., O'Connor, D. T., Risbrough, V. B., & Team, M. R. S. (2014). Heart rate variability characteristics in a large group of active-duty marines and relationship to posttraumatic stress. *PSYCHOSOMATIC MEDICINE, 76*(4), 292.

Miu, A. C., Heilman, R. M., & Miclea, M. (2009). Reduced heart rate variability and vagal tone in anxiety: trait versus state, and the effects of autogenic training. *Autonomic Neuroscience, 145*(1-2), 99-103.

Möltner, A., Hölzl, R., & Strian, F. (1990). Heart rate changes as an autonomic component of the pain response. *Pain, 43*(1), 81-89.

Montgomery, G. H., DuHamel, K. N., & Redd, W. H. (2000). A meta-analysis of hypnotically induced analgesia: How effective is hypnosis? *International Journal of Clinical and Experimental Hypnosis, 48*(2), 138-153.

Moon, E., Lee, S.-H., Kim, D.-H., & Hwang, B. (2013). Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. *Clinical Psychopharmacology and Neuroscience, 11*(3), 137.

Mortola, J. P., Marghescu, D., & Siegrist-Johnstone, R. (2015). Respiratory sinus arrhythmia in young men and women at different chest wall configurations. *Clinical Science, 128*(8), 507-516.

Moseley, G., & Butler, D. S. (2015). Fifteen years of explaining pain: the past, present, and future. *The Journal of Pain, 16*(9), 807-813.

Mostoufi, S. M., Afari, N., Ahumada, S. M., Reis, V., & Wetherell, J. L. (2012). Health and distress predictors of heart rate variability in fibromyalgia and other forms of chronic pain. *Journal of psychosomatic research, 72*(1), 39-44.

Moulin, D. E., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A., . . . Morley-Forster, P. K. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Research and Management, 19*(6), 328-335.

Murphy, M. J., Mermelstein, L. C., Edwards, K. M., & Gidycz, C. A. (2012). The benefits of dispositional mindfulness in physical health: a longitudinal study of female college students. *Journal of American College Health, 60*(5), 341-348.

Nahit, E. S., Hunt, I. M., Lunt, M., Dunn, G., Silman, A. J., & Macfarlane, G. J. (2003). Effects of psychosocial and individual psychological factors on the onset of musculoskeletal pain: common and site-specific effects. *Annals of the Rheumatic Diseases, 62*(8), 755.

Nash, J. M., & Thebarge, R. W. (2006). Understanding psychological stress, its biological processes, and impact on primary headache. *Headache: The journal of head and face pain, 46*(9), 1377-1386.

Navratilova, E., Morimura, K., Xie, J. Y., Atcherley, C. W., Ossipov, M. H., & Porreca, F. (2016). Positive emotions and brain reward circuits in chronic pain. *Journal of Comparative Neurology, 524*(8), 1646-1652.

Neff, R. A., Wang, J., Baxi, S., Evans, C., & Mendelowitz, D. (2003). Respiratory sinus arrhythmia. *Circulation research, 93*(6), 565-572.

Nesvold, A., Fagerland, M. W., Davanger, S., Ellingsen, Ø., Solberg, E. E., Holen, A., . . . Atar, D. (2012). Increased heart rate variability during nondirective meditation. *European journal of preventive cardiology, 19*(4), 773-780.

Nickel, P., & Nachreiner, F. (2003). Sensitivity and diagnosticity of the 0.1-Hz component of heart rate variability as an indicator of mental workload. *Human Factors, 45*(4), 575-590.

Nyklíček, I., Mommersteeg, P., Van Beugen, S., Ramakers, C., & Van Boxtel, G. J. (2013). Mindfulness-based stress reduction and physiological activity during acute stress: A randomized controlled trial. *Health Psychology, 32*(10), 1110.

Ochsner, K. N., Zaki, J., Hanelin, J., Ludlow, D. H., Knierim, K., Ramachandran, T., . . . Mackey, S. C. (2008). Your pain or mine? Common and distinct neural systems supporting the perception of pain in self and other. *Social Cognitive and Affective Neuroscience, 3*(2), 144-160.

Oke, S. L., & Tracey, K. J. (2009). The inflammatory reflex and the role of complementary and alternative medical therapies. *Annals of the New York Academy of Sciences, 1172*, 172.

Ospina, M. B., Bond, K., Karkhaneh, M., Buscemi, N., Dryden, D. M., Barnes, V., . . . Shannahoff-Khalsa, D. (2008). Clinical trials of meditation practices in health care: characteristics and quality. *The Journal of Alternative and Complementary Medicine, 14*(10), 1199-1213.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguière, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cerebral Cortex, 12*(4), 376-385.

Otis, J. D., Keane, T. M., & Kerns, R. D. (2003). An examination of the relationship between chronic pain and post-traumatic stress disorder. *Journal of rehabilitation research and development, 40*(5), 397-406.

Ottaviani, C., Thayer, J. F., Verkuil, B., Lonigro, A., Medea, B., Couyoumdjian, A., & Brosschot, J. F. (2016). Physiological concomitants of perseverative cognition: A systematic review and meta-analysis. *Psychological Bulletin, 142*(3), 231.

Pal, G. K., & Velkumary, S. (2004). Effect of short-term practice of breathing exercises on autonomic functions in normal human volunteers. *Indian Journal of Medical Research, 120*(2), 115.

Palta, P., Page, G., Piferi, R. L., Gill, J. M., Hayat, M. J., Connolly, A. B., & Szanton, S. L. (2012). Evaluation of a mindfulness-based intervention program to decrease blood pressure in low-income African-American older adults. *Journal of Urban Health, 89*(2), 308-316.

Parswani, M. J., Sharma, M. P., & Iyengar, S. S. (2013). Mindfulness-based stress reduction program in coronary heart disease: A randomized control trial. *International journal of yoga, 6*(2), 111.

Pellissier, S., Dantzer, C., Canini, F., Mathieu, N., & Bonaz, B. (2010). Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology, 35*(5), 653-662.

Peng, C. K., Henry, I. C., Mietus, J. E., Hausdorff, J. M., Khalsa, G., Benson, H., & Goldberger, A. L. (2004). Heart rate dynamics during three forms of meditation. *International journal of cardiology, 95*(1), 19-27.

Perakakis, P., Taylor, M., Martinez-Nieto, E., Revithi, I., & Vila, J. (2009). Breathing frequency bias in fractal analysis of heart rate variability. *Biological psychology, 82*(1), 82-88.

Perciavalle, V., Blandini, M., Fecarotta, P., Buscemi, A., Di Corrado, D., Bertolo, L., . . . Coco, M. (2017). The role of deep breathing on stress. *Neurological Sciences, 38*(3), 451-458.

Pereira, E. A. C., Lu, G., Wang, S., Schweder, P. M., Hyam, J. A., Stein, J. F., . . . Green, A. L. (2010). Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain. *Experimental neurology, 223*(2), 574-581.

Perlman, D. M., Salomons, T. V., Davidson, R. J., & Lutz, A. (2010). Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion, 10*(1), 65.

Pertovaara, A. (2013). The noradrenergic pain regulation system: a potential target for pain therapy. *European journal of pharmacology, 716*(1), 2-7.

Phongsuphap, S., Pongsupap, Y., Chandanamattha, P., & Lursinsap, C. (2008). Changes in heart rate variability during concentration meditation. *International journal of cardiology, 130*(3), 481-484.

Pieper, S., Brosschot, J. F., van der Leeden, R., & Thayer, J. F. (2007). Cardiac effects of momentary assessed worry episodes and stressful events. *PSYCHOSOMATIC MEDICINE, 69*(9), 901-909.

Pieper, S., Brosschot, J. F., van der Leeden, R., & Thayer, J. F. (2010). Prolonged cardiac effects of momentary assessed stressful events and worry episodes. *PSYCHOSOMATIC MEDICINE, 72*(6), 570-577.

Pittig, A., Arch, J. J., Lam, C. W. R., & Craske, M. G. (2013). Heart rate and heart rate variability in panic, social anxiety, obsessive–compulsive, and generalized anxiety disorders at baseline and in response to relaxation and hyperventilation. *International Journal of Psychophysiology, 87*(1), 19-27.

Pollatos, O., Füstös, J., & Critchley, H. D. (2012). On the generalised embodiment of pain: how interoceptive sensitivity modulates cutaneous pain perception. *PAIN®, 153*(8), 1680-1686.

Porges, S. W. (1995). Cardiac vagal tone: a physiological index of stress. *Neuroscience & Biobehavioral Reviews, 19*(2), 225-233.

Porges, S. W., & Byrne, E. A. (1992). Research methods for measurement of heart rate and respiration. *Biological psychology, 34*(2-3), 93-130.

Pramanik, T., Sharma, H. O., Mishra, S., Mishra, A., Prajapati, R., & Singh, S. (2009). Immediate effect of slow pace bhastrika pranayama on blood pressure and heart rate. *The Journal of Alternative and Complementary Medicine, 15*(3), 293-295.

Quintana, D. S., & Heathers, J. A. J. (2014). Considerations in the assessment of heart rate variability in biobehavioral research. *Frontiers in psychology, 5*, 805.

Radloff, L. S. (1991). The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *Journal of youth and adolescence, 20*(2), 149-166.

Rahman, Q. A., Janmohamed, T., Pirbaglou, M., Ritvo, P., Heffernan, J. M., Clarke, H., & Katz, J. (2017). Patterns of user engagement with the mobile app, Manage My Pain: results of a data mining investigation. *JMIR mHealth and uHealth, 5*(7).

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science, 277*(5328), 968-971.

Raj, S. R., Brouillard, D., Simpson, C. S., Hopman, W. M., & Abdollah, H. (2000). Dysautonomia among patients with fibromyalgia: a noninvasive assessment. *The Journal of Rheumatology, 27*(11), 2660-2665.

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., . . . Sluka, K. A. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain, 161*(9), 1976-1982.

Randich, A., Thurston, C. L., Ludwig, P. S., Timmerman, M. R., & Gebhart, G. F. (1991). Antinociception and cardiovascular responses produced by intravenous morphine: the role of vagal afferents. *Brain research, 543*(2), 256-270.

Ray, W. J., Sabsevitz, D., Pascalis, V. D., Quigley, K., Aikins, D., & Tubbs, M. (2000). Cardiovascular reactivity during hypnosis and hypnotic susceptibility: three studies of heart rate variability. *International Journal of Clinical and Experimental Hypnosis, 48*(1), 22-31.

Rivat, C., Becker, C., Blugeot, A., Zeau, B., Mauborgne, A., Pohl, M., & Benoliel, J.-J. (2010). Chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. *Pain, 150*(2), 358-368.

Robertson, D., Low, P. A., & Polinsky, R. J. (2011). *Primer on the autonomic nervous system*: Academic Press.
Robison, M. K., Gath, K. I., & Unsworth, N. (2017). The neurotic wandering mind: An individual differences investigation of neuroticism, mind-wandering, and executive control. *The Quarterly Journal of Experimental Psychology, 70*(4), 649-663.
Roger, K. (1995). *Experimental Design: Procedures for the Behavioral Sciences, Third Edition*. Monterey, California: Brooks/Cole Publishing.
Rojahn, J., & Gerhards, F. (1986). Subjective stress sensitivity and physiological responses to an aversive auditory stimulus in migraine and control subjects. *Journal of behavioral medicine, 9*(2), 203-212.
Rosenbloom, B. N., Khan, S., McCartney, C., & Katz, J. (2013). Systematic review of persistent pain and psychological outcomes following traumatic musculoskeletal injury. *Journal of pain research, 6*, 39.
Rosser, B. A., & Eccleston, C. (2011). Smartphone applications for pain management. *Journal of telemedicine and telecare, 17*(6), 308-312.
Sachs-Ericsson, N., Cromer, K., Hernandez, A., & Kendall-Tackett, K. (2009). A review of childhood abuse, health, and pain-related problems: the role of psychiatric disorders and current life stress. *Journal of Trauma & Dissociation, 10*(2), 170-188.
Sakakibara, M., Takeuchi, S., & Hayano, J. (1994). Effect of relaxation training on cardiac parasympathetic tone. *Psychophysiology, 31*(3), 223-228.
Sawatzky, R. G., Ratner, P. A., Richardson, C. G., Washburn, C., Sudmant, W., & Mirwaldt, P. (2012). Stress and depression in students: the mediating role of stress management self-efficacy. *Nursing research, 61*(1), 13-21.
Schopflocher, D., Taenzer, P., & Jovey, R. (2011). The prevalence of chronic pain in Canada. *Pain Research & Management, 16*(6), 445–450.
Schramm, S. H., Moebus, S., Lehmann, N., Galli, U., Obermann, M., Bock, E., . . . Katsarava, Z. (2015). The association between stress and headache: A longitudinal population-based study. *Cephalalgia, 35*(10), 853-863.
Searle, R. D., & Simpson, K. H. (2010). Chronic post-surgical pain. *Continuing Education in Anaesthesia, Critical Care & Pain, 10*(1), 12-14.
Segerstrom, S. C., & Nes, L. S. (2007). Heart rate variability reflects self-regulatory strength, effort, and fatigue. *Psychological science, 18*(3), 275-281.
Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Frontiers in psychology, 5*.
Sharp, T. J., & Harvey, A. G. (2001). Chronic pain and posttraumatic stress disorder: mutual maintenance? *Clinical psychology review, 21*(6), 857-877.
Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*(1), 169-191.
Slade, G. D., Diatchenko, L., Bhalang, K., Sigurdsson, A., Fillingim, R. B., Belfer, I., . . . Maixner, W. (2007). Influence of psychological factors on risk of temporomandibular disorders. *Journal of dental research, 86*(11), 1120-1125.
Soer, R., Vos, D., Hofstra, B., & Reneman, M. F. (2014). Heart coherence training combined with back school in patients with chronic non-specific low back pain: first pragmatic clinical results. *Applied psychophysiology and biofeedback, 39*(3-4), 259-267.

Sommer, C., & Kress, M. (2004). Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neuroscience letters, 361*(1-3), 184-187.

Sood, A., & Jones, D. T. (2013). On mind wandering, attention, brain networks, and meditation. *EXPLORE: The Journal of Science and Healing, 9*(3), 136-141.

Sowder, E., Gevirtz, R., Shapiro, W., & Ebert, C. (2010). Restoration of vagal tone: a possible mechanism for functional abdominal pain. *Applied psychophysiology and biofeedback, 35*(3), 199-206.

Steiner, T. J., Birbeck, G. L., Jensen, R. H., Katsarava, Z., Stovner, L. J., & Martelletti, P. (2015). Headache disorders are third cause of disability worldwide. In: BioMed Central.

Stronks, D. L., Tulen, J. H. M., Pepplinkhuizen, L., Verheij, R., Mantel, G. W. H., Spinhoven, P., & Passchier, J. (1999). Personality traits and psychological reactions to mental stress of female migraine patients. *Cephalalgia, 19*(6), 566-574.

Tan, G., Jensen, M. P., Thornby, J. I., & Shanti, B. F. (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain, 5*(2), 133-137. doi:10.1016/j.jpain.2003.12.005

Tang, Y.-Y., Ma, Y., Fan, Y., Feng, H., Wang, J., Feng, S., . . . Li, J. (2009). Central and autonomic nervous system interaction is altered by short-term meditation. *Proceedings of the national Academy of Sciences, 106*(22), 8865-8870.

Tateishi, Y., Oda, S., Nakamura, M., Watanabe, K., Kuwaki, T., Moriguchi, T., & Hirasawa, H. (2007). Depressed heart rate variability is associated with high IL-6 blood level and decline in the blood pressure in septic patients. *Shock, 28*(5), 549-553.

Tavares, B. S., de Paula Vidigal, G., Garner, D. M., Raimundo, R. D., de Abreu, L. C., & Valenti, V. E. (2017). Effects of guided breath exercise on complex behaviour of heart rate dynamics. *Clinical physiology and functional imaging, 37*(6), 622-629.

Tefikow, S., Barth, J., Maichrowitz, S., Beelmann, A., Strauss, B., & Rosendahl, J. (2013). Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. *Clin Psychol Rev, 33*(5), 623-636. doi:10.1016/j.cpr.2013.03.005

Telles, S., Raghavendra, B. R., Naveen, K. V., Manjunath, N. K., Kumar, S., & Subramanya, P. (2013). Changes in autonomic variables following two meditative states described in yoga texts. *The Journal of Alternative and Complementary Medicine, 19*(1), 35-42.

Terkelsen, A. J., Mølgaard, H., Hansen, J., Finnerup, N. B., Krøner, K., & Jensen, T. S. (2012). Heart rate variability in complex regional pain syndrome during rest and mental and orthostatic stress. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 116*(1), 133-146.

Terry, P. C., Lane, A. M., & Fogarty, G. J. (2003). Construct validity of the Profile of Mood States—Adolescents for use with adults. *Psychology of sport and exercise, 4*(2), 125-139.

Thayer, J. F. (2009). Vagal tone and the inflammatory reflex. *Cleve Clin J Med, 76*(Suppl 2), S23-26.

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews, 36*(2), 747-756.

Thayer, J. F., Friedman, B. H., & Borkovec, T. D. (1996). Autonomic characteristics of generalized anxiety disorder and worry. *Biological psychiatry, 39*(4), 255-266.

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of affective disorders, 61*(3), 201-216.
Tracey, K. J. (2002). The inflammatory reflex. *Nature, 420*(6917), 853.
Tracey, K. J. (2009). Reflex control of immunity. *Nature Reviews Immunology, 9*(6), 418-428.
Tracey, K. J., & Huston, J. M. (2014). Inhibition of inflammatory cytokine production by cholinergic agonists and vagus nerve stimulation. In: Google Patents.
Tracy, L. M., Ioannou, L., Baker, K. S., Gibson, S. J., Georgiou-Karistianis, N., & Giummarra, M. J. (2016). Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *Pain, 157*(1), 7-29.
Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., . . . First, M. B. (2015). A classification of chronic pain for ICD-11. *Pain, 156*(6), 1003.
Treede, R. D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., . . . Serra, J. (2008). Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology, 70*(18), 1630-1635.
Turan, G., Ar, A. Y., Kuplay, Y. Y., Demiroluk, O., Gazi, M., Akgun, N., & Celikoglu, E. (2016). Analgesia Nociception Index for perioperative analgesia monitoring in spinal surgery. *Brazilian Journal of Anesthesiology (English Edition)*.
Turk, D. C. (2002). A diathesis-stress model of chronic pain and disability following traumatic injury. *Pain Research and Management, 7*(1), 9-19.
Turk, D. C., & Monarch, E. S. (2002). Biopsychosocial perspective on chronic pain. *Psychological approaches to pain management: A practitioner's handbook, 2*, 3-29.
v Hippel, C., Hole, G., & Kaschka, W. P. (2001). Autonomic profile under hypnosis as assessed by heart rate variability and spectral analysis. *Pharmacopsychiatry, 34*(03), 111-113.
van Wilgen, C. P., & Keizer, D. (2012). The sensitization model to explain how chronic pain exists without tissue damage. *Pain Management Nursing, 13*(1), 60-65.
Verkuil, B., Brosschot, J. F., de Beurs, D. P., & Thayer, J. F. (2009). Effects of explicit and implicit perseverative cognition on cardiac recovery after cognitive stress. *International Journal of Psychophysiology, 74*(3), 220-228.
Verkuil, B., Brosschot, J. F., Gebhardt, W. A., & Thayer, J. F. (2010). When worries make you sick: a review of perseverative cognition, the default stress response and somatic health. *Journal of Experimental Psychopathology, 1*(1), jep-009110.
Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Aboyans, V. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet, 380*(9859), 2163-2196.
Wallace, L. S., & Dhingra, L. K. (2014). A systematic review of smartphone applications for chronic pain available for download in the United States. *Journal of opioid management, 10*(1), 63-68.
Weissman-Fogel, I., Dashkovsky, A., Rogowski, Z., & Yarnitsky, D. (2008). Vagal damage enhances polyneuropathy pain: Additive effect of two algogenic mechanisms. *Pain, 138*(1), 153-162.
Wells, R. E., Burch, R., Paulsen, R. H., Wayne, P. M., Houle, T. T., & Loder, E. (2014). Meditation for migraines: a pilot randomized controlled trial. *Headache: The journal of head and face pain, 54*(9), 1484-1495.

Whitehead, W. E., & Palsson, O. S. (1998). Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. *Gastroenterology, 115*(5), 1263-1271.
Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage, 47*(3), 987-994.
Williams, A. C. d. C., & Craig, K. D. (2016). Updating the definition of pain. *Pain, 157*(11), 2420-2423.
Williamson, J. B., Lewis, G., Grippo, A. J., Lamb, D., Harden, E., Handleman, M., . . . Porges, S. W. (2010). Autonomic predictors of recovery following surgery: a comparative study. *Autonomic Neuroscience, 156*(1-2), 60-66.
Wöber, C., Holzhammer, J., Zeitlhofer, J., Wessely, P., & Wöber-Bingöl, Ç. (2006). Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. *The Journal of Headache and Pain, 7*(4), 188-195.
Wobst, A. H. K. (2007). Hypnosis and surgery: past, present, and future. *Anesthesia & Analgesia, 104*(5), 1199-1208.
Woolf, C. J. (2010). What is this thing called pain? *J Clin Invest, 120*(11), 3742-3744. doi:10.1172/JCI45178
Wu, S.-D., & Lo, P.-C. (2008). Inward-attention meditation increases parasympathetic activity: a study based on heart rate variability. *Biomedical Research, 29*(5), 245-250.
Yasuma, F., & Hayano, J.-i. (2004). Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? *Chest, 125*(2), 683-690.
Yüksel, R., Ozcan, O., & Dane, S. (2013). The effects of hypnosis on heart rate variability. *International Journal of Clinical and Experimental Hypnosis, 61*(2), 162-171.
Zautra, A. J., Johnson, L. M., & Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *Journal of consulting and clinical psychology, 73*(2), 212.
Zeidan, F., Emerson, N. M., Farris, S. R., Ray, J. N., Jung, Y., McHaffie, J. G., & Coghill, R. C. (2015). Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia. *Journal of Neuroscience, 35*(46), 15307-15325.
Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. *Neuroscience letters, 520*(2), 165-173.
Zeidan, F., Johnson, S. K., Gordon, N. S., & Goolkasian, P. (2010). Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. *The Journal of Alternative and Complementary Medicine, 16*(8), 867-873.
Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain mechanisms supporting the modulation of pain by mindfulness meditation. *Journal of Neuroscience, 31*(14), 5540-5548.
Zucker, T. L., Samuelson, K. W., Muench, F., Greenberg, M. A., & Gevirtz, R. N. (2009). The effects of respiratory sinus arrhythmia biofeedback on heart rate variability and posttraumatic stress disorder symptoms: A pilot study. *Applied psychophysiology and biofeedback, 34*(2), 135.

Appendix A. Study I

Study Consent Form
TITLE: AN EXPLORATION OF ATTENTIONAL BIAS, MEDITATION AND MIGRAINES WITH THE USE OF HEART RATE VARIABILITY AND EYE TRACKING MEASURES

INVESTIGATORS: Dr. Paul Ritvo, Dr. Joel Katz

You are being asked to take part in a research study. Before agreeing to take part in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, potential harms/risk/discomforts, and the benefits associated with this study. It also describes your right to refuse to participate or to withdraw from any part of the study at any time.

In order to decide whether you wish to participate in this research study, you should understand enough about it to make an informed decision. This is known as the informed consent process. Please ask the researcher to explain any words you do not understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Purpose:
You have been asked to participate in a study designed to examine the physiological effects of mindfulness meditation and migraines. Heart rate variability (HRV) and eye tracking measurements will be taken.

Procedure:
Your participation in this study will entail a time commitment of 90 hours. If you agree to participate in this study, you will be asked to provide your up-to-date medical history during the prescreening. These questions will help the researcher determine if you are eligible to participate in the study. Feel free to ask the researcher to clarify the questions, if necessary.

Protocol:
If you choose to partake in this study, you will be asked to complete 5 questionnaires, complete a cognitive task and listen to a 10-minute recording related to mindfulness meditation.

Questionnaires:

(i) The Demographic Questionnaire

(ii) The Kentucky Inventory of Mindfulness Skills (KIMS) Questionnaire: evaluating whether or not certain statements are applicable to you (e.g., I'm good at finding the words to describe my feelings).

Cognitive Task:
You will be asked to solve a pattern consisting of four alphanumeric characters presented at the top of the screen that will be followed by a 5th character. You will be asked to click either "True" or "False", respectively, depending on whether or not the 5th character follows the same pattern as the previous four characters. Heart rate variability and eye tracking measures will be taken during this task.

Listening Task:
You will be asked to sit quietly and still for 10-minutes while listening to a recording related to mindfulness meditation. Heart rate variability measures will be taken during this task.

Potential Harms, Risks or Discomforts:
Some of the questions ask about private matters such as whether or not you have been clinically diagnosed with a mental disorder or if you have any illnesses/diseases. In addition, there is no risk for undergoing ECG recordings or using the eye tracker, however, some participants may feel uncomfortable performing a cognitively demanding task while attached to various pieces of equipment.

Potential Benefits:
There are no substantial benefits associated with participating in this study. We hope this investigation will lead to a better understanding of the physiological effects of mindfulness meditation and migraines.

Confidentiality:
All information obtained during the study will be held in strict confidence to the fullest extent possible by law. In no case will your personal information be shared with any individuals or groups without your expressed written consent. The experimental data acquired in this study may—in an anonymized form that cannot be connected back to you—be used for teaching purposes, be presented at meetings, published, shared with other scientific researchers or used in future studies. Your name or other identifying information will not be used in any publication or teaching materials without your specific permission. Your information provided online will be password-protected and only research staff will have access to this information. Data will be retained for five years after publication of the study results.

Participation:
Your participation in the study is voluntary; you have the right not to participate, not to answer any questions and/or to terminate participation anytime without prejudice. Your refusal to participate or your withdrawal from the study will not affect your relationship with the researcher or with York University. If you decide to withdraw from the study and you wish us to destroy the information and data you provided, we will do so upon your request.

Questions:
If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Paul Ritvo by telephone at ------- ext. ----- or by e-mail (-----). This research study has been reviewed and approved by the Human Participants Review Sub-Committee (Certificate #: 2015-218), York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research
Ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact Ms. Alison Collins-Mrakas, Manager, Research Ethics, Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone ------ or e-mail ------

Legal Rights and Signatures:

I, _____, consent to participate in this research study. I have understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Name of Participant	**Signature of**	**Date**
Name of Person Obtaining Consent	**Signature of Person Obtaining Consent**	**Date**

Problems Sets for Pattern Recognition Task.
Underlined character appears at the second stage (after 9 seconds). Wrong answer feedback trials are in **bold**.

Trial 1: 14 48 88 140 400
Trial 2: AB AZ AC AX AY
Trial 3: F1 D3 C5 E7 B9
Trial 4: 90 09 19 96 69
Trial 5: AG NA CL OH CO
Trial 6: 18 56 72 27 63
Trial 7: A1 91 B1 81 C1
Trial 8: 26 66 36 96 16
Trial 9: SH CH ST TH SC
Trial 10: US CA RU UK VU
Trial 11: 12 21 32 45 59
Trial 12: 44 2 56 8 22 4
Trial 13: AT AN AM AD AH
Trial 14: 54 78 96 12 62
Trial 15: UI UO UA UI UE
Trial 16: 3e 4A 1b 6U 7i
Trial 17: PI IP OP PE AP
Trial 18: 13 26 49 82 116
Trial 19: T2 F5 N9 S7 E8
Trial 20: OR OP OS OW OX
Trial 21: 31 24 53 46 75
Trial 22: 4T T6 7T T8 9T
Trial 23: MU NU PI XI OM
Trial 24: 10 25 50 75 0
Trial 25: CT CH CK CL CR
Trial 26: 11 3 13 6 15 9

Appendix B. Study II

Informed Consent Form- Breath Awareness Study

DR. JOEL KATZ
------- Ext.

ABID AZAM, PHD3

VERED LATMAN, PHD1

Department of Clinical Psychology / Human Pain Mechanisms Lab

4700 KEELE ST TORONTO ON CANADA M3J 1P3 T 416 123 4567
EXT 12345
F 416 123 4567
email@yorku.ca www.yorku.ca

Purpose of the Research: The aim of the present study is to evaluate the effects of a mobile-based 'breathing task' on heart-rate variability and mood. Furthermore, the study aims to examine individuals' present awareness and mind-wandering.

What You Will Be Asked to do in the Research: You will be asked to complete a few mobile- and paper-based questionnaires, as well as a brief breathing task administered via a mobile app while you are being monitored for your heart rate and respiration. The administration of these tests will take place over a single session, which will last about an hour and a half.

Risks and Discomforts: We do not foresee any risks or discomfort from your participation in the research.

Benefits of the Research and Benefits to You: There are no major benefits that may reasonably be expected to result from this study, except the knowledge that you are contributing to graduate education and the advancement of science.

Voluntary Participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence your relationship with York U, the researchers, or any other group associated with the project.

Withdrawal from the Study: You can stop participating in the study at any time, for any reason, if you so decide. If you decide to stop participating, you will still be eligible to receive the promised credit for agreeing to be in the project. Your decision to stop participating, or refusal to answer particular questions, will not affect your relationship with the researchers, York

University, or any other group associated with this project. In the event you withdraw from the study and you do not wish the investigators to use your data, please let them know and the data will be destroyed.

Risks: You may experience some distress from answering some of the questions. Should you feel any distress as a result of participating in the present study you may contact the York University Personal Counselling Services at 416-736-5297.

Confidentiality: All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research. Psychophysiological and questionnaire data will anonymized (will not contain personal identifying information) and will be stored on a password protected laptop with TrueCrypt encryption software under a password accessible partition on the hard disk. The mobile app data will be anonymized with a 3 digit number representing each unique participant, and no identifying information will be entered into the mobile app. All paper-based data will be safely stored in a locked facility and only research staff will have access to this information. Data will be securely stored for 5 years after publication of study results. Confidentiality will be provided to the fullest extent possible by law.

Questions About the Research? If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Katz either by telephone at 416- 736-2100, extension 40557 or by e-mail (jkatz@yorku.ca). This research has been reviewed and approved by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:
I, consent to participate in conducted by. I have understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature Date

Participant

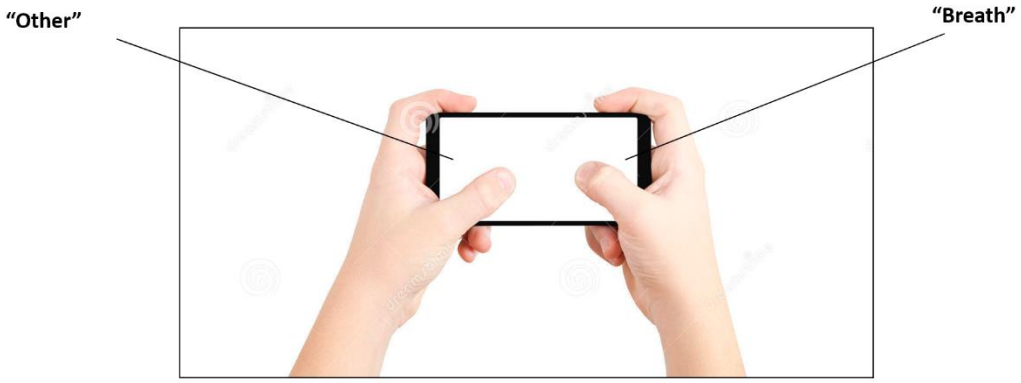
Signature Date

Person obtaining consent

Mindfulness Meditation App Task Instructions:

The purpose of this breathing practice involves attending to your breathing, and noticing what you're attending to by pressing buttons indicating 'breath' or 'other' on a mobile phone at the sound of a tone.

1. Sit comfortably in your chair with your back straight. Your neck should be relaxed, with your chin slightly tucked in.
2. Hold the mobile phone with two hands resting comfortably on your lap, and place your thumbs above (but not touching) the screen as the image below displays:



3. Close your eyes.
4. For the duration of the task, take full breaths and try and be aware of your breathing sensations, including any or all of the following aspects of breathing:
   - The feeling of the air passing through your nostrils and throat
   - The movement of your in- and out-breath at your chest and torso
   - The sound of the air as you breathe in and out
   - The temperature (coolness or warmth) of the in- and out-breath
   - **JUST DO YOUR BEST TO KEEP ATTENDING TO THE BREATH**

5. At various times, the phone will sound a tone. Press **'Breath'** if in that moment your attention was on your breath, and **'Other'** if in that moment your attention was on other experiences (e.g. thoughts, feelings, physical sensations).
6. Return your attention to your breath after pressing a button. This task will be 12 minutes long, please remain seated with your eyes closed until the end of the task.

Trial Exercise: "First, let's start with a one minute practice to help you get used to pressing the buttons. Remember, press 'Breath' if you were aware of your breath in the moment you hear a tone, or 'Other' if you were attending to any thoughts, emotions, or sensory and physical experiences."

Breathing Only Task Instructions:

The purpose of this breathing practice involves attending to your breathing and noticing the object(s) of your attention at any given moment.

1. Sit comfortably in your chair with your back straight and both hands comfortably placed on your lap. Your neck should be relaxed, with your chin slightly tucked in.
2. Close your eyes.

3. For the duration of the task, try and be aware of your breathing sensations, including any or all of the following aspects of breathing:

- The feeling of the air passing through your nostrils and throat
- The movement of your in- and out-breath at your chest and torso
- The sound of the air as you breathe in and out
- The temperature (coolness or warmth) of the in- and out-breath
- **JUST DO YOUR BEST TO KEEP ATTENDING TO THE BREATH**

4. Return your attention to your breath when you have noticed your attention has been elsewhere. This task will be 12 minutes long, please remain seated with your eyes closed until the end of the task.

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ **Time:** _____

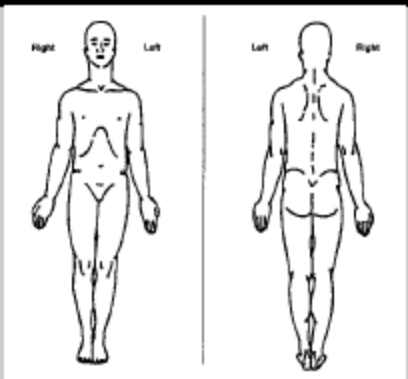
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Mind Wandering Questionnaire (MWQ)

Please rate how frequently you experience the following:

1= almost never
2= very infrequently
3=somewhat infrquently
4=somewhat frequently
5=very frequently
6=almost always

I have difficulty maintaning focus on simple or repetitive work	1 2 3 4 5 6
While reading, I find I haven't been thinking about the text and must therefore read it again	1 2 3 4 5 6
I do things without paying full attention	1 2 3 4 5 6
I find myself listening with one ear, thinking about something else at the same time	1 2 3 4 5 6
I mind wander during lectures or presentations	1 2 3 4 5 6

Mind Wandering Inventory

We are interested in your experiences while doing the breath attention task. Please read each item and indicate the response that best represents how frequently you experienced it during the breath attention task. Please use the following 5-point scale when rating each item in the provided boxes.

① – Never
② – Rarely
③ – Sometimes
④ – Often
⑤ – Very often

During the breath attention task …

☐ I worried about things that might happen in the future

☐ I thought I should be doing better on the breath attention task

☐ I was aware of outside noises

☐ I was aware of my breath

☐ I thought about the future

☐ I thought positively about things that happened in the past

☐ I was aware of pain in my body

☐ I felt bored

☐ I thought positively about things that might happen in the future

☐ I had daydreams or fantasies involving others

☐ I thought about pain in my body

☐ I thought about solutions to my problems

☐ I thought about unpleasant bodily sensations

☐ I had conversations with my "inner voice"

☐ I felt sleepy

☐ I imagined having conversations with others

☐ I was aware of pleasant body sensations

☐ I experienced images of colors/shapes or other non-verbal experiences

☐ I was simultaneously aware of my breath and another experience(s)

☐ I thought about how difficult it was to attend to my breath

- [ ] I thought about things that I need to do
- [ ] I was aware of unpleasant feelings/emotions
- [ ] I wished I was doing something other than the breath attention task
- [ ] I thought about past experiences
- [ ] I noticed how awake I felt
- [ ] I worried about things that happened in the past
- [ ] I was aware of pleasant thoughts/emotions
- [ ] I had daydreams or fantasies involving me
- [ ] I thought about when the tone was going to occur next
- [ ] I thought about my performance on the breath attention task
- [ ] I counted to myself
- [ ] I was aware of experiences that I cannot label or describe
- [ ] I thought about new ideas
- [ ] I noticed how attentive I was
- [ ] I "heard" music in my head
- [ ] I thought about how easy it was to do the breath attention task

Please list any other experiences you had during the breath attention task

_____

_____

_____

Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	☐	☐	☐	☐
Feeling hot	☐	☐	☐	☐
Wobbliness in legs	☐	☐	☐	☐
Unable to relax	☐	☐	☐	☐
Fear of worst happening	☐	☐	☐	☐
Dizzy or lightheaded	☐	☐	☐	☐
Heart pounding/racing	☐	☐	☐	☐
Unsteady	☐	☐	☐	☐
Terrified or afraid	☐	☐	☐	☐
Nervous	☐	☐	☐	☐
Feeling of choking	☐	☐	☐	☐
Hands trembling	☐	☐	☐	☐
Shaky / unsteady	☐	☐	☐	☐
Fear of losing control	☐	☐	☐	☐
Difficulty in breathing	☐	☐	☐	☐
Fear of dying	☐	☐	☐	☐
Scared	☐	☐	☐	☐
Indigestion	☐	☐	☐	☐
Faint / lightheaded	☐	☐	☐	☐
Face flushed	☐	☐	☐	☐
Hot/cold sweats	☐	☐	☐	☐

Center for Epidemiologic Studies Depression Scale (CES-D)

Date: _____

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you've felt this way during the **past week**. Respond to all items.

Place a check mark (✓) in the appropriate column. **During the past week...**	**Rarely or none of the time (less than 1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**All of the time (5-7 days)**
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not "get going."				

Source: Radloff, L.S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*: 385-401.

Scoring for Center for Epidemiologic Studies Depression Scale (CES-D)

Directions: Do not score if missing more than 4 responses. 1) For each item, look up your response and corresponding score (0-3). 2) Fill in the score for each item under the last column labeled "Score." 3) Calculate your Total Score by adding up all 20 scores.

During the past week...	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)	Score
1. I was bothered by things that usually don't bother me.	0	1	2	3	
2. I did not feel like eating; my appetite was poor.	0	1	2	3	
3. I felt that I could not shake off the blues even with help from my family.	0	1	2	3	
4. I felt that I was just as good as other people.	3	2	1	0	
5. I had trouble keeping my mind on what I was doing.	0	1	2	3	
6. I felt depressed.	0	1	2	3	
7. I felt that everything I did was an effort.	0	1	2	3	
8. I felt hopeful about the future.	3	2	1	0	
9. I thought my life had been a failure.	0	1	2	3	
10. I felt fearful.	0	1	2	3	
11. My sleep was restless.	0	1	2	3	
12. I was happy.	3	2	1	0	
13. I talked less than usual.	0	1	2	3	
14. I felt lonely.	0	1	2	3	
15. People were unfriendly.	0	1	2	3	
16. I enjoyed life.	3	2	1	0	
17. I had crying spells.	0	1	2	3	
18. I felt sad.	0	1	2	3	
19. I felt that people disliked me.	0	1	2	3	
20. I could not "get going."	0	1	2	3	
				Total Score:	

Scoring Results: Total Score of 16 or higher is considered depressed.
If your score indicates depression, see a health care/mental health professional for further evaluation and treatment. Bring these test results to your appointment.

Abbreviated POMS (Revised Version)

Name: _____ Date:

Below is a list of words that describe feelings people have. Please **CIRCLE THE NUMBER THAT BEST DESCRIBES HOW YOU FEEL RIGHT NOW**.

	Not At All	A Little	Moderately	Quite a lot	Extremely
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn Out	0	1	2	3	4
Unhappy	0	1	2	3	4
Proud	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4
Sad	0	1	2	3	4
Active	0	1	2	3	4
On-edge	0	1	2	3	4
Grouchy	0	1	2	3	4
Ashamed	0	1	2	3	4
Energetic	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Restless	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4
Competent	0	1	2	3	4
Annoyed	0	1	2	3	4
Discouraged	0	1	2	3	4
Resentful	0	1	2	3	4
Nervous	0	1	2	3	4
Miserable	0	1	2	3	4

	Not At All	A Little	Moderately	Quite a lot	Extremely
Confident	0	1	2	3	4
Bitter	0	1	2	3	4
Exhausted	0	1	2	3	4
Anxious	0	1	2	3	4
Helpless	0	1	2	3	4
Weary	0	1	2	3	4
Satisfied	0	1	2	3	4
Bewildered	0	1	2	3	4
Furious	0	1	2	3	4
Full of Pep	0	1	2	3	4
Worthless	0	1	2	3	4
Forgetful	0	1	2	3	4
Vigorous	0	1	2	3	4
Uncertain about things	0	1	2	3	4
Bushed	0	1	2	3	4
Embarrassed	0	1	2	3	4

THANK YOU FOR YOUR COOPERATION

PLEASE BE SURE YOU HAVE ANSWERED EVERY ITEM

Citation:
Grove, J.R., & Prapavessis, H. (1992). Preliminary evidence for the reliability and validity of an abbreviated Profile of Mood States. *International Journal of Sport Psychology, 23*, 93-109.

Five Facet Mindfulness Questionnaire (FFMQ)

Please rate each of the following statements with the number that best describes *your own opinion* of what is *generally true for you.*		Never or very rarely true	Rarely true	Sometimes true	Often true	Very often or always true
FFQM 1	When I'm walking, I deliberately notice the sensations of my body moving. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 2	I'm good at finding words to describe my feelings. (D)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 3	I criticize myself for having irrational or inappropriate emotions. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 4	I perceive my feelings and emotions without having to react to them. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 5	When I do things, my mind wanders off and I'm easily distracted. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 6	When I take a shower or bath, I stay alert to the sensations of water on my body. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 7	I can easily put my beliefs, opinions, and expectations into words. (D)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 8	I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 9	I watch my feelings without getting lost in them. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 10	I tell myself I shouldn't be feeling the way I'm feeling. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 11	I notice how foods and drinks affect my thoughts, bodily sensations, and emotions. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 12	It's hard for me to find the words to describe what I'm thinking. (D-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 13	I am easily distracted. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 14	I believe some of my thoughts are abnormal or bad and I shouldn't think that way. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 15	I pay attention to sensations, such as the wind in my hair or sun on my face. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 16	I have trouble thinking of the right words to express how I feel about things. (D-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 17	I make judgments about whether my thoughts are good or bad. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 18	I find it difficult to stay focused on what's happening in the present. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Never or very rarely true	Rarely true	Sometimes true	Often true	Very often or always true
FFQM 19	When I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 20	I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 21	In difficult situations, I can pause without immediately reacting. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 22	When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words. (D-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 23	It seems I am "running on automatic" without much awareness of what I'm doing. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 24	When I have distressing thoughts or images, I feel calm soon after. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 25	I tell myself that I shouldn't be thinking the way I'm thinking. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 26	I notice the smells and aromas of things. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 27	Even when I'm feeling terribly upset, I can find a way to put it into words. (D)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 28	I rush through activities without being really attentive to them. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 29	When I have distressing thoughts or images, I am able just to notice them without reacting. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 30	I think some of my emotions are bad or inappropriate and I shouldn't feel them. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 31	I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow. (OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 32	My natural tendency is to put my experiences into words. (D)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 33	When I have distressing thoughts or images, I just notice them and let them go. (NR)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 34	I do jobs or tasks automatically without being aware of what I'm doing. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 35	When I have distressing thoughts or images, I judge myself as good or bad depending what the thought or image is about. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 38	I pay attention to how my emotions affect my thoughts and behavior. OBS)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		Never or very rarely true	Rarely true	Sometimes true	Often true	Very often or always true
FFQM 37	I can usually describe how I feel at the moment in considerable detail. (D)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FFQM 38	I find myself doing things without paying attention. (AA-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
FFQM 38	I disapprove of myself when I have irrational ideas. (NJ-R)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Scoring:
(Note: R = reverse-scored item)

Subscale Directions	Your Score TOTAL	Your score item Avg.
Observing: Sum items 1 + 6 + 11 + 15 + 20 + 26 + 31 + 36		
Describing: Sum items 2 + 7 + 12R + 16R + 22R + 27 + 32 + 37.		
Acting with Awareness: Sum items 5R + 8R + 13R + 18R + 23R + 28R + 34R + 38R.		
Nonjudging of inner experience: Sum items 3R + 10R + 14R + 17R + 25R + 30R + 35R + 39R.		
Nonreactivity to inner experience: Sum items 4 + 9 + 19 + 21 + 24 + 29 + 33.		
TOTAL FFMQ (add subscale scores)		

NOTE: Some researchers divide the total in each category by the number of items in that category to get an average category score. The Total FFMQ can be divided by 39 to get an average item score.

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment, 13*(1), 27-45.

2a. Protocol Compliant Analyses

These analyses included participants who experienced issues with the Mindfulness Meditation App (and henceforth practiced MM without it) as MMA- participants, according to a per protocol analytical approach. Four participants from the CP group and 1 participant from the SC group were included as MMA- instead of MMA+ in the ensuing analyses.

Primary results

Three-way ANOVA indicated a significant main effect of phase [$F(2, 374) = 29.32$, $p < 0.001$, $\eta_p^2 = 0.14$], and significant group x phase [$F(4, 374) = 4.70$, $p = 0.001$, $\eta_p^2 = 0.05$], and condition x phase [$F(2, 374) = 7.05$, $p = 0.001$, $\eta_p^2 = 0.04$], interaction effects, but the group [$F(2, 374) = 2.48$, $p = 0.09$], condition [$F(2, 374) = 1.67$, $p = 0.20$], group x condition [$F(4, 374) = 7.05$, $p = 0.40$] and the three-way interaction [$F(4, 374) = 2.20$, $p = 0.07$] effects were not significant.

Baseline HRV. The two-way interaction of group x phase was significant, [$F(2, 374) = 4.70$, $p = 0.001$, $\eta_p^2 = 0.05$]. The simple interaction effect of group was significant at rest phase [$F(2, 187) = 6.50$, $p = 0.002$, $\eta_p^2 = 0.07$]. As expected, HF-HRV was higher in SC (M = 6.48, SD = 1.16) than CP (M = 5.92, SD = 0.88, $p < 0.01$, $d = 0.52$) and DA (M = 5.95, SD = 0.94, $p < 0.01$, $d = 0.49$) groups.

Hypothesis 1a: Higher HRV in CP and DA receiving MMA+. The simple simple main effect of condition during the MM phase was significant for the CP group [$F(1, 374) = 4.72$, $p = 0.01$], but not the DA [$F(1, 374) = 2.80$, $p = 0.10$] or SC [$F(1, 374) = 0.23$, $p = 0.63$] groups. The planned comparison indicated HF-HRV was significantly higher in the MMA- condition compared to the MMA+ for CP ($p = 0.01$, $d = 0.67$), contrary to the hypothesis (Table 6).

Hypothesis 1b: Greater HRV increases from stress to MM for CP and DA receiving MMA+. The simple simple main effect of phase in the MMA+ condition was significant for the SC group [$F(2, 374) = 5.75$, $p < 0.005$, $\eta_p^2 = 0.06$], but not the CP [$F(2, 374) = 1.76$, $p = 0.18$] or DA [$F(2, 374) = 1.13$, $p = 0.33$] groups. Planned comparisons indicated HF-HRV significantly increased from the stress to MM phase in SC group receiving MMA+ ($p < 0.005$, $d = 0.25$). Conversely, the simple simple main effect of phase in the MMA- condition was significant for the CP [$F(2, 374) = 27.16$, $p < 0.001$, $\eta_p^2 = 0.23$], DA [$F(2, 374 = 15.53$, $p < 0.001$, $\eta_p^2 = 0.14$], and SC [$F(2, 374) = 3.24$, $p < 0.01$] groups. Planned comparisons indicated HF-HRV increased significantly from the stress to MM phase in the MMA- condition for CP ($p < 0.001$, $d = 0.41$), DA ($p < 0.01$, $d = 0.35$), and SC ($p < 0.01$, $d = 0.21$) groups.

Table 6. Means and standard deviations of log-transformed high-frequency heart rate variability in study groups and conditions

	Rest	Stress	MM
All participants (n=193)			
MMA+ (n=94)	6.20 (1.10)	6.09 (1.06)	6.36 (0.97)
MMA- (n=99)	6.16 (1.03)	6.26 (0.93)	6.68 (0.98)
Total (N=193)	6.18 (1.06)	6.18 (1.00)	6.52 (0.99)
Chronic Pain			
MMA+ (n=23)	5.97 (1.00)	6.08 (0.95)	6.24 (0.71)
MMA- (n=27)	5.90 (0.77)	6.21 (1.10)	6.82 (0.98)[b, d]
Total (n=50)	5.94 (0.87)	6.15 (1.03)	6.56 (0.91)
Depressive-Anxious			
MMA+ (n=27)	5.99 (1.08)	5.96 (0.99)	6.15 (1.11)
MMA- (n=32)	5.94 (0.82)	6.19 (0.79)	6.59 (0.84)[b, d]
Total (n=59)	5.95 (0.94)	6.07 (0.89)	6.38 (0.99)
Sub-Criteria			
MMA+ (n=44)	6.44 (1.14)	6.17 (1.16)	6.55 (0.99)[c]
MMA- (n=42)	6.53 (1.20)	6.36 (0.91)	6.65 (1.07)[d]
Total (n=86)	6.48 (1.16)[a]	6.27 (1.05)	6.60 (1.02)

Note. [a]$p < 0.001$ for SC vs. CP & DA at rest; [b]$p < 0.005$ for SC of stress vs. MM in MMA+; [c]$p \leq 0.001$ for CP, DA, & SC of stress vs. MM in MMA-. [d]$p < 0.001$ for MMA+ vs. MMA- in CP. All comparisons were planned and Bonferroni-corrected.

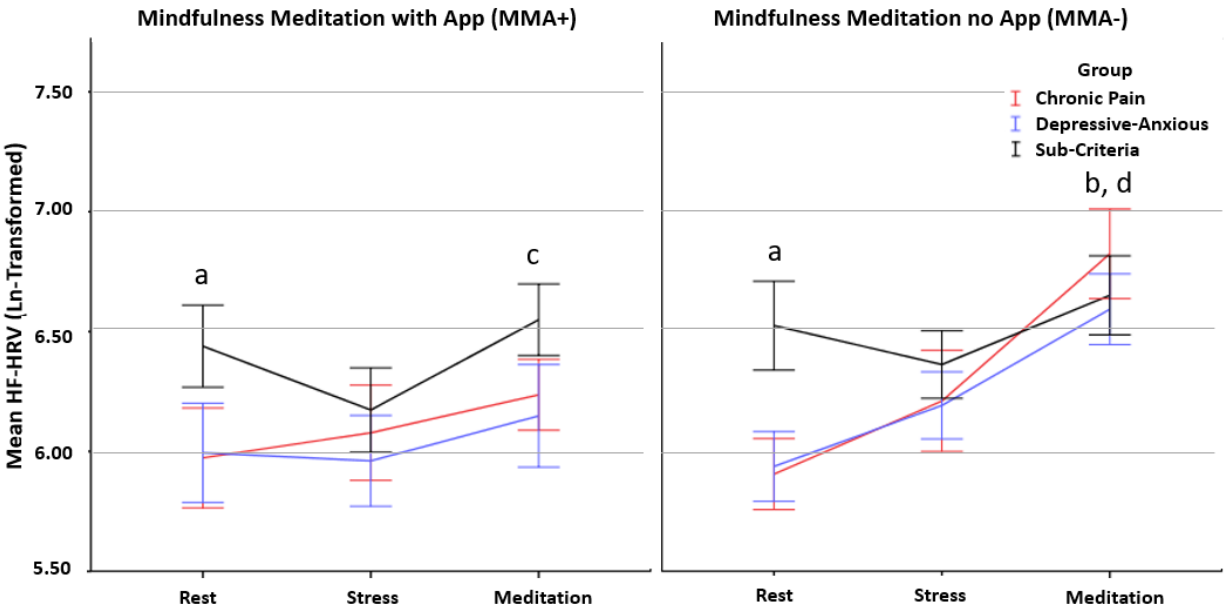


Figure 4. Mean plots of high-frequency heart rate variability (HF-HRV; Ln-transformed) in study groups and conditions across experimental phases. Error bars represents standard errors. a: $p < 0.01$ for SC vs. CP and SC vs. DA at rest; b: $p < 0.01$ for stress vs. MM in MMA- for SC, CP, and DA groups; c: $p < 0.005$ for stress vs. MM in MMA+ for SC group; $^{d}p < 0.001$ for MMA+ vs. MMA- in CP.

Appendix C. Study III

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A Randomized-Controlled Trial of a Novel Perioperative Acceptance and Commitment Therapy and Clinical Hypnosis Program for Postsurgical Pain and Opioid Weaning

Principal Investigator: Hance Clarke, Anesthesiologist, Medical Director of Transitional Pain Service

Co-Investigator: Aliza Weinrib, Ph.D., Clinical Psychologist, Transitional Pain Service

Contact Information: Department of Anesthesia and Pain Management
3 Eaton North
Toronto, Ontario
M5G2C4
---------- ext. ----

Introduction:
You are being asked to take part in a research study. Please read the information about the study presented in this form. The form includes details on study's requirements, risks, and benefits that you should know before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study principal investigator or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Background/Purpose:
After surgery, pain is a normal part of the recovery period. One of the main methods of pain management used in the hospital is opioid medication (also known as "pain killers" or "narcotics.") You may already be taking opioid medication or you may start taking it after surgery.

Opioid medications are useful in providing you with pain relief, but they don't relieve all of the pain. In addition, opioid medications have side effects, like constipation, nausea and itchiness. There are also growing concerns about taking high doses of opioid medication for a long time – for example, the concern that people can become dependent or addicted to it. You may have heard about this on the news or in the newspaper, and you may have some concerns about this medication.

We want to help patients at UHN to need less opioid medication, while being more comfortable. Therefore, we have developed a new program using clinical hypnosis for pain relief. If you participate in this program, you will be offered the same choices

regarding pain medication as if you are not participating at this program, but you may naturally need less medication.

Clinical hypnosis is a method of deeply relaxing, focusing inward, and harnessing the power of your imagination. Clinical hypnosis has been found to reduce acute and chronic pain. When you participate in hypnosis, it feels a lot like deep relaxation. In addition, acceptance and commitment therapy is a kind of cognitive behavioral therapy that has been shown to help people to cope with pain, reduce distress, and do more of what matters to them.

People often have questions about hypnosis. It is important to know that you will be in control of yourself and your actions at every moment – there is no way in which the therapist will control you. The therapist provides choices and suggestions, which may be helpful to you in finding pain relief. This will not affect your medical care. We plan on enrolling a total of 92 participants at Toronto General Hospital.

Study Design:

This is a randomized-controlled study. If you decide to participate you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor your doctor can choose what group you will be in. You will have a 1 in 2 chance of being given access to the hypnosis program before surgery and for one month after surgery. If you are randomly assigned to the control group, you will receive the guided hypnosis audio recordings one month after surgery, when they can still be helpful to you in reducing discomfort and stress, and improving the quality of your sleep. Your doctor will not know which group you are in. In an emergency, if your study assignment needs to be identified, the doctor can get this information.

If you are selected to be in the hypnosis treatment group, we will teach you before surgery how to deeply relax. We will provide you with audio recordings that have been developed by a pain psychologist at Toronto General Hospital in order to provide you with guidance on psychologically preparing for surgery, coping with pain and finding pain relief after your surgery, improving sleep, calming your mind and body, and moving forward with life after surgery. This intervention is offered in addition to the pain medication that you will receive and may potentially serve to enhance the effectiveness of your pain medication and pain coping in general.

You will be provided with audio recordings that you can listen to at your convenience, both at home and in hospital. In addition, a therapist will guide you through the “Preparing for Surgery” hypnosis in-person at the hospital before your surgery, and a therapist will visit you one time after your surgery while you are in hospital in order to practice with you and coach you. The hypnosis audio tracks can be provided to you via downloading or streaming them from the internet from a link that we will provide.

One month after surgery (once all study data collection is completed), all patients can have access to the audio recordings developed by our UHN pain experts, which can help you with relaxation, pain relief, improved sleep.

Study Visits and Procedures

If you agree to participate in this research study, you will be asked to record how frequently you practiced with the hypnosis recordings before and after your surgery on a tracking form and return this to us at the end of the study. In addition, you will be asked to complete questionnaires about your pain, mood, sleep, and daily functioning before surgery, one week after surgery, and one month after surgery. These questionnaires will take 20 minutes to complete. Lastly, you will be asked to undergo a brief assessment of your heart rate and breathing rate during rest and relaxation periods before surgery and at one month after surgery.

Risks:

Taking part in this study has risks. Some of these risks we know about. There is a possibility of risks that we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

Risks of Hypnosis

The main risk of hypnosis is that it may not work for everyone. Rarely, participants in clinical hypnosis report dizziness, drowsiness, headache or anxiety; however, these effects are generally brief and mild. We do not recommend hypnosis for people living with serious mental illness involving hallucinations and/or delusions (e.g., schizophrenia) or dissociation (e.g., dissociative identity disorder), as it may exacerbate their symptoms. Do not listen to the hypnosis recordings while driving or operating heavy machinery.

Risk of Questionnaires

Some questions that you may be asked may make you uncomfortable. You do not have to answer any questions that make you uncomfortable.

Benefits:

You may or may not directly benefit from being in this study. The hypnotherapy provided to you before and after your surgery may help you to cope with your post-surgical pain, improve mood, and optimize your sleep and activity levels. Information learned from this study may help to improve care for other patients undergoing the same surgery as you in the future.

Confidentiality:

If you agree to join this study, the study investigator and the team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could identify you and includes your:

- Name and address

- Medical records that include information on the types of medical conditions you have
- Pain ratings after surgery, pain medication after surgery, and time to discharge from hospital
- The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years.

Research Information in Shared Clinical Records

If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. Only the study team will be allowed to look at your records. The study team can tell you what information about you will be stored electronically and may be shared outside of the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines:

- Representatives of the University Health Network (Häuser) including the UHN Research Ethics Board

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study. Your name will be made anonymous and replaced with an identification number on all completed questionnaires.

Voluntary Participation and Withdrawal:

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and change your mind later. You may refuse to answer any question you do not want to answer. You may leave the study at any time without affecting your medical care. If you decide to leave the study, the information that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission.
We will give you new information that is learned during the study that might affect your decision to stay in the study. This intervention is offered in addition to the pain medication that you will receive and may potentially serve to enhance the effectiveness of your pain medication and pain coping in general. Information from this study will be used to improve the quality of pain management care that other patients who have surgeries receive in the future.

Costs and Reimbursement:

You will not have to pay for any of the materials involved with this study.
You will be reimbursed $20 for your parking travel costs to attend the assessments.

Rights as a Participant:
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Conflict of Interest:
The study investigators have an interest in completing this study. Their interests should not influence your decision to participate in this study. You should not feel pressured to join this study.

Questions about the Study:
If you have any questions, concerns or would like to speak to the study team for any reason, please call: Aliza Weinrib, Ph.D., Clinical Psychologist, Department of Anesthesia & Pain Management ---- ext. ----.

If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be offered a signed copy of this consent form.

Consent:
This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

Print Study Participant's Name	Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent	Signature	Date

Contacting Pharmacy
We would like to understand if learning how to use clinical hypnosis to relax and reduce pain impacts how much pain medication is needed by patients for one month after surgery. In order to track how much pain medication is used by patients in this study for one month after surgery (including after you have left the hospital), we are asking for your consent to contact your pharmacy one month after your surgery to obtain information on your pain medication

prescriptions. You can participate in the study without consenting to sharing information from your pharmacy and pharmacist.

Do you permit us to contact your pharmacy to obtain your pain medication information?
☐ **YES** ☐ **NO**

<u>If yes, please complete the additional consent form for communication from the pharmacy to the UHN research team.</u>

Was the participant assisted during the consent process? ☐ **YES** ☐ **NO**
If **YES**, please check the relevant box and complete the signature space below:

☐ The person signing below acted as an interpreter for the participant during the consent process and attests that the study as set out in this form was accurately interpreted and has had any questions answered.

_____	_____	_____
Print Name of Interpreter	Signature	Date

_____	_____
Relationship to Participant	Language

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

_____	_____	_____
Print Name of Witness	Signature	Date

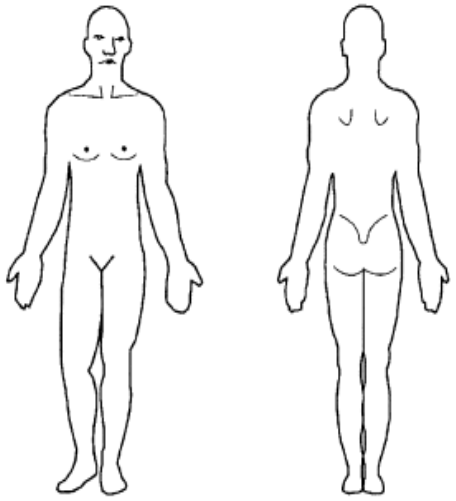
_____
Relationship to Participant

BPI-SF

1. Throughout most of our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?

   YES NO

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its **WORST** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the last 24 hours

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

Please circle the one percentage that most shows how much **RELIEF** you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

a. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

b. Mood

0	1	2	3	4	5	6	7	8	9	10

Does not interfere										Completely Interferes

c. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

d. Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

e. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

f. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

g. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

Heart Rate Variability & Respiration during Rest and Relaxation

Had caffeinated drinks in last 2 hrs? □ Yes □ No

Smoked in last 2 hrs? □ Yes □ No

Exercised in last 24 hrs? □ Yes □ No

Had alcohol in last 24 hrs? □ Yes □ No

Medications:

□ For hypertension (e.g. beta-blockers, calcium channel blockers, diuretics)
Name(s): _____ *Last taken*: _____

□ For depression/anxiety (e.g. tricyclic antidepressants, SSRI, anxiolytics/benzodiazepine)
Name(s): _____ *Last taken*: _____

□ For nasal congestion (e.g. Sudafed, Neo-Synephrine)
Name(s): _____ *Last taken*: _____

Setup:

- Positive (+) lead on patient's lower left rib bone towards the side
- Negative (–) lead on right collar bone (mid-clavicle)
- Ground (o) lead on lower right rib bone towards the side
- Secure respiration belt at patient's diaphragm (~2 inches below sternum). Adjust for comfort.

Instructions:

"For the first part of this test I will ask you to simply rest in your chair for 5 minutes. Please be seated comfortably with your eyes closed, try not to speak or make sudden movements, and I'll let you know when 5 minutes are up."
[Start: End:]
"In this last part, please close your eyes, and follow the instructions provided for the next 10 minutes. Stay seated comfortably, try not to speak or make sudden movements, and I'll let you know when 10 minutes are up."
[Start: End:]

Relaxation Measures

Measure	**Ratings** None										Extreme
Relaxation Level before Rest	0	1	2	3	4	5	6	7	8	9	10
Relaxation Level after Rest	0	1	2	3	4	5	6	7	8	9	10
Relaxation Level in Relaxation session*	0	1	2	3	4	5	6	7	8	9	10

** ask after relaxation session, based on how they felt towards the end of the relaxation session.*

Additional Notes

Completed by: _____ Date: _____