Mindfulness-Based Stress Reduction (MBSR) and Chronic Neuropathic Pain (CNP): A pilot fMRI neuro-imaging analysis in breast cancer survivors

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ABSTRACT

A significant subset of women plagued with breast cancer continue to experience chronic neuropathic pain (CNP) long after undergoing cancer treatment. Medical interventions such as pharmacotherapy and/or surgery have been most widely used to abate painful symptoms with limited efficacy. Other alternatives are required given a heavy reliance on pharmaceuticals can lead to tolerance, dependence and severe side effects. Possibilities include cognitive behavioural therapy (CBT), physical therapy, and mindfulness interventions to supplement pharmacotherapies. Mindfulness practice in particular has been offered to a variety of chronic pain groups including breast cancer patients, however evidence is lacking to support its effectiveness in CNP for breast cancer survivors (BCS). The purpose of the present study was to explore the benefits a mindfulness-based stress reduction program (MBSR) may have on altering the underlying neuronal correlates linked with pain-related symptoms associated with CNP in BCS. The primary objective was to investigate how mindfulness training might possibly mediate the brain's capacity for emotional reactivity, white matter integrity, and activation of the default mode network (DMN) and how these changes may correlate with levels of pain severity and pain interference, improving overall quality of life. To achieve these results, several brain imaging techniques were used in order to observe the correlation between the subjective experience of pain and the objective manifestation of brain changes that may be potentiated by MBSR training. A total of 23 participants were placed in either an 8 week MBSR intervention group (n=13) or a waitlist control group (n =10). All women were scanned with MRI before and after the 8 week intervention regardless of group allotment. The following neuroimaging modalities were used for each scanning session: resting state fMRI (rsfMRI) to monitor changes to functional connectivity in the default mode network (DMN); Diffusion Tensor Imaging (DTI) to assess the structural integrity of white matter tracts; and the Emotional Stroop Task (EST) to examine emotional reactivity in response to pain related stimuli. Exploratory results from

this pilot study indicate that improvements to functional connectivity were apparent in the MBSR group relative to control, indicative of more efficient communication in areas related to attention, self-awareness, emotion regulation and pain. Improvements were also noted as increased cerebral white matter health and reduced emotional reactivity to pain related stimuli in the group of MBSR trained participants relative to control. Additionally, these functional and structural changes correlated with the self-reported pain measures in the MBSR group, suggesting that the MBSR group demonstrated improvements to ratings of pain severity and pain interference whereas the opposite occurred with the control group. The results have been interpreted as improvements to patients' perception of pain and quality of life post MBSR training, however, were not limited to the subjective experience of pain. The inclusion of neuroimaging modalities provides objective and empirical support for MBSR training as it highlights the underlying brain mechanisms that were altered as part of MBSR treatment. Ultimately, the evidence suggests that MBSR could be incorporated as part of the treatment protocol for women experiencing CNP post breast cancer treatment.

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INTRODUCTION

Breast Cancer

Breast cancer accounts for 25% of all cancers women face, making it the most common (Canadian Cancer Statistics Advisory Committee, 2018). Over the last 3 years (2020-2022), breast cancer was consistently expected to be the second most diagnosed cancer in Canada, accounting for 25% of new cancer cases every year (Brenner et al., 2020; Brenner et al., 2022; www.cdn.cancer.ca). The incidence of breast cancer has increased significantly for women under 40 since 2000 with evidence suggesting that there is now an increased risk of the disease in younger cohorts (Heer et al., 2020). Survival rates fluctuate and are dependent on age and stage of cancer. Overall, patients are surviving longer however are often left with debilitating symptoms after treatment that negatively impact quality of life (QoL). The incidence and prevalence of breast cancer give credence as to why breast cancer is highly feared among women, and presents as a significant barrier to screening behaviour (Andersen et al., 2003).

Breast cancer not only affects women physically, but also causes psychosocial distress, impacting many domains of QoL. A general assessment of one's QoL may include several factors, however most notably encompasses the level of individual physical functioning, psychological well-being (including anxiety and depression) and the extent to which they experience social support (Perry, Kowalski & Chang, 2007). Moreover, every individuals' experience with breast cancer is considerably different, i.e., when they were diagnosed, treatments undergone (surgery, chemotherapy, radiation therapy), psychological adjustments to the illness and prognosis, as well as prospects of survivorship among other pre-existing medical conditions and additional factors (Bodai & Tuso, 2015). The combination of these distinct variables results in a unique individual experience with the disease and is equally considered a contributing factor to the extent to which

their QoL is impacted. The totality of the experience from diagnosis to treatment can be overwhelming, and often results in psychosocial distress including depression, anxiety and panic disorders (Baumeister et al., 2010; Reich, Lesure & Perdrizet-Chevallier, 2008; Hewitt, Herdman, & Holland, 2004). Typically patients feel a strong emotional upheaval upon diagnosis manifested as shock, sadness, and/or anxiety, more so than any other medical diagnosis (Shapiro et al., 2001). Understandably, the immediate and long term impacts of this disease have been a primary clinical and research question.

Modern treatment techniques for breast cancer are dependent on stage of cancer upon diagnosis, and usually combines treatment options such as surgery with radiotherapy, chemotherapy with or without antracyclines and taxanes, and endocrine therapy with aromatase inhibitors (AIs) (Canadian Cancer Society). Although, these treatment types may lead to a plethora of complications and subsequent negative side effects. Breast cancer treatments, like chemotherapy and radiation, may instigate long-term symptoms including fatigue, headaches, decline in cognitive functioning, cardiovascular toxicity, pulmonary complications, ovarian dysfunction, bone density loss, lymphedema, and symptoms of ongoing chronic pain lasting for months to years after initiation of therapy (Agrawal, 2014). Chemotherapy may additionally result in premature menopause and infertility, sexual dysfunction, osteoporosis, and vasomotor symptoms while radiotherapy has been implicated with cardiotoxicity, essentially causing damage to the heart tissue and the vascular system (Molina, Barton, & Loprinzi, 2005; Wang et al., 2019). Most cancer treatments result in some form of post treatment pain. Epidemiological surveys report that up to 25% of patients with cancer-related chronic pain indicate that the pain is connected to chemotherapy, radiation therapy, hormone therapy or surgery (Payne, 2000). While presently, patients are more likely to successfully recover from cancer and long-term survival rates continue

to rise, most survivors unfortunately continue to battle with intractable pain as an aftermath to treatment (Ewertz & Jensen, 2011). The underlying cause of this type of pain becomes resistant to pharmacotherapy leaving sufferers with enduring pain, sometimes lasting for the remainder of their lives.

According to estimates from the International Association for the Study of Pain (IASP), the general prevalence of pain in breast cancer patients can range between 40-89 percent (International Association for the Study of Pain, 2011). More recent estimates suggest approximately 20-50% generally complain about experiencing pain, meanwhile this estimation rises to 90% for patients in terminal stages or with metastatic cancer (Langford et al., 2015; Van den Beuken-van Everdingen et al., 2016). Additionally, 20-50% of women experience *chronic* pain in the breast, arm and shoulder after undergoing treatment related to the disease, persisting often for three to five years, or more (Bokhari & Sawatsky, 2009). These symptoms continue to plague survivors leaving more than half struggling with pain indefinitely. This pain is often due to neuronal dysfunction and is classified as chronic neuropathic pain (CNP) (Jung et al., 2003; Bokhari & Sawatsky, 2009). In order to better comprehend the roots of CNP however, we must first consider the influence of chronic pain more broadly.

Chronic Pain

The mysticism and complexity underlying the root of pain is one of the longest standing challenges in the history of medicine. Traditionally, the presence of pain was useful in aiding physicians to surmise where the symptoms of pain originated from in order to properly assess and treat the primary complaint of the patient. However, the traditional means of assessment and treatment become flawed when pain “becomes intractable, no longer serves a useful purpose and then becomes through its mental and physical effects, a destructive force” (Bonica, 1953).

Chronic pain is considered a multidimensional condition, affecting multiple constructs such as sensory, cognitive, and affective mechanisms (Moayedi & Davis, 2013), rendering it extremely difficult to treat. Chronic pain is defined as pain that persists for more than the normal course of healing, generally for more than 3 months, and is associated with significant emotional distress and/or functional disability (Merskey & Bogduk, 1994). According to the National Institute for Health and Care Excellence (NICE) guidelines published in 2021, chronic pain may be characterized as either chronic primary pain or chronic secondary pain depending on its origin. Chronic primary pain (CPP) is classified exclusively as a disease of its own accord unless another diagnosis would better account for the presenting symptoms. Chronic secondary pain is the result of an underlying disease such as cancer-related, osteoarthritis, ulcerative colitis, and/or musculoskeletal pain. Irrespective of classification however, all forms of chronic pain are known to cause distress and disability requiring appropriate assessment and treatment.

Today, chronic pain has become one of the most commonly reported reasons for seeking medical attention. It affects nearly 50 million adults in the United States of America, according to the 2016 National Health Interview Survey (Dahlhamer et al., 2018), and approximately 7.6 million Canadians from the 2019 Health Survey results (Canadian Pain Task Force). Persistent chronic pain may result from various neurological conditions such as spinal cord injury, stroke, multiple sclerosis and Parkinson's disease, among various other non-neurological medical conditions and cancers (Borsook, 2012; Boland & Ahmedzai, 2017). Given the extent of medical treatments required which contribute to work absenteeism, chronic pain has emerged as a significant medical, social, and economic burden (Chou et al., 2015) with an enormous financial cost to the health care system (Phillips, 2009). As of 2019, treatment of chronic pain had a combined total direct and indirect cost of $38.2 - $40.3 billion in Canada. Direct costs, including

physician's services, prescriptions and hospital inpatient and outpatient care, represent over 10% of total combined health care expenditures in the country (Canadian Pain Task Force, March 2021).

Types of Chronic Pain

Chronic pain may manifest in several forms and in numerous regions within the body. To supplement a primary or secondary classification, it is more commonly divided into two broad categories, namely neuropathic pain, or nociceptive pain (Nicholson, 2006). Neuropathic pain occurs when nerves of the somatosensory system are damaged from trauma or disease whether peripherally or centrally. It originates from nervous system lesion or nerve dysfunction (disturbances to the nerves) and spontaneously transmits pain signals to the spinal cord and brain (Colloca et al., 2017). This type of chronic pain is often described as sharp, stabbing, shooting, burning or felt as electrical sensations.

Nociceptive pain on the other hand occurs when receptors within the nervous system (nociceptors) are activated when the body experiences injury peripherally in tissues and/or organs (Treede et al., 2008). Nociceptors within the body detect painful stimuli and send this information to the spinal cord and brain for interpretation and response. Nociceptive pain may be further categorized as either visceral or somatic pain, which transit through divergent pathways to ultimately reach the spinal cord (Boezaart et al., 2021). Visceral pain originates within major internal organs, and only organs containing nociceptors may elicit this type of deep visceral pain. Alternatively, somatic pain is often related to joint injury or arthritic conditions. It is caused by injury to parts of the body such as skin, ligaments, tendons, muscles, joints and bones. Somatic pain types may include musculoskeletal, arthritic, fibromyalgia, bone fracture, and some types of back pain (Boezaart et al., 2021).

In 2019, the World Health Organization (WHO) accepted the International Classification of Diseases (ICD)-11th edition as the first to include a functional definition of "chronic pain" as a disease and has officially classified chronic pain into 6 sub-categories; chronic cancer pain, chronic post-surgical or post-traumatic pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain. Given this designation, it becomes possible to treat chronic pain as a primary disease requiring concerted treatment, contrasted to prior treatment of symptoms of an underlying condition, thus rendering the approach to pain management more intentional and potentially integrative.

Pain Management

Historically, the traditional means of chronic pain management has included medical intervention whether opioid medication and/or surgery. Opioids function on both central and peripheral pain pathways in order to inhibit pain perception. However, the long-term benefits of opioid use for chronic pain conditions are disputed (Chou, 2013). It was found that long-term use of opioids was associated with increased psychological distress and presents serious risk of misuse (Potter & Marino, 2013). The benefits of opioids also have a tendency to decline with prolonged use (Krashin, Sullivan & Ballantyne, 2013) and patients using opioids long-term may develop endocrine abnormalities such as decreased testosterone, progesterone, estradiol, and cortisol changes in response to stress (Katz & Mazer, 2009). Aside from the typical side effects that accompany opioid use such as constipation, sedation, and tolerance, its use may ultimately lead to additional unintended negative consequences such as psychological dependence, opioid-induced hyperalgesia (Brush, 2012), addiction (Rosenblum et al., 2008) and death (Dydyk, Jain, & Gupta, 2022).

In the United States, the prevalent opinion among medical professionals is that the long-term use of opioid therapy for the treatment of chronic pain, is "contraindicated by the risk of addiction, increased disability and lack of efficacy over time" (Rosenblum et al., 2008). Opioid use can be traced back to more than 5,000 years and has been one of the earliest and most commonly used medicines (Booth, 1996). It was used unrestrictedly throughout the early twentieth century for common ailments (headaches, insomnia, anxiety, cough etc.). However, at the tail-end of the twentieth century, the use of opioids expanded significantly, continuing an upward trend lasting to this day. This increased the prevalence of nonmedical use of prescription opioids, and resulted in significant opioid abuse, physical drug dependence, and severe opioid withdrawal symptoms (Kosten & Baxter, 2019), ultimately rendering the mass distribution of opioids an epidemic. Unfortunately, physical drug dependence often transpires with the abrupt cessation of opioids, or in the case of rapid dose reduction without proper medical supervision. These withdrawal symptoms include aches and pains, muscle spasms, tremors, abdominal cramps, nausea, anxiety, irritability, insomnia, heart pounding, hot flashes/chills, among others (Wesson & Ling, 2003). Symptoms typically abate when the opioid administration is tapered down slowly in a controlled environment and with the administration of safe and effective counter treatments. Although physical dependence is certainly concerning, addiction is of grave concern as it becomes characterized as a chronic illness (Rosenblum et al., 2008) with misuse severe enough to be classified as an opioid use disorder (OUD) (Ahrnsbrak et al., 2017; Dydyk, Jain, & Gupta, 2022). Some patients treated with opioids may develop severe psychological distress and behavioural disturbances, highlighting the development of the addictive disorder. The withdrawal process may also exacerbate the initial chronic pain symptoms once opioid use is no longer recommended in individual patient care, and this may draw patients back to opioid-use in order to abate the difficult

to bear withdrawal symptoms (Kosten & Baxter, 2019). Clearly, the long-term use of opioids as treatment for chronic pain symptoms is arduous and controversial given the concerns surrounding potential side-effects, long-term drug efficacy, as well as the potential for drug abuse and addiction (Savage et al., 2003). Consequently, it becomes crucial for physicians to monitor patient progress, and also carefully assess patient potential for dependency or addiction when recommending extended opioid treatment. Although negative consequences of opioid consumption are evident, rates of misuse were low and not frequently reported among cancer survivors (Jairam et al., 2020).

As a result of the growing concerns surrounding the traditional means of treatment, a multidisciplinary/interdisciplinary approach has become more commonly advocated to address symptoms and enhance outcomes. Behavioural pain management interventions rose to prominence in 1976, with the introduction of psychosocial and physical therapy interventions (Fordyce, 1976). Rather than solely viewing pain through the lens of the disease model, Fordyce offered the perspective that clinical pain could be interpreted from a behavioural or learning/conditioning model which presented a modernized approach to diagnosis and pain management. Given that pain may be overtly observed when a patient demonstrates pain-related behaviours (an indication of the presence of pain), responses to pain are in essence observable behaviours (whether respondents or operants). Fordyce posited that these behaviours may arise as a result of 1) nociception, neuropathic or neurophysiological stimuli, 2) anticipated consequences (behavioural learning) or 3) contingent consequences met (positive or aversive) (Fordyce, 1984). As behavior is influenced by cognitive processes, behavioural and cognitive strategies are not mutually exclusive, thus cognitive-behavioural methods simultaneously blossomed as an assessment perspective in relation to chronic pain. In fact, Melzack & Wall (1965) highlighted the importance of psychosocial and physiological processes as primary contributors to the processing of pain within the Gate Control

Theory of pain, detailed further below (Moayedi & Davis, 2013). The psychosocial aspect of this model in particular contributed greatly towards patients' pain perception as negative mood states amplify the intensity of sensory output (Gatchel, 2005; Gatchel & Howard, 2008). The further interpretation and discussion of this framework laid the foundation towards a biopsychosocial model for the treatment of chronic pain disorders, which is more readily used today (Engel, 1977, 1980; Gatchel et al., 2007). This approach characterizes pain and disability as a complex dynamic across biological, social and psychological factors and has emerged as the preferred assessment and treatment model for pain management with chronic pain sufferers (Engel, 1980; Gatchel, 2004; Gatchel & Howard, 2008). The biopsychosocial method is an integrative approach which explains individual variability to pain as an intricate dynamic between underlying biological (genetics and disease markers, hormones, physiological reactivity, innate pain modulating mechanisms) (Suls & Rothman, 2004), psychological, social, cognitive, and affective measures as contributing agents in pain assessment and management (Gatchel & Maddrey, 2004). Psychological elements include our beliefs, behaviours and cognitions, attention and emotion (Cieza, & Bickenbach, 2015). These systems can be modulated by psychological techniques in pain control, anti-stress programs, behavioural talk and group therapies as well as education on life quality improvement (rehabilitation, exercise, nutrition, social influences and support networks and/or pain management classes) (Havelka, Despot Lucanin & Lucanin, 2009). Social components integrate the contributions of social support, relationship satisfaction, social network size, work, healthcare and financial security (Suls & Rothman, 2004). Physical activity and diet also play a key role in how individual pain may be modulated (Hoeger Bement & Sluka, 2016; Law & Sluka, 2017; Bjorklund, 2019). Social support contributions are vital for coping with and buffering against stress, and any deficiency may exacerbate pain by releasing stress hormones continuing the

cyclical pattern of pain, and perpetuate cortisol dysfunction (Hostinar & Gunnar, 2015; Hannibal & Bishop, 2014). The long-term effectiveness of a biopsychosocial interdisciplinary approach to pain assessment and management has reported improved outcomes on pain severity and pain interference (Oslund et al., 2009) and is more effective than medication use alone. Although this approach has gained sustained prominence and demonstrated effectiveness, significant barriers remain to the effective management of cancer-related pain.

Barriers to Pain Management

Inadequate pain management practices have led to the improper and under-management of cancer pain. Poor pain management practices have left some patients with moderate to severe pain with insufficient treatment of agonizing symptoms (Kwon, 2014). Barriers to pain management may be interrelated to several fundamental components including the patient, the treating clinician and/or the health care system (Paice, Toy & Shott, 1998). The potential for successful treatment is heavily reliant upon the fortuitous chemistry and interaction of these systems. A thorough investigation and comprehension of individual contributing factors including personal history is necessary in order to achieve a successful pain management treatment plan and ultimately a prosperous outcome. However, specific factors may influence the patients' perspective such as general antecedent factors (age, gender), cognitive and affective factors, and intrinsic belief systems (Kwon, 2014). A commonly held patient belief is that pain is inevitable and thus some are hesitant to report their truest level of experienced pain to medical practitioners (Sherwood et al., 2000). One of the most common patient-related barriers is the fear of addiction when using analgesics (Melzack, 1990), along with the fear of becoming tolerant to the medication (Sherwood et al., 2000). Additionally, it is common to think that side-effects of medication are inevitable and unmanageable (Ferner, 2014). As such, the Barriers Questionnaire (BQ) was conceptualized to

assess patient barriers to the optimal management of cancer pain (Gunnarsdottir et al., 2002). A proper assessment of individual characteristics and adequate patient/practitioner communication may provide patients with realistic expectations relating to drug efficacy and side effects improving adherence to analgesic regimen (Schug & Stannard, 2011). Additionally, clinician-related and health-care barriers include more broad knowledge deficits (medications and side effects) (Jacobsen et al., 2007), inadequate pain assessment capabilities, and regulatory obstacles (institutional barriers, scrutiny) (Paice, Toy, & Shott, 1998; Glajchen; 2001; Jacobsen et al., 2009).

The successful treatment of chronic pain is clouded by specific barriers in addition to significant challenges with the identification, and management of isolated patient symptoms. The matter is further complicated by a lack of candid patient-practitioner communication. As discussed, chronic pain is commonly generalized into two broader categories (nociceptive versus neuropathic) that maintain their own challenges relating to pain management. Chronic neuropathic pain (CNP) has been documented as more challenging than nociceptive pain to treat, given reports of higher dose requirements of analgesics are generally required for treatment (Benedetti et al., 1998). As the intent of this thesis is to investigate the impact on a patient group suffering from CNP, we will now look further into the specifics of what CNP consists of and how it may impede a sustainable standard of QoL.

What is Chronic Neuropathic Pain?

A particularly insidious pain condition, CNP is estimated to affect approximately 7-10% of the general population (Mulvey et al., 2014) and up to 30-50% of BCS (Bokhari & Sawatzky, 2009). As defined by Merskey and Bogduk in 1994, neuropathic pain is “pain initiated or caused by primary lesion or dysfunction in the nervous system”. It originates from neuronal dysfunction resulting from extensive damage to nerve fibers (Jung et al., 2003), affecting the somatosensory

system (Leysen et al., 2018) and it often persists indefinitely (Bredal et al., 2014).

Chronic neuropathic pain is caused by lesion or disease to the somatosensory system whether peripherally or centrally (Finnerup, Kunner & Jensen 2021). The somatosensory system is the underlying system that allows for the perception of pain, pressure, temperature, movement and vibration (Colloca et al., 2017). The intricate network of nerves originates at the skin as an entry point, and communicate with the muscles, joints, and fascia which include a multitude of receptors (thermoreceptors, mechanoreceptors, chemoreceptors, nociceptors) that communicate with the spinal cord and brain (Colloca et al., 2017). When lesions exist or disease occurs, this complex system of integrated communication gets disrupted and loss of sensation and pain ensues (Finnerup, Kunner & Jensen, 2021). Given the injury may originate peripherally or centrally, there are some conditions commonly associated with CNP such as metabolic disease, viral infections (such as HIV), leprosy, exposure to toxins, autoimmune conditions, neurological conditions and cancers (Colloca et al., 2017; Scholz et al., 2019). However, an important distinction in CNP, is the combination of sensory loss and pain either with or without sensory hypersensitivity in the area of pain (Finnerup, Kunner & Jensen, 2021).

The IASP has classified CNP into two major categories; central or peripheral neuropathic pain. Central neuropathic pain stems from spinal cord, brain injury, stroke, or pain associated with multiple sclerosis, whereas peripheral neuropathic pain may be a result of trigeminal neuralgia, peripheral nerve injury, painful polyneuropathy, postherpetic neuralgia and painful radiculopathy (Scholz et al., 2019). The diagnosis of CNP requires a minimum history of 3 months of painful symptoms resulting from nervous system injury or disease and a “neuroanatomical plausible distribution of the pain,” including negative and positive sensory symptoms (Sholz et al., 2019). “Negative” symptoms present as decreased loss of sensation and “positive” symptoms are

demonstrative of evoked pain or hyperalgesia which indicate the involvement of the somatosensory nervous system and the underlying innervated organ of the affected structure (Sholz et al., 2019).

Living with CNP is often debilitating and may have a profound negative impact on QoL and psychological functioning. For example, for many individuals living with CNP the intensity of pain becomes so severe that it is often crippling, significantly impacting activities of daily living, and forces many towards unemployment or to part-time work (Jung et al., 2003). CNP is also commonly comorbid with depression and anxiety, thus patients experiencing neuropathic pain are more likely to exhibit increased anxiety in addition to sleep disturbance (Carlson et al., 2004; Pace et al., 2009; McCarberg & Billington, 2006). Pain catastrophizing is an "exaggerated negative mental set brought to bear during actual or anticipated painful experience" (Sullivan et al., 2001). Pain catastrophizing typically incorporates three dimensions as identified by Sullivan such as: magnification of perceived threat, helplessness and rumination (Sullivan et al., 2001). The tendency to ruminate over negative experience, for instance the inability to stop thinking about the pain, in conjunction with fearing the meaning of pain and the development of an attitude of hopelessness, is associated with higher rates of depression, anxiety, social impairment and physical disability (Bishop & Warr, 2003). These maladaptive thinking patterns account for a significant portion of distress in CNP which consequently results in further catastrophizing and worsening of subjective symptom severity negatively impacting QoL (Khan et al., 2011; Toth 2014). Adopting a negative response style such as catastrophizing, becomes commonplace and adds to the magnitude of already debilitating symptoms experienced as sequelae to primary disease.

As indicated, breast cancer is the most prevalent cancer diagnosis experienced among

women and is the most significant leading cause of chronic peripheral neuropathic pain (Caraceni & Portenoy 1999; Leysen et al., 2018). Neuropathic pain specifically, marks the most predominant pain type when compared to nociceptive and central sensitization pain, accounting for 25% of breast cancer survivor pain (Leysen et al., 2018). Chronic neuropathic pain resulting from cancer treatment, is most commonly caused by complications due to chemotherapy, radiation, surgical injury, or other cancer related processes (Jung et al., 2003). In BCS, it manifests as phantom breast pain, intercostobrachial neuralgia, or painful neuroma and presents as sensations of burning, numbness, shooting pain and tingling (Ramesh, Shukla & Bhatnagar, 2009). Phantom breast pain is typically experienced as severe acute post-operative (mastectomy) pain and is described as the sensation of residual breast tissue and pain in the breast that was previously removed (Ramesh, Shukla & Bhatnagar, 2009). Intercostobrachial neuralgia manifests as pain in the breast and/or upper arm that is attributable to nerve damage during surgery with or without axillary dissection (Jung et al., 2003). Additionally, neuromas are catalyzed by an abnormal growth of nerve tissue when peripheral nerves are severed or injured. Should nerves become damaged following mastectomy surgery in breast cancer treatment, a neuroma may develop causing hypersensitivity and pain of the breast, chest, or arm (Jung et al., 2003).

CNP Management

The traditional model of patient care encompasses disease-specific treatment. However, optimal patient care demands attention to all factors contributing to the experience of pain and related disability. In order to treat pain with quality pain management practices, treatment should incorporate assessments that delineate the predominant pain mechanisms, however, not only are biomedical evaluations necessary, but equally important are measures that are psychosocial in nature. Psychological as well as social components have contributed to pain severity, emotional

distress, work disability, in addition to treatment response in persons experiencing chronic pain (Jamison & Edwards, 2012). Evidence is supportive of a biopsychosocial model and that psychosocial factors in particular are inherent in chronic pain (Williams, 2013). This approach enables a holistic evaluation and treatment of an individual's level of overall suffering (Payne, 2000).

For persons living with CNP, pain management becomes crucial, but unfortunately the limited understanding of its pathology has made successful integrative treatment challenging. According to the WHO, pharmacotherapy constitutes the main treatment for cancer related pain in 85-90 percent of patients (Satija et al., 2014). In 2007, Moulin et al. developed the standard Canadian guideline for pharmaceutical management of neuropathic pain, which was more recently revised by Mu et al. (2018). These guidelines include four lines of medical intervention (Figure 1) and are based on the evidence of drug efficacy, side effect profile, ease of use, and cost-effectiveness. The first line of intervention is generally accepted amongst medical professionals, however if inadequate, additional lines may be added to supplement the treatment plan. The first line of treatment includes tricyclic antidepressants and anticonvulsants, including gabapentinoids and serotonin-norepinephrine reuptake inhibitors (Mu et al., 2018). Tricyclic antidepressants block reuptake of serotonin and norepinephrine availability and essentially modulate pain signal pathways (Moraczewski & Aedma, 2022). However, caution is required with respect to side-effects related to this drug class in that bladder retention, and sedation may become pertinent issues (Hatch, 2018). Gabapentinoids are also widely used for CNP among chronic pain and other pain groups, however the drug contains sedative effects on the central nervous system, along with dizziness, gait instability and feeling of intoxication (Goodman & Brett, 2017).

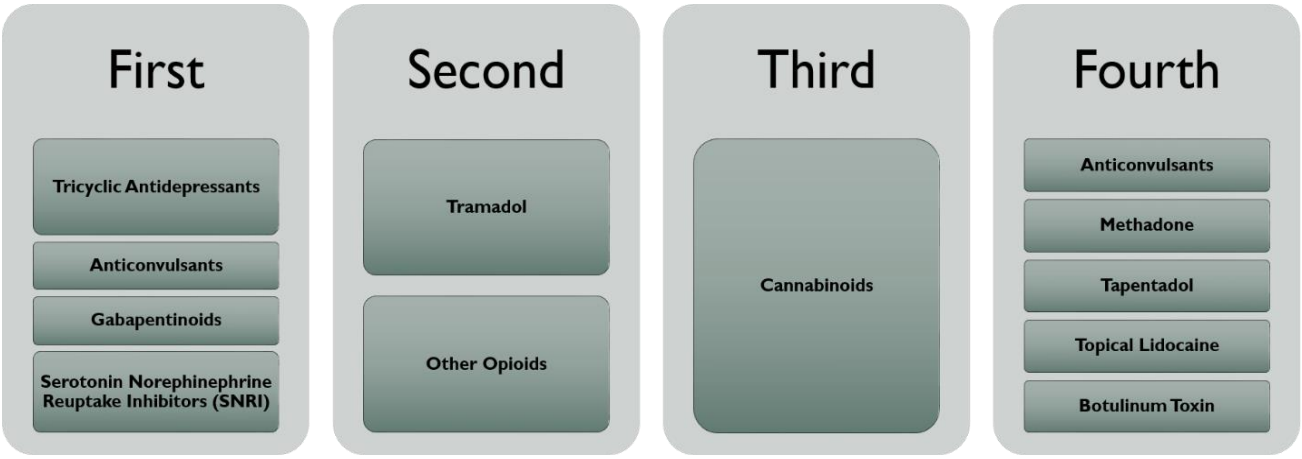
The addition of tramadol and other opioids encompasses the secondary line of

intervention, while cannabinoids are now recommended as a third-line (Mu et al., 2018). Opioids, as discussed earlier, are one of the most readily prescribed pain medications for CNP. They are potent analgesics that may result in pathological, physiological and psychosocial impacts, and CNP is noted to respond less favorably to opioids (Smith & Meek, 2011), thus their use in treatment of CNP remains controversial (Rosenblum et al., 2008). Tramadol also modulates serotonin and norepinephrine reuptake, however it is a less potent opioid agonist as it has a lower affinity for the u-opioid receptor. Thus the potential for overdose and addiction is less to that of other opioids, making it a more favourable alternative to prescribe (Pathan & Williams, 2012; Grond & Sablotzki, 2004; Radbruch, Grond, & Lehmann, 1996). Cannabinoids on the other hand, modulate endogenous cannabinoid receptors, and thus as an extension, are potentially able to modulate pain and mood (Hatch et al., 2018). The fourth and final line of medical intervention introduces, methadone, tapentadol, topical lidocaine, and botulinum toxin (Mu et al., 2018). Methadone is a synthetic opioid while tapentadol is a modernized opioid that offers analgesic effects, with common side effects similar to other opioid administration (Toombs & Kral, 2005). Its use is considered fourth line since it has limited studies demonstrating effectiveness with neuropathic pain (Mu et al., 2018). Within this algorithm of pharmacological pain management, the addition of subsequent agents is considered sequentially dependent on patient symptoms and degree of relief, however physicians must also continuously consider contraindications and patient safety (Mu et al., 2018).

Although considered the primary means of treatment, pharmacotherapy alone is not able to successfully abate painful symptoms associated with CNP, as the majority of patients continue to experience debilitating pain even while taking medication (Harden & Cohen, 2003), and evidence of efficacy of opioids in the treatment of neuropathic pain is not convincing (Gaskell et al., 2016;

Stannard et al., 2016). Additionally, there is the risk of adverse reactions, as well as opioid tolerance, dependency, misuse, addiction and overdose (England & Franklin, 2012). Thus, physicians are left with critical decisions for effective pain management strategies that ensure safe use and patient protection from risk.

Figure 1.
Guidelines for four lines of medical intervention (Mu et al., 2018)



It is generally accepted that CNP is extremely difficult to treat, and that comorbidities such as anxiety, depression or sleep disturbances are important factors in the potential outcome for patients. Evidence suggests that approximately 50% of individuals experience only partial relief from CNP symptoms with medication, and in many cases adverse effects make treatment intolerable (Finnerup et al., 2015). As referenced earlier, a multidisciplinary or interdisciplinary approach to chronic pain management is vital and presently, is more readily used. Holistic, and/or alternative interventions, such as psychological intervention (i.e., CBT), physiotherapy, and even exercise programs, may be beneficial in treatment of chronic pain (Mills, Torrance, & Smith, 2016; Kress et al., 2015; Williams et al., 2020). Psychological interventions may be particularly essential to include as part of a treatment plan, given the high rate of comorbid mental health issues with CNP (McCarberg & Billington, 2006; Moulin et al., 2007). Studies have demonstrated

the positive benefit that CBT may have on chronic pain groups (Turk, Swanson, & Tunks, 2008, Scascighini et al., 2008). One example contrasted the effects of either a physical therapy session, CBT, behavioural medicine rehabilitation coupled with physical therapy and CBT, or a treatment as usual group might have on pain within a chronic spinal cord pain group (Scascighini et al., 2008). After a treatment period of 4 weeks, results demonstrated that women in either the CBT or the behavioural medicine group had reported better QoL outcomes than women in the treatment as usual group, although these significant differences were not observed for men. The results highlighted not only the effectiveness of CBT treatment on QoL outcomes, but also indicated that a sex difference may exist, which may have an implication on how men and women respond differently to alternative interventions. Additionally, Jensen et al. demonstrated that a multidisciplinary approach coupling a behavioural medicine rehabilitation program with CBT (13-14 hours per week) and behavior-oriented physical therapy (20 hours a week) yielded the most optimistic results for chronic spinal cord pain, consistent at 18-month follow up (Jensen et al., 2001). The CBT treatment was intended to improve patients' ability to manage their pain and enhance quality of life and included cognitive coping techniques, breaking vicious cycles, goal setting, problem solving, applied relaxation, and activity planning. This study also corroborated that sex differences are apparent in the literature, as women in the CBT and behavioural medicine rehab program reported significantly better results on health related QoL at 18-month follow up whereas no differences were apparent in men when compared to the control group.

Physical therapy (PT) is also considered an important modality in conjunction with pharmacotherapy. An evaluation of patients with chronic pain indicated that two-thirds of the patients included in the review were using some form of non-pharmacological treatment such as massage (30%), acupuncture (13%), and physical therapy (21%) to treat their pain (Mills,

Torrance & Smith, 2016). Some PT treatments include hot and cold, ultrasound, short wave diathermy, low frequency currents, laser, transcutaneous electrical nerve stimulation (TENS) and neurostimulation techniques (deep brain and transcranial magnetic stimulations) for pain modulation (Akyuz & Kenis, 2013; Rennie, 2010; NICE). However, ultrasound and short wave diathermy have not been as readily recommended for patients with CNP, and massage therapy use for CNP is still under investigation pending further supportive evidence (Akyuz & Kenis, 2013; Ownby, 2006; Norrbrink & Lundeberg, 2011; Basar & Erhan, 2020). The TENS technique has shown the most potential for effectively treating neuropathic pain, as it activates central nerve mechanisms inciting analgesia, although its use also requires further evidence (Basar & Erhan, 2020; Vance et al., 2014). Its effectiveness seems to rely on several factors such as intensity of stimulation, frequency, duration, as well as how many consecutive sessions the patient takes part in (Vance et al., 2014; Akyuz & Kenis, 2013).

Exercise is well-known for improving overall physical and mental health. Its effectiveness as an intervention is also being considered for those experiencing CNP. As demonstrated by Li and Hondzinski (2012), routine exercise such a strength-stability training, or aerobic exercise were impactful additions to pharmaceutical treatment for patients with peripheral neuropathy, a form of CNP. The potential gains are many including enhanced vascular health, reduced risk of hypertension, increased antioxidant defenses, reduced risks of cancers, increased cardiorespiratory endurance, reduced depression and anxiety, improved sleep, improved cognition, and enhanced physical functioning (Piercy et al., 2018). Routine exercise in fact was shown to preserve and promote the function of peripheral nerves in peripheral neuropathy (Balducci et al., 2006). A systematic review on the subject has indicated that steady exercise programs were exceptionally beneficial in reducing pain in chronic low back pain sufferers, patients with fibromyalgia, and

knee osteoarthritic condition groups (Chiang et al., 2016). More broadly, varying levels of exercise demonstrate that active individuals had a reduced risk of experiencing neuropathic pain, however further study is required to determine how dose factors such as frequency, intensity, and type have an impact. It seems that regular physical activity reduces the risk of chronic pain by 10-15% in those younger than 65 (Landmark et al., 2011), however further research is needed to establish how it may help persons with CNP cope.

As previously noted, the contemporary model of pain management is more integrative, taking into consideration physiological, psychosocial, and social factors (Turk & Monarch, 2002). The multitude of symptoms accompanying CNP and the complexity of the underlying disease dictates that a multidisciplinary approach is best suited to fully benefit from complementary treatment modalities. It is important to consider all sequelae that are associated with chronic pain, including biological and psychosocial comorbidities to fully address the specific contributions to a patient's experienced pain and to attempt to restore their optimal health and level of functionality. Some adjunctive therapies may offer support and potential relief, however an individual's subjective level of experienced pain (physiological and behavioural response) (Follin & Charland, 1997), the underlying etiology as well as approach to pain assessment and management may have an impact on how successful selected treatments may be (Wells, Pasero & McCaffery, 2008). How does one's perceptions of their own experience of CNP alter their approach to tackling and managing these painful symptoms? In order to appreciate the underlying complexities involved with how we process pain, it is essential to review one of the most influential models depicting our internal processes when struggling with pain.

Theories of Pain

Several theoretical models have been posited as explaining the basis of pain perception.

Some of the most historical theories include the Specificity Theory of Pain, Intensity Theory of Pain, Pattern Theory of Pain, and the Gate Control Theory (Gatchel & Howard, 2008; Moayedi & Davis, 2013; Trachsel, Munakomi, & Cascella, 2022). The Specificity Theory of Pain, one of the most primitive theories of pain, indicates there are dedicated pathways present for each somatosensory modality, essentially each modality has specific receptors coupled with associated sensory fibers that are sensitive to only one specific stimulus (Moayedi & Davis, 2013; Trachsel, Munakomi, & Cascella, 2022). For example, mechanical stimuli are processed only by mechanoreceptors which then project to mechanoreceptor neurons in the spinal cord or brainstem (Moayedi & Davis, 2013). Contrarily, the Intensity Theory indicates that specificity of distinct pathways does not exist, however it is the number of impulses in neurons which determines the level of intensity of a painful stimulus, thus an emotional response to stimulus (Trachsel, Munakomi, & Cascella, 2022). It describes pain as an emotion that occurs when a stimulus is stronger than what could be expected (intense and long lasting) and is not necessarily a unique sensory experience (Moayedi & Davis, 2013). The Pattern theory of Pain suggests that nerves that are implicated in pain detection, are also capable of detecting other stimuli and sensations (Lele et al., 1954). This theory is contrary to the theory of specificity, in that specific nerve fibers capable of interpreting a specific sensation of pain do not exist (Trachsel, Munakomi, & Cascella, 2022). It indicates that the pattern activity of any painful experience is interpreted at the neuronal level within the brain, which has been detected and transmitted to the brain by similar nerves irrespective of type or location of the painful stimuli (Moayedi & Davis, 2013; Trachsel, Munakomi, & Cascella, 2022). Our brains are capable of deciphering this pattern, and essentially correlate the pattern of activity with the painful sensation (Melzack, 2005).

The Gate Control Theory of Pain postulated by Melzack and Wall (1965) expands upon the

inaccuracies and deficiencies of the earlier pain models and explains the underlying interaction between the peripheral and central nervous systems that are capable of oscillating the sensation of pain to either activate more perceived pain intensity or lessen it. It postulates that neuronal synapses within the central nervous system (beginning at the spinal cord) act as "gatekeeper" neurons which may transmit action potentials to tertiary neurons in the midbrain and cortex, where pain is perceived (Melzack & Wall, 1965). Accordingly, the sensation of pain is determined by the interaction between these various components within specific locations of the spinal cord prior to traveling to the brain (Trachsel, Munakomi, & Cascella, 2022).

Although these theories have historical significance and popularity in furthering the understanding of pain, they do not allow for the ability to cognitively control for neuronal impulses. If the continued perception of pain is only regulated at a synaptic level, it is possible that chronic pain may remain eternally "stuck" within a prolonged cycle of intense neuronal activation, or enduring specific receptor stimulation. Research has clarified that unique nerve receptors do exist for various types of sensation, thus discrediting earlier theoretical models (Marzvanyan & Alhawaj, 2021; Trachsel, Munakomi, & Cascella, 2022; Moayedi & Davis, 2013). Although the above theories may offer some foundation with respect to how pain is perceived, a prominent theory suggests how cognitive appraisal may have a vital impact on continued suffering (Philips, 1987) and as such may be most relevant to the pain experienced by BCS especially given the prominence of fear of cancer recurrence (Turk & Wilson, 2010; Hall et al., 2019).

The fear avoidance model of chronic pain describes the perception of threat related to the cascade of events after pain (Figure 2). It is actively investigated and corroborated in research findings and suggests how one may progress from the experience of acute pain to a vicious cycle of entrapment and chronic suffering (Vlaeyen, 2015; Vlaeyen & Linton, 2000; 2012). Framed

within the biopsychosocial perspective, it posits how the experience of acute pain may lead to chronic disability (Gatchel et al., 2007). It recognizes and acknowledges how important patient beliefs are in accordance with their pain and emphasizes how fear when integrated with beliefs ultimately results in avoidance (Fordyce, 1976; Turk, Meichenbaum, & Genest, 1983; Philips, 1987). Fear coupled with avoidance, evolves into a behavioural pattern that is asynchronous with the underlying pathology, resulting in a magnified perception of pain (Philips, 1987). The real experience of pain sets in motion cognitive, emotional and behavioural responses that may exacerbate pain and lead to eventual disability.

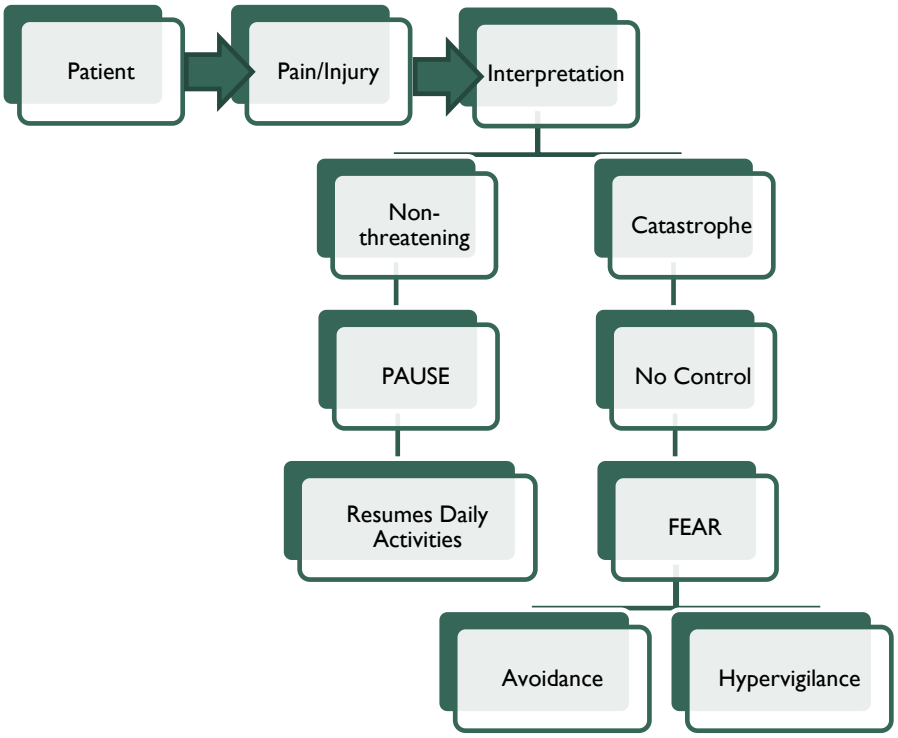
At the core of the fear-avoidance model is the patients' dyssynchronous perception and interpretation of their own pain (Lethem et al., 1983; Vlaeyen et al., 1995). When pain is interpreted as non-threatening, an individual is typically able to resume their activities of daily living after a short pause and equates expectations to actual experience (Crombez et al., 2000, 2012). However, when a painful event is interpreted as catastrophic, an individual may suffer from irrational and debilitating fear of re-injury, (Philips, 1987; Vlaeyen et al., 1995) and thus overestimate future pain and its possible consequences. As such, patients hold negative and biased beliefs about pain and are unable to continuously assess if their personal expectations are in line with actual experience/reality given overwhelming fear of reoccurrence. When a catastrophic interpretation sets in, serious pathology develops, as the individual's perceived locus of control (LOC) diminishes. The LOC relates to the patient's belief in their own ability to influence their illness and minimize experienced pain by thoughts and actions (internal processes), versus controlled by external events (Rotter, 1954, 1966; Crisson & Keefe, 1988). The cognitive processing of our LOC is pivotal to the experience of pain as internalized processing is associated with lowered symptoms and improved treatment outcomes (Lipchick, Milles, & Covington, 1993).

Research is indicating that a relationship between LOC and catastrophizing exists, as higher internal LOC is associated with decreased pain and intensity/unpleasantness in conjunction with reduced catastrophizing through training (Thompson, Terry, & Rhudy, 2015). The fear-avoidance model outlines that the approach to pain catastrophizing is what leads to an excess of fear of pain/injury to the point of complete avoidance of physical activity (Gatchel et al., 2007). Catastrophizing is impactful and pervasive even within healthy community members as evidenced by behavioural avoidance in healthy samples when faced with cognitively challenging tasks (Wijenberg et al., 2021). Since avoidance is limiting in that expectation is not rivalled by actual experience, the expectation of future pain is overestimated along with any potential negative consequences associated with the activity.

Attentional processes play a pivotal role in this scenario as one resorts to continuously scanning their bodies for any signals of pain or injury (Crombez et al., 1998). When the individual is automatically attending to pain or pain-related information from their bodies, other information within the environment is often ignored as limited resources remain available to attend to the environment. This dynamic presents the hypervigilance aspect to the model (Crombez et al., 2005). Hypervigilance is a state of increased alertness, thus making one very sensitive to their surroundings as the subconscious mind is anticipating danger. Hypervigilance to pain is a crucial component of the fear-avoidance model as it is associated with significant disability (Vlaeyen & Linton, 2000; 2012). Avoidance and hypervigilance may offer some benefit in the shorter term as they provide an immediate protection from further imminent injury (Crombez et al., 2012). However, in the long-term, this strategy is not self-serving as avoidance and hypervigilance resulting from pain-related fear predicts disability and are both mentally and physically taxing as patients are less able to shift attention away from pain-related information (McCracken et al.,

1998). Since activities are generally avoided, aspects of self, both physical and mental, are slowly deteriorating, perpetuating the vicious cycle of inactivity, disability, and long-term suffering. The interminable cycle of inactivity leads to physical deconditioning resulting in being even more vulnerable to future pain as the pain threshold is ultimately lowered (Verbunt, Smeets, & Wittink, 2010). Avoidance behaviours cultivates an inability to pursue previous valued activities, spiraling into reduced positive experiences, reduced social activity, and eventually leading to affective distress (Crombez et al., 2012).

Figure 2.
Fear-Avoidance Model of Pain (Adaptation of Vlaeyen & Linton's model, 2000; 2012)



This extensively accepted model outlines how an acute experience of pain may become devastating and crippling in short course. It has been thoroughly researched, readily adopted and has been judged as credible by patients themselves given its ability to resonate with their personal

experiences (Eccleston, Williams, & Rogers, 1997). It is not unconditionally embraced, however offers an explanation as to how pain and suffering may become chronic. In treating the "what" it is crucial to understand the "why", and this model offers us a glimpse at the potential for why and how our perceptions may guide our judgements of an internalized pain experience. Although it is essential to establish a foundation for how and why chronic pain may emerge, treatment of the debilitating symptoms accompanying the experience is of paramount importance. A promising treatment for CNP, namely mindfulness, is explored further in this monograph.

Mindfulness-Based Interventions

Mindfulness is defined as the ability to reflect on the present moment in an open and intentional manner, and it is this ability that empowers those suffering to alter the perception of pain as transient passing events, making space for acceptance (McCracken & Vowles, 2014). While some unfortunately experience constant debilitating pain, mindfulness based interventions (MBI) allow for the acceptance of this state. At its core, mindfulness is centered on "paying attention in a particular way; on purpose, in the present moment, and non-judgmentally" (Kabat-Zinn, 1994, p.4).

Interventions in mindfulness have demonstrated improvements to QoL outcomes and are well-documented as supporting the management of chronic pain conditions (Kabat-Zinn, 1982) as well as anxiety, depression and other symptoms associated with the condition (Hofmann et al., 2010; Niazi & Niazi, 2011). These include reducing the tendency to react emotionally and ruminate on physical sensations and associated thoughts (Goldin et al., 2012), minimizing the unpleasantness and intensity associated with nociceptive pain (Brown & Jones, 2010; Grant & Rainville, 2009), as well as immediate clinical reductions in pain and overall reduction in neuropathic and affective pain at follow-up (Brown & Becerra, 2017).

A commonly used MBI for chronic pain conditions is Mindfulness-Based Stress Reduction (MBSR), a group-based intervention program originally developed by Dr. Kabat-Zinn as a method to assist those adapting to chronic illness (Kabat-Zinn, 1982; Bishop, 2002). The typical MBSR program is approximately eight weeks in length, with each weekly session lasting 2.5 hours, and the addition of one full-day retreat session at the 6th week mark of the course. During the weekly sessions, an assortment of mindfulness skills are explored including deep breathing, body-scan meditation, sitting meditation, hatha yoga, and walking meditation among others (Baer, 2005). The objective is to aid participants in focusing their attention on feelings and sensations throughout the sessions, while redirecting attention as it shifts. As feelings and emotions naturally arise, participants are guided towards observing and noticing these sensations in a nonjudgmental fashion. In addition to weekly group sessions, homework is assigned where participants are expected to conduct daily individual exercises for approximately 45 minutes per day (Baer, 2005).

In the original seminal study of MBSR, the intervention resulted in approximately a 33% reduction in pain and general body problems in more than 50% of chronically ill, including both cancer pain and CNP participants, after the 10 week course (Kabat-Zinn, 1982). However, analyses were not completed separately, thus very little attention has been given to the effect of mindfulness training for CNP specifically. Systematic review and meta-analyses have determined studies rated as either fair or good quality, indicate that mindfulness intervention was associated with significant positive effects on depressive symptoms and quality of life overall, as well as physical functioning and self-reported pain (Hilton et al., 2017; Khoo et al., 2019). In some studies, mindfulness practice has proven to effectively reduce pain (Liu et al., 2018) and to significantly change the perception of pain intensity (Ussher et al., 2014; Morone et al., 2016). Following Kabat-Zinn's initial example, researchers have recognized a correlation amongst

mindfulness interventions and altered brain processes, thereby providing symptom relief by modulating the experience of pain (Nakata, Sakamoto, & Kakigi, 2014).

Distinctive psychological and neural mechanisms are suggested as elements in regulating symptoms of chronic pain (Cherkin et al., 2016). Researchers have proposed a link between emotions and pain as being relevant in understanding the underlying processes associated with mindfulness that contribute to pain reduction. A continued mindfulness practice may ameliorate the psychological correlates of pain (Reiner, Tibi & Lipsitz, 2013), and reduce the subjective experience of pain, feelings of unpleasantness and intensity (Brown & Jones, 2010; Grant & Rainville, 2009). Brain imaging studies have also highlighted that pain may be mediated by areas related to the cognitive reframing of sensory stimuli and nociceptive processing, and affective regulation (contralateral primary somatosensory cortex, anterior cingulate cortex, anterior insula, orbitofrontal cortex and thalamic regions) and that meditation is linked to reduced pain-related activation in these regions (Zeidan et al., 2011, 2012). Variations ensuing from MBSR training have been observed in brain regions related to attention control, emotional regulation and self-awareness (Zeidan et al., 2011, 2016; Tang & Leve., 2016). However, minimal research explores the influence of mindfulness on subjective pain experience ratings for individuals coping with CNP. The vast majority of research to date has focused primarily on broad outcomes of global distress, QoL, and psychological well-being (measures of depression and anxiety) in several chronic pain patient groups (Hilton et al., 2017; Reiner, Tibi & Lipsitz, 2013). As such, some clinical research composed of diverse age demographics, have realized statistically significant reductions in pain severity and a trend towards reducing pain interference after mindfulness intervention.

In one such example, a group of 957 older adults (minimum of 60 years old) with chronic

pain were given a brief mindfulness intervention including weekly body scan meditations. The treatment group showed statistically significant reduced pain intensity after the 6-week program and at the 6-week follow-up assessment (Zhou, Peng, & Xie, 2018), increased mindfulness measures (acting with awareness, and nonreactivity to inner experience), and trended towards reducing pain interference. The mindfulness body scan intervention in this study comprised of a 10-minute weekly group session, and unaccompanied 10 minute daily homework exercises. The obtained results stipulate reduced ratings of pain intensity with a modified short course in mindfulness exercise, indicating that even brief exposure to a mindfulness regimen is capable of commanding a significant effect. This specific contribution to the literature also recommended that body scan meditations are an essential component to mindfulness meditation as they direct focused attention to bodily sensations and the breath simultaneously. Subsequent research has corroborated a similar effect with simply introducing body scan meditations within older patient groups suffering from chronic lower back pain (Morone et al., 2016).

The literature has established that mindfulness is beneficial and exhibits pain-altering properties within several distinct presentations of chronic pain. Research suggests broad outcomes are possible in those experiencing chronic tension-type headaches (Cathcart et al., 2014). Taking part in a modified mindfulness-based therapy program (over 3 weeks) was shown to effectively decrease headache frequency in a group of 42 chronic tension-type headache sufferers, for at least 12 months (Cathcart et al., 2014). Similarly, notable reductions in chronic pain and mood disturbances such as depression, stress, and emotional reactivity were expressed in a case study example examining the effects of mindfulness on CNP following a stroke (Brown & Becerra, 2017). The participant, a 62 year old female, had remarkably been experiencing symptoms of CNP for 18 years prior to the study. She participated in daily mindfulness practice for 12 weeks and

ultimately demonstrated a clinically significant reduction in pain following the program. Overall, an abatement of continuous, neuropathic and affective pain was observed immediately post treatment, although results were mixed for long-term follow up. It is important to consider that these results represent the impact to one individual case who had experienced prolonged CNP for over 18 years without relief, and therapeutic expectancies for improvement cannot be ruled out, thus, caution is required for generalized extrapolation. Although, supportive wide-ranging results have been obtained from a systematic review that noted improvements to pain rating and depressive symptoms alike. The review included 30 randomized controlled trial (RCT) studies examining the application of mindfulness meditation for the treatment of chronic pain without discriminating for type or source of pain and realized overall low-quality evidence that meditation practice was associated with decreased pain intensity, depression and an improvement to overall QoL (Hilton et al., 2017). Adverse events were noted to be rare, however the majority of studies did not capture this data. The authors advised that more rigorous and well-designed RCT studies are required given that common limitations across studies included small sample sizes, poor methods reporting, inadequate statistical power, and neglecting to report their power calculations.

Comparably, the use of mindfulness meditation coupled with cognitive therapy resulted in significant reductions in average daily pain in a group with painful diabetic peripheral neuropathy (PDPN) (Hussain & Said, 2019). Diabetic neuropathy is one of the most commonly associated microvascular complications arising from nerve damage related to diabetes and includes symptoms typical of CNP such as numbness, tingling and pain, among others such as continence issues (Hussain & Said, 2019; Galer, Gianas, & Jensen, 2000). One study comparing mindfulness to progressive relaxation noted differences between treatment types, however the most significant results were observed when compared to the control group. Some participants (n=36) completed a

mindfulness based cognitive therapy program while a second group (n=37) participated in progressive muscle relaxation therapy. Meanwhile the control group (n=32) participants were simply instructed to sit quietly and relax for 20 minutes. Both the mindfulness and the progressive relaxation groups reduced their daily average pain compared to baseline, and the mindfulness group expressed the most significant reduction in daily pain when compared to the control group. The authors proposed that using cognitive reappraisal to separate sensation of pain from the internal alarm reaction was an essential factor contributing to the reduction in suffering observed in the mindfulness group (Hussain & Said, 2019). This was mediated by the ability to alter their attention from proprioception to detached observation, incited by mindfulness meditation. More recently, researchers have validated the mediating properties of mindfulness explicitly with the MBSR program on painful diabetic peripheral neuropathy (PDPN) with 62 participants, noting that such training garnered improved pain severity, pain interference, and the physical variable within the health-related quality of life (HRQoL) questionnaire after 3 months (Rozworska et al., 2020). Similarly, participation in a MBSR program, reduced pain catastrophizing, depression and stress, and also improved QoL variables with continued improvement 12 weeks post mindfulness training in a group (n=30) experiencing PDPN when compared to controls (n=32) (Nathan et al., 2017). The authors attempted to increase the clinical relevance and added value of MBSR by optimizing pharmacotherapy treatment for up to 5 months prior to the MBSR program, which was achieved when compared to usual care and resulted in improved function and reduced pain.

When considered in conjunction, these examples illuminate the capacity mindfulness treatment may have on improving the perception of pain intensity, severity, and interference, contributing factors to overall QoL. The trend towards abating painful symptoms is similarly promising for CNP groups given the above-stated studies noted reductions in painful symptoms

within varying chronic pain condition groups. Although limited, recent studies have suggested that mindfulness may have an impact on CNP intensity (Brown & Becerra, 2017). Theoretically, a proposed ideology is that continued mindfulness practice would enable a spontaneous uncoupling of the sensory mechanism of pain from cognitive and emotional mechanisms, leading to reduced sensation of pain (Reiner, Tibi & Lipsitz, 2013). In their research, Reiner et al. recognized two potential theories focused on how MBIs may have an impact on pain intensity. The two facets they proposed are increased acceptance of pain, and detachment from the cognitive/emotional aspects of pain. Reductions in pain intensity may be mediated by increasing openness and acceptance to the existence of pain, which inspires less avoidance and increased valuable action when perceiving pain. Alternatively, they also posited that mindfulness intervention may enable a detachment from cognitive and emotional aspects of pain, which in turn reduces the perception of pain intensity, improves the ability to self-regulate and ultimately results in improved quality of life (Reiner, Tibi & Lipsitz, 2013). Although mindfulness-based stress reduction has become more widely accepted as treatment of chronic pain conditions, it is important to juxtapose traditional means of therapy and treatment such as Cognitive Behavioural Therapy (CBT) with mindfulness as an example.

How does MBSR compare to CBT?

As discussed, mindfulness intervention is now more readily used as a promising intervention for chronic pain groups. However, the gold standard treatment protocol typically includes the addition of psychological therapy using Cognitive Behavioural Therapy (CBT). The underlying premise of CBT maintains that maladaptive cognitions is what contributes and supports emotional distress and behavioural issues (Beck, 1970). These maladaptive cognitions include beliefs about the self, the world, and the future and become automatic thought patterns that arise within a set of specific circumstances (Hofmann et al., 2012). By changing the maladaptive

cognitions, the pillar of CBT supports that these changes will extend to emotional distress, inaccurate beliefs and disrupted behavioural patterns (Beck et al., 1979; Driessen & Hollon, 2010). Therefore the goal of CBT is to identify and replace maladaptive patient cognitions, emotions and behaviours with more adaptive ones (Gatchel & Rollings, 2012). The emphasis of CBT is placed on the patients' attitudes, beliefs and expectations, and by using problem solving and relaxation to assist patients' ability to shift from being passive, reactive and helpless to being active and resourceful (Turk, Meichenbaum, & Genest, 1983). In so doing, patients become active participants in this process and are taught to challenge and re-conceptualize thoughts and patterns, and to modify feelings of hopelessness, helplessness and passivity. It is consistently used in a wide range of psychological disorders such as personality disorders, anxiety and depression, addiction and substance abuse, stress management, as well as chronic pain groups; the evidence-base of its effectiveness is very strong (Hofmann et al., 2012). With respect to chronic pain, CBT treatment has been tailored to aspects that accompany CNP and are addressed as part of treatment, such as pain catastrophizing, and avoidance of activity (fear-avoidance). The ultimate objective is to assist patients in gaining mastery over their pain, and improve overall QoL by improving their mood, level of activity, and reducing disability (Turk et al., 2010).

Morley, Eccleston, and Williams' (1999) meta-analysis, found that CBT catalyzed improvements in multiple dimensions of chronic pain (coping, pain behavior, social functioning). Additionally, McCracken and Turk's literature review detected predictors of treatment outcomes for CBT and associated negative emotional responses to pain, perceptions of disability, and orientation toward self-management as favourable predictors for positive outcomes. This notion supports the matching of treatment protocols to patient characteristics in order to best attend to patients' needs by offering the most appropriate and effective management strategies (McCracken

& Turk, 2002). When incorporated as part of an interdisciplinary approach, CBT has emerged as the psychosocial treatment of choice for chronic pain and is the most stable, widely used and well-studied form of psychotherapy (Gatchel et al., 2014).

Although it is one of the most studied and supported means of psychotherapy, limited research has compared CBT treatment to MBSR directly. However, a recent systematic network meta-analysis of RCT studies evaluating the effectiveness of CBT treatment compared to MBSR in improving physical functioning and reducing pain intensity in patients with chronic pain, unearthed one such example (Khoo et al., 2019). The review included 13 additional studies comparing CBT to control groups, and 7 studies investigating MBSR compared to controls, where outcome measures of interest included physical functioning, pain intensity, emotional functioning, and patient's global impression of change (PGIC). Results comparing CBT to MBSR indicated that although both treatment types demonstrated benefits to physical functioning, pain intensity and depressive symptoms respectively, no significant differences were apparent on these measures when contrasting the two types of treatment. Additionally, the singular study with direct comparison had not found any significant differences in functional limitations and self-reported pain between the two treatment options, however noted greater improvements in pain intensity and functional limitations overall (Cherkin et al., 2016). Although, the CBT group demonstrated marginal improvements to depressive symptoms over the MBSR treatment (Khoo et al., 2019). Understanding a notable gap in the literature exists, a recent study compared a variation of mindful treatment, Mindful Self-Compassion (MSC), to CBT treatment directly investigating clinical outcomes in patients with chronic pain. Of the total 123 patients assigned to either the MSC (n=62) or CBT (n=61) groups, results inferred that the novel intervention of self-compassion improved symptoms of anxiety, pain interference and pain acceptance even more so than CBT

(Torrijos-Zarcera et al., 2021). Notwithstanding, simultaneously contrasting treatment types remains seriously unexplored, and as such it is not feasible to adequately assess which intervention may be superior or most beneficial for CNP at this time. This further emphasizes the clinical perspective to date that a multidisciplinary approach to pain management is essential as a successful outcome depends on the individual's level of responsiveness as some treatments may offer superior improvement and results.

It is promising to observe marginal to significant improvements in abating painful symptoms, reducing pain severity and lessening the impact of pain interference along QoL variables within chronic pain and neuropathic pain groups. Although research examining CNP may be limited, the examples of chronic pain groups within the literature have associated mindfulness use to the mediation of painful symptoms associated with chronic pain. The goal of this thesis is to examine the underlying neural mechanisms supporting MBSR, and if such an intervention may ameliorate painful symptoms associated with CNP as a consequence to breast cancer treatment. This merits an investigation of MBSR treatment in breast cancer patients and survivors.

MBSR in Breast Cancer

Mindfulness interventions have shown effectiveness in the treatment of the physical and psychological distress that may accompany breast cancer. Many women who receive a breast cancer diagnosis report this as a particularly devastating emotional experience (Stark & House, 2000). Such a diagnosis, along with the demands of treatment that follow, leave a significant emotional impact adversely affecting QoL well beyond diagnosis and treatment (Longman, Braden & Mishel, 1999). In addition to physical pain, it may also increase psychological distress symptoms such as stress, anxiety, uncertainty, mood related symptoms, and fear of cancer

recurrence (Conley, Bishop, & Anderson, 2016; Epplein et al., 2011) as well as dysregulate immune function (Witek-Janusek et al., 2008).

Empirical evidence stipulates that MBSR is effective in reducing physical symptoms such as pain and fatigue, and improving overall QoL (Lengacher et al., 2016; Henderson et al., 2012). It has also proven especially beneficial to women with breast cancer who continue to harbor psychological symptoms after diagnosis, such as emotional distress, by reducing symptoms of stress and low mood (Speca et al., 2000). In one study, mindful practice was associated with reduced physical pain severity in women with breast cancer, in addition to reducing psychological variables of pain such as anxiety and depression, increasing QoL overall (Lengacher et al., 2016).

A systematic review on the matter investigated the mechanism supporting the ability of mindfulness to modify both physical and psychological symptoms may be due to its influence on the perception of pain (Ngamkham, Holden & Smith, 2019). The evidence presaged that generally speaking, patients with cancer believe it is the obligation of the physician to determine how to alleviate cancer pain (Czerw et al., 2017), and how the patient appraises the perception and meaning of pain influences pain experiences. The six studies included in the systematic review had compatible yet distinct mindfulness training programs (MBSR, Mindfulness-Based Cognitive Therapy (MBCT) & Mindfulness Awareness Practice (MAP)) with varying lengths of administration and yet consistently determined that the practice facilitated a shift in focus from pain, increasing pain tolerance. One of the highlighted studies, an RCT evaluating the efficacy of an adapted MBSR program in improving multiple QoL variables (physical as well as psychological symptoms), had indicated improvements to symptoms of anxiety, fear of recurrence, fatigue severity and interference (Lengacher et al., 2016). Meanwhile, a 6–week MBSR intervention consisting of 84 females primarily focused on self-regulation of arousal to stressful

circumstances and symptoms, had comparably expressed improved psychosocial and physical functioning for breast cancer patients. The results validated enhanced mood and indicators of physical and emotional QoL, along with decreased symptoms of depression, anxiety, cognitive deficits, fear of reoccurrence and fatigue (Lengacher et al., 2009, 2016; Conley, Bishop, & Anderson, 2016). The authors concluded on an underlying theme whereby mindfulness meditation may be an effective tool for altering the perception of pain associated with cancer (breast cancer and colon cancer) given its ability to moderate the emotional appraisal of pain (Brown & Jones, 2010). Cognitive reappraisal is conceivably accomplished by altering where the patient's attention lies, focusing less on their pain, and attending more towards tolerance and acceptance (Brown & Jones, 2010), which are primary objectives of mindfulness intervention. A challenging feat nonetheless, as cancer pain and treatment are known to impair cognitive functioning such as attention and memory (Attal et al., 2014). The practice of mindfulness has been correlated to increased activity in brain regions implicated in the regulation of nociceptive pain processes as well as with cognitive reframing and attentional control (Zeidan et al., 2011; Tang et al., 2012a). Additionally, an important and contributing factor to cognitive function and performance such as sustained attention and memory consolidation, is that of sleep quality and sleep deprivation (Alhola & Polo-Kantola, 2007; Maquet, 2001; Stickhold, 2005). It has been estimated that approximately 30-60 % of patients with cancer experience insomnia over an 18-month period following cancer surgery with an even greater prevalence in patients with breast cancer (42-69%) (Savard et al., 2011). Although this represents a significant proportion of cancer patients, conversations are not systematically taking place with health care practitioners given predominant barriers, and when they are, the most commonly offered solution is typically pharmaceutical (Savard, et al., 2022). Savard et al., have suggested a stepped care approach to CBT for insomnia

(CBT-I) could be a feasible means of addressing this issue, although some barriers to offering this treatment as part of routine care remain (Savard et al., 2021).

Concurrently, the literature also extends the understanding of how sleep quality might have an impact on the sustained level of mindfulness with BCS. One such study invoked mindfulness as having the most significant direct influence on fatigue in BCS, noting that it is an important contributing factor in effectively reducing sleep disturbances (Ikeuchi et al., 2020). The authors compared self-report questionnaire responses with clinical records from 249 participants and reported that fatigue maintains a strong direct relationship with mindfulness in BCS, and may be indirectly impacted by pain, anxiety, depression, loneliness and sleep quality. This is a significant finding, as it has been determined that fatigue is often highly correlated with QoL variables such as anxiety, depression and pain (Thornton, Andersen & Blakely, 2010; Ho et al., 2015) and the majority of research on sleep reports a positive correlation between pain intensity and degree of sleep disturbance (Morin, Gibson, & Wade 1998). This is noteworthy as frontal brain areas are vulnerable to insufficient sleep, and both attention and working memory are linked to the proper functioning of frontal lobes (Harrison, Horne & Rothwell, 2000; Thomas et al., 2000; Naghavi & Nyberg, 2005). Given that attention may be impaired with lack of quality sleep, cognitive reappraisals of pain may not be as successful thus perpetuating the pain cycle. Even so, mindfulness appears to have restorative features in helping to improve sleep quality for those with chronic insomnia (Ong et al., 2014).

A potential benefit of MBSR training with breast cancer patients was undertaken by Witek-Janusek (2008) where participation in an 8-week MBSR program decreased cortisol levels and restored immune function in 38 women diagnosed with early stage breast cancer. Although the ability to draw conclusion is limited given the study design, women who enrolled in the MBSR

program during their cancer treatment reported more improvement in their overall QoL, exhibited some restored immune functionality, and indicated improvements to comprehensive coping effectiveness (Witek-Janusek et al., 2008). The non-randomized controlled design was specifically interested in how MBSR may impact immune function in women with early-stage breast cancer who had not received chemotherapy treatment. Women in the MBSR group (n=38) had decreased plasma cortisol levels and restoration of Natural Kill Cell Activity (NKCA), a measure of immune function, when compared to a non-treatment group (n=28) after 8-weeks of mindfulness training. They posited that a reduction in circulating cortisol levels may have contributed to the immune changes that were observed. This study builds upon earlier results from Carlson et al., (2004), where participation in an 8-week MBSR program had decreased physical symptoms associated with stress in breast cancer patients, however also noted fluctuations in cortisol levels. Uniquely, the authors observed that hormone levels fluctuated as a result of the training and could possibly contribute to beneficial changes to the hypothalamic-pituitary-adrenal (HPA) axis functioning, a system known for mediating and regulating the effects of stress and immune response. They also re-iterated additional support for significant improvements to sleep quality while undergoing treatment, a crucial variable relating to QoL as noted above (Carlson et al., 2004).

Living with symptoms of chronic pain is a significant concern for women who have already undergone painful and debilitating breast cancer treatment. This experience has altered patients' sensitization to pain, and increased the likelihood of developing psychological distress impacting aspects of general health overall and quality of daily living. Mindfulness has sustained improvements to both physical and psychological well-being rendering the practice a legitimate potential solution to alleviate symptoms associated with CNP that accompany breast cancer treatment. However, in addition to understanding its mechanisms, furnishing empirical evidence is

crucial in validating its use as a supplement to pharmacotherapy and alternative treatments. Neuroimaging provides such a venue for empirical study.

Neuroimaging and Neuropathic Pain

Brain imaging tools have been used in clinical diagnosis and as empirical support in research depicting structural as well as functional brain characteristics. Magnetic Resonance Imaging (MRI), is an imaging method that enables an in-depth examination of brain structure and function. Using several modalities of MRI (including functional MRI (fMRI), resting state fMRI (rsfMRI) and diffusion tensor imaging (DTI)), the primary objective of this thesis was to explore the impact of MBSR on CNP in BCS by capturing functional and structural brain changes post-treatment in an effort to elucidate the neural mechanisms substantiating these modifications.

functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is used to quantify changes in brain activity by detecting the patterns and movement of oxygenated blood in response to neural activation (Toma & Nakai, 2002). This effect is measured using the blood oxygen level dependent (BOLD) signal, which is altered in response to neuronal activation. As a brain region is activated, oxygen consumption and blood flow increase arising from the spontaneous demand in energy (Barinaga, 1997). While neurons are static and inactive, a deoxygenation process occurs where oxygenated blood is converted within the capillaries of the brain at a continuous rate. This process invokes differing magnetic properties between the levels of oxygenated and deoxygenated blood, the first being diamagnetic and the latter paramagnetic. Once neurons are activated, an influx of oxygen floods the region, tipping the balance of oxygenated versus deoxygenated blood. It is this change in magnetic signal, providing good spatial and temporal resolution (Matthews & Jezzard, 2004), that ultimately is measured using fMRI (Huettel, Song, & McCarthy, 2008). This signal

allows for the identification of activity in specific brain regions related to behaviours when coupled with a cognitive task. Consequently, it is the process used for generating a neural map of brain activation during a cognitive task.

The experience of "allodynia", the sensation of pain in response to exposure to a typically non-noxious stimuli, has been studied using fMRI. Allodynia is essentially the elicitation of a sensation of pain with a stimulus, one that is not typically pain-related (Moisset & Bouhassira, 2007), and is rendered by applying a thermal stimulus (hot or cold), or a mechanical stimulus (brush) to the area of the body that experiences pain (Peyron et al., 2004; Schweinhardt et al., 2006). Participants with known allodynia had their pain evoked by the application of a thermal of mechanical stimulus, while undergoing fMRI study. Using the output BOLD signal, fMRI studies have delineated multiple processes associated with pain intensity while receiving noxious stimuli (allodynia), and has suggested that subjective pain experiences may be mediated by areas of the brain (ACC, anterior insula, somatosensory cortex, orbitofrontal cortex and thalamic regions) activated for affective regulation and cognitive reframing of sensory stimulation (Zeidan et al., 2011; Nakata, Sakamoto, & Kakigi, 2014).

Research in fMRI has been beneficial in demonstrating that pain is processed via a fluid system comprised of layered interacting networks and is biased by individual subjective experience. The processing of pain has been described as taking place in a series of interconnected neural regions known as the pain matrix (Melzack, 1999). Based on the review conducted by Moisset and Bouhassira (2007), an outlined pattern of activation within the described matrix in participants experiencing neuropathic pain was made apparent using fMRI in response to evoked allodynia. The pain matrix has generally included the activation of lateral pain systems, including the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and insular cortices.

However, it also includes the activation of the medial representational pain system such as the anterior cingulate cortex (ACC), insula, and the medial thalamus. Additionally, other brain regions identified as activated during the processing of pain include the motor cortex, prefrontal cortex (PFC), basal ganglia and brainstem (Chiesa & Serreti, 2010).

The matrix theory of pain has been well established, and reflects how the actual experience of pain is rather complex and multidimensional, being influenced by cognitive, emotional and physical factors (Trachsel, Munakomi, & Cascella, 2022). Brain regions associated with pain are often described within various subsystems known as the sensory-discriminative subdivision (processes the sensory aspects of pain), the affective-motivation subdivision (processes the affective qualities of emotional preparedness of pain), and finally a cognitive-evaluative system (Peyron, Laurent & Garcia-Larrea, 2000; Kupers & Kehlet, 2006). The sensory-discriminative aspects of pain represent the lateral system while the affective-emotional system is related to the medial system, and the cognitive-evaluative mainly represented in the prefrontal cortices (Petrovic et al., 2000; Peyron et al., 1998).

Moreover, as part of the brain's processing of pain, the nociceptive matrix has been identified as a necessary entryway in provoking physiological pain. This matrix contains spinothalamic projections, and includes the posterior thalamus (ventral posterior, centrolateral, mediodorsal and posterior nuclei groups) (Garcia-Larrea & Peyron, 2013). The nociceptive experience of pain is capable of persisting with or without conscious awareness as it may be activated during sleep, coma and vegetative state (Batsuji et al., 2012; Kassubek et al., 2003). Although identified as an entry point, it is not exclusive to the pain experience as neuropathic pain is associated with multiple layers of integrated networks, as highlighted above. A transition takes place from the nociceptive matrix to conscious awareness of pain leading to a second-order matrix

that includes the posterior parietal, prefrontal and anterior insular areas. The joint activation of these two networks is required for the conscious perception of pain (Garcia-Larrea & Peyron, 2013). It has been found that the intensity of the nociceptive stimulus affects the magnitude of the brain's response in the regions identified as part of the pain matrix (Baliki & Apkarian, 2015).

Research using fMRI has further contributed to understanding the neural mechanisms of mindfulness. A systematic review conducted by Chiesa and Serreti (2010) illuminated a consistent pattern of neural activation related to mindfulness in long-term meditation practitioners. Their findings proposed that mindfulness meditation practice overall increased activation of the PFC, and the ACC, and enhanced thickness to cerebral areas related to attention (PFC, anterior insula) in long-term meditators. The review included 52 RCT studies that focused on neurobiological data and clinical outcomes on persons with mental health and/or clinical disorders. They concluded that practitioners of mindfulness meditation are more engaged in an equilibrated mind-body interaction, which may facilitate reduced emotional reactivity to negative emotions or physical pain. Additionally, long-term meditation practice may offer protection from cognitive decline by inhibiting the decline of grey matter volume, as well as protection against decreases to attentional performance that come with age (Chiesa & Serreti, 2010).

The practice of mindfulness has been associated with increased neural activation in the anterior insular and cingulate cortices, brain regions involved with cognitive appraisal (Opialla et al., 2015) and balancing of nociceptive pain processes (Coghill et al., 1999), as well as the orbitofrontal cortex which is involved with the cognitive reframing of sensory experiences (Zeidan et al., 2011; Nakata, Sakamoto, & Kakigi, 2014). Tang and Leve (2016) have further elucidated more specifically, the neural mechanisms supporting aspects of the complex mental state of mindfulness. Their review included several brain regions that consistently demonstrated more

efficient activation as a result of mindfulness intervention related to attention control (ACC, PFC, and striatum) (Peterson & Posner, 2012), emotional regulation (PFC and limbic brain regions) (Phelps et al., 2004) and self-awareness (insula, MPFC, PCC and the precuneus) (Tang & Leve, 2016; Tang, Holzel & Posner, 2015). The ACC and the PFC are brain mechanisms that are highly implicated and associated with controlling attention (Friedman & Robbins, 2022; Menon & D'Esposito, 2022) while the limbic related areas (insula, hippocampus, corpus callosum) are more implicated with emotional regulation (Rajmohan & Mohandas, 2007; Tang et al., 2012a; Tang & Leve, 2016), further validating the relationship mindfulness has with attentional control and emotional regulation.

Mindfulness intervention (MBSR) has also been examined using fMRI in clinical samples with those diagnosed with social anxiety disorder (SAD) and generalized anxiety disorder (GAD). The results have demonstrated less brain activity was present in areas related to self-referential processing, visual attention, and language processing (dorsomedial prefrontal cortex (dmPFC) (Han et al., 2010), medial prefrontal cortex (mPFC) (Paneri & Gregoriou, 2017) and the left inferior frontal gyrus) (Ishkhanyan et al., 2020) as well as reductions on scores of social anxiety, depression, rumination, and state anxiety in those affected by SAD following intervention (Goldin & Gross, 2010). For study participants exhibiting symptoms of GAD, the MBSR group when compared to a stress management education program, exhibited a stronger functional connectivity between the amygdala and the bilateral dorsolateral and bilateral dmPFC and the dorsal ACC following MBSR training (Holzel et al., 2013). This was the first study of its kind to observe a modified connectivity between the amygdala and prefrontal regions of the brain following MBSR training. The authors posited that the positive connectivity may be attributed to an engagement in active monitoring and control of arousal. These patterns of brain activity imply that mindfulness

training is associated with reduced activation as a response to sad emotional information and could potentially enhance emotional self-regulation (Farb et al., 2010).

This line of research is beginning to conceptualize that significant changes in neural pattern activation are present when practicing mindfulness meditation in several interconnected brain regions. Mindfulness meditation requires multiple aspects of mental function and the integration of complex interactive brain networks. As a result of the emerging literature, core components of meditation practice have been identified as attention control, emotional regulation and self-awareness. Given the results thus far, there is evidence implicating mindfulness training as impetus for changes in neuronal activation. However, limitations do exist, and further investigation is essential to demonstrate the potential for mindfulness intervention within this particular clinical sample (BCS). This thesis, a sub-study of a larger RCT, relied on task specific, as well as resting state brain activity fMRI techniques, to determine how MBSR training may impact the underlying pattern of brain activation in women who continue to experience CNP post breast cancer treatment.

Emotional Stroop Task (EST)

fMRI makes it possible to assess neural activity during attention and emotional reactivity to an emotional stroop task (EST). In the EST, participants are required to respond to word colours while attempting to ignore the context of the presented words, whether neutral or emotional. The EST is a measure of selective attention to emotional stimuli in the face of cognitive interference. It enables the measurement of cognitive control in the face of emotionally-valenced words (Williams, Matthews & MacLeod, 1996). Essentially, this task is used to assess neural activation when attention is engaged during an elicited emotional task. It is capturing participants' ability to inhibit the distraction of emotional information thus, measuring cognitive control in the face of

interference by capturing and comparing response time latency between emotional and neutral words. By measuring participants' ability to inhibit the distraction of emotional information (presented words), the task aligns with one of the primary goals of the MBSR program, emotional and cognitive regulation (Baer, 2005). The demands on executive functioning for this task, such as cognitive control and emotional inhibition, are high (Hart et al., 2010; Song et al., 2017). Researchers have found that the PFC plays a significant role in recruiting cognitive control during the EST. Particularly, the DLPFC (including the middle frontal and inferior frontal gyri) is significantly activated while attempting to maintain attention (Compton et al., 2003; Song & Hakoda, 2015), in addition to the dorsal part of the ACC (Ruff et al., 2001). The ACC in particular has been implicated with a form of attention required to regulate both cognitive and emotional processing (Bush et al., 2000) and is closely connected to the mPFC. According to a meta-analysis conducted by Phan et al. (2002) investigating emotional activation in PET and fMRI, it was determined that the mPFC had a general role in emotional processing as it was most commonly activated in emotional tasks across studies included in the review. It appears the mPFC is activated with the cognitive aspects associated with emotion, attention and appraisal (Drevets & Raichle, 1998) and top-down cognitive control may help modulate emotional processing (Ochsner et al., 2009). Consequently, these specific brain regions that are recognized as crucial components in the attention and regulation of emotional information, overlap regions identified as part of the pain matrix noted earlier (Iannetti & Mouraux, 2010; Garcia-Larrea & Peyron, 2013).

The EST task has been validated and systematically used within chronic pain populations to determine the extent to which patients attend to pain-related information (Crombez et al., 2000; Andersson, & Haldrup, 2003; Roelofs et al., 2002; Compton et al., 2003). It is widely used within various clinical and non-clinical populations as it is a non-invasive objective measure of cognitive

interference. It is also an advantageous measure since the emotional words used may be specifically selected and are matched to assess the distinct pathology (for example; anxiety, depression, obsessive-compulsive disorder, and post-traumatic stress disorder) (Ben-Haim et al., 2016). There is evidence that an attentional bias exists for negative and pain-related words causing cognitive interference given the inability to simultaneously process a second stimulus (Derbyshire, Vogt, & Jones, 1998). Additionally, cognitive interference is more pronounced when pain-related information (words) are grouped together in a block design (Compton et al., 2003; Ben-Haim et al., 2016). Patients in a clinical pain population demonstrated increased task-evoked responses in brain regions associated with attention, emotional processing, motor planning and performance, while exhibiting slower reaction times on the EST task (Weissman-Fogel et al., 2011). The results from this particular fMRI study, suggested that slower reaction time on the EST task, was related to unsynchronized recruitment of attentional/cognitive processing areas. Coping with the severity of chronic pain demands attention, and patients demonstrated a decoupling of activation between the prefrontal and cingulate cortex, as well as the amygdala and cingulate cortex (Weissman-Fogel et al., 2011).

Resting State fMRI (rsfMRI)

Resting-state fMRI (rsfMRI), is a distinct technique used to detect differences in functional connectivity in brain regions while at rest and in the absence of an explicit task or during mind-wandering (Menon & Uddin, 2010). Researchers have recognized several brain networks activated during rest such as the default mode network (DMN), salience network (SN) and the central executive network (CEN) (Parkinson et al., 2019). The DMN involves the posterior cingulate cortex (PCC), mPFC, precuneus, and the ventral anterior cingulate cortex (vACC) (Greicius, 2003; Andrews-Hanna et al., 2010) as well as the lateral anterior temporal and the posterior parietal lobe,

and sometimes the hippocampus (Buckner et al., 2008). The DMN accounts for increased low frequency activation during mind-wandering and self-reflection on past or future events (Zhou & Lei, 2018) while the SN (insula and the anterior cingulate gyrus) orients attention internally or externally based on sensory and limbic inputs while concurrently mediating between networks (Menon & Uddin, 2010). The CEN (involving dorsolateral prefrontal cortex (DLPFC), ACC and dmPFC is most implicated with external directed thinking, processing of information and executive functioning tasks such as attention, working memory, language and processing of visual information (Parkinson et al., 2019; Bressler & Menon, 2010).

Using resting state neuroimaging, studies have linked meditation with reduced activation in the DMN in experienced meditators (Brewer et al., 2011) and mind-wandering with increased activation patterns (Mason et al., 2007). As a result of mindfulness training, specific brain regions linked to the DMN, including the angular gyrus middle temporal regions, and precuneus, have shown deactivation (Tomasino et al., 2013). These brain regions associated with the DMN are usually engaged during mind-wandering or resting state (Menon & Uddin, 2010), however the deactivation of the DMN is consistent with the objectives of meditation in maintaining concentration on the present moment. These findings have been replicated within the literature and have concluded that meditation results in a reduction in default mode processing at rest, and even relative to an active task in experienced meditators (Garrison et al., 2015).

In further resting state analyses, a reduction in pain was expressed in a pain-afflicted group post mindfulness training (Su et al., 2016) and increased connectivity was observed in areas highly related to attention, the anterior insular cortex (AIC) and the dorsal anterior mid-cingulate cortex (daMCC). Some researchers have postulated that an increased AIC - daMCC connection could be the impetus for the participants' altered perception of pain since their co-activation is linked to

attention, cognitive control and emotional regulation processes (Sterzer & Kleinschmidt, 2010). Additionally, attentional processes are engaged during mindful observation as a result of the increased activation of the dmPFC (Frewen et al., 2010). These increased activation patterns support the impact of meditation on the internal emotional self-reflection processes that recruit the AIC, daMCC, and also the dmPFC, a component of the CEN.

Diffusion Tensor Imaging (DTI)

Diffusion Tensor Imaging (DTI), a structural MRI modality, has also been used to elucidate the neural mechanisms supportive of MBSR and thus may be beneficial in the study of CNP and brain structure adaptation. More specifically, DTI is a neuroimaging technique where structural white matter integrity and anatomical connectivity patterns are observed by capturing molecular changes of water protons (Dong et al., 2014; Kupers & Kehlet, 2006). DTI is used to characterize magnitude, anisotropy and orientation of water molecules. Two measures of structural integrity that are obtained with DTI are mean diffusivity (MD) and fractional anisotropy (FA) (Gustin et al., 2011; Bennett et al., 2010). The FA values are used to analyze white matter tracts by describing the degree of directional diffusivity or "anisotropy" of water. Subsequently, a measure of whole-brain white matter integrity (whole-brain FA) can be calculated by obtaining global water diffusion over white matter tracts (Alexander et al., 2007). Scores of FA range from 0-1 with 1 being the healthiest white matter value possible.

The average degree of water diffusion in a brain region, the mean diffusivity (MD), provides a measure of tissue structure and cellular integrity (Dong et al., 2014). A reduction in MD indicates less water movement in a particular region while an increase suggests greater water movement. When less water movement is present, this signifies increased tissue barriers, potentially attributable to neuronal sprouting and cellular proliferation. Meanwhile, greater water

movement is facilitated by decreased tissue barriers, whether caused by cell death, demyelination or axonal loss (Gustin et al., 2010; Iannucci et al., 2001).

Gustin et al., utilized DTI to determine whether neuropathic pain following spinal cord injury was associated with changes in brain anatomy and connectivity (Gustin et al., 2010). They offered that undergoing neuropathic pain resulted in changes in MD to a number of brain regions connected to pain processing; DLPFC, left anterior insular cortex, premotor cortex, ventroposterior (VP) thalamus and the left amygdala. These brain changes were significantly correlated with the intensity of pain symptoms reported by participants, demonstrating a remarkable relationship between the reported areas and pain processing. Additionally, investigations evaluating DTI in peripheral nerve fiber injury have demonstrated significant changes to FA values (Boyer et al., 2015) and that FA was significantly reduced following lumber spine injury in compressed nerve roots, which correlated with pain and depression scores (Hughes et al., 2019). Research with DTI is gaining momentum and is delineating underlying connectivity of pivotal brain regions resulting from painful injury. Given this potential, the inclusion of DTI analysis in this study will support the measurement of anatomical integrity and message transmission, and how these may correlate to experience of pain and QoL metrics.

Experimental Design

Given the high rates of CNP post breast cancer treatment, as well as the modest benefits achieved from pharmacotherapy, complimentary treatments are needed. However, empirical evidence is imperative prior to them being readily accepted. Given that the experience of pain is very subjective, the present study offered an objective assessment of pain perception via a comprehensive neuroimaging examination of the impact MBSR might have in BCS with CNP. Although neural mechanisms underlying mindfulness have been well researched over the last

decade, it is consequential to examine how the use of mindfulness may impact psychological health and well-being in a variety of clinical populations with unique symptom manifestations, CNP in this instance.

The findings of this study may illuminate the underlying neural correlates that coincide with pain management for persons living with CNP especially so for BCS who have already suffered the stressful experience involved with a cancer diagnosis and cancer-related treatment. This undertaking will further expand the limited literature available relating to the efficacy of MBSR as an adjunctive non-pharmacological treatment of CNP in breast cancer patients. The objective is to provide further foundation towards a multidisciplinary approach to pain management for breast cancer patients, as traditional pharmacotherapy treatment alone is costly, has limited efficacy, and includes potentially severe consequences while attempting to abate painful daily experiences and improve QoL overall.

The present study sample was taken from a larger RCT study that was designed as a repeated measures between-group design. This design allowed for control of several factors that would have incited increased variability between participants, as we were able to assess directly how participants responded to treatment over time. Participants for the main study were recruited from The Ottawa Hospital as part of a research undertaking investigating the effects of an interdisciplinary program (including MBSR) on QoL variables in BCS with CNP (registered on clincialtrials.gov NC02758197). The primary study assessed pain-related disability (assessed via the Brief Pain Inventory-Screening Form (BPI-SF)) as the primary outcome measure, with additional measures for QoL as secondary outcome measures including; Neuropathic Pain Symptom Inventory (NPSI), Profile of Mood States Scale (POMS-2A), Patient Global Impression of Change Scale (PGIC), Perceived Stress Scale (PSS), Pain Catastrophizing Scale (PCS), and

biomarkers for stress (hair cortisol), and telomere length. Upon initial consent and confirmation of presence of CNP, participants received optimized medical treatment by a chronic pain specialist at The Ottawa Hospital Pain Clinic. Study coordinators completed group randomization in four batches of 27 patients each (16 patients assigned to MBSR; 11 patients assigned to the wait-list control arm). Group allocations were computer generated by a statistician at the Ottawa Methods Centre who was not associated with the study; patients were randomly allocated within strata to wait-list or MBSR using the method of optimal batch-wise minimization (Faes et al., 2012). Frequencies and proportions were calculated for categorical variables including cancer and pain characteristics and were incorporated into the stratification factors intended for randomized treatment allocation. Allocations were balanced for pain severity categorized as <6 (moderate pain) and 7-10 (severe pain) on the BPI-SF (Tan et al., 2004, Dworkin et al., 2010), as well as type of pain (40% chemotherapy-induced, 60% postmastectomy induced). Group allotment was concealed from treating physicians, investigators, research assistants, neuroimaging staff and data analysts and thus remained blind to the randomization of groups for the duration of the study. No significant between group (MBSR intervention and wait-list control) differences were identified at baseline. Following pharmaceutical treatment stabilization, baseline data was collected which included completion of questionnaires and biomarker sampling followed by the fMRI/MRI segment used for this thesis. This included women who volunteered to take part in the neuroimaging component, and who were MRI compatible (no metal implants, pacemakers, recent surgery, metal dental work, or claustrophobia). All assessments were repeated two weeks following the completion of the 8-week MBSR program or an equal amount of time for the wait-list controls.

Hypotheses

fMRI during EST

Research conducted to date suggests the experience of CNP would increase brain activation in brain areas related to pain and emotional processing, such as the anterior cingulate, insula, mPFC, DLPFC, OFC, daMCC, and the AIC (Compton et al., 2003). Additionally, the literature indicates that mindfulness has been associated with the deactivation of complimentary brain regions associated with emotional regulation and processing, and memory (PFC, insula, somatosensory cortex, precuneus, cingulate gyrus) (Zeidan et al., 2012). By using fMRI, we are able to assess how the mindfulness intervention would be associated with significant changes in neural activation for areas associated with pain and emotional processing (PFC, amygdala, somatosensory cortex and the anterior cingulate). Thus, we expected to see decreased activation in these brain regions for the MBSR group following the intervention however, we did not anticipate these changes would be apparent in the wait-list control group.

1) Given that altering attention and emotional reactivity are cornerstones to MBSR, it was hypothesized for the current study, that the introduction of the MBSR program would reduce participants' emotional reactivity to pain related stimuli (words projected on a screen during the EST, further described below), whereas no change to emotional reactivity was expected in the control group.

rsfMRI

Following the intervention, it was expected that resting state results would highlight significant differences in functional connectivity within the DMN brain regions when comparing participants in the MBSR versus the control group. The DMN includes brain regions that are not engaged when undergoing a specific task, however, are active during rest and self-referential

processing. The functioning of the DMN is altered from the experience of chronic pain however it is also altered from experience with mindfulness (Baliki et al., 2008, 2014; Loggia et al., 2013; Malfliet et al., 2017; Harrison et al., 2019). Research on the resting state has specified that experienced meditators have decreased functional connectivity within DMN regions involved with self-referential processing and emotional appraisal, while also increased connectivity in other areas such as the dmPFC, and right inferior parietal lobule (Taylor et al., 2013). More recently, results have revealed that functional connectivity was strengthened between right ACC and left anterior insula in a group of healthy volunteers exposed to 8 weeks of MBSR (Gan et al., 2022).

2) As a result, we hypothesized that there would be increased functional connectivity in brain regions related to the DMN that are associated with the modulation of pain following the MBSR program. Regions included in the DMN were hypothesized to be less active after the MBSR in the intervention group compared to controls, and we anticipated the control group would remain unchanged.

DTI

Changes to white matter integrity in areas associated with pain processing have been elucidated as they relate to CNP (Gustin et al., 2011). Although the literature examining modifications to white matter correlating with MBSR are limited, some preliminary results are indicative of increased white matter microstructure (decreased diffusivity and increased FA) associating the PCC and DLPFC with MBSR training (Kral et al., 2019). Laneri et al. have also stipulated white matter connectivity changes via FA microstructure alteration in five brain regions of interest related to mindfulness meditation; thalamus, insula, amygdala, hippocampus and anterior cingulate cortex (Laneri et al., 2016).

3) In the current study, it was hypothesized that fluctuations in the DTI measures for the

MBSR group exemplified by increased FA value for these same brain regions related to mood, self-monitoring, pain and emotional regulation would be apparent. We hypothesized that no changes would be exhibited in the control group.

Pain Measures & Mindfulness

Evidence suggests that MBSR is an effective tool for improving pain intensity (Cramer et al., 2012; Reiner, Tibi & Lipsitz, 2013), pain acceptance (La Cour & Peterson, 2015), and QoL (Nathan et al., 2017). It was expected that the introduction of an MBSR intervention would result in significant improvement to participants' subjective rating of pain severity and interference, thus enhancing QoL for BCS suffering from CNP. The inclusion of the two measures from the larger RCT was considered in order to provide further context to the above mentioned fMRI hypotheses. We included both measures of pain intensity and severity, as assessed using the BPI, and the measure for Mindfulness (FFMQ) to determine how they might correlate to the neuroimaging results. From the larger RCT, using the BPI to assess pain, a change score with a reduction of >1 was deemed clinically significant and interpreted as an amelioration to pain severity and minimized interference with daily living (Dworkin et al., 2005; 2009).

4) It was hypothesized that the wait-list control group would not realize any betterment in their BPI scores from time 1 to time 2 while the MBSR group would have lower BPI scores following the intervention, signifying an improvement to levels of pain severity and interference. Additionally, participants within the MBSR group would have noted increases to their ratings of Mindfulness on the FFMQ questionnaire, resulting from the mindfulness training received, while control group participants were not expected to increase their mindfulness ratings.

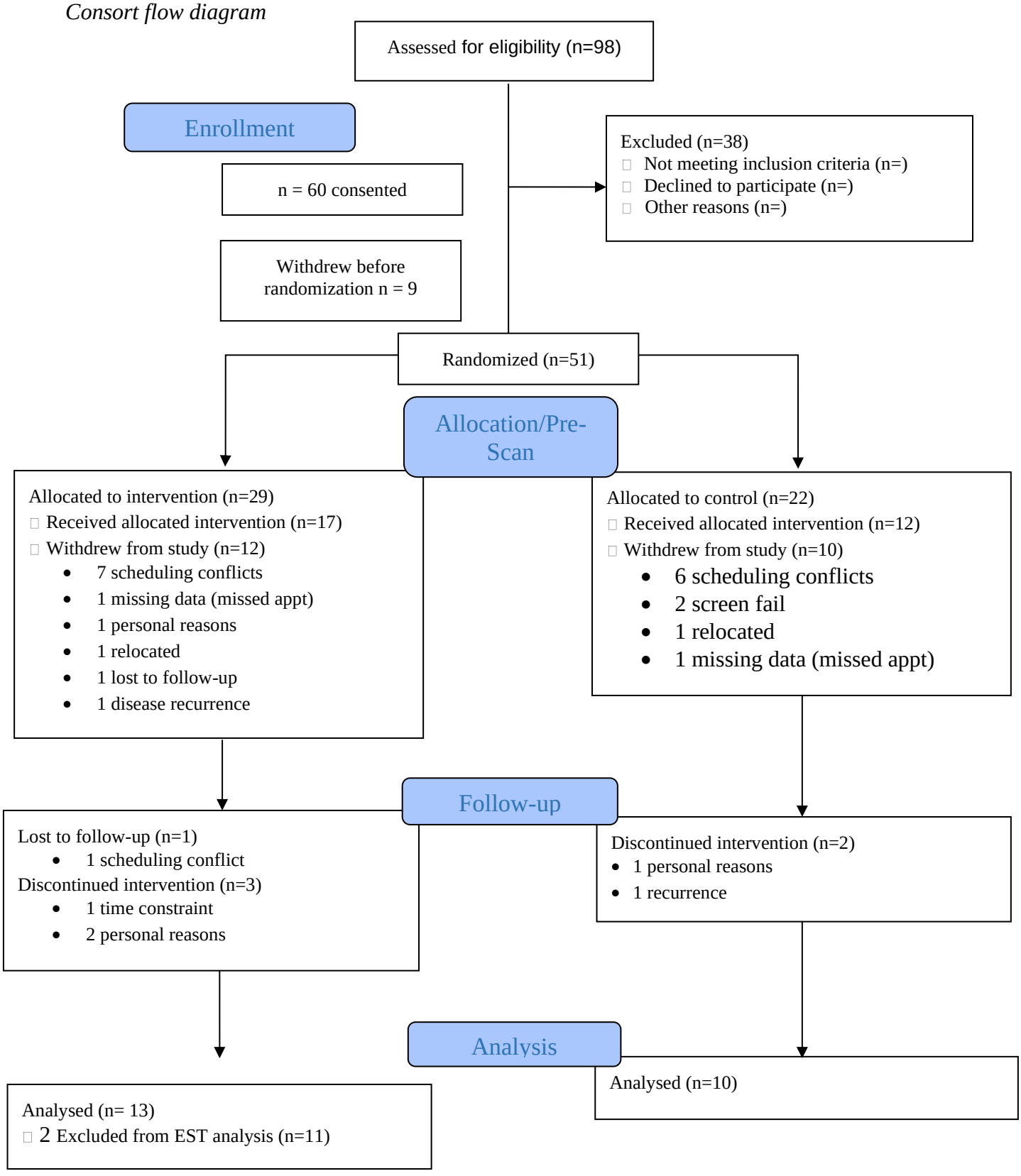
METHODS

Participants

The required sample size for this study was 24 participants (12 in a control group and 12 in the MBSR group) and was determined considering previously established precedents for neuroimaging research. Using the most common general guidelines for fMRI studies, an ideal number of participants is 12 per group, which gives 80% power at the single voxel level with *p=.05* (Desmond & Glover, 2002). We maintained strong *a priori* hypotheses that allow for analyses with fewer participants and due to the within subject design, are not as limited by this specific power analysis.

In total, we achieved a sample size of N=23 of BCS with two participant groups, the MBSR intervention group (n=13) ages 37-81, and the waitlist control group (n=10) ages 45-69 after considering factors of exclusion (Figure 3). The mean age of the intervention group was 49.92 (SD =12.32) and the mean age of the control group was 56.5 (SD= 8.11). Two participants were not able to complete the EST task due to vision problems and thus for that analysis we had n=11 for the MBSR group and n=10 for the control group. All participants were one year post-treatment for breast cancer whether surgery and/or chemotherapy (type was not controlled for). The groups did not differ significantly for age, ethnicity, employment, or education. As mentioned, group allocation was concealed from the researchers, only research coordinators were aware of group allotment.

Figure 3.
Consort flow diagram



Procedures

This study was a small segment of the larger RCT study described earlier investigating the effects of a MBSR intervention on pain disability, psychological well-being and QoL in BCS (Shergill et al., 2022). The RCT study was approved by The Ottawa Hospital and The Ottawa University Research Ethics Boards. Prior to study enrolment, researchers had obtained written informed consent from all participants.

Participants were recruited from the Cancer Centre and the Pain Clinic at the Ottawa Hospital on a referral basis. Poster advertisements at the Maplesoft Survivorship Cancer Centre and the Wellness Beyond Cancer program were used as a means of recruitment. All participants were screened for suitability and inclusion based on the following eligibility criteria: female breast cancer survivor 1-year post-treatment from first cancer occurrence, currently experiencing neuropathic pain that had lasted for over 6 months (induced by surgery or chemotherapy), and a baseline pain severity of >4 (moderate to severe) on the BPI-SF. All participants received recommendations for medical optimization and received confirmation of pharmacological treatment stability (minimum of 2 weeks) by a pain specialist prior to randomized group allocation. Prospective participants with metal implants, pacemakers, recent surgery (within the past month), metal dental work (excluding fillings), and/or claustrophobia were excluded from the neuroimaging segment of the study. Participants for this study were also required to be right-handed as a standard practice for neuroimaging research and to ensure a comparable sample.

The intervention (MBSR program) was introduced after initial completion of questionnaires and took place over the course of eight consecutive weeks. Each session was approximately 2.5 hours long with one full day session during the sixth week of the program. According to study protocol for the larger RCT, the MBSR training was offered to participants in

groups of 6 to 12 women. Thus, women who had participated in the fMRI component of our study took part in the MBSR training alongside participants from the larger RCT study. There were five facilitators of the MBSR sessions who had experience in chronic pain, formal MBSR training, in addition to experience leading MBSR groups. All sessions were recorded to ensure appropriate adherence to the established MBSR protocol. A registered psychotherapist with more than 5 years of experience with MBI's assessed treatment fidelity, and reviewed a random selection of the session's recordings. A sampling of 12% of sessions were listened to and treatment adherence was assessed according to the Mindfulness Based Interventions: Teaching Assessment Criteria Scale (MBI:TAC), and the Mindfulness-Based Relapse Prevention Adherence and Competence scale. Participants were required to complete the BPI questionnaires in English or French and to attend seven out of nine MBSR sessions (English only) in order to be included in the analyses. All waitlist control participants were offered participation to the MBSR treatment following the waiting period, although these women were not scanned upon completion of their participation in the intervention. All participants were compensated $50.00 for their participation at each time point.

Primary Outcome Measure (Neuroimaging)

Neuroimaging data was collected using a 3T Siemens TRIO scanner at The Ottawa Hospital Civic Campus. Participants laid supine on the bed of the scanner with their head immobilized in a 32-channel head coil. Scanning consisted of several sequences, including a conventional T1-weighted spin echo localizer that was acquired to then prescribe a subsequent 3D FLASH (TR/TE 11.2/21 ms, flip angle 60, field of view (FOV) 26x26 cm, 256x256 matrix, slice thickness 1.5 mm) volume acquisition for structural analyses. Two fMRI sequences were acquired, an emotional stroop task (described below) and a 5 minute resting state scan (participants were

instructed to keep eyes closed and think of nothing in particular for the 5 minutes) using a $T2^*$-weighted echo planar pulse sequence (TR/TE 3000/34 ms, flip angle 90°, FOV 24×24 cm^2, 128×128 matrix, slice thickness 4 mm, 38 slices). The final sequence was diffusion weighted for DTI analyses. The diffusion sequence was a fluid attenuated inversion recovery (FLAIR) double-refocused spin echo sequence with 30 diffusion tensor images acquired with b-value = 1000s/mm^2 and one non-diffusion (TR=12000ms, TE=98ms, slices number = 76, slice thickness = 2mm, field of view (FOV) = 192 mm).

Participants were expected to remain in the scanner for a 45-minute session at two time points while all scans were collected. This same procedure took place at both baseline time point and post-MBSR training or equivalent time for wait-list controls. Participants were equally compensated ($50.00) for their participation in the scanning session at each time point.

Emotional Stroop Task

In the EST task used for this study, words were presented sequentially to participants in one of two consecutive blocks; one block consisting of pain-related words (such as cancer pain and pain in general) which was contrasted with blocks of neutral words. Words used for the present study were taken from previous research (Pearce & Morley, 1989; Bradley & Lang, 1999) and were matched for frequency and length parameters. Participants were presented with a series of 4 blocks of pain-related emotional words which alternated with 4 blocks of neutral words for a total of 8 blocks. Each block was administered in alternating order, always beginning with a neutral block, followed by a pain-related block and this ordered presentation was consistent for all participants. Examples of emotionally charged pain-related words include; failure, hopeless, depressed, and agonizing, while examples of the neutral words were as follows; applause, footnotes, unit and actor. For reference, the remaining words used in the task are located in

Appendix A. Word presentation using this block design was chosen as research has suggested that emotional words are far more difficult to avoid when grouped together (Compton et al., 2003) and thus would maximize potential for specificity of results.

Participants were trained on how to use two separate two-button response pads (fitted for left and right hands) outside the scanner and once again while inside the scanner. This ensured participants were sufficiently trained and had achieved 100% response accuracy during the training sessions prior to advancing to the scanner task. Response accuracy was also determined for the trials themselves with a minimum requirement of 80% accurate responses per participants in order to be included for analyses. With the assistance of the response pads, participants were instructed to read the words they observed on a projected screen via a specialized mirror, and identify and select the colour of the word that corresponds with the colour on the response pad as quickly as possible. All words were presented in an equal selection of the 4 colours of the response pads; red, yellow, green, or blue thus ensuring the same number of each possible colour responses for each of the two conditions. Participants were instructed to read the words internally and then indicate the colour of the word presented as quickly as possible by selecting the corresponding coloured button on the pad. Participants' responses were captured within 1000 m-seconds for each presented word (whether the participant had responded or not). Errors as well as omissions were both captured. Each word block contained 16 words and was a total of 33 seconds long. Each trial lasted 2000 m-seconds and consisted of a 300 m-seconds fixation point followed by a 1700 m-seconds presentation of the word. A nine second rest period was interjected between each alternating word block that included a crosshair with a picture of the response pads to remind participants of the location of corresponding response pad colours. In total, the task consisted of 256 trials and took seven minutes to complete. Reaction times and number of errors were recorded

with the assistance of a fiberoptic response device.

Figure 4.
Example of training screen for the EST including response pad button location

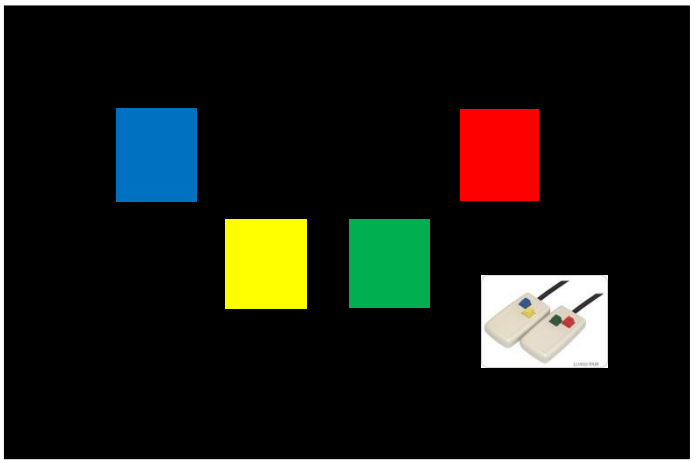
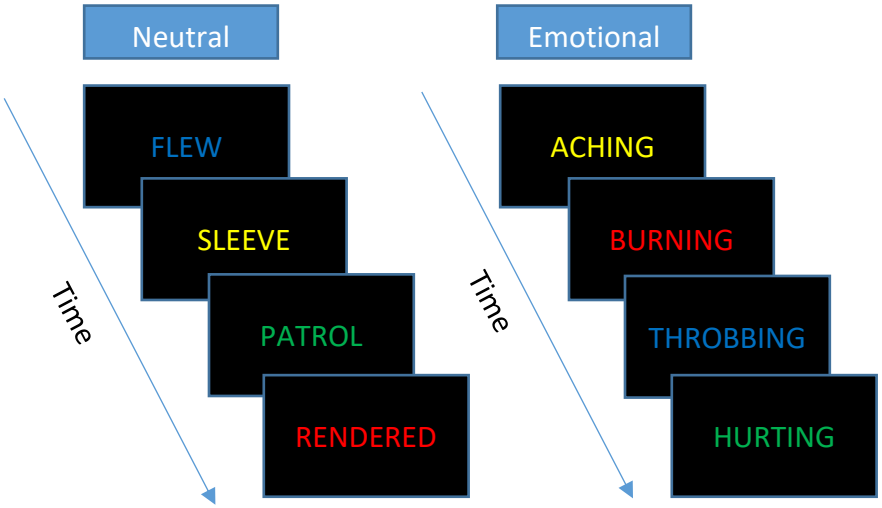


Figure 5.
Experimental array of example words used in EST



Secondary Outcome Measures

Several questionnaires were administered to participants as part of the larger study, however from these, two were incorporated into this thesis which include, the BPI-SF

questionnaire (Cleeland, 2009), and the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006). The BPI-SF is often used in clinical practice and allows for a focused evaluation of pain. It measures individual subjective pain to assess the level of interference and severity that pain has on daily functioning related to affective impacts and activity. Participants are asked to complete a daily rating of their worst, least, average, and current pain intensity over the course of seven consecutive days. They are also asked to self-report on how much their pain interferes with 7 domains of daily functioning including; general activity, mood, walking ability, normal work, relationships with others, sleep, and general enjoyment of life. For example, participants are asked to rate their pain on average, their pain right now, and their pain at its worst within the last 24 hours on a Likert scale from 0 (no pain), to 10 (pain as bad as you can imagine). The BPI-SF has good reliability and validity, with alpha coefficients of .85 for the severity scale and .88 for the interference scale (Tan et al., 2004). The BPI is widely used in research to assess cancer pain and has reported benefits of using the measure with hospitalized patients with cancer, noting its usefulness in identifying pain mechanisms (Cleeland, 2009; Andersson et al., 2020).

The FFMQ is a 39-item questionnaire that measures five aspects of trait mindfulness; non-reactivity to inner experience, observing, describing, acting with awareness, and non-judging of experience. Participants are asked to deem how true they believe each statement resonates with them using a 5-point Likert scale. Some example questions include; “I criticize myself for having irrational or inappropriate emotions”, and “I watch my feelings without getting lost in them”. The FFMQ has been found to have adequate to good reliability, with alpha coefficients between 0.75 and 0.91 for all subscales. The construct validity of the FFMQ has been assessed and validated as having good psychometric properties (Baer et al., 2008), and adequate to good reliability with alpha coefficients ranging from.75 to .91 and has been previously used as an assessment tool in

breast cancer research (Zimmaro et al., 2020).

Data Analysis

Clinical Measures

Analysis for the FFMQ consisted of tabulating total scores for the 39 item questionnaire, and comparing difference scores across the 5 sub scales (Observing, Describing, Acting with Awareness, Nonjudging of inner experience, Nonreactivity to inner experience). The subscales were coded in standard and reversed scoring (depending on the question) as per the scoring guide, and summed together for a total FFMQ score. The Shapiro-Wilk test was used to examine the normality of the data in both groups, and results indicate that both groups were normally distributed. The Levene's test was also used to confirm that both groups had equal variances.

To analyze the BPI results, a mean interference score was calculated for each of the seven pain interference items, as well as a mean of the four pain severity items. For each time point, a mean score per participant was determined across a consecutive 7-day rating period, where daily BPI scores were captured. Difference scores were calculated for the BPI-SF between the two time points, comparing mean differences between the pain interference and pain severity subscales. The Shapiro-Wilk test was applied to examine the normality of pain interference and pain severity scores for each group. The normality test indicated that the pain severity scores were normally distributed in each group (all $p > 0.05$), however, pain interference scores were not normally distributed in either group post intervention (all $p < 0.05$). Both groups had equal variance of pain severity scores ($p > 0.05$). As a result, a mixed ANOVA analysis was applied to pain severity scores using the ANOVA-test function, and a non-parametric mixed ANOVA analysis was applied for the pain interference scores using the eZ Perm function in R studio.

EST Analysis

Statistical Parametric Mapping 12 (SPM12) was used to post-process the fMRI EST data and to perform the statistical analyses specific to this dataset. The functional images were reconstructed and whole brain images were realigned to correct for motion by employing the procedure of Friston et al. (1996). Images were then spatially normalized to match the echo planar imaging template provided in SPM12. Images were smoothed with an 8mm full-width at half-maximum Gaussian filter following spatial normalization. First level analyses were performed for each participant using these images representing the different conditions of the EST where motion correction was applied as a regressor. Data was analyzed using a general linear approach to identify voxels with activity that co-varied in time with components of the experimental design. The contrast of interest used for comparison was the subtraction of brain activity of the pain-related emotional blocks minus the neutral control blocks (average of pain-related words, including all responses, minus average of neutral words, including all responses (errors or correct)). Group comparisons were then performed for second level, random effects analyses (Hatchard et al., 2021).

A whole brain analysis with a full factorial 2-way ANOVA was conducted to examine the interaction effect (Group × Time) or main effects of either group or time at a set threshold of $p_{uncorr} = 0.05$, with a cluster-wise correction at $p_{FWE} = 0.05$ and a set cluster size larger than 10 voxels. All blocks (emotional and neutral) were included for the whole brain-analysis comparison, rest periods were not captured nor included as no responses were possible during rest periods. A region of interest (ROI)-based approach was applied for further post hoc analyses in the regions showing a significant interaction effect or main effect. ROIs were defined based on the significant interaction effect or main effect result from the whole brain analysis, and the parametric estimated

activation values were extracted using the Marsbar toolbox (Hatchard et al., 2021).

Performance data for the EST was also captured, specifically reaction time (RT) and errors. In order to remain consistent with the fMRI analyses, RT differences were calculated subtracting averaged neutral words reaction time from averaged affective words (RTaffective − RTneutral) as the dependent variable. The RT difference measures colour-naming latency between the averages of emotional blocks and the neutral blocks. The effect is a result of longer naming latencies to ink colour of emotional words rather than neutral words and is assessing cognitive performance under the exposure of emotional content. This recommended analysis is based upon emotional words being processed more slowly given the greater cognitive interference for emotional information as described earlier (Compton et al., 2003). A mixed ANOVA analysis was performed with Group as the between-subject factor and Time as the within-subject factor (Hatchard et al., 2021).

Functional Connectivity Analyses – rsfMRI

Resting-state fMRI data pre-processing and functional connectivity (FC) analysis were conducted using Data Processing Assistant for rsfMRI (DPARSF) and SPM12 in MATLAB 2017a. rsfMRI images of each participant were first realigned to correct for head motion, co-registered with the anatomical image and smoothed in space using a three-dimensional 4-mm full width at half maximum Gaussian kernel. Images were then normalized to standard Montreal Neurological Institute (MNI) space and re-sampled with isotropic $3 \times 3 \times 3$ mm^3 voxel size. Linear band pass filter at 0.01~0.08 Hz was used to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise. Nuisance covariates including the six head motion parameters, global mean signal, white matter and CSF signal were regressed out from the data (Smith et al., 2021).

The seed-to-voxel approach was applied for the FC analysis at the whole brain level. As

the main hub of the DMN, the PCC was defined as the seed using an automated anatomical labeling region of interest library through the WFU Pickatlas tool-box (http://fmri.wfubmc.edu/software/PickAtlas). For each participant, the mean BOLD fMRI signal time series was extracted from the seed and used as the regressor in the FC analysis. The correlation coefficients between the time series of the seed region and other brain areas were grouped into an individual FC map and transformed into a z-score through a Fisher's r-to-z transformation to improve the normality of the correlation coefficients. These z-transformed individual FC maps were then entered into the second-level group analysis using paired t-tests to explore the within-group differences of the FC between two test sessions for each group, and using two sample t-tests to compare FC differences between groups during the first (pre-MBSR scan) and the second (post-MBSR scan) resting state scans. For the paired sample t-tests within-group results, the threshold was set at a significance level of voxel-wise uncorrected $p < 0.005$ and family-wise error (FWE) corrected $p < 0.05$ at the cluster level. Additionally, the two sample t-tests between-group comparison (MBSR compared with controls), had a threshold set at a relatively liberal level due to the small sample size of voxel-wise uncorrected $p < 0.01$ and FWE corrected $p < 0.05$ at the cluster level. The activation cluster size was more than 30 voxels for all analyses (Smith et al., 2021).

DTI Analysis

Raw data was analyzed using the functional MRI of the brain (FMRIB) software library. Each diffusion-weighted image was affine-aligned to its corresponding b0 image using FMRIB's linear image registration package (FLIRT v5.4) to correct for motion artifacts and attenuate eddy current distortions. For each participant, brain masks of each brain b0 image were generated using the brain extraction tool (BET v2.1) with fractional threshold, f=0.1 and a vertical gradient, g=0.

The FMRIB's diffusion toolbox (FDT v2.0) was then used to fit the tensor at each brain voxel and estimate the eigenvalues of the tensor from which the FA values were derived.

Voxelwise whole-brain analysis of the FA data were carried out using Tract-Based Spatial Statistics (TBSS v1.2). Nonlinear registration of FA images into 1x1x1 MNI152 standard space were performed through direct registration to the FMRIB58_FA template using FNIRT. The transformed individual FA images were averaged to create a mean FA image, which was then thinned in order to produce a mean FA skeleton representing the centre of white matter tracts common to all participants (threshold FA value of 0.2). The aligned FA images for each participant were projected back onto this mean skeleton in order to account for residual misalignments between participants after the initial nonlinear regression.

Baseline and post-treatment FA comparisons were conducted using a voxel-wise statistical repeated-measures analysis with a threshold-free cluster enhancement (TFCE) correction for regions of interest (ROI). TFCE was used to avoid having to arbitrarily define an initial cluster-forming threshold (Nguyen et al., 2013). The multiple comparisons correction (MC) was also performed on the whole-brain results to control for type 1 error. Due to the small sample size, a liberal MC threshold was applied from $p < 0.06$ to $p < 0.05$ levels, to explore results. A two-sample unpaired T test-randomized pipeline was applied, for the comparisons between the two groups (MBSR vs Control) during the baseline and post-MBSR sessions. For comparisons of within group participants, the two-sample paired T test-randomized pipeline was applied between the baseline and post-MBSR sessions. The FA values for interested regions were extracted using the fslmath function based on the TBSS whole-brain results for further analysis (Mioduszewski et al., 2020).

RESULTS

Participants

All participants (N=23) were female, Caucasian breast cancer survivors with mean ages of 49.92 for the MBSR group (n=13) and 56.5 for the control group (n=10) and no significant differences between groups (t = 1.716, p = .102) (Table 1). Again, two of the participants were unable to complete the EST so for the EST analysis N=21 (MBSR n = 11, control n =10). Employment status statistics are provided in Table 1 below, and although there were no significant differences between groups (t = -.836, p = .413) of noteworthy mention, the MBSR group was made up of 38% participants who were on disability and 30% who were not working (unemployed or retired), while the control group had 40% who were either unemployed or retired, and no participants on disability leave. There was no significant difference between groups with respect to years of pain experienced (t = .930, p = .364) with mean years of pain at 3.12 for the MBSR group and 3.53 for the control group (Table 1).

Table 1.
Participant demographics at baseline for all 23 participants

Variable	**MBSR (n=13)**	**CONTROL (n=10)**
Age Mean (SD)	49.92 (12.32)	56.5 (8.11)
Ethnicity (%)		
Caucasian	13 (100%)	10 (100%)
Employment Status		
Full-Time	5 (38%)	6 (60%)
Unemployed	3 (23%)	1 (10%)
Retired	1 (7%)	3 (30%)
Disability	4 (30%)	
Years of pain		
Mean	3.12	3.53
Range	1 - 5.5 (4.5)	1.5 - 7 (5.5)

Clinical & Pain Measures

BPI

No significant differences were observed between groups during either scanning session when comparing BPI scores (Table 2). Both pain severity and pain interference were significantly decreased after the 8-week training program in the MBSR group, meanwhile the opposite effect was observed in the control group (although not significantly) as their scores were increased on both measures when comparing the two scanning sessions (Table 3).

Pain Severity

Comparative analyses (ANOVA) indicated that there were no significant interaction effects observed for Group X Time (F (1,21) = 2.031, p = 0.169) nor significant main effects of Group (F(1,21) = 0.032, p = 0.859) or Time (F (1, 21) = 0.198, p = 0.661). Paired sample t-tests were conducted in order to explore the effect of pain severity might have within groups and a determination was made that pain severity had decreased for the MBSR group (p< 0.025) and had increased slightly for the control group.

Pain Interference

No significant between-group differences were observed when comparing the Control and the MBSR groups at either time point for pain interference (F (1, 21) = .198, p = 0.661). Table 3 below indicates between group differences for each scan (Table 3). However, a significant interaction of Group X Time was detected for the pain interference scores (F (1,21) = 4.898, p = 0.038). The simple effects of Group and Time were examined, and results indicated that pain interference scores in the MBSR group were significantly decreased after the MBSR training (Mean = 3.35, SD ± 2.62) contrasted with before training results (Mean = 4.24, SD ± 2.46)

(p=0.05). No significant differences were found in the control group between the two time points (Mean = 3.13 *SD* ± 2.17; Mean = 3.58 *SD* ± 2.44; p = 0.146).

Table 2.
Mean change scores between groups by subject (BPI)

	Pain Severity (Ps)		**Pain Interference (Pi)**	
Subject	Scan 1	Scan 2	Scan 1	Scan 2
CONTROL				
13	3.4	4.3	4.0	5.8*
32	1.7	2.5	3.1	1.58*
37	2.1	2.9	0.5	1.5*
40	3.4	1.8*	5.2	6.7*
41	1.8	2.2	1.4	1.9
42	3.4	2.0*	8.0	8.3
53	2.4	2.2	2.8	2.3
69	1.5	1.2	2.7	2.0
85	1.3	1.9	2.1	2.6
114	0.9	1.9*	1.5	3.1*
MBSR				
21	2.1	2.7	3.6	2.9*
29	3.4	2.9	4.4	5.1
33	2.2	1.5	4.7	6.5*
43	4.0	3.9	7.4	5.4*
57	2.6	2.5	3.8	2.4*
61	3.5	3.3	6.5	6.4
63	1.5	1.3	3.1	2.8
64	2.5	0.8*	8.7	8.0
65	3.2	1.9*	0.9	0.7
79	0.9	0.5	4.5	0.6*
89	1.4	1.2	5.7	1.6*
113	2.3	2.3	1.0	0.4
115	2.7	2.8	0.8	0.7

Note: A mean change score of >1 is deemed clinically significant on the BPI indicated by an asterisk.*

Table 3.
Within and Between group differences at both testing sessions (BPI)

		Pain Severity (Ps)		**Pain Interference (Pi)**	
		Pre	Post	Pre	Post
MBSR	Mean	2.48	2.12	4.24	3.35
	SD	.897	1.02	2.46	2.63
	Within-group		$p = 0.025$*		$p = 0.038$*
CONTROL	Mean	2.19	2.29	3.13	3.57
	SD	.929	.836	2.17	2.43
	Within-group		$p = 0.374$		$p = 0.113$
Between - Group		$p = 0.451$	$p = 0.679$	$p = 0.274$	$p = 0.831$

Note: Within-group and between group differences in BPI score for both scans. Statistically significant results indicated by (*) at p< 0.05

FFMQ

A mixed ANOVA analysis was used to analyze the FFMQ data, and it was determined that a significant interaction existed for the effects of Group and Time ($F(1,21) = 2.952$, $p = 0.043$). A simple effects analysis for each variable (Group, Time) was conducted, and established that the MBSR group had significantly increased their overall level of mindfulness as indicated by the FFMQ scores post MBSR training ($F = 4.65$, $p < .007$). Given the pairwise comparisons, significant mean differences were noted in all subscales of the FFMQ in the MBSR group, with nonreactivity to inner experience ($p <. 001$) and non-judging of experience ($p = .009$) noted as the most significant subscales. Meanwhile no differences were observed in the Control group between time points, as well, no between group differences were noted between the Control and MBSR group at either time point (Table 4). Overall, the FFMQ change score (post-MBSR minus pre-MBSR) was significantly higher in the MBSR group compared to controls post intervention) (MBSR Mean = 20.77, *SD* ± 4.65; CONTROL Mean = 3.2, *SD* ± 75.3, t = -3.38, $p = 0.003$). FFMQ scores were significantly increased in the MBSR group after treatment (Mean = 135.92, *SD*± 25.57) contrasted with baseline measures (Mean = 115.15, *SD* ± 24.65) ($p = 0.05$), and no

differences were evident in the control group when comparing time points; PRE (Mean= 124.70 *SD* ± 21.11) compared to POST (M= 127.90, *SD* ± 23.77) (Table 4).

Table 4.
Post-hoc analysis of FFMQ scores

		PRE	POST	Time difference
MBSR	Mean SD	115.15 24.65	135.92 25.57	*p.adj. = 0.012**
CONTROL	Mean SD	124.70 21.11	127.90 23.77	*p.adj. = 0.610*
Group difference		*p.adj. = 0.452*	*p.adj. = 0.480*	

Note: P value was adjusted by Bonferroni correction. Statistically significant results indicated by asterisk (*) at p < 0.05.

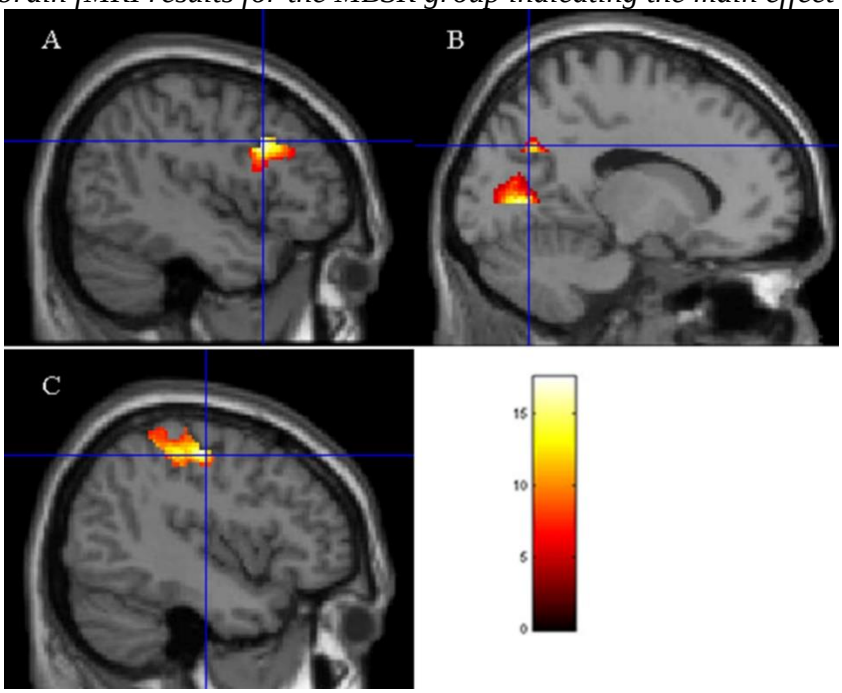
fMRI during EST

Results obtained from the EST indicate that no significant interactions were apparent at the whole brain level between Group and Time at the given threshold, nor main effect of Group on brain activation in response to the contrast of interest (pain-related vs neutral words). However, a significant main effect of time was observed in left cortical brain regions, including the precuneus (Pcu), lingual gyrus, middle temporal gyrus (MTG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), postcentral gyrus, and the precentral gyrus. A main effect of time was also observed at the given threshold in the anterior cingulate cortex/middle frontal cortex (ACC/MFC) and middle cingulate cortex (MCC).

In an effort to further investigate the Time difference as indicated by the main effect (Time), the parametric estimate activation values of these regions were extracted for each participant. The normality and homogeneity of variances of the data were tested (p's > 0.05), and subsequently a mixed ANOVA analysis was performed using the regional activation values. This

analysis proposed a main effect of Time on the activation observed in these regions by the whole brain analysis for all participants (F (1,19) = 24.95, $p < 0.001$, partial $\eta^2 = 0.4584$, post hoc power > 0.999). Subsequently, a one-way MANOVA was applied to express the Time effect in brain activation in all regions for both groups, the outcome is indicated in Table 5 below. The post-MBSR activation had significantly decreased when contrasted with the pre-MBSR results in all the reported regions (Figure 6).

Figure 6.
Whole brain fMRI results for the MBSR group indicating the main effect of Time.



Note: *Demonstrates where activity was significantly reduced when comparing post to pre-MBSR in the MBSR group. The blue crosshairs indicating the most significantly different voxel within a cluster.* ***A*** *Left dorsolateral prefrontal cortex (x y z = -44 14 44);* ***B*** *left precuneus (x y z = -18 -64 32) and left cuneus (x y z = -14 -72 4);* ***C*** *left postcentral gyrus (x y z = -42 -16 50).*

Given the ANOVA results, in order to further clarify which group demonstrated the most substantial changes in brain region activation differences for both time points, subsequent post hoc analyses were completed. For the MBSR group, the brain activation post-MBSR had significantly decreased when contrasted with the pre-intervention results in all reported regions. The control

group had a significant time effect difference in left ACC/MFC, MCC, precentral, MTG and lingual regions. The changes to activation that were unique to the MBSR group were in the MFG, IFG, Pcu, postcentral gyrus and calcarine. These results are specifically laid out in Table 6 below and have been published in *Mindfulness* (Hatchard et al., 2021).

Table 5.
Main effect (Time) on brain activation

Region	Mean ± SD		*p* adj.
	PRE	POST	
Left Middle Frontal Gyrus (MFG)	0.29 ± 0.39	- 0.03 ± 0.25	0.001**
Left Inferior Frontal Gyrus (IFG)	0.26 ± 0.32	0.01 ± 0.38	0.019*
Left Precuneus (Pcu)	0.10 ± 0.09	- 0.04 ± 0.15	0.001**
Left Postcentral	0.09 ± 0.21	- 0.07 ± 0.18	0.004**
Left Calcarine	0.10 ± 0.19	- 0.04 ± 0.15	0.004**
ACC/MFC	0.30 ± 0.31	- 0.03 ± 0.31	0.002**
MCC	0.14 ± 0.22	- 0.11 ± 0.25	0.001**
Left Precentral	0.18 ± 0.21	- 0.06 ± 0.26	0.001**
Left Middle Temporal Gyrus (MTG)	0.19 ± 0.14	0.00 ± 0.20	<0.001***
Left Lingual	0.10 ± 0.08	- 0.02 ± 0.13	<0.001***

*Note: P value was adjusted through a MANOVA. Statistically significant results are marked by asterisk at * p <0.05; ** p<0.01*

Table 6.
Post hoc analysis of Main effect (Time) on brain activation by group

Region	MBSR			CONTROL		
	Mean ± SD					
	PRE	POST	*p* adj.	PRE	POST	*p* adj.
Left.MFG	0.25 ± 0.26	- 0.03 ± 0.27	0.023*	0.32 ± 0.50	- 0.04 ± 0.24	0.060
Left IFG	0.23 ± 0.16	0.004 ± 0.32	0.048*	0.30 ± 0.45	0.02 ± 0.45	0.176
Left Pcu	0.10 ± 0.14	- 0.05 ± 0.1	0.019*	0.10 ± 0.13	- 0.02 ± 0.22	0.149
Left Postcentral	0.11 ± 0.22	- 0.11 ± 0.15	0.014*	0.07 ± 0.21	- 0.02 ± 0.20	0.338
Left Calcarine	0.08 ± 0.13	- 0.06 ± 0.13	0.018*	0.12 ± 0.24	- 0.02 ± 0.17	0.140
ACC/MFC	0.23 ± 0.18	- 0.02 ± 0.35	0.046*	0.39 ± 0.41	- 0.03 ± 0.29	0.016*
MCC	0.09 ± 0.16	- 0.17 ± 0.28	0.014*	0.20 ± 0.26	- 0.05 ± 0.20	0.026*
Left Precentral	0.18 ± 0.21	- 0.03 ± 0.23	0.030*	0.19 ± 0.22	- 0.08 ± 0.30	0.033*
Left MTG	0.20 ± 0.13	0.02 ± 0.20	0.017*	0.18 ± 0.15	-0.03 ± 0.20	0.018*
Left Lingual	0.09 ± 0.09	- 0.03 ± 0.11	0.016*	0.12 ± 0.06	- 0.01 ± 0.16	0.026*

*Note: P value was adjusted through a MANOVA. Statistically significant results are marked by asterisk at * $p < 0.05$; ** $p < 0.01$*

Reaction Time

The Shapiro-Wilk test was used to examine the normality of the Reaction Time (RT) data and revealed that each group was normally distributed (all $p > 0.4$). We also applied the Levene's test to assess and validate that equality of variances was achieved in both groups (all $p > 0.05$). A mixed ANOVA was utilized to determine the interaction and main effects of Group and Time on RT differences. No significant interaction was found (Group x Time) ($F(1,19) = 2.936$, $p = 0.102$), however a significant main effect of Time was noted ($F(1,19) = 6.983$, $p = 0.016$, partial $\eta^2 = 0.269$, post hoc power = 0.93). Reaction time results are indicated in Table 7 below. No significant main effect for Group was found (F (1,19) = 0.474, $p = 0.499$). A simple effects analysis was conducted to examine further the effect of time. The RT difference was increased in the post intervention scan (17.52 ± 38.12 ms) compared to the pre-intervention scan (-17.59 ± 44.58 ms)

across both groups ($p = 0.02$). A simple effects analysis was conducted for each group to determine the variance of the main effect of time within each group separately. The RT in the control group was significantly increased during the post-intervention scan (25.22 ± 48.83 ms) compared to the pre-intervention scan (-33.77 ± 37.58 ms) ($p = 0.009$), meanwhile this difference was not observed in the MBSR group when comparing pre-intervention (-2.89 ± 46.95 ms) to post intervention scans (10.52 ± 25.45 ms) ($p = 0.506$). This indicated that the control group was slower in responding to pain-related affective words compared to neutral words during the second scan. Errors of omission and commission were also captured, noted in Table 8 below, however were not statistically significant.

Table 7.
Response times for Emotional Stroop Task (ms)

		Control	MBSR
Pre-intervention	Affective	795.60 ± 103.2	787.50 ± 94.86
	Neutral	829.37 ± 90.06	790.38 ± 103.6
	$RT_{affective}$- $RT_{neutral}$	- 33.77 ± 37.58	- 2.89 ± 46.95
Post-intervention	Affective	817.53 ± 112.21	761.00 ± 110.7
	Neutral	792.31 ± 98.11	750.48 ± 116.5
	$RT_{affective}$- $RT_{neutral}$	25.22 ± 48.8	10.52 ± 25.5
Time difference $RT_{affective}$- $RT_{neutral}$		$p = 0.009$*	$p = 0.506$

*Note: Statistically significant results are marked by asterisk at * p <0.01*

Table 8.
Mean errors of omission and commission during EST

	CONTROL		**MBSR**	
	EMOTION	NEUTRAL	EMOTION	NEUTRAL
PRE				
Error omission	3.2	3.6	2.8	3.3
Error commission	0.9	0.9	1	1.5
POST				
Error omission	2.2	2.2	1	1.4
Error commission	1.5	2.7	1.9	1.4

Note: Mean errors between emotional pain-related blocks and neutral blocks comparing controls to MBSR intervention pre and post MBSR. No significant between groups or within group changes were noted.

rsfMRI

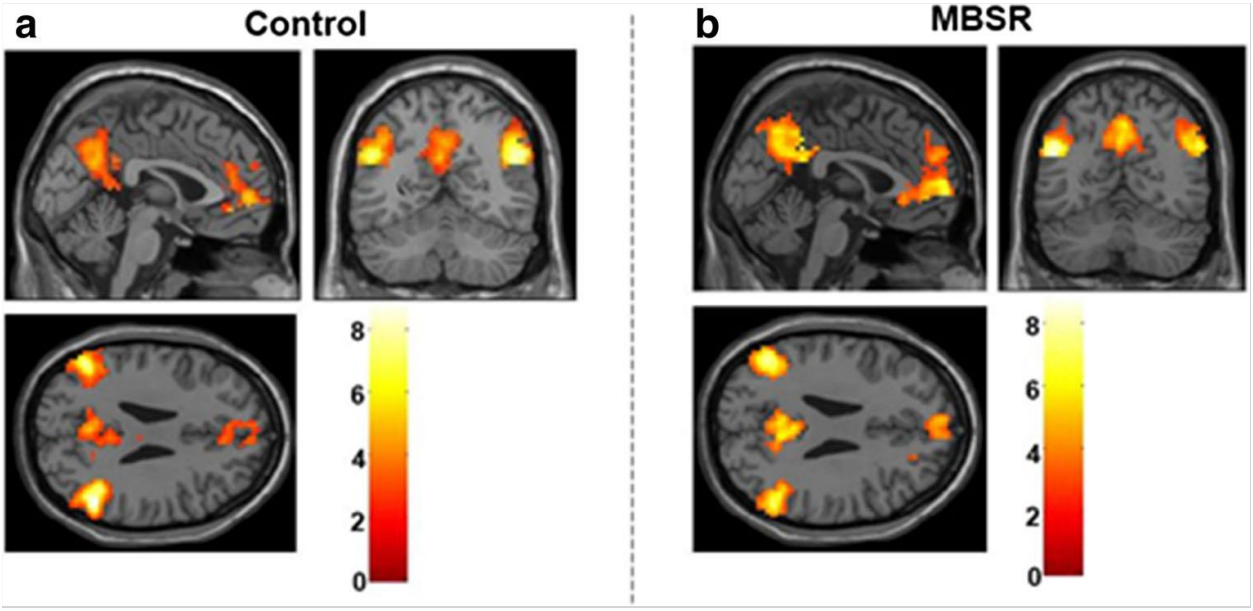
No significant interaction (Group x Time) was observed at the whole brain level at the given threshold (uncorrected $p < 0.005$ at the voxel-wise level, and FWE corrected $p < 0.05$ at the cluster level) when comparing within group differences during the resting state scan. However, since the anticipated outcome was specific to the MBSR group participants having altered FC post intervention, we further conducted a paired sample t-test. The paired sample t-test was applied to investigate the PCC seed region FC changes between the two scans obtained within both groups. Our results demonstrated powerful increases to FC between the PCC seed region and other regions identified as part of the DMN; the ACC, mPFC and the bilateral angular gyri within the parietal cortex in both groups (Table 9). Increased DMN functional connectivity in the PCC seed region when comparing post-intervention to pre-intervention scans was observed in both the Control and the MBSR groups (Figure 7).

Table 9.
rsfMRI results for PCC seed FC during post scan

Hemisphere	Region	MNI Coordinate			Peak T	Cluster-level FWE corrected p value
		x	y	z		
CONTROL (Increased FC)						
Left	ACC/mPFC	-3	54	3	5.25	<0.001
Right	ACC/mPFC	9	48	12	6.17	<0.001
Left	Angular	-54	-63	27	7.99	<0.001
Right	Angular	51	-54	24	8.91	<0.001
MBSR (Increased FC)						
Left	ACC/mPFC	-9	45	-3	5.51	<0.001
Right	ACC/mPFC	3	60	3	8.09	<0.001
Left	Angular	-48	-63	24	7.97	<0.001
Right	Angular	57	-57	24	7.32	<0.001

Note: Statistical inferences were performed at a threshold of uncorrected $p < 0.005$ at the voxel-wise level, and FWE corrected $p < 0.05$ at the cluster level. ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex.

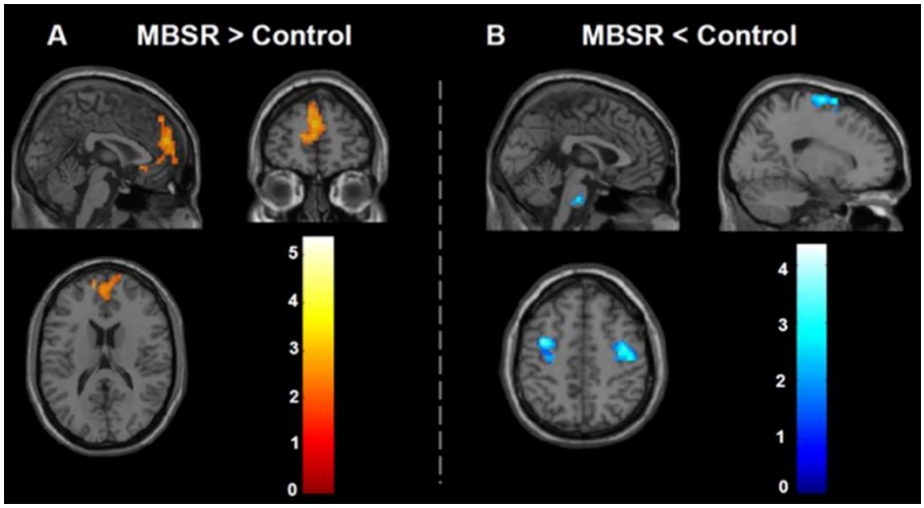
Figure 7.
Increased PCC seed FC in post-MBSR versus pre-MBSR scans



Note: a. Increased DMN FC in CONTROL group. b. increased DMN FC in MBSR group. Threshold set at uncorrected $p < 0.005$ at whole brain level, and $p < 0.05$ at cluster level. Activation cluster size > 30 voxels.

Between group differences were also investigated, and it was determined that no significant FC difference was observed between groups at baseline at the given threshold (uncorrected $p < 0.01$ at the voxel-wise level, and FWE corrected $p < 0.05$ at the cluster-level). Comparing the second scan results, significant PCC seed region FC differences were observed between groups (Table 10). The results indicate that the MBSR group had an observable increase to FC between the PCC and ACC/mPFC, compared to controls (Figure 8). However, FC had also decreased between PCC and the bilateral precentral gyrus, right superior frontal gyrus and the pons in the MBSR group compared to the control group.

Figure 8.
Functional connectivity (FC) changes between groups at second scan



Note: A) FC change between PCC and medial prefrontal cortex in the MBSR group compared with the control group; B) FC change between PCC and pons, right SFG, and bilateral precentral gyrus compared with the control group. Threshold was set at uncorrected $p < 0.01$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level. Activation cluster size > 30 voxels

Table 10.
rsfMRI FC differences between control and MBSR groups during second scan

Hemisphere	Region	MNI Coordinate			Peak *T* score	Cluster-level FWE corrected *p* value
		x	y	z		
MBSR > Control in PCC FC						
Left	ACC/mPFC	-6	27	-6	4.61	0.021
MBSR < Control in PCC FC						
Left	Precentral	-36	0	51	5.05	0.014
Right	Precentral	39	-6	48	3.78	0.036
Right	SFG	15	-6	72	4.57	0.033
Left	Pons	-15	-33	-33	4.19	0.001
Right	Pons	9	-24	-39	4.36	0.001

Note: Statistical inferences were performed at a threshold of uncorrected $p < 0.01$ at the voxel-wise level, and FEW corrected $p < 0.05$ at the cluster level. PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; SFG, superior frontal gyrus. Activation cluster size >30 voxels

A Pearson's correlation analysis was completed in order to further investigate the relationship between the noted FC changes and the BPI scores. We analyzed the BPI change scores between both sessions across both groups and contrasted these results to the between group differences observed in the post-MBSR time point. The FC values between the reported regions from the between group difference results (PCC and the ACC/mPFC) at the post-MBSR scan, were extracted using the Marsbar toolbox in order to complete the Pearson's correlation analysis. The Pearson's correlation investigated the relationship between FC changes and BPI score changes (post-intervention minus pre-intervention MBSR values) for all participants. Using this analysis, we had determined that the increased connectivity between PCC and ACC/mPFC was shown to be negatively correlated with the decrease in pain severity scores ($r = -0.57$, $p < 0.005$). This result demonstrated that the greater FC in these areas was associated with lower pain severity following the post-MBSR session for all participants. Additionally, the decreased FC between the PCC and the bilateral precentral gyrus was positively correlated with the changes observed in the pain severity scores ($r = 0.51$, $p = 0.014$). This indicated that reduction in FC between the PCC and bilateral precentral regions was associated with higher pain severity during the post-MBSR scans.

DTI

No significant difference in FA between groups was observed at either the pre or post intervention sessions. Additionally, there was no significant difference apparent between the pre and post intervention scans for the control group at the given threshold (TFCE FWE corrected $p < 0.06$ to $p < 0.05$). However, results specified, as we had expected, increased FA in multiple brain regions at the post intervention scan when compared to pre-intervention for the MBSR group. As indicated in Table 11 below, the most significant increases in FA values occurred in left subcortical brain region clusters including the external capsule (EC_L), uncinate fasciculus

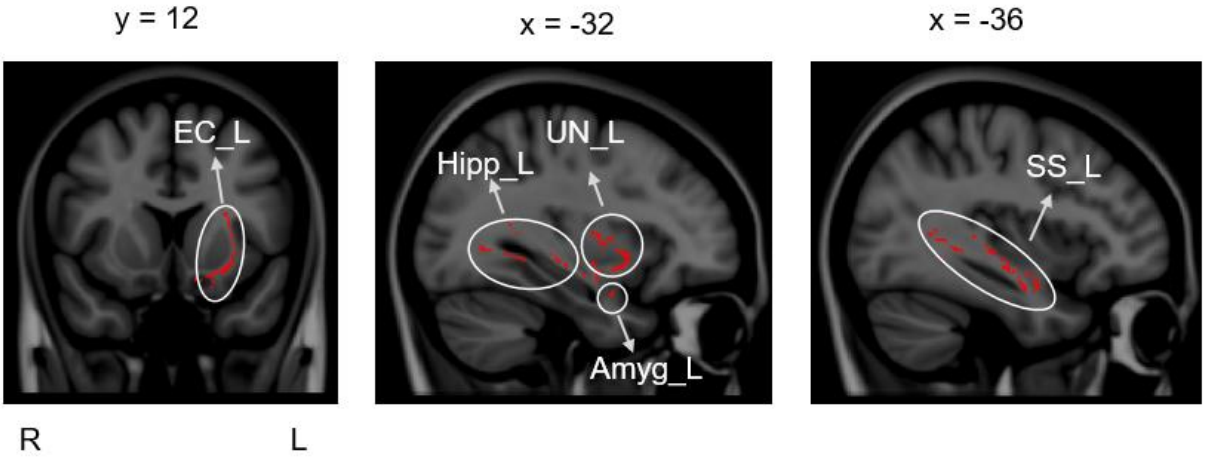
(UN_L), (Amyg) amygdala, and hippocampus cingulum (Hipp_L) as well as the left sagittal stratum (SS_L), after MC (Figure 9). The sagittal stratum (SS) consists of multiple regions and networks which includes the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the posterior thalamic radiation. These clusters were observed to be approaching significance after multiple comparisons. When using a region of interest (ROI) analysis, the FA values were extracted for the MBSR group exclusively at both time points and the difference in these values was contrasted using a Bonferroni correction. Given this post-hoc analysis, all the reported tracts demonstrate greater FA when comparing post intervention to pre-intervention results for the MBSR group (Table 11).

Table 11.
Whole brain FA values for the MBSR group (differences between Pre and Post scans (post> pre)

WM Label	Voxel-Wise						FA value in ROIs		
	Cluster Size	MNI Coordinates			Peak Cluster		Mean (SD)		
		x	*y*	*z*	*t* score	*p* value	PRE	POST	*p* value
EC_L	87	-30	10	-7	4.09	0.052	0.49 (0.05)	0.55 (0.03)	0.006
UN_L	87	-31	4	-1	4.18	0.052	0.29 (0.05)	0.34 (0.05)	0.016
SS_L	101	-38	-32	2	5.25	0.052	0.59 (0.05)	0.66 (0.04)	0.001
Hipp_L	31	-34	-34	-12	3.54	0.058	0.58 (0.08)	0.63 (0.04)	0.046
Amyg	28	-35	-10	-35	3.72	0.058	0.31 (0.04)	0.37 (0.08)	0.031

Note: peak cluster p value tfce multiple comparison correction. FA value in ROIs p value, 2-tailed Bonferroni correction. EC L – external capsule left, UN_L – uncinate fasciculus left, SS_L – sagittal stratum left, hip L – hippocampus left, Amyg – amygdala.

Figure 9.
Regions of increased FA in the MBSR group post MBSR intervention.

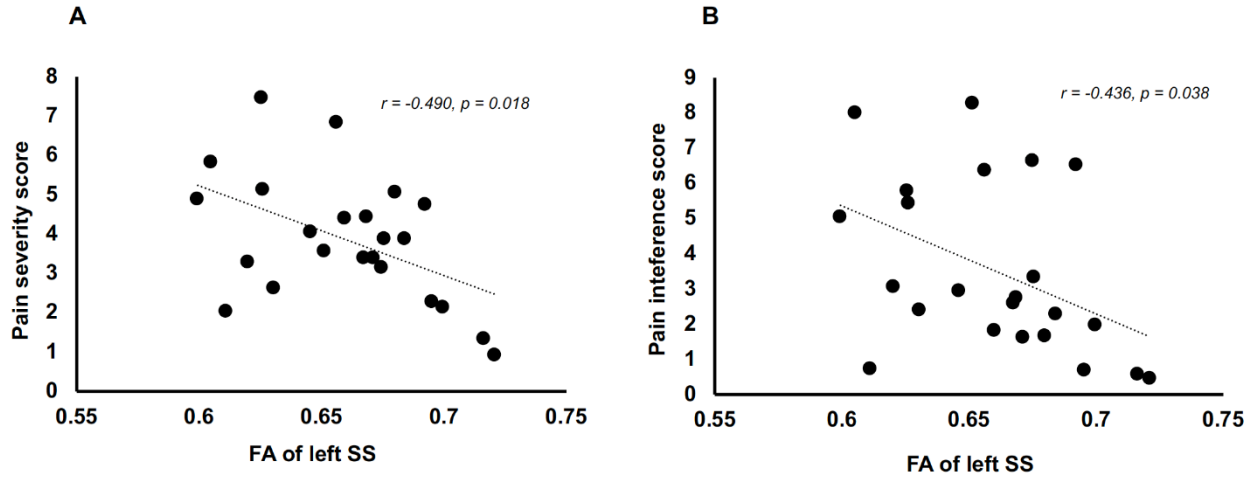


Note: Results are FWE-corrected at p < 0.06. L = Left; R = Right; EC = external capsule; Hipp = hippocampus; UN = uncinate fasciculus; Amyg = amygdala; SS = Sagittal stratum.

Correlations

A Pearson's correlation analysis was applied to further investigate the relationship between the obtained FA values and the scores obtained on the BPI (pain severity and interference). The FA values were extracted from the five brain regions where significant differences were observed using the fslmath function and correlated with the BPI scores obtained during both testing sessions. A negative correlation was confirmed for the FA changes of the left SS and both pain severity (r = -0.49, p = 0.018) and pain interference (r = -0.436, p = 0.038) scores during the post-intervention scan for MBSR participants (Figure 6). This correlation result recognized that a higher FA value in the SS was associated with a decreased BPI score. These results are represented visually in Figure 10 below and were published in the Journal of Cancer Survivorship (Mioduszewski et al., 2020).

Figure 10.
DTI Correlations observed in MBSR participants between BPI scores and FA (post-scan)



Note: A. Negative correlation between pain severity score and the FA of the left SS during post-scan. B. Negative correlation between pain interference score and the FA of the left SS during the post-scan

DISCUSSION

Breast cancer is on the rise as the second most diagnosed cancer in women (Brenner et al., 2022). Unfortunately, there is also an increase in diagnosis of CNP after treatment for breast cancer (Ilhan et al., 2017). After experiencing and surviving breast cancer diagnosis and treatment, these women continue to struggle with intense pain affecting sensory, cognitive and emotional aspects of daily life (Jensen, Chodroff, & Dworkin, 2007) in addition to constant fear that their cancer may once again return (Simard et al., 2013: Sun et al., 2019). Neuropathic pain is associated with poor health on every health domain (physical, psychosocial, and social) (Smith et al., 2007; Jensen, Chodroff, & Dworkin, 2007) and robs individuals of true joy and appreciation for life while simultaneously having significant economic implications with respect to the burden of treatment and inability to work (Chou et al., 2015). Unfortunately, the use of pharmacotherapy to treat CNP symptoms is not only an enormous financial cost to the health care system, but it has also left patients with unrelieved pain and affected their ability to maintain employment. In addition, many patients are obligated to consume multiple drugs simultaneously, increasing the need to manage a polypharmacy of substances along with their correlating potential side effects.

Evidence now suggests that chronic pain is recognized as a biopsychosocial phenomenon that requires a combination of alternative forms of therapy such as CBT, rehabilitation and exercise which are more effective than medication use alone (Bevers et al., 2016). A multimodal approach is essential since as the initial injury resolves, patients continue to experience lasting painful symptoms in addition to psychological and social stressors (Sokol, Pines & Chew, 2021). Mindfulness is now recommended as a suitable therapy for chronic pain, having been validated as a successful pain management treatment plan within chronic pain groups since the early 1980's. However, mindfulness intervention has not received sufficient notable attention within a CNP

context, thus results demonstrating its potentially beneficial effects in this setting are lacking; this is precisely what was explored in this study.

The primary objective of the present study was to determine, through the use of various neuroimaging modalities, the underlying neural correlates of CNP that may be improved by the introduction of a mindfulness program. This undertaking was essential to supplement the very limited research within this specific sample of BCS with CNP, and to determine to what extent complimentary treatment options may support the management of CNP symptoms other than relying exclusively on pharmacotherapy. This study examined the underlying brain structure changes in the DMN, white matter, and functions relating to emotional reactivity and regulation in conjunction with patient-reported outcomes on perceived pain and mindfulness, as analyzed in the main RCT study. The differences in pain scores were explored as important outcomes to provide further context to the fMRI/MRI results, and thus determine correlations between the objective imaging results and the subjective patient-reported outcomes. The expectation was that upon completion of a MBSR program, women within the intervention group would experience functional and structural brain changes correlating with enhanced QoL by way of reductions to pain intensity and severity. The preliminary results of this pilot study within this particular clinical sample have been promising by corroborating the literature on mindfulness to date and demonstrates that mindfulness may play a role in the top-down regulation of pain (Namjoo et al., 2019). Similarly, mindfulness is a known mechanism for training our attention to adjust focus away from emotional judgement and rumination on pain, and rather shifts our attention towards acceptance. In this study, the MBSR group had reduced pain severity and pain interference and increased their mindfulness scores after 8 weeks of training compared to their pre-intervention results, although no significant differences were observed between groups. Exploratory analyses

indicated that significant brain changes were also apparent in the resting state FC of DMN regions, FA of white matter in left subcortical regions, and reduced emotional reactivity to pain related stimuli for the treatment group. The following is a summary and interpretation of the results.

Summary of Results

It was expected that a significant change score in pain would become apparent as measured by the BPI, with a clinically significant change indicative of having an impact on QoL (Dworkin et al., 2009). Results pertaining to the clinical measure of pain in the MBSR group indicated that both pain severity and pain interference were significantly decreased after the 8-week mindfulness program with mean scores shifting from 2.49 to 2.12 for pain severity, and decreasing from 4.24 to 3.35 for pain interference. Meanwhile the opposite effect was observed in the control group who increased their scores on both measures when comparing the first and second scans (although not significantly) with mean scores increasing from 2.19 to 2.29 on the pain severity scale and 3.13 to 3.57 on pain interference. Similar results are observed in the literature where multiple outcome measures of pain have been significantly improved for patients with chronic pain who practice mindfulness (Cherkin et al., 2016; Morone et al., 2016; Ussher et al., 2014). In fact, the MBSR program was originally designed for chronic pain patients in order to help improve the self-directed management of chronic pain by "uncoupling" the sensory from the cognitive/emotional components (Kabat-Zinn, 1982). As a result, evidence supports the positive implications of detachment from cognitive and affective interpretations of pain, and have noted that pain intensity is consistently reduced for mindfulness intervention participants when compared to controls (Reiner, Tibi, & Lipsitz, 2013). With the results obtained from the present study, we corroborate similar findings, indicating a relationship between mindfulness and pain irrespective of experienced or novice meditators (Grant et al., 2010; Lutz et al., 2013). As Reiner et al., indicated,

the subjective experience of pain is modulated by the psychological correlates of pain and MBSR is meant to target these pain correlates in order to improve functioning and minimize distress, rather than removing or avoiding the pain (Reiner, Tibi & Lipsitz, 2013). Our preliminary neuroimaging findings support the positive effects of the 8-week mindfulness course on specific brain regions related to pain and emotional processing, expanding the clinical groups who may benefit (women with CNP following BC treatment).

rsfMRI Results

The rsfMRI exploratory results from this study support a positive effect of MBSR on communication within the DMN, in areas related to attention, self-awareness, emotion regulation and pain. More specifically, the results demonstrated that the MBSR group had more efficient communication within the DMN and less of a requirement for communication between the DMN and the descending pain and motor networks when compared to the controls as indicated by reduced functional connectivity within these brain regions.

The increased connectivity between the posterior functional hub of the DMN, the PCC, and the medial frontal regions (ACC/MPFC) suggest facilitation of the cognitive and emotional regulation of pain. The PCC is identified as a major node in the DMN and has widespread connectivity with regions involved in attentional control, including prefrontal and frontoparietal networks. The PCC region is a pivotal component benefiting from mindfulness training given results of greater PCC grey matter concentration in meditators compared to controls in prior studies (Holzel et al., 2011). Leech et al., (2012) also suggest that the PCC and its connections work to regulate the balance of internal and external directed cognition (Leech, Braga & Sharp, 2012). Further, the PCC resting state connectivity with the ACC and the mPFC in particular represents part of the attentional network for self-referential processing (Gusnard et al., 2001). A

study involving patients with ongoing chronic pain provides an example demonstrating the relationship between the ACC and pain activation. Participants performing real-time fMRI learned to exhibit voluntary control over localized brain activation of the ACC that correlated with their experience of pain in real-time fMRI (rtfMRI) (De Charms, et al., 2005). They used attention and control, much like the regulation of attention associated with mindfulness, to increase and decrease activation of the ACC that in turn impacted the severity of their pain. The increased activity in the mPFC has also been linked with perception of acute pain (Seminowicz & Moayedi, 2017), and processing the affective and cognitive components of pain (Bushnell et al., 2013; Naser & Kuner, 2018). As well, the mPFC, including the ACC, has recently been declared as a "central hub" for the comorbidities that are associated with chronic pain, like depressive mood (Kummer et al., 2020). The mPFC exerts top-down regulation of sensory and affective aspects of pain and is thus described as a promising region for psychosocial interventions (Lee et al., 2015; Kummer et al., 2020).

A recent review on rsfMRI data indicated that neural signatures of mindfulness are beginning to emerge as the integrated studies reviewed reveal mindfulness is related to FC in the DMN, frontoparietal network (FPN) and SN (Sezer, Pizzagalli, & Sacchet, 2022). More specifically, FC changes related to mindfulness include increased connections between the PCC (key component of the DMN) and the DLPFC (part of the FPN). This connection seems to relate to increased abilities of attention and control. Additionally, results from this review have indicated increased connectivity between the ACC and DMPFC (DMN) in addition to decreased connectivity in the rostral ACC and the amygdala, which represents a change to emotional regulation after mindfulness intervention, as well as decreased FC between the cuneus and the SN, which has been suggested as being related to self-awareness. Finally, increased FC between the

dorsal ACC (SN) and the anterior insula (SN) has been observed and interpreted as changes to the perception of pain relief (Sezer, Pizzagalli, & Sacchet, 2022). The review has synthesized key underlying neural signatures related to attention, control, self-awareness, emotional regulation and pain relief that are emerging as neuroimaging research incorporating mindfulness expands.

Our resting state results had also determined that decreases in FC were apparent between the PCC seed region and the bilateral precentral gyri, right superior frontal gyrus and the pons in the MBSR group however not in the controls. The pons is a critical component of emotional (affective) regulation (Vollmayr et al., 2000; Cannon et al., 2007) and is part of the descending pain pathway. Mills et al., investigated FC in CNP patients and observed increased FC between the ACC and the pons suggesting a means to transfer noxious stimuli from the brainstem to higher brain regions (Mills et. al., 2018). The reduced connectivity between the pons and the PCC observed in the present study may suggest that the MBSR contributed to a reduction in pain processing. Similarly, the reduced FC between the PCC and bilateral precentral gyri positively correlated with the pain severity scores for the MBSR group, supporting that mindfulness may affect non-reactivity to pain, as has been suggested by Parkinson, Kornelsen, & Smith (2019). The results in the FC between the PCC and the right superior frontal gyrus is consistent with the literature that has found this relationship exists in experienced meditators (Taylor et al., 2013). As such, it is possible that the MBSR program may have been able to contribute to the altered perception of pain by facilitating focused attention on acceptance and less on negative pain experiences.

With continued practise, experienced meditators are able to alter their resting functional connectivity, especially in areas that are related to the DMN, indicative of control over mind wandering and executive functioning (Garrison et al., 2015; Vishnubhotla et al., 2021). With

improvement to connectivity in these areas, one is able to not only improve executive control but also emotional regulation, ultimately improving resiliency to stress (Ochsner & Gross, 2005). These findings further support the top-down regulation that is mediated by meditation. A form of top-down emotional regulation, cognitive re-appraisal, is proposed to manipulate the input to the emotion-generative system, by way of actively attending to emotional stimuli and reinterpreting it in order to modify emotional impact (Gross, 1998). In the absence of cognitive re-appraisal, the system would be reliant on lower emotion brain regions and thus lack active recruitment of prefrontal cortex or higher order brain processes. As indicated by the results, we observed increased connectivity to the prefrontal regions (mPFC), an indication that top–down regulation equated to emotional regulation may have been present. Consequently, we have noted that MBSR has an impact on frontal subnetworks which are responsible for self-awareness, top-down emotional regulation (cognitive reappraisal) and the regulation of pain while simultaneously reducing connectivity to motor regions and the descending pain pathway (Goldin & Gross, 2010; Guendelman, Madeiros & Rampes, 2017; Zeidan & Vago, 2016; Martucci & Mackey, 2018). This promotes the individual's ability to harness their innate system for self-regulation and is encouraging as an empowering tool to re-interpret the sensation of pain (Gawande et al., 2018; Grady & Gough, 2014).

DTI Results

The role of white matter is to enable efficient information processing and communication throughout the brain (Fields, 2010). In the present study, white matter integrity, as measured using DTI, was positively altered for the MBSR group where FA increased in left subcortical regions post MBSR training. The most significant change was reported in the sagittal stratum, with

increases in FA also observed in the external capsule, uncinate fasciculus, amygdala, and the hippocampus cingulum. These regions are subsequently described as follows:

- The sagittal stratum is a longitudinal fiber system connecting the occipital lobe to the rest of the brain and includes fiber tracts from the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and posterior thalamic radiation (Jellison et al., 2004).
- The external capsule also includes multiple association fibers, such as the superior longitudinal fasciculus, inferior front-occipital fasciculus and the arcuate fasciculus (Boekel & Hsieh, 2018).
- The uncinate fasciculus is identified as the white matter pathway that joins the temporal lobe to the orbitofrontal cortex and contributes to the emotional experience of pain perception (Von Der Heide et al., 2013; Oishi et al., 2014; Tian et al., 2016). These connections also contribute to language and visual perception, as well as integrating cognitive and emotional information into decision-making and emotional responding (Beer et al., 2006; Rolls, 2004).
- Lastly, the amygdala and hippocampus are implicated with the stress response and regulation of the affective aspects of pain, and information to and from both these regions is transported via fibers contained within the uncinate fasciculus, the network for emotional experiencing of pain (McEwen, Nasca & Gray, 2016; Saur et al., 2008).

Changes to FA values may result from a variety of factors, for instance alterations to myelination, axonal density, axonal diameter, and axonal membrane integrity (Taubert, Villringer, & Ragert, 2011). Increases to the FA value indicate healthier white matter, whether protective or

regenerative and are indicative of a change in the diffusion of water molecules attached to fiber bundles (Thomason & Thompson, 2011). Reductions in FA are related to the normal aging process (Sala et al., 2012). Therefore, the higher FA values are interpreted as increased (or protective) health within white matter tracts suggesting that the mindfulness training received by the MBSR group mediated this improvement. This is in accordance with Doll et al., who have shown that some large-scale brain networks, which allow for widespread communication within the brain (CEN, SN, attention and limbic), have been identified as potential targets for modification through mindfulness training (Doll et al., 2015).

Very few studies have examined the impact of mindfulness meditation on white matter integrity, however our results align with the understanding that increased FA indicates structural remodeling of white matter in a positive way, for instance for skill acquisition and memory consolidation (Liu et al., 2015; Pan et al., 2020). Cross sectional data comparing non meditators to experienced meditators demonstrated significantly higher FA values for several brain regions of interest (ROI) such as the thalamus, insula, amygdala and hippocampus with experienced meditators. Additionally, the increase in FA reported was observed in the left ROI's, similar to our findings. The authors also suggested that mindfulness meditation could be a protective factor for the FA decline typically occurring with age (Laneri et al., 2016).

In general, evidence has concluded that specific brain regions are typically altered by meditation practise such as the ACC, PCC, MPFC, insula, hippocampus and amygdala (Holzel et al., 2011). Additionally, from an anatomical likelihood estimation (ALE) meta-analysis completed by Fox et al., researchers identified certain brain regions as demonstrating consistent alterations within meditation groups including the bilateral hippocampus (memory consolidation), the ACC and mid cingulate (self and emotional regulation), left sensorimotor cortex (exteroception and

interoception), frontopolar cortex (meta-awareness), superior longitudinal fasciculus, and corpus callosum (intra- interhemispheric communication) (Fox et al., 2014). From our post hoc analyses, the left hippocampus cingulum and amygdala were specifically noted in the present study as having increased FA in the MBSR group. These brain regions are identified as essential factors in emotion regulation and increases one's ability to exemplify a nonreactive stance to inner activity and experience, one of the five facets of mindfulness (Holzel et al., 2011). An increase in FA to these regions post MBSR training may indicate how mindfulness treatment improves one's ability to manage stress, as both the amygdala and the hippocampus are implicated with the stress response. Ultimately, reducing anxiety and stress may also result in reduced pain perception (Hansen & Streltzer, 2005).

Our preliminary findings were also supported by Luders et al. who indicated that meditators had improved structural connectivity when compared with controls in the entire brain within major projection pathways (Luders et al., 2011). They had analyzed and compared 20 various fiber tracts between meditators and controls and found that meditators had greater and most improved white matter structural integrity. The most significant findings echo what was determined in the present study, whereby they detected the longitudinal fasciculus (superior) and the uncinate fasciculus as demonstrating the largest group differences (Luders et al., 2011). Similarly, Holzel's research demonstrated that the uncinate fasciculus was found to have improved FA in highly stressed participants after having completed an MBSR program (Holzel et al., 2016). The alterations to the external capsule were also observed in Boekel's study, and given the profound and vast association fibers projected through this region, changes to its microstructure have been associated with emotional regulation as well as cognitive dysfunction (Boekel & Hsieh, 2018).

The present study noted the most significant changes were apparent in the sagittal stratum, which were also negatively correlated to pain interference and severity. This major white matter bundle has fiber projections from parietal, occipital, cingulate and temporal regions to subcortical and brainstem structures with complex internal (optic radiations) and external layer compositions corresponding to fibers of the superior and inferior longitudinal fasciculus (Maldonado et al., 2021). Although these results were the most significant finding of the DTI analyses, similar findings are currently lacking in the MBSR literature. Nonetheless, some research examining integrative body-mind training (IBMT) has signaled positive changes to axial diffusivity (AD) (interpreted as improved axonal density) in the sagittal stratum region after 4 weeks of training. However, no significant FA findings were observed in the sagittal stratum (Tang et al., 2012b).

It is of particular interest that the changes observed in the present study were all indicated in the left hemisphere specifically. This may have potentially been explained if all participants had had surgery or pain only on one side of their bodies, this however was not the case. All women were right-handed to ensure a comparable sample, however language lateralization as evidenced by the literature may also explain the left lateralized results (Piervincenzi et al., 2017). Given the lack of substantiated evidence, it is difficult to interpret this lateralization with certainty. One possible explanation is related to positive valence and acceptance that is fostered with MBSR, as these appear to be more left lateralized. Perhaps the MBSR intervention enhanced the left sided white matter tracts specifically due to the characteristics of the intervention (Davidson et al., 2003). This explanation of positivity and acceptance is strengthened by the correlation results revealing a negative relationship between FA and pain severity and pain interference scores on the BPI. Significant improvements to vast white matter tracts relating to pain, attention, emotional regulation and sensory symptoms (Malfliet et al., 2017; Liu et al., 2018) may help to improve

message communication between networks, and ultimately assist with the re-evaluation and interpretation of pain.

EST Results

The results of this pilot study are aligned with previous research and indicate support for how MBSR may improve emotional reactivity and attention in conjunction with the neural mechanisms that underlie these changes. Mindfulness constitutes training in interoception and significant reductions in brain activity were observed in brain regions related to pain, emotional regulation, and cognitive processing following the MBSR intervention. A significant reduction in BOLD activity was apparent in the MBSR group across left cortical brain regions related to pain and emotional processing during an emotional reactivity task where participants were challenged by emotional stimuli (pain-related words). The reduced activation was primarily apparent in left regions associated with visual attention (precuneus, primary visual cortex) in addition to the left somatosensory and dorsolateral prefrontal cortices. The precuneus is a brain region involved in several complex functions, such as memory, integration of information, cue reactivity, mental imagery and affective responses to pain (Borsook, Malaki & Burstein, 2015). Reduced activation in the precuneus region has been associated with reduced pain perception and higher trait mindfulness (Harrison et al., 2019). The primary somatosensory cortex is responsible for processing afferent somatic information from the body (proprioception, nociception, and temperature) (Borich et al., 2015) and is most commonly activated in chronic pain conditions (Alomar & Bakhaider, 2018). Given a reduction in emotional activation to this brain region we can infer that the pain-related words may have become less salient post-MBSR. The DLPFC on the other hand is implicated with executive functions such as decision making, mood regulation, language processing, sustaining and monitoring the focus of attention, and working memory

(Hertrich et al, 2021; Petrides, 2000; Levy & Goldman-Rakic, 2000). While some have found contrary results, i.e., increases in activation in the right DLPFC with the introduction of mindfulness meditation (Tomasino & Fabbro, 2016), their results were indicative of a mind at rest. We have interpreted our initial results of the attenuated activity observed in the MBSR group to suggest a possible reduced requirement for executive control over emotions and emotional stimuli and altered pain perception. This is supported by results obtained from Gard et al., suggesting that decreased activation in the lateral prefrontal cortex was associated with pain modulation and the increased ability of "letting go" facilitated by reducing cognitive control through mindfulness practice (Gard et al., 2012).

It is promising that during an engaged emotional task, the participants in the present study were able to achieve a reduction in activation to this pivotal brain region (DLPFC) responsible for executive function and reappraisal of negative stimuli (Ochsner et al., 2002). Our understanding is that this may have been potentiated by the deliberate and intentionally focused mindfulness training received by the MBSR group. The control group did not show unique regions of reduced activity during the EST at the second imaging session however results indicate slower reaction times to emotionally charged pain-related words, while this reaction time difference was not observed with the MBSR group. The reaction time results are difficult to interpret as we did not observe significant variability between the pain-related and neutral words used in the study. This may have been the result of the small sample size, thus a larger sample size would be required in future research. It is conceivable that the MBSR group retained the ability to become less reactive overall and thus more resilient to the affective cues as presented during the emotional task given the decreased neural activation.

These results overlap generalized research on mindfulness meditation and emotional interference on a cognitive task. Ortner, Kilner and Zalazo found that participants with more experience with mindfulness meditation displayed less cognitive interference when presented with unpleasant affective images, thus mindfulness attenuates prolonged reactivity to emotional stimuli. This suggests that experienced practitioners are able to disengage their attention from emotional information and redirect their attention to environmental or in this case cognitive information in the task (Ortner, Kilner & Zelazo, 2007). A process model of emotional regulation suggested five distinct regulation strategies such as situation selection, situation modification, attentional deployment, cognitive change and response modulation (Gross, 1998). It seems that attentional deployment is more readily influenced by mindfulness meditation by using cognitive control to control negative rumination patterns (Ramel et al., 2004) as well as attention regulation and allocation (Slagter et al., 2009). Although, limited research is available that objectively identifies the specific brain regions that are responsible for these attentional shifts, the current study has been able to offer some preliminary mechanisms, and as such substantiates further research in this area.

Results obtained from the current study indicate higher scores on the FFMQ in the MBSR group, signifying that the intervention group had increased their overall level of mindfulness on 5 subscales (non-reactivity to inner experience, observing/noticing, acting with awareness, describing and non-judging of experience). The intervention group had significantly increased their level of mindfulness as a direct outcome of the 8-week MBSR program whereas this effect was not apparent in the control group. The most significant changes in the MBSR group were noted in the subscales of non-judging of experience and nonreactivity to inner experience, which was not observed in the control group. This finding may be supported by the rsfMRI results where reductions in FC between the PCC and bilateral central gyri also correlated with participants'

interpretation of pain severity scores and suggested an enhanced ability of non-reactivity to pain in the MBSR group (Parkinson, Kornelsen & Smith, 2019). Additionally, when considered in collaboration with the FFMQ scores, we noted that the MBSR group had lower pain interference scores on the BPI indicating that a relationship between altered pain perception and mindfulness was present yet absent with controls. We can postulate that the MBSR group had significantly increased their levels of mindfulness and thus by extension may have reduced their ratings on the BPI as attribution to the mindfulness training and its modulating effects on pain-related brain areas as discussed. However, further research is needed (e.g. mediation analyses) prior to firmly concluding its mediating properties.

In summary, the present pilot study results indicate changes were observed in areas specific to processing sensory information such as touch, temperature and pain, nociception and proprioception, and affective responses to pain as demonstrated by the EST. It is possible that given the increased connectivity in resting state networks as well, that these emotional and functional connections overlap the underpinnings of mindfulness teachings. The increased FC observed in our study from the resting state analyses, may indicate that improvements were made to the DMN networks ability to attend to emotional impulses, regulate self-referential mental activity, control internally directed thinking, and improve executive functions such as decision making. The same was evident for increased FA, as portrayed through the structural DTI scans, to the left subcortical areas (sagittal stratum, external capsule, amygdala, hippocampus) that are important for emotional processing, emotional memory, emotional regulation, affective-perceptual and cognitive–evaluative forms of empathy, arousal and sensorimotor functions. Overall, these results may suggest that changes apparent in the DMN brain regions, responsible for facilitating

focused attention, increased efficiency within regulating networks related to pain, emotional regulation, visual attention and cognitive processing over time, as a result of MBSR training.

These findings shadow the fear avoidance model as posited by Fordyce in 1976, whereby the introduction of the mindfulness intervention enables the individual to reframe their cognitive, emotional, and behavioural responses to the experience of pain altering the extent of the exaggerated perception of pain. Since at the core of the fear avoidance model is the patient's interpretation of pain, mindfulness offers patients the opportunity to an open and alternative interpretation. In lieu of focused attention on potential future re-injury or an expectation of pain, mindfulness guides the individual to focus on the present moment and to re-direct their attention on acceptance through such practices as breathwork. In accordance with the model, this training may serve as the basis for approaching pain as nonthreatening and minimize a catastrophizing mentality, an interesting perspective for future study. Since attentional processes play a key role in the assessment of pain, mindfulness enables the patient to focus attention on breathing, openness and nonreactivity to inner experience in order to divert automatically attending to pain and pain-related feedback, and instead choosing to focus attention on breathing and acceptance.

Synthesis of Results

We have observed that MBSR has the potential to alter the DMN, alter how we react to pain-related stimuli with healthy emotional regulation and improve executive functioning ability, resulting in decreased pain severity and pain interference in a CNP group. Additionally, in a short program of 8 weeks, MBSR training demonstrated that it may impact cerebral white matter integrity and potentially serve as a protective factor in managing constant chronic pain. It is difficult to succinctly interpret these results without accounting for extraneous variables, however one explanation may be, that the difference may reflect the MBSR group's learned ability to

attentively engage in heightened emotional regulation over time and thus possess more resilience to salient affective cues. Whereas the control group's results were in accordance with not having had the advantage of receiving the tailored program. Although the preliminary results are supportive of improvements to neural mechanisms potentially resulting from mindfulness training, given the small sample size and the design of our pilot study, results should still be interpreted with caution.

Comparing the results obtained via the three neuroimaging modalities, we observed a commonality between the structural results obtained from the DTI analyses, and the functional results of the EST. Both had illuminated the impact of mindfulness on specifically left subcortical and cortical brain regions. These results correlated with data obtained from the pain scores and effectively rendered the emotional stimuli less salient and reduced the overall perception of pain in the MBSR group. As discussed, the left lateralization of results may be attributable to handedness (all right-handed) or possibly emanating from the effects of MBSR in encouraging acceptance. However, according to the valence hypothesis suggested by Davidson, the pattern of activation and hemispheric dominance is dependent on the emotional valence of a stimulus (Davidson, 1995). Davidson offered that left hemisphere was dominant for positive emotions, whereas the right is for processing negative emotions based on the evidence of numerous neuroimaging studies. Therefore, there is a possibility that the MBSR intervention incited more positivity in the participants as the program was interpreted with positive valence, resulting in improved structural and functional activation within left cortical and subcortical areas, building upon relative hemispheric dominance for processing positive emotions. Although, the fMRI resting state analyses did not reciprocate left lateralization, the debate persists as to whether or not Davidson's hemispheric model should be interpreted as absolute brain asymmetry, or relative dominance. Our results support the perspective

that whole hemispheric interpretation is much too general and anatomic specificity is still required given our varied hemispheric results (Alves et al., 2008; Wager et al., 2003).

This study was centered on the impact MBSR training would have on a group of women post breast cancer experiencing CNP. Although the literature to date outlines that sex differences within chronic pain groups do exist, there is insufficient research to indicate if sex differences would remain consistent in a sample of men and women with CNP adhering to a MBSR treatment plan. As stated earlier, some sex differences have been reported in the literature, specifically, in a group undergoing a PT/CBT treatment protocol, where women had significantly improved on QoL outcomes, and men had shown no difference (Jensen et al., 2001). In Zhou et al. (2018), the authors had also realized sex was a statistically significant factor correlating with the prevalence of chronic pain in a sample of 957 Chinese seniors. Females were reported as having a higher pain prevalence than older male adults, and these findings were consistent with other samples studied in both the US and Brazil (Johannes et al., 2010; De Moraes Vieira et al., 2012). There may be underlying biological mechanisms that could account for this variance in womens' experience of pain versus men, such as hormonal and/or psychosocial factors predisposing women to higher pain prevalence (Wissenfeld-Hallin, 2005). Given the significantly lower incidence of breast cancer in men compared with women (1 in every 100 diagnoses – www.cancer.org), it was not the intention of this study to include men and examine sex as a variable. This would require further investigation and should be incorporated into the objectives of future studies as it would be important to determine if receptiveness to MBSR within a CNP group would also vary concurrently with the variability of pain.

Limitations

There are several limitations to this study that need to be taken into consideration when interpreting the results. The first relates to the sample size of the study. The sample for this study was rather small and consisted of exclusively Caucasian women within a wide age range. The researchers were limited by the number of recruits from the larger RCT study, as only volunteers who met MRI compatibility requirements were included, and we were unable to recruit additional participants beyond the participants who were selected as part of the larger RCT study. Relatedly, a participant bias may have occurred since the women who volunteered for the neuroimaging portion may have demonstrated enhanced eagerness to participate, as this required 2 separate, time-consuming visits to the MRI scanner. It is possible that our results may indicate an overestimation of the intervention effect given this participant bias. This may also explain the MBSR groups noted improvements to self-reported pain measures related to treatment expectancy for improvement. Additionally, participants within the control group likely withheld from seeking out any alternative forms of pain relief thus this may have accentuated their perception of pain. Although the total sample size for the neuroimaging research was small (n=23), the effect was still detectable after multiple comparisons, thus speaking to its relevance as an exploratory study that merits further research. Despite the difficulty and nature of neuroimaging research, it is nonetheless recommended that future research within this clinical sample include larger sample sizes with varied demographic characteristics to better extrapolate results.

Relating to the sample, it would also have been recommended to have a healthy control group in addition to the wait-list controls. Our wait-list control group participants were also recruited from the larger RCT study and were offered the MBSR program upon completion of the data collection relevant for the study. Given the limitations inherent with a RCT with a wait-list

control condition, it is challenging to succinctly surmise at the true mediator for improvements to reported pain was in fact the MBSR program, and a healthy control or active control group would have provided more insight into the mediating mechanisms. It was impossible to complete neuroimaging scans with the wait-list control group upon completion of the MBSR program, as it was not financially viable and scanner time was no longer available. This would have provided further substantiation of the results, with greater power. Similarly, long-term follow-up of the study participants would have provided an excellent opportunity to monitor the lasting effects of the MBSR, however resource constraints did not allow for this.

Additionally, there was one noted outlier in the study, aged 81 years old, which could have potentially skewed the study findings regardless of normality of the age demographic. In order to determine if her participation and inclusion represented a true outlier, analyses were conducted both including and excluding her results. The obtained results remained unaltered. Her structural scans also demonstrated support for adequate brain health, and her performance on the EST matched that of the other study participants with similar response times and recorded errors.

There are certain invaluable variables which we were unable to control for in this study, for example, time since surgery, type of breast cancer treatment received (radiation/chemotherapy), doses of chemotherapy received, type of chemotherapy drugs, current medication, and menopausal status. Other factors potentially influencing results relate to any prior affective disturbances (anxiety, depression, post-traumatic stress disorder) as well as any potential cognitive impairment relative to chemotherapy treatment and affective distress. These considerations were not captured or controlled for within the neuroimaging component and is also reflective of why neuroimaging research is crucial in order to provide objective measures to further clarify subjective results. Additionally, a wide array of protocols exist within the realm of this research making it difficult

for a true comparison to the current literature. For example, different protocols exist for administering the rsfMRI sequence, including eyes open or eyes closed instruction. Also, there are various adaptations to the MBSR program within the literature, where not all are consistent with the original MBSR curriculum as initiated by Dr. Jon Kabat-Zinn. For instance, as this study was related to a chronic pain patient group, attention and priority were placed on pain in the body during the mindfulness exercises. Additionally, the MBSR intervention in our study was delivered by five health care professionals (psychologists and social workers) with formal MBSR training, and various teacher training background and years of experience. The intent was to ensure all teachers had a minimum of 5 years of teaching experience however two exceptions were made; one facilitator was a post-doctoral student who was certified to teach mindfulness intervention and secondly a graduate student who had more than 5 years of experience with mindfulness-based interventions and two years of teaching experience. This inconsistency most likely did not impact the study results, since all teachers maintained a standard curriculum throughout the sessions. Additionally, this situation is representative of a real-world scenario, and mimics what would occur outside the context of research.

The choice of words used during the Emotional Stroop Task may also be considered a confounding variable. The words chosen encompassed both pain-related words as well as negative emotional words, however more stringent use of exclusively pain-related words would have provided more specificity to the study results, making them more readily interpretable and possible to extrapolate.

The experience of pain and specifically CNP, is extremely subjective and multifactorial where no individual experience is alike. This fact limits the extrapolation of the study results to a larger population, as consistency of symptoms and experience is difficult to achieve. It is

unrealistic to expect a perfectly consistent and uniform sample in this context, as is the case with most research. Thus, repeating the study with a larger sample size would account for the variability of individual experience and minimize the potential impact of such a confound. Given that each individual has their own unique experiences, it is equally possible that some participants may have experienced adverse events while taking part in the MBSR intervention. This aspect was included as part of the larger RCT, and no adverse effects were reported. Nonetheless, it is important to include assessments of adverse events in future research in order to capture potentially negative side effects in a timely manner while taking part in collaborative mindfulness sessions. For instance, some participants may have been severely traumatized in their past and the act of simply focusing and paying attention could trigger unconscious emotional turmoil potentially placing the participant in a compromising situation. A participant may be ill prepared, unwilling to vocalise or incapable of processing difficult emotions within the open group format of the intervention (Farias et al., 2020). This aspect of MBSR is only beginning to germinate with respect to proper investigation and would be an important assessment to include moving forward with mindfulness research.

Clinical Implications

Adverse effects of breast cancer are long lasting, thus trying to reduce immediate term and long-term side effects is an important undertaking. The results of this study are exciting in that they support the growing body of evidence which suggests that mindfulness practise may alleviate pain by changing their relationship to and altering the perception of pain and cultivating acceptance. This was supported by the increased FC in brain regions, an alteration in the FA of white matter, and improved emotional regulation which correlates to a reduction in the sensation of pain in women with CNP. Given CNP is very difficult to treat with standard pharmacotherapy,

it is crucial to discover ways to treat the debilitating symptoms with adjunctive therapy. This study helps to support the literature in the discovery of the mitigating effects MBSR may have on debilitating and life-altering illnesses such as CNP, where focused attention and training can alter the functioning and structure of the brain, thus improving overall QoL, and rendering patients less dependent on pharmaceuticals.

General Conclusion

Given the challenges faced with prescribing the appropriate pharmacological treatments, and the cost burden associated with chronic pain on our health care system, it is promising to observe the positive impacts a short course in MBSR may have on ameliorating debilitating painful symptoms without great monetary investment. Also, understanding that the experience of pain is very subjective, it is crucial to have an objective measure of the neural basis of CNP in order to better comprehend the underlying mechanisms of pain, and what may contribute to its effective management. This underlines the importance of objectivity in research, and in this case, justifies the use of fMRI/MRI as an objective measure to assess how MBSR treatment is supportive of altering the perception of pain at the neuronal and microstructural level.

It is imperative to investigate the manners in which we may enhance QoL in this patient group, bringing more acceptance and peace to their lives so they may know joy once more and live with less pain. Given that individual experience of pain is so unique, it is important to assess personal experience to tailor treatment plans that improve the likelihood of success. Mindfulness practise is an intervention that should be evaluated under each circumstance for its potential benefits as psychotherapeutic treatment as witnessed in this study, but also for its versatility. There are a variety of meditation programs available, along with various ways of practising mindfulness. It is possible to engage a mindful mindset while taking part in a myriad of daily activities.

As mentioned, the treatment of CNP is extremely difficult, given underlying medical conditions, or co-morbidities that may occur as a result of the primary disease. Although this study demonstrates that MBSR training may be a promising treatment for aspects of CNP, it is also important to maintain a multidisciplinary approach to address all aspects of the individual suffering with the disease and its comorbidities. There is no one-size-fits all approach to tackling CNP, however this study demonstrates that MBSR may be used to ameliorate symptoms associated with CNP and that MBSR training may be offered in conjunction with alternative treatments including pharmacotherapy, physiotherapy, CBT among others. This study highlights the potential for including MBSR as part of the repertoire of treatments that should be weighed, considering patient symptoms, abilities and needs. As the literature supports a multidisciplinary approach to pain management for chronic pain and CNP, we can propose the inclusion of the MBSR program or similar mindfulness programs into an interdisciplinary/multidisciplinary strategy for treatment and research of CNP post breast cancer given the results of this study.

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Appendix A

Table of words used for the Emotional Stroop Task (EST)

Cont1	Emo1	Cont2	Emo2	Cont3	Emo3	Cont4	Emo4
Develop	Failure	Communing	Irritable	Context	Anxious	Air	Die
Applause	Hopeless	Patrol	Lonely	Binoculars	Humiliation	Nonchalant	Mastectomy
Footnotes	Throbbing	Hail	Dull	Surprised	Nightmare	Cookout	Assault
Coasted	Pounding	Flew	Wretched	Suggestion	Punishment	Candlestick	Uncomfortable
Rattling	Tiring	Flowed	Sore	Inspired	Rejected	Wealth	Scream
Astonished	Unbearable	Defining	Hurting	Bathtub	Violent	Nation	Defeat
Agreeable	Depressed	Closest	Nagging	Spring	Cancer	Glance	Brutal
Rides	Grief	Waterskiing	Overwhelmed	Lighthouse	Frightened	Chimney	Torture
Upper	Sharp	Accent	Sorrow	Gallon	Breast	Glamour	Surgery
Sleeve	Aching	Vehicle	Worried	Pretty	Damage	Actor	Tumor
Accumulate	Agonizing	Rendered	Tender	Fragrance	Suffocate	Guaranteed	Disability
Limitless	Punishing	Mention	Dreadful	Friend	Trauma	Knowledge	Terrified
Note	Fear	Profusely	Gnawing	Tick	Pain	Fries	Panic
Prime	Angry	Bleaching	Exhausting	Rabbit	Crisis	Kitten	Suffer
Descend	Burning	Boyish	Sickening	Nature	Guilty	Canoe	Shame
Insects	Killing	Unit	Dead	Family	Attack	Excellence	Distressed