Individual Differences in Emotional Disposition, Psychological Factors, and Central Mechanisms in the Development and Maintenance of Persistent Pain

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Declaration

I confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged.

The research presented in Chapters 3-6 have been reported in articles that are published, under review, or are currently in preparation for submission:

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Mitigating Circumstances

Due to the Covid-19 pandemic, the structure and quality of this research was mitigated. Experimental testing which involved direct contact between humans was halted for over a year. During the time advised to work from home, I decided to carry out a systematic review and meta-analyses which was loosely related to the theme of my thesis. As time went on it became clear that in order to complete a PhD in the required time, I would have to change its contents from the original plans.

My thesis consequently consists of a secondary analysis, the meta-analyses I was working on, and two studies using data that had been collected. When testing stopped, data for 44 participants had been collected. As a result, two of the studies in this thesis had a reduced sample size (Study Two and Study Three).

Originally, the final study in my thesis had intended to explore the effectiveness of Cognitive Behavioural Therapy (CBT) and aimed to identify individual differences in why some people might respond with greater success to psychological treatment than others. As this study split the 44 participants into two groups (an experimental and control group), it was deemed that not enough data had been collected for it to be analysed. As a result, a systematic review and meta-analyses took the place of this final study. Data collection for the CBT project continues today (26/04/2022).

I, therefore, request that the examiners take these mitigating circumstances into account when assessing the coherence of my thesis, the sampling adequacy of Studies 2 and 3, and the references towards appropriate psychological intervention (CBT).

Table of Contents

1. Abstract

Pain is a complex multifaceted experience. Pathology does not always correlate to symptomatology, with many individual differences being involved in the genesis of chronic pain. Identifying some of the factors associated with pain will help to build a model for vulnerability and inform on targeted interventions.

Study one compared a large chronic pain population to a healthy population for differences in psychosocial factors in the workplace. The results indicated that, compared to healthy individuals, people in pain reported significantly poorer relationships with their managers and colleagues, felt they were discriminated against, felt subjected to more threats and abuse, and were not as appreciated for their efforts. Interestingly, they felt more competent in their job role and reported greater job security.

Study two assessed whether attending to a painful stimulus (intrinsic attention to pain) was associated with a 'pro-nociceptive' phenotype (characterised by enhanced temporal summation and less efficient conditioned pain modulation). The results showed that endogenous pain modulatory mechanisms were responsible for 39% of the variation in intrinsic attention to pain.

Study three correlated Five-Factor Mindfulness Questionnaire (FFMQ) scores with rates of sensitisation to a repetitive/consistent pain stimulus over a brief paradigm. The findings revealed that people who scored low on the FFMQ were at higher risk of sensitisation to pain.

Study four examined the construct validity of the Central Sensitisation Inventory (CSI) by meta-analysing correlations of the CSI with measures of nociceptive responsivity (Quantitative Sensory Testing) and psychological constructs (anxiety, depression, stress etc). The CSI was strongly correlated with psychological constructs and showed weak/no association to nociception.

Overall, this thesis suggests that a wide range of biopsychosocial factors contribute towards pain. Workplace environment, endogenous modulatory mechanisms, trait mindfulness and

psychopathology should be considered when building a model to help predict vulnerability and inform on targeted intervention, to improve resilience to pain.

2. Introduction

2.1. The Problem of Pain

2.1.1. Acute Pain

Acute pain can be described as a necessary evil; although seemingly unpleasant it serves to protect the body from external harm e.g., removing one's hand from a flame to avoid getting burnt. In the first instance, acute pain acts as the alarm system that helps us to avoid potentially harmful or noxious stimuli by taking evasive action (the avoidance system). The second function of acute pain is to protect injuries from further insult so that the injured area is under minimal stress while it repairs (the restorative system) (Grahek, 2011). This is why people might walk with a limp when they are faintly injured, or why a bruised/cut area becomes more sensitive. Such pain acts as additional sensitivity to remind us to be particularly careful with the injured area, so that it has time to repair itself and recover efficiently. When these systems are absent it can lead to disastrous consequences, such as in the case of Miss C, who was born with congenital analgesia. Her inability to feel pain led to extensive skin and bone trauma that directly resulted in her death (Baxter & Olszewski, 1960). Pain is therefore nature's most sophisticated self-protective psychophysical system.

2.1.2. The Transition from Acute to Chronic pain

A functional pain system is not so simple; sometimes it goes wrong. People's avoidance systems may become overly sensitive (sensitisation) which, although it serves an important survival function, can become demoralising when patients are subjected to constant outbursts of pain in innocuous settings (Patel, 2019). Or, more commonly, the restorative or repair system goes wrong whereby pain continues to persist long after the injured area has fully recovered (i.e., chronic pain) (Grichnik & Ferrante, 1991; Rosenbloom et al., 2013). Little was understood as to why some people develop this persistent pain and others do not, but with recent developments in research, we are beginning to grasp the bases for such individual differences. This topic will be addressed throughout this thesis.

2.1.3. The Costs of Chronic Pain

Chronic Pain (CP) is characterised as pain that lasts beyond three to six months (Merskey et al., 1994). CP is a problem that accompanies many disorders and physical conditions ranging from fibromyalgia and osteoarthritis to migraines and low back pain. It is often regarded as a co-morbidity, or a symptom of another condition (van Hecke et al., 2013). But recently, CP has been classified as a disease by the International Association for the Study of Pain (IASP), with its own taxonomies and definition (Merskey, 2008). It is one of the most common reasons people seek medical treatment and can be a great burden on people at both individual and societal level, not to mention its imposed economic costs'. It is estimated that 20% of adults in Europe live with chronic pain which seriously impacts their daily activities, social life and work (Breivik et al., 2006). In 1992, approximately 8 million adults in the UK reported their chronic pain to be moderate to severely disabling (Von Korff et al., 1992), with recent research indicating that these numbers have grown to just under 28 million adults in the UK who currently live with chronic pain (Fayaz et al., 2016). Overall, chronic pain costs the UK economy approximately £10 billion per year, with its economic impact being greater than most other health conditions (Maniadakis & Gray, 2000). Gaskin and Richard (2011), using the Medical Expenditure Panel Survey, identified about 100 million adults in the US, who were affected by chronic pain (Gaskin & Richard, 2011). Then, extrapolating figures on medical expenses and lost work productivity, they estimated that chronic pain costs the US somewhere between $560 to $635 billion. This eclipses the estimated annual costs of heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion), based on statistics published by the 'National Heart, Lung, and Blood Institute' and American Diabetes Association (American Diabetes Association, 2008; National Heart & National Institutes of Health (U.S.), 1976).

Overall, the cost of chronic pain is huge, imposing a great socioeconomic burden on society. Despite these figures, the impact of chronic pain may still be underestimated. Studies that attempt to calculate a cost associated with pain, do this by cumulating medical costs of treatment, disability

cheques, tax revenue, legal fees, working days lost, and estimations of lost productivity due to debilitation (Gaskin & Richard, 2011; Maniadakis & Gray, 2000; Mayer et al., 2019; Phillips, 2009). These studies, however, do not incorporate the humanistic or psychosocial costs that people with chronic pain face.

2.1.4. Humanistic Costs of Chronic Pain

A World Health Organisation (WHO) survey of primary care patients across 15 countries found that 22% of patients had pain lasting for over 6 months, which affected patient's quality of life and ability to carry out daily activities. They found that people with chronic pain were more likely to be anxious or depressed (Gureje et al., 1998). The monetary costs of chronic pain, however enormous, merely touch the tip of the iceberg when considering the personal suffering that accompanies chronic pain.

One of the major problems for people with chronic pain is the disparity between symptomatology and pathology, making cases so difficult to diagnose and treat. Diagnostic tests often come back reporting no identifiable issue (Maus, 2010) and people without pain can have seemingly severe spinal abnormalities (Jensen et al., 1994). This makes accurate diagnosis extremely difficult. For instance, a review of spinal degeneration imaging found that for 20-year-old patients who expressed no symptoms of pain: 37% had disk degeneration, 30% had a disk bulge and 29% had disk protrusion (Brinjikji et al., 2015). There are also severely painful conditions such as fibromyalgia, migraines, and chronic low back pain where no aetiological cause can be easily identified. This makes medical professionals susceptible to type one diagnostic errors (a chronic pain diagnosis, without appropriate symptomatology), as well as type two errors (failing to diagnose a condition due to lack of observable injury). Consequently, a doctor may be unsure of how to treat a patient, meaning they will often refer them somewhere else e.g., a physiotherapist. Patients are often passed from specialist to specialist without ever receiving a clear diagnosis (Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior, 1987).

A lack of clear diagnosis as to the source of experienced pain can lead to severe frustration in patients, with the feeling that there is no one able to identify the cause of their problem, let alone being able to treat it (Frank, 2004). A European survey on chronic pain reported that 40% of chronic pain patients were not satisfied with their treatment and 36% were not satisfied with their doctors (Breivik et al., 2006). This frustration mounts as they may begin to fear that there is no cure for their pain, which can lead to an overwhelming sense of hopelessness (Orbach, 1994). This frustration can be carried into the workplace with no diagnosis, meaning that companies and managers are reluctant to give sympathy or any lenience to the employee in chronic pain, owing to a lack of understanding (Rasmussen et al., 2014).

Physically, as the pain persists, people may develop fear-avoidance behaviours out of fear of further injuring themselves (Vlaeyen & Linton, 2012). See section 2.2.2. for more details on the fear-avoidance model of pain. The impact on a person's quality of life can be immense. People in pain often find it difficult to get comfortable, which can interfere with normal sleeping patterns (Finan et al., 2013) and contribute towards chronic fatigue as a co-morbidity (Jackson & Bruck, 2012). Work and home life are affected as menial tasks become more difficult and concentration lapses (Dueñas et al., 2016). Pain rumination begins to occur as people in chronic pain become unable to think of anything other than their insufferable pain (Edwards et al., 2011). Friends and family are often unaware and misunderstand their struggle (Wernicke et al., 2017); they may not be able to acknowledge that a person can be in pain without any clear presence of an injury (broken bone, torn tissue). Coinciding with this, people in pain have powerful incentives to stifle their groans as they do not want to burden others (Kowal et al., 2012), meaning patients often suffer in silence (Watkins et al., 2006). This can lead to feelings of social isolation (Harris, 2014). They feel pressure to stay at work and/or return to work prematurely (Wainwright et al., 2013), and fear they are missing out on the life they used to live (Dysvik & Furnes, 2018; McCracken & Vowles, 2006).

These hardships can often wear someone down, and lead to persistent pain rumination (Buenaver et al., 2012; Sullivan et al., 2004; Van Damme et al., 2004). Ruminating has a substantially negative impact on mental health, particularly depression (Bair et al., 2003; Fishbain et al., 1997) and anxiety (Asmundson & Katz, 2009). In the most severe cases, chronic pain can lead to debilitating feelings of hopelessness and even suicidal thoughts (Tang & Crane, 2006), as patients see no cure in sight, no signs of improvement, and deal with seemingly clueless practitioners. 22% of people with chronic pain feel their doctors never ask them about their pain and 20% believe that their pain is not even viewed as a problem (Breivik et al., 2006). Unsurprisingly, people with chronic pain often become angry and frustrated, which, over time, has led to a social stigma against 'difficult' chronic pain patients (Cohen et al., 2011). This, in turn, leads to further feelings of isolation and loneliness, which can only exacerbate the pain experience further (Jaremka et al., 2013); social support being a prominent factor in people's abilities to cope with pain (López-Martínez et al., 2008).

Work productivity begins to wane as people with chronic pain may take considerable time off work. This can cause animosity between employers and employees (Hesselius et al., 2009), as the workloads of co-workers are increased or work is not getting done. As a result, people in pain feel pressure to return to work prematurely, despite knowing they will face physical difficulties (Chou et al., 2018). As the cause of the pain is often unidentifiable (Amirdelfan et al., 2014), and there is a lack of visible tissue damage or broken bones, it is hard for doctors to estimate how long patients should be out of work for (Wrapson & Mewse, 2011). Without a concrete diagnosis, peers and managers may have little sympathy, and question the legitimacy of an employee's pain (Rasmussen et al., 2014). People in pain often find it hard to make decisions (Apkarian et al., 2004), and some may find it increasingly difficult to return to work. They may have concerns over job stress, high physical demands, job dissatisfaction, an unsupportive workplace, fear of doing further damage and fear having to request modifications to help accommodate their condition (Shaw et al., 2009). They may believe that they will be scrutinised by their peers and feel the need to catch up for lost time, but are scared that their bodies will not be able to cope with the increased workload (Shaw et al.,

2009). Thus, feelings of anxiety continue to accumulate which further exacerbates the pain and stress experienced. This accumulation of psychosocial stressors alongside physiological symptoms leads to a vicious cycle of exacerbation, that makes chronic pain so resistant to treatment.

2.1.5. Individual Differences in Susceptibility to Chronic Pain

Whilst the 21st century has seen a heightened focus on psychological health within treatment, chronic pain treatment still often follows a pathological diagnosis (Cohen et al., 2013; Gatchel et al., 2014; Lovell, 1995; Tu et al., 2005). Most current strategies of treating pain (analgesics, surgery) do not acknowledge the role of psychological factors, but target putative tissue damage as the primary source of pain. In many cases, traditional surgical and pharmacological treatment strategies have been deemed insufficient for managing chronic non-cancer pain (Turk et al., 2011), with psychological/multi-modal treatment being required. Surgery can be unnecessarily invasive (DuBois et al., 2017) and lead to further complications i.e., chronic post-surgical pain (Macrae, 2008; Stahel et al., 2017). Long term use of opiate-based painkillers can lead to increased tolerance, subsequent addiction and dependence (Society, 1997). For example, Hojsted et al. (2010) conducted two methods for diagnosing opioid addiction, finding that either 14.4% or 19.3% of chronic pain patients met the diagnostic for opioid addiction, depending on the method used (Højsted et al., 2010). Similarly, Skurtveit et al. (2011) identified that 191 out of 686 (28%) regular opioid users, taken for chronic pain, engaged in problematic behaviours indicative of addiction (Skurtveit et al., 2011).

Promoting fewer problematic solutions to treating chronic pain should be imperative. One possible way to safely reduce cases of chronic pain may be to identify those who are susceptible to developing chronic pain early. The use of interventions can then be encouraged at an early stage to reduce the risk of transition from acute to chronic pain, before pain becomes psychologically entrenched and more resistant to treatment. Exploring individual differences in pain response could help us to understand why this transition to chronic pain occurs in some but not others. If markers

for pain vulnerability can be identified in laboratory settings, they may be useful for indicating who is at risk for developing chronic pain.

Moreover, if possible markers which indicate vulnerability to pain can be identified on an individual basis, such information would be useful for tailoring intervention programmes which focus on improving function and emotional wellbeing, with realistic expectations of recovery. For most pain patients, identifying key psychosocial factors will expand the range of therapeutic options to improve the efficacy of treatment and to help the patient regain control of their symptoms and their impact. Given the complexities of different chronic pain disorders and the limited availability of suitable care, several pain patients have been insufficiently served by the health-care system (Jegan et al., 2017). It would therefore be beneficial to identify possible risk factors of exacerbation and offer relevant reassurance as a precursor to exploring treatment options. Recognising psychosocial factors which could exacerbate pain in individuals could be repositioned as opportunities to develop more effective interventions. Yet, it should be noted that the mere existence of factors associated with the development and maintenance of pain do not necessarily predict the development of chronic pain, and the absence of risk factors does not guarantee successful adaptation to chronic pain (Ramírez-Maestre & Esteve, 2013). In fact, research has shown that interventions tailored towards targeting specific risk factors are rarely more beneficial than usual care (Kent & Kjaer, 2012). Less is known, however, about possible psychosocial factors that are protective and could inform on favourable interventions for pain. Focusing on positive psychology for pain resilience and coping may hold an important key for informing on effective protective strategies, to promote successful adaptation (Jegan et al., 2017).

Many studies have suggested that there are individual differences in how individuals process and respond to pain. For instance, clinical evidence has revealed that tissue damage has little to no correlation with the intensity of pain experience (Balagué et al., 2012; Bogduk, 2012; Cheung et al., 2009; Register et al., 2012). Some people report to the clinic with severe tissue damage, despite

experiencing very little pain at all, while other patients report debilitating pain with only minimal tissue damage. Some people appear more susceptible to developing chronic pain than others. For example, only a third of lower back pain patients continue to experience problems 12 months later. For osteoarthritis, no link has been found between damage severity and pain, and only 34% of diabetic neuropathy patients develop painful neuropathy (Abbott et al., 2011; Denk et al., 2014; Dieppe & Lohmander, 2005; Maher et al., 2017). In cases of non-specific low back pain, there seems to be no identifiable cause that can account for pain (Chenot et al., 2017). This suggests great complexity and inconsistencies in chronic pain development. Fibromyalgia is another chronic pain condition where there is no obvious aetiological cause. For many years, researchers have tried to identify a peripheral cause for fibromyalgia in patients, but these efforts have to date been unsuccessful. The diagnostic criteria for fibromyalgia cover a wide range of symptoms which can be similar to other conditions. This wide range indicates that there are no mechanistic explanations for the symptoms experienced by patients (Bidari et al., 2018; Mease et al., 2008). Fibromyalgia can show different disease expressions in people and can even change over time (Häuser et al., 2017). A patient may at one point be diagnosed with the fibromyalgia label but at another time be diagnosed with more local complaints such as low back pain, headache, temporomandibular joint disorder, or irritable bowel syndrome (Egloff et al., 2015; Sluka & Clauw, 2016). Core symptom variation both within a patient over time, as well as between patients, produces considerable perplexity in a fibromyalgia diagnosis (Häuser et al., 2017; Perrot et al., 2012).

Observable damage does not appear to directly translate to severity of pain, therefore relying on observation for pathology alone is unreliable. There appear to be many factors that can enhance or reduce the intensity of pain experienced. Chronic pain has been associated with many psychological components e.g., pain catastrophising (Dong et al., 2020), rumination (Eccleston et al., 2001), poor sleep quality (Finan et al., 2013), stress (Burke et al., 2017), depression (Sheng et al., 2017), and anxiety (Woo, 2010). Some of the factors which enhance our risk of developing health issues such as chronic pain are modifiable, either through targeted intervention and therapy, or changing lifestyle.

Modifiable factors that are associated with chronic pain include: mental health, other co-morbidities of pain, lifestyle factors (which include unhealthy behaviours such as smoking, drinking alcohol, obesity), physical activity or lack of exercise, sleep, nutrition, and general health status (Bergman et al., 2004; van Hecke et al., 2013). Pain is an emotional and social experience. To seek effective treatment, these modifiable health factors should be discussed between patients and healthcare professionals.

One important factor which can be modified, but one which the chronic pain patient cannot always control, is social support. A growing body of evidence suggests that social support can reduce pain in both experimental and clinical settings. For instance, social support is associated with reduced use of analgesic medication and reports of less pain during childbirth (Hodnett et al., 2011). Noxious stimuli are also perceived as less painful in laboratory settings when participants were accompanied (Brown et al., 2003). These reports, however, may have been influenced by a social desirability bias. An example of this bias may be presented in a study which found that a male-male dyadic had the most profound effect on reductions in pain intensity (Edwards et al., 2017), which could be a result of typical male stoicism.

Interestingly, however, the study also indicates that pain reports were lower when a friend was in the next room (Edwards et al., 2017). This finding suggests that simply knowing that a friend is nearby has a buffering effect on pain. There is also evidence for the beneficial impact of social support coming from clinical studies that examine pain disability and recovery from painful conditions. Social support is associated with greater attendance of treatment sessions, less affective stress, greater life control , lower disability levels and better clinical outcomes (Che et al., 2018; Holtzman et al., 2004; Oraison & Kennedy, 2021; Ozbay et al., 2007; Richmond et al., 2018). Furthermore, neuroscience research has highlighted a strong overlap of neural pathways involved in the experience of physical and social pain (e.g. social exclusion or rejection) (Eisenberger et al., 2003; Sturgeon & Zautra, 2016), suggesting the two have a significant influence on each other.

There are some factors that increase vulnerability to pain which are non-modifiable. These include female sex and age (Tsang et al., 2008), cultural and socioeconomic background, history of trauma/injury/interpersonal violence, and genetic or inherited factors (van Hecke et al., 2013). One factor that may play a pertinent role in amplifying pain and the stress-response, which is arguably modifiable, is employment status and occupational factors. Issues such as employer and co-worker responses to pain can have a large role in the level of stress an individual feels and the extent to which pain interferes with life. In Study One, we examine which psychosocial factors that people with chronic pain face in the workplace, which might interfere with their life and contribute towards greater levels of stress.

There is a significant overlap between those who are unable to work due to disability or illness, and those experiencing chronic pain (Elliott et al., 1999). It is well documented that people with disabilities are stigmatised against and experience discrimination (Au & Man, 2006; Draper et al., 2011; Antonak & Livneh, 2000). Individuals with chronic pain may perceive poor job control, feel pressure to return to work and fear that they might cause further pain/risk re-injury at work(fear-avoidance; Vlaeyen et al., 2016). All these occupational risk factors can contribute to the development and maintenance of persistent pain (Shaw et al., 2006). Discrimination against chronic pain in the workplace is understudied. In the first study of this thesis, presenteeism and the potential for discrimination against chronic pain in the workplace was assessed. Strategies for potential workplace modification to combat these social co-morbidities of pain is then discussed.

One key component of pain facilitation which may be modifiable through psychological intervention, is how people attend to pain (Bantick et al., 2002; Pincus & Morley, 2001). It is important to understand how individual differences in attention to pain may affect pain modulatory mechanisms. Attending to pain with a negative focus and maladaptive cognition (i.e., catastrophising and rumination), is associated with pain facilitation and chronic pain (Buenaver et al., 2012; Burns et al., 2015; Dong et al., 2020). Whilst more mindful practices of attending to pain and therapies

promoting acceptance (such as Acceptance and Commitment Therapy – see section 2.2.2), reduces negative affect and can lead to better clinical outcomes (Cash et al., 2015; Hughes et al., 2017; la Cour & Petersen, 2015; Morone et al., 2016). Understanding individual differences in attention to pain may be critical in identifying people who are susceptible to acute to chronic pain transition and understanding why others might be more resilient. To date, little research has examined the extent to which attention to pain plays a role in adaptation to painful conditions and acute to chronic pain transition. If the extent to which people attend to pain is an indicator of vulnerability to pain facilitatory mechanisms, it may be suggestible to focus efforts on interventions aimed at attention regulation which improve resilience to pain (e.g., mindfulness training and cognitive behavioural therapy), which focuses on changing negative thoughts surrounding pain.

We are interested in knowing which individual differences may increase or decrease the risk of transition to chronicity. Yet, it is unclear from many cross-sectional studies whether factors such as pain catastrophising, rumination, stress, depression and attending to pain, are strictly involved in the development of chronic pain, or whether they occur as a result of chronic pain, or both (Ellegaard & Pedersen, 2012; Tsang et al., 2008; Woo, 2010). Some of the most compelling research that allows us to observe the factors involved in this transition from acute to chronic pain, are case reports of chronic post-surgical pain (CPSP). As the onset of an invasively painful procedure is known, pre- and post-surgery assessments can be run to help understand, and predict, why some patients will suffer from chronic pain months after surgery. Some recover within a few weeks, while others are left living in pain for months, years, or even their entire life. Since the prevalence of CPSP is 5-10% worldwide, with over 230 million people undergoing surgery every year (Weiser et al., 2008), it would be of great benefit to identify what it is about those 5-10% that has led to chronicity. This is especially important as the annual cost of new cases of CPSP is in the hundreds of billions of dollars (Weiser et al., 2008). If markers to suggest why some people are more susceptible to developing chronic pain can be identified before surgery takes place, it may be possible to implement

interventions aimed at reversing this transition pre- and post-surgery, before pain becomes chronic (psychologically entangled) and more difficult to treat.

A risk factor identified to increase the risk of CPSP is the type of surgery, particularly surgery that involves damage to nerves (Katz & Seltzer, 2009; Kehlet et al., 2006), though it is worth noting that not all CPSP is neuropathic (Steyaert & Lavand'homme, 2018). The most decisive factor in predicting CPSP appears to be pain itself. This comprises of intensity of acute postoperative pain (Fletcher et al., 2015; Katz et al., 1996; Pinto et al., 2018; VanDenKerkhof et al., 2012; Wang et al., 2016), the time spent in severe pain immediately following surgery (Fletcher et al., 2015), pain intensity in the weeks following surgery (Aasvang et al., 2010; Chidambaran et al., 2017; Choinière et al., 2014) and any referred pain in other body parts (Gerbershagen et al., 2014; VanDenKerkhof et al., 2012), along with the presence (VanDenKerkhof et al., 2012) and intensity (Choinière et al., 2014; Fletcher et al., 2015; Wang et al., 2016) of any chronic pain existing prior to surgery. From a psychological perspective, perioperative depression (Attal et al., 2014; Brandsborg & Nikolajsen, 2018), anxiety (Brandsborg & Nikolajsen, 2018; Choinière et al., 2014; Pagé et al., 2015; Pinto et al., 2018; VanDenKerkhof et al., 2012), pain catastrophising (Burns et al., 2015; Pinto et al., 2018) and posttraumatic stress symptoms (Kleiman et al., 2011) can also predict CPSP. Finally, high levels of consumption of analgesics post-surgery was associated with more intense CPSP and if a patient used opioids prior to surgery, this was associated with an increased risk of CPSP (Rozet et al., 2014; VanDenKerkhof et al., 2012) potentially due to opioid induced hyperalgesia (Fletcher & Martinez, 2014; Rivat & Ballantyne, 2016). Once more, several of these psychosocial risk factors also predicted the likelihood of opioid misuse post-surgery, including anxiety and depression (Brummett et al., 2017) and pain catastrophising (Goesling et al., 2016).

If risk factors before and after surgery were better managed, there would be a better chance of preventing this transition from acute to chronic pain from happening. This would help to reduce medical costs and facilitate earlier discharge (Huang et al., 2015, 2016; Katz et al., 2015). Katz et al.

(2019) recently implemented a multi-modal prevention approach, which identified patients that were at high risk of developing CPSP based on risk factors: perioperative pain, opioid use, and negative affect including; depression, anxiety, pain catastrophising, and posttraumatic stress disorder–like symptoms (Katz et al., 2019). When these patients were identified early and were given comprehensive care which targeted these risk factors, improvements were seen in pain intensity, pain catastrophising, pain interference, symptoms of anxiety and depression, and opioid use. The multi-modal clinical services included medication optimisation by anaesthesiologists, physical therapy and acupuncture after surgery, and psychological interventions which included education of pain, mindfulness training, hypnosis, and a brief form of cognitive behavioural therapy (CBT known as 'Acceptance and Commitment Therapy' (Katz et al., 2019).

Although research points towards the success of multi-disciplinary pain clinics, gaining access to quality pain management remains difficult for many patients. Specialised clinics and relevant professionals are unacceptably dispersed and waiting times can be extremely long (Lynch et al., 2007, 2008; McGhie & Grady, 2016). This lack of availability of effective care adds to the psychological deterioration people with chronic pain go through; well-being, quality of life, pain severity and healthcare costs all being associated with longer waiting times (Lynch et al., 2008). Moreover, research suggests that psychological co-morbidities associated with chronic pain often occurs sooner than when patients can be seen and officially diagnosed (Dickenson et al., 2013; Treede et al., 2015). By the time a patient with a complex pain disorder finally gets access to the appropriate help, it is likely that a vicious cycle of physiological problems and psychosocial stressors has already become entrenched in their lives. Frustration, hopelessness, catastrophising, rumination, anxiety, depression and poor sleep may have already begun to take place, exacerbating the problem of pain. This psychological facilitation is one of the reasons why chronic pain is so resistant to treatment.

Some of the processes by which these risk factors might act include a negative interpretation bias, whereby individuals with chronic pain appraise ambiguous situations in a negative or threatening way (Edwards & Pearce, 1994; McKellar et al., 2003; Pincus et al., 1994, 1996). One study found that adolescents who reported greater pain showed a negative interpretation bias towards ambiguous events and this negative bias mediated the association between recent pain and pain catastrophising (Heathcote et al., 2016). Perceiving ambiguous information as a threat can play a maintaining and facilitatory role in the development of chronic pain, with anxiety sensitivity and pain catastrophising feeding negative interpretation biases which collectively play an important role in the perception of pain (Keogh et al., 2004; Keogh & Cochrane, 2002). Furthermore, interpretation bias has been implicated as a cognitive mechanism underlying vulnerability to pain, mediating the relationship between emotional responses and pain outcomes (Keogh et al., 2004; Keogh & Cochrane, 2002). Experimental studies have shown that adolescents can show biases in the way they attend to and remember pain related information (Beck et al., 2011; Koutantji et al., 1999), and these biases are likely related to catastrophising cognitions about the experience and potential consequences of pain (Asmundson et al., 2012; Noel et al., 2015; Vervoort et al., 2013). This suggests that negative interpretation biases towards attention to, and memory of, pain may be related to higher risk of developing pain in the youth. Contemporary models which explore negative interpretation bias and perceiving pain as a threat will be discussed in greater detail in section 2.2.2.

The key to improving clinical outcomes could be to improve accessibility to early interventions that address these pain facilitatory factors before pain becomes chronic, psychologically entrenched and more difficult to treat. One way of improving accessibility to treatment could be by identifying high risk individuals early on, so that appropriate treatment can be pursued during the early stages of pain onset/development. What is needed is a better understanding of the early mechanisms by which psychological factors might affect the response to acute pain, and which factors might be involved in acute pain transitioning to chronic pain. If people who are better at coping with acute and persistent pain can be identified in laboratory settings, it may translate to the development of

high-risk profiles of pain facilitation and vulnerability to acute to chronic pain transition. Identifying some of the mechanisms underlying pain vulnerability on a case-by-case basis may also be informative for targeted intervention programmes.

2.1.6. Summary

Acute pain is a sophisticated self-protective psychophysical system. Sometimes, however, acute pain can become chronic, causing great stress and suffering. Chronic pain is a complicated multi-faceted phenomenon with many physiological, psychological, behavioural, and social components. It is not just a symptom that occurs alongside a condition, but classified as a disease in its own right, with great health and societal implications of a global concern. The overall cost of chronic pain is larger than any other chronic condition and the personal detriment within each case can be immense. Due to an ageing population and workforce, this problem is only likely to grow. While clinical outcomes for treating pain remains inadequate for a large proportion of patients.

The nature of chronic pain is complex; the amount of tissue damage does not always equate to the intensity of pain and co-morbidities such as depression, anxiety and increased stress, often occur alongside chronic pain. These co-morbidities create a vicious cycle where pain creates stressors, and these stressors make pain worse. If pain is not treated early, pain and these psychosocial stressors are likely to become entangled, leading to a greater risk of pain facilitation, treatment resistance and chronicity. This is a major problem as specialist health professionals for pain are sparse and general practitioners are not always properly educated on the complexities of pain. Consequently, people in chronic pain often face long waiting times and do not get appropriate treatment early enough, running the risk that chronicity develops before a patient is even seen.

By the time pain becomes chronic, it is too late for certain interventions to be beneficial, and the pain then becomes more difficult to treat. Changes in mental processes such as catastrophising, fear avoidance and negative bias, may have already begun to become schematised. To address this problem, it would be appropriate to understand the mechanisms behind vulnerability or resilience to

pain at an acute stage. Identifying modifiable factors related to pain resilience at an acute stage will further our understanding of why some people are vulnerable to develop chronic pain. Given the complex individual differences and multiple mechanisms that contribute towards pain at both an acute and chronic level, building a model for identifying vulnerability to pain is extremely difficult. We are currently at the early stages of attempting to build such a model and the studies in this thesis will contribute towards that literature. Knowledge on resilience to pain could also help suggest appropriate measures for prevention. Exploring psychosocial factors and mechanisms that underlie pain facilitation/inhibition may therefore be informative for tailoring specific intervention programmes on a case-by-case basis.

2.2. Formulation of Pain

2.2.1 Early Theories of Pain

To understand the transition from acute to chronic pain, the role of psychological facilitation, and how to combat it; we must first familiarise ourselves with the underlying mechanisms that generate pain. We will then be in a better position to understand how psychosocial stressors interact with pain modulatory mechanisms, to facilitate chronic pain development and maintenance.

Early theories of pain, such as the Cartesian model and specificity theory (Moayedi & Davis, 2013), postulated that sensory nerves directly sent pain signals form the periphery to the brain, much like the ringing of a bell (Figure 1). These theories were pivotal as they were the first to suggest that the brain was involved in the pain experience.

Figure 1

Cartesian Model Depicting the Sensation of Pain Travelling Directly from the Periphery to the Brain.

These early theories, however, downplayed the role of psychological factors in the processing and experience of pain. They described the brain simply as a receiver of this straight-line transmission of input from the pain location. Recent research studies and clinical evidence, however, has revealed that tissue damage has little to no correlation with the intensity of pain experienced (Balagué et al., 2012; Bogduk, 2012; Cheung et al., 2009; Register et al., 2012). There are several psychological factors associated with pain intensity, other than the degree of tissue damage. For instance, the degree to which one attends to pain (Bantick et al., 2002; Pincus & Morley, 2001), prior learning about pain (Goubert et al., 2011; Wiech et al., 2014), social context (Eisenberger et al., 2011;

Montoya et al., 2004) and emotional mood (Villemure & Bushnell, 2009; Wiech et al., 2014), have all been identified as factors that can influence pain intensity.

The Cartesian model can be particularly questioned when we consider phantom limb syndrome, in which the location of pain is felt at the site of a non-existent, or amputated, limb. In these circumstances, the pain cannot be physically derived from tissue in the periphery as the tissue does not exist. The model also cannot account for instances where people feel pain without apparent injury, such as in the case of tension headaches and migraines. Nor can the model explain why pain can persist long after any putative tissue damage has healed. This is all suggestive of a more complex system than just a straight-line communication between pain receptors and the brain.

Developments in scientific understanding and technology over the 19th century have allowed us to expand on this early anatomical explanation of pain transmission. Melzack and Wall proposed that psychological facilitation and inhibition of pain occurs through ascending and descending systems, which centrally modulate pain in the dorsal horn; otherwise known as the 'pain-gate' (Melzack & Wall, 1965). Subsequently, they proposed the 'gate-control theory of pain', whereby various neurotransmitters in the dorsal horn have the ability to block or facilitate the transmission of pain signals from the periphery to the brain. This theory is still supported and widely accepted today (Dickenson, 2002; Mendell, 2014). The 'Neuromatrix of Pain' model was later suggested by Ronald Melzack as an extension of gate-control theory, in an effort to explain phantom limb syndrome (Melzack, 1990). The model proposes that the experience of pain is the result of ascending and descending pain systems working together, with modulatory input provided by specific regions of the brain and spine. The model is a prime example of 'pattern' theory that viewed pain as the product not just of pain receptors transmitting direct signals via sensory nerves to the brain (specificity theory), but of a wide range of central and peripheral interactions. Within this model of a neuromatrix, Melzack proposed the concept of a 'neurosignature', which postulated that the intensity of a painful stimulus is modulated by sensory input and experiential variables, creating a

unique pain experience according to the individual. Wager and colleagues expanded on this concept by using fMRI to identify a specific neural signature for the magnitude, and spatial pattern, of the perception of acute pain, which seemed to generalise across participants (Wager et al., 2013). They found that somatic-specific regions such as the somatosensory cortex, ventrolateral thalamus and dorsal posterior insula encompassed the neural signature for pain, along with anterior insula and anterior cingulate cortex which are activated across many psychological processes. The neural signature provides an exciting conceptual development, which moves the discussion away from nociceptors and peripheral mechanisms to a network that incorporates cortical processes such as perception, personalisation, memory, and attention to pain. The progression of these theories of pain will now be discussed in further detail.

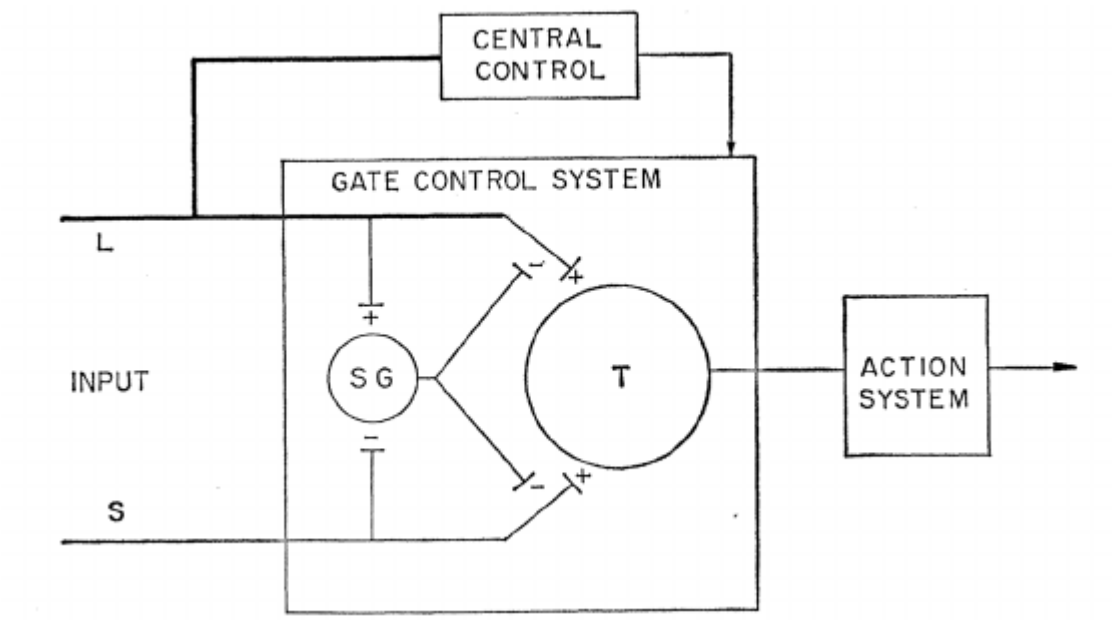
To understand the evolution of theories of pain, we must start at the beginning, with the sensory nerve endings that detect a noxious stimulus. The name given to these nerve endings is 'nociceptors', which are nerve endings that are specialised for identifying noxious stimuli. The existence of nociceptors was proposed speculatively in 1907 (Sherrington, 1907), but research providing physiological evidence for their existence was not published until 1967 (Burgess & Perl, 1967); shortly after Melzack and Wall published 'The Gate Control Theory of Pain' (Melzack & Wall, 1965). Burgess and Perll (1967) discovered that out of a total of 513 primary afferent fibres, only 74 of them responded to noxious stimulation. Later, Bessou and Perl (1969) identified polymodal nociceptors, which responded to different modalities (cold, heat, chemical and mechanical) (Bessou & Perl, 1969). Gate theory proposes that all the nociceptors of primary afferent fibres in the periphery, project towards the dorsal horn (coined 'the gate' to the central nervous system), where they synapse on to transmission cells and inhibitory and excitatory interneurons, that inhibit/facilitate transmission cell activity (Mendell, 2014; Takazawa & MacDermott, 2010). The transmission cells then send the pain signal up the spinothalamic tract to the brain (Christensen & Perl, 1970).

Each of the primary afferent fibres has different properties (Dubin & Patapoutian, 2010; Yam et al., 2018): A-beta fibres are large in diameter and are highly myelinated (Abraira & Ginty, 2013), allowing for quick conduction from the peripheral to central nervous system. These fibres have low activation potentials, that respond to light touch. They are responsible for conveying tactile sensory information to the central nervous system and brain (Abraira & Ginty, 2013). A-delta fibres are much smaller in diameter and are thinly myelinated (Abraira & Ginty, 2013). This means that they conduct more slowly than A-beta fibre and have greater activation potentials, which respond to noxious thermal and mechanical stimuli. C-fibres are the smallest of the fibres with no myelination (Abraira & Ginty, 2013). This means they have the highest activation potentials and conduct sensory information the slowest. Their activation threshold is so high that they only respond to nociceptive, or 'painful' stimuli. The A-beta and C fibres are both responsible for carrying nociceptive signals to the dorsal horn, coined the 'pain gate' by Melzack and Wall (Melzack & Wall, 1965).

The 'pain gate' is the first central region the nociception signal encounters, that is subject to modulation. The gate possesses inhibitory and excitatory neurotransmitters, which can either amplify the pain signal or decrease it (Melzack & Wall, 1965). Melzack and Wall postulated that the primary afferent signal is received within the dorsal horn of the spinal cord, by the substantia gelatinosa (SG) & central-transmission cells (T-cells). The SG is posited as a modulatory region, which can regulate the afferent signal before it influences the T-cells. T- cells are then responsible for projecting this post-modulatory signal up to the brain. The existence of gate control is widely accepted today, but the physiological specifics remain open for contest and experimentation (Ropero Peláez & Taniguchi, 2015; Wall, 1978).

Figure 2

Schematic Diagram Depicting 'The Gate Theory of Pain'.



Note.L: Large diameter fibres, S: Small diameter fibres, SG: Substantia Gelatinosa, T: Central transmission cells. From 'Pain Mechanims: A new theory' by R. Melzack and P. Wall, 1965, Science, 150(3699), p. 971-978.

Pain modulation can occur at this stage of afferents ('the gate'), when A-beta fibres compete with signals from smaller fibres carrying pain signals (A-delta and C fibres). As the A–beta fibres conduct and transmit their signal to the dorsal horn quicker, they block off access through the gate for the slower conducting pain fibres (Mendell, 2014). A-beta fibres do this by giving off collaterals in the dorsal horn, which stimulate an inhibitory neuron to release GABA, at the synapse between the primary and secondary afferent neuron (Yam et al., 2018). GABA can inhibit the transmission of neurotransmitters, glutamate and substance P, which are responsible for transmitting the nociceptive signal, from the primary to the secondary afferent neurons (Kendroud et al., 2021; Yam et al., 2018). An example of this is the classic case of banging one's knee. The instinctive response is to rub the knee to temporarily reduce the pain. This reduction in pain occurs because the gate is

being overloaded with tactile sensory information carried by the quick conducting A-beta fibres; this releases GABA which blocks access of the gate to the pain carrying A-delta and C-fibres.

The gate theory gives an example of how an ascending pain signal (transmission from the nociceptor to the brain) can be modulated at the dorsal horn. However, gate theory proposes that once the T-cells transmit this post-modulatory signal up the spinal cord towards the brain, signifying the beginning of the modulatory process, not the end. The brain still has the ability to transmit signals back down to the dorsal horn, which can either open or close the gate, to inhibit or facilitate pain transmission (Fields, 1999; Ossipov et al., 2010, 2014). Melzack and Wall propose that cognitive factors such as: distraction, positive mood, mindfulness, etc. can contribute towards closing the gate, while cognitions such as: catastrophising, anxiety, fear, etc. can open the gate and facilitate pain transmission. The text book example of gate theory in practice comes from anecdotal scenarios whereby soldiers report not feeling their injuries on the battlefield until afterwards (Beecher, 1946). From a psychological perspective, gate theory suggests that because the brain is busy prioritising how best to survive, the pain gate effectively shuts until there is a more suitable time to pay attention to the pain signals.

Once the pain signal synapses to the secondary afferent neuron in the dorsal horn, the neuron decussates over to the contralateral side of the spinal cord (Al-Chalabi et al., 2021). Here the signal will ascend up the spinothalamic tract (anterolateral system), to the thalamus (Al-Chalabi et al., 2021; Willis et al., 2001). The signal primarily travels to an area called the ventral posterior lateral (VPL) nucleus, or the ventral posterial Inferior Nucleus (VPI) in the thalamus (Al-Chalabi et al., 2021). It then synapses with a third order neuron where it can go to the cingulate gyrus, anterior Insula and somatosensory cortex (S1 and S2) (Bushnell et al., 2013). Along the way to the thalamus, the secondary neuron will also project to areas of the brainstem such as: the reticular formation, parabrachial nucleus, periaqueductal grey matter (PAG), hypothalamus, and the superior colliculus (Benarroch, 2012; Gauriau & Bernard, 2002). The signal that breaks off to the parabrachial nucleus is

projected up to the amygdala, which is responsible for emotions such as fear and anger within pain (AbuHasan et al., 2021). The hypothalamus controls our autonomic nervous system i.e., changes in our heart rate, blood pressure, respiration etc and all the autonomic aspects of pain (Saper & Lowell, 2014). A primary region which receives the pain signal is the reticular formation (Martins & Tavares, 2017), which is one of the primary regions responsible for attention and consciousness (Mangold & M Das, 2021), hence why people become so aware of pain when it occurs. The reticular formation sends signals upwards to the thalamus which again, stimulates almost the entire cerebral cortex, including the cingulate gyrus, anterior insula, and the somatosensory cortex (Martins & Tavares, 2017). The collateral, however, that we are most interested in, (that lies in the brainstem), is the fibres that go to the periaqueductal grey (PAG). This region is largely responsible for controlling the descending modulatory pain system, capable of inhibiting pain signals (Millan, 2002; Reynolds, 1969; Waters & Lumb, 1997; Yeung et al., 1977).

The invention of non-invasive brain imaging techniques, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), has allowed us to track activity in the brain during specific tasks. The scientific community is therefore in a better position to understand the role of specific brain regions in pain. Neuroimaging studies over time have revealed that there is not one specific region of the brain that interprets pain or is responsible for it. Research has identified a 'Pain Matrix' that is consistently activated during the administration of painful stimuli, with increasing activation correlated with increased pain intensity (Legrain et al., 2011). Following a large scale review of pain studies in 1999, the prominent brain regions which appear to be involved in the 'Pain Matrix' were the: thalamus, primary and secondary somatosensory (S1 & S2), insular, prefrontal cortices (PFC), and the anterior cingulate cortex (ACC) (Peyron et al., 2000). Later studies also included the amygdala, parietal cortices, and regions in the brainstem associated with descending modulation: PAG, RVM & locus coeruleus. (Apkarian et al., 2005; Denk et al., 2014; May, 2009; Price, 2000; Tracey & Mantyh, 2007).

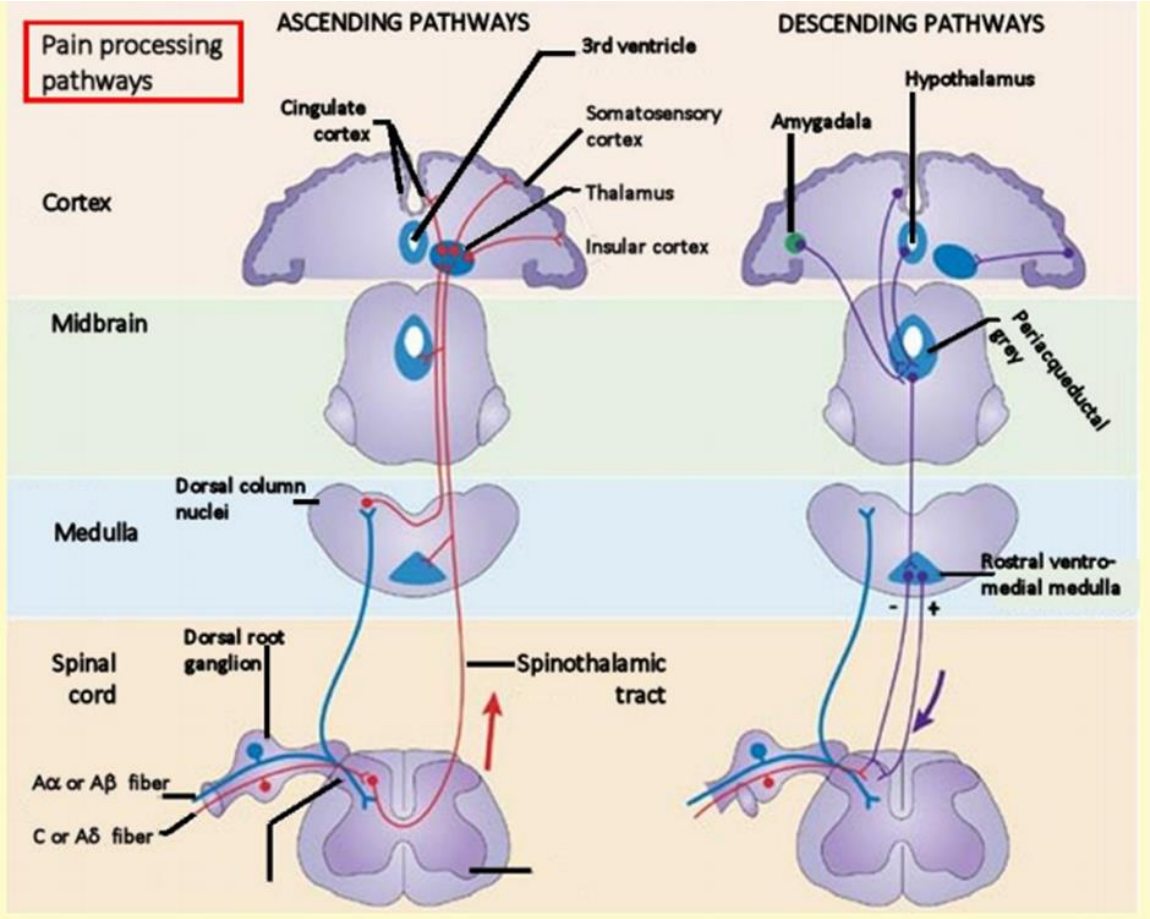
Although the existence of a 'Pain Matrix' appears to be consistently found in neuroimaging studies, a question of reverse inference remains; as when pain occurs the matrix is activated, however, the activation of the matrix does not always mean that pain has occurred. For instance, a study found the pain matrix to be activated during nociceptive, non-nociceptive, auditory and visual stimuli (Mouraux et al., 2011). Furthermore, social rejection and empathy to pain have also been found to activate the pain matrix (Eisenberger et al., 2003; Singer et al., 2004; Valeriani et al., 2008). One study even revealed that in an individual born with congenital analgesia, the pain matrix was activated during nociceptive stimulation, despite the participant being unable to feel pain (Salomons et al., 2016). It seems that although there is specificity in output, the brain's involvement is far less specific. For instance, there are several regions of the brain (e.g., ACC, insula), whose primary function is not pain, that consistently contribute to the experience of pain (an account far more consistent with a pattern view like 'Neuromatrix'). So, while pain is the product of a complex mix of contributions from many of these players, and no one piece of this network is solely responsible for pain, or even a particular aspect of pain; we can speak about the likely contribution of some of these regions to the overall experience.

So far, research corresponds the thalamus as the central receiver of the ascending pain signal, acting as the control centre which co-ordinates and integrates with all other regions involved in the pain experience (Ab Aziz & Ahmad, 2006; Al-Chalabi et al., 2021; Willis et al., 2001). The insular, amygdala and ACC, all appear to be related to the emotional aspects of pain and pain intensity (Loeser & Treede, 2008; Price, 2000). The prefrontal cortex with how one makes sense of pain (Apkarian et al., 2005; Atlas & Wager, 2012), and the somatosensory cortex with identifying the location of pain in the body (Bushnell et al., 1999; Haggard et al., 2013). The PAG, RVM and locus coeruleus, have recently emerged as key centres of pain modulation, capable of triggering descending opioidergic, serotonergic and noradrenergic systems (Ossipov et al., 2010, 2014). Each of these brain regions are highly interconnected, making up the 'pain matrix'.

Descending modulation of pain occurs at the PAG in the midbrain (Ossipov et al., 2010, 2014). The PAG draws on information from cortical regions (Tracey & Mantyh, 2007), and transmits fibres which activate the locus coeruleus, which is rich in norepinephrine (Mokhtar & Singh, 2021; Schwarz & Luo, 2015). The PAG also communicates with nuclei in the reticular formation (primarily responsible for attention and awareness) called the nucleus reticularis gigantocellularis, which are rich in serotonin (Beitz, 1982; Martins & Tavares, 2017). As well as these nuclei, they also stimulate the raphe nucleus magnus in the rostro-ventricular medulla (RVM), which are also rich in serotonin (Cui et al., 1999; Ossipov et al., 2010; Westlund & Willis, 2012). These noradrenergic and serotonergic neurotransmitters carried by neurons all come together and descend down to the dorsal grey horn, where they synapse in the substantia gelatinosa (the 'pain gate') (Vasquez & Vanegas, 2000; Xie et al., 2009). This is where the serotonin and norepinephrine are released to stimulate small inhibitory neurons, which release endogenous opioids such as: enkephalins, endorphins and dynorphins (Basbaum, 1984; Shenoy & Lui, 2021). Activation of opioid receptors at the interneuronal level produces hyperpolarisation of the neurons. This hyperpolarisation results in the inhibition of the firing and release of substance P (a neurotransmitter involved in pain transmission), thereby blocking pain transmission (Kendroud et al., 2021). This is just a simple version of the descending nature of the system which begins with the PAG descending to the dorsal horn. The actual system is much more complex, with opioids found throughout the central nervous system, being able to modulate pain transmission at various points. For example, one region only briefly mentioned in this thesis is the RVM in the brainstem which is closely interconnected with the PAG and plays a key role in descending modulation. The RVM has the ability to induce pain facilitatory or pain inhibitory mechanisms, through on and off cells (Heinricher et al., 2009).

Figure 3

Diagram Showing the Ascending and Descending Pain Pathways.



The experience of pain is made up of the result of these ascending and descending pain systems. The main sites for which pain signals can be modulated are at the dorsal horn (by inhibiting the transmission of substance P and glutamate) (Wall, 1978; Zieglgänsberger, 2019) and the PAG (which controls descending pain modulation and the opioidergic system) (Ossipov et al., 2010, 2014). The PAG is integrated with and influenced by higher order cognitive and emotion centres in the brain. These include, the prefrontal cortex, somatosensory cortex and amygdala; in a highly sophisticated system of neurons (Hadjipavlou et al., 2006; Helmstetter et al., 1998; Ossipov et al., 2010).

Activity in the amygdala, insular, and prefrontal and anterior cingulate cortices, all appear to be related to the cognitive, attentional & emotional processes that occur during nociception (Berntson

et al., 2011; Bushnell et al., 2013). Activity levels within these regions is subject to differing personality characteristics (Adelstein et al., 2011; Mulders et al., 2018) such as: the anticipation of pain, experience of pain, attention, mental health, genetics, and lifestyle (Coghill, 2010; Fillingim et al., 2008; Linton & Shaw, 2011; Lumley et al., 2011; van Hecke et al., 2013). All these factors appear to have an impact on why pain is so subjective and can be experienced with different levels of intensity and unpleasantness (i.e., why pathology does not always correlate to symptomatology). Individual differences in brain structure and activity levels can influence the efficiency of ascending and descending pathways (Ossipov et al., 2014; Yang & Chang, 2019), with psychological factors having a large impact on pain modulation (facilitation or inhibition) (Linton & Shaw, 2011; Tracy, 2017). Individual differences in pain modulation, influenced by psychological factors and brain activity, could help explain why some people are vulnerable to the development and maintenance of chronic pain, and others are not. Since the reticular formation (responsible for attention and consciousness) and PAG (responsible for descending inhibition) are in close communication with each other, we hypothesise that attention to a painful stimulus will be associated with pain modulatory mechanisms. This will be explored within the second study of this thesis.

2.2.2. Contemporary Models of Pain

The International Association for the Study of Pain describes pain as *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"* (Raja et al., 2020, p.14). This definition importantly expresses that pain is not just a sensory experience, but an emotional experience as well. Psychological factors such as: personality, attention, expectations, and cognitions should be considered when evaluating pain. Moreover, neuroimaging studies have identified a neural signature of multiple brain regions being activated during painful stimulation (Apkarian, 2013; Wager et al., 2013). This neural signature suggests a complex interplay of cognitive processes in the pain experience. Wager et al. (2013) reported a neural signature for brain activity during pain that had 90% sensitivity to predict reported pain, was

specific to pain, and at an individual level was consistent across scanners and studies (Wager et al., 2013). The identification of such a neural signature forms a basis for understanding neurophysiological processes which might underlie different types of pain and may hold the key to targeting treatment for neuropathologic conditions. Though, it may be questioned whether this neural signature developed in laboratory studies on acute pain will generalise to patients with chronic pain (Farmer et al., 2012)

What the neural signature does affirm, is that not one region of the brain is responsible for pain, but there is a complex interplay between brain regions and synaptic activity at the level of the spine and the location of any injury, which contribute towards the pain experience. Cortical processes and cognitive evaluations appear to be influenced by the presence of persistent pain, with brain structural and functional differences being associated with the development of chronic pain (Farmer et al., 2012; Kamping & Flor, 2012). This suggests that the presence of pain can change the way people think and perceive the world.

Experimental studies have investigated interactions between neurocognitive processes, and ways in which negative behavioural and cognitive responses (such as pain-related fear and anxiety), are acquired (Crombez et al., 2013; Meulders & Vlaeyen, 2012; Wiech et al., 2008). These studies suggest that the intensity of pain is determined by the extent to which it is perceived as a threat, with psychological factors such as: anticipation, attention, and memory, contributing strongly to the pain experience.In addition to these psychological factors involved in the perception of pain and the response to it, there is also a large social component (Hadjistavropoulos et al., 2011; Jensen et al., 2011), with psychosocial factors being reported to play an important role in the determination of pain intensity and pain-related outcomes (Clay et al., 2010). The IASP definition of pain has recently been criticised for not including social components of the pain experience (Williams & Craig, 2016). Chronic pain, after all, can have a devastating impact on work, as people might have to change their occupational duty or lose their job as a result of their symptoms (Breivik et al., 2006; Patel et al.,

2012). It can also affect a person's social interactions and restrict their ability to take part in leisure activities (Ojeda et al., 2014; Porter et al., 2008), which can have a consequential effect on mental health and one's ability to deal with stress (Dueñas et al., 2016; Ojeda et al., 2014).

These wide-ranging findings implore a biopsychosocial framework for understanding the genesis of chronic pain. There are many contemporary models of pain which shed light on the facilitation of pain and development of chronicity within a biopsychosocial framework. These models include: the fear-avoidance model (Vlaeyen et al., 2016), the cognitive-affective model (Eccleston & Crombez, 1999), acceptance and commitment model (Hughes et al., 2017), the diathesis-stress model (Turk, 2002), and central sensitisation (Latremoliere & Woolf, 2009).

The fear-avoidance model offers an explanation as to why symptomatology does not always correlate with pathology. Vlaeyen et al. (2016) proposed that people in pain often avoid activities or movements due to the fear that they may re-injure themselves or make their pain worse. This can perpetuate into a downward spiral of increased avoidance and disability (Vlaeyen et al., 2016). The model describes several ways in which pain-related fear can lead to disability. These include negative appraisals including catastrophic thinking and emotions such as anxiety and depression. The fear of further pain/re-injury affects attention processes, which can lead to hypervigilance and consequent escape and avoidance behaviours. Activity avoidance can then lead to occupational/social isolation, physical degeneration, disability and further fear; in a vicious cycle (Turk & Wilson, 2010; Zale et al., 2013). The model posits an opposing pathway in which some individuals will confront their pain experience with no fear allowing them to become more engaged in active coping, thus improving daily function. This model offers an explanation as to why some people might develop chronic pain and others do not. Support for this model is given from studies finding that high levels of pain-related fear are associated with aversion from physical activity, hypervigilance of pain-related sensations and distraction from normal cognitive functioning (Herbert et al., 2014; Marshall et al., 2017; Suhr & Spickard, 2012; Vlaeyen & Linton, 2000).

Anticipation of pain is a key factor of fear-avoidance. Numerous studies have suggested that recurrent episodes, past experiences and a person's memory of pain can sensitise an individual into anticipating greater pain and taking part in more pain-avoidance behaviours (Feuerstein & Beattie, 1995; Fordyce et al., 1984; Vlaeyen et al., 1999; Waddell et al., 1993). Waddell and colleagues proposed that *"the fear of pain and what we do about it is more disabling than the pain itself"* (Waddell et al., 1993, p.164). Empirical evidence supports the notion that fear avoidance behaviours are a powerful predictor of chronic disability (Al-Obaidi et al., 2000; Keen et al., 1999; Klenerman et al., 1995; Waddell et al., 1993).

The dilemma with the fear-avoidance model is that the function of pain is to demand attention (Eccleston & Crombez, 1999). Pain is considered to be a useful warning signal which leads to appropriate behavioural responses in dealing with injury. It can therefore be very difficult to ignore pain, even when there is little that can be done to alleviate it (e.g., cancer pain). Fear avoidance, therefore, has evolutionary significance as it promotes survival and the avoidance of harm, albeit sometimes at the expense of quality of life. The amount of attention given to pain likely has a lot to do with the extent to which pain is considered a threat. The fear avoidance model suggests that some people may be more vigilant to possible signals of pain or injury. Research that investigates mechanisms by which some individuals are more vigilant to pain would be useful to understand the extent to which hypervigilance is driven by physiological mechanisms. Research should also help identify whether and which emotional and/or cognitive responses are involved in attention to pain. This thesis will explore the role that endogenous modulatory mechanisms, characteristic of a 'pro-nociceptive' phenotype, play in attention to pain.

Crombez and Eccleston proposed a cognitive affective model for the interruptive function of pain (Eccleston & Crombez, 1999). They too proposed that ongoing behaviour can be interrupted by pain dependent on the extent to which pain is perceived as a threat. They posited that various cognitive factors (e.g., motivation, catastrophising, hypervigilance) and affective factors (e.g., novelty and

intensity of a stimulus) both have a modulatory influence on attention to pain. All these factors contribute towards the extent to which individuals anticipate and perceive pain as a threat (Eccleston & Crombez, 1999; Legrain et al., 2009; Torta et al., 2017; van Ryckeghem & Crombez, 2018). The extent to which people attend to pain appears to have many relevant determinants. It is not just the strength of the stimulus but also the social context and our cognitive evaluation of a stimulus. For instance, Beecher (1946) reported that during battle, some soldiers denied any pain, despite extensive wounds. This suggests that the function of pain may have been overridden by the higher threat value of the surrounding battle. Moreover, one experiment demonstrated the distraction of highly difficult cognitive tasks significantly reduced the perceived intensity and unpleasantness of nociceptive stimuli, compared to low difficulty tasks (Rischer et al., 2020). Similarly, financial compensation for completing a dot-probe task reduced pain intensity in high catastrophisers (Verhoeven et al., 2010). This suggests that pain competes for attention with other tasks based on distract ability, and motivationally relevant goals.

Another important model which addresses individual differences in motivation, and the extent to which people attend to pain or interpret it as a threat, is the acceptance and commitment model. This model suggests that psychological flexibility and cognitive interpretation are key factors in our behavioural response to pain. The key concepts of the model are to encourage people with pain to avoid futile attempts to control pain, and instead focus on the things they can control such as taking part in valued activities, embracing the world around them, and pursuing important life goals. In support of this model, studies have found that pain-related acceptance leads to higher physical functioning and less emotional distress (McCracken, 1998; McCracken et al., 1999; McCracken & Eccleston, 2003).

It would be useful to understand whether natural levels of acceptance towards pain can be assessed. One characteristic that promotes acceptance is mindfulness. People who are trained to be mindful are encouraged to direct attention to the present moment in a non-judgmental and accepting

manner (Bishop et al., 2004). High levels of mindfulness suggest psychological flexibility and greater acceptance of adversity/stress (Silberstein et al., 2012). One way in which to assess how a characteristic such as mindfulness is associated with responses to pain in terms of acceptance is using an individual differences approach i.e., Examining whether trait mindfulness, or more specifically the self-reported capacity to adapt emotionally and attentionally is associated with pain experience during repeated/prolonged exposure to a painful stimulus. We adopted this approach in a study, reported in Chapter 5.

The diathesis-stress model highlights the role of lifestyle and contextual factors which supplement a genetic predisposition to generate psychological stress and pain. The model suggests that individuals with a history of major life adversity, anxiety or depressed mood, and those who report greater levels of stress, are at greater risk of developing chronic and disabling pain (Crook et al., 2002; Linton, 2000; Pincus et al., 2002). The model integrates cognitive factors such as catastrophising, anxiety sensitivity, anticipation of pain and injury, fear avoidance, causal attribution, self-efficacy and operant conditioning, with pre-disposing characteristics and physical pathology (Turk, 2002). Anxiety sensitivity is positioned as a dispositional characteristic within the diathesis-stress model. Anxiety sensitivity refers to the fear of behaviours or sensations associated with the experience of anxiety, and evaluating these sensations as a threat (Mantar et al., 2011). People with high anxiety sensitivity misinterpret bodily sensations elicited by a thought or event (e.g., palpitations and nausea) as dangerous, consequently causing further anxiety. This heightened attention towards bodily sensation leads to a great sense of arousal. As a result, individuals with high anxiety sensitivity may be primed (hypervigilant) such that minor painful stimuli can be amplified. Studies have shown that people with high anxiety sensitivity are more likely to engage in pain-related fear-avoidance behaviours, had greater cognitive disturbances and were likely to use greater quantities of analgesic medication (Asmundson et al., 1999; Asmundson & Norton, 1995; Asmundson & Taylor, 1996).

Anticipation of pain was alluded to earlier when discussing the fear avoidance model i.e., that the threat of pain can instigate preparatory responses, which prime the attentional system (hypervigilance), and encourage fear-avoidance behaviours. Self-efficacy refers to an individual's perception of their lack of ability to cope with pain and associated problems. Causal attributions refer to when a patient attributes the original cause of pain to a traumatic accident and consequently avoids all activities related to that incident. Operant condition suggests that activity such as work and physical activity may not be as reinforced as pain behaviours that inspire attention from a spouse or a health professional. Catastrophising is characterised by overtly negative thoughts, that magnify the threat value of pain and make someone feel helpless in the presence of pain. The diathesis-stress model proposes that this large set of psychological factors interacting with trauma and genetic predisposition may be key to understanding the development and maintenance of chronic pain. Both physical pathology and psychological factors, such as anxiety sensitivity and negative affectivity, may enhance susceptibility to developing chronic pain (Flor et al., 1990). The diathesis-stress model suggests that a pathological pre-disposition alone is insufficient to predict chronic pain and disability. Cognitive factors (i.e., anticipation of pain, expectations, causal attributions), fear-avoidance behaviours, and operant reinforcement are all important. It is the individual's processing of pain-related information that results in anticipatory anxiety and avoidance behaviours. All these biological, psychological, and social factors contribute towards the pain experience. The practical implication of this model is that it proposes a multi-disciplinary approach which targets lifestyle, contextual and cognitive factors in the recovery process. It promotes extensive screening to understand a patient's history, lifestyle and the role contextual factors play in vulnerability to pain.

The biopsychosocial model is a widely accepted theory that incorporates biological, psychological and sociological factors (Engel, 1977). Examples of biological factors includes the severity of the health condition, hormones, and genetics. Psychological factors include: mood, anxiety sensitivity, pain catastrophising, anticipation of pain, fear avoidance, etc. Social factors include: gender roles,

ethnic identity, discrimination, social support and health care provider bias. The biopsychosocial model of pain promotes a multi-disciplinary approach to treating chronic pain. The primary aim is to treat physical pain and improve overall functionality, accounting for potential barriers in recovery. Multi-modal care should be tailored to each individual and may include primary care, physical therapy, psychiatric care, occupational therapy, and case management.

Recently, the IASP definition of pain was revised to, *"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"* (Raja et al., 2020, p.14). The definition now describes pain as a multi-faceted phenomenon with sensory and emotive properties, but has been criticised for not including a social component (Williams & Craig, 2016). Intriguingly, the definition states that in some cases pain does not even require actual tissue damage. One of the mechanisms which helps to explain how this might be possible is discussed in the next section (central sensitisation).

2.2.3. Summary

Over the last century or so, our understanding of pain mechanisms has improved. The disparity between symptomatology and pathology is becoming more explainable. There is not just a direct link between an injury site in the body and a receptive site in the brain, but a complex myriad of peripheral and central mechanisms that work together to create the pain experience. Melzack and Wall were instrumental in developing our understanding of pain mechanisms, initially proposing the gate control theory of pain, which remains influential today. Recent expansions on this model suggest that, following detection by nociceptors, primary nerve fibres in the periphery carry pain signals to the spinal cord, then up to the brain via the spinothalamic tract. These transmissions are subjected to modulation via neurotransmitters in the dorsal horn as they ascend towards the brain, but descending input from the brain and PAG also influences inhibitory and facilitatory neurotransmitters in the dorsal horn. The dorsal horn therefore, acts as a gate at which ascending facilitation and descending inhibition of pain takes place. The pain experience is largely determined

by the post-modulatory transmission of these ascending and descending mechanisms. One key element of this gate is that psychological factors such as: attention, relaxation, anxiety and depression, can assist in opening or closing the gate. Contemporary models of pain suggest psychological formulations by which risk factors might contribute towards the development of chronic pain. These models incorporate the biological, psychological, and sociological components of the pain experience. Exploring how human psychology influences pain facilitatory and inhibitory mechanisms, would be helpful for improving our understanding of how chronic pain develops in some people but not others, and could help inform on targeted intervention strategies.

2.3. Central Sensitisation

2.3.1. What is Central Sensitisation?

The International Association for the Study of Pain (IASP) describes central sensitisation as:

"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input." (Loeser & Treede, 2008, p.476).

The prevalence of central sensitisation occurring after strokes and spinal cord injuries is understandable, as these are injuries that directly involve the nervous system and its structure (Carlton et al., 2009). What is more difficult to explain is why central sensitisation occurs, in cases such as fibromyalgia, migraines and common low back pain, when there are no clear structural implications to the central nervous system (CNS) or surrounding tissue.

Central sensitisation has been strongly associated with chronic pain disorders such as chronic low back pain (Flor et al., 1997), neck pain (Chua et al., 2011), whiplash injuries (Banic et al., 2004), chronic tension headaches (Bendtsen, 2000; Coppola et al., 2013), migraines (Stankewitz & May, 2009), rheumatoid arthritis (Meeus et al., 2012), osteoarthritis (Arendt-Nielsen et al., 2010), endometriosis (Bajaj et al., 2003), fibromyalgia (Staud, 2006), injuries resulting from motor accidents

(McLean et al., 2005), slow recovery from surgery (Fernandez et al., 2010), irritable bowel syndrome (Verne & Price, 2002) and chronic fatigue (Meeus & Nijs, 2007).

Central sensitisation occurs when the CNS reaches a persistent state of heightened sensitivity, primed by progressively decreasing thresholds of primary afferent nociceptors, often following repeated exposure to a painful stimulus. (Campbell et al., 1979; Gybels et al., 1979; LaMotte et al., 1983). The recommended model of treatment for chronic pain in cases of central sensitisation therefore involves addressing central factors, not just structural tissue damage in the periphery; a concept patients are often perplexed by.

To understand how this occurs, the function of pain must be considered. As aforementioned in 'Section 1.1.1. – Acute pain', acute nociceptive pain is a sophisticated self-preserving psychophysical system; although seemingly unpleasant, it serves to protect the body from external harm i.e., removing one's hand from a flame to avoid getting burned. The second function of acute pain is to monitor and protect injuries from any further damage, so that the injured area is under minimal stress while it repairs (Grahek, 2011). This is why people might walk with a limp when they are faintly injured or a bruise/cut area becomes more sensitive. This pain or additional sensitivity reminds us to be particularly careful with the injured area, so that it has time to repair itself and recover efficiently. If people were not able to feel pain, they would be less primed to protect themselves, potentially leading to fatal consequences as seen in cases of congenital analgesia (Baxter & Olszewski, 1960).

A mechanism behind this protective function of acute pain is the sensitisation of the nociceptive system that occurs after an injury or painful event. After an injury, lower action potentials are required to activate nociception and subsequent inputs are amplified (Woolf & Salter, 2000; Woolf & Walters, 1991). This is because noxious stimulation can cause cellular changes to occur at receptor sites in the CNS- particularly the dorsal horn and brain, leading to a state of hypervigilance (Curatolo et al., 2006; Schwartzman et al., 2001). The function of neurons and circuits within nociceptive

pathways are enhanced, synaptic efficacy and membrane excitability are increased, while pain inhibitory mechanisms are reduced. This results in an augmented action potential output and an amplified state of pain facilitation (Latremoliere & Woolf, 2009). When noxious input to the injured area deceases and tissue damage recovers, this state of hypervigilance should return to normal (baseline), having served its purpose of protecting the injured area.

However, pain is not always so simple, sometimes it goes wrong. Occasionally, pain continues to persist long after the injured area has fully recovered i.e., chronic pain that lasts over six months. Central sensitisation offers an explantion for why this pain might persist, as when putative tissue damage has healed, this heightened state of sensitivity remains. Essentially, the function of neurons, circuits and nociceptive pathways remain enhanced, as the central nervous sytem has now been re-wired for overprotection. The purpose of this phenomenon was that this enhancement of sensitivity in nociceptive pathways, would serve a protective function to prevent further harm and promote the indivdual to exercise additional caution. When this protective system remains in place long after injury and the respective tissue damage has healed, however, it means unnecessary pain and sensitivity for the patient. This remaining state of hypervigilance causes the CNS to amplify the interpretation of sensory signals resulting in persistent and elevated levels of pain and discomfort. Modern models of chronic pain have hypothesised that central sensitisation is heavily involved in acute to chronic pain transition and serves as a key maintenance factor for chronic pain (Latremoliere & Woolf, 2009).

There are two main manifestations of central sensitisation: allodynia and hyperalgesia. Allodynia is pain due to a stimulus that does not normally provoke pain. Hyperalgesia is increased pain from a stimulus that normally provokes pain. Primary hyperalgesia describes pain sensitivity that occurs directly in the damaged tissues and secondary hyperalgesia describes pain sensitivity that occurs in surrounding undamaged tissues; a hallmark of central sensitisation being increasingly widespread pain. The sensitivity caused by central sensitisation creates a perception that a real noxious stimulus

causing harm may be present i.e., that there is some tissue damage. There is a heightened attention towards pain or hypervigilance to pain and somatic sensation. This hypervigilant state causes individuals to be excessively ready and selectively draw their focus towards pain-related information (Rollman, 2009). The immediate threat value of pain and pain related cues is increased, with pain-related fear (fear-avoidance) and catastrophic thinking often being found to be strong predictors of hypervigilance to pain (He et al., 2014; McWilliams & Asmundson, 2007; Quartana et al., 2009). This formulation of central sensitisation brings forward the question of whether clinical conditions of chronic pain such as chronic low back pain and fibromyalgia, (which are not linked to clear peripheral pathology), are reflective of this mechanism of hypervigilance.

The mechanism of central sensitisation supports that pain experience is not just a straight-line transmission of nociceptive input to the brain; it suggests another dimension by which peripheral input can be distorted by its degree, duration and spatial extent. The magnitude of pain is amplified by the CNS, instead of exclusively being driven by noxious input in the periphery. As pain signals can be distorted by the CNS, an important question remains as to whether there are individual differences in people's propensity for developing central sensitisation. The ability to identify diagnostic criteria and risk factors for central sensitisation will assist greatly in phenotyping patients for treatment that focuses on de-sensitising hyperexcitable central nervous systems.

2.3.2. Risk Factors for Central Sensitisation

There are likely psychological, biological and environmental factors involved in the predisposition to, and exacerbation of central sensitisation. Low and high pain thresholds determined by genetics may have a direct relationship with central sensitisation (James, 2013). Pain hypersensitivity has also been linked to psychophysiological factors including the stress-response. Experimental evidence on animals (Alexander et al., 2009; Imbe et al., 2006) and humans (Kuehl et al., 2010; Rivat et al., 2010), as well as prospective studies on humans (Slade et al., 2007) suggest a large bidirectional interaction

between stress and pain. Similarly, anxiety, pain catastrophising and rumination about pain, have all been linked with lower pain thresholds (Hirsh et al., 2008; Sullivan et al., 2004).

A common thread between these negative psychological/cognitive processes and pain sensitivity is hypervigilance. If people have undergone a process of central sensitisation, whereby their perceived threat for somatic and painful stimuli has increased; it is likely that they will become fixated on pain and other aversive stimuli, with a greater likelihood of perceiving situations as threatening. This exaggerated vigilance to threat does not just allude to increased sensitisation to pain but likely leads to negative distorted thinking such as catastrophising, rumination, increased stress and anxiety sensitivity. There is likely a bi-directional relationship between these hypervigilant thoughts and central sensitisation. Negative distorted thoughts contribute towards hypervigilance (Leeuw et al., 2007). This state of psychological hypervigilance likely enhances somatic and painful sensations due to increased threat value, while the presence of amplified pain only leads to further fear-avoidance behaviours.

This notion of stress and psychological factors influencing vulnerability to chronic pain is supported by the increased likelihood of chronic pain occurring when there is a prior history of depression, anxiety and trauma (Häuser et al., 2013; McLean et al., 2005; Nahit et al., 2003; Talbot et al., 2009). The common denominator between all these conditions is the central nervous system. It is not that these conditions make people more likely to get injured or contract an illness, but that they all alter the state of the central nervous system. The state of the central nervous system can interfere with the normal trajectory of pain and the healing process. The concept is that people who have an emotional disposition that appropriates stress are more likely to respond negatively to pain and nociception, because pain after all is a stressor.

Individual differences in psychological state can affect many areas of life and have an accumulative impact on quality of life. For instance, people prone to anxiety may stay up at night worrying. This limited sleep can enhance the state of fragility to stressors, further increasing anxiety. Quality of

sleep has been linked with stress and heightened sensitivity to pain, with insomnia being a common co-morbidity of chronic pain (Azevedo et al., 2011; Chiu et al., 2005). After prolonged periods of poor sleep, people tend to become more irritable and stressed (an amplification factor). This can lead to heightened sensitivity of biological and nervous system functions. Behaviours such as anxiety and poor sleep can therefore serve as amplification factors which increase the likelihood of stressors (such as the onset of pain) becoming more difficult to deal with. This amplification of pain via psychological factors is just one of the mechanisms likely involved in the genesis of chronic pain. Chronic pain is then likely to cause discomfort and disturb sleep, thus a vicious cycle is created, where pain causes poor sleep and poor sleep makes pain worse (Smith & Haythornthwaite, 2004). This is an interactive cycle which likely occurs between chronic pain and several other psychophysiological disorders involving the CNS including: depression, anxiety and stress (Chapman et al., 2008; Kroenke et al., 2011; Lerman et al., 2015; Williams et al., 2003).

Currently, it is unclear whether people are born with a susceptible predisposition to central sensitisation and consequently chronic pain, or whether the introduction of chronic pain leads to central sensitisation. Some factors are predisposing factors which create an initial susceptibility to central sensitisation, while other factors play a role in the exacerbation of central sensitisation following the onset of pain. It is likely that similar factors are involved at both stages e.g., depression, anxiety, poor sleep and stress. Some of the factors that might exclusively occur after pain onset are pain catastrophising and fear avoidance. Ultimately, all these stressors have the ability to increase the reactivity of the central nervous system, increasing the likelihood of central sensitisation (Curatolo et al., 2006; Diatchenko et al., 2006).

2.3.3. Diagnosing Central Sensitisation

It is extremely difficult to diagnose central sensitisation by the IASP definition, as examining the responsiveness of nociceptive neurons in the central nervous system would be an invasive procedure. Some models within research labs involving capsaicin, thermal, pressure and electrical

stimuli, have attempted to measure areas of allodynia and secondary hyperalgesia as a proxy for central sensitisation. These measures, however, have not been widely used for diagnosis in clinic settings (Quesada et al., 2021). A major reason for this is that expensive specialist equipment is often required, with specific training and time needed to make such evaluations. Additionally, some of these tests involve using von Frey filaments and pressure gauges that require patients to report their own level of sensitivity surrounding an area of stimulation. It would be difficult to assume that specific surface areas calculated for allodynia and hyperalgesia, following a painful stimulus, were indicative of central sensitisation on a case-by-case basis. There would be an impractical cut-off point for suggesting CS in one patient but not another. In other words, there is no accepted standard for what an abnormal score indicative of central sensitisation would be. The identification of increased responsiveness of nociceptive neurons would require a baseline measure for each individual, to assess whether responsivity had increased on a case by-case basis. It would be impractical to carry out such measures on healthy people throughout their lifetime.

One easy-to-use method that has been developed to help identify central sensitisation is the 'Central Sensitisation Inventory' (CSI) (Neblett et al., 2015). This questionnaire is based on self-report answers to questions that are associated with the risk factors previously mentioned i.e., depression, anxiety, stress, sleep etc. Although the CSI is a useful clinical tool in evaluating possible psychological pain facilitation and overall hypervigilance, due to its indirect nature, it is a leap to assume that this inventory can reliably identify the occurrence of increases in nociceptive responsivity. This thesis questions the suitability of this self-report inventory for diagnosing such a psychophysical mechanism. While sensitivity to pain and psychological facilitation may be closely aligned, one should not be used to determine the presence of the other. We will assess whether the CSI maps on to psychophysical measures associated altered pain processing i.e., Quantitative Sensory Testing (QST). Or, whether the questionnaire more accurately represents an amalgamation of psychological risk factors associated with chronic pain (e.g., anxiety, depression stress etc.). If the latter is found to be the case, it suggests that the CSI does not truly measure central sensitisation i.e., the increased

responsiveness of nociceptive neurons. It may, however, offer clinical utility by suggesting a mechanism behind a patient's complex and often difficult to diagnose condition, which could help them to legitimise their pain.

QST such as pain thresholds, temporal summation (TS) and conditioned pain modulation (CPM), have been found to build a phenotype ('pro-nociceptive'), which can predict pain facilitation/central sensitisation (O'Brien et al., 2018; Yarnitsky et al., 2013). TS and CPM are psychophysical assessments that have been linked with mechanisms of ascending facilitation and descending inhibition, respectively (Mackey et al., 2017). TS is investigated by comparing a noxious stimulus to a serially presented stimulus of the same strength. Typically, an increasing intensity of pain occurs with prolonged exposure in a phenomenon known as 'wind-up' (D'Mello & Dickenson, 2008). Wind-up occurs when repeated nociceptive input transmitted via c-fibres to the dorsal horn, result in an increased frequency of secondary spinal firing from the dorsal horn; leading to increased pain intensity and consequently lowering the activation potential required for pain. A characteristic of central sensitisation is when this 'wind-up' sensation can progress into a persistent state of high reactivity. CPM is a human psychophysical assessment based on the concept of 'pain inhibits pain', derived from the diffuse noxious inhibitory control (DNIC) mechanism found in animal studies (Le Bars et al., 1979). CPM is associated with endogenous analgesia mechanisms and is said to quantify the efficiency of endogenous inhibition of pain (Damien et al., 2018; Ohara et al., 2005; Yarnitsky et al., 2012). CPM can be measured in humans by evaluating the experience of pain before and after it is inhibited, by the inducement of pain at a proximally distal anatomical site. For example, via the application of a thermal test stimulus to the leg, and a hot water bath as a conditioning stimulus, applied to the hand (Yarnitsky et al., 2008, 2012)

CPM and TS have both been successful tools in predicting post-surgical pain (Petersen et al., 2015; Weissman-Fogel et al., 2003, 2009; Wilder-Smith et al., 2010). Chronic pain disorders are associated with less efficient CPM (Lewis et al., 2012; Staud, 2012; Yarnitsky, 2015), as well as enhanced TS

(Arendt-Nielsen et al., 2010; Sarlani et al., 2004; Staud et al., 2014; Weissman-Fogel et al., 2003). Since modern models of chronic pain have hypothesised central sensitisation to be a key factor in the maintenance of chronic pain (Latremoliere & Woolf, 2009), it is likely that these mechanisms play a role in central sensitisation susceptibility. Investigating psychological factors associated with these pain mechanisms, measurable via TS and CPM, may be useful for identifying people who are vulnerable to central sensitisation and acute to chronic pain transition. One factor of interest in this thesis is how attention to pain may influence these ascending and descending modulatory systems. If a modifiable characteristic, such as attention, is associated with a 'pro-nociceptive' phenotype it may suggest that endogenous pain facilitatory and inhibitory mechanisms can be moderated; through attention regulation training (i.e., mindfulness-based training or CBT).

2.3.4. Central Sensitisation, Cognitions and Emotions

When central sensitisation occurs and the nervous system becomes highly reactive, this may not just be related to sensitivity to pain. it may also be associated with our emotions. For instance, central sensitisation has been associated with cognitive disorders such as anxiety, depression and emotional distress (Adams & Turk, 2015; Clark et al., 2019). This occurs because the central nervous system is not just responsible for transmitting sensory sensations like pain to the brain; it also governs modulatory processes driven by our thoughts and emotions (Critchley et al., 2013; Garland, 2012). There is also a question of causality and co-morbidity between pain, emotions, and central sensitisation. Most likely, there is a bi-directional relationship whereby our emotional state influences central sensitisation and vice versa. It makes sense that people who are stuck in a highly reactive state of central sensitisation are likely to be nervous or anxious, with low thresholds for pain. Contrary to this, people who are better able to relax perceive things as less threatening and approach ambiguous stimuli in a more accepting manner, could be more resilient to central sensitisation. One key determinant of an individual's vulnerability to pain facilitation might be the extent to which people attend to pain and become fixated on it, versus their ability to regulate

attention and/or disengage from pain when it occurs. Regulating attentional processes by disengaging from pain or ultimately viewing pain as less unpleasant (i.e., approaching it in an accepting manner), could help to resist the development of an excitatory pain-stress cycle, which occurs in the mindset of many chronic pain patients.

If catastrophising is the act of being unable to disengage from pain and dwelling on it with great negativity, mindfulness would be its functional antithesis. Mindfulness is an attentional regulatory process, which promotes awareness of the current context in an open and accepting manner (Chiesa & Serretti, 2009; Kabat-Zinn, 1982). Neural findings suggest that mindfulness alters pain through a unique mechanism, simultaneously involving increased attention to sensory input, but reduced evaluative and negative affective responses (Harrison et al., 2019; Salomons & Kucyi, 2011). Therefore, like catastrophising, mindfulness is associated with an attentive engagement with pain, but it differs by actively regulating any negative association. It can be seen as a state i.e., mindfulness meditation, or as an intrinsic trait that people naturally engage (Brown & Ryan, 2003). High trait mindfulness is associated with lower chronic pain severity (Petter et al., 2014), higher pain thresholds (Zeidan et al., 2016) and lower levels of pain catastrophising (Bento et al., 2018; Prins et al., 2014).

When referring to mindfulness as a trait, in this case it refers to the extent to which someone naturally tends towards properties of mindfulness. A trait is defined as a distinguishing quality which indicates an inherited or environmentally determined characteristic, which is expressed over an extended period of time. Trait mindfulness refers to the "*innate capacity of paying attention to present-moment experiences with an open and non-judgmental attitude*" (Tang & Tang, 2020,p.26). It is distinct from state mindfulness, which describes the experience of non-judgmental present-focused awareness induced from mindfulness practice/meditation (Medvedev et al., 2017). Thus, trait mindfulness is the extent to which one's natural tendencies are reflective of these mindfulness techniques, without any prior training. The FFMQ is a widely used measure of trait mindfulness

(Carpenter et al., 2019; Cosme & Wiens, 2015; Harrison et al., 2019; Kiken et al., 2015). Using the FFMQ to assess mindfulness as a trait is important as assessments could help identify if an individual is likely to be vulnerable to persistent pain when it occurs, and can give an indication through which mechanisms the individual is vulnerable. Meta-analytic evidence shows that FFMQ scores can be changed through mindfulness training (Kiken et al., 2015; Quaglia et al., 2016), and mindfulness meditation is associated with beneficial response to pain (Hilton et al., 2017). identifying trait mindfulness as a vulnerability for pain sensitisation may have implications for suggesting appropriate treatment for some individuals.

Measuring mindfulness with the FFMQ means that cross-sectional research exploring the association between mindfulness and pain can be carried out, without the need for mindfulness behavioural interventions (MBIs). For reference, MBIs are a successful treatment option for chronic pain associated with increased pain thresholds and reduced negative pain-related biases, such as catastrophising (Turner et al., 2016; Zeidan et al., 2010, 2012). However, we are not interested in whether meditative practices can reduce pain sensitisation here. Instead, we want to study universal markers that can be measured in anyone, without the need for training. We are focused on studying individual differences in trait personality characteristics that might lead to a naturally enhanced vulnerability or resilience to pain, which is likely an important factor in acute to chronic pain transition (Hasenbring et al., 2001). The FFMQ allows us to assess whether a person's natural tendency to be mindful, without any meditative training, is associated with differential responses in pain sensitisation. In this thesis we will assess the extent to which trait mindfulness is associated with sensitisation to pain over a brief time period.

2.4. Principle Questions

2.4.1. Overview

This thesis aims to contribute to the literature by exploring social and psychological factors that could help predict which individuals are vulnerable to the transition of acute to chronic pain. The

importance of psychosocial factors is highlighted in the first section of this thesis. Chronic pain causes a lot of stress and problems in everyday life. These stressors, in turn, exacerbate pain, creating a vicious cycle of chronicity which is hard to break out of. Due to lack of available resources, people are often unable to get the help they need right away. This enhances the risk of developing chronic pain. Psychological stressors such as: anxiety, depression, hopelessness, social stigma, catastrophising, and poor sleep, begin to facilitate pain in to becoming something much more difficult to treat. We are interested in exploring what every day psychosocial factors in the workplace contribute towards this negative pain experience.

We also know that psychological factors contribute towards the pain experience and directly influence ascending and descending modulatory mechanisms. Exploring Individual differences in acute pain resilience might help us to better understand why some people develop chronic pain and others do not. Identifying areas for vulnerability could also help inform on strategies for targeted interventions. Further knowledge of how psychological factors influence pain mechanisms in healthy subjects, may provide clues to suggest individual differences in coping with pain following onset; during a critical time where acute pain could become chronic. In this thesis we will assess whether attending to pain (intrinsic attention to pain) and properties of attention regulation (trait mindfulness) are associated with laboratory measures of pain facilitation and inhibition in healthy subjects.

Assessing pain sensitisation in laboratory settings may be useful for understanding individual differences in resilience to pain. However, these paradigms are not always cost-effective, nor pragmatic, to conduct on patients in a clinical setting. Clinicians are likely to rely on self-report questionnaires that patients can quickly fill out themselves, without the need for any expensive or specialist equipment. We aim to explore some of the limitations and assumptions that these self-report questionnaires can make. We will assess the extent to which the 'Central Sensitisation Inventory' accurately reflects the mechanism of central sensitisation, defined as an increased

responsiveness of nociceptive neurons. We will therefore highlight the disparity between laboratory measures of a construct (central sensitisation) and how this term has been adapted for use in clinics (self-report questionnaire), causing a form of construct drift across disciplines.

2.4.2. What Psychosocial Stressors in the Workplace are Associated with Chronic Pain?

As reviewed above, chronic pain has many stressors associated with it, which can exacerbate pain and make it worse. In this study we aimed to investigate how chronic pain affects individuals within the workplace. We did this by examining psychosocial variables in a large sample of individuals in the European workforce. We conducted a cross-sectional analysis of 2,384 individuals with chronic pain, and 2,263 individuals without pain. The two groups were compared on the following psychosocial factors: supervisor support, job responsibility, team cohesion, discrimination, threats/abuse, job competency, job reward, sexual harassment, stress, and job security.

This was of interest because a lot is known about the impact of pain in terms of medical costs and missed work, but less is known about its impact when individuals are present for work. The paper adds to the literature on the overall costs of pain by offering a novel approach to measuring the indirect personal and societal costs of 'presenteeism', that are often overlooked when totalling overall costs of pain in the workplace. Identifying some of the additional issues that people in chronic pain face could shed light on some of the psychosocial factors that exacerbate pain. The findings could also offer important information for guiding workplace interventions to help people with pain, and maximise productivity across the workplace. We hypothesised that chronic pain would be associated with greater psychosocial stress and poorer relations in the workplace.

2.4.3. Is Attention to Pain Associated with Endogenous Modulatory Mechanisms?

Conditioned pain modulation (CPM) and temporal summation (TS) are psychophysical assessments viewed as a proxy for measuring the efficiency of ascending and descending modulatory circuitry (Lewis et al., 2012; Yarnitsky et al., 2013). CPM measures an individual's ability to inhibit a peripheral

nociceptive stimulus represented by the method of 'pain inhibits pain' (Moont et al., 2010) . TS measures 'wind-up', which represents an individual's ability to facilitate an ongoing peripheral nociceptive stimulus. Together, these two measures make up a pronociceptive phenotype, associated with endogenous pain facilitation (Yarnitsky et al., 2013). We also know that people differ in their ability to disengage from pain when it occurs (Kucyi et al., 2013). This is of interest because although pain captures attention, attentional disengagement may be able to override pain mechanisms. For example, Beecher (1959) reported that some soldiers denied any pain despite extensive wounds, most likely due to their attention being required elsewhere for survival. In Study Two, we were interested in assessing how modulatory circuitry can influence the extent to which individuals attend to pain. We were able to assess intrinsic attention to pain (IAP) in 44 healthy participants by measuring the extent to which participants' attention was focused on pain during noxious stimuli. We could then investigate correlations between IAP scores, TS, and CPM to test whether individual differences in propensity to attend to pain was associated with a pro-nociceptive phenotype. We hypothesised that attention to pain will be associated with pain facilitation and disinhibition (a pronociceptive phenotype).

2.4.4. Is Trait Mindfulness Associated with Sensitisation to Pain?

In this paper we were interested in examining individual differences in sensitisation to pain over a brief paradigm. While we do not know yet if adaptation over a short period is related to adaptation over a longer period i.e., chronic pain, this study may be relevant for understanding individual differences in how people respond when they experience persistent pain. One study that suggests these shorter paradigms may be relevant for chronic pain prediction identified that sensitivity to painful stimulation was associated with chronic pain (Vierck et al., 2014), while another study identified that coping behaviours were rudimentary in acute to chronic pain transition (Hasenbring et al., 2001). We specifically wanted to investigate how trait mindfulness, a psychological characteristic associated with beneficial responses to pain, was associated with rates of sensitisation

over a short time period (approx. 26 minutes). We explored how trait mindfulness influences adaptation to an ongoing stimulus. 44 healthy participants carried out the FFMQ. These five facets of mindfulness were then correlated against rates of sensitisation. Participants went through three separate days of pain assessment. For each pain assessment, participants received 44 pre-calibrated painful stimulations of the same temperature and duration. Ratings for intensity and unpleasantness were recorded after blocks of 11 stimuli each. Rates of sensitisation were recorded by evaluating the change in ratings across the four time points. FFMQ scores were correlated with these sensitisation rates. We hypothesised that low trait mindfulness would be associated with enhanced rates of sensitisation, and high trait mindfulness would be associated with greater resilience/habituation to the stimulus. If our hypothesis is correct, this study could inform on which individual differences factors facilitate coping with persistent pain in the short-term. The study informs future research on assessing the role of trait mindfulness in acute to chronic pain transition.

2.4.5. Is the Central Sensitisation Inventory a reliable assessment of the increased responsiveness of nociceptive neurons?

Central Sensitisation is defined as “an increased responsiveness to nociceptive neurons to either normal or sub-threshold input” (Loeser & treede, p.426). It was a mechanism discovered in animal studies, but no gold standard measure has accurately been able to assess central sensitisation in humans (Schuttert et al., 2021). The term central sensitivity syndrome was developed to give a label for ‘medically unexplained’ pain conditions (Yunus, 2007), which all had common psychological co-morbidities. These included depression, anxiety, and stress (Adams & Turk, 2015; Clark et al., 2019), all of which are factors associated with chronic pain (Woo, 2010). Central sensitisation is thought to be a likely underlying cause of many unexplained chronic pain conditions (Nijs et al., 2021). Although psychological facilitation and sensitivity to nociception are closely linked, one does not define the other. In this systematic review, we aim to explore the extent to which the easy to implement self-report questionnaire the ‘central sensitisation inventory’, accurately reflects an increase in

nociceptive responsiveness, or whether it measures sensitivity in a broader/psychological sense. We suggest that this inventory assumes that psychological factors associated with central sensitivity syndromes (such as anxiety, depression, stress, etc.) are used to assess central sensitisation in clinics. We hypothesise that the questionnaire may not truly reflect nociceptive responsiveness, and therefore does not accurately represent the canonical (pre-clinical) definition of central sensitisation. If this is found to be the case, we will consequently discuss a notion of 'construct drift'. Construct drift is where the diagnosis of central sensitisation and its meaning within clinical settings has drifted from its original mechanistic definition of nociceptive responsiveness, to one of a more emotional/psychological vulnerability. A reason for this drift may be that 'central sensitisation' is a term clinicians can use to legitimise a person's pain, and offer a central mechanistic explanation when there is no visible aetiological cause apparent.

2.5. References

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3. Study One: Attending Work with Chronic Pain is Associated with Higher Levels of Psychosocial Stress

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Attending Work with Chronic Pain is Associated with Higher Levels of Psychosocial Stress

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3.1. Abstract

Background & Aims

Much is known about the impact of pain in terms of medical costs and missed work. Less is known about its associations when individuals are present for work. This study examines 'presenteeism' by analysing the psychosocial costs of pain in the workplace, using the 2015 European Working Conditions Survey (EWCS).

Methods

We conducted cross-sectional analysis of 2,384 individuals with chronic pain, and 2,263 individuals without pain (matched by age and sex), using data from the European Working Condition Survey (2015). We compared groups in terms of the following psychosocial factors: Supervisor Support, Job Responsibility, Team Cohesion, Discrimination, Threats/Abuse, Job Competency, Job Reward, Sexual Harassment, Stress, and Job Security. The groups were also compared in terms of days lost due to illness.

Results

People with pain were 64% less likely to view their job as rewarding (OR .61, 95% CI .57-.65), 47% more likely to be subjected to threats/abuse in the workplace (OR .68, 95% CI .63-.73), 30% more likely to report poor supervisor support (OR .77, 95% CI .73-.82), and 28% more likely to perceive discrimination in the workplace (OR .78, 95% CI .71-.85). People with pain missed approximately nine more days of work per year than the non-pain respondents.

Conclusions

Chronic pain was associated with lower vocational fulfilment, and feelings of being ostracised in the workplace. These findings suggest that the presence of pain in the workplace goes well beyond lost productivity due to absenteeism.

3.2. Introduction

The economic burden of chronic pain is huge, costing the US an estimated 560-635 billion dollars in 2010, due to a combination of medical costs and productivity lost (Gaskin & Richard, 2011). Absenteeism (lost productivity due to absences from work) is a well-documented cost of chronic pain (Darr & Johns, 2008; Harrison & Martocchio, 1998; Johns & Xie, 1998). Less is known about presenteeism, whereby unhealthy employees are physically present at work but unable to perform at full capacity. Research has shown that presenteeism is positively related to burnout (Caverley et al., 2007; Demerouti et al., 2009; Koopman et al., 2002), and it is claimed that working while ill can cause a greater aggregate loss of productivity than being absent (Collins et al., 2005). The annual cost of presenteeism due to pain may substantially outweigh the cost of absenteeism (Nagata et al., 2018; van Leeuwen et al., 2006). This may be due to burnout exacerbating pain and leading to greater disability, or it could be because people who attend work with pain experience conflict with peers due to disability bias and discrimination. This can lead to lower levels of morale and productivity across the workplace (Draper et al., 2011; Grant et al., 2019). Learning to manage presenteeism effectively, so that it doesn't lead to burnout and workplace disruption, could provide a competitive advantage for employers (Hemp, 2004). Research that identifies some of the issues workers with chronic pain face, which might have an impact on workplace productivity, would be informative for guiding healthy workplace interventions and improving return-to-work outcomes.

Studies that do tally lost productivity costs due to presenteeism are primarily based on employees' self-reported productivity or approximate valuation methods that are difficult to verify (Johns, 2009; Lensberg et al., 2013). Assessing the overall impact and cost of presenteeism involves understanding the different ways pain patients might struggle while at work. Chronic pain can be invisible to employers, yet its psychological and social impact can be immense (Dueñas et al., 2016; Smith & Osborn, 2007). People in chronic pain often receive no clear medical diagnosis, making managers less likely to offer sympathy or accommodation (Rasmussen et al., 2014), and increasing the chances

that these people will continue to work through pain and/or feel pressured into returning to work prematurely (Wainwright et al., 2013). In turn, this can result in increased job stress, high physical demands, job dissatisfaction, an unsupportive workplace and more subsequent days off (Shaw et al., 2009). Further absenteeism may be an act of fear avoidance that promotes disability, disuse, and fear of discrimination from co-workers. Individuals with chronic pain may feel guilty, frustrated, and even a burden to colleagues, leading to a detrimental effect on their own mental health and a decline in morale across the workplace. Colleagues become frustrated with having to pick up the sufferers workload as productivity levels wane, due to both absenteeism and presenteeism (Lack, 2011; Ree et al., 2019).

While presenteeism has clear psychosocial and financial costs, these costs remain difficult to quantify. We are interested in exploring some of the indirect psychosocial costs that go above and beyond monetary loss which constitute a broader definition of presenteeism. This study aims to specify how chronic pain affects individuals within the workplace, by examining psychosocial variables in a large sample of individuals in the European workforce.

3.3. Method

European Working Conditions Survey - Participants

Data were taken from the sixth and most recent European Working Conditions Survey (EWCS), collated in 2015 (*Sixth European Working Conditions Survey*, 2015). Ethical approval for the EWCS was provided by INRAEUROPE and participants gave informed consent. Analysis conducted for this paper was performed on a fully anonymised and publicly available version of this data. Further information on how data was collected can be found at: https://www.eurofound.europa.eu/surveys/european-working-conditions-surveys.

In total, 43,850 participants were interviewed face-to-face across 35 European countries. These included the 28 EU Member States; plus, Albania, Turkey, Switzerland, the Former Yugoslav Republic of Macedonia, Montenegro, Norway and Serbia. In most countries, the target sample size was 1,000. To reflect the larger workforce in larger countries, the target was increased to 1,200 in Poland, 1,300 in Spain, 1,400 in Italy, 1,500 in France, 1,600 in the UK and 2,000 in Germany and Turkey. Countries were also offered the opportunity to top-up their sample. This offer was taken up by Belgium, Slovenia and Spain, which led to sample sizes of 2,500, 1,600 and 3,300 respectively.

Participants chosen were a random sample of people in employment, representative of the working population in each EU country. This population included all active employed and self-employed persons aged 15 years and over (16 or older in Bulgaria, Norway, Spain and the UK). People were classified as employed if they had worked for pay or profit for at least an hour in the week preceding the interview (International Labour Organization definition), or if they were not working but had jobs from which they were temporarily absent. All retirees, unemployed people and homemakers were excluded. Non-Europeans were included on the condition that they were interviewed in the respective language of the country which they worked.

A multi-stage, stratified, random sample of the working population was taken in each country to deliver a clustered sample. Depending on the availability of high-quality registers, sampling was carried out using individual-level, household-level and address-level registers. Or through enumeration, using a random-walk approach. Country-level samples were stratified by region and degree of urbanisation. In each stratum, primary sampling units (PSUs) were randomly selected proportional to size. Subsequently, a random sample of households was drawn in each PSU. Finally, unless individual-level registers were used, in each household, the selected respondent was the person in work who would have their birthday next.

The survey consisted of a questionnaire that was administered in a face-to face interview. The respondents were interviewed at home and the questionnaire comprised of 106 multiple-part questions that covered information on types of contracts, various health outcomes, and several aspects of working conditions. This included the physical environment, psychosocial working conditions, work-station design, working hours, work organisation and social support at work. Only questions that imposed a potential psychosocial or cognitive impact to an individual within the workplace were considered for analysis.

Pain and non-pain samples were selected from the original EWCS 2015 data. Although there were no direct questions about chronic pain, we have inferred pain status from a question on chronic health conditions, doing our utmost to ensure that our chronic pain group consists only of individuals with pain as their primary chronic health issue. Participants that indicated they had one or more of the following: headaches, backache, muscular pains in shoulders, neck and/or upper limbs (arms, elbows, wrists, hands etc.) or muscular pains in lower limbs (hips, legs, knees, feet etc.) over the past 12 months, and who indicated that they had an illness/health problem that has persisted for longer than 6 months, were classified as having pain. To minimise the number of participants whose primary persistent health problem wasn't pain, we excluded individuals who endorsed other illnesses or health problems such as; hearing problems, skin problems, Injuries or any 'others' in the

past 12 months. We did not exclude individuals with anxiety or fatigue, given their high levels of co-morbidity with pain. In order to reduce the possibility that findings were driven by the inclusion of individuals with anxiety and chronic fatigue as their primary chronic health issue, a parallel analysis was carried out excluding these individuals.

The non-pain sample was identified as participants who reported no illness or health problems over the last 12 months and no persistent health problems lasting over 6 months. The total sample that was deducted from the EWCS 2015 original Data set (43,850 participants) suitable for analysis, was 18,022. This sample consisted of 4,254 respondents with pain and 13,768 without pain.

Measures

The first step in analysing the data was to recode relevant questions such that 1 on a Likert scale indicated the most positive response for each question, allowing for directional interpretations in later analyses. Secondly, in order to manage the large number of variables and ensure that items tapping the same latent construct were grouped together, questions related to workplace costs (46 items in total) were selected for a Principal Components Analysis (PCA). A PCA was chosen as the primary objective was to reduce a large set of variables to a smaller more interpretable set. Once these items underwent a varimax rotated PCA, related items could be consolidated into suitable psychosocial factors, for a more coherent analysis. A scree Test was used to limit the number of components. This was done by ranking eigenvalues of the components' eigenvectors, derived from the variance-covariance matrix. Psychosocial factors with eigenvalues greater than one were regarded as significant for this study. Each varimax rotated factor is comprised of items that yield a high co-variance. Varimax rotated factor loadings below 0.4 co-variance were excluded from the factor. If factor scores overlapped (i.e., an item scored >0.4) for more than one factor; the lower factor score was disregarded. Internal consistency for each of the factor scores were examined using Cronbach's alpha. Participants with missing data for our variables of interest were discarded from all analyses. The primary reason for missing data was the exclusion of self-employed individuals from

many of the psychosocial variables examined. This ensured that our sample consisted only of people who were employed and paid a salary within an agency, ensuring that a hierarchical management structure was part of the social context. Following a Chi square test to assess age and sex differences between the pain and non-pain samples (see Results), the two samples were matched by age and sex leaving a pain sample of 2,384 and a non-pain sample of 2,263.

To obtain odds ratios and assess the contribution of pain to differences in our workplace variables, we ran a binary logistic regression for each factor. Tests were Bonferroni-corrected to account for multiple comparisons. Psychosocial factors that survived Bonferroni correction were put into a one way between-subjects multivariate analysis of covariance to determine whether the factors were significant as part of a model (i.e., did not explain variance already accounted for by other factors).

To confirm previous findings that pain is associated with higher levels of absenteeism, a t-test was carried out to assess whether individuals with pain missed more working days than individuals without pain. An ANOVA was conducted to investigate whether any observed differences in psychosocial variables were a function of individuals with pain having different job characteristics (e.g., part-time/full-time work, hours worked, carrying or moving heavy loads, working with computers, sitting, dealing with clients, level of education etc). A parallel logistic regression was conducted to include substantive job characteristics as additional co-variates. All statistical analyses were carried out using SPSS 25.

3.4. Results

Participant Characteristics

There was a relatively even distribution of men (5,191) and women (4,865) across the whole sample, with a high preponderance of women in the pain group. The pain group was 57.4% female, significantly greater than the proportion in the non-pain group ($\chi^2(1, N = 10{,}056) = 102.87$, $p < .001$). On average, the mean age of the pain sample was significantly higher than that of the non-pain sample ($\chi^2(66, N = 10{,}021) = 646.70$, $p < .001$) (Table 1). These findings are consistent with previous findings that females and an older population are more likely to live with chronic pain (Fayaz et al., 2016; Yang et al., 2016). To ensure that age and sex were not confounders, case-control matching was used to create a new dataset that matched the pain and non-pain sample by age and sex, leaving a pain sample of 2,384 and a non-pain sample of 2,263. An ANOVA test showed that age ($F(1,4637) = 2.79$, $p = .095$) and sex ($F(1,4644) = .11$, $p = .736$) did not significantly differ between the pain and non-pain sample.

Table 1

Descriptive Statistics of Age and Sex in Pain vs Non-Pain Population.

	Males	Females	Missing	Total	Mean Age (n=10,021)
Pain	1014	1369	1	2,384	46.35 (n=2380)
Non-Pain	4177	3496	3	7,676	39.62 (n=7641)
All	5191	4865	4	10,060	41.22

Note. N is lower in age group as some people refused to give their age.

Six job characteristics appeared to be significantly associated with the pain sample. These were part-time work, fewer hours worked, carrying or moving heavy loads more frequently, sitting more frequently, dealing with people outside the workplace more frequently and a lower level of education (see Table 2). However, the effect sizes for all but one of these factors are small. The job

characteristic most substantively found in the pain group was carrying or moving heavy loads (F(1, 4,642) = 159.00, p<0.001).

Table 2

Descriptive Stats of Job Characteristics in Pain vs Non-Pain Group.

	Total	Pain Group	Non-pain Group	Df	F	Sig	ETA squared
	Mean (SD)	Mean (SD)	Mean (SD)				
Part time or full time (low score = more likely to work part-time)	1.79(.41)	1.78 (0.41)	1.80 (0.40)	4,462	3.44	.064	.001
Hours worked per week	36.55(10.47)	36.7 (11.08)	36.4 (9.79)	4,601	.931	.335	<.001
Carrying or moving heavy loads (low score = more frequently)	5.86 (1.66)	5.56 (1.84)	6.17(1.38)	4,642	159.00	<.001	.033
Sitting (low score = more frequently)	4.25 (2.17)	4.22 (2.17)	4.28(2.17)	4,642	.89	.346	<.001
Dealing directly with people who are not employees at your workplace (low score = more frequently)	3.85 (2.41)	3.70 (2.39)	4.00 (2.42)	4,638	17.84	<.001	.004
Working with computers, laptops, smartphones etc (low score = more frequently)	4.17(2.41)	4.15 (2.44)	4.19 (2.37)	4,641	.29	.591	<.001
Level of education (low score = lower level of education)	6.79 (2.99)	6.65 (3.02)	6.95 (2.96)	4,312	11.25	.001	.003
Is your household able to make ends meet? (Low score = very easily)	3.12 (1.33)	3.27(1.35)	2.96 (1.20)	4,627	70.57	<.001	.015

Principal Components Analysis

A Principal Components Analysis (PCA) was carried out across the 46 items that were selected from the EWCS based on their relevance to psychosocial association to quality of life and workplace adjustment. The varimax-rotated factor loadings (items) were then inspected for conceptual coherence, to ensure that the eventual factor solution yielded interpretable psychosocial factors (Table 3). One item did not load on to any psychosocial factors (89H – "If I were to lose or quit my current job, it would be easy for me to find a job of similar salary"). The table also shows the variance explained by each factor.

Table 3

Principal Components Analysis for Factor Scores with Alpha Reliability

	Varimax Rotated Factor scores	Rotated Variance Explained (%)	Alpha Reliability for Factor Scores
1 – Supervisor Support		22.52	.90
Q63f - Your immediate boss encourages and supports your development	0.80		
Q63e - Your immediate boss provides useful feedback on your work	0.81		
Q63b - Your immediate boss gives you praise and recognition when you do a good job	0.78		
Q63d- Your immediate boss is helpful in getting the job done	0.76		
Q63c - Your immediate boss is successful in getting people to work together	0.76		
Q63a - Your immediate boss respects you as a person	0.63		
Q70a - Employees are appreciated when they have done a good job	0.54		
2 - Job Responsibility		6.95	.81
Q61n - You can influence decisions that are important for your work	0.76		
Q61d - You are involved in improving the work organisation or work processes of your department or organisation	0.7		
Q61i - You are able to apply your own ideas in your work	0.71		

Q61e - You have a say in the choice of your work colleagues	0.68		
Q61c - You are consulted before objectives are set for your work	0.66		
Q61f - You can take a break when you wish	0.57		
3. Team Cohesion		5.16	.84
Q70f - In general employees trust management	0.52		
Q70c - Conflicts are resolved in a fair way	0.57		
Q70d - Work is distributed fairly	0.59		
Q70b - The management trusts the employees to do their work well	0.58		
Q70e - There is good cooperation between you and your colleagues	0.72		
Q89d - I generally get on well with my work colleagues	0.59		
Q61a - Your colleagues help and support you	0.45		
4 – Discrimination		4.88	.69
Q72c - Over the past 12 months at work, have you been subjected to any of the following - discrimination linked to nationality	0.67		
Q72b - Over the past 12 months at work, have you been subjected to any of the following - discrimination linked to race, ethnic background or colour	0.73		
Q72e - Over the past 12 months at work, have you been subjected to any of the following -discrimination linked to religion	0.68		
Q72g - Over the past 12 months at work, have you been subjected to any of the following - Discrimination linked to sexual orientation	0.65		
Q72f - Over the past 12 months at work, have you been subjected to any of the following - Discrimination linked to disability	0.56		
Q72d - Over the past 12 months at work, have you been subjected to any of the following - Discrimination on the basis of your sex	0.52		
Q72a - Over the past 12 months at work, have you been subjected to any of the following - Age Discrimination	0.43		
5 - Threats/Abuse in the Workplace		4.41	.74
Q80c - Over the last month, during the course of your work have you been subjected to any of the following – threats	0.79		
Q80a - Over the last month, during the course of your work have you been subjected to any of the following - verbal abuse	0.73		
Q80d - Over the last month, during the course of your work have you been subjected to any of the following - humiliating behaviours	0.71		
Q81c - Over the last month, during the course of your work have you been subjected to any of the following - bullying/harassment	0.60		

Q81a - Over the last month, during the course of your work have you been subjected to any of the following - physical violence	0.60		
6 – Perceived Competence		3.04	0.74
Q61j - You have the feeling of doing useful work	0.72		
Q61h - Your job gives the feeling of work well done	0.71		
Q61k - You know what is expected of you at work	0.69		
Q61g - You have enough time to get the job done	0.51		
7 - Job Reward		2.87	.80
Q89a - Considering all my efforts and achievements in my job, I feel I get paid appropriately	0.73		
Q89e - The organisation I work for motivates me to give my best job performance	0.61		
Q89c - I receive the recognition I deserve for my work	0.62		
Q89b - My job offers good prospects for career advancement	0.65		
8 - Sexual Harassment		2.66	.69
81b - Over the past 12 months, during the course of your work have you been subjected to any of the following- Sexual Harassment	0.86		
80b - Over the last month, during the course of your work have you been subjected to any of the following- Unwanted Sexual attention	0.84		
9 - Workplace Stress		2.32	.47
Q61m - You experience stress in your work place	0.75		
Q61o - Your job requires that you hide your feelings	0.75		
10 - Job Security		2.24	1.00
Q89g - I might lose my job in the next 6 months	0.66		

The PCA analysis yielded 10 psychosocial factors with eigenvalues above 1. Cronbach Alpha scores below 0.6 suggest that the items within the factor may not be measuring the same underlying construct. This is seen under the work stress factor (Alpha = .47). This factor was therefore discarded from the analysis.

To determine whether chronic pain had a significant association on any of these psychosocial factors, we compared pain and non-pain groups using a logistic regression analysis for each factor (see Table 4). For parallel analysis including heavy lifting as a co-variate (see supplementary Table 4a in appendix section).

Table 4

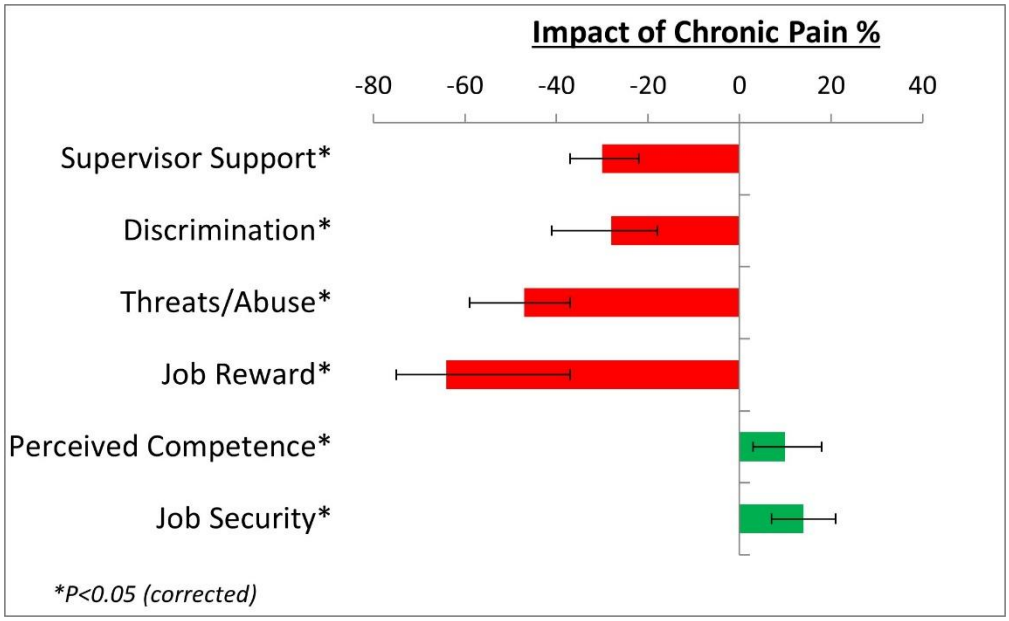
Logistic Regression Showing Impact of Chronic Pain on Each Psychosocial Factor

Component/Factor	Beta	SE	Sig.	OR	95% CI
Supervisor Support	-.26	.03	<.001	.77	.73-.82
Job Responsibility	-.03	.03	.381	.97	.92-.1.03
Team Cohesion	-.01	.03	.836	.99	.94-.1.06
Discrimination	-.25	.04	<.001	.78	.71-.85
Threats/Abuse	-.39	.04	<.001	.68	.63-.73
Job Competency	.10	.03	.005	1.1	1.03-1.18
Job Reward	-.50	.03	<.001	.61	.57-.65
Sexual Harassment	-.03	.03	.395	.97	.91-1.04
Job Security	.13	.03	<.001	1.14	1.07-1.21

After Bonferroni correction (0.05/10, $p<0.005$), three psychosocial factors were non-significant (Job responsibility, Team cohesion and Sexual harassment) and were not analysed further. The other six psychosocial factors were significantly influenced by pain (see Figure 1). These same factors remained significant in our parallel analysis with individuals with anxiety and chronic fatigue removed (see Supplementary Table 1), indicating that these findings were likely not driven by those individuals. Similarly, the inclusion of 'heavy lifting' as a co-variate did not influence the findings (see Supplementary Table 2).

Figure 1

Effect of Chronic Pain on Factor



Note. Odds Ratios Converted to Percentages

After inverting odds ratios for negative effects where appropriate, the significant findings of a logistic regression analysis for each factor were carried out as our core analyses. This showed that respondents with pain were 64% less likely to report their job as rewarding (OR .61, 1/.61 = 1.64), 47% more likely to be subjected to threats and/or abuse in the workplace (OR .68, 1/.68 = 1.47), 30% more likely to report poor supervisor support (OR .77, 1/0.77 = 1.30), and 28% more likely to perceive discrimination in the workplace (OR .78, 1/.78 = 1.28). On the other hand, the respondents with pain were 10% more likely to report good job competency (OR, 1.10) and 14% more likely to report greater job security (OR, 1.14). There were no significant differences between the pain and non-pain respondents for Job Responsibility (OR, 0.97, p = .381), Team Cohesion (OR, 0.99, p=.836) and Sexual Harassment (OR, 0.97, p = .395), after Bonferroni correction. All Odds ratios and 95% confidence intervals can be found in Table 4).

To examine the unique contribution of each of the significant psychosocial factors obtained from the univariate analyses, a multivariate model (MANOVA) including all significant psychosocial factors was conducted (see Table 5). The model of psychosocial factors (Supervisor Support, Discrimination, Threats/Abuse, Perceived Competence, Job Reward and Job Security was associated with chronic pain *(F(6, 4640) =88.07, p < .001; Wilk's Λ = 0.898, partial η^2 (eta) = .102*). All psychosocial factors remained significant within the model.

Table 5

MANOVA Comparing Pain vs Non-Pain Populations for Each Factor.

Factor	Group				F	P	Partial ETA Squared
	Pain Group		Non-pain Group				
	M	SD	M	SD			
Supervisor Support	.22	1.18	-.03	.92	63.64	<.001	.014
Discrimination	.11	1.27	-0.70	.66	36.51	<.001	.008
Threats/Abuse	.28	1.38	-.098	.77	131.34	<.001	.027
Job Competency	-.16	.94	-.10	.93	4.90	.027	.001
Job Reward	.34	1.05	-.11	.95	235.48	<.001	.048
Job Security	-.12	1.17	.00	1.06	14.95	<.001	.003

In order to address the possibility that the results could be influenced by violations of normality assumptions, tests were conducted to assess violations of normality. Following the PCA, a Shapiro-Wilk test showed that data were not normally distributed for supervisor support (W(4647) = .95, p<0.01), discrimination (W(4647) = .29, p<0.01), threats/abuse (W(4647) = .55, p<0.01), perceived competence (W(4647) = .97, p<0.01), job reward (W(4647) = .99, p<0.01), and job security (W(4647) = .97, p<0.01). These tests suggest violations of normality across the data and therefore the assumptions for parametric tests were not met for all variables.

A one-way non-parametric Kruskal-Wallis test was therefore conducted to ascertain whether any differences observed between the pain vs non-pain groups on reported work-related factors were significant. A Kruskal-Wallis test showed that there was a statistically significant difference between

the pain and non-pain sample for supervisor support ($H(1) = 35.92$, $p<0.01$), discrimination ($H(1) = 14.90$, $p<0.01$) ,threats/abuse, ($H(1) = 16.39$, $p<0.01$) job reward ($H(1) = 228.352$, $p<0.01$) and job security ($H(1) = 23.21$, $p<0.01$) scores. Perceived confidence scores were not significantly different for the two sample populations ($H(1) = 2.79$, $p=0.095$). The findings of the non-parametric test did not change the pattern of results from the logistic regression and MANOVA analyses reported above.

Out of the total sample of 4,647 that completed the selected questions, 4,317 went on to answer another question about the number of working days they missed over the past 12 months. An exploratory T-test was carried out to compare working days missed for the pain vs non-pain respondents. People with pain missed three times as many days (Mean=13.69, SD = 28.96) of work per year than the non-pain respondents (Mean=4.36, SD = 12.88), which was significant ($t(4,315) = 13.44$, $p <.001$, $D = 0.40$).

3.5. Discussion

The study sheds light on some of the hidden costs of pain above and beyond absence from work and medical costs. Consistent with previous studies of absenteeism (Besen et al., 2015; Ihlebæk et al., 2006), individuals with pain missed three times as many days as individuals without pain. To assess the association of pain when individuals do show up for work (presenteeism), we compared individuals with and without pain on ten psychosocial factors: Supervisor Support, Job Responsibility, Team Cohesion, Discrimination, Threats/abuse, Job Competency, Job Reward, Sexual Harassment, Stress and Job Security. The respondents with pain reported less reward for their efforts, poorer supervisor support and higher rates of threats and abuse. Identifying these key aspects of presenteeism helps us to better understand the overall cost of chronic pain.

These findings are consistent with previous literature demonstrating the association between pain and poor relationships with managers in the work place (Hämmig, 2017), discrimination (Coole et al.,

2010), threats/abuse (Sabbath et al., 2014; Yang et al., 2016), greater stress levels (Ellegaard & Pedersen, 2012), and feelings of underappreciation/ low reward (Siegrist, 1996). Moreover, Nixon et al (2011) conducted a meta-analysis across 79 studies and found that workplace stressors such as organisational constraints, interpersonal conflict, role conflict, role ambiguity, and lack of control were all related to physical symptoms (Nixon et al., 2011). Psychosocial factors such as these have a negative effect on productivity in the workplace (Chang et al., 2009; Cocker et al., 2013; Lohela-Karlsson et al., 2010; Rosen et al., 2010), with presenteeism often leading to burnout (Caverley et al., 2007; Demerouti et al., 2009; Koopman et al., 2002). One explanation for the feelings of discrimination/ abuse, poorer supervisor relations, stress and underappreciation in this study may be due to pain respondents' appraisals of employer concerns about productivity.

In this study we can see that two considerable psychosocial stressors; discrimination and threats/abuse, were associated with pain. Sabbath et al (2014) found similar results in a survey of 1,497 care workers. They found that injury prevalence was associated with being yelled at, for experiencing hostile/offensive gestures, and for being sworn at (Sabbath et al., 2014). There is an increasing body of evidence that suggests bullying and hostile-work environments are associated with poorer health (Khubchandani & Price, 2015; Lu et al., 2014; Vignoli et al., 2015; Yang et al., 2016). As these studies are cross-sectional, it is difficult to establish the directionality of the relationship between pain and social stress in the workplace, let alone the question of causality. The default presumption would be that pain is causing interpersonal issues, as pain regularly leads to socially detrimental behaviours such as frustration and depression (Dow et al., 2012; Fishbain, 2003). On the other hand, Nixon et al's (2011) meta-analyses included 7 longitudinal studies indicating that workplace stressors may precede chronic pain development (Nixon et al., 2011). It is also the case , that such stress could exacerbate and maintain pain (Fischer et al., 2016; Glaros et al., 2016; Li et al., 2017). It is possible that the relationship between pain and stress creates a negative feedback loop where pain causes interpersonal issues but is, in turn, exacerbated by those issues. As the present

study was also cross-sectional, this issue of causality between chronic pain and psychosocial factors applies, though again, it is likely that the two exacerbate each other.

Another notable finding of this study is the negative association of chronic pain with employee-supervisor relations. Studies have found that managers have limited awareness of employee pain and it is rarely openly discussed (Larsen et al., 2018). Managers habitually do not consider pain amongst employees a problem (Rasmussen et al., 2014), which is surprising given that a Danish study found that over 70% of the employees in a workforce had attended work despite experiencing considerable pain or sickness during the past year (Hansen & Andersen, 2008). One explanation that would reconcile these opposing points is that managers may have difficulty distinguishing chronic pain disorders from common day to day pain problems that most people experience at some point in their lives. This may be particularly important as studies have shown that management behaviour can significantly influence how an employee handles pain at work (Dellve et al., 2007; Sterud et al., 2014; Wynne-Jones et al., 2011). 'The Healthy Workplace Campaign' was introduced to reduce workplace bullying in America, holding the employer accountable for an abusive work environment, which encouraged the employer to actively reduce hostility within the workplace (Richardson et al., 2016). Similar campaigns may hold the key to reducing the negative psychosocial association with chronic pain across the workplace (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011; Rodwell & Demir, 2012; Vignoli et al., 2015). The requirement for public and occupational health strategies to reduce and manage chronic pain is becoming increasingly important as the workforce is continuing to grow older, becoming more susceptible to health issues (Delloiacono, 2016; Heidkamp & Christian, 2013).

Our study shows the negative association between pain and psychosocial factors in the workplace. The incorporation of campaigns that promote a work culture for handling pain could be of great benefit; helping to accommodate employees who struggle with pain and provide opportunities for trustful communication concerning employee health and possibilities for workplace adjustment. If

campaigns can focus on creating a friendly environment which aids people in pain, it may be possible to address some of the psychosocial issues identified in this study. There is much literature that endorses the value of such strategies (Barnes et al., 2008; Dellve et al., 2007; Johansson & Lundberg, 2004; Linton et al., 2016; Vries et al., 2012). For instance, employers report several advantages for accommodating employees with chronic health problems, with social inclusion having a positive effect on both productivity levels and employee health (Hartnett et al., 2011). Similarly, good leadership and a friendly social environment have been linked with enhanced productivity levels (Haynes, 2007; Lohela-Karlsson et al., 2010).

The findings that people with pain perceived greater competence and security in their work suggests that people with pain did not feel that pain affected their job performance negatively. Although, a non-parametric test also found that perceptions of job competence did not significantly differ between the pain and non-pain group. A possible explanation for the counterintuitive finding, related to job security, is that that people with pain, who were regularly absent and had strained relationships with their colleagues/supervisors, may have read into their working rights more thoroughly and became more aware of the rules surrounding job security. The unexpected finding related to job competence may be explained if we consider the limitations and biases of self-report questionnaires. Responses may be subject to social desirability bias as people in pain do not want to divulge that they might not be as competent in their job. This may be particularly pertinent as self-report questionnaires were completed via a face-to-face interview where participants may have felt judged. Regarding social context, Individuals in pain may overall be more prone to negative reporting bias that leads them to report greater pain and greater social hardship in the workplace. For instance, if during the time of reporting, respondents had been going through a particularly painful time, negative reporting bias may have occurred in relation to their pain and work relationships. Contrary to this, respondents with pain who feel discriminated against may feel they have to work harder due to higher expectations and unhelpful peers (Russinova et al., 2011). An intriguing area for a follow up investigation would be directly testing the possibility that people in

pain are confident in their own abilities but feel a sense of injustice as they perceive being ostracised by colleagues and underappreciated for their efforts.

A limitation of the study was that little direct information about pain conditions was collected in the European Working Condition Survey. As such, the presence of chronic pain was inferred from participants reporting they had been diagnosed with a health condition related to pain in the past 12 months, which had lasted more than six months. To mitigate the possibility that the observed workplace issues were due to a health condition other than pain, we excluded individuals who endorsed chronic health problems other than pain. Due to the high overlap between chronic pain and fatigue and anxiety symptoms, our primary analysis retained these individuals if they also endorsed pain symptoms, but we ran a parallel analysis without these individuals to confirm that our findings were not driven by either the inclusion or exclusion of individuals with comorbid anxiety or fatigue. Despite these steps, we cannot exclude the presence of some false positives in our sample. Moreover, there was no information on graded levels of pain intensity within the pain sample, where pain severity may ultimately be the most important factor in presenteeism and decreased productivity levels (Deyo et al., 2015). An experimental paradigm designed for purpose would allow for more reliable data and greater accuracy. In addition to this, the data are retrospective and obtained all at the same time so the temporal relationship between pain and psychosocial factors are unknown, we are therefore unable to determine causality between pain and psychosocial stressors. Moreover, the findings are subject to self-reported questionnaires which may have led to people with pain reporting greater hardship within the workplace and social desirability bias, leading to reports of greater competence at their job.

While we have noted the limitations of our selection criteria for chronic pain, it is noteworthy that more than half of the workers with pain were women and the mean age for workers with pain was older than workers without pain. As the workforce is ageing and people are working later into their life, workers with chronic pain will likely increase. If these findings are further verified, they suggest

that employers will face greater psychosocial issues related to chronic pain in future and further social disparity may occur between pain and non-pain samples if this issue is not addressed. As outlined above, campaigns such as the 'healthy workplace campaign' have been launched in America to successfully combat such issues.

This study detailed some of the psychosocial factors that should be considered when evaluating the costs of presenteeism. Some studies suggest that the costs of presenteeism may be considerably higher than those of absenteeism (Collins & O'Sullivan, 2015; Nagata et al., 2018). These comparisons, however, do not consider further potential losses if individuals with pain were to stay away from work. When considered in this light, presenteeism could be regarded as an act of organisational citizenship which garners praise. This view does not focus on productivity loss, but on productivity gained compared to absenteeism (Johns, 2009). In terms of further study, these evaluations should be considered within the context of the impact of working in a stressful psychosocial environment for pain, and whether such an environment might result in more missed work, higher medical costs, or even reduced productivity of non-affected team members. This study attempted to identify some of the issues of presenteeism that may influence productivity levels within the workforce more broadly. Future study should seek to quantify the effects of these issues on productivity.

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3.6. Appendix

Supplementary Table 1:

Logistic Regression Comparison of Pain Population With and Without Co-morbidities Against Each Factor.

	Pain population with Anxiety and Fatigue as co-morbidities (n=2,384)					Pain Population without Anxiety and Fatigue as co-morbidities (n=863)				
Factor	Beta	SE	Sig.	OR	95% CI	Beta	SE	Sig.	OR	95% CI
Supervisor Support	-.26	.03	<.001	.77	.73-.82	-0.14	0.04	0.001	0.87	.81-.95
Job Responsibility	-.03	.03	.381	.97	.92-.1.03	0.04	0.04	0.378	1.04	.96-1.12
Team Cohesion	-.01	.03	.836	.99	.94-.1.06	0.12	0.04	0.006	1.13	1.04-1.23
Discrimination	-.25	.04	<.001	.78	.71-.85	-0.15	0.05	0.002	0.86	.78-.95
Threats/ Abuse	-.39	.04	<.001	.68	.63-.73	-0.22	0.05	0.000	0.80	.74-.88
Job Competency	.10	.03	.005	1.10	1.03-1.18	0.10	0.05	0.039	1.10	1.01-1.20
Job Reward	-.50	.03	<.001	.61	.57-.65	-0.31	0.04	0.000	0.73	.78-.80
Sexual Harassment	-.03	.03	.395	.97	.91-1.04	0.01	0.05	0.833	1.01	.92-1.11
Job Security	.13	.03	<.001	1.14	1.07-1.21	0.19	0.04	0.000	1.21	1.11-1.31

Note. Age and sex were used as co-variates.

Supplementary Table 2

Logistic Regression Showing Impact of Chronic Pain on Each Factor (With Heavy Lifting as Co-variate)

	Logistic Regression excluding lifting heavy loads as Co-variates					Logistic Regression including lifting heavy loads as a Covariates				
Component/Factor	Beta	SE	Sig.	OR	95% CI	Beta	SE	Sig.	OR	95% CI
Supervisor Support	-.26	.03	<.001	.77	.73-.82	-0.24	0.03	<.001	0.79	.74-.84
Job Responsibility	-.03	.03	.381	.97	.92-.1.03	-0.01	0.03	0.881	1.00	.94-1.06
Team Cohesion	-.01	.03	.836	.99	.94-.1.06	-0.01	0.03	0.771	0.99	.93-1.05
Discrimination	-.25	.04	<.001	.78	.71-.85	-0.24	0.04	<.001	0.79	.73-.86
Threats/Abuse	-.39	.04	<.001	.68	.63-.73	-0.37	0.04	<.001	0.69	.64-.74
Job Competency	.10	.03	.005	1.1	1.03-1.18	0.12	0.04	<.001	1.13	1.06-1.21
Job Reward	-.50	.03	<.001	.61	.57-.65	-0.47	0.03	<.001	0.63	.59-.67
Sexual Harassment	-.03	.03	.395	.97	.91-1.04	-0.02	0.03	0.544	0.98	.92-1.05
Job Security	.13	.03	<.001	1.14	1.07-1.21	0.14	0.03	<.001	1.15	1.16-1.25

Supplementary Table 4a

Logistic Regression Showing Impact of Chronic Pain on Each Factor (Age and Sex as Co-variates)

Component/Factor	Beta	SE	Sig.	OR	95% CI
Supervisor Support	-.26	.02	<.001	.77	.74-.81
Job Responsibility	-.05	.02	.045	.95	.90-.99
Team Cohesion	-.07	.02	.005	.94	.89-.98
Discrimination	-.14	.02	<.001	.87	.83-.91
Threats/Abuse	-.32	.02	<.001	.72	.69-.76
Job Competency	.12	.03	<.001	1.13	1.08-1.19
Job Reward	-.40	.02	<.001	.67	.64-.70
Sexual Harassment	-.03	.02	.206	.97	.93-1.02
Job Security	.14	.03	<.001	1.15	1.10-1.21

4. Study Two: Intrinsic Attention to Pain is Associated with a Pro-nociceptive Phenotype

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Intrinsic Attention to Pain is Associated with a Pro-nociceptive Phenotype

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4.1. Abstract

Evidence suggests that attention to pain is a product of both incoming sensory signals and cognitive evaluation of a stimulus. Intrinsic Attention to Pain (IAP) is a measure that captures an individual's natural tendency to attend to a painful stimulus, and may be important in understanding why pain disrupts cognitive functioning in some individuals more than others. In this study we explored the extent to which IAP was associated with the modulation of incoming sensory signals characteristic of a 'pro-nociceptive' phenotype: Temporal summation (TS) and conditioned pain modulation (CPM). We found that IAP was positively correlated with TS and CPM. A regression model showed that TS and CPM explained 39% of the variance in IAP scores. Both mechanisms appear to contribute independently to the propensity to attend to pain. These findings highlight that modulatory mechanisms at the spinal/supraspinal level exert a strong influence on an individual's ability to disengage from pain.

Summary:

Capacity for modulation of incoming nociceptive signals is a determinant of our tendency to attend to pain.

4.2. Introduction

Individuals differ in their capacity to endogenously modulate nociceptive input. Yarnitsky et al. (2013) proposed a 'pro-nociceptive' phenotype associated with nociceptive facilitation, consisting of enhanced temporal summation (TS), and/or less efficient conditioned pain modulation (CPM)(Yarnitsky et al., 2013). TS is a measure of 'wind-up' or enhancement of pain with prolonged nociceptive exposure; with accumulating intensity drawing increased attention to the stimulus, facilitating adaptive response (D'Mello & Dickenson, 2008). CPM is based on the concept of 'pain inhibits pain' derived from diffuse noxious inhibitory control (DNIC) in animal studies (Le Bars et al., 1979). CPM is said to quantify the efficiency of endogenous inhibition of pain (Damien et al., 2018; Ohara et al., 2005). In Yarnitsky's conceptualisation, the two modulatory mechanisms contribute independently towards a 'pro-nociceptive' phenotype, likely due to the ascending facilitatory component of TS (Price, 1972; Price et al., 1977) and the descending inhibitory component of CPM (Le Bars, 2002). This suggests there are measurable individual differences in how people modulate an incoming nociceptive stimulus at the spinal and supra-spinal level.

Pain is an alarming signal and naturally captures attention to facilitate adaptive avoidance of harm (Fields, 2006). Field's motivation-decision model suggests that the degree to which attention is captured by pain, may be a function of the competing salience of current contextual factors other than the nociceptive stimulus (Fields, 2006). For instance, Beecher (1946) reported that during battle, some soldiers denied any pain despite extensive wounds. This was a likely result of their attention being required elsewhere for survival (Beecher, 1946). Experimentally, the distraction of highly difficult cognitive tasks significantly reduced the perceived intensity and unpleasantness of nociceptive stimuli, compared to low difficulty tasks (Rischer et al., 2020). Additionally, when participants were financially compensated for taking part in tasks, this had a suppressing effect on pain intensity (Verhoeven et al., 2010), suggesting motivational goals may be a factor in attending to pain.

Attention to pain is likely not a simple function of pain intensity and the contextual factors external to the individual. Melzack and Casey (1968) postulated that cognitive evaluation could modulate the sensory-discriminative and motivational-affective dimensions of pain. For instance, distraction can alleviate pain, whilst maladaptive cognitions such as rumination and catastrophising can exacerbate it (Johnson, 2005; Quartana et al., 2007; Schreiber et al., 2014). Subsequently, Eccleston and Crombez (1999) proposed the 'cognitive-affective' model, highlighting that interruptive attention towards pain is driven by perceived threat level. This encompasses the intensity, novelty, and predictability of a threatening pain stimulus, their level of somatic awareness and whether they catastrophise about pain (Eccleston & Crombez, 1999).

There appear to be many cognitive and contextual factors that influence engagement with pain, but no studies, to our knowledge, have explored the role of spinal/supraspinal mechanisms in attention to pain. Studying CPM and TS in relation to attention to pain can give us an idea of the extent to which attention to pain is driven by the sensory/discriminative output of modulatory activity in the spinothalamic tract, or whether other mechanisms are predominantly involved.

A previous study found 'intrinsic attention to pain' (IAP- the likelihood that people focus on 'pain' or 'something else' during nociceptive stimulation) was stable within individuals across time; with a high intraclass correlation(Kucyi et al., 2013). IAP was associated with their performance on a cognitive task during the presence of pain (Kucyi et al., 2013), suggesting that there areindividual differences in the likelihood that pain will distract from cognitive functioning. Neurologically, IAP is associated with functional and structural connectivity between the medial prefrontal cortex and periacqueductal-gray, suggesting an individual's propensity to attend to pain might be a function of the interplay between cortical evaluative processes and endogenous modulation of incoming sensory signals.

To date, however, little research has explored the role of the endogenous modulatory processes in how likely an individual is to be distracted by pain. This study therefore investigated whether (and how) a 'pro-nociceptive' phenotype is associated with trait-like attention to pain.

4.3. Method

Participants

44 healthy participants (23 female; M_{age}=23.57, S.D.=5.50) were recruited and received payment for their participation. The study was approved by the University of Reading Ethics Committee. Informed consent was provided by each participant. This study was part of an ongoing study involving 13 experimental sessions: One sensory/cognitive assessment, one imaging session, 11 examining prolonged pain exposure per participant. All data for this study was collected during the initial sensory assessment.

Materials

Evaluation of IAP, TS and CPM involved thermal stimuli being administered by a 30x30mm thermode (PATHWAY, Medoc, Israel) to the centre of the right calf. The baseline temperature for stimuli used in all testing was 32°C, and the ramp up rate was 8°C/second. For CPM and TS, participants verbally rated pain intensity on a Numerical Rating Scale (NRS) ranging from 0 ('no pain') to 10 ('extremely painful'). For IAP, participants provided verbal ratings indicating "to what degree were your thoughts/feelings about pain or something else?" using a 4-point Likert scale provided on paper (2='only pain', 1='mostly pain', -1='mostly something else', -2='only something else').

IAP

Participants received 10 thermal stimuli (5/10NRS – calibrated as a 20s stimulus rated between 4 and 6 - if a rating was given outside these values the stimulus was adjusted by 0.5°C and the test was

repeated) of 20 seconds(s) duration each, and each with a 30s interstimulus interval. After each stimulus, participants provided IAP ratings. IAP scores were calculated by averaging all ten scores.

Temporal Summation

Based on previous paradigms (Suzan et al., 2015), a calibrated (5/10NRS) thermal stimulus was applied for 120s. Every 10s participants were verbally prompted to state pain intensity using the NRS. TS scores were calculated by subtracting the first score from the last score in the series. A high TS score indicated greater sensitisation.

Conditioned Pain Modulation

Based on previous paradigms (Yarnitsky et al., 2012), the test stimulus was a calibrated 6/10 thermal stimulus applied to the right calf. The conditioning stimulus was submersion of the left hand in a 46.5°C water bath (Julabo, TW20). The test stimulus was first applied in isolation, with pain ratings from the leg recorded 3 times, at 10s intervals over a 30s stimulus. Following this, the hand was submerged in the water bath, with 3 pain ratings from the hand recorded at 10s intervals over a 30s stimulus, checking everyone rated the conditioning stimulus as non-zero (i.e. painful). Finally, the test and conditioning stimuli were presented simultaneously with pain ratings from the leg recorded 3 times, at 10s intervals over a 30s stimulus. The CPM score was calculated by subtracting the average pain rating from the test (leg) stimulus during simultaneous presentation, from the average rating from the test stimulus only condition. A high CPM score indicated more efficient inhibition of pain.

Analysis

Regression models were used to explore whether IAP was associated with CPM and TS, both individually and modelled together. For visualisation purposes, we calculated a composite pro-nociception score by adding TS scores (high facilitation) to reverse coded CPM scores (low inhibition), following z-transformation of both scales (The IAP scale was not z-transformed). A

Pearson's correlation analysis was carried out to explore the association between IAP and pro-nociception score. All statistical analyses were carried out using SPSS 25 (IBM Corp., Armonk, USA) with the significance level set to $p<0.05$.

Missing Data

Four participants were unable to keep their hand in the bath for the entire CPM task, so the final analysis includes the data of 40 participants. A missing values analysis indicated that Little's (1988) test of Missing Completely at Random (MCAR) was not significant, $\chi 2 = 1.38$, DF = 2, p = .501. Therefore, the data were considered missing completely at random.

4.4. Results

Following a Cooks Distance analysis removing three outliers (Cook, 1977), Table 1 shows that TS ($t(36)=11.08$, $p<0.001$) and CPM ($t(36)=4.91$, $p<0.001$) were significant. IAP was positively correlated with TS ($r(35)=0.36$, $p=.008$) and negatively correlated with CPM ($r(35)=-0.54$, $p=.001$). The correlation between CPM and TS was non-significant ($r(35)=.22$, $p=0.187$). The regression model showed that TS and CPM explained 39% of the variance in IAP scores ($F(2,34)=10.98$, $p<0.001$, $r=0.63$, 95% CI [0.19, 1.58], $R^2=.39$). CPM and TS remained significant predictors within the model (Table 2). Zero order and partial correlations within this model were roughly equivalent, indicating that the two measures explained unique portions of the variance in IAP. A post hoc power analysis revealed the observed power of this study, given a probability level of $\alpha=0.05$, a sample size of $N=37$ and an observed $R^2=0.39$ is 0.99. (GPower 3.1.9.6).

Table 1

Descriptive Stats for Temporal Summation and Conditioned Pain Modulation

	Mean	SD	T	Df	P-value	Correlation with IAP (r)	P-value
TS1 (initial rating)	2.46	1.61	11.08	36	.000	0.01	.943
TS12 (last rating)	7.24	2.06				.56	.000
CPM – Average rating (test stimulus only)	5.09	1.75	4.91	36	.000	.08	.632
CPM – Average rating (test and conditioning stimulus)	3.88	1.86				-.54	.001

Note: Paired Samples T-test to show difference between first and last pain rating in TS paradigm. Correlation between IAP and first and last TS rating. For conditioned pain modulation (CPM) descriptive stats showing leg ratings for the test stimulus only and for test stimulus when conditioning stimulus was added. Paired samples T-test to show difference between test-only and test + conditioning paradigm. Correlations between IAP and test-only and test + conditioning paradigm.

Table 2

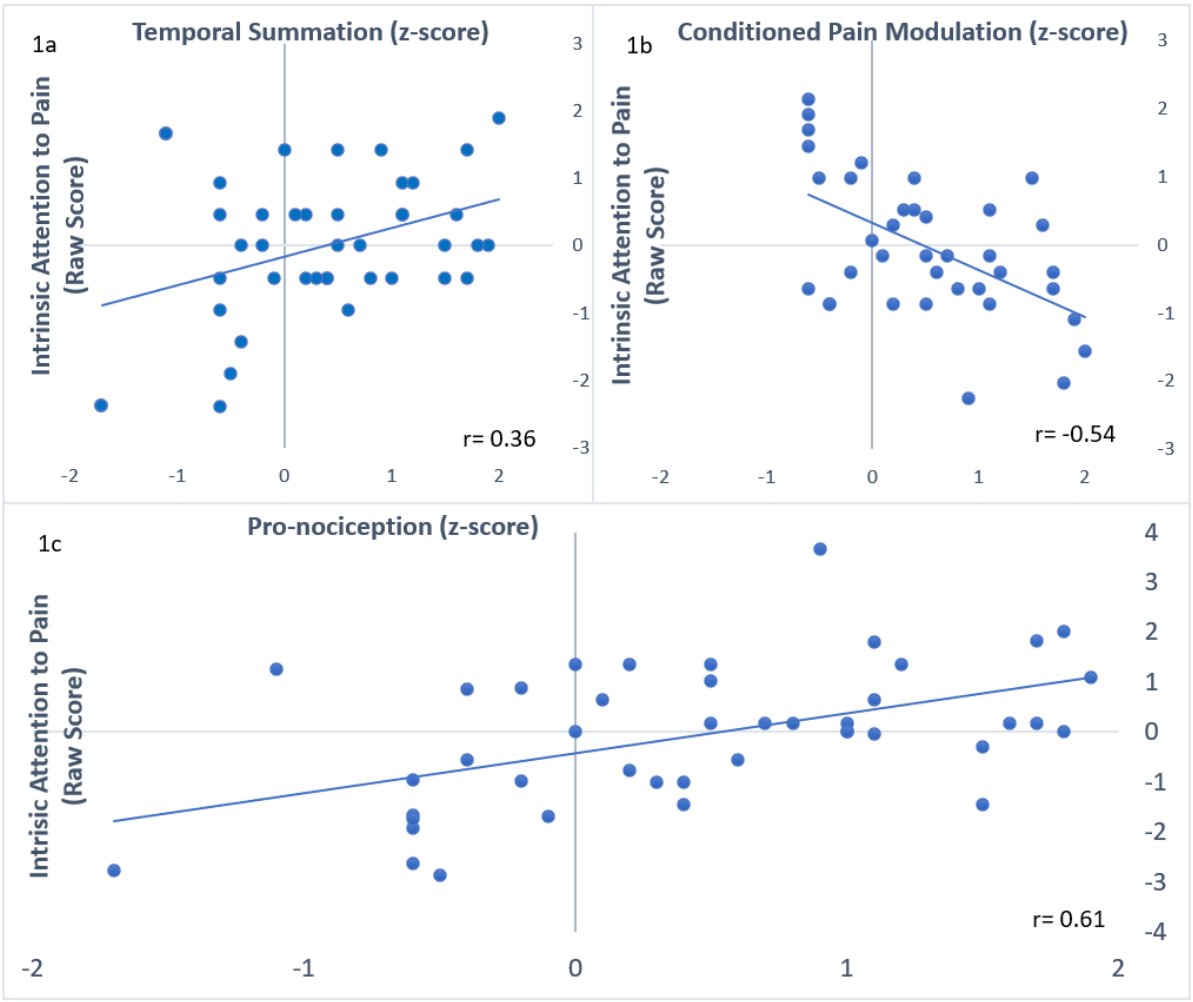
IAP regression with CPM and TS

	B	95% CI	SE B	β	T	P-value	Zero-order	Partial
Constant	.34	[-1.97, .87]	.26		1.28	0.210		
CPM	-.25	[-1.87, -0.15]	.08	-0.47	-3.41	0.002	-0.54	-0.46
TS	.10	[-.41, -.10]	.04	0.33	2.39	0.023	0.43	0.38

The Pro-nociception score was correlated with IAP score (r(35)=.61, R^2=.37 - Figure 1). This correlation was consistent with variance explained in our regression model.

Figure 1:

Scatterplots Showing IAP correlations with Temporal Summation (1a), Conditioned Pain Modulation (1b) and Pro-nociception score (1c). IAP, Intrinsic Attention to Pain



To check for robustness the regression model was re-run including outliers ($F(2,37)=8.47$, $p<0.001$, $r=0.56$, $R^2=.31$). IAP and TS were significantly correlated ($r(38)=0.43$, $p=.023$), as were IAP and CPM ($r(38)=0.50$, $p=.001$).

4.5. Discussion

This study examined the degree to which attention to pain is associated with endogenous mechanisms that modulate incoming sensory signals. We found an individual's IAP was associated

with both TS and CPM. Both mechanisms appear to contribute to pain engagement relatively independently of each other, together accounting for 39% of the variance of attention to pain. This suggests modulation of spinal/supraspinal pain signals does significantly influence how we attend to pain, but other factors (e.g., higher order cognitive processes) may also contribute strongly, as 61% of the variance in IAP is left unaccounted for.

TS occurs when a high frequency of action potentials in the presynaptic neuron, elicits postsynaptic potentials that summate with each other (Dubin & Patapoutian, 2010), increasing pain perception. A previous study found that this 'wind-up' was associated with activation of the ipsilateral and contralateral thalamus, medial thalamus, S1, bilateral S2, mid- and posterior insula, rostral and mid-anterior cingulate-cortex (Staud et al., 2008). These are regions that have been previously implicated in attention studies (Løvstad et al., 2012; Menon & Uddin, 2010; Tokoro et al., 2015).

Less efficient CPM was also associated with IAP. CPM is strongly influenced by descending inhibitory signals from brainstem regions such as the periaqueductal-gray (Bannister & Dickenson, 2017; Damien et al., 2018; Harper et al., 2018; Willer et al., 1990). Periaqueductal-gray activity has also been linked with IAP (Kucyi et al., 2013). This suggests the observed correlation maybe related to overlapping mechanisms in the brainstem. It is likely that multiple factors influence attention to pain and pain inhibition. These may include evaluative cognitions involved in decision making, assessment of risk/reward versus pain, or punishment avoidance (Becker et al., 2018).

Yarnitksy acknowledges a 'pro-nociceptive' phenotype consisting of two QST measures. This may not present a complete picture of an individual's vulnerability to pain and could be supplemented with additional measures to achieve more precise characterisation (Yarnitsky et al., 2013). These results support this suggestion by demonstrating that propensity to attend to pain is a function of processes such as wind-up and DNIC included in the 'pro-nociceptive phenotype'. These factors, however, do not fully explain individual differences in IAP.

As 61% of the variance in IAP is left unaccounted for, it is likely that higher order cognitive processes account for a large portion of this variance. In support of this, research examining whether CPM is prone to cognitive attention found that there was a significant further pain inhibition when CPM and distraction were combined compared to CPM alone (Moont et al., 2010). This finding suggests that CPM and distraction are two distinct mechanisms that can inhibit pain, both with attentional properties. It is likely that attention to pain is a complex phenomenon that reflects the engagement of multiple systems. In support of this notion, several studies have found that distraction inhibits pain more effectively in males (Keogh & Eccleston, 2006; Quiton & Greenspan, 2007; Unrod et al., 2004; Weisenberg et al., 1995), suggesting differential underlying mechanisms for pain inhibition across sexes.

There are a few limitations to this study. Firstly, the scale used for IAP used a four-point Likert scale. This was so that participants did not choose a mid-point score, encouraging participants to assess whether their thoughts were directed towards or away from pain. Yet, a limitation of the scale is, that, with four rather than five (or other) choices, the observed results can be distorted as it forces a choice when a participant may not have an opinion, or their opinion is neutral. Secondly, despite showing a strong correlation with IAP, the methodology of CPM can be questioned as criticisms over the reliability of this paradigm have emerged over recent years (Bossmann et al., 2016). This problem is made worse by a relative lack of standardisation in methodology being used across studies. Our study followed the initial protocol set by Yarnitsky (Yarnitsky et al., 2008), which the pro and anti-nociception pain modulation profiles are based on. However, paradigms that use two thermal stimuli such as the one in this study, have been found to have a lower test-retest reliability (ICC= 0.34-0.39), compared to other paradigms. Finally, due to the COVID-19 pandemic, testing was halted early on this study, resulting in a reduced sample size. Yet, due to the strength of the correlations, a post-hoc sensitivity analysis indicates that the findings are sufficiently powered

Yarnitksy and colleagues mention in their paper that his proposed components for a pro-nociceptive phenotype may be “too simple” (Yarnitsky et al., 2013, p.665), welcoming the suggestion of additional factors that supplement the phenotypic profile to “achieve more precise correlates of clinical pain” (Yarnitsky et al., 2013, p.665). We suggest IAP as an appropriate measure to supplement this model of a nociceptive phenotype. Yarnitsky’s model was originally proposed to help identify suitable treatment approaches reflective of the patient’s TS or CPM response. For example, those with enhanced TS would benefit more from gabapentinoids or NMDA blockers such as ketamine, which inhibit neuronal sensitisation. Patients with less efficient CPM would benefit more from serotonin and/or nor-epiniephrine reuptake, that augment descending inhibition by spinal monoamine reuptake inhibition. This model for recommending appropriate treatment is greatly reductionist, by necessity as we are a long way off from building a successful model for treatment recommendation. Including IAP measures in this model could lead to treatments that address attentional properties of pain facilitation including mindfulness based training, or CBT. In other words, the involvement of IAP as a supplementary factor in this pain modulation profile introduces a biopsychosocial approach which does not just address neurobiological imbalances. Instead, it incorporates cognitive factors such as attention and experience of pain that should be addressed when trying to modify the pain experience.

Given that an individual’s propensity to attend to pain is directly related to their ability to maintain cognitive function while experiencing pain, further investigation of the factors that contribute to IAP will provide clinically relevant clues as to why some individuals are able to maintain adaptive function despite living with pain. We should, however, treat the extrapolation of studies on healthy volunteers in laboratory settings inducing acute pain to have clinical significance with caution. Further research on this novel design of IAP should be conducted on clinical populations.

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5. Study Three: Low Trait Mindfulness is Associated with Enhanced Sensitisation to Nociception

Manuscript in preparation

Low Trait Mindfulness is Associated with Enhanced Sensitisation to Nociception

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5.1. Abstract

Introduction

Mindfulness based training is associated with beneficial responses to pain in both laboratory and clinical settings. Mindfulness, however, can also be a trait. Trait mindfulness has been associated with acute pain processing; higher pain thresholds and lower levels of pain catastrophising. In this study, we want to assess how trait mindfulness influences individual response to a prolonged/repetitive stimulus, as this may be more relevant for assessing the role of mindfulness in coping with pain (potentially relevant for acute to chronic pain transition). In the same way mindfulness meditators can cultivate an attitude of acceptance and reduced anticipation towards impending stimuli, we expected those with high trait mindfulness to be better able to attenuate to a prolonged/repetitive stimulus.

Method

44 Healthy participants (23 female; mean age= 23.57, S.D.=5.50) came to the laboratory for 3 experimental sessions on separate days. During each session, participants would receive 44 painful thermal stimuli (7/10 NRS) to the left calf. Average pain ratings for pain intensity and unpleasantness were recorded every 11 stimuli (x4 time points). Each participant also completed the Five Facet Mindfulness Questionnaire.

Results

Trait mindfulness was negatively associated with pain sensitisation over time, in terms of pain unpleasantness (r=-.298, p=.05), and a negative trend was shown for pain intensity (r=-0.276, p=0.07). Mindfulness facets related to self-acceptance and emotional resilience were most strongly correlated to pain sensitisation over time; non-judgemental inner activity was associated with pain unpleasantness (r=-.358, p = 0.017) and non-reactivity with pain intensity (r=-.321, p =0.034).

Conclusion

Low trait mindfulness was associated with enhanced sensitisation to pain. People who scored higher on trait mindfulness were better at coping to a prolonged/repetitive stimulus over time. Low attributes of non-judgemental inner activity and non-reactivity were most strongly associated with enhanced pain sensitisation, two components that are targeted through open-monitoring meditation. Future studies may explore how open-monitoring meditation influences pain sensitisation paradigms such as the one in this study, whether it helps people who score low or high on these two facets and whether such an interaction can be translated into studies on chronic pain populations.

5.2. Introduction

Mindfulness based training is associated with beneficial responses to pain in both laboratory and clinical settings (Cherkin et al., 2016; Kabat-Zinn, 1982; Morone et al., 2016; Reiner et al., 2016). Mindfulness interventions train patients to focus their attention on their current environment and regulate their cognitive and emotional responses (Bishop et al., 2004; Ludwig & Kabat-Zinn, 2008; Salomons & Kucyi, 2011). Experienced practitioners appear to undergo robust changes that allow them to process nociceptive information in a unique manner by cultivating an attitude of acceptance and reduced anticipation towards impending stimuli. This promotes health benefits such as enhancements in cognitive control, emotion regulation, positive mood and acceptance (Brown & Jones, 2010; Reiner et al., 2016; Zeidan, 2015).

Research indicates that mindfulness training has a varied response across studies, being successful for some but not others (Reiner et al., 2013; Rosenzweig et al., 2010). Whilst there is a burgeoning literature focusing on mindfulness-based training, less attention is given to mindfulness as a trait; a psychological characteristic that may influence individual differences in pain response. Examining trait mindfulness allows us to measure an individual's natural ability to be mindful, without any prior training. Experiments assessing trait mindfulness can reduce confounding variables such as quality and quantity of meditative training, which may influence pain responses and contribute to this variability in success. Exploring trait mindfulness in the context of pain allows for a cross-sectional design to help evaluate which facets of mindfulness may influence how people modulate pain.

High trait mindfulness suggests attentional focus is naturally guided towards the present moment and negative emotions are more innately regulated. Importantly, we know that high trait mindfulness has been associated with higher pain thresholds and lower levels of pain catastrophising (Bento et al., 2018; Harrison et al., 2019; Prins et al., 2014; Zeidan et al., 2016). This indicates that trait mindfulness is beneficial to acute pain processing. Paradigms assessing sensitisation to pain over time, however, may be more relevant for examining the context of

individual differences in coping/adapting to pain over time; an important component involved in acute to chronic pain transition (Hasenbring et al., 2001).

Ultimately, we know a lot about the benefits of using mindfulness as an interventional tool, but less is known about its predictive utility. If we can learn more about how trait mindfulness influences pain modulation, we may be better able to identify those who are most at risk to pain sensitisation, and those who would benefit most from mindfulness-based interventions. In this study we are interested in whether trait mindfulness is associated with rate of sensitisation to pain in healthy participants. Subjective changes in sensory and emotional components of pain will be recorded at intervals throughout prolonged/repetitive painful stimulation. We expect that those naturally high in trait mindfulness would be better at distress tolerance and coping with pain, in a similar way to experienced meditators.

5.3. Method

Participants

44 Healthy participants (23 female; M_{age}= 23.57, S.D.=5.50) were recruited for this study. The data used for this study was part of a larger study involving 13 experimental sessions per participant, for which recruitment is still ongoing. The larger study involved: a battery assessment (one session), MRI brain imaging (one session), behavioural questionnaires, natural aptitude for pain sensitisation/habituation over three sessions, and an eight-session cognitive behavioural training paradigm.

Participants were recruited by advertisements that were circulated around the University of Reading, offering an amount of £10 per hour for their participation. All participants reported that they did not suffer from any chronic pain issues, nor were they taking any regular pain medication. The study complied with the Declaration of Helsinki (2013) and its protocol was approved by the

Local Ethics Committee of the University of Reading (UREC). Informed consent was provided by each participant before commencing their participation in the study.

Materials

Participants came to the laboratory for three experimental sessions on separate days ($M^{duration}$= 5.20 days (range 3-13 days). Each of these involved thermal stimuli being administered to the centre of the left calf generated by a MEDOC Pathway thermal stimulator (Medoc Medical Systems, Ramat Yishai, Israel) applied via a 30x30cm ATS thermode. The baseline temperature of the thermode was set to 32°C and the ramp up rate to the testing stimulus was set to 8°C/second for all assessments. During each session the participant would receive 44 painful stimuli for 8 seconds (s) calibrated at 7/10 Numerical Rating Scale (NRS) pain percept (20s intervals). Average pain ratings for pain intensity and pain unpleasantness were recorded after a series of 11 stimuli, which was repeated four times, giving us 4 timepoints at which pain intensity and unpleasantness ratings were collected. Participants were asked to verbally rate the perceived intensity on a NRS ranging from 0 ('no pain') to 10 ('extremely painful'). Unpleasantness used the same scale ranging from 0 ('not unpleasant') to 10 ('extremely unpleasant'). Each participant also completed the self-reported Five Facet Mindfulness Questionnaire (FFMQ) prior to the final session. The test consists of 39 items using a 5-point Likert scale (1='never', 5 ='very often'), that measure five facets of mindfulness (observation, description, acting with awareness, non-judgemental inner experience and non-reactivity).

Analyses

To check for baseline differences of trait mindfulness, FFMQ scores were correlated against the initial recording of pain intensity and unpleasantness across each of the three sessions. Using the slope function in Excel, the four time points measuring pain intensity and unpleasantness were converted into slope scores for each session based on the regression line of the four data points. Each participant had three slope scores for both pain intensity and unpleasantness. To explore a possible time-sensitive habituation or sensitisation effect across sessions, partial correlations were

run between the slope scores for the first and last session controlling for number of days between to check whether duration of days between the first and last session significantly influenced the consistency of the slopes. First and last slope scores were chosen as they had the largest difference in means. Subsequently, a reliability analysis was run to assess whether the three slope scores were consistent across sessions. The three slopes could then be collapsed to give a more reliable measure of within-session sensitisation. The average slope score for each participant was then correlated against FFMQ scores.

Missing Data

There was no missing data in this study.

5.4. Results

Trait mindfulness did not significantly influence baseline ratings for both pain unpleasantness and intensity across any of the sessions (see Table 1). The first and last unpleasantness slope were significantly correlated ($r(42)=0.66$, $p<.001$), and controlling for days between the correlation was very similar ($r(42)=0.65$, $p<.001$). For intensity, the first and last slope were also significantly correlated ($r(42)=0.69$, $p<.001$), when controlling for days between the results were again very similar ($r(42)=0.68$, $p<.001$). This strongly suggests that number of days between sessions did not significantly affect the gradient of the sensitisation slopes within sessions, meaning there was little to no sensitisation affect across sessions in terms of rate of sensitisation.

Once we established that days between sessions did not affect sensitisation rates, we could explore the reliability of slopes by checking for consistency. For unpleasantness, a high degree of reliability was found between the three slopes for unpleasantness ratings. The average measure intraclass correlation (ICC) was .87 with a 95% confidence interval from .78 to .93 ($F(40,80)= 7.59$, $p<.001$). A high degree of reliability was also found between the three slopes for pain intensity ratings. The

average measure ICC was .89 with a 95% confidence interval from .81 to .93 ($F(40,80)= 8.97$, $p<.001$).

As the three slopes for both unpleasantness and intensity were consistent across sessions, we could collapse the slopes to create an average and more reliable measure of sensitisation rate for each participant. The collapsed unpleasantness sensitisation slopes were significantly correlated with FFMQ scores $r(42)=-.30$, $p=.05$. The collapsed intensity sensitisation slopes were not significantly correlated with FFMQ scores ($r(42)=-.28$, $p=.070$), although a trend is shown. Low trait mindfulness was associated with greater rates of sensitisation, particularly for pain unpleasantness.

The FFMQ can be broken down into 5 components; observing, describing, awareness, non-judgmental inner experience and non-reactivity (see Table 2). Unpleasantness sensitisation was most strongly associated with non-judgmental inner experience ($r(42)=-.32$, $p=.034$). Intensity sensitisation was most strongly associated with non-reactivity ($r(42)=-.36$, $p=.017$).

Table 1

Correlations to Show FFMQ did not Influence Baseline Pain Ratings Across All Three Sessions

		Correlation	Sig. (2-tailed)
Session 1	Intensity	-0.05	0.761
	Unpleasantness	-0.08	0.61
Session 2	Intensity	-0.07	0.642
	Unpleasantness	0.02	0.914
Session 3	Intensity	-0.16	0.294
	Unpleasantness	0.03	0.836

Table 2

Sensitisation Associations with Facets of Trait Mindfulness

	Unpleasantness sensitisation slope		**Intensity sensitisation slope**	
	Correlation	Sig.	Correlation	Sig.
Observing	-0.02	0.887	-0.11	0.479
Describing	-0.24	0.120	-0.25	0.107
Awareness	-0.03	0.854	-0.03	0.863
Non-judge	-0.36	0.017	-0.18	0.257
Non-react	-0.23	0.126	-0.32	0.034
FFMQTOTAL	-0.30	0.050	-0.28	0.070

Power Analysis

A post hoc power analysis revealed the observed power of this study given a probability level of *α=0.05*, a sample size of *N=44* and a medium effect size of r=0.3 is *0.53*. (GPower 3.1.9.6). This power analysis indicates that the study is underpowered. The explanation for this is that data collection was stopped early due to health and safety concerning the ongoing Covid-19 pandemic.

5.5. Discussion

The findings of the study show that low trait mindfulness in individuals (scored by the FFMQ) was associated with an increased sensitisation to painful stimulations over time (approx. 26 minutes). The components of mindfulness that were most strongly associated with rate of sensitisation were non-judgmental inner experience (not letting the inner critic take a toll on our happiness and positive state of mind) and non-reactivity (active detachment from negative thoughts and emotions so that we can accept their existence and choose not to react to them).

People with low trait mindfulness seemed to have greater difficulty in regulating their emotional response as unpleasantness ratings increased significantly over time. Notably, pain intensity ratings also increased at a similar rate, but these findings failed to meet statistical significance. Overall, people with high trait mindfulness were able to maintain or even habituate their perceived level of

unpleasantness and intensity, whereas those with low trait mindfulness became more sensitive as the stimuli persisted. This complements findings from trained mindfulness studies where experienced practitioners were able to cultivate an attitude of acceptance towards impending stimuli (Brown & Jones, 2010). Individuals high in trait mindfulness seem more able to acclimatise to the stimuli in the same way as experienced meditators. One speculative explanation for this may be that those with low trait mindfulness sensitise to repeated stimuli due to enhanced anticipation and expectation of the impending stimuli as they lack active mechanisms of acceptance (Gard et al., 2012), compared to those with high trait mindfulness.

The components of the FFMQ that were significantly correlated with pain responses over time were non-judgemental inner experience and non-reactivity. Non-judgmental experience is associated with self-acceptance for oneself. Non-reactivity refers to active detachment from negative thoughts and emotions so that we can accept their existence and choose not to react to them. Non-reactivity makes way for emotional resilience and restores mental balance (McManus et al., 2012). In our study, these correlations with pain response weren't statistically larger than correlations with other factors (e.g., describing - the way we label our experiences and express them in words to ourselves and others), so strong claims about specificity can't be made, but they were the strongest. Non-reactivity was most strongly correlated with intensity sensitisation and non-judgemental experience was most strongly correlated with unpleasantness sensitisation. This is an interesting observation as it corresponds with studies on meditational practice. For example, Grant & Rainville (2009) evaluated the effects of trained mindfulness on experimentally induced pain. When practicing mindfulness, meditators were able to reduce pain sensitivity for both sensory and affective aspects of pain. More specifically, Perlman et al (2010) found that open monitoring meditation, which could regulate negative affect through a mechanism of non-judgmental, non-reactive awareness of sensory experience, was able to significantly reduce self-reported pain unpleasantness. Based on this, our findings suggest that interventions that influence non-reactivity and non-judgemental experience, such as open monitoring meditation, may be beneficial for modulating pain response.

Future directions could explore the specificity of these two facets (non-reactivity and non-judgemental experience); whether they are consistently seen to influence pain responses over time, whether they are abnormally low in chronic pain patients, and whether they can be addressed by open monitoring meditation.

It is likely that some of the cortical and supraspinal mechanisms between experienced meditators and high trait mindfulness are similar. One study conducted in our lab did find similarities in neural observations between high trait mindfulness and meditative practice, in response to painful stimulation (Harrison et al., 2019). We found that high trait mindfulness was associated with greater functional connectivity between the precuneus and somatosensory cortices, as well as weaker connectivity between the precuneus and medial prefrontal cortex. A deactivation that has been repeatedly observed in neural studies on meditative practice (Brefczynski-Lewis et al., 2007; Brewer et al., 2011; Farb et al., 2007; Taylor et al., 2013). One explanation for the likelihood of these neural similarities and modulatory mechanisms is that those who regularly practice mindfulness begin to integrate the meditative state with their normal state, thus high mindfulness becomes a permanent trait in experienced meditators. In support of this, experienced meditators scored highly on trait mindfulness (Baer et al., 2008), and appear to go through permanent neural changes which alters the way they process nociceptive information, even when in a non-meditative cognitive state (Grant et al., 2011; Lutz et al., 2013; Taylor et al., 2013).

One practical question to ask is who would benefit most from mindfulness interventions. People low in trait mindfulness may have a deficiency allowing for the most room for improvement. On the other hand, people high in trait mindfulness may be better equipped to learn and harness the abilities taught through trained mindfulness. One study found that individuals high in trait mindfulness pre-treatment, benefitted most from mindfulness-based stress reduction training (including a greater enhancement in trait mindfulness [Shapiro et al., 2011]). Although, it must be noted that the sample size in this study was small.

It may suggest that individuals with high trait mindfulness be identified so that they can undergo meditative practice to achieve higher levels of mindfulness and pain resilience. Further research exploring the specificity of open monitoring meditation, regarding its beneficial impacts on high versus low trait mindfulness individuals, would be useful. This scientific knowledge would be particularly important prior to surgery, helping to minimise the risk of surgery related sensitisation and post-surgical chronic pain in select individuals.

Trait mindfulness is an important psychological factor to consider when exploring responses to painful stimuli. Assessing trait mindfulness as a self-report measure, prior to any pain or negative affect associated with pain setting in, allows us to predictively assess patients for vulnerability to pain sensitisation following pain onset. The main finding of our study is that individual differences in trait mindfulness influence adaptation to pain over the course of approximately 26 minutes of painful stimulation in laboratory settings. While we do not yet know if adaptation over a short period is related to adaptation over a longer period (i.e., chronic pain), our findings may be relevant for understanding individual differences in how people psychologically respond when they experience the onset of persisting pain. The data suggests that trait mindfulness may be able to influence pain facilitatory/inhibitory mechanisms at an acute stage. One study that suggests these shorter paradigms may be relevant for chronic pain prediction identified that sensitivity to painful stimulation was associated with chronic pain (Vierck et al., 2014). Another study identified that coping behaviours were elementary in acute to chronic pain transition (Hasenbring et al., 2001).

It should be emphasised, however, that pain sensitisation that occurs in healthy participants in a controlled environment is very different to the psychological facilitation and social problems that accompany chronic pain. This study is unable to account for psychological processes such as catastrophising and fear-avoidance, which often develop alongside chronic pain and contribute towards sensitisation and hypervigilance. Generalisations of pain sensitisation towards clinical relevance in this study should therefore be interpreted with caution and follow up studies involving

clinical populations should be considered. The data lead to an intriguing hypothesis for future work to explore the role of trait mindfulness in susceptibility/resilience to acute to chronic pain transition. One way of investigating this further may be to assess the association between trait mindfulness and chronic post-surgical pain, taking FFMQ measures prior to surgery and assessing associations between trait mindfulness' and recovery times/post-surgical complications. One study, for instance, identified that FFMQ was an accurate predictor of post-operative pain in gynaecologic oncology patients undergoing minimally invasive hysterectomy (Weston et al., 2020).

There were, however, a number of limitations to this study. Firstly, all questions related to non-judgemental inner experience were negatively loaded, while all questions related to non-reactivity were positively loaded. Interpreting negative subscale scores of non-judgemental inner experiences which are recoded to give positive scores, such that high scores are related to high levels of self-acceptance, should be interpreted with caution. Just because someone reports to never disapprove of themselves one cannot derive that they always approve of themselves. Moreover, having some sub-scales being phrased negatively and other scales being phrased positively opens the possibility of a leading questions bias that encourages participants to score in opposing directions on different sub-scales. This is particularly important as some facets consisted of both negatively and positively loaded questions (e.g., 'describe items'). The questionnaire therefore includes leading questions posed in opposite directions across the facets, which could skew the results disproportionately. Additionally, we should emphasise that the interpretation of pain sensitisation to acute pain in laboratory settings is largely different to clinical populations. Chronic pain patients are subjected to emotional and social experiences of hardship which, over time, may impact on their resilience and coping to persistent pain, which this study is unable to account for given the lab-based acute pain induction. Finally, due to the ongoing pandemic, testing for this study was halted early, resulting in a reduced sample size and possibly underpowered findings.

To conclude, these findings suggest that sensitisation to a stimulus over time is influenced by individual levels of trait mindfulness. To better clarify the role of trait mindfulness in chronic pain development, more prospective studies that assess trait mindfulness prior to surgery should be carried out, as low trait mindfulness may be associated with chronic post-surgical pain. Additionally, those with high trait mindfulness may benefit most from mindfulness-based training that promotes active mechanisms of acceptance such as open monitoring meditation, reducing negative expectations and regulating emotional affect. More longitudinal studies exploring whether those with high trait mindfulness who received open-monitoring training had more positive responses post-surgery, compared to those low in trait mindfulness, would provide further clarity. We speculate that mindfulness training should be recommended as an early intervention, allowing for neural changes to permanently take place, facilitating high trait mindfulness and a more resilient response to persistent pain.

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5.7. Appendices

Five Facet Mindfulness Questionnaire

Description:

This instrument is based on a factor analytic study of five independently developed mindfulness questionnaires. The analysis yielded five factors that appear to represent elements of mindfulness as it is currently conceptualized. The five facets are observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience. More information is available in:

Please rate each of the following statements using the scale provided. Write the number in the blank that best describes your own opinion of what is generally true for you.

1 2 3 4 5

never or very rarely true rarely true sometimes true often true very often or always true

_____ 1. When I'm walking, I deliberately notice the sensations of my body moving.

_____ 2. I'm good at finding words to describe my feelings.

_____ 3. I criticize myself for having irrational or inappropriate emotions.

_____ 4. I perceive my feelings and emotions without having to react to them.

_____ 5. When I do things, my mind wanders off and I'm easily distracted.

_____ 6. When I take a shower or bath, I stay alert to the sensations of water on my body.

_____ 7. I can easily put my beliefs, opinions, and expectations into words.

_____ 8. I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted.

_____ 9. I watch my feelings without getting lost in them.

_____ 10. I tell myself I shouldn't be feeling the way I'm feeling.

_____ 11. I notice how foods and drinks affect my thoughts, bodily sensations, and emotions.

_____ 12. It's hard for me to find the words to describe what I'm thinking.

_____ 13. I am easily distracted.

_____ 14. I believe some of my thoughts are abnormal or bad and I shouldn't think that way.

_____ 15. I pay attention to sensations, such as the wind in my hair or sun on my face.

_____ 16. I have trouble thinking of the right words to express how I feel about things

_____ 17. I make judgments about whether my thoughts are good or bad.

_____ 18. I find it difficult to stay focused on what's happening in the present.

_____ 19. When I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it.

_____ 20. I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.

_____ 21. In difficult situations, I can pause without immediately reacting.

_____ 22. When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words.

_____ 23. It seems I am "running on automatic" without much awareness of what I'm doing.

_____24. When I have distressing thoughts or images, I feel calm soon after.

_____ 25. I tell myself that I shouldn't be thinking the way I'm thinking.

_____ 26. I notice the smells and aromas of things.

_____ 27. Even when I'm feeling terribly upset, I can find a way to put it into words.

_____ 28. I rush through activities without being really attentive to them.

_____ 29. When I have distressing thoughts or images I am able just to notice them without reacting.

_____ 30. I think some of my emotions are bad or inappropriate and I shouldn't feel them.

_____ 31. I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.

_____ 32. My natural tendency is to put my experiences into words.

_____ 33. When I have distressing thoughts or images, I just notice them and let them go.

_____ 34. I do jobs or tasks automatically without being aware of what I'm doing.

_____ 35. When I have distressing thoughts or images, I judge myself as good or bad, depending what the thought/image is about.

_____ 36. I pay attention to how my emotions affect my thoughts and behavior.

_____ 37. I can usually describe how I feel at the moment in considerable detail.

_____ 38. I find myself doing things without paying attention.

_____ 39. I disapprove of myself when I have irrational ideas.

Scoring Information:

Observe items: 1, 6, 11, 15, 20, 26, 31, 36

Describe items: 2, 7, 12R, 16R, 22R, 27, 32, 37

Act with Awareness items: 5R, 8R, 13R, 18R, 23R, 28R, 34R, 38R

Nonjudge items: 3R, 10R, 14R, 17R, 25R, 30R, 35R, 39R

Nonreact items: 4, 9, 19, 21, 24, 29, 33

6. Study Four: Do “Central Sensitisation” questionnaires Reflect Measures of Nociceptive Sensitisation or Psychological Constructs? A Systematic Review and Meta-Analyses:

Manuscript in preparation

Protocol published in ‘Pain Reports’

Adams G, Harrison R, Gandhi W, van Reekum CM, Wood-Anderson D, Gilron I, Salomons TV. (2021). Do “central sensitization” questionnaires reflect measures of nociceptive sensitization or psychological constructs? Protocol for a systematic review. Pain Reports, 6:4, e962. DOI: 10.1097/PR9.0000000000000962

Do “Central Sensitisation” questionnaires Reflect Measures of Nociceptive Sensitisation or Psychological Constructs? a Systematic Review and Meta-Analyses:

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Author Contributions: GA, RH, WG, CMvR, IG and TVS helped prepare and write the protocol.

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PROSPERO registration: (CRD42021208731).

6.1. Abstract

Central sensitisation (CS) is defined as an increased nociceptive responsiveness due to sensitisation of neurons in the central nervous system, usually the result of prolonged nociceptive input or a disease state associated with noxious inputs (e.g., polyarthritis). The concept of CS has recently been adopted in clinical assessments of chronic pain, but its diagnosis in humans may now include a wide range of hypervigilant responses. The purpose of this review is to ascertain whether self-report questionnaires linked with CS are associated with enhanced nociceptive responses, or whether they measure sensitivity in a broader sense (i.e., emotional responses).

According to our published, PROSPERO-registered review protocol, a predefined search of studies that involve the Central Sensitisation Inventory (CSI) and/or Pain Sensitivity Questionnaire (PSQ) correlated with either nociceptive sensory tests or emotional hypervigilance was conducted on MEDLINE, PsychINFO and Web of Science. Correlations between the CSI/PSQ with our primary outcomes were extracted and meta-analysed using the Hunter-Schmidt method.

A Review of 66 studies totalling 13,284 participants found that the CSI (but not the PSQ) strongly correlated with psychological constructs: Depression, anxiety, stress, pain catastrophising, sleep and kinesiophobia. The CSI and PSQ showed weak/no correlations with experimental measures of nociceptive sensitivity: pain thresholds, temporal summation or conditioned pain modulation. The PSQ did, however, correlate strongly with phasic heat and tonic cold pain tests.

The studies reviewed did not provide sufficient evidence that self-report measures reflect CS. The CSI is an indicator of psychological hypervigilance as opposed to assessing the increased responsiveness of nociceptive neurons.

6.2. Introduction

Central sensitisation (CS) is defined by the International Association for the Study of Pain (IASP) as "increased responsiveness of nociceptive neurons in the central nervous system to either normal or subthreshold afferent input," (Loeser & Treede, 2008, p. 476). CS has been linked with a multitude of chronic pain disorders in humans (La Touche et al., 2018; Lluch et al., 2018; Meuus & Nijs., 2007; Roussel et al., 2013; Sanchis et al., 2015; Yunus., 2007), with 'Central Sensitivity Syndrome (CSS)' being a recently developed diagnosis for several unexplained pain disorders (e.g., fibromyalgia and temporomandibular disorder) for which CS is thought to be the underlying cause (Yunus., 2008). As of yet, there is no conclusive method of accurately establishing the presence of CS in humans (Quesada et al., 2021), although quantitative sensory testing (QST) is used to assess the dynamic modulation of nociceptive signals, which can suggest the presence of CS (Arendt-Nielsen & Yarnitsky., 2009; Williams., 2018). QST measures consist of pain threshold tests, temporal summation (a measure of 'wind-up' or enhancement of pain with prolonged nociceptive exposure (Dubin & Patapoutian., 2010) and conditioned pain modulation (said to quantify the efficiency of endogenous inhibition of pain (Damien et al., 2018).

Although QST allows for a comprehensive assessment of pain sensitivity profiles, it often involves select training, expensive lab equipment and sufficient time where the patient's presence is required in the lab, making testing difficult at a clinical level (Role et al., 2006). Self-report questionnaires would make a pragmatic alternative assessment of CS in clinics, allowing for quick and convenient assessment at little cost. To serve this purpose, however, these questionnaires would need to demonstrate acceptable associations with known measures of CS to show sufficient construct validity.

A self-report questionnaire that is widely used in the assessment of central sensitisation is the Central Sensitisation Inventory (CSI). The CSI was designed to identify patients who have symptoms that may be related to CS, such as fibromyalgia, neck injury, temporomandibular joint

disorder or migraine/tension headaches (Neblett et al., 2015). It has been shown to reflect a reliable and valid psychometric instrument for identifying individuals vulnerable to pain (Mayer et al., 2012).

The Pain sensitivity questionnaire (PSQ), however, may more directly measure the sensory facilitation involved in CS (Ruscheweyh et al., 2009). It focuses more on respondents imagining situations that involve nociceptive input and predicting how they would react. The questions are posed to measure sensitisation to sensory input, but the degree to which it reflects a top-down component influenced by personality type or disposition, remains open. More specifically, whether it reflects these psychological profiles to the same degree as the CSI is a germane question in terms of understanding how closely related and psychometrically distinct these measures are.

We are interested in exploring the degree to which the CSI and PSQ reflects CS as an "increased responsiveness of nociceptive neurons" (Loeser & Treede, 2008, p. 476) . The CSI appears to focus on hypersensitivity in a broader sense, including anxiety and depression, as well as cognitive impairment. The use of the term 'central sensitisation' has expanded to include psychological profiles rather than centrally enhanced nociceptive responsivity. Thus, we are interested in exploring the CSI's contribution to a form of construct drift across disciplines. Construct drift may have been allowed to occur as the diagnosis of CS has clinical value in giving patients a central mechanism that legitimises their pain. This diagnosis, however, may not truly represent the canonical (pre-clinical) mechanism of CS that the title of the questionnaire would suggest. Instead, the questionnaire may reflect a broader definition of sensitivity which includes psychological states such as depression, anxiety and stress.

The meta-analyses of available studies examined whether self-report measures (the PSQ and/or CSI) aligned more closely with QST measures/experimental measures of nociceptive sensitivity or psychological questionnaires such as anxiety, depression, stress etc. In doing so, we aim to assess

and compare the two questionnaires in terms of the degree to which they assess nociceptive sensitisation or emotional sensitisation.

6.3. Methods

Sources of Evidence

We searched MEDLINE, PsychINFO and WebofScience from their inception until June 2021. Two separate searches were conducted including both the CSI and PSQ. One search reviewed these questionnaires for sensory correlates (e.g., QST). The second search reviewed their correlations with psychological questionnaires (e.g., anxiety, depression, pain catastrophising etc). Any duplicates within both searches were removed.

Search Terms

Search 1 terms:

('Quantitative Sensory Testing' or 'wind-up' or 'temporal summation' or 'conditioned pain modulation' or 'pain threshold' or 'pain ratings' or 'hyperalgesia' or 'allodynia' or 'offset analgesia' or 'widespread pain' or 'evoked pain' or 'experimental pain' or 'pain tolerance') AND ('central sensitization inventory' or 'central sensitisation inventory' or 'pain sensitivity questionnaire')

Search 2 terms'

('depression' or 'anxiety' or 'stress' or 'catastrophizing' or 'rumination' or 'neuroticism' or 'personality' or 'abuse' or 'trauma') AND ('central sensitization inventory' or 'central sensitisation inventory' or 'pain sensitivity questionnaire')

Eligibility Criteria

Only human studies were eligible for inclusion. They must have been written in English and an original peer-reviewed experiment (i.e., not a dissertation, case study or review article). Finally, studies must have included at least one of the CSI or PSQ instruments. The CSI and/or PSQ must be correlated against at least one psychological or sensory measure of interest.

Study Screening

Two independent reviewers assessed studies for eligibility (GA and WG). Initially, titles and abstracts were screened using excel, and full-text screening was performed on citations felt to be potentially eligible. Both authors were required to agree for inclusion. We excluded studies that did not satisfy our inclusion criteria. Discrepancies between the reviewers were resolved by discussion and consensus, with a third reviewer being consulted in cases of disagreement. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of this process is provided (Fig.1).

Assessment of risk of bias in included studies

For each study included in the review, a modified version of the quality appraisal process proposed by Hayden et al. (2006) was conducted by two independent authors (GA, WG/RH). This was to evaluate potential sources of bias across 5 domains: participation bias, publication bias, attrition, methodological quality and statistical analysis. We assessed the following for each study: (1) Were potential sources of participation bias considered and addressed? (2) Was there any missing data regarding the variables of interest (3) Was the methodology of the variable of interest of a standardised quality? (4) Was the desirable statistical analyses performed? (5) Was the sample size adequate? Each category was assigned a low, unclear, or high risk of bias and presented with a Risk of bias summary. Disagreements between reviewers were resolved by discussion and consensus. A third reviewer (WG/RH) was consulted where assessments could not be agreed upon.

Analysis of Participation Bias

Specific sources of participation bias were identified i.e., age and sex characteristics of the population sample, as well as population samples that excluded participants based on mental health, physical health or medication being taken.

Study Descriptives

Our primary outcomes were correlations between the CSI total score and/or the PSQ total score with sensory measures associated with CS. These include QST measures; temporal summation, pain thresholds and tolerance, and any measure related to nociceptive hypersensitivity or widespread pain. We were also interested in exploring the extent to which self-report questionnaires may be predictive of descending aspects of modulation (impaired inhibition), therefore including conditioned pain modulation as a measure of interest.

The second outcome measure was correlations between the CSI and/or the PSQ and psychological factors. These included questionnaires that assess depression, anxiety, stress, pain catastrophising, abuse, trauma, mindfulness, neuroticism or personality and any other measure related to emotional hypersensitivity.

The review included studies that correlate the PSQ/CSI with sensory and/or psychological measures. In studies that involved an intervention, measures were only considered if they were assessed at baseline.

Data Extraction and Management

One reviewer (GA) extracted relevant data from each study (correlation coefficient *r*, and number of participants *n*). If these values were not given within the paper, authors were contacted to provide the relevant correlation coefficient. A second reviewer (DW-A) checked the extracted data. Data extracted from each citation included information about the study design, the correlation coefficients age, sex and number/type of participants.

Sample sizes (*n*) and correlation scores (*r*) on primary outcomes were extracted from papers or via responses collected from emailing corresponding authors and presented to show individual study characteristics. Only data that provided sample size and a correlation value were included. Only Spearman's rank and Pearson's correlation were considered eligible so that meta-analyses could be conducted.

Data Synthesis

CSI correlations were extracted for each construct separately; depression, anxiety, stress, pain catastrophising, kinesiophobia and sleep. Meta-analyses were conducted if at least 3 studies reported findings for a related construct. Each meta-analysis was made up of a combination of instruments for that construct e.g., correlates with CSI and anxiety will include CSI against STAI Trait and State, the Anxiety component of the Depression Anxiety stress scale (DASS-21), the anxiety component of the Hospital Anxiety and Depression Scale (HADS), etc.).

Meta-analyses for quantitative sensory measures were conducted for each measure separately: Pressure pain threshold, heat pain threshold, conditioned pain modulation, and temporal summation were separately meta-analysed against CSI. If studies reported two correlations for one construct e.g., multiple body sites taken for pain threshold or trait and state anxiety scores were reported for anxiety, scores were averaged together.

Data Visualisation

Data for individual studies were reported in Table 1 to show individual study characteristics. This table was presented in four sections; CSI with psychological constructs, CSI with nociceptive measures, PSQ with psychological constructs, and PSQ with nociceptive measures. Meta-analyses findings were presented in table format with a summary of the effect size on the right of the table. Any other findings with insufficient data for a meta-analysis were reviewed narratively where appropriate.

Primary Analysis

Meta-analyses consisted of Sample sizes (*n*) and correlation scores (*r*) on primary outcomes extracted from papers or via response from emailing corresponding authors and will be presented in a table. These values were then input into a meta-analysis to give a weighted mean correlation using the Hunter-Schmidt method (Schmidt & Hunter., 2015). Statistical Software StatsDirect version 3.3.5 was used to calculate weighted mean correlations, to test for heterogeneity and to perform subgroup analysis [StatsDirect Statistical Analysis Software. 2021]. Weighted mean correlations were

calculated to measure the overall strength of a correlation between the PSQ/CSI and each construct. A sub-group analysis was performed where applicable to assess and compare the relative strength of our correlations of interest for chronic pain patients versus healthy controls.

Tests for Heterogeneity

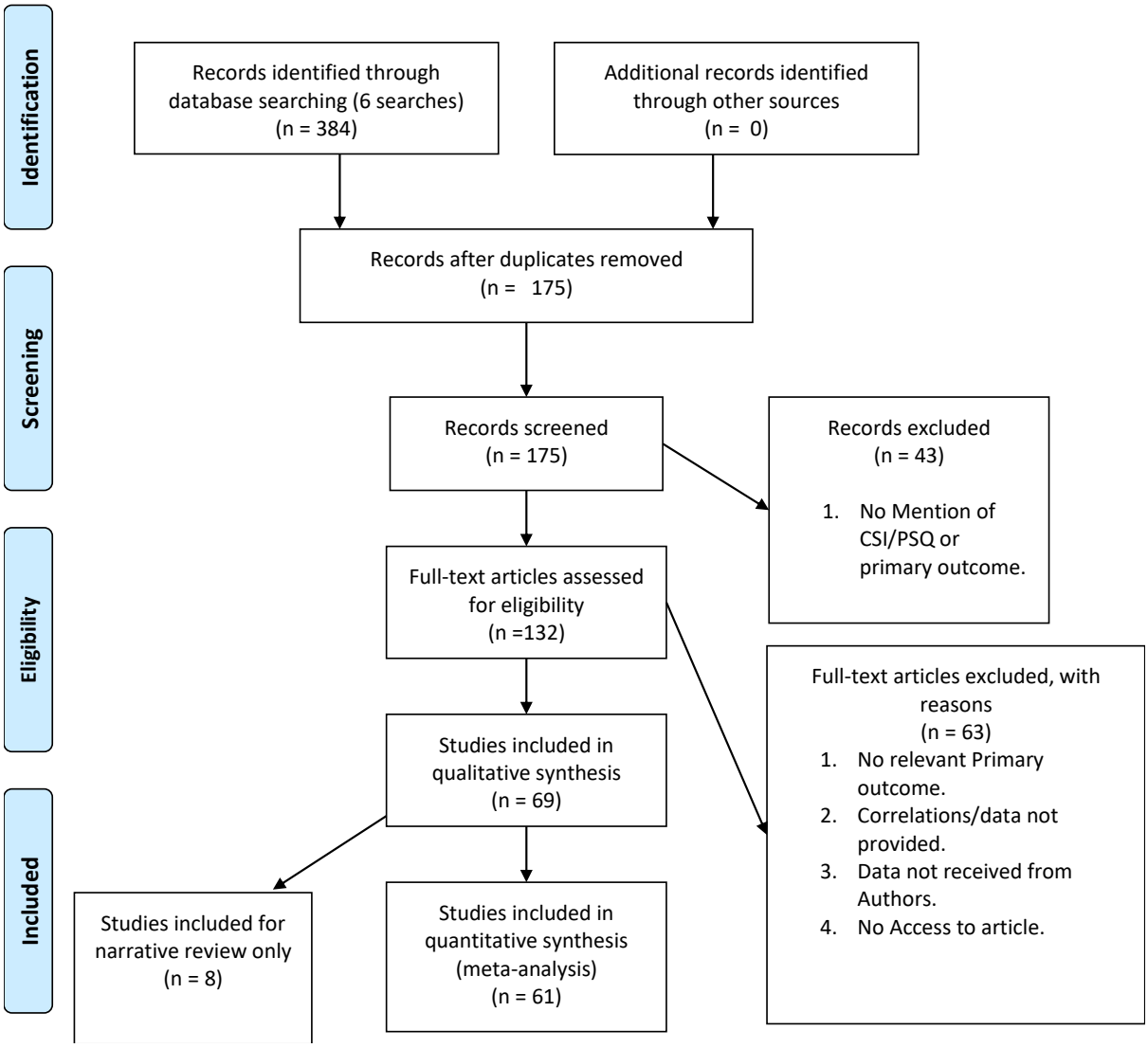
The Chi-squared (X^2) test was used to measure statistical heterogeneity across studies. Significant heterogeneity (p<0.05) is an indicator of clinical and methodological heterogeneity. The I^2 statistic was calculated to report heterogeneity as a percentage (Deeks et al., 2019; Higgins et al., 2003). A value of 0% implies no observed heterogeneity, 1 to 40% indicates low heterogeneity, 30% to 60% suggests moderate heterogeneity, 50% to 90% signifies substantial heterogeneity, and 75% to 100% is considered heterogeneous (Higgins et al., 2003).

6.4. Results

After excluding duplicates, the initial literature search identified 175 articles (Fig 1). 49 of these articles appeared eligible after full screening. A further 74 corresponding authors were emailed for specific correlations (either the PSQ or CSI with our variables of interest) as data were collected but not reported within their publication. 20 authors responded and provided the correlates of interest. Therefore, a total of 69 studies were eligible for quality appraisal/bias assessment (see Figure 1 for further details).

Figure 1

Flowchart to Show the Process of Inclusion Eligibility for Meta-analyses



Risk of Bias

All 69 studies included in the review went through an assessment of quality and risk of bias. The results are presented in Figure 2. An additional breakdown of participation bias is presented in Figure 3.

1. Participation Bias – Many studies showed participation bias. This reflects some common exclusion criteria that occur in studies that measure pain sensitivity e.g., neuropathic pain patients are often excluded as well as individuals with any mental health disorders or people taking any medication as this may affect their responsivity to stimuli. We ran a separate assessment to showcase the common characteristics which were excluded from study populations. The 'other' column was primarily made up of participants being excluded due to cognitive deficits (see Bias Assessment 2).
2. Missing data- A few studies reported missing data. This was in part due to incomplete questionnaires or participation dropout. Data not being reported for all the participants (e.g., reporting for pain patients but not healthy controls) was reflected in their bias assessment.
3. Standardised method - Most studies conducted a standardised method. The questionnaires were standardised for CSI, PSQ and psychological correlates and if sensory measures were taken, the method was of standardised quality. We could check this by assessing whether studies employed protocols from previously published work, or how homogenous protocols were across studies. Two studies were excluded due to a lack of methodological standardisation (Mcintyre et al., 1992; Wachtel et al., 2014)
4. Desirable statistics- Most studies provided Pearson's correlations for our variables of interest, but a few provided Spearman's rank correlations. If the study had undergone the relevant methodology but did not provide Pearson's or Spearman's correlations, we contacted the authors to provide data for one of these correlations. Synthesised results could then be analysed comparatively and included in meta-analyses. One study gave partial correlations and was therefore excluded (Melotti et al, 2018).
5. Sample Size- 63 out of 69 studies had an adequate sample size- a power calculation based on r=0.3 indicated that the sample size should have been 43 or over. Anything lower than n=43 was flagged. However, all studies were included for weighted meta-analyses. Low sample

sizes simply reflected less influence in a weighted meta-analysis. Yet, these small sample sizes may be relevant when reviewing less frequent correlations that were not suitable for meta-analysis i.e., narrative review.

Figure 2

Bias Assessment (Quality Assessment)

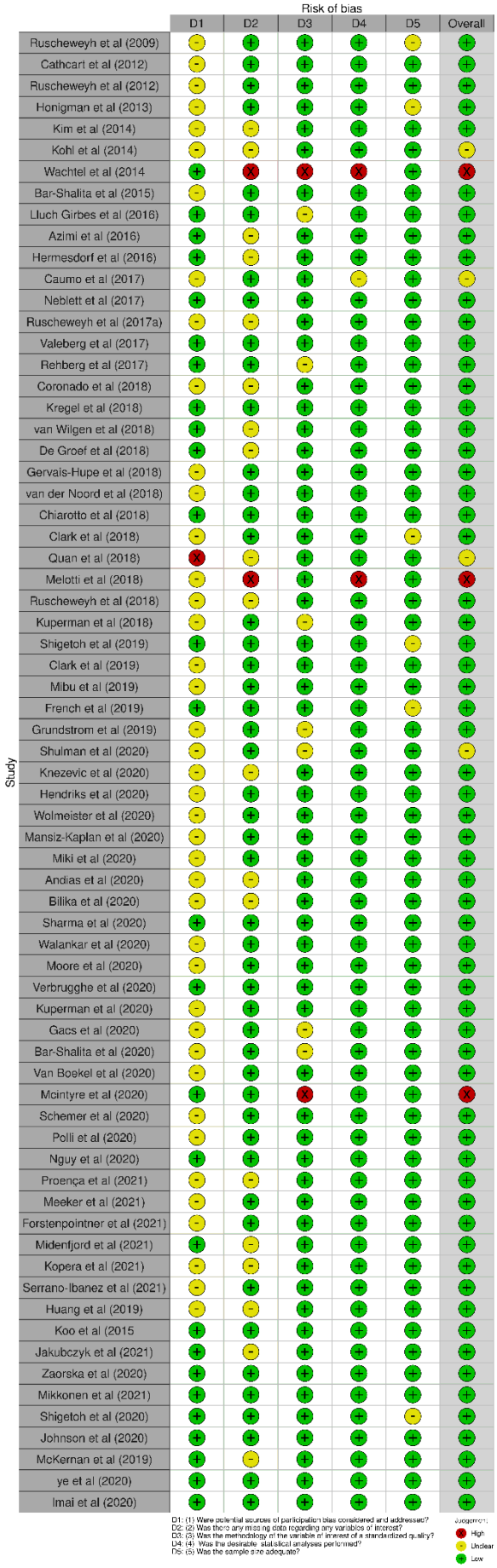
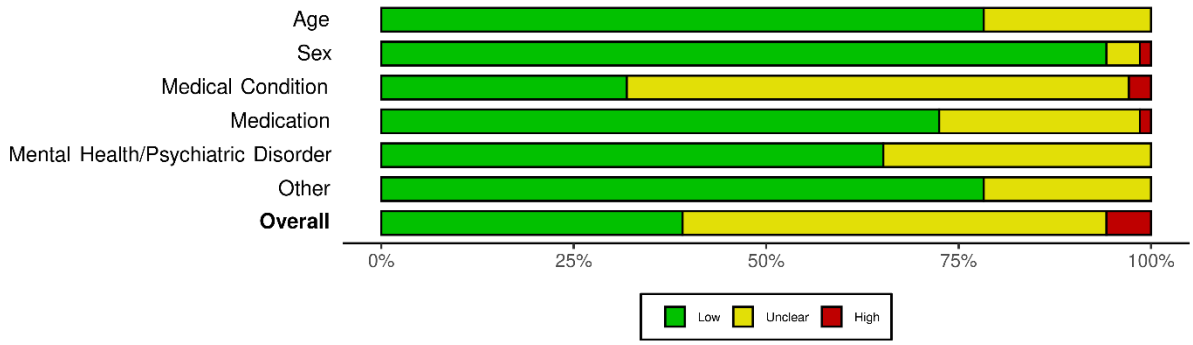

Risk of bias
D1
D2
D3
D4
D5
Overall
Study
Ruscheweyh et al (2009)
Cathcart et al (2012)
Ruscheweyh et al (2012)
Honigman et al (2013)
Kim et al (2014)
Kohl et al (2014)
Wachtel et al (2014
Bar-Shalita et al (2015)
Lluch Girbes et al (2016)
Azimi et al (2016)
Hermesdorf et al (2016)
Caumo et al (2017)
Neblett et al (2017)
Ruscheweyh et al (2017a)
Valeberg et al (2017)
Rehberg et al (2017)
Coronado et al (2018)
Kregel et al (2018)
van Wilgen et al (2018)
De Groef et al (2018)
Gervais-Hupe et al (2018)
van der Noord et al (2018)
Chiarotto et al (2018)
Clark et al (2018)
Quan et al (2018)
Melotti et al (2018)
Ruscheweyh et al (2018)
Kuperman et al (2018)
Shigetoh et al (2019)
Clark et al (2019)
Mibu et al (2019)
French et al (2019)
Grundstrom et al (2019)
Shulman et al (2020)
Knezevic et al (2020)
Hendriks et al (2020)
Wolmeister et al (2020)
Mansiz-Kaplan et al (2020)
Miki et al (2020)
Andias et al (2020)
Bilika et al (2020)
Sharma et al (2020)
Walankar et al (2020)
Moore et al (2020)
Verbrugghe et al (2020)
Kuperman et al (2020)
Gacs et al (2020)
Bar-Shalita et al (2020)
Van Boekel et al (2020)
Mcintyre et al (2020)
Schemer et al (2020)
Polli et al (2020)
Nguy et al (2020)
Proença et al (2021)
Meeker et al (2021)
Forstenpointner et al (2021)
Midenfjord et al (2021)
Kopera et al (2021)
Serrano-Ibanez et al (2021)
Huang et al (2019)
Koo et al (2015
Jakubczyk et al (2021)
Zaorska et al (2020)
Mikkonen et al (2021)
Shigetoh et al (2020)
Johnson et al (2020)
McKernan et al (2019)
ye et al (2020)
Imai et al (2020)
D1: (1) Were potential sources of participation bias considered and addressed?
D2: (2) Was there any missing data regarding any variables of interest?
D3: (3) Was the methodology of the variable of interest of a standardized quality?
D4: (4) Was the desirable statistical analyses performed?
D5: (5) Was the sample size adequate?
Judgement
High
Unclear
Low

Figure 3

Bias Assessment (Participation Bias)



Overall, the quality assessment for studies selected for this review showed that they were of good quality with a low risk of bias. Three studies were excluded due to a non-standardised method being used, or data not being given in the required format for correlational meta-analyses (Mcintyre et al., 2020; Melotti et al., 2018; Wachtel et al., 2014).

There were some concerns over participation bias (Figure 2), due to certain types of chronic pain patients being excluded in several studies (n=46) based on their medical condition e.g., neuropathy. Patients on pain medication were excluded in several studies (n=19), patients with mental health or psychiatric disorders were excluded in a number of studies (n=24), and individuals with cognitive deficits were also excluded in studies (n=12). This exclusion criteria may appear biased, but it is typical across studies that examine pain populations as medical conditions, medication, cognitive deficits and mental health; which can all interfere with the pain processing/Interpretation of pain. (Khera & Rangasamy., 2021; Lautenbacher & Krieg., 1994; Vanegas et al., 2010). Similarly, due to the typical nature of chronic pain populations, some study populations were predominantly female, and the mean age was high (over 60).

Only one study was identified as high risk, in any of the assessed domains on participation bias. The reason for this was, that in one study of a Chinese population, women on contraception were excluded from the sample (Quan et al., 2018). The study, however, was still included for further

analysis as research has found that oral contraception pills can alter neural pathways and impact pain processing (Vincent et al., 2013).

Excluded studies

Two studies were excluded due to a lack of methodological standardisation (Mcintyre et al., 2020; Wachtel et al., 2014) and one study gave partial correlations and was therefore excluded (Melotti et al., 2018).

Data Extracted

The surviving 66 studies included a total of 13,284 participants. 7,470 participants took the Central Sensitisation Inventory across 37 different studies and 5,531 took the Pain Sensitivity Questionnaire across 30 different studies (one study included both questionnaires [Coronado et al.,2018]). 31 studies containing a total of 6,885 participants provided correlations for the CSI with at least one psychological primary outcome. 16 studies consisting of 1,857 participants provided correlations for the CSI with at least one sensory primary outcome. 25 studies consisting of a total of 4,482 participants provided correlations for the PSQ with at least one psychological primary outcome. 16 studies consisting of a total of 3,375 participants provided correlations for the PSQ with at least one primary sensory measure. All extracted correlations can be seen in tables 1a-d.

Table 1a-d shows the extracted data for each of these studies (Table 1a shows all extracted correlations for CSI with psychological primary outcomes, Table 1b for CSI with sensory primary outcomes, Table 1c for PSQ with psychological primary outcomes and Table 1d for PSQ with sensory primary outcomes). All tables provide data for age, sex and subject population for each study if it was provided. Note that if multiple correlations of the same or very similar constructs were provided for a study, (which only occurs when trait anxiety and state anxiety are reported within the State and Trait Anxiety Inventory [STAI]), the values were averaged together as these two measures have high intercorrelation (Ramanaiah et al., 1983). Similarly, if measures for multiple body sites were

recorded for PPT, HPT, CPM etc., the multiple correlations per study were averaged together to give a mean correlation score for that construct. This was because intraclass correlations for pain measures across different body sites have been found to be high (Cronbach's alpha values >.80) (Lacourt et al., 2012; Mailloux et al; 2021). This meant that one correlation score for each construct was provided for each population, which could be used for meta-analysis.

Table 1a

Table Shows Correlations Extracted from Studies that Correlate the CSI Total Score with Psychological Constructs.

Study	N	Subject Population	Age (SD)	Sex (Female)	Psychological Construct								Questionnaires
					Dep	Anx	Cat	Stress	Sleep	Kin	Other		
					r	r	r	r	R	r	Measure	r	
Coronado et al. (2018)	78	Shoulder Pain Patients	39.0 (14.5)	46%	0.64	0.66		0.67			Brief Resilience Scale Positive Affect Negative Affect	-0.29 -0.11 0.67	BRS, PANAS, DASS-21
Hendriks et al. (2020)	125	Chronic Whiplash Patients	40.24 (11.26)	57%	0.56	0.54		0.66			4DSQsomatization	0.68	4DSQ
Kregel et al. (2020)	116	Chronic Spinal Pain Patients	39.92 (12.52)	62%			0.46						PCS
van Wilgen et al. (2018)	114	Chronic Pain Patients	46.73 (15.95)	56%			0.27						PCS
Wolmeister et al. (2020)	150	Patients Undergoing Surgery	58.2 (12.1)	58%				0.51					B-MEPS
De Groef et al. (2018)	146	Breast Cancer Survivors	56.8 (9.9)	100%			0.48						PCS
Gervais-Hupe (2018)	133	Knee Osteoarthritis Patients	63.5 (10.7)	56%			0.30				Somatization Anxio-depressive Symptoms	0.76 0.58	HADS (a+d), PCS, PHQ-15
Miki et al. (2020)	238	Pre-surgical Low Back Pain Patients	63.50 (16.0)	43%	0.49	0.50	0.54						HADS (a+d), PCS
van der Noord et al. (2018)	198	Chronic Pain Patients	46.8 (15.5)	58%	0.67	0.65	0.39						SCL-90, PCS
Andias et al. (2020)	1,435	Adolescents with Pain	16.30 ± 1.17	64%	0.60	0.59	0.49	0.65	0.46	0.46			PCS, DASS-21, TSK, BaSIQs

Bilika et al. (2020)	250	200 Chronic Pain Patients + 50 Healthy Controls	49.35 (14.70) 27.90 (8.71)	62% 50%			0.68					PCS
Chiarotto et al. (2018)	220	Chronic Pain Patients	54.5 (15.5)	79%	0.55	0.71						HADS (a+d), PCS
Shigetoh et al. (2019)	20	Musculoskeletal Pain Patients	67.5 (15.6)	60%	0.58	0.66	0.54			0.83		HADS (a+d), PCS, TSK
Clark et al. (2018)	21	Chronic Low Back Pain Patients	43	76%		0.63					Sensory Sensitivity (SSv) Sensation Seeking (SSk)	0.57 - 0.53	AASP
Clark et al. (2019)	165	Chronic Low Back Pain Patients	45 (12)	76%		0.46					Sensory Sensitivity Sensation Avoiding Low Registration Sensation Seeking Profile	0.63 0.48 0.54 - 0.23	AASP, STAI (t)
Sharma et al. (2020)	100	Musculoskeletal Pain Patients	42.01 (14.61)	67%			0.50						PCS
Walankar et al. (2020)	80	Chronic Shoulder Pain Patients	NA	48%			0.71			0.66			PCS, TSK
Verbrugghe et al. (2020)	101	Chronic Low Back Pain Patients	44.2 (9.6)	61%				0.36		0.26			PSS, TSK
Neblett et al. (2017)	763	Chronic Spinal Pain	46.8 (10.6)	35%	0.60				0.23		Abuse History PASS	0.11 0.34	BDI, ISI, PASS and abuse history

Mansiz-Kaplan et al. (2020)	64	Adolescents with Chest Pain	15.0 (1.8)	84%	0.64	0.75			Childhood Trauma	0.57	HADS (a+d), CTQ
Knezevic et al. (2020)	399	Chronic Pain Patients	52.76 (12.58)	67%			0.37	0.50			MOS, PCS
Caumo et al. (2017)	285	Chronic Pain + Healthy Controls	NA	87%			0.68				PCS
Imai et al. (2020)	201	Chronic and Non-Chronic Pain Patients	71.8 (8.8)	NA	0.50		0.33				GDS15, PCS
Polli et al. (2020)	26	Healthy Controls	52.0(10.90)	100%		0.14	0.52				PCS, BAI
Polli et al. (2020)	28	Pain Patients	48.0(9.44)	100%		0.78	0.26				PCS, BAI
Nguy et al. (2020)	52	Parkinson's Disease Patients	67.8(7.80)	31%	0.46	0.42		0.41			HADS (a+d), PSQI
Midenfjord et al. (2021)	401	All Participants Healthy, Chronic Pain and Irritable Bowell Syndrome Patients	31.0	73%	0.55	0.66					HADS (a+d)
Midenfjord et al. (2021)	111	Healthy Volunteers	25.0	59%	0.32	0.43					HADS (a+d)
Midenfjord et al. (2021)	36	Chronic Pain Patients	44.0	92%	0.56	0.75					HADS (a+d)

Serrano Ibanez et al. (2021)	398	Chronic Pain Patients	53.03(8.76)	92%					DASS	0.44	DASS-21
Mikkonen et al. (2021)	229	Musculoskeletal Pain Patients	NA	73%	0.62			0.46			TSK, DEPS
Shigetoh et al. (2020)	43	Musculoskeletal and Central Pain Patients	72.2(12.9)	77%	-0.02	0.48	0.37				PCS, HADS (a+d)
Johnson et al. (2020)	181	Chronic Pain Patients	44.62(14.06)	80%	0.60	0.61			Childhood Sexual Abuse	0.32	HADS(a+d), CATS
									Childhood Punishment	0.44	
									Childhood Neglect	0.50	
McKernan et al. (2019)	175	Chronic Pain Patients	44.89(14.23)	80%					Trauma History Questionnaire	0.28	CTQ
									PCL (PTSD checklist)	0.65	

Anx = Anxiety, Cat = Pain Catastrophising, Dep = Depression, Kin = Kinesiophobia. n = number of participants, r = extracted correlation

*Questionnaire Key: **4DSQ** = Four-Dimensional Symptom Questionnaire, **AASP** = Adolescent/Adult Sensory Profile, **BAI** = Beck Anxiety Inventory, **BaSIQs** = Basic scale of Insomnia Complaints and Quality of Sleep, **BD** = Becks Depression Inventory, **B-MEPS** = Brief Measure of Emotional Pre-operative Stress, **BRS** = Brief Resilience Scale, CTQ = Childhood Trauma Questionnaire, DASS-21 = Depression Anxiety Stress Scale, DEPS = Depression Scale, GDS15 = Geriatric Depression Scale, **HADS (a+d)** Hospital Anxiety and Depression Scale, **ISI** = Insomnia Sleep Index, **MOS** = Medical Outcomes Study Sleep Scale, **PANAS** = Positive and Negative Affect Schedule, **PASS** = Pain Anxiety Sensitivity Scale, **PCS** = Pain Catastrophising Scale, **PSS** = Perceived Stress Scale, **PHQ-15** = Patient Health Questionnaire, **PSQI** = Pittsburgh Sleep Quality Index, **SCL-90** = Symptom Checklist 90, **STAI (t+s)** State and Trait Anxiety Inventory, **TSK** = Tampa Scale of Kinesophobia.*

Table 1b

Table Shows Correlations Extracted From Studies That Correlate the CSI Total Score with Nociceptive Measures.

Study	N	Subject Population	Age (SD)	Sex (Female)	Nociceptive Measure										
					PPT		HPT		CPM		TS		WP	Other	
					r	avg r	r	avg r	R	avg r	r	avg r	r	Measure	r
Coronado et al. (2018)	78	Shoulder Pain Patients	39.0 (14.5)	46%	-0.13 -0.09 -0.13	-0.12	-0.08 0.13	0.03						Suprathreshold	-0.03
Shulman et al. (2020)	30	Chronic Pain Patients	15.2 (1.9)	75%										Offset Analgesia	-0.05
Shulman et al. (2020)	32	Healthy Participants	15.3 (2.1)	72%										Offset Analgesia	-0.24
Hendriks et al. (2020)	125	Chronic Whiplash Patients	40.24 (11.26)	57%	-0.11 -0.20	-0.17					0.03 -0.01	0.01			
Kregel et al. (2020)	116	Chronic Spinal Pain Patients	39.92 (12.52)	62%	-.26 -.24 -.28 -.26	-0.26			0.02	0.02					
van Wilgen et al. (2018)	114	Chronic Pain Patients	46.73 (15.95)	56%									0.58		
Wolmeister et al. (2020)	150	Patients Undergoing Surgery	58.2 (12.1)	58%	-0.29	-0.29			0.01	0.01				Pressure Pain Tolerance	-0.20
De Groef et al. (2018)	146	Breast Cancer Survivors	56.8 (9.9)	100%	-0.30	-0.30								Index of	-0.14

													Widespread Hyperalgesia	
Gervais-Hupe. (2018)	133	Knee Osteoarthritis Patients	63.5 (10.7)	56%	-0.24 -0.26	-0.25		0.19	0.19	0.07 0.09	0.08	0.40		
Mibu et al. (2019)	104	Chronic Low Back Pain Patients	58.4(14.2)	74%	-0.09	-0.09				0.09	0.09	0.25		
Mibu et al (2019)	50	Knee Osteoarthritis Patients	66.7 (7.7)	90%	-0.16	-0.16				-0.13	-0.13	0.27		
French et al. (2019)	36	18 Greater Trochanteric Pain Syndrome Patients + 18 Healthy controls	54.5 (23)	83%	-0.55 -0.57 -0.52 -0.52 -0.54 -0.36 -0.27 -0.44	-0.47								
Lluch Girbes et al. (2016)	53	Knee Osteoarthritis Patients	70.2 (7.4)	64%									Area of pain	0.46
Moore et al. (2020)	134	Knee Osteoarthritis Patients	64.63 (7.80)	61%	-0.39 -0.40 -0.37	-0.39		0.28	0.28	0.18 0.21	0.19		Manual Tender Point Count Number of Painful Sites	0.45 0.43

Polli et al. (2020)	26	Pain Patients	52.0(10.90)	100%	0.02	0.02	0.11 -0.66 0.73	0.06			0.10	0.10	0.25	Cold Pain Neck Cold Pain Hand Cold Pain Leg	-0.15 0.07 -0.07
Polli et al. (2020)	28	Healthy Participants	48.0(9.44)	100%	-0.33	-0.33	-.36 -.39 .15	-0.20			0.32	0.32	0.47	Cold Pain Neck Cold Pain Hand Cold Pain Leg	0.38 0.37 0.35
Proença et al. (2021)	31	Healthy Participants	33.0	71%	-0.05 -0.10 -0.02	-0.06			0.08 0.24 0.17	0.16					
Proença et al. (2021)	115	Temporomandibular Disorder	37.0	83%	-0.10 -0.08 -0.09	-0.09			-0.04 -0.06 0.03	-0.02					
Johnson et al. (2020)	181	Chronic Pain Patients	44.62(14.06)	80%									0.52		
McKernan et al. (2019)	175	Chronic Pain Patients	44.89(14.23)	80%									0.55		

CPM = Conditioned Pain Modulation, HPT – Heat Pain Threshold, PPT = Pressure Pain Threshold, TS – Temporal Summation, WP = Widespread Pain. n = number of participants, r = extracted correlation, avg r = average of extracted r correlations (multiple body sites per study).

Table 1c

Table Shows Correlations Extracted from Studies that Correlate the PSQ Total Score with Psychological Constructs.

Study	N	Subject Population	Age (SD)	Sex (female)	Psychological Construct						Questionnaires
					Dep	Anx	Cat	Stress	Other		
					r	avg r	r	r	Measure	r	
Coronado et al. (2018)	78	Shoulder Pain Patients	39.0 (14.5)	46%	0.14	0.31		0.14	BRS Positive Affect Negative Affect	-0.39 -0.16 0.31	BRS, PANAS, DASS-21
Kuperman et al. (2020)	130	Mild Traumatic Brain Injury Patients	37.0 (12.0)	44%	0.23	0.16	0.48	0.23			PCS, HADS (a+d), PSS
Ruscheweyh et al. (2009)	47	Healthy Participants	25 (4)	61%	0.24	0.17	0.45				PCS, BDI, STAI (t+s)
Ruscheweyh et al. (2017)	65	Chronic Pain Patients	49.3 (12.3)	74%	0.25	0.27					BDI, STAI (t+s), PCS
Honigman et al. (2013)	29	Healthy Participants	27.6 (3.4)	48%		0.51	0.46				PCS, STAI (t+s)
Quan et al. (2018)	182	Healthy Participants	39.9 (14.6)	74%	0.00	0.10	0.27				PCS, STAI (t+s), BDI
Bar-Shalita et al. (2015)	250	Healthy Participants	27.3 (3.77)	50%			0.24		SRQ	0.31	PCS, SRQ
Azimi et al. (2016)	101	Lumbar Disc Herniation Patients	52.4 (9.1)	54%			0.81				PCS
Hermesdorf et al. (2016)	735	Depression Patients	49.72 (7.30)	59%	0.11	0.16					Ham (a+d)
Catchart et al. (2012)	53	Chronic Tension	45.5 (13.4)	66%				0.34			DASS-21

		Headache Sufferers								
Gacs et al. (2020)	226	Healthy Participants	30.5 (10.3)	64%				Past Negativity Past-Positivity Present-Fatalism Present Hedonism Future-Orientation	0.20 0.02 0.16 -0.15 -0.14	ZTRI
Kim et al. (2014)	72	Degenerative Spinal Disease patients	65.87 (8.14)	63%			0.38			PCS
Bar-Shalita et al. (2020)	204	Healthy Participants	27.4 (3.71)	49%				Aversive Hedonic Extraversion Neuroticism Agreeableness Conscientiousness Openness to Experience	0.29 0.04 0.05 0.29 -0.13 -0.07 -0.15	SRQ
Grundstrom et al. (2019)	37	Persistent Pelvic Pain	26.4 (5.9)	100%	0.27	0.19				HADS (a+d)
Grundstrom et al. (2019)	55	Healthy Participants	30.2 (5.6)	100%	0.34	0.18				HADS (a+d)
Rehberg et al. (2017)	198	Breast Cancer Patients	57.5 (12.5)	NA	0.12	0.13				BDI, STAI (t+s)
Kuperman et al. (2018)	100	Mild Traumatic Brain Injury Patients	36 (12.5)	42%	0.17	0.11	0.31			PCS, HADS (a+d)

Kuperman et al. (2018)	80	Healthy Participants	43 (14.3)	53%	0.08	0.03	0.23			PCS, HADS (a+d)
Ye et al. (2020)	64	Healthy Participants	NA	52%		0.14	0.19			PCS, STAI (t+s)
Schemer et al. (2020)	112	Healthy Participants	23.36(4.0)	100%	-0.10		0.15			BDI, PCS
Meeker et al. (2021)	64	Healthy Participants	NA	NA	-0.01	0.11	0.50			CES-D, PCS, STAI-T
Forstenpointner et al. (2021)	555	Pain, Painless and Healthy Participants	NA	NA	0.11	0.16	0.30			PCS, HADS (a+d)
Forstenpointner et al. (2021)	332	Pain Patients	59.0 (15.5)	51%	0.01	0.10	0.25			PCS, HADS (a+d)
Forstenpointner et al. (2021)	112	Healthy Controls	43.3 (13.0)	62%	0.12	0.11	0.14			PCS, HADS (a+d)
Kopera et al. (2021)	110	Non-Alcohol Use Disorder Patients	40.6 (8.1)	NA	0.09			DERS	-0.17	BDI, DERS
Kopera et al. (2021)	144	Alcohol Use Disorder Patients	44 (11.2)	NA	0.14			DERS	0.21	BDI, DERS
Huang et al. (2019)	136	Pain Patients	44	36%	0.13		0.25	PANAS	0.07	PANAS, BDI, PCS
Huang et al. (2019)	157	Healthy Controls	44	36%	0.11			PANAS	0.15	PANAS, BDI
Koo et al. (2015)	58	Pain Patients	41.3 (14.5)	64%			0.26	PASS	0.11	PCS, PASS
Jakubczyk et al. (2021)	165	Alcohol Use Disorder Patients	44(11.2)	12%		0.19				BSI
Jakubczyk et al. (2021)	110	Non-Alcohol Use Disorder Patients	40.6(8.1)	26%		0.16				BSI

Zaorska et al. (2020)	165	Alcohol Use Disorder Patients	25.7(9.6)	12%	0.19	CTQ	0.139	BSI, CTQ

Anx = Anxiety, Cat = Pain Catastrophising, Dep = Depression, Kin = Kinesiophobia. n = number of participants, r = extracted correlation, avg r = average of STAI (trait and state)

*Questionnaire Key: **BD** = Becks Depression Inventory **BRS** = Brief Resilience Scale, **BSI** = Brief Symptom Inventory, **CES-D** = Centre for Epidemiologic Studies Depression Scale, **CTQ** = Childhood Trauma Questionnaire, **DASS-21** = Depression Anxiety Stress Scale, **DERS** = Difficulties in Emotion Regulation Scale, **HADS (a+d)** = Hospital Anxiety and Depression Scale, **PANAS** = Positive and Negative Affect Schedule, **PCS** = Pain Catastrophising Scale, **PSS** = Perceived Stress Scale, **SRQ** = Sensory Responsiveness Questionnaire, **STAI (t+s)** State and Trait Anxiety Inventory*

Table 1d

Table Shows Correlations Extracted From Studies that Correlate the PSQ Total Score with Nociceptive Measures.

Study	**N**	**Subject Population**	**Age (SD)**	**Sex (Fem)**	**Nociceptive Measure**									
					PPT		HPT		CPM		TS		Other	
					r	avg r	r	avg r	R	avg r	r	avg r	Measure	r
Coronado et al. (2018)	78	Shoulder Pain Patients	39.0 (14.5)	46%	-0.14 -0.27 -0.25	-0.22	-0.17 0.17	0.00					Suprathreshold	0.15
Kuperman et al. (2020)	130	Mild Traumatic Brain Injury Patients	37.0 (12.0)	44%	-0.25	-0.25	-0.30	-0.30	-0.13 0.31	0.09	0.15 0.16	0.16	Mean Area of Injured Pain Number of Painful Body Areas	0.26 0.28
Ruscheweyh et al. (2009)	47	Healthy Participants	25.0 (4.0)	61%									Experimental Pain Threshold	.03

									Score	
									Experimental Pain Intensity Rating Score	0.56
									PinPrick	0.39
									Phasic Heat47	0.51
									Phasic Heat48	0.54
									Tonic Heat	0.43
									Tonic Cold	0.47
									Cold Pressor	0.42
Ruscheweyh et al. (2015)	65	Chronic Pain Patients	49.3 (12.3)	74%	-0.29	-0.29	-0.45	-0.46	Tonic Cold	0.68
									Pinprick (512 mN)	0.38
									Phasic Heat 47°C	0.63
									Phasic Heat 48°C	0.67
Quan et al. (2018)	182	Healthy Participants	39.9 (14.6)	74%					Electrical Pain Threshold	0.30
									Pain Tolerance	0.23
									Fixed Pain Stimulation	0.50
Hermesdorf et al. (2016)	735	Depression Patients	49.7 (7.3)	59%	-0.21	-0.21				
Grundstrom et al. (2019)	37	Persistent Pelvic Pain	26.4 (5.9)	100%	-0.43	-0.43	-0.63	-0.63	Cold Pain Threshold	0.56
Grundstrom et al. (2019)	55	Healthy Participants	30.2 (5.6)	100%	-0.15	-0.15	-0.09	-0.09	Cold Pain Threshold	0.08
Van Boekel et al. (2020)	262	Healthy Participants		57%	-0.05	-0.05			Pressure Pain Threshold- NRS	0.40
									Electrical Pain Tolerance (n=132)	-0.17
									Electrical Pain	0.24

												Tolerance NRS (n=132)	
Ruscheweyh et al. (2012)	46	Mixed Chronic Pain Patients	50 (13)	74%	-0.29	-0.30	-0.51	-0.51				Phasic Heat (47°C)	0.72
												Phasic Heat (48°C)	0.76
												Pinprick (512 mN)	0.40
												Tonic Cold	0.76
Valeberg et al. (2017)	48	Healthy Participants		44%			−0.15	−0.15				Cold Pressor Pain Intensity rating	0.36
												Cold Pressor Pain Tolerance	-0.30
Rehberg et al. (2017)	198	Breast Cancer Patients	57.5 (12.5)						-0.18	-0.18		Electrical Pain Threshold	-0.29
												Pain Intensity Heat (hot water bath)	0.33
Ruscheweyh et al. (2018)	501	Population-Based Participants	52.9 (8.2)	52%	-0.17	-0.17							
Kohl et al. (2014)	60	Fibromyalgia Patients	51.4 (9.4)	100%								Heat Pain Tolerance	-0.52
Kuperman et al. (2018)	100	Mild Traumatic Brain Injury Patients	36 (12.5)	42%					-0.21 0.33	0.06	0.12	0.12	Electrical Pain tolerance	-0.27
Kuperman et al. (2018)	80	Healthy Participants	43 (14.3)	53%					0.03 -0.11	-0.04	0.30	0.30	Electrical Pain Tolerance	-0.01
Meeker et al. (2021)	64	Healthy Participants					-0.29	-0.29					Warm Detection Threshold	-0.08

Forstenpointner et al. (2021)	555	Pain, Painless and Healthy Participants			-0.09	-0.09	0.04	0.04		0.03	0.03	Cold Detection Threshold Warm Detection Threshold Temperature Sensory Limen Cold Pain Threshold Mechanical Pain Threshold Mechanical Pain Sensitivity Mechanical Detection Threshold Vibration Detection Threshold	-0.10 0.12 0.11 0.01 0.04 0.07 0.10 -0.08
Forstenpointner et al. (2021)	332	Pain Patients	59.0 (15.5)	51%	-0.07	-0.07	-0.01	-0.01		0.03	0.03	Cold Detection Threshold Warm Detection Threshold Temperature Sensory Limen Cold Pain Threshold Mechanical Pain threshold Mechanical Pain Sensitivity Mechanical Detection Threshold	-0.04 0.06 0.05 0.07 -0.05 0.04 0.02

											Vibration Detection Threshold	0.01
Forstenpointner et al. (2021)	112	Healthy Controls	43.3 (13.0)	62%	-0.07	-0.07	0.07	0.07		-0.04	-0.04	Cold Detection Threshold	-0.09
												Warm Detection Threshold	-0.08
												Temperature Sensory Limen	0.06
												Cold Pain Threshold	-0.04
												Mechanical Pain Threshold	-0.01
												Mechanical Pain Sensitivity	0.18
												Mechanical Detection Threshold	0.06
												Vibration Detection Threshold	0.08

CPM = Conditioned Pain Modulation, HPT – Heat Pain Threshold, PPT = Pressure Pain Threshold, TS – Temporal Summation. n = number of participants, r = extracted correlation, avg r = average of extracted r correlations (multiple body sites per study).

Study Characteristics

Psychological Measures

Psychological correlates with PSQ or CSI that were provided for at least three studies were included in meta-analyses; these were depression, anxiety, pain catastrophising, stress, sleep, and kinesiophobia. The questionnaires used to assess depression were the Depression Anxiety Stress Scale (DASS-21) (Lee, 2019), the four-dimensional Symptom Questionnaire (4DSQ) (Terluin et al., 2006), the Hospital Anxiety and Depression Scale (HADS-D) (Zigmond & Snaith., 1983), the Symptom Checklist 90 (SCL90-D) (Bonicatto et al., 1997), Beck's Depression Inventory (BDI) (Schotte et al., 1997), the Depression Scale (DEPS) (Poutanen et al., 2010), the Centre for Epidemiologic Studies Depression Scale (CES-D), and the Geriatric Depression Scale (GDS-15) (Radloff,1977) and the Hamilton Anxiety Rating Scale (HAM-D) (Maier et al., 1988). The questionnaires used to assess anxiety were DASS21 (Lee, 2019), 4DSQ (Terluin et al., 2006), HADS-A (Zigmond & Snaith., 1983), SCL90-A (Bonicatto et al. 1997), the State and Trait Anxiety Inventory (STAI) (Metzger, 1976), the Brief Symptom Inventory (BSI) (Franke et al., 2017), the Beck Anxiety Inventory (BAI) and the HAM-A (Maier et al, 1988). The questionnaire used to assess pain catastrophising was the pain catastrophising scale (PCS) (Osman et al., 1997). The questionnaires used to assess stress were the DASS-21 (Lee, 2019), the Perceived Stress Scale (PSS) (Lee, 2012), 4DSQ (Terluin et al., 2006) and the Brief Measure of Emotional Preoperative Stress (B-MEPS) (Wolmeister et al., 2020). The questionnaires used to assess sleep were the Medical Outcomes Study Sleep Scale (MOS) (Allen et al., 2009), the Basic Scale of Insomnia Complaints and Quality of Sleep (BaSIQs) (Allen Gomes et al., 2015), and the Insomnia Severity Index (ISI) (Morin et al., 2011). The questionnaire used to assess kinesiophobia was the Tampa Scale of Kinesiophobia (TSK) (Tkachuk & Harris, 2012).

Other questionnaires that reported correlations with CSI/PSQ in fewer than three studies were included for narrative review but not in the meta-analysis. These were: the Brief Resilience Scale (BRS) (Smith et

al., 2008), the Patient Health Questionnaire (PHQ-15) (Kroenke et al., 2002), the Adolescent/Adult Sensory Profile (AASP) (Brown et al., 2001), the Sensory Responsiveness Questionnaire (SRQ) (Bar-Shalita et al., 2015), the Difficulties in Emotion Regulation Scale (DERS) (Bjureberg et al., 2016), the Positive and Negative Affect Schedule (PANAS) [Crawford & Henry, 2004), the Pain Anxiety Sensitivity Scale (PASS) (McCracken et al., 1992), the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997) and the Child Abuse and Trauma questionnaire (CATS) (Sanders & Becker-Lausen, 1995).

Nociceptive Sensory Measures

Sensory correlates suitable for meta-analysis included Pressure Pain Threshold (PPT), Heat Pain Threshold (HPT), Conditioned Pain Modulation (CPM), Temporal Summation (TS) and Widespread Pain. Methods that were not carried out regularly enough for meta-analyses (i.e., fewer than three studies reported correlations for these measures) included: suprathreshold (pain rating associated with the 5th heat pulse out of a series of 5 heat pulses [46°C]) (Coronado et al., 2018), offset analgesia (Shulman et al., 2020), pain tolerance (electrical, pressure or thermal) (Forstenpointner et al., 2021; Kohl et al., 2014; Kperman et al., 2020; Quan et al., 2018; Valeberg et al., 2017; Van Boekel et al., 2020; Wolmeister et al., 2020), area/number of pain sites (Lluch et al., 2018; Moore et al., 2020), cold pain threshold (Grundstroem et al., 2019), electrical pain threshold (Rehberg et al., 2017), and tonic heat (Ruscheweyh et al., 2009). Correlations for the CSI/PSQ with these measures can be found in tables 1a-d.

The methodologies for the nociceptive measures included in the meta-analysis were considered standardised and generally consistent, although, they did show slight variations in some cases, as outlined below.

Pressure Pain Threshold

In most cases for PPT, a digital or handheld mechanic pressure algometer was used to apply pressure through a 1cm² probe. The main variation in PPT was in the rate of pressure applied, being between

0.1kg/s to 1kg/s. The body site for which the PPT was applied varied across studies, though it was consistently applied to muscles. Participants were asked to report the moment that the increasing pressure became painful or unpleasant.

Heat Pain threshold

For Heat Pain threshold, a thermode was applied to various body sites depending on the study, consistently applied to muscles. In all studies, the thermode started at a baseline temperature (commonly 32°C) and was increased at a varied rate between 0.5°C/s to 1.5°C/s across studies. Participants were asked to report the moment that the increasing heat became painful or unpleasant.

Conditioned Pain Modulation

For CPM, the conditioning stimulus was most regularly a cold-water bath applied to the opposite hand of the test stimulus. One study used a thermode to elicit cold pain (Gervais-Hupe et al., 2018), and another used a hot water bath (Rehberg et al., 2017). Most commonly the test stimulus was a pre-determined pressure applied to a body part on the opposite side of the conditioning stimulus, using a pressure algometer. One study used a combination of pressure and heat pain (Kuperman et al., 2020), and another used electrical stimuli applied to the right sural nerve (Rehberg et al., 2017). One study used PPT as the test stimulus and Ischemic compression using a Sphygmomanometer, which was used as the conditioning stimulus (Proenca et al., 2021). The average pain ratings for the test stimulus given during the conditioning stimulus condition (both test and conditioning stimulus simultaneously administered) were subtracted from the average pain ratings of the test stimulus only condition, to give a CPM score.

Temporal Summation

TS was often calculated by applying a pre-determined pressure intensity, using a pressure algometer, to a body site (body sites varied across studies) for several repetitions (commonly 10 consecutive stimulations) at a rate of 1/second. The first pain rating in the series was subtracted from the final pain rating to give a TS score. One study used this same paradigm, as well as a similar paradigm using electrical stimulation (Kuperman et al., 2020). Another study applied a 60g von Frey filament to the forearm and knee for four stimulations, the stimulus was then applied for 30 stimulations at a rate of 1/second. The initial pain rating was subtracted from the second to give a TS score (Gervais-Hupe et al., 2018).

Widespread Pain

Widespread pain measures consisted of the Widespread Pain Index (WPI) (Dudeney et al., 2018) and the Michigan Body Map (MBM) (Brummett et al., 2016), which are both questionnaires used to assess the number of painful body sites and areas of pain across the body.

Phasic Heat

Phasic heat stimulation was administered at 47°C or 48°C for five seconds. The average of four ratings collected at the set temperature of 47/48°C was used as phasic pain rating. If Phasic Heat rating was carried out at two temperatures, the average of these two scores was taken as the Phasic heat score.

Tonic Cold

A thermode surface oscillated around 3°C (0.5 Hz, amplitude: ±1°C) for 60s. The average of the ratings over the four-time points and four measurements (twice on each hand) was used as the tonic cold pain rating.

Pinprick Stimulation

Pain intensity ratings of pinprick stimuli were obtained from the volar forearm using a weighted pinprick stimulator (force: 512 mN).

Summary

All studies included in this review were assessed for methodology and were considered standardised by at least two reviewers. Though it should be noted that, in general, there was a certain level of heterogeneity in methodology across studies involving nociceptive sensory measures, particularly with CPM.

Meta analyses:

The results of the meta-analyses are reported in Table 2. Studies reporting data for sub-set samples instead of a total (e.g., patients and healthy controls) were entered into the meta-analyses as separate correlations as they reflected separate populations. In a separate sub-analysis, they were divided appropriately to compare findings for pain patients with healthy participants (see Table 3).

Table 2

Meta-analyses for CSI and PSQ with Psychological and Sensory Measures.

Outcome Measures	Studies	N of Populations	Total N of Participants	Weighted mean correlation [95% CI]	Heterogeneity	Strength of Correlation
	All Participants – CSI					
Depression	[5,21,25,47,55,57,85,95–97,103–105,132,133]	15	4,248	0.58 [0.54-0.62]	χ^2 = 52.66, df = 14 (P <0.001); I^2 = 61.3%	Strong
Anxiety	[5,21–23,25,47,57,85,95,96,103–	16	3,295	0.60 [0.56-0.63]	χ^2 = 58.35, df = 15 (P < 0.001); I^2 = 72%	Strong

	105,110,132, 133]					
Pain Catastrophising	[5,14,20,32,43,55,62,64,66,96,105,110,131–133,150,151]	17	3,812	0.48 [0.43-0.54]	χ^2 = 82.56, df = 16 (P < 0.001); I^2 = 82.6%	Moderate-Strong
Stress	[5,25,47,147,153]	5	1,889	0.62 [0.56-0.69]	χ^2 = 27.79, df = 4 (P < 0.001); I^2 = 80.2%	Strong
Sleep	[5,62,103,104]	4	2,649	0.40 [0.29-0.51]	χ^2 = 44.57, df = 3 (P < 0.001); I^2 = 92.8%	Moderate
Kinesiophobia	[5,97,133,147,150]	5	1,865	0.46 [0.40-0.53]	χ^2 = 16.08, df = 4 (P = 0.003); I^2 = 80%	Moderate-Strong
Pressure Pain Threshold	[25,32,40,43,47,66,94,98,110,112,153]	14	1,272	-0.22 (-0.28 to -0.17)	χ^2 = 17.37, df = 13 (P = 0.183); I^2 = 24.2%	Weak
Heat Pain Threshold	[25,110]	3	132	-0.01 (-0.12 to 0.09)	χ^2 = 1.16, df = 2 (P = 0.558); I^2 = 0%	No Effect
Conditioned Pain Modulation	[43,66,98,112,153]	6	679	0.10 [0.01-0.19]	χ^2 = 9.09, df = 5 (P = 0.106); I^2 = 45.5%	Weak
Temporal Summation	[43,47,94,98,110]	7	600	0.09 [0.01 – 0.16]	χ^2 = 6.07, df = 6 (P = 0.415); I^2 = 0%	None-Weak (negligible)
Widespread Pain	[43,94,110,151]	6	455	0.39 [0.23-0.50]	χ^2 = 10.53, df = 5 (P = 0.061); I^2 = 54.9%	Moderate
	All Participants– PSQ					
Depression	[25,38,44,49,53,65,70,70,90,113,117,120,121,127]	17	2,985	0.11 [0.08-0.15]	χ^2 = 16.71, df = 17 (P = 0.474); I^2 = 0%	Weak
Anxiety	[25,38,44,49,52,56,69,70,90,113,117,1	18	2,859	0.16 [0.14-0.19]	χ^2 = 9.65, df = 17 (P = 0.918); I^2 = 0%	Weak

	20,121,157,161]					
Pain Catastrophising	[9,11,38,52,53,59,69,70,90,113,121,127,157]	15	1,980	0.32 [0.25-0.40]	χ^2 = 48.97, df = 14 (P < 0.001); I^2 = 82.6%	Moderate
Stress	[19,25,69]	3	261	0.23 [0.15-0.30]	χ^2 = 1.39, df = 2 (P = 0.49); I^2 = 0%	Weak
Pressure Pain Threshold	[25,38,44,49,69,120,122,123,144]	10	2,464	-0.17 [-0.22 to -0.12]	χ^2 = 13.94, df = 9 (P = 0.124); I^2 = 35.6%	Weak
Heat Pain Threshold	[25,38,44,69,120,122,143]	9	1,078	-0.11 [-0.25 to 0.02]	χ^2 = 46.77, df = 8 (P < 0.001); I^2 = 84.8%	Weak
Conditioned Pain Modulation	[69,70,117]	4	508	-0.04 [-0.15 to 0.07]	χ^2 = 7.00, df = 3 (P = 0.072); I^2 = 57.2%	No Effect
Temporal Summation	[38,69,70]	4	865	0.08 [-.00 to 0.17]	χ^2 = 6.36, df = 3 (P = 0.095); I^2 = 53.6%	None-Weak (negligible)
Phasic Heat	[120–122]	3	158	0.64 [0.54 to 0.73]	χ^2 = 3.03, df = 2 (P = 0.219); I^2 = 31.9%	Strong
Tonic Cold	[120–122]	3	158	0.64 [0.51 to 0.77]	χ^2 = 6.1, df = 2 (P = 0.047); I^2 = 63%	Strong
Pin Prick Stimulation	[120–122]	3	158	0.39 [0.38 to 0.40]	χ^2 = 0.02, df = 2 (P = 0.991); I^2 = 0%	Moderate

Central Sensitisation Inventory

When Cohen's standards for effect sizes are applied (Cohen, 1988), the CSI showed moderate to strong correlations with psychological questionnaires. Depression (r=0.58, 95% CI [0.54-0.62]), anxiety (r=0.60, 95% CI [0.56-0.63]), pain catastrophising (r=0.48, 95% CI [0.43-0.54]), stress (r=0.63, 95% CI [0.56-0.69]), sleep (r=0.40, 95% CI [0.29-0.51]) and kinesiophobia (r=0.46, 95% CI [0.40-0.53]) all showed moderate-

strong weighted correlations with the CSI. There was not sufficient data to conduct a meta-analysis on childhood trauma, somatisation, and personality type (sensory profile and brief resilience scale) and negative affect. Yet, they all showed moderate-strong correlations with CSI (Clark et al., 2019; Clark et al., 2018; Coronado et al., 2018; Hendriks et al., 2020; Johnson et al., 2020; Mansiz-Kaplan et al., 2020; McKernan et al., 2017) (see Table 1A). Overall, these findings suggest that the CSI correlates strongly with psychological factors.

CSI shows a weak negative correlation with PPT (r=-0.22, 95% CI [-0.28 to -0.17]), no correlation with HPT (r=-0.01, 95% CI [-0.12-0.09]) and a weak/negligible correlation with CPM (r=0.10, 95% CI [0.01-0.19]) and TS (r=0.09, 95% CI [0.01-0.16]). This suggests that CSI scores are a weak/negligible predictor of how an individual might respond to nociceptive sensory testing. The correlations between the CSI and sensory measures: PPT, HPT, CPM and TS, are substantially weaker than their correlations with psychological constructs. Widespread pain was moderately correlated with the CSI (r=0.39, 95% CI [0.23-0.50]). Area of pain, number of pain sites and manual tender point count were also moderately correlated with the CSI (r= 0.46, $p<0.01$; r=0.45 $p<0.01$; r=0.43 $p<0.01$; respectively) (see Table 1B).

Pain Sensitivity Questionnaire

The PSQ showed weak correlations with psychological questionnaires; depression (r=0.11, 95% CI [0.08-0.15]), anxiety (r=0.16, 95% CI [0.14-0.19]) and stress (r=0.23, 95% CI [0.15-0.30]), and a moderate correlation with pain catastrophising (r=0.32, 95% CI [0.25-0.40]). Regarding measures that did not provide sufficient data for meta-analyses, the Brief Resilience Scale (BRS) showed a moderate negative correlation with PSQ in one study (Coronado et al., 2018). Negative affect neuroticism aversiveness, past negativity and sensory responsiveness showed weak-moderate positive correlations with the PSQ (Bar-Shalita et al., 2020; Bar-Shalita et al., 2015; Coronado et al., 2018; Gacs et al., 2020) (See Table 1C).

The PSQ showed a weak negative correlation with PPT (r=-0.17, 95% CI [-0.22 to -0.12]) and HPT (r=-0.11, 95% CI [-0.25 to 0.02]) a negligible correlation with TS (r=0.08, 95% CI [-0.00 to 0.17]) and no correlation with CPM (r=-0.04, 95% CI [-0.15 to 0.07]). The PSQ was, however, strongly correlated with Phasic heat (r=0.64, 95% CI [0.54-0.73]) and tonic cold (r=0.64, 95% CI [0.51-0.77]) and moderately correlated with pin prick stimulation (r=0.39, 95% CI [0.38-0.40]). This suggests that the PSQ does assess what it is designed for and can predict how people might respond to painful stimulations.

Comparison of the PSQ and CSI

The correlations between the CSI and depression (Z= 23.10, p<0.001), anxiety (Z= 20.74, p<0.001), pain catastrophising (Z= 6.90, p<0.001) and stress (Z= 7.64, p<0.001), were significantly stronger than their correlations with the PSQ. There was no significant difference between the CSI and PSQ correlations for nociceptive sensory measures; PPT (Z= -1.50, p= 0.066), HPT (Z= 1.08, P= 0.141) and TS (Z= 0.19, P= 0.425). CPM showed weak/no correlations with both the CSI (r=0.10, 95% CI [0.01-0.19]) and PSQ (r=-0.04, 95% CI [-0.15 to 0.07]).

Moderator analyses

For meta-analyses where high heterogeneity was found (i.e., I^2 was above 50%) (Higgins et al., 2003), a moderator analysis was performed to assess whether correlations were influenced by the varied populations in each study. A weight-least squares regression was carried out to assess if the correlations were influenced by: age, sex, type of assessment used (e.g., different variations of depression questionnaires), whether the data were published or retrieved by email, and type of population (chronic pain patients or healthy participants). A weighted least-squares regression analysis was used because this method tends to be the most accurate method for identifying moderator variables (Steel et al., 2002). The correlation between sleep and CSI (our highest score of heterogeneity at 92.8%) was moderated by sex (F=26.22, B=0.964, p=0.036) and publication/retrieval of data (F=27.62, p=0.034). The

retrieved data (weighted mean correlation = 0.24, SD = 0.04) had a substantially lower mean compared to the published data (weighted mean correlation = 0.47, SD = 0.02), suggesting a potential file drawer effect. Correlations between CSI and Anxiety (F=5.59, p=0.032) and Depression (F= 4.45, p=0.053) were moderated by type of population (chronic pain or healthy participants). The correlation between the PSQ and pressure pain threshold (F=4.94, p=0.053) was also moderated by type of population. The PSQ's correlation with CPM was moderated by Age (F= 65.87, B=-0.985, p=0.015). CPM, TS and tonic cold correlations with the PSQ may have also been subject to high heterogeneity (Higgins et al., 2003), due to the small number of studies incorporated in the meta-analysis (von Hippel, 2015). The heterogeneity for CSI with stress, sleep and kinesiophobia may also be inflated due to the small number of studies being included for meta-analysis (von Hippel, 2015).

Healthy Controls vs Pain Patients

There was insufficient data to run meta-analyses to compare healthy controls against chronic pain patients for the CSI. Only two studies involving healthy participants correlated CSI with psychological constructs, and anxiety was the only measure taken by both studies (Midenfjord et al., 2021,Polli et al., 2020) (r=0.43, p<0.01 and r= 0.14, p=0.50 respectively);with the latter study having a small sample size (n=26). The two lowest correlations for anxiety across all studies were for these two with healthy populations. Similarly, Midenfjored et al. (2021) reported a correlation for CSI with Depression (r=0.32, p<0.01), which is considerably lower than the meta-analytic average (r=0.58, 95% CI [0.54-0.62]). This suggests that correlations for the CSI with psychological questionnaires may be stronger in pain patients compared to healthy participants, although due to the low number of studies along with their small sample sizes, this is inconclusive. More studies involving healthy participants are required to confirm this finding. The small sample sizes for healthy controls reporting lower correlations could help account for some of the high heterogeneity in our findings (von Hippel, 2015).

Only three studies correlated the CSI with nociceptive sensory correlates for healthy participants (Polli et al., 2020; Proenca et al., 2021; Shulman et al., 2020). Of these, PPT was the only sensory measure recorded in more than one study (r=-0.33, p=0.09; and r=-0.06, p=0.60, respectively) (Polli et al., 2020; Proenca et al., 2021), with both of these studies having a small sample size (n=28 and n=31, respectively). There was insufficient data to make any clear conclusions about whether healthy participants and pain populations differed in their correlations for CSI and nociceptive sensory measures (QST).

There was sufficient data to run meta-analyses comparing chronic pain patients versus healthy participants for the PSQ's correlations with several of our primary outcomes. The meta-analyses for these comparisons can be seen in Table 3.

Table 3

Comparison of Healthy controls and Chronic Pain Patients (PSQ).

Outcome Measures	Population	Studies	N of Populations	Total N of participants	Weighted mean correlation [95% CI]	Heterogeneity	Strength of Correlation
Depression	Chronic pain population	[25,38,44,53,70,70,117,120]	8	1,076	0.12 [0.06-0.18]	χ^2 = 8.21, df = 7 (P = 0.314); I^2 = 14%	Weak
	Healthy Participants	[38,44,53,70,90,113,121,127]	8	809	0.05 [-0.02 to 0.13]	χ^2 = 10.15, df = 7 (P = 0.180); I^2 = 31.8%	No-effect
Anxiety	Chronic pain population	[25,38,45,70,70,117,120]	7	940	0.15 [0.10 – 0.19]	χ^2 = 4.31, df = 6 (P = 0.634); I^2 = 0%	Weak
	Healthy Participants	[38,44,52,70,90,113,121,157]	8	633	0.13 [0.06 – 0.19]	χ^2 = 5.48, df = 7 (P = 0.601); I^2 = 0%	Weak

Pain Catastrophising	Chronic pain population	[9,38,59,69,70]	7	929	0.36 [0.23 – 0.49]	χ^2 = 37.35, df = 6 (P < 0.001); I^2 = 90.7%	Moderate
	Healthy Participants	[11,38,52,53,70,90,113,121,127,157]	10	1097	0.25 [0.19 – 0.31]	χ^2 = 11.57, df = 9 (P = 0.239); I^2 = 27.4%	Weak-Moderate
PPT	Chronic pain population	[25,38,44,69,120,122]	6	688	-0.18 [-0.26 to -0.09]	χ^2 = 8.53, df = 5 (P = 0.129); I^2 = 42%	Weak
	Healthy Participants	[38,44,144]	3	429	-0.07 [-0.10 to -0.03]	χ^2 = 0.44, df = 2 (P = 0.803); I^2 = 0%	None-Weak (negligible)
HPT	Chronic pain population	[25,38,44,70,120,122]	6	688	-0.17 [-0.34 to 0.00]	χ^2 = 33.55, df = 5 (P<0.001); I^2 = 86.7%	Weak
	Healthy Participants	[38,44,90,143]	4	279	-0.08 [-0.22 to 0.05]	χ^2 = 5.41, df = 3 (P = 0.144); I^2 = 44.8%	None-Weak (Negligible)
CPM	Chronic pain population	[69,70,117]	3	428	-0.04 [-0.22 to 0.04]	χ^2 = 7.01, df = 2 (P=0.03); I^2 = 71.5%	No Effect
	Healthy Participants	[70]	1	80	r= -0.04		No-Effect
TS	Chronic pain population	[38,69,70]	3	562	0.07 [0.02 to 0.14]	χ^2 = 1.71, df = 2 (P = 0.42); I^2 = 0%	None-Weak (Negligible)
	Healthy Participants	[38,70]	2	192	0.10 [-0.13 to 0.33]	χ^2 = 5.29, df = 1 (P = 0.022); I^2 = 81.3%	Weak

Overall, correlations between the PSQ and psychological and sensory measures were stronger for chronic pain patients compared to healthy participants, though not always significantly so. The only measure where the healthy participants showed a stronger correlation was TS, however, these

correlations were not significantly different (Z = -0.36, p= 0.360). Pain catastrophising (Z= 2.72, p= 0.003) and PPT (Z= -1.81, p= 0.035) showed significantly stronger correlations for chronic pain patients than healthy controls. Depression (Z= 1.51, P= 0.065), Anxiety (Z= 0.40, p= 0.346), HPT (Z= -1.28, p= 0.100) and CPM (Z= -0.42, p= 0.338) did not show significantly different correlations between chronic pain and healthy subject populations.

In regards to heterogeneity, with the exception of TS (which only had two studies that assessed healthy controls and was therefore vulnerable to high heterogeneity due to a small number of studies being used in the meta-analyses [von Hippel, 2015]), heterogeneity was below the suggested benchmark for substantial heterogeneity in healthy controls (I^2=50%) (Higgins et al., 2003). The overall higher heterogeneity found in the chronic pain group suggests that type of pain may be an important factor that moderates our correlations. To conclude, high heterogeneity in some of our findings appears to be down to different target populations being used across studies with characteristics such as age, sex and type of pain having a moderating influence on correlations.

6.5. Discussion

We found that the CSI was strongly correlated with psychological measures (anxiety, depression, pain catastrophising, stress, sleep, and kinesiophobia). In contrast, it was not or only weakly correlated with QST measures; pain thresholds, TS and CPM were all found to be low in their correlation to the CSI (all r's<0.3). Only the extent of widespread pain as a sensory measure reached a moderate correlation with the CSI, which differs in methodology from the other 'sensory' measures, as it does not involve experimental lab testing of nociception. Compared to the CSI, the PSQ showed significantly lower correlation coefficients with psychological constructs. For their correlations with sensory measures (QST), there was no significant difference between the two questionnaires. The PSQ was, however, associated with measures of pain where participants were asked to rate a set painful stimulus: phasic

heat, tonic cold and pinprick stimulation. Therefore, there is evidence to suggest that PSQ does measure what it was designed for i.e., sensitivity to pain. But there is no evidence to suggest either questionnaire is a useful tool for identifying CS or pain modulatory capacity, based on their correlations with QST.

There is a lack of data that assesses the association between the CSI and human surrogate models of CS (measures specifically designed in an attempt to quantify the 'increased responsiveness of nociceptive neurons in the central nervous system to either normal or subthreshold afferent input,' [Loeser & Treede, 2008]). Quesada et al. (2021) provided a review and practical guide of different models of CS in humans, finding that there were more than a dozen methods used to induce hyperalgesia and allodynia (characteristics of CS), including intradermal or topical capsaicin, low or high-frequency electrical stimulation and thermode induced heat injury. Duration and area of hypersensitivity were subsequently measured to examine the presence of CS (Quesada et al., 2021). We found none of these measures of CS to be assessed alongside the CSI or PSQ in this review. More studies should be conducted to directly examine correlations between the CSI and these measures of CS. While we acknowledge that QST measures are not direct measures of CS, for this review, they were the best measures available for identifying pain facilitatory mechanisms of a 'pro-nociceptive' phenotype that are associated with chronic pain (Yarnitsky et al., 2013), which might suggest the presence of CS (Williams, 2018).

As a result, this review is limited to QST measures (TS, CPM and pain thresholds) as the primary form of physical assessment for CS. QST is a largely standardised method, used to evaluate sensory profiles in response to stimuli, assessing the functional integrity of small and large nerve fibre afferents and central somatosensory pathways (Cruz-Almeida et al., 2014; Kim et al., 2015; Verberne et al., 2013). One of these measures that is considered a particular indication of CS, is TS [Arendt-Nielsen, 2015; Staud et al., 2007). TS assesses the 'wind-up' that occurs from repetitive stimulation of peripheral c-fibres and is thought to reflect summation mechanisms of dorsal horn neurons (Li et al., 1999, Staud et al., 2007). We would therefore expect self-report assessments related to CS (such as CSI) to be strongly correlated with

TS. However, this review has revealed that the CSI and TS show only a very weak correlation *(r=0.09),* which is likely to be of low clinical relevance. The PSQ shows a similarly weak correlation with TS *(r=-0.08)*. Low correlations between CPM and the two questionnaires were found. CPM is said to quantify the efficiency of endogenous inhibition of pain based on the concept of 'pain inhibits pain' (Moont et al., 2010),derived from diffuse noxious inhibitory control in animal studies (Damien et al., 2018; Le Bars et al., 1979; Ohara et al., 2005). There is no evidence to suggest either of these questionnaires could be used to help identify underlying mechanisms of pain facilitation or inhibition in humans.

There is currently no optimal method for measuring CS in humans and most assessments require specialist equipment that would be time-consuming to use in clinical settings. The CSI may have been developed as an easy-to-use tool to help identify CS in clinical populations. However, in developing this self-report questionnaire, the diagnosis of an underlying mechanism (CS), based on our review, may have been overly assumptive.

The CSI is a self-report questionnaire designed to identify patients who have conditions related to CS such as: fibromyalgia, temporomandibular disorder or migraine/tension headaches (Neblett, 2018). The CSI consists of two parts. Part A includes 25 questions related to common CSS symptoms such as: fatigue, depression, poor sleep, lack of concentration and general sensitivity. Part B determines if the patient has been diagnosed with certain CSS disorders or related disorders, such as: chronic fatigue syndrome, migraines, fibromyalgia etc. (Mayer et al., 2012). The CSI has been shown to be a useful and valid measure for screening patients diagnosed with CSS (Neblett er al., 2015). A 2014 study by Neblett et al found the CSI accurately identified 82.8% of participants as having CSS, whereas 54.8% of participants were correctly identified as not having CSS. It appears that the CSI validates a diagnosis of CSS, but the diagnosis of CSS is not scientifically precise itself. Neblett et al (2014) stated that a diagnosis of CSS relied on tender point evaluations being conducted on people suspected of having fibromyalgia and trigger point evaluations for patients suspected of having myofascial pain syndrome. There are

therefore some assumptions made about the presence of CS in these cases to begin with, with tender and trigger point evaluations being used to confirm the presence of CS. These measures would not be sufficient to accurately identify an 'increased responsivity of nociceptive neurons. The CSI asks if the patient has been diagnosed with certain CSS disorders and/or shows associated symptoms, so intercorrelation between the two would be expected to be high. Therefore, although the CSI validates the diagnosis of CSS, we question whether either diagnostic accurately identifies 'an increased responsiveness of nociceptive neurons' (Loeser & Treede, 2008).

The items within the CSI were developed based on a large body of literature that shows associations between somatic sensation and emotional health (Ahles et al., 1991; Kroenke & Mangelsdorff, 1989; Lydiard et al., 1993; Mayer et al., 2012; Sperber & Dekel., 2010). The inventory was proposed to help identify patients with CSS (Neblett et al., 2013). CSS is presented as a family of disorders described as 'medically unexplained' with no clear aetiological cause (Yunus, 2008), including fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, migraine and tension headache and myofacial pain syndrome [Kindler et al., 2011; Phillips & Clauw, 2011; Yunus, 2015; Yunus, 2007). These conditions share a characteristic of common co-morbidities which include depression, anxiety, insomnia, fatigue, difficulty concentrating and trauma (Arnold et al., 2006; Henningsen et al., 2003; Phillips & Clauw., 2011; Spiegel et al., 2015; Yunus, 2015; Yunus, 2007). Thus, unsurprisingly, the CSI has strong corelations with other validated self-report measures of psychological constructs (e.g., anxiety, depression, stress etc.), which is cited as evidence for convergent validity (Neblett, 2018). The development and validation of the CSI is presented in a two-part study that identifies that the CSI has high test-retest reliability, and that fibromyalgia patients scored higher on the CSI than a normative group (Mayer et al., 2012). A systematic review also reported that the CSI generates reliable and valid data to measure the severity of symptoms related to CS (Scerbo et al., 2018). These studies that claim to validate the CSI, however, do not provide direct evidence that the CSI is a measure of amplified

nociceptive response, as its title suggests. A recent review recommends that data using the CSI should be interpreted with caution as so far there is no evidence to suggest that the CSI is a valid indicator of CS (Schutter et al., 2021). The CSI therefore appears to be developed as a tool to help identify symptoms related to CSS. No self-report tool, however, can identify the physiological mechanism of CS. These meta-analyses give evidence supporting that the CSI has strong psychometric properties but, despite its name, does not measure CS (the increased responsiveness of nociceptive neurons).

We included the PSQ in these meta-analyses to determine whether a questionnaire that directly asks people how they would respond to specific painful stimuli in everyday life may be more reflective of central sensitisation (increased responsiveness to stimulation). We found that the questionnaire was not associated with QST measures but one lab (Ruscheweyh et al., 2015; Ruscheweyh et al., 2009; Ruscheweyh et al., 2012) consistently found that the PSQ was associated with pain intensity ratings to a set stimulus e.g., phasic heat, tonic cold and pinprick stimulation. The PSQ was predictive of how people might respond to a painful stimulus or situation but, according to our data, it was not/weakly associated with QST measures. Therefore, there is no evidence to suggest that the PSQ is a good assessment of CS or a 'pro-nociceptive' phenotype.

One study, included in this review, that compared the CSI and PSQ on emotional and nociceptive measures of sensitivity, was conducted on 78 patients with shoulder pain (Coronado et al., 2018). Similar to our findings, the CSI was strongly correlated with depression, anxiety, stress and negative affect and weakly correlated with nociception (pressure pain threshold, heat pain threshold and suprathreshold). They found weaker correlations between the PSQ and psychological measures, but a slightly higher correlation between the PSQ and nociceptive measures, albeit not likely strong enough to be of clinical relevance. They concluded that it is too difficult to isolate mechanisms of pain sensitivity via self-report, a conclusion that our extended review supports.

The CSI has utility within clinics in screening and diagnosis for proposed CSS's (Neblett et al., 2015). What this review suggests, however, is that the link between this diagnosis and CS may require re-consideration. The CSI, or a CSS diagnosis, does not appropriately identify the mechanisms of CS as its title suggests. The definition of CS states an increased responsiveness of nociceptors in the central nervous system to either normal or sub-threshold afferent input (Louw et al., 2017), resulting in hypersensitivity to stimuli (Latremoliere & Woolf, 2009), increased responsiveness to non-noxious stimuli (Loeser & Treede, 2008), increased pain responses evoked by stimuli outside the area of injury, and an expanded receptive field (Dahl & Kehlet, 2006). It appears that there has been a jump in translation from CS identified in pre-clinical studies and the term used in this inventory. The CSI more broadly assesses sensitisation from a psychological/emotional perspective and presumes that the scores in this inventory reflect the mechanism of 'increased responsiveness of nociceptive neurons', identified in pre-clinical animal studies (Latremoliere & Woolf, 2009).

Our findings suggest that the CSI is a useful tool for assessing the overall psychological and emotional sensitivity of a patient, as opposed to identifying any underlying mechanism related to CS. It may be that CS and emotional sensitivity are closely linked (Curatolo et al., 2006; Diatchenko et al., 2006), but the CSI loads almost exclusively on emotional sensitivity, rather than on measures of nociceptive response. It appears that a form of construct drift regarding the definition of CS has occurred across disciplines where patients in clinics have been assumed to be suffering from CS based on their psychological difficulties alongside pain. One possible explanation for this is that when pain is difficult to diagnose in the absence of an identifiable aetiological cause, it becomes tempting for clinicians to propose a mechanism for these 'difficult patients'. It allows the clinician to finally diagnose the patient. From the patient's perspective, a diagnosis offers relief that legitimizes their pain. We question whether they are accurately being diagnosed with CS or whether they have simply been given a new label for 'psychogenic pain'. Being given the label of CS offers a physiological basis to legitimatise a patient's pain

so that patients are not to believe that the pain is all in their head, which a diagnosis of psychogenic pain can often be interpreted as (Covington, 2000). Based on the findings of this review, there is no evidence to suggest it would be appropriate to associate patients who score highly on the CSI with CS (the specific nociceptive mechanism). CS in patients' needs to be more clearly evidenced using methods other than currently available self-report measures. The reason being that two different treatment approaches would be recommended for those with a psychological vulnerability and for people whose nociceptive pathways have been altered.

Seemingly, CS has undergone a transition in its meaning with overall sensitivity to: sounds, light, touch, odours, and emotions, along with cognitive deficits such as poor concentration and poor short-term memory being incorporated into this definition (Curatolo et al., 2006; Phillips & Clauw, 2011; Yunus, 2007). These may all occur due to a process of 'wind-up' regulating the central nervous system into a persistent state of high reactivity. However, there is no evidence to suggest that these forms of sensitivity are due to increased responsiveness of nociceptors in the central nervous system to either normal or sub-threshold afferent input (CS). The term CSS, when diagnosed via the CSI, likely refers not to CS definitively, but to an overall sensitivity or hypervigilant state which is associated with pain. This hypervigilant state seemingly has no identifiable aetiological cause and has been associated with CS, perhaps in part due to the CSI being used as a diagnostic tool.

One interesting observation and possible limitation is the lack of data that assesses the CSI with electrical and thermal stimuli. Similarly, few studies explore the relationship between CSI and psychological or nociceptive sensitivity in healthy participants. This suggests that the questionnaire is largely used in clinical populations with only certain mechanical instruments available to assess CS. More research is required in laboratory settings that can further assess the association between the CSI and CS. As aforementioned data on nociceptive measures was also restricted to QST, with to our knowledge, no studies assessing the CSI/PSQ against measured areas of allodynia/hyperalgesia. Future research

should include the CSI with human surrogate models of CS using thermal, electrical and capsaicin models that induce measurable areas of hyperalgesia/allodynia (Quesada et al., 2021), and the assessment of both healthy participants and pain patients. There is clearly a need for more data to assess the relevance of the CSI related to CS and on what basis of research the questionnaire was formulated. If the CSI was a good tool for identifying CS, we would expect high scores on the CSI to be reflected in neuropathic pain patients who have clinical signs of CS. Strikingly, however, we found that neuropathic pain patients are typically excluded from studies incorporating the CSI.

Another limitation is comparing correlations of nociceptive sensitivity in laboratory settings to self-report questionnaires. It is likely that any negative bias or social desirability bias introduced when completing one questionnaire is likely to be replicated in another by the same individual. For instance, biases associated with depression driven by an exaggerated negative view of themselves and their level of function (Geisser et al., 2000) will be reported across questionnaires which include items to capture a self-view construct. On the other hand, respondents may not be able to assess themselves accurately with regards to the PSQ - where they make a judgement of how they might respond in specific painful situations. Some respondents may give a more self-desirable answer, or are unable to portray themselves accurately due to restrictive rating scales. These biases and inaccuracies in self-report may skew data particularly when we are comparing self-report answers to complex peripheral CNS processes such as TS and CPM carried out in laboratory settings. Other limitations include only selecting English language empirical publications, which may have meant that several otherwise valid studies were not included in the meta-analyses. We also found weaker correlations between sleep and CSI in retrieved data compared to data that were published, which had a significant moderating influence on the meta-analytic correlations. As 54 out of 74 authors who were contacted for data did not respond, there is a considerable possibility of reporting bias whereby small/non-significant correlations between these factors may not have been reported

To conclude, it is too difficult to isolate mechanisms of CS via self-report instruments currently available (The CSI or PSQ). The CSI appears to identify people with a psychological vulnerability that is associated with pain, rather than CS itself. It may be valuable in identifying a hypervigilant state that is common in many chronic pain patients. On its own, however, we question its utility as a tool for identifying CS, as defined by an "increased responsiveness of nociceptive neurons" (Loeser & Treede, 2008, p.476). More research is required to develop an optimal method for identifying CS in humans, with these models being used to assess the construct validity of the CSI as an accurate indicator of CS. The PSQ does appear to correlate with experimental measures of pain sensitivity, not QST, albeit these measures are conducted by one particular lab group (Ruscheweyh et al., 2015; Ruscheweyh et al., 2009; Ruscheweyh et al., 2012). More studies assessing the validity of the PSQ with experimental measures of nociception should be conducted by different lab groups. Overall, there is no evidence to suggest either self-report questionnaire is suitable for assessing CS in humans or identifying a 'pro-nociceptive' phenotype, based on QST measures.

Other

The review protocol has been previously published (Adams et al., 2021) and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=208731) prepared in accordance with recommendations specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Page et al., 2020).

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6.7. Appendices

Central Sensitization Inventory: Part A

Name:_____ Date: _____

Please circle the best response to the right of each statement.

1	I feel tired and unrefreshed when I wake from sleeping.	Never	Rarely	Sometimes	Often	Always
2	My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
3	I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
4	I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
5	I have problems with diarrhea and/or constipation.	Never	Rarely	Sometimes	Often	Always
6	I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
7	I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
8	I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
9	I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
10	I have headaches.	Never	Rarely	Sometimes	Often	Always
11	I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Sometimes	Often	Always
12	I do not sleep well.	Never	Rarely	Sometimes	Often	Always
13	I have difficulty concentrating.	Never	Rarely	Sometimes	Often	Always
14	I have skin problems such as dryness, itchiness, or rashes.	Never	Rarely	Sometimes	Often	Always
15	Stress makes my physical symptoms get worse.	Never	Rarely	Sometimes	Often	Always
16	I feel sad or depressed.	Never	Rarely	Sometimes	Often	Always
17	I have low energy.	Never	Rarely	Sometimes	Often	Always
18	I have muscle tension in my neck and shoulders.	Never	Rarely	Sometimes	Often	Always
19	I have pain in my jaw.	Never	Rarely	Sometimes	Often	Always
20	Certain smells, such as perfumes, make me feel dizzy andnauseated.	Never	Rarely	Sometimes	Often	Always
21	I have to urinate frequently.	Never	Rarely	Sometimes	Often	Always
22	My legs feel uncomfortable and restless when I am trying to goto sleep at night.	Never	Rarely	Sometimes	Often	Always
23	I have difficulty remembering things.	Never	Rarely	Sometimes	Often	Always
24	I suffered trauma as a child.	Never	Rarely	Sometimes	Often	Always
25	I have pain in my pelvic area.	Never	Rarely	Sometimes	Often	Always
					Total=	

Central Sensitization Inventory: Part B

Name: _____

Date: _____

Have you been diagnosed by a doctor with any of the following disorders?

Please check the box to the right for each diagnosis and write the year of the diagnosis.

		NO	YES	Year Diagnosed
1	Restless Leg Syndrome			
2	Chronic Fatigue Syndrome			
3	Fibromyalgia			
4	Temporomandibular Joint Disorder (TMJ)			
5	Migraine or tension headaches			
6	Irritable Bowel Syndrome			
7	Multiple Chemical Sensitivities			
8	Neck Injury (including whiplash)			
9	Anxiety or Panic Attacks			
10	Depression			

Pain Sensitivity Questionnaire

This questionnaire contains a series of questions in which you should imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be. Let 0 stand for no pain; 1 is an only just noticeable pain and 10 the most severe pain that you can imagine or consider possible. Please mark the scale with a cross on the number that is most true for you. Keep in mind that there are no "right" or "wrong" answers; only your personal assessment of the situation counts. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness.

1. Imagine you bump your shin badly on a hard edge, for example, on the edge of a glass coffee table. How painful would that be for you?

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

2. Imagine you bum your tongue on a very hot drink.

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

3. Imagine your muscles are slightly sore as the result of physical activity.

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

4. Imagine you trap your finger in a drawer.

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

5. Imagine you take a shower with lukewarm water.

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

6. Imagine you have mild sunburn on your shoulders.

0 = not at all painful 10 = most severe pain imaginable

0 1 2 3 4 5 6 7 8 9 10

7. Imagine you grazed your knee falling off your bicycle.

0 = not at all painful 10 = most severe pain imaginable

0—— 1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10

8. Imagine you accidentally bite your tongue or cheek badly while eating.

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

0 = not at all painful 10 = most severe pain imaginable

9. Imagine walking across a cool tiled floor with bare feet.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

10. Imagine you have a minor cut on your finger and inadvertently get lemon juice in the wound.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

11. Imagine you prick your fingertip on the thorn of a rose.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

12. Imagine you stick your bare hands in the snow for a couple of minutes or bring your hands in contact with snow for some time, for example, while making snowballs.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

13. Imagine you shake hands with someone who has a normal grip.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

14. Imagine you shake hands with someone who has a very strong grip.

0 = not at all painful 10 = most severe pain imaginable

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

15. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles.

0 = not at all painful 10 = most severe pain imaginable

0 1 2 3 4 5 6 7 8 9 10

16. Imagine you are wearing sandals and someone with heavy boots steps on your foot.

0 = not at all painful 10 = most severe pain imaginable

0 1 2 3 4 5 6 7 8 9 10

17. Imagine you bump your elbow on the edge of a table (”funny bone”). **0 = not at all painful 10 = most severe pain imaginable**

0 1 2 3 4 5 6 7 8 9 10

7. General Discussion:

7.1. Overview:

The overall aim of this thesis was to investigate some of the individual differences that might be involved in the development and maintenance of persistent pain. As reviewed in section 2.2 ('Formulation of Pain'), mechanisms by which pain can be modulated have received a lot of interest over the past few decades. Psychological factors that can cause a predisposition to pain vulnerability and pain facilitation, remain an area of great importance. The primary focus of this thesis was to assess some of the biopsychosocial factors associated with pain facilitation and chronic pain. Factors included 1) which psychosocial stressors in the workplace (where we spend the majority of our time) are associated with chronic pain, 2) whether modulatory mechanisms (characteristic of a 'pro-nociceptive' phenotype) were associated with how we attend to pain, 3) whether psychological factors such as how we regulate attention (mindfulness) are associated with pain facilitation/sensitisation, and 4) how psychological factors are used to help identify complex chronic pain conditions, and whether this is appropriate. In this chapter, I will briefly review the findings of three empirical studies and one systematic review, evaluate their contribution to the wider literature, explore clinical considerations and future directions, and discuss the strengths and limitations of each study. I will also present a section on the overall limitations and future recommendations of the thesis.

7.2 Review of Studies:

7.2.1 Study One: Attending Work with Chronic Pain is Associated with Higher Levels of Psychosocial Stress

Study One comprised a secondary analysis that aimed to assess some of the psychosocial issues people with chronic pain face in the workplace. The findings revealed that people who suffered from persistent pain perceived poorer relationships with their managers, felt they were discriminated

against, felt they were more likely to be subjected to threats and abuse, and were much less likely to feel rewarded for their efforts. Surprisingly, the pain population also felt they were more competent and had greater job security in the workplace. A possible explanation for these positive impacts of pain (particularly job security), may be a reflection of their understanding of workplace regulations; owing to individual research on employee rights relating to pain and disability. On the other hand, people with pain may report higher job competency as they feel they must work harder to combat the discrimination they undergo in the workplace.

Overall, the issues associated with chronic pain appeared to be social in nature. Chronic pain was associated with poor workplace relations (less supervisor support, more threats and discrimination), and feelings of underappreciation. We discussed in section 2.1.4., how feelings of loneliness, isolation and social rejection can exacerbate pain (Eisenberger et al., 2003; Harris, 2014; Jaremka et al., 2013; López-Martínez et al., 2008). While we cannot assume causality in this paper, the findings highlight that chronic pain is associated with poor relationships. This is cause for concern as social support has been shown to be a substantial buffer for the negative impact of harmful beliefs about pain, and is associated with better adjustment to chronic pain (Edwards et al., 2016; Sturgeon & Zautra, 2016). Considering the fear-avoidance model of pain; social factors that people with chronic pain face in the workplace, such as: feelings of abuse, discrimination, and poor support - may lead to further avoidance behaviours (i.e., promoting absence from work, isolation, and further disuse and disability).

A vicious cycle of chronic pain occurs, as people who feel isolated may be more sensitive and prone to chronic pain (Wolf & Davis, 2014); given the importance of social support in improving clinical outcomes. The study calls for better workplace schemes to support people with chronic pain. Such schemes should not just target individuals with chronic pain, but should educate the wider workplace on disability bias and discrimination against chronic pain, while encouraging social support. For instance, research shows that individuals who exhibit lower knowledge about chronic

pain also hold more negative attitudes towards people with pain (Odenigbo et al., 2019). The key to reducing discrimination and disability bias in the workplace, therefore, may lie in educating the wider workforce.

Steenstra et al. (2017) conducted a systematic review on prognostic factors for return to work and found that when a workplace offered modified duties or workplace accommodation, it can improve return to work outcomes (Fransen et al., 2002; Steenstra et al., 2017; Turner et al., 2008). The review concludes that physical factors in the workplace are important regarding return to work, but the psychosocial work environment is understudied (Steenstra et al., 2017). The study in this thesis sheds some light on the psychosocial issues of chronic pain faced in the workplace, with implications that people in pain might benefit from a supportive work environment. 'The Healthy Workplace Bill' was introduced in America to reduce: abuse, discrimination and bullying (some of the psychosocial issues identified in this study); encouraging the employer to take responsibility and actively reduce hostility within the workplace (Richardson et al., 2016). Future research should assess the efficacy of healthy workplace campaigns, which hold the employer accountable for an abusive work environment. Such campaigns should focus on improving accommodation for people in pain, promote healthy behaviours and coping strategies, and educating the wider workforce on chronic pain and other health issues. Invoking employer responsibility in these areas could improve return-to-work outcomes, and increase productivity and morale across individuals in the whole workforce.

7.2.2. Study Two: Intrinsic Attention to Pain is Associated with a Pronociceptive Phenotype

With Study Two, we aimed to take a closer look at an individual's ability to endogenously modulate nociceptive input via know pain mechanisms, temporal summation (TS) and conditioned pain modulation (CPM). TS is investigated by comparing a noxious stimulus to a serially presented stimulus of the same strength (Suzan et al., 2015). Typically, increased percept of pain occurs with prolonged exposure in a phenomenon known as 'wind-up'(Latremoliere & Woolf, 2009,). CPM is a psychophysical assessment based on the concept of 'pain inhibits pain' (Moont et al., 2010), derived

from diffuse noxious inhibitory control (DNIC) in animal studies (Le Bars et al., 1979). CPM is associated with endogenous analgesia mechanisms and is said to quantify the efficiency of endogenous inhibition of pain (Damien et al., 2018; Ohara et al., 2005; Yarnitsky et al., 2012). Yarnitsky and colleagues proposed that a pronociceptive phenotype associated with nociceptive facilitation, consisted of enhanced TS, and/or less efficient CPM (Yarnitsky et al., 2013). We were interested in assessing the extent to which intrinsic attention to pain is associated with this 'pro-nociceptive' phenotype i.e., how endogenous ability to modulate pain influences how we attend to pain. We measured pro-nociception by assessing temporal summation ('wind-up') to a constant thermal stimulation over 120s, and a CPM paradigm of a thermal conditioning stimulus applied to the hand inhibiting a thermal test stimulus applied to the leg. IAP was measured by assessing the extent to which participants thoughts were directed towards painful stimulations using a four-point Likert scale. We found that those whose thoughts became fixated on a painful stimulus, were more likely to have this 'pro-nociceptive' phenotype, characteristic of enhanced TS and less efficient CPM. In this study, TS and CPM explained 39% of the variance in intrinsic attention to pain scores, suggesting that endogenous mechanisms play a considerable role in how we attend to pain. Given that evidence has suggested that this pronociceptive phenotype is associated with chronic pain (Rabey et al., 2015; Yarnitsky et al., 2013), future research could assess whether people who have chronic pain are likely to have a high intrinsic attention to pain.

As 61% of the variance in IAP is left unexplained (i.e., not explained by modulatory mechanisms assessed by TS and CPM), there are likely higher-order cognitions which influence how we attend to pain and become fixated on it. In the next paper we look at an affective style of attention regulation to examine how trait mindfulness can influence how we respond and adapt to ongoing pain.

7.2.3. Study Three: Low Trait Mindfulness is Associated with Enhanced Sensitisation to painful Stimulation

In Study Three, we examined how trait mindfulness might influence the extent to which individuals sensitise or habituate to a prolonged and repetitive stimulus over a short time period. We selected trait mindfulness because of its association to pain resilience and attention regulation (Bento et al., 2018; Harrison et al., 2019). Mindfulness-based training can have tremendous benefits for patients suffering from chronic pain (Zeidan et al., 2011; Zeidan & Vago, 2016). Less, however, is known about trait mindfulness and how it might influence adaptation to an ongoing painful stimulus. Our study assessed FFMQ scores (used to measure trait mindfulness), prior to participants receiving a series of 44 painful stimulations, with subjective measurements (0-10 NRS) being take for pain intensity and unpleasantness at four-time intervals. This paradigm was repeated three times to assess for reliability. Subsequently, average scores across the three were carried forward for analysis. The study found that those who scored low on the FFMQ were more likely to sensitise to painful stimulation over a short protocol of repetitive/persistent pain. Conversely, those who scored highly were less likely to sensitise and, in some cases, habituated to the painful stimuli. These findings suggest that an affective style characterised by how we regulate attention can influence the extent to which we are vulnerable or resilient to persistent pain. Such attention regulation may be particularly important at the critical stage of acute to chronic pain transition, as high levels of trait mindfulness appear to increase resilience to pain at an acute stage. Future research should examine whether the FFMQ is a useful tool in identifying people who are susceptible to developing chronic pain or assessing individual differences in coping with pain over a longer period of time.

7.2.4. Study Four: Do "Central Sensitisation" Questionnaires Reflect Measures of Nociceptive Sensitization or Psychological Constructs?

In Study Four we focused on central sensitisation. Central sensitisation can be defined as an increased responsiveness of nociceptors in the central nervous system to either normal or sub-threshold afferent input. Central sensitisation leads to: hypersensitivity to stimuli (Louw et al., 2019), increased responsiveness to non-noxious stimuli (Loeser & Treede, 2008), increased pain response

evoked by stimuli outside the area of injury, and an expanded receptive field (Dahl & Kehlet, 2006). The Central Sensitisation Inventory (CSI) is used to help identify people with central sensitivity syndromes (CSS). Central sensitisation (increased responsiveness of nociceptors) is presumed to be the primary underlying factor in the development and maintenance of chronic pain in patients with CSS. These syndromes have been associated with many psychological factors: stress, anxiety, pain catastrophising, depression, sleep quality and trauma (Adams & Turk, 2015; Bettini, 2016; Campbell et al., 2015; Moeller-Bertram et al., 2014).

Three databases (PubMed, PsycINFO and WebofScience) were searched for CSI and PSQ correlations with nociceptive measures (e.g., Quantitative Sensory Testing, Threshold, Temporal Summation, Conditioned Pain Modulation etc.), and psychological constructs (e.g., depression, anxiety, stress, pain catastrophizing, poor sleep quality and kinesophobia). Using the Hunter-Schmidt method (Schmidt & Hunter, 2015), the extracted correlations were meta-analysed for each construct separately. The meta-analyses demonstrated that the CSI used to identify central sensitisation, more accurately maps on to psychological factors of distress/hypervigilance (e.g., depression, anxiety, stress, etc.), compared to any measurable indicators of increased nociceptive sensitivity (e.g., pain thresholds, temporal summation, conditioned pain modulation, etc.).

While emotional and nociceptive sensitivity are strongly associated (Lumley et al., 2011), we emphasised that one should not be used to interpret the presence of the other, i.e., they should not be evaluated synonymously. The CSI appears to assess psychological constructs under the name of central sensitisation, which by definition, is a purely physical mechanism. A form of construct drift seems to have occurred across disciplines, which the CSI contributes towards. A reason for this construct drift might be that providing a diagnosis of central sensitisation to patients with no clear aetiological cause (but who suffer from emotional distress due to pain), gives patients a potential mechanism which legitimises their pain. Central sensitisation may be a clinically preferred term to

'psychogenic pain', which is a commonly unaccepted term by patients who mistakenly interpret this diagnosis as meaning the pain is all 'in their head' (Covington, 2000).

7.2.5. Summary

These studies provide evidence that there are many psychological, social and behavioural factors associated with pain facilitation and the presence of pain, supporting that a biopsychosocial approach should be considered when trying to understand and manage the complexities of chronic pain.

These studies suggest some of the factors that contribute towards susceptibility to developing and maintaining pain, and help towards building a model for vulnerability. They also give some indication of the areas that people with pain may benefit from targeted intervention. For example, if there is a social element to pain, where individuals with pain perceive negative bias and discrimination in the workplace, they may benefit from workplace interventions that educate the wider workforce on social support. An unsupportive work environment can lead to models of pain formulation such as fear-avoidance, where avoidance behaviours are enhanced by the fear of discrimination and hostility in the workplace.

Similarly, understanding more about the extent to which attention to pain and how people regulate attention to pain, can inform on an individual's natural ability to facilitate or inhibit pain. Future research should assess the malleability of these psychological and social characteristics and explore the extent to which targeting them can help intervention strategies to improve resilience to pain. It is well established that there are many factors that contribute towards the experience of pain. This thesis contributes to the literature by giving a brief depiction of some of the biological, psychological, and social elements of the biopsychosocial model of pain. The relevance and individual contribution of each study to the wider literature is discussed in the next section.

7.3. Contribution to the Literature

This body of literature highlights the role of psychological factors and social context in chronic pain. Study one reveals that people in pain are subjected to discrimination and negative bias in the workplace. The study complements existing literature that health-related stigma affects sustainable employment and well-being at work (van Beukering et al., 2021). Employers and the general workforce (without pain) hold negative attitudes towards people in pain, which decreases the likelihood that these individuals will be supported at work (Biggs et al., 2010; Foitzek et al., 2018; Glozier, 1998; Krupa et al., 2009). This lack of support only serves to enhance the psychosocial stress associated with pain. Studies on social isolation and lack of support show repeated associations with chronic pain and stress (Harris, 2014; López-Martínez et al., 2008; Montoya et al., 2004). Due to stigma, individuals are likely to lose motivation to work and may fear working altogether. This study, for instance, found that people in pain took considerably more days off work than those without. If we consider this in the context of the fear-avoidance model; people who withdraw from work and avoid achieving goals altogether are likely to develop: catastrophic thoughts, fear of returning to work, and avoid pro-active behaviours which can lead to further disuse and disability. This loss of motivation can lead to additional social stress factors such as: low income, anxiety, depression and social isolation; which all enhance the risk of chronicity (Crook et al., 2002; Linton, 2000; Pincus et al., 2002). People in pain who undergo stigma at work are susceptible to a vicious excitatory cycle, where the burden of persistent pain contributes to emotional distress and this stress can make their pain worse.

Across the literature on disability in the workplace, several studies revealed that employers were likely to hold stigmatising attitudes towards their employees; with lack of knowledge of their disabilities being a primary reason for the negative affect on disabled employees (Coffey et al., 2014; Dolce & Bates, 2019; Foitzek et al., 2018; Lindsay et al., 2019). This could be due to lack of knowledge about the condition or about suitable workplace accommodation. An alarming amount of studies portray that employers believe that people with disabilities were incompetent, less productive, and less reliable (Dolce & Bates, 2019; Gladman & Waghorn, 2016; Russinova et al.,

2011; Scheid, 2005; Stergiou-Kita et al., 2016; Thomas et al., 2019). Workers with disabilities are regularly being forced to accept lower wages and experience lack of recognition (Russinova et al., 2011). Poignantly, one study revealed that with appropriate workplace accommodation, there was no difference in functional ability between employees with or without disabilities (Lindsay et al., 2019). This may be particularly pertinent in the case of chronic pain as people with disabilities that are invisible, appear to have more challenges with receiving workplace accommodation, compared to people with visible disabilities (Teindl et al., 2018).

The discriminating beliefs of employers appear to be replicated in co-workers of those people with disabilities. Again, stigmatisation is often related to lack of knowledge (Foitzek et al., 2018), and the belief that those with disabilities are less productive and reliable within the workplace (Oud, 2019; Zhu et al., 2016). Another negative belief that co-workers had was that specialist workplace accommodation was unfair (Krupa et al., 2009; Russinova et al., 2011). Co-workers sometimes refuse to collaborate with people with disabilities or assist them with work (Russinova et al., 2011). This can contribute towards a toxic work environment. In some cases, co-workers may have held those with disabilities to a higher standard, ignoring their limitations, as they felt they had to work harder to prove their competency (Russinova et al., 2011). This may explain why this study found that people in pain perceived themselves to be more competent in their job than those without pain. The presence of a disability, mental condition, or chronic pain appear to have a negative impact on relations in the workplace. Unequal treatment can lead to increased tension, frustration, strained relationships, abuse, and discrimination. This can make it difficult for people with aversive conditions to maintain the motivation required to perform their job (Obara-Gołębiowska, 2016; Teindl et al., 2018, 2018).

Since most of the literature on stigmatisation on health conditions in the workplaces discusses stigma towards disability, mental health, obesity, and contractual diseases such as HIV, Study One adds to the literature on stigmatisation by assessing some of the workplace concerns of people with

chronic pain. The findings of our study suggest that people with chronic pain undergo a similar pattern of workplace discrimination and stigmatisation.

Something must be done to help improve workplace relationships and enhance productivity across the workplace. Hanisch et al. (2016) conducted a systematic review that assessed the effectiveness of anti-stigma campaigns at the workplace. They found tentative evidence that interventions addressing stigmatisation towards people with mental illness can result in greater knowledge and lead to more supportive behaviour from colleagues. A recent systematic review, however, found that there is no conclusive evidence to support any specific return-to-work intervention for workers with chronic pain (Wegrzynek et al., 2020). They found that multi-disciplinary efforts comprising of psychological, physical and workplace elements; were the most effective intervention for people with chronic pain. This finding is supported in a similar systematic review on the effectiveness of workplace interventions in return-to-work for musculoskeletal, pain related and mental health conditions (Cullen et al., 2018). They provided evidence that single domain focused interventions showed mixed results on return-to work outcomes, but multi-modal interventions were effective. Future research needs to explore the extent to which implementing appropriate workplace accommodation and anti-stigma campaigns in a multi-modal approach can positively influence employees' attitudes, knowledge, and supportive behaviour. Campaigns should aim to help people with aversive conditions such as chronic pain, by improving workplace cohesion and thus increasing all-round productivity.

Following a quantitative and qualitative review on work-based return to work interventions (Franche et al., 2005), the Institute for Work and Health posted advice on the Seven '*Principles*' for Successful Return to Work (*Seven "Principles" for Successful Return to Work*, 2014). The principles ensure that intervention programmes do not just target the individual. To get the best out of workplace interventions, they ensure that employers are held responsible, that the wider work force is educated and that no-one is disadvantaged. The review suggests that widespread knowledge of

these principles could inform stakeholders such as management and human resources personnel on the beneficial impact of workplace intervention programmes and effective methods for combatting presenteeism.

If we consider the biopsychosocial model of pain, Study One addresses some of the social factors that contribute towards the pain experience. Study Two of this thesis takes a closer look at some of the biopsychological mechanisms involved in the endogenous modulation of pain and the role these mechanisms play in cognitive engagement towards pain. Although social and psychological factors are displayed as prominent factors that exacerbate the pain experience, I wanted to show that endogenous biological mechanisms are also a key factor in vulnerability to pain.

Study Two found that an individual tendency to attend to pain was associated with sensory/discriminative modulatory mechanisms, assessed by TS and CPM. It is understandable that prolonged nociception and an increasing number of action potentials culminating in the dorsal horn (temporal summation), would be associated with greater attention towards pain. After all, the purpose of nociception is to protect oneself from immediate danger, therefore greater nociception (summation) should lead to heightened attention towards the stimulus. This increasing intensity of pain, or heightened attention, motivates threat avoidance behaviours as quickly as possible.

The cognitive-affective model for the interruptive function of pain considers motivations and the novelty of a stimulus as a modulatory factor for whether pain is perceived as a threat (Eccleston & Crombez, 1999). Motivation may have played a key role in the variance in attention to pain. As if participants were contextually motivated by a current goal (e.g., an imminent assignment deadline), their mind may more easily wander away from pain. Participants who underwent painful stimulation in a laboratory study on pain may have been differentially distracted by motivational goals at the time. Contextually, some participants may have believed that the stimulus could cause damage to their skin, while others may have known that the experiment would not be ethically allowed to do so. Some participants may have been distracted by an imminent deadline or more simply were

wondering what they might cook for dinner, while others were not distracted from the stimulus as it was perceived as more threatening.

The findings of this study showed that the extent to which we attend to pain is significantly influenced by endogenous mechanisms, although 61% of the variance in attention to pain is left unaccounted for. Other than motivational goals, distraction is another cognitive factor that plays a role in the extent to which we attend to pain. Some people are naturally more easily distracted than others (Forster & Lavie, 2016). Distraction reduces sensitivity to pain by introducing stimuli that compete for attentional resources (Fernandez & Turk, 1989). Those that are easily distracted are therefore less likely to fixate on pain. Experimental studies have shown that engagement with a cognitive task can significantly reduce the perceived intensity and unpleasantness of nociceptive stimuli (McCaul & Malott, 1984; Rischer et al., 2020).

Arguably, CPM could inhibit pain simply via the conditioning stimulus distracting from the test stimulus. However, research looking into whether CPM is due to cognitive attention manipulation found that there was a significant further pain inhibition when CPM and distraction were combined, compared to CPM alone (Moont et al., 2010). This suggests that CPM and distraction are two distinct mechanisms that can inhibit pain. Additionally, several studies have found that distraction inhibits pain more effectively in males (Keogh & Eccleston, 2006; Quiton & Greenspan, 2007; Unrod et al., 2004; Weisenberg et al., 1995), suggesting differential underlying mechanisms for pain inhibition across sexes. These studies support that attention to pain is a complex phenomenon that reflects the engagement of multiple systems.

Attention to pain may also require evaluative cognitions such as decision making, assessment of risk/reward versus pain, or punishment avoidance. These cognitions typically involve the amygdala and prefrontal cortex (Anticevic et al., 2010; Gupta et al., 2011), and two higher centres in the brain found to predict individual differences in CPM efficiency (Bogdanov et al., 2015). These findings suggest that there is a neural component to CPM that can influence modulatory efficiency.

Furthermore, the amygdala and prefrontal cortex are highly interconnected with the periaqueductal gray (PAG); an area of the brain which is rich in opioids and plays a large role in descending pain inhibition (Ossipov et al., 2014).

A recent study found that high resting connectivity between the PAG and cortical pain processing regions were correlated with greater CPM efficacy (Harper et al, 2018). Intrinsic attention to pain has also been associated with higher structural and dynamic resting state connectivity between the PAG and default mode network, representing a tendency towards disengaging from pain (Kucyi et al., 2013). These neural inferences suggest that attention to pain may be linked to modulatory efficiency, via activity in the PAG and higher centres in the brain. However, it may be presumptuous to assume such neural inferences from the behavioural data presented in this study. The data simply tells us that modulatory spinal mechanisms can account for almost a third of the variance in attention to pain. Further research looking into the neural components of attention to pain may help us to address the remaining variance.

One maladaptive cognition where people struggle to disengage from pain, is pain catastrophising (Crombez et al., 1998; Quartana et al., 2009; Van Damme et al., 2004). Catastrophising has been found to moderate the association between CPM and pain ratings (Goodin et al., 2009), as well as been associated with enhanced TS (Carriere et al., 2019; Edwards et al., 2006; Rhudy et al., 2011). The degree of individual differences in pain catastrophising and its impact on modulatory processes, pain thresholds and chronicity, give a clear indication of the role cognitions play in how we respond to pain and how attention to pain is maintained, enhanced or dissipated (Quartane et al, 2009; Leung, 2012).

In relation to the fear-avoidance model of pain, the extent to which people attend to pain should be related to the extent to which pain is perceived as a threat. Some individuals may be more vigilant to possible signals of pain or injury. The findings of this study (Study Two) suggest that modulatory supraspinal mechanisms have a strong relevance for vigilance to a noxious stimulus. Maladaptive

modulatory mechanisms may therefore contribute to hypervigilance and enhanced perception of threat. Yet, individuals who attend to pain in laboratory settings may just have greater survival function. To speculate that cognitive factors such as catastrophising and fear come into play in a laboratory assessment which briefly assesses attention towards a painful stimulus, may be over generalised. The wider literature, however, suggests that multiple cognitive systems are involved in pain engagement.

One model that may be relevant in the extent to which people attend to pain during a brief protocol is the acceptance and commitment model (Hughes et al., 2017). Psychological flexibility, avoiding attempts to control pain, and focusing on things that can be controlled such as valued activities, pursuing important life goals, and embracing the surrounding environment, likely reduces attentive engagement with pain. A form of psychological state that could influence how individuals regulate their attention and embrace an attitude of acceptance, is through mindfulness techniques. Mindfulness is a cognitive state or trait that encourages attention to the present moment in an accepting manner (Bishop et al., 2004). It requires individuals to enhance their attentional focus on current surroundings, while regulating their emotional response. Attention distorting cognitions such as pain catastrophising can be successfully treated through psychotherapeutic interventions such as mindfulness based training and CBT (Majeed et al., 2018; Prins et al., 2014; Schütze et al., 2010, 2018).

We found that a 'pro-nociceptive' phenotype, associated to poor clinical outcomes and chronic pain, may be influenced by the extent to which one attends to pain. This led on to a follow-up study where we were interested in whether the ability to regulate attention would have an impact on sensitisation and vulnerability to pain. We therefore examined how mindfulness, proposed as a beneficial disposition for regulating attention (Bishop et al., 2004), could regulate the perceived salience and unpleasantness of pain over a brief protocol.

The findings showed that characteristics of trait mindfulness, assessed via the FFMQ, were associated with greater resilience to pain within a brief protocol. People who scored lower on the FFMQ were susceptible to pain sensitisation over time. Existing literature on the mindfulness questionnaires and pain response have revealed that high scores of mindfulness are associated with higher pain thresholds and lower levels of pain catastrophising (Bento et al., 2018; Harrison et al., 2019; Prins et al., 2014). This study adds to the literature by providing one of likely multiple coping strategies for how individuals might adapt to ongoing pain, during a brief protocol. The study suggests that people who are naturally more mindful have coping mechanisms that might be more effective during the early stages of pain onset. Whether this translates to more resilience to developing chronic pain is unknown. Chronic pain, as we have discussed, involves extensive formulation which usually involves a complex myriad of biological, social, and psychological factors. The stress and disability associated with chronic pain is far removed from laboratory experiments using a thermal stimulus in controlled settings. Though, the study does provide an interesting finding which requires follow up. Future research should assess whether the FFMQ is predictive of future chronic pain in longitudinal studies, and should be assessed prior to invasive surgery, in order to assess for prevalence of chronic post-surgical pain development. One study that does examine this found the FFMQ was effective in predicting post-operative pain in gynaecologic oncology patients, undergoing minimally invasive hysterectomy (Weston et al., 2020). More studies should be carried out to validate this finding.

The facets of mindfulness that were associated with sensitisation/resilience to pain were non-judgemental inner experience and non-reactivity. These two facets most strongly align with acceptance compared to the others. Non-judgemental inner experience includes questions such as: "*I criticise myself for having irrational or inappropriate emotions*" and "*I believe some of my thoughts are abnormal or bad and I should not think that way*", while non-reactivity includes questions such as: "*I perceive my feelings and emotions without having to react to them*" and "*when I have distressing thoughts or images, I am able just to notice them without reacting*" (Five Factor

Mindfulness Questionnaire, 2014). The other items are more related to noticing body sensations and surroundings (Observing), the ability to express one's feelings and find the right words (describing) and one's general ability to maintain focus or get distracted (Act with awareness). It therefore seems that people who are more accepting of themselves and have the ability to block out negative thoughts, also seem to be more resilient to pain. This may be because they have an active mechanism of acceptance that allows them not to become negatively fixated on pain or catastrophise. Possibly, they accept the pain in laboratory settings and do not see it so much as a threat, just as they do not see 'irrational or inappropriate thoughts or emotions' as a threat. This feeds into the fear-avoidance/cognitive-affective models of pain (Eccleston & Crombez, 1999; Vlaeyen et al., 2016), as those who are more mindful appear to be more accepting of external and noxious stimuli, and more capable of internally reducing the threat value of pain. Thus, they are less likely to fear pain, catastrophise, or engage in avoidance behaviours that lead to hypervigilance, disuse, and disability. The study suggests that people who scored low on the FFMQ became more hypervigilant to pain over time. People who score high in mindfulness are more accepting of the painful stimuli and may therefore be more likely to engage in confrontational behaviours that promote recovery.

There is a body of literature that support this mechanism of acceptance in highly mindful people. For instance, research has found questionnaires assessing mindfulness and acceptance to be highly correlated (de Boer et al., 2014; Y. Li et al., 2021; McCracken & Zhao-O'Brien, 2010). Also, Bishop et al.'s (2004) proposition of the operational definition of mindfulness conceptualises mindfulness as a non-judgmental, present-centred awareness in which thoughts, feelings and sensations that present themselves in the attentive field become acknowledged and accepted (Bishop et al., 2004). Research on mindfulness meditation suggests practitioners are able to cultivate an attitude of acceptance and reduced anticipation towards impending stimuli (Brown & Jones, 2010; Kabat-Zinn et al., 1985; Reiner et al., 2016; Zeidan & Vago, 2016).

Open monitoring meditation is a form of mindfulness that works by regulating negative affect through a mechanism of non-judgmental, non-reactive awareness of sensory experience and been associated with significant reductions in pain unpleasantness for practitioners (Lutz et al., 2013; Perlman et al., 2010). The benefits of open monitoring meditation further suggest the role of the two facets, 'non-judgmental inner experience' and 'non-reactivity', as important characteristics which can influence coping mechanisms and pain resilience. Meditators who regularly practiced open monitoring meditation had reduced anticipatory activation in the anterior insula, with baseline activation being correlated with meditator experience (Lutz et al., 2013). These neural findings support other studies which found that reducing expectations, and accepting impending pain, is a primary mechanisms by which mindfulness is able to reduce pain (Brown & Jones, 2010; Harrison et al., 2019; Lutz et al., 2013; Perlman et al., 2010)

Although this study does not suggest that people who score high on mindfulness questionnaires are less likely to develop chronic pain, it does suggest that they have a similar mechanism of acceptance that experienced practitioners are able to cultivate. One study that supports similarities between trait and trained mindfulness showed that trajectories of mindfulness acquired through meditation, can predict changes in trait mindfulness (Kiken et al., 2015). Similarly, neural activations for people who scored highly on the FFMQ (Harrison et al., 2019), have been found with experienced practitioners (Brefczynski-Lewis et al., 2007; Brewer et al., 2011; Farb et al., 2007; Taylor et al., 2013). This is important as mindfulness meditation techniques have repeatedly been found to significantly reduce pain in experimental and clinical settings (Cherkin et al., 2016; Kabat-Zinn, 1982; Morone et al., 2016; Reiner et al., 2016). This study, therefore, may contribute to the literature on risk/resilience factors for chronic pain by identifying a characteristic which can be easily assessed, and suggests vulnerability to pain sensitisation. Furthermore, the study posits a desirable characteristic which could enable people to become more resilient and accepting of pain when it occurs. In other words, if patients are able to adopt a more accepting view of themselves and their surroundings may be less likely to sensitise to pain over time. To support this hypothesis, future

research should assess whether training in non-judgemental inner experience and non-reactivity, reduces sensitisation to pain over time, in healthy subjects. Similar studies involving clinical populations are also required to assess the generalisability of these findings for clinical application.

These findings are in line with contemporary models of pain, particularly the acceptance and commitment model, as the two facets of the FFMQ that were related to self-acceptance were associated with resilience to pain. Furthermore, the functional premise of mindfulness-based training is to cultivate an accepting attitude towards external stimuli (Brown & Jones, 2010). Individuals who are highly mindful are likely to be more accepting of the negative thoughts and threats that occur around them. Support for a mindfulness-acceptance-commitment-based approach stems from the study of athletic performance. The approach does not focus on controlling, eliminating, or suppressing internal states of negative thoughts and emotions. Instead, facilitation of positive behavioural outcomes is enhanced through targeting the development of mindful acceptance of internal experiences, along with clarification of motivational goals. The technique has been successful in improving athletic performance, as well as decreasing experiential avoidance behaviours, and sports anxiety (Dehghani et al., 2018). The findings of the studies in this thesis and the wider literature gives supporting evidence for the acceptance and commitment model. People who approach aversive situations in an accepting manner appear to have better coping mechanisms for pain (Esteve et al., 2007; McCracken & Vowles, 2006; McCracken & Zhao-O'Brien, 2010). Knowledge of acceptance-related processes should expand the range of psychological treatment methods, improve coping skills, and ultimately enhance resilience to pain.

This thesis also takes a deeper look into how prominent psychological factors have now become in the identification and diagnosis of chronic pain conditions which are difficult to explain. Psychological factors have become so intertwined with complicated pain disorders that it appears they are being used as markers to identify complex pain mechanisms. The final study in this thesis gives an example of how this may have occurred and discusses whether it is appropriate.

Central sensitisation has been strongly associated with many chronic pain conditions and is thought to be a key maintenance factor in chronic pain. It is defined as an "*increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input*" (Loeser & Treede, 2008, p. 476). Central sensitisation has been proven in animal studies which are able to assess the increasing excitability of neurons in the spinal cord (Woolf, 1983), by assessing changes in electrophysiological recordings (Arendt-Nielsen et al., 2018; Hunt et al., 2018). These assessments, however, cannot be performed in humans (Schuttert et al., 2021). The principles found in animal studies have to some degree been extrapolated to humans, in order to help explain chronic pain disorders without any clear aetiological explanation (Arendt-Nielsen et al., 2018).

Neblett et al. (2013) attempted to build an inventory that could be used to identify patients with central sensitivity syndromes (CSS). The inventory was built on the basis of a family of disorders with no identifiable aetiological cause often described as, 'medically unexplained' (Neblett, 2018; Neblett et al., 2013; Yunus, 2008). Proposed CSS conditions include: fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, migraine and tension headache, and myofacial pain syndrome (Kindler et al., 2011; Phillips & Clauw, 2011; Yunus, 2007, 2015). The conditions hold a familiar characteristic of hypersensitivity to stimuli. Other types of disorders, of which pain is not a primary component, have been added to the CSS family. These include: restless leg syndrome, post-traumatic stress disorder, and multiple chemical sensitivity (Phillips & Clauw, 2011; Yunus, 2007). All these disorders have a large amount of co-morbidity with psychiatric disorders including: depression, anxiety, insomnia, fatigue, difficulty concentrating, trauma etc. (Arnold et al., 2006; Henningsen et al., 2003; Phillips & Clauw, 2011; Spiegel et al., 2015; Yunus, 2007, 2015). It was within this framework that the CSI was developed.

The CSI is therefore designed to identify co-morbidities associated with proposed CSS, without necessarily assessing an increased responsiveness of nociceptive neurons. It is arguably largely a measure of emotional/psychological sensitivity, that is often found in 'medically unexplained'

chronic conditions. These psychological disorders can, however, be present without pain. It is, therefore, possibly an inadequate measure to quantify CS or indicate its presence in pain patients. Quantitative sensory testing has been suggested as a proxy for measuring central sensitisation in humans (Harte et al., 2018). These tests can be used assess for altered pain processing. Assessments include threshold tests which may indicate allodynia or hyperalgesia, conditioned pain modulation which quantifies impaired inhibition of pain, and temporal summation which assesses ascending facilitation of pain. This thesis evaluated the CSI correlations with QST measures and found that the CSI was not a good indicator of altered pain processing.

A recent review affirms that a gold-standard procedure for assessing central sensitisation in humans is still yet to be found (Schuttert et al., 2021). In the review, a variety of definitions used for central sensitisation with ambiguous terminology is identified across studies. For instance, a new definition for central sensitisation was proposed in 2019 as the "*hyperexcitability of the central nervous system*" (den Boer et al., 2019, p.1). This definition assumes that hyperexcitability of nociceptive neurons is predominantly altered by central, and not peripheral systems. This definition undermines the research and clinical evidence; that altered sensation can be caused peripherally (Roth et al., 2021). Schuttert et al. (2021) conclude in their review that a unified definition for central sensitisation has not been used across human studies.

The findings of the study in this thesis provide supporting evidence that there is no gold standard measure of central sensitisation in humans and precludes towards this notion of a construct drift, where multiple definitions are being used for central sensitisation in humans. The findings suggest that the self-report questionnaire that was formulated to help identify central sensitisation in humans (the CSI) is more relatable to den Boer's et al. (2019) definition of "*hyperexcitability of the central nervous system*" (den Boer et al., 2019, p.1). This would explain why psychological constructs such as depression, anxiety and stress, which are related to the central nervous system, are so highly correlated with the CSI. As the findings showed weak/no correlations with quantitative sensory

measures, the findings suggest the CSI is not a reliable measure for assessing pain processing mechanisms related to nociceptive sensitivity. The CSI, therefore, does not honour the original definition of central sensitisation – "*the increased responsiveness of nociceptive neurons to their normal or subthreshold input*" (Loeser & Treede, 2008, p.476).

In the Schuttert et al. (2021) review, they state that CSI is often used as a measure for assessing central sensitisation, but data including the CSI should be interpreted with caution as they were unable to identify any scientific evidence for the value of the CSI as an indicator of central sensitisation. The study in this thesis is the first to compile data that compares the CSI to other "human-assumed central sensitisation" measures. Our study suggests that depending on the definition used for central sensitisation, there is insufficient evidence to support the CSI as a valid measure of central sensitisation in humans. Study Four suggests that the CSI may be an appropriate measure for assessing psychological and emotional sensitivity associated with pain, which may align more with the definition of "*hyperexcitability of the central nervous system"* (den Boer et al., 2019, p.1). The theory here being that individuals who are psychologically vulnerable have hyperexcitable central nervous systems, associated with an increased perception that pain or other aversive stimuli is threatening (hypervigilance).

This research calls for unity in the definition of central sensitisation, and the production of a gold-standard for assessing its presence in humans. To develop this gold standard, it would be advisable to first conduct research that specifically demonstrates central sensitisation in humans.

7.4. Contribution of Findings to Models

This body of work supports the use of more contemporary biopsychosocial models in the treatment of pain. Physiological mechanisms, social factors, emotional disposition, and psychology were all observed to play a role in the experience of pain. According to this research, people who are hypervigilant to pain, have an emotional disposition to be less mindful, experience psychological difficulty (e.g., anxiety, depression, stress, etc.), and receive poor social support may be at higher risk

of experiencing persistent pain. These studies support the importance of addressing psychosocial factors in reducing the negative impact of pain, and in line with previous research, suggest that psychosocial factors may be key contributors to the development of chronic pain (Hruschak & Cochran, 2018; Jensen et al., 2011; Kendall, 1999; Linton & Shaw, 2011; Seth & Gray, 2019) .

People who are in pain and don't turn up to work as much may be engaging in fear-avoidance behaviours as they avoid work and believe that co-workers are discriminative and even abusive towards them. High levels of fear-avoidance has been linked to a long term risk of absence from work (Jay et al., 2018), with absence from work likely having a detrimental impact on workplace relations (Sanders, 2004). This work is in line with previous research on the fear avoidance model; that activity avoidance can lead to occupational/social isolation, which can have a further negative impact on physical degeneration, disability and fear (Turk & Wilson, 2010; Zale et al., 2013). An approach of acceptance and commitment (Hughes et al., 2017), would be a healthier approach both in terms of accepting pain and focusing on things that one can control, such as promoting active engagement with healthy coping behaviours.

Attention to pain appears to be largely influenced by endogenous modulatory factors, which expands on the cognitive affective model for the interruptive function of pain (Eccleston & Crombez, 1999). The model posits that pain engagement is determined by the threat value of a stimulus based on various cognitive (e.g., motivation, catastrophising, hypervigilance) and affective factors (e.g., novelty and intensity of a stimulus). This body of work expands on this model by indicating that attention to pain is partly due to ascending and descending mechanisms at the spinal and supraspinal level. Endogenous modulatory mechanisms therefore play a significant role in determining the threat value of a painful stimulus. A 'pro-nociceptive' phenotype being associated with attention to pain is supportive of a diathesis stress-model (Turk, 2002), suggesting that hypervigilance is, in part, due to physiological mechanisms that are innate. These mechanisms, however, can differ in efficiency from person to person and have been linked to the development of

chronic pain (Yarnitsky et al., 2008). We suggest that a large portion of these individual differences in pain facilitation/inhibition are due to emotional disposition and psychological factors such as trait mindfulness, anxiety, depression, stress, etc.

There is an overarching theme of hypervigilance being a prominent factor involved in pain throughout this thesis. This body of work supports that the experience of pain may be largely due to the perceived threat value of pain proposed by the fear avoidance (Vlaeyen et al., 2016) and cognitive affective models (Eccleston & Crombez, 1999). Firstly, people in pain report more social hardship in the workplace (this could be due to experiences of disability bias from disgruntled co-workers, or could be a mechanism of hypervigilance driven by fear-avoidance thoughts leading to enhanced sensitivity). Secondly, a 'pro-nociceptive' phenotype linked with chronic pain and poor surgical outcomes (Yarnitsky et al., 2008) was associated with greater attention (hypervigilance) towards pain. Thirdly, a lack of mindfulness (ability to regulate attention [Lutz et al., 2008]) was corelated with sensitisation to pain. Finally, constructs associated with hypervigilance, such as anxiety and stress (Kimble et al., 2014), were related to chronic pain measures and the proposed mechanism of central sensitisation. Thus, this thesis supports literature that hypervigilance is a key contributor to the presence of chronic pain (Asmundson et al., 2004; Crombez et al., 1999, 2005; He et al., 2014; Herbert et al., 2014; Vossen et al., 2018).

Overall, this thesis contributes towards the importance of a biopsychosocial approach to understanding the development, maintenance, and treatment of chronic pain. Consistent with previous research (Innes, 2005; Jensen et al., 2011; Martinez-Calderon et al., 2018; Shaw et al., 2013), psychological and social factors are identified as key factors related to the persistent experience of pain.

7.5. Clinical Considerations and Future Directions

Study One portrays some of the social components of pain. Lack of support and social discrimination are associated with chronic pain. The study calls for better workplace adjustment and accountability

to be put on employers to build a safe workplace for people with pain and other health issues. From a clinical standpoint, it promotes extensive screening of lifestyle, workplace and the role of contextual factors in a patient's life, and how social factors might contribute towards the experience of pain. Study Two introduces a biopsychological element as endogenous spinal and supra-spinal mechanisms appear to play a considerable role in attention towards pain. Study Three demonstrates the role of psychology further. Individuals with an affective style of taking a more accepting stance of the world and the difficulties that present themselves may be more resilient to pain. Study Four demonstrates how emotions such as depression, anxiety and stress are regarded as strong co-morbidities of pain mechanisms. Together these papers point towards a biopsychosocial approach for addressing pain.

A clinical consideration is the development of a battery assessment that could help to identify which types of individuals are likely to show pain faciliatory mechanisms, which enhance the likelihood of acute to chronic pain transition. Such a battery should involve measures associated with occupational stress and social context, a 'pro-nociceptive' phenotype (IAP, TS and CPM), trait mindfulness (FFMQ), and other psychological constructs known to be associated with chronic pain such as anxiety, depression, stress and pain catastrophising (Choi et al., 2021; de Heer et al., 2014; Dong et al., 2020; Kadimpati et al., 2015; Sheng et al., 2017). Such work has recently taken place in our lab at Reading University. We are developing a modulatory capacity assessment battery (MCAB) to quantify an individual's ability to process and modulate pain. We believe that a battery assessment may be the key to suggesting high-risk people for developing chronic pain, and identifying areas for targeted interventions. Currently, the MCAB consists of multiple components including an initial sensory assessment, during which multiple psychophysical tests are carried out to create a pain profile. These tests include pain thresholds, TS, CPM, and IAP assessments. Thus, characteristics of a 'pro-nociceptive' phenotype are identified. We then run an imaging session where resting-state data and a detailed T1 anatomical scan is collected, followed by an imaging task where participants receive 44 painful stimuli. During the task, participants register their perceived

level of pain intensity at four-time intervals. This task allows us to see the neurological differences between people who sensitise to a stimulus versus people who habituate to a painful stimulus over time. This rate of sensitisation/habituation was found to be a consistent and reliable individual difference identified in the mindfulness study (Study Three). Psychological questionnaires can be used to identify the personality types associated with pain sensitisation and pain facilitatory mechanisms. These questionnaires include the Becks Depression Inventory (Schotte et al., 1997), the State and Trait Anxiety Inventory (Metzger, 1976), the Perceived Stress Scale (Lee, 2012), the Pittsburgh Sleep Quality Index (Buysse et al., 1989), and the Pain Catastrophising Scale (Sullivan et al., 1996). We also include our questionnaire on trait mindfulness (Five Factor Mindfulness Questionnaire, 2014), found to be associated with pain sensitisation. In addition to these questionnaires, we also include the BEM Sex-Role Inventory (Holt & Ellis, 1998) as the lab have already published on how gender roles may introduce a recruitment bias in experimental studies, with an underrepresentation of males who identify with traditional feminine traits (Mattos Feijó et al., 2018). Other questionnaires include questions on individual coping strategies (Carver et al., 1989), emotion regulation (Gross & John, 2003), general self-efficacy (Schwarzer & Jerusalem, 1995.), personality type (the Big Five Inventory [Alansari, 2016]) and the assessment of motivational systems (BIS/BAS [Carver & White, 1994]). So far, we have begun to examine the clinical utility of the MCAB within an experimental clinical trial investigating a new form of embolization surgery for treating knee osteoarthritis. Additionally, we have begun to examine whether the MCAB can be used predictively regarding psychological interventions in their treatment of persistent pain and secondary hyperalgesia. The goal is to identify a profile for individuals who are likely to sensitise to a stimulus over time as a proxy for acute to chronic pain transition i.e., identifying those who might me vulnerable to developing chronic pain, due to lack of resilience once pain onset occurs. We are also interested in exploring whether we can identify certain behavioural, psychophysical and neurological traits that might suggest a beneficial response to psychological intervention (CBT), using the same battery assessment.

Not only do the studies in this thesis contribute towards the literature on identifying possible risks for developing and maintaining pain, they also provide implications for developing successful intervention. These studies give a small insight into how different components of the biopsychosocial model work together to facilitate the pain experience. Study One introduces psychosocial factors that play a role in the context of pain. Study Two introduces biopsychological mechanisms that play a role in how we attend to pain. Study Three explores affective style by introducing how facets of trait mindfulness are associated with vulnerability/resilience to pain. Study Four introduces the role of central sensitisation and psychological mood states that contribute towards pain. Overall, this thesis displays that there are many factors that can contribute towards pain. Not all of these factors may need to be present for chronic pain to develop, and there are many reasons why some people develop chronic pain and others do not. This thesis, however, suggests some areas that could be targeted during intervention to improve resilience to pain in some individuals. A battery assessment as described above may be useful for tailoring targeted interventions. Understanding areas where patients might be struggling most e.g., social relationships at work, or low levels of mindfulness and self-acceptance, would help health practitioners to identify possible areas of vulnerability. Identifying markers for vulnerability would be useful for encouraging discussions between patients and clinicians, to help tailor treatment programmes on an individual basis.

An intervention model we may consider in light of these studies is the Working Model of Adjustment to Chronic Illness (WMAC) (Moss-Morris, 2013). The WMAC is a biopsychosocial approach to improving adjustment to chronic disease which attempts to address many of the factors that make the pain experience so complex. It incorporates the assessment of personal background (e.g., early life experiences, personality, values, life goals, etc.), social and environmental background (e.g., availability of health care, social support, work-environment, etc.) and illness specific factors (e.g., symptoms, degree of disability, pain related stress, treatment regime and side effects). WMAC also explores the role of key critical events such as the development of initial symptoms and diagnosis,

the perceived threat value of the diagnosis, and how the condition affects behaviours and cognitions related to the self. The model emphasises adjustment to ongoing stressors such as managing social relationships with friends, colleagues, and healthcare professionals, preserving autonomy while acknowledging limits and accepting lifestyle changes, potential disability, and symptoms. The model uses a cognitive behavioural approach to target cognitions, emotions, and behavioural responses to psychosocial and cognitive stressors. The model posits that successful adjustment to the emotional and physical disruption caused by pain/illness will enhance: self-efficacy, improve acceptance, encourage perceived social support, increase engagement in good health behaviours and activity levels, and promote adherence to medical and self-management regimes; resulting in good psychological, physical and social adjustment.

7.6. Strengths and Limitations:

7.6.1. Study One - Attending Work with Chronic Pain is Associated with Higher Levels of Psychosocial Stress:

A limitation for Study One is that the survey was not designed to be fit for purpose. A chronic pain population was deducted using multiple questions within the questionnaire. Some were based on chronicity and others on health symptoms. One question asked whether participants had been diagnosed with a health condition in the last 12 months. Another question was whether respondents had a health condition that lasted six months. The combination of these two questions were used to identify the presence of a chronic health issue. There was another multi-answer questionnaire that required respondents to report symptoms. All reported health symptoms that were not associated with pain were eliminated. It was therefore deducted that those respondents currently had a pain-related health condition that lasted for over six months. A supplementary analysis was run to include the presence of anxiety and chronic fatigue, as these are common co-morbidities of pain. The results were robust to the inclusion or exclusion of these health conditions as co-morbidities. Thus, the findings are likely reflective of a chronic pain population. A cross-sectional or prospective study,

(designed fit for purpose), to examine vocational fulfilment and social interactions of employees with chronic pain versus healthy co-workers', would provide further clarity.

In addition to this, there was no way of identifying graded severity of pain within our sample, which may have been the most important factor in presenteeism and reduced productivity levels (Hartnett et al., 2011). Grading levels of pain would provide another interesting co-variant to explore, particularly as this sample compared a deduced pain sample versus a healthy sample which may have been emphatically healthy, as they reported no health conditions over the past 12 months. We must also consider the possibility that due to the self-reported nature of the questionnaire that there could be some negativity bias where individuals who report health issues may also be more likely to report greater hardship within the workplace.

A strength of this study was, however, that it passed repeated checks for robustness. Including and excluding for anxiety and chronic fatigue as co-morbidities was robust. This was similarly the case for including/excluding the job characteristic most strongly associated with chronic pain as a co-variate (moving heavy loads). The results were found not to be driven by those individuals.

Given the scale of data collection, another strength of the study was that a large sample consisting of multiple ethnicities was used, matching for age and sex across the two groups. To improve the validity of these findings or to check for changes over time, a secondary analysis can be run with a new (equally large) sample every five years, as data is re-collected every five years using a different sample.

7.6.2. Study Two - Intrinsic Attention to Pain is Associated with a Pro-nociceptive Phenotype:

One limitation of this study is that the IAP paradigm is a fairly novel approach that has only been conducted a few times in our lab. A high intraclass correlation across sessions was found in one study (Kucyi et al., 2013) yet more studies using this paradigm across different labs, would be useful to explore further associations and confirm its validity.

CPM is a paradigm used to help identify individuals with reduced pain inhibition and has been associated with outcomes related to surgery (Yarnitsky et al., 2008), and maintenance of chronic pain conditions (Lewis et al., 2012). Nonetheless, criticisms of the reliability and efficacy of this paradigm have begun to emerge over recent years. Interclass correlation coefficients have been reported to greatly fluctuate between 0.10 - 0.76 (Bossmann et al., 2016). If CPM is intended for clinical use, understanding this lack of reliability is essential. One explanation is that CPM test-retest reliability appears to be higher when there is a short time interval between tests (Gehling et al., 2016). Another explanation is that despite its popular use within the literature base, there is not much standardisation in the method used to conduct CPM, with a variety of modalities being used for the test and conditioning stimulus. Studies have been conducted to assess the influence of stimulus type on reliability. The combination of two heat stimuli, which was used in this study, was found to have the lowest test-retest reliability (ICC= 0.34-0.39) (Granovsky et al., 2016; Wilson et al., 2013), despite being the original method adopted as the standardised procedure on which a wealth of research was subsequently conducted (Yarnitsky et al., 2008). To address this, the European Pain Federation (EFIC) held a consensus meeting on CPM to propose a suitable standardised method to promote the reliable application of this tool (Yarnitsky et al., 2015).

In Study Two, using the equipment we had available in the lab, we followed the standardised protocol for CPM initially set by Yarnitsky (Yarnitsky et al., 2008), which was found to be an effective tool for clinical assessment. Additionally, all assessments (IAP, TS and CPM) were carried out within the same 1-hour session, eliminating any chance that time-intervals between tests would become a confounding factor (Gehling et al., 2016).

7.6.3. Study Three - Low Trait Mindfulness is Associated with Enhanced Sensitisation to Nociception:

Study Three examines a paradigm that assesses whether people habituate or sensitise to a stimulus over time, and whether trait mindfulness influences this rate of sensitisation/habituation. In this

study, we assess the course of sensitisation over a 26-minute paradigm. One limitation of the study is that we infer that this course of sensitisation may be representative of how people might respond to chronic painful conditions. This paradigm of 26 minutes of repetitive painful stimulation may not be a true reflection of the lifespan of pain mechanisms during the period of acute to chronic pain transition which takes place over a period of months.

Although we do not know whether this sensitisation over a short period of time translates to adaptation to pain over a longer period (i.e., chronic pain), these findings do shed light on psychological differences in how people inherently cope with persistent pain, at an acute stage. There has also been research to suggest that responses to these shorter paradigms are associated with chronic pain (Vierck et al., 2014). Another study found that coping behaviours that come with a more mindful attitudes are influential in acute to chronic pain transition (Hasenbring et al., 2001). Clinical research that supports this theory found that the FFMQ was effective in predicting post-operative pain in gynaecologic oncology patients undergoing minimally invasive hysterectomy (Weston et al., 2020). Yet more studies assessing the clinical utility of the FFMQ are required to confirm it's utility.

Other limitations include the negative/positive positioning of different facets. All questions related to 'non-judgmental inner experience' and acting with awareness are negatively loaded, whilst questions related to 'non-reactivity' and observing, are positively loaded. Questions related to 'describing' contains a mixture of negative and positively loaded questions. This introduces a possible bias due to leading questions, and lack of consistency in their directionality. Lastly, due to the COVID-19 pandemic, data collection was stopped early resulting in a reduced sample size and underpowered findings.

7.6.4. Study Four - Do "Central Sensitisation" questionnaires Reflect Measures of Nociceptive Sensitisation or Psychological Constructs? a Systematic Review and Meta-Analyses:

Study Four suggests that the CSI is strongly made up of psychological constructs in its assessment of central sensitisation. It appears the majority of studies that use the CSI are conducted on clinical populations. Thus, there has been a limited number of healthy subjects used in studies, and pain evoking stimulation has not been explored in association with CSI regularly enough or across different modalities e.g., thermal, or electrical pain. Interestingly, neuropathic pain patients are typically excluded from experimental pain studies due to abnormal pain reporting. This is particularly alarming given that central sensitisation is a likely mechanism contributing to neuropathic pain (Campbell & Meyer, 2006; Latremoliere & Woolf, 2009).

We compared the CSI with the PSQ for its relative associations with nociceptive and emotional sensitivity. We found that there were mixed reports with the PSQ and its association with nociceptive stimulation. It appears not to be associated with measures of quantitative sensory testing, but is moderately/strongly associated with static pain responses. All of these high correlations are found within the same lab group. More studies assessing the association between PSQ and responses to painful stimulation are required.

For the purposes of this thesis, we are mainly interested in the results of the CSI, with the findings suggesting that there is an overemphasis on psychological vulnerability when assessing for central sensitisation. One limitation may be that for psychological constructs the CSI (a questionnaire) was correlated against other questionnaires (depression, anxiety etc.). This may be a confounding variable in why these correlations were so high compared to the CSI's correlations with experimental pain measures of nociceptive sensitivity. However, if correlations were likely to be high simply due to both measures being questionnaires, we would also expect the correlations between the PSQ and psychological constructs to be higher. One possible confounder between the questionnaires is that the CSI and other measures of emotion (e.g., anxiety, depression, and stress questionnaires) are more prone to negative reporting bias. This may be because imagining how you would react in a painful situation does not reflect current mood; some individuals may even report with a social

desirability bias as reporting high tolerance of pain can be interpreted as a sign of strength. Reporting on the CSI and measures of anxiety, depression, stress etc. are more susceptible to current mood and therefore may be more highly correlated. Other limitations also include that only studies written in English were included, and there was potential for a file-drawer effect with a large number of authors not reporting data and not responding to requests for data. This is particularly noteworthy since the retrieval of data by email correspondence, compared to data being reported in publication, was a moderating variable in one of the meta-analyses.

7.7. Limitations of the Thesis and Future Recommendations

The inferences drawn from Studies Two and Three with respect to interventions should be interpreted with caution. Impactful inferences are made based on findings derived from experimentally induced pain on healthy volunteers. As discussed in the WMAC, there are many social and psychological complexities to the pain experience that are difficult to induce or control for in laboratory settings. Chronic pain often involves a long detrimental process which can involve pain catastrophising, fear avoidance, discrimination, rumination, and social isolation, to name a few. Healthy volunteers in these studies were predominantly young students paid to volunteer, who confirmed that they were not on any pain medication, nor did they have a condition that might interfere with pain perception. Assessing how these individuals attend to pain and cope with pain over a brief paradigm, within a laboratory, may have limited value to informing us on the maladaptive coping mechanisms that occur during adjustment to chronic conditions. Future research could assess whether the correlations found in Studies Two and Three are replicable in clinical settings. Such replications would enhance generalisability, but it should still be noted that laboratory-based acute pain with ethical guidelines is different from chronic debilitating pain. Despite the caution provided with respect to the generalisability of these studies to daily life and chronic pain conditions, it is still important to simulate chronic pain conditions as best we can in laboratory settings with healthy participants. This is because we aspire to identify mechanisms

including those derived from an individual difference approach, which may play a role during acute to chronic pain transition. We are currently at the early stages of trying to build a model that could help inform on risk and appropriate treatment. Though these experiments may not be generalisable to clinical settings, they provide important indicators of individual differences in pain responses at a very early stage of pain onset. Whilst we do not yet know the degree to which these laboratory studies in healthy individuals are applicable, it is still appropriate to understand individual differences of pain responses in healthy individuals. Understanding these individual differences may be informative when pain onset occurs at the pre-chronic stage and adaptation begins to take place.

Another limitation of Studies Two and Three is that testing was halted by the COVID-19 pandemic. Consequently, the sample sizes were smaller than expected, and possibly underpowered in Study Three. Originally, Study Four intended to examine whether an eight-session pain specific CBT programme might accumulatively reduce salience and unpleasantness of pain. Due to the ongoing COVID-19 pandemic, testing on this project was halted and the meta-analyses on the CSI was conducted instead. A brief rationale of how CBT relates to other studies in this thesis is given below.

CBT for pain is a structured psychotherapeutic approach which trains patients to actively control their pain and associated negative affect through cognitive restructuring (Thorn, 2004; Turk et al., 1984). In patients with fibromyalgia, CBT has been found to significantly reduce negatively distorted attention processes such as catastrophising and rumination more effectively than the recommended pharmacological treatment and treatment as usual at a primary care level (Alda et al., 2011). One goal of this intervention is to promote the use of learned coping strategies to gradually trickle into everyday life in a spontaneous manner. This potentially has an implication on the tendency to disengage from pain. Research suggests that CBT for pain led to increased resting connectivity between the PAG and the default mode network (DMN) in individuals with chronic pain (Shpaner et al., 2014). The DMN is a network of interacting brain regions that are active when a person does not focus on a given task or stimulus (other than keeping their eyes open). One study found that DMN

activations were attenuated during disengagement from pain, and fluctuations in functional connectivity between the DMN and PAG were able to track the tendency to disengage from pain (Kucyi et al., 2013). A follow up study showed that CBT could reverse the impact of repeated pain exposure on the brain over time. The authors found enhanced resting functional connectivity between areas of the DMN and prefrontal cortex over time (Kucyi et al., 2016). These neural changes in brain systems relevant to spontaneous pain-attention interactions suggest that CBT could help some individuals to develop strategies to disengage from pain.

Furthermore, Williams et al. (2020) conducted a Cochrane review evaluating the effectiveness of psychological therapies for chronic pain (Williams et al., 2020) . They found that CBT had small positive effects on disability and distress, with evidence of these positive effects being maintained after a 6-month follow up. The review suggests that CBT is a useful approach in the management of chronic pain. However, the small-moderate effect sizes found across studies, do have large standard deviations, suggesting that CBT has had a substantially positive impact on some patients while having little to no impact on others. One of the conclusions of the Cochrane review is that to improve outcomes, future research should explore sources of variation in treatment effects.

Although the overall effect is positive, CBT is a pain management technique that appears to be more effective in some people than others. It would, therefore, be useful to create an assessment battery that could help predict successful response to pain specific CBT. The study originally proposed for this thesis intended to examine which components of CBT are beneficial, and for which individuals do they work for. Two groups were administered different protocols of CBT. One protocol was designed to improve interpersonal relationships and the other was pain specific CBT. Prior to group allocation, participants were subjected to a series of assessments like those outlined in the assessment battery mentioned previously (see section 7.4.). This type of research focusing on the development of a successful battery assessment to identify patients best suited for CBT should help with tailoring treatment strategies for individuals. Ultimately, future research may indicate that such

a battery may lead to improving clinical outcomes whilst also saving health professional's valuable time and resources.

7.8. Conclusion

The work in this thesis aimed to contribute to the available literature on psychological variables involved in vulnerability to pain. Study One demonstrates an association between chronic pain and social conflict within the workplace. Causality cannot be confirmed, but the findings support research that suggests people in chronic pain feel isolated and ostracised by their peers (Dueñas et al., 2016; Wolf & Davis, 2014). These feelings of frustration and isolation are only likely to cause stress and exacerbate any existing health issues (including pain) further (Mushtaq et al., 2014). The findings suggest a strong association between chronic pain and psychosocial hardship.

Study Two takes a more mechanistic approach that demonstrates that endogenous pain faciliatory and inhibitory mechanisms influences our tendency to attend to pain. Individuals with a 'pro-nociceptive' phenotype, characterised by enhanced TS and less efficient CPM, are likely to attend to a stimulus i.e., become fixated on pain. These two mechanisms have been linked to increased sensitivity to pain, less beneficial post-surgical outcomes, and chronic pain. Therefore, the extent to which we attend to pain could be an important factor in individual differences for pain resilience/vulnerability. IAP may be a useful measure to help identify people with a 'pro-nociceptive' phenotype, who might be vulnerable to developing chronic pain (acute to chronic pain transition). It also offers a potentially modifiable characteristic which can influence endogenous pain modulatory mechanisms.

Study Three indicates that the way people think and process the world around them (regulate attention) can influence how they respond to ongoing pain over a short time period (26 minutes). The study reports that trait mindfulness, measured via the FFMQ, has an influence on the rate at which individuals sensitise to a painful stimulus over time. The data suggests that people who score highly on trait mindfulness are less likely to sensitise to a painful stimulus i.e., a psychological

resilience to persistent pain. Those who score low on trait mindfulness are more likely to sensitise to a stimulus over time i.e., they have a vulnerability to persistent pain. Trait mindfulness measured via the FFMQ, therefore, may be a useful tool for helping to identify individuals who might be less resilient to persistent pain onset and more vulnerable to acute to chronic pain transition.

Study Four assesses the utility of two questionnaires, the PSQ and the CSI. We are primarily interested in the CSI as it is proposed as a measure of central sensitisation. In this paper, we discuss how the definition of central sensitisation may have adapted across disciplines. CS was originally proposed as an enhanced nociceptive response at a cellular level (Latremoliere & Woolf, 2009). It appears though that the definition has been moderated in clinics to include sensitivity in a broader sense (i.e., when people are diagnosed with central sensitisation, they are likely to be sensitive to many other senses including emotion, not just nociception). We conducted this study to assess whether a tool used to help identify 'Central Sensitisation' (the CSI) truly reflected nociceptive measures that suggest central sensitisation, or whether the diagnosis was inferred from an amalgamation of psychological constructs associated with central sensitisation and CSS e.g., depression, anxiety, stress etc. We found that the CSI showed strong associations with psychological constructs and no/weak associations with nociceptive measures of altered pain processing (temporal summation, pain thresholds, conditioned pain modulation). The importance of psychological constructs, therefore, seem overemphasised in the identification of central sensitisation within the CSI.

Overall, this thesis discusses the importance of psychology in identifying vulnerability to pain. Psychological and social factors, the way we attend to pain and affective style all appear to play a role in our resilience/vulnerability to pain. Even diagnostic tools such as the CSI have been developed, that heavily rely on psychological constructs (such as anxiety, depression, stress, etc.), to help identify individuals with chronic pain and mechanistic vulnerability (central sensitisation).

Albeit, we do criticise the use of self-report questionnaires being used to measure peripheral CNS processes.

The work detailed in this thesis contributes to building a successful battery assessment that will help to identify healthy people who might be at risk of developing chronic pain. The existence of a predictive assessment could help inform clinicians and patients of the risk of developing chronic pain in the future. The battery assessment will include questionnaires on affective style, psychological constructs, psychophysical mechanisms (IAP, CPM, TS and pain thresholds), as well as exploring neural mechanisms using MRI. We are currently running a large-scale study that uses the multiple components of this proposed battery assessment to identify individuals who may be vulnerable to pain sensitisation over time. We are also interested in whether a similar battery assessment can help identify a phenotype, neural biomarkers, or an 'affective style' that responds successfully to pain specific CBT. This is important because a Cochrane review suggests that CBT appears to be an effective pain management strategy for some people, but not others (Williams et al., 2020). Identifying a profile for people who may be at high risk of developing chronic pain, and respond beneficially to CBT, may substantially refine national health resources and expenditure.

7.9. References:

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