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An Experimental and Clinical Investigation of Psychological and Neural Factors Associated with Individual Differences in Pain and Pain Modulation

Thesis submitted for the degree of Doctor of Philosophy

School of Psychology and Clinical Language Sciences

Centre for Integrative Neuroscience and Neurodynamics

University of Reading

Richard Harrison

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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. In chapter two, data was collected by clinical staff in the obstetrics and gynaecology department at the Royal Berkshire Hospital as part of a clinical evaluation and medical audit. Permission to analyse the data and disseminate it within this thesis and publication was confirmed with the Royal Berkshire Foundation Trust Research & Development team. Further, chapters 3 and 4 contain analysis on the same subset of participants, and data collection for this study was started whilst volunteering in the CINN pain lab, prior to the start of my PhD.

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"Nothing of me is original. I am the combined efforts of everyone I've ever known"

Chuck Palahniuk

The research presented in chapters 2-4 is either published or in preparation for submission.

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Harrison, R., Gandhi, W., Salomons, T.V. (in preparation). Conditioned Pain Modulation (CPM) is associated with heightened connectivity between the periaqueductal grey (PAG) and the descending pain modulation network.

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Abstract

Chronic pain is a multi-faceted condition comprising of pathological, psychological and biological influences. This poses a significant problem to accurate assessment and treatment, with symptomology commonly not matching pathology. It is also unclear why some individuals develop chronic pain, while others appear resilient. Identifying individual differences in pain processing and modulation may be one method to help identify individuals who are susceptible to pain. Consequently, this thesis examined pain, its assessment and management in a clinical setting and individual differences in pain response in a laboratory setting.

Study one evaluated pain ratings from hysteroscopy patients, to understand the prevalence of pain. Clinician estimates of pain were used to examine the accuracy of clinical pain assessment and how this related to pain management. Despite being considered a minimally-painful procedure, we found that patients' pain ratings varied substantially, and were inversely correlated with clinician estimates. Our results indicate that hysteroscopy should not be advertised as a minimally-painful procedure. Advancing pre-surgical assessments to predict individuals at risk of developing pain could have important clinical implications.

Individual differences in pain behaviour and response were examined in studies two and three, using resting-state connectivity in healthy controls. Study 2 investigated dispositional mindfulness, alongside sensory and cognitive pain variables. Trait mindfulness was associated with beneficial pain responses. Mindfulness was also associated with higher functional connectivity to the somatosensory cortex, and lower connectivity to the prefrontal cortex, with a precuneus seed. Our results may suggest that trait mindfulness is associated with increased sensory, present-moment focus, facilitating more effective pain management.

Study 3 investigated Conditioned Pain Modulation (CPM), which quantifies the efficiency of descending modulation circuitry. Our results indicate that high CPM is associated with increased connectivity between pain modulatory and processing regions. Taken together, this research suggests that clinical assessments may benefit from psychometrics quantifying individual differences in their intrinsic ability to manage pain, to detect patients vulnerable to pain.

Chapter 1. Introduction

1.1. Problem of Pain

When investigating pain in the laboratory, it is crucial to understand the scope of this problem in the real-world. This not only emphasises the importance of this research, but also helps inform the direction of our studies based on specific challenges encountered by patients and clinicians alike. Chronic pain is one of the most prevalent and costly problems in the world today. In Europe, it is estimated that 20% of adults are currently living with chronic pain (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006) and the associated societal costs are calculated to be around €200m per annum (Tracey & Bushnell, 2009). However, there is a strong narrative suggesting that chronic pain historically has been seen more as a co-morbid condition, rather than a primary condition in its own right (van Hecke, Torrance, & Smith, 2013). As a result, the impact of chronic pain on the global burden of disease is frequently underestimated (Croft, Blyth, & van der Windt, 2010). A recent influential review by pain research leaders, Irene Tracey & Katherine Bushnell, has also aided in reconceptualising the perspective of pain from a syndrome to a disease, thus specifying our focus and, hopefully, improving the accuracy of future epidemiological investigation (Tracey & Bushnell, 2009). As assessments improve, the underestimation of chronic pain may be corrected. Alongside a persistently increasing global life expectancy and the finding that prevalence of generic (Elliott, Smith, Penny, Smith, & Chambers, 1999) and disabling (Thomas, Mottram, Peat, Wilkie, & Croft, 2007) chronic pain increase with age, this suggests that the burden of chronic pain will continue to grow in stature as a global health burden.

When evaluating the importance of pain research, it is important to not just limit the rationale to purely fiscal, financial & epidemiological domains. There is also a tremendous humanistic burden associated with pain. Anecdotally, the prospect of severe pain as a response to the most mundane tasks is something non-sufferers would struggle to comprehend. Those who have suffered an acute back injury may have experienced first-hand what it's like having to grit their teeth when

contemplating getting out of bed, making a cup of tea or getting up from a chair. However, when this problem is chronic, it can persist, on average, for 10.7 years and can sometimes be life-long (Moulin, Clark, Speechley, & Morley-Forster, 2002), making the burden several magnitudes higher. While the rate of major depression in the general population is estimated to be around 5-8% (Kessler et al., 2003), within chronic pain populations, this number is estimated to be around 30-54% (Banks & Kerns, 1996; Sullivan, Reesor, Mikail, & Fisher, 1992).. Additionally, chronic pain has been associated with psychological distress (Croft et al., 1995), sleep dysfunction (Sayar, Arikan, & Yontem, 2002), anxiety (Asmundson & Katz, 2009; McWilliams, Cox, & Enns, 2003), post-traumatic stress disorder (Demyttenaere et al., 2007) and alcohol/substance abuse (Alford et al., 2016). Most worryingly, suicidal ideation in chronic pain sufferers is 3 times higher on average relative to non-sufferers (McWilliams et al., 2003) and a 10 year longitudinal study found that chronic back pain patients were 10 times more likely to commit suicide than age-, smoking- & social status-controlled non-sufferers (Penttinen, 1995). This is a pertinent indicator for the importance of research on how psychology may influence the experience of pain and how progress in this field could have implications for the existence of pain in the real-world.

While the lived experience of chronic pain is evidently burdensome for patients, this is intensified due to challenges with clinical assessment and treatment. Typically, pain is clinically first assessed by patient self-report. Following the traditional medical model, the clinician will then perform tests to examine for an observable abnormality that could explain the aetiology of the patient-reported pain. This pathological approach will then determine what treatment, if any, the patient is given. Issues with pain assessment and treatment have long been identified within the pain literature, highlighting that in 1997, approximately 50-70m Americans were being undertreated (or not treated at all) for painful conditions (Krames & Olson, 1997). This statistic represented approximately 18-26% of the general population at the time (U.S. Bureau of the Census, 1998) and is a trend that has continued, and potentially even magnified, into the present day. In addition to treatment, challenges are also present within the assessment of the condition. 22% of chronic pain patients feel that their Doctor never asks them about their pain, while 20% believe that their Doctor

does not view their pain as a problem. As such, not only are chronic pain patients impeded by their condition on a daily basis, but challenges in assessment may also act as barriers to accessing treatment. Based upon this premise, examining and evaluating pain assessment is a core feature of this body of work. Understanding clinical processes within assessment, as well as underlying mechanisms in healthy controls, may help us identify areas in which this process can be improved or modified. When outlining the problem of pain for those struggling to live with a diagnosis of chronic pain, statistics only serve to describe part of the picture. Patients with lower back pain (LBP) reported that doctors sometimes present the prospect of a bleak future, which generates anxiety, pessimism and hopelessness in the patient (Corbett, Foster, & Ong, 2007). Analysis also revealed that patients felt their medical professionals viewed them as demanding, difficult & drug-seeking (White & Seibold, 2008). Although the use of analgesia was common, concerns about dependency, side effects and their impact on the patients view of their 'self' was widely reported (Bunzli, Watkins, Smith, Schütze, & O'Sullivan, 2013). With regards to the aetiology of pain, healthcare professionals who infer a psychological cause of pain can elicit negative feelings that the patient's integrity is being questioned (Bunzli et al., 2013). While biomedical explanations provided by clinicians often led to passivity and avoidance of treatment in patients (Walker, Holloway, & Sofaer, 1999), patients who did not receive a suitable aetiological explanation, felt at risk of their condition not being believed (Campbell & Guy, 2007; Holloway, Sofaer, & Walker, 2016) and experienced a deleterious effect upon their belief in the medical model (diagnosis-treatment-cure). This fuelled feelings of anxiety due to an uncertain future, as well as anger and frustration towards the medical professionals involved (Bunzli et al., 2013).

These criticisms of a predominantly pathological approach & concerns of limitations in aetiological explanation are especially relevant when examining chronic pain. When treating pain, it is important to understand the potential disparity between symptomology & pathology. Whilst the 21st century has seen a heightened focus on psychological health within treatment, chronic pain treatment still often gravitates towards a pathological diagnosis (Cohen, 2005; Gatchel, McGeary, McGeary, & Lippe, 2014; Lovell, 1995; Tu, As-Sanie, & Steege, 2005). Although a subset of

patients suffering from an entirely peripherally derived source of pain may benefit from this approach, when evaluating variability in clinical outcomes, we must also evaluate those who do not benefit. For treatment, it has recently been postulated that traditional surgical & pharmacological treatment strategies are insufficient for managing chronic non-cancer pain (Turk, Wilson, & Cahana, 2011) and that psychological, or combinative, therapies are required. Additionally, medical assessment reliant upon pathology alone is also vulnerable to inaccuracy. A review of spinal degeneration imaging found that for asymptomatic 20-year olds (participants not suffering from back pain), 37% have disk degeneration, 30% have disk bulge and 29% have disk protrusion. For 80-year olds, the prevalence for these diagnoses increase to 96%, 84% and 43%, respectively (Brinjikji et al., 2015). While these observations leave medical professionals susceptible to diagnostic type 1 errors (a chronic pain diagnosis, without appropriate symptomology), incongruence between symptoms and pathology can also put them at risk of type 2 errors; failing to diagnose a true patient, due to a lack of observable injury. This is one of the key challenges faced in the treatment of chronic pain and one of the key perspectives in this body of work is to further understand how psychology may influence pain and pain modulation, and to explore the variability in pain across individuals.

Assessment is a key factor for patients gaining access to management for a chronic pain condition. In 2013, IASP submitted a declaration stating that access to pain management is a fundamental human right (Cousins & Lynch, 2011), a call echoed by WHO and the United Nations (Lohman, Schleifer, & Amon, 2010). However, access to pain management is associated with unacceptably long waiting times, which are associated with deterioration of psychological-wellbeing, health-related quality of life, higher severity of pain and greater cost to the health system (Lynch et al., 2007, 2008; McGhie & Grady, 2016; McGhie, 2014). . Collectively, chronic pain is a complex dynamic medical condition, with day-to-day fluctuations in presentation and a wide range of clinical co-morbidities (Pincus, Burton, Vogel, & Field, 2002; Schneider et al., 2012; Thibault, Loisel, Durand, Catchlove, & Sullivan, 2008). It has also been shown that the underlying neuropsychological changes associated with chronic pain states sometimes appear sooner than

chronic pain can be officially diagnosed (<3 months) (Dickenson, Berkman, Arch, & Lieberman, 2013; Rolke et al., 2006; Treede et al., 2015). Given the complications in gaining access to treatment, this means that by the time a patient gains access to treatment, it is conceivable that their chronic pain entangled within a combination of auxiliary physical & psychological issues. A vicious cycle of pain, psychopathology, frustration and hopelessness that would plausibly contribute to the deleterious effect of chronic pain on an individual. This cycle also presents challenges for assessment and relies upon co-ordinated multi-disciplinary treatment across multiple medical domains.

Investigating the influence of individual differences in pain response, could have huge implications for assessment and would inevitably improve our understanding on chronic pain as a whole. It is still unclear why subsets of patients appear to be vulnerable to developing chronic pain while others (often the majority) do not. For instance, within diabetic neuropathy, a minority of patients (34%) develop painful neuropathy and for lower backpain patients, only a third continue to experience persistent chronic pain for 12 months or more and, for osteoarthritis, no link has yet to be found between extent of damage severity and pain (Abbott, Malik, Van Ross, Kulkarni, & Boulton, 2011; Denk, McMahon, & Tracey, 2014; Dieppe & Lohmander, 2005; Maher, Underwood, & Buchbinder, 2017). Given that the extent of observable damage does not necessarily directly translate to severity of pain, relying on observation for pathology alone is unreliable. Based on this premise, identifying why some patients may be susceptible to chronic pain is a crucial area for pain research. Understanding the mechanisms behind pain sensitivity is one possible method for achieving this. Increasing our knowledge of individual differences in pain processing, and more specifically the psychological appraisal of pain, could help develop tools for early prediction of chronic pain and thus facilitate preventative interventions.

2.1.1. Summary

Chronic pain is a multi-faceted condition, comprising of pathological, psychological and biological influences. It is also a global health concern associated with massive societal and healthcare costs. As our population continues to age, it is anticipated that the burden of pain will continue to increase. The impact of pain on the individual is severe, with patients often reporting all aspects of their life being detrimentally impacted by their condition. Additionally, chronic pain is associated with a wide range of co-morbidities, such as depression and anxiety, adding to the complexity of this condition. Unfortunately, chronic pain treatment is usually reported to be inadequate, as supported by highly variable and generally poor clinical outcomes. While there is an array of possible explanations for variable treatment response, one contributing factor may be that the multi-faceted nature of chronic pain represents a challenge for clinical assessment. Specifically, the traditional medical model prioritises the isolation of a pathological trigger to explain patient-reported symptoms, in order to diagnose and treat. This is often challenging in chronic pain conditions where the pathological basis commonly does not match the described symptomology, or in some cases, is entirely absent.

One potential strategy that may help address this is issue is to increase the breadth of these assessments to match the multiple levels associated with chronic pain, thereby increasing the accuracy and comprehensiveness of clinical assessments. Learning more about individual differences in pain response could be crucial in improving our assessments and could help inform why only subsets of patients develop chronic pain It is evident across conditions such as painful diabetic neuropathy, lower backpain and postoperative chronic pain, that while most patients achieve a pain-free recovery, a minority of patients develop chronic pain. Studying the phenomenon of pain in healthy controls allows us to identify traits that may predict pain response, which could have clinical implications for identifying the minority of patients who could be vulnerable to developing chronic pain. For instance, this could facilitate the development of preventative interventions prior to chronic pain developing, for example in the case of post-

operative chronic pain. Alternatively, in instances where the pain is inevitable, being able to predict individuals at risk of developing chronic pain could improve access to treatment for these patients before their pain develops into co-morbidities, lifestyle deficits and frustration.

1.2. Pain Mechanisms

1.2.1. Peripheral mechanisms

Understanding the multi-faceted experience of pain requires knowledge of how the underlying mechanisms function to generate it. As described within Rey's account of the History of Pain (Rey, 1998), early philosophical thinking provided insight to the experience of pain, during a period where science was not yet equipped to validate the theories. One of the initial pain mechanism hypotheses was postulated by Renes Descartes. Facilitated by his research on animal and human dissection, the Treatise of Men offered an early-scientific insight to the anatomy and physiology of the human experience. Within this, Descartes suggested that, while the experience of pain was generated in the periphery, the signal was passed along nerve fibres, until it reached the brain. The analogy used was that of a hammer hitting a hand, triggering the pulling of a cord between the hand and the brain, leading to a bell ringing in the brain corresponding to the sensation of pain. In fact, Descartes viewed the brain solely "as a bell to be rung by tugging on a string in the periphery". Although this premise suggests that the brain is merely a passive receptor for pain, this dualistic supposition was ahead of its time and laid the foundation for a development of research into pain mechanisms. Within the late 18th century, this work was advanced by the lesser-known Pierre Jean Georges Cabanis who proposed three psychophysiological components involved in the experience of pain (Rey, 1998). Firstly, he insisted that pain does not represent a solely physiological reaction to an external stimulus but can be generated spontaneously in the brain. Secondly, he suggested that the perception of pain is reliant upon the mental activity of the perceiver, inclusive of emotional state. Thirdly, he viewed the conscious awareness of pain to be the product of a competitive model of external & internal feelings. Within this model, weaker feelings can be

absorbed within stronger ones, and therefore, the sensory experience of pain would need to be potent enough to overrule the experience of internal feelings to become consciously experienced. Conversely, the sensation elicited by a nociceptive stimulus can be overridden by a compelling internal state. Within this body of work, it could be said that the concept of pain modulation was created, providing the foundation for modern scientific descriptions of pain mechanisms.

Arguably, the most prominent of the original pain scientists were Ronald Wall & Patrick Melzack. Not only has their work been critical in focussing the progression of pain science, but has also been of utility in subdivisions of science such as medicine, veterinary science, art & humanities and social sciences (Katz & Rosenbloom, 2015). Melzack & Wall's magnum opus is said to be their 1965 publication introducing the "Gate Control Theory of Pain" (Melzack & Wall, 1965). Fundamentally, they proposed that pain is transmitted via a peripheral nerve through the spinal cord and is subject to modulation intrinsically via nerves, or via control in the brain. Their theory detailed that a nociceptive signal was transmitted up the spinal cord and into the brain via a *transmission gate* and that the extent to which this gate was open, facilitated a heightened experience of pain. However, the key component was that the brain can transmit signals which can close the gate to reduce or prevent signals from being sent to the brain (lower pain sensitivity) or the opposite, to open the gate and increase the signal (higher pain sensitivity). They also postulated that passive factors can contribute to closing the gate (distraction, positive mode, deep breathing, etc) and opening the gate (catastrophisation, anxiety, fear, etc).

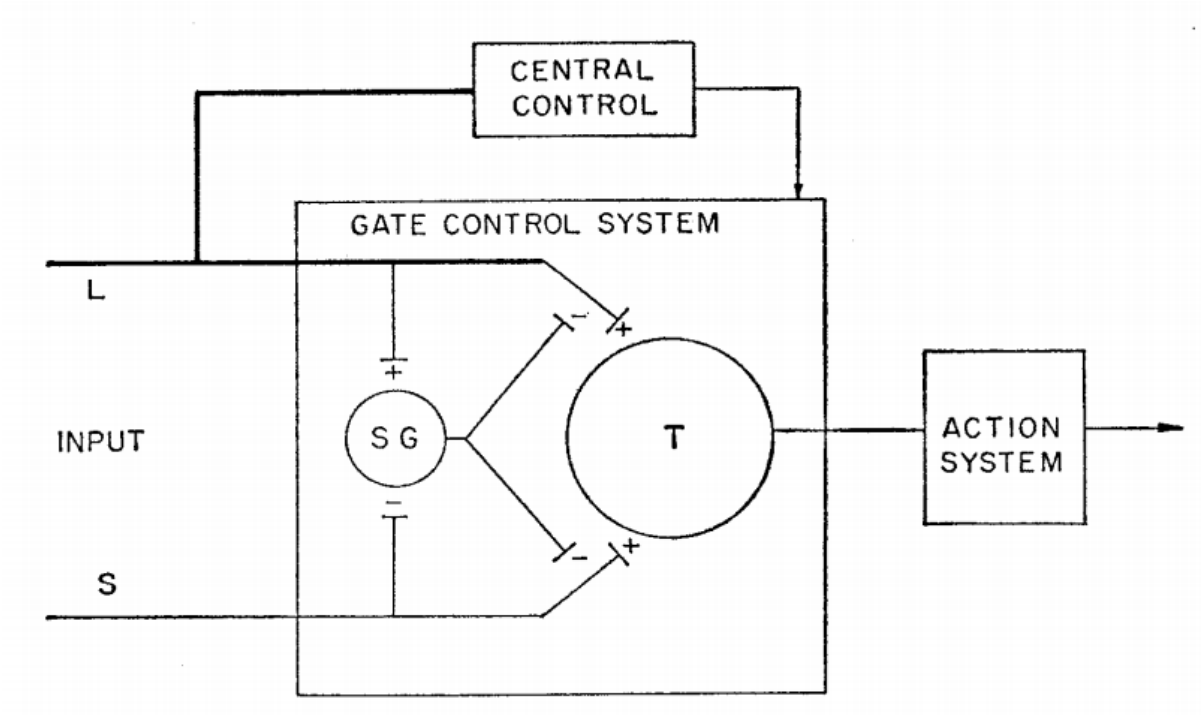

Figure 1. *Schematic drawing for The Gate Control Theory of Pain. L: Large-diameter fibres, S: Small-diameter fibres, SG: Substantia Gelatinosa, T: Central-transmission cells. From "Pain Mechanisms: A new theory" by R. Melzack and P. D. Wall, 1965, Science, 150(3699), p. 971-978. Reprinted with permission from AAAS*

As well as a concept, Melzack & Wall also proposed a potential mechanism underlying this function (Figure 1) (Melzack & Wall, 1965). Stimulation of the skin at the periphery leads to the signal being transmitted via one of two types of neurons; small- or large- diameter fibres. This signal is received within the dorsal horn of the spinal cord by the substantia gelatinosa (SG) & central-transmission cells (T-cells). The former is seen as a modulatory region which can regulate the afferent signal before it influences the T-cells which, in turn, are responsible for co-ordinating the response and perception to the painful event. Regarding the two types of fibres, activity within large fibres can increase the inhibitory effect of the SG, whereas small fibre activity decreases this effect. As a product of this mechanism, there is also a central control mechanism, triggered by afferent activity, which activates selective brain processes to further influence the modulatory properties within the gate control mechanism. Crucially, at the terminus of this ascending mechanism, once the T-cell has transmitted the post-modulatory signal up the spinal cord towards

this brain, this signifies the start of the modulatory process, not the end. At this point, the brain continues to be involved in processing the signal and the abstraction of the information.

While the specifics of this mechanism have been altered over the decades, many say that the theory has stood the test of time (Dickenson, 2002; Mendell, 2014) and has been critical to the development of modern pain science & uncovering the reality of pain mechanisms. In line with Melzack & Wall's proposition, the current perspective views the experience of pain to be an emergent property of the combination of an ascending & descending pain signal, via the input of multiple types of fibres, with further input provided from specific regions within the brain.

One concept which was missing from Melzack & Wall's model was the presence of a "pain-specific" neuron. The principle held within Gate Theory was that the control system allowed for multiple peripheral neurons to discharge, forming an accumulative response to intense stimulation, which superseded the requirement of a specific high-threshold afferent fibre. However, while the term "nociceptor" was first coined at the turn of the 20th century (Sherrington, 1906), it wasn't until 1967 that the first study was published demonstrating electrophysiological evidence of their existence (Burgess & Perl, 1967). This study demonstrated that out of 513 primary afferent fibres, 74 of them only responded to damaging mechanical stimulation and these were classified as nociceptors. This was later followed up with the identification of polymodal nociceptors, which responded across different modalities (heat, cold & ischemia) (Bessou & Perl, 1969). Later, as the research within this field developed, it was found that nociceptors project towards the dorsal horn, where they synapse amongst marginal cells which are specialised for noxious stimuli (Christensen & Perl, 1970). At this point, the signal then transcends into the spinothalamic tract (Willis, Zhang, Honda, & Giesler, 2001), a sensory pathway from the skin to the thalamus, which would provide access to cortical processes. The nature of this nociception-specific pathway, from receptor via marginal cells up to the spinothalamic tract, initially appeared to contradict the core premise of gate theory. However, subsequent investigation into the dorsal horn identified that, while the marginal

cells are specific for nociception, wide dynamic cells process both nociceptive & non-nociceptive input (Mendell, 1966), thus facilitating the integration of Gate Theory and the discovery of nociceptors (Mendell, 2014).

Today, our current understanding of pain mechanisms has stemmed from these developments, although the complexities of human cell biology mean a full understanding of this process is a long way off (Purves et al., 2001). The ascending pain pathway is initiated within the periphery when a nociceptor is stimulated via an aversive thermal, mechanical or chemical stimulus. There are primarily two different types of axon associated with these nociceptors; a-fibres (mostly Aδ) or c-fibres (Woolf & Ma, 2007). The speed of action potential transmission is directly correlated with myelination & the diameter of the axon. A-fibres are large & myelinated allowing for the transmission of action potentials between 5-30 metres/sec (Dubin & Patapoutian, 2010). Stimulation of a-fibres represents the first stage of the pain experience, which is sharp, nearly instantaneous & intense. C-fibres are smaller, unmyelinated neurons with a much slower transmission rate (~2m/s) and are associated with slower, duller & less intense feelings of pain. Each type of fibre is also associated with a predominant modality type; a-fibres are usually heat- or mechanosensitive, while c-fibres are usually polymodal (Tracey, 2017). These excitatory nociceptors release glutamate, amongst other peptides such as substance P, and synapse to first order neurons within the dorsal root ganglion (DRG). This axon then transitions and penetrates the spinal cord, via the dorsal root, ultimately terminating within the dorsal horn. From here, the signal can deviate across multiple pathways depending on which area of the dorsal horn the axons terminate in (D'Mello & Dickenson, 2008). In relation to the spinothalamic tract, the first order neuron projects to a second order neuron, which decussates across the midline of the spinal cord and ascends contralaterally towards the thalamus & brainstem (Figure 2). The neurons ultimately synapse with third order neurons in the ventral posterolateral (VPL) nucleus of the thalamus, and from here, signals can be transmitted across the cortex.

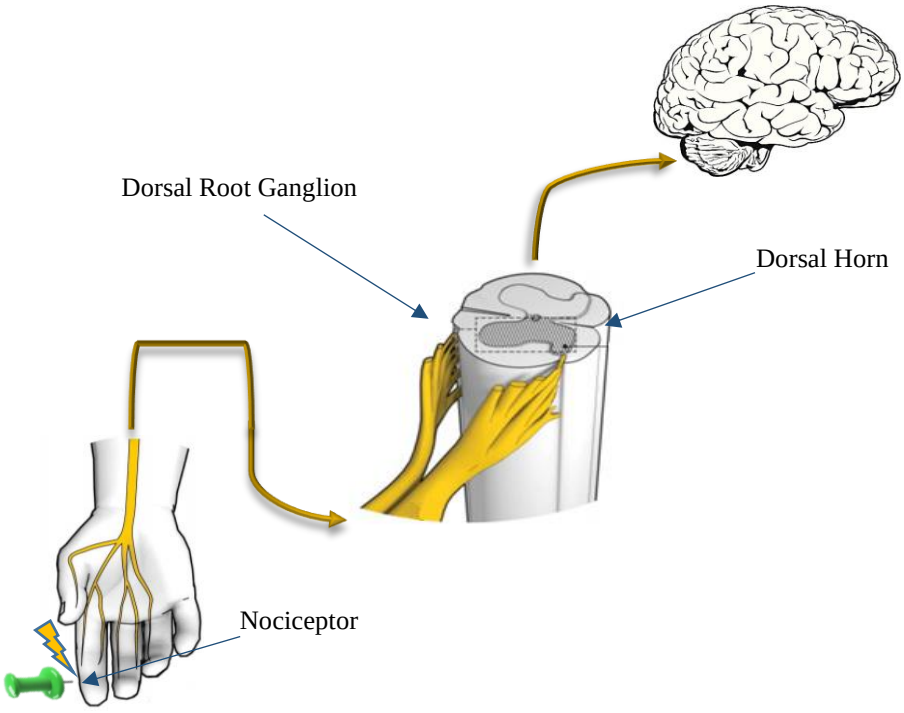

Figure 2. *Transmission of nociceptive signal into the ascending pain pathway. Adapted from "Neural Circuits of Pain" by C. Piers and R.P Seal, 2016, Science, 354(6312), 578-584. Reprinted with permission from AAAS.*

In addition to ascending pathways, it is also crucial to understand the presence of descending pain pathways, originating from the brain and descending the spinal cord. When nociceptive information enters the dorsal horn, it's subject to modulation from numerous mechanisms. This is due to the premise that the brain is not a passive endpoint for sensory information, instead it can process and interpret information, and make adjustments when required. The role of the brain in the pain experience can be observed intuitively across a range of situations we have likely all experienced. Attention can be directed away from pain actively, such as when finishing up a strenuous workout or preparing to rip a plaster off a wound. But this influence can also be seen passively, such as when someone is completing garden-work and observing that they had cut yourself but didn't notice at the time as they were busy focussing on the task at hand. Outside of the mundane & everyday experiences, we can also presuppose that from an evolutionary perspective, this mechanism would have benefitted survival instincts by allowing the brain to suppress the salience of pain to facilitate escape or defence whilst injured.

There has also been research in both animals & humans indicating that the efficiency of the descending pathway may be related to those who are susceptible to developing chronic pain (De Felice et al., 2011; Granovsky, 2013; Granovsky & Yarnitsky, 2013; Lewis, Heales, Rice, Rome, & McNair, 2012; Sevcik et al., 2006; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). This has stimulated growth within mechanistic pain research to identify the pathways involved in descending modulation, as well as trying to better understand how they relate to psychological processes & individual differences. This work was started in the early 20th century when Charles Sherrington identified the involvement of the brain in the experience of pain (Sherrington, 1906). Sherrington observed that the severance of the spinal cord in mice led to an enhanced nociceptive reflex with exposed to a painful stimulus. He hypothesised that this was due to an active involvement of the brain in the interpretation and modulation of the painful signal (Sherrington, 1906). This work was later developed via pharmacological & electrophysiological work in animals, which identified that the stimulation of the periaqueductal grey (PAG) facilitated an analgesic (or pain-relieving) response, and that subcortical structures, namely the PAG & Rostroventral Medulla (RVM), are involved in the descending modulation of spinal nociceptive processing (Millan, 2002). Lastly, using diffuse tensor imaging (DTI), these subcortical brainstem regions were found to be integrated with higher order regions such as the amygdala, hippocampus and somatosensory & prefrontal cortices (Hadjipavlou, Dunckley, Behrens, & Tracey, 2006).

The expansive involvement of a wide-range of psychological processes in the interpretation of pain presents a major challenge for clarifying the brains involvement, but a basic opioidergically-sensitive descending modulatory network has thought to be identified. As described, the primary juncture for ascending and descending signals is within the dorsal horn of the spinal cord and, as such, is seen as the terminus for the descending pathway. Cortical input represents the starting point for descending modulation and will be discussed in full in section 1.2.2, but this information is thought to be first integrated within the PAG. The PAG is thought to be the source of opioid-mediated descending pain inhibition (Waters & Lumb, 1997; Yeung, Yaksh, & Rudy, 1977) and

was originally demonstrated to endogenously modulate pain when stimulated via electrode (Reynolds, 1969; Tsou & Jang, 1964).

Importantly, the PAG has been shown to project and receive descending input from higher/cortical regions, such as the prefrontal cortex, somatosensory cortex and amygdala (Helmstetter, Tershner, Poore, & Bellgowan, 1998; Ossipov, Dussor, & Porreca, 2010), as well as ascendingly from lower brainstem/spinal regions, such as parabrachial nuclei & dorsal horns (Gauriau & Bernard, 2002; Waters & Lumb, 1997). This indicates that the PAG is able to modulate pain, both, centrally and via the spinal cord. While a key node within the descending modulatory system, the PAG itself has few projections directly to the dorsal horn (Vasquez & Vanegas, 2000; Xie, Huo, & Tang, 2009) and is thought to stimulate a modulatory effect via the raphe neurons (serotonergic), rostral ventromedial medulla (RVM; opioidergic), the ventral tegmental area (VTA; dopaminergic) and locus coeruleus (LC; noradrenergic) (Cui et al., 1999; Omelchenko & Sesack, 2009; Ossipov et al., 2010; Vasquez & Vanegas, 2000; Westlund & Willis Jnr, 2012). Currently, the mechanistic perspective identifies the PAGs projections to the RVM being of interest. The RVM represents the final common relay in the descending pathway between the cortex and spinal cord (Ossipov et al., 2010), and is known to exert a bidirectional effect capable of, both, inhibiting and facilitating the experience of pain (Heinricher, Tavares, Leith, & Lumb, 2009). The combination of the nodes within this pathway allow the incoming peripheral signal to be modulated within the spinal cord, thus influencing the perceived intensity, or unpleasantness, of the painful stimulus.

Ultimately, our understanding of pain mechanisms has developed greatly over the last 100 years. We are now able to explain how the severity of an injury may not directly correlate with the felt sensation of pain. The globally-accepted definition of pain, via the International Association for the Study of Pain (IASP), states that pain is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey et al., 2002). This definition describes a multi-faceted phenomenon involving emotions,

unpleasantness, verbal description and no requirement of tissue damage. Considering this, the interaction and combination of ascending and descending pain signals allows us to explain how situations, personalities or motivations are compulsory when evaluating our pain experience. However, while animal experimentation and electrophysiology have provided us with detail of the pathways, our understanding of the higher processes that influence the descending signal are still not fully understood. The brain, as a complex organ, still presents a black box to pain science and remains a key target for improving our understanding of the human experience, and struggle, with pain.

1.2.2 Brian mechanisms

Our understanding of the neural basis of pain has developed greatly since the invention of non-invasive brain imaging, in particular, electroencephalography (EEG) & functional magnetic resonance imaging (fMRI). From these developments came the identification of the "pain matrix"- a collection of anatomically distinct brain regions joined together as a network, which are involved in processing various dimensions of pain (Figure 3). These regions have been identified due to consistent activation across pain studies, as well as correlated activity associated with increased pain intensity (Legrain, Iannetti, Plaghki, & Mouraux, 2011). A large-scale review in 1999 synthesised data from 68 studies on experimental & clinical pain and concluded that the main components of the pain network were the thalamus, primary and secondary somatosensory (S1 & S2), insular, anterior cingulate cortex (ACC) and prefrontal cortices (PFC) (Apkarian, Bushnell, Treede, & Zubieta, 2005). These regions have formed the foundation of the pain matrix, with later studies proposing the inclusion of the amygdala, parietal cortices and PAG, alongside other brainstem regions such as the RVM & locus coeruleus (May, 2009; Peyron, Laurent, & Garcia-Larrea, 2000; Price, 2000; Tracey & Mantyh, 2007).

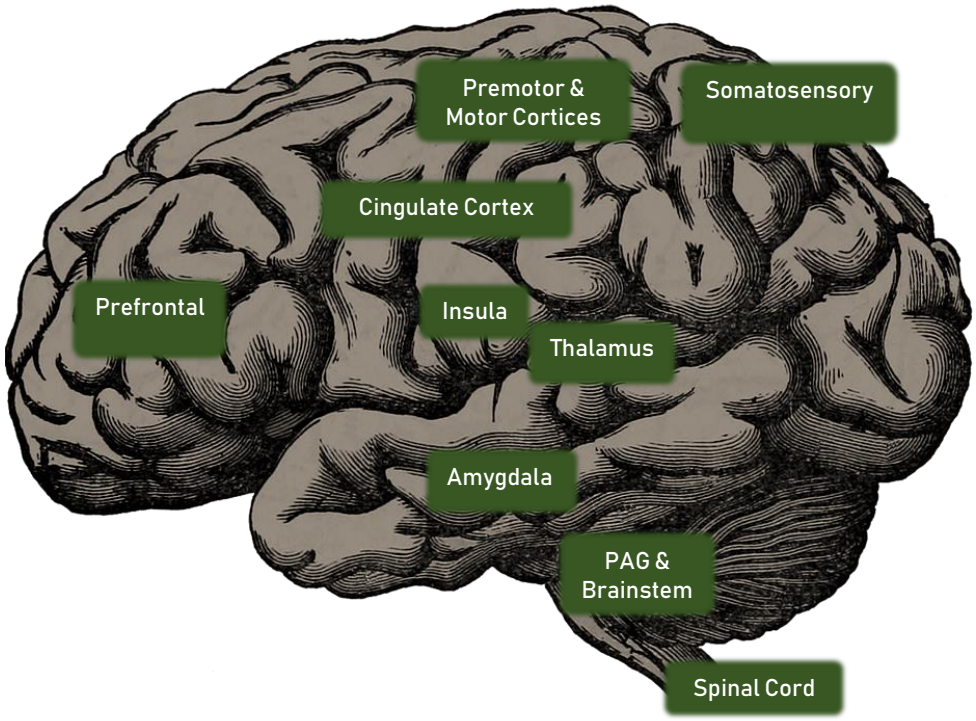

Figure 3. *Primary nodes within the "pain matrix" activated in response to nociceptive stimulation & processing.*

Whilst this pattern of neural activity is reliably found when administering a nociceptive stimulus, years of neuroscientific research examining the specificity of the pain matrix have raised genuine concerns. This theory has been challenged on the basis that it may be a product of reverse inference (Iannetti & Mouraux, 2010; Salomons, Iannetti, Liang, & Wood, 2016). For example, it is a logical premise to state that when the band Motörhead played the Hammersmith Apollo, beer stocks within the local vicinity ran out. However, it is fallacious reasoning (upon the premise of reverse inference) to deduce that when beer stocks in Hammersmith run low, Motörhead must be playing at the Apollo. In relation to neuroscience, we can state that when in pain, the pain matrix is activated. We cannot, however, state that when the pain matrix is activated, the individual is experiencing pain. One highly influential study examined the neural basis of a variety of aversive and non-aversive stimuli within fMRI, in an attempt to elucidate the specificity of the pain matrix (Mouraux, Diukova, Lee, Wise, & Iannetti, 2011). The results of this study provided a strong argument against the specificity of the pain matrix, demonstrating that nociceptive, non-nociceptive, auditory & visual stimuli all activate regions within the pain matrix. Additionally,

empathy to pain (Singer et al., 2004; Valeriani et al., 2008) and social rejection (Eisenberger, 2003) have also been found to activate the pain matrix. Tellingly, pain matrix activation has even been shown to be intact following nociceptive stimulation in patients experiencing congenital insensitivity to pain (Salomons et al., 2016). Intuitively, we know the experience of pain to be a holistic & multi-faceted phenomenon, influenced by attentional, cognitive and emotive processes, alongside an array of other features. Therefore, when imaging the neural basis of this, it is logical to expect the utilisation of auxiliary or generic processes to be involved in the experience and, therefore, the mechanism. So, while the pain matrix is not a redundant concept, as these regions are actively involved in processing pain, it is difficult to disentangle which areas are related specifically to pain (if any), as opposed to generic processes. Consequently, more specific hypotheses-driven research into pain mechanisms is now encouraged to expand upon this.

In an attempt to breakdown the amorphous experience of pain, one approach is to examine separate features of the experience in isolation. For example, if someone were to stub their toe, we would expect the 'pain matrix' to be activated as they are processing nociceptively-related information (where did they hit it/how hard did they hit it/does it feel damaged etc), but also non-nociceptively-related information (are they balanced/what did they hit/is anyone near them etc). Within an experimental setting this process remains the same, and the interaction of nociceptive and non-nociceptive processing would lead to a heterogenous pattern of activation, whereby specific function is difficult to detangle. However, if we were to compare nociceptive stimulation in isolation, to the same stimulation in combination with a complex cognitive task, we would be able to target the experimental focus on the neural mechanism underpinning pain modulation, which is a core feature of interest in this current body of work. We know that a subjective experience of pain is formed via a combination of ascending and descending signals, the latter of which originating in the cortex (Ossipov et al., 2010). Not only would targeting our investigations to the influence of such cortical processes on this mechanism allow us to better understand the neural underpinnings of pain, but also help us understand apparent innate individual differences which facilitate

vulnerability to chronic pain. Therefore, mechanistically, one key area of focus is on the descending pain modulation system (DPMS).

The DPMS is a network that ultimately regulates the nociceptive signal at the level of the spinal dorsal horn (Denk et al., 2014). Due to the number of varying processes which can contribute to this mechanism of action (for example, attentional vs emotional distraction), there is currently an array of identified descending modulatory regions and pathways, but each operates as a bidirectional loop between the cortex and the spinal cord, via the brainstem (Bushnell, Čeko, & Low, 2013; Millan, 2002). The bidirectional nature of this network facilitates or alleviates the experience of pain depending on the situation. For example, if an individual is interpreted to be in a fight or flight environment, it is beneficial to downregulate the nociceptive signal and decrease the experience of pain, thus facilitating the utilisation of resources towards escaping the situation (Williams, 2016). Conversely, the enhancement of the nociceptive signal would lead to a heightened and consistent pain state, which may be a contributing factor to chronic pain and pain sensitivity. For example, it has been proposed that persisting pain within nerve injury is associated with alterations in the function of the DPMS (Ossipov et al., 2010; Porreca, Ossipov, & Gebhart, 2002). Within this study, chronic pain following nerve injury was associated with a reduction in inhibitory influences in the dorsal horn, alongside increases in facilitatory action. While the experience of pain is a product of multiple processes emanating from the cortex, the key areas are thought to be the ACC, insula, somatosensory and dorsolateral prefrontal cortices (dlPFC), the amygdala, thalamus and hypothalamus within the subcortex and the PAG and RVM in the brainstem (Denk et al., 2014). Processes within the amygdala, hypothalamus and prefrontal and cingulate cortices are associated with cognitive, attentional & emotional states that interact with the nociceptive processing (Bushnell et al., 2013). Therefore, activity within these regions is likely affect by the trait and state characteristics of the individual.

Ultimately, the pain experience is also impacted via psychological factors whose processes originate within the brain. Influences such as emotion, attention and cognition can influence the final expression of pain and are each associated with a variety of distinct (yet overlapping) mechanisms. It's been suggested that alterations in the amygdala-PFC network, via disturbances in sleep quality and mood control, impact how pain is modulated via nuclei in the brainstem (Denk et al., 2014). The associative effects on how the nociceptive stimulus is inhibited or facilitated via these processes could represent a vulnerability to the development and maintenance of chronic pain.

1.2.3. Summary

Early developments in our understanding of pain formulated the idea that pain and injury are not directly correlated and that the brain is involved in its interpretation. This provided Melzack & Wall with a foundation to propose their Gate Control Theory of Pain. They suggested that pain is transmitted via a peripheral nerve through the spinal cord where it is subject to modulation intrinsically via nerves, or via control in the brain. One key element of this theory was that the opening and closing of the gate could be facilitated by psychological factors, such as relaxation, anxiety or catastrophising. The discovery of nociceptors, specialised for detecting aversive stimuli, alongside Gate Theory, led to development of mechanistic breakdowns of the pain pathways. These can be classified into two groups; ascending and descending pathways. The ascending pathway begins via detection in the periphery, transmission into the dorsal horn of the spinal column, and then up the spine and into the brain (for example, via the spinothalamic tract). The descending pathway originates in the brain, projects through the PAG and then indirectly into the spinal cord, via a number of different regions, associated with a range of neurotransmitters. Investigation into structural pathways is highly suited to electrophysiological and animal experimentation, and as such, has been described in fine detail over the past 50 years. However, due to the complexity of the brain and human psychology, cortical involvement in the descending pathway, and how this contributes to pain modulation, still requires further research. Further examination of the brains

involvement in this process may help us understand how an individual's capability to modulate the ascending signal of a noxious stimulus may be associated with how people manage chronic pain in clinical settings.

Advances in brain research have led to the identification of a collection of brain regions that are involved in the processing of pain. These regions are often reported to be the thalamus, amygdala, periaqueductal grey (PAG), primary and secondary somatosensory (S1 & S2), insular, anterior cingulate (ACC), parietal and prefrontal cortices (PFC) (Apkarian et al., 2005). Originally, these regions were designated as the "pain matrix". However, as activation of the pain matrix has shown to be active in patients with congenital sensitivity to pain, as well as in response to non-noxious stimuli, the specificity of the pain matrix has since been asserted to be a product of reverse inference.

Ultimately, within the pain matrix, it is difficult to disentangle which areas are related specifically to pain (if any), as opposed to generic processes, such as attention, cognition, emotion or sensation. As such, more specific, targeted hypotheses are now encouraged for expanding on this. One concept of interest when examining intrinsic ability to manage pain is the concept of pain modulation. The combination of the ascending and descending pathways in pain processing elicit the experience of pain. Psychological factors associated with resilience are associated with cortical processes and examining how these cortical influences contribute to pain modulation is one method to investigate the psychology of innate individual differences in pain. For example. processes within the amygdala, hypothalamus and prefrontal and cingulate cortices are associated with cognitive, attentional & emotional states that interact with the nociceptive processing (Bushnell et al., 2013). This is especially pertinent as these areas are identified within the descending pain modulation system, which is a network of regions key to the process of modulating pain. Examining how individual differences related to pain processing may be associated with

underlying differences in the DPMS, is a good strategy for understanding how effective, intrinsic pain management may be represented neurologically.

1.3. Pain Assessment

As illustrated, pain is a complex, multi-faceted phenomena, with no direct causal link to nociception. It can vary wildly across individuals, time-points and locations. Even within chronic pain patients, pain can be known to fluctuate across the days, weeks and months, despite no known alterations in pathology (Schneider et al., 2012). Moreover, due to the lack of specificity in the neural markers underlying pain, there is currently no objective test available to detect or evaluate pain. The challenges in assessing pain, alongside the clear utility that accurate assessments would bring, have led to a range of different methods being proposed to quantify different aspects of the pain experience. The complexity of pain means that it cannot be accurately represented via the use of a single number, and for a detailed assessment, it must be evaluated across multiple levels. For clinical assessment, it has been proposed that diagnoses should be based on pain mechanism, not just symptom (Woolf, 2004). This is based on the premise that differences in clinical symptoms represent differences in the abnormalities of the underlying pathophysiological mechanisms of pain processing (Rolke et al., 2006). However, regarding our current understanding of these mechanisms our knowledge is incomplete and, within the methodology of assessment in particular, many issues remain to be addressed (Cruz-Almeida & Fillingim, 2014).

For the purposes of description, pain assessment can be categorised into four domains; *the periphery, descending pathways, psychology & the brain*. One crucial note when attempting to designate distinct clusters is that these domains are not orthogonal towards one another. For example, when quantifying thresholds in the periphery and pain catastrophising via psychometrics, it is important to note that each is likely to affect the other. But, these tools can either be used in

combination to describe the amalgam of the entire pain experience, or individually, to isolate specific mechanisms within the experience of pain if required.

1.3.1 The Periphery

Assessment of pain in the periphery can be assessed using static quantitative sensory testing (sQST) and represents the simplest approach to describing an individual's pain profile. Traditionally, sQST involves administering thermal (heat/cold) or mechanical stimuli (tactile/vibration/pressure) (Cruz-Almeida & Fillingim, 2014) and performing three main tests; sensory detection thresholds, pain thresholds & pain tolerance. The first two tests use supra- and super-threshold stimulation to provide a proxy for the intensity of a stimulus required to elicit either the detection of sensory stimulation (sensory detection) or painful stimulation (pain threshold). The latter test, quantifying pain tolerance, is completed via exposure to a noxious stimulus where the participant is required to maintain exposure until the pain becomes intolerable, at which point they can withdraw from the stimulus. Taken together, these sQST measures can provide a basic sensory profile for an individual consisting of sensory and nociceptive sensitivity (Figure 4). One clear advantage of this approach is that these tests are quick to complete, require little expertise for data collection and provide an impression of the basal state of the nociceptive system. Beneficially, these tests are associated with the good-excellent reliability, representing the most reliable of the psychophysical assessment tools (Marcuzzi, Wrigley, Dean, Adams, & Hush, 2017).

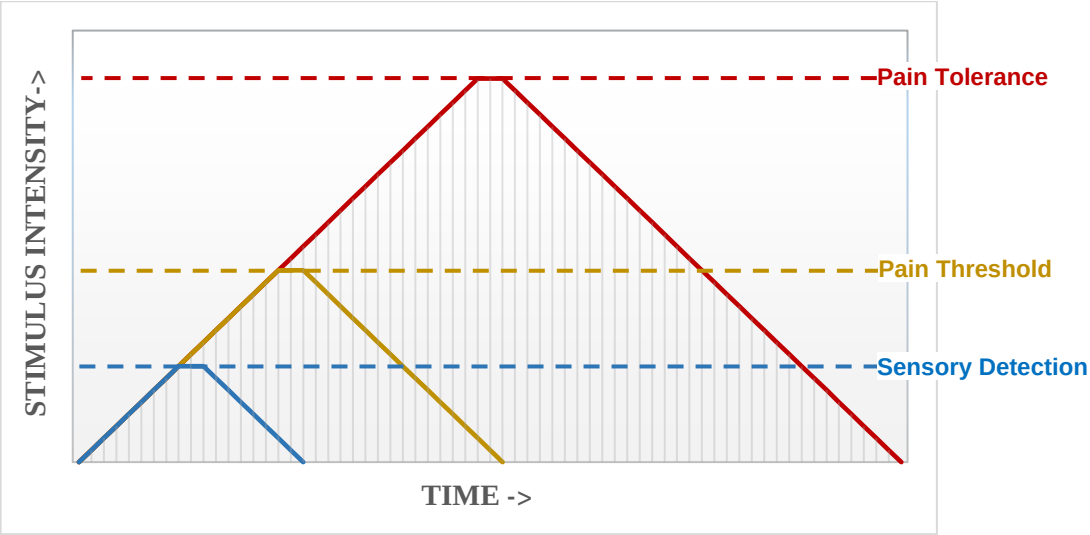

Figure 4. *Static QST assessments and their relation to sensory detection & pain sensitivity*

While sQST assessments require involvement of the entirety of the neuroaxis, from the periphery to the brain, their outcomes can be used to make direct observations of peripheral sensitivity. Within clinical research, thresholds can be used to detect sensory loss in peripheral nervous system disorders (Masson & Boulton, 1991; Ponirakis et al., 2016; Ziegler, Mayer, & Gries, 1988), compare intra-individual pain sensitivity (i.e. affected vs non-affected areas) (Coronado, Kindler, Valencia, & George, 2011; Coronado, Simon, Valencia, & George, 2014) or as pre-surgical acute pain assessment (Yang et al., 2019). Within research settings, pain thresholds provide an experimental variable that is a proxy for pain sensitivity. This can be used to investigate the impact of pain on various tasks (Dunbar et al., 2012; Nisbett & Schachter, 1966), to understand clinical conditions in relation to controls (Adler & Gattaz, 1993; Granges & Littlejohn, 1993) and to investigate associations between pain and underlying neurology (Coghill, Sang, Maisog, & Iadarola, 2017; Peyron et al., 2000), amongst many other applications. Pragmatically, these techniques can also be used to further increase the quality of other, more complex, behavioural assessments. For example, the calibration of pain thresholds and ratings of pain intensity to static stimuli are often required for the application of more complex psychophysical assessment used to investigate other mechanisms involved in pain.

1.3.2. Ascending & Descending Pathways

One benefit of sQST methods is that the simplicity of the design allows an experimenter to direct their conclusions to the periphery. However, dynamic quantitative sensory testing (dQST) can use peripheral stimulation within more complex designs to provide insight about deeper mechanisms within the neuroaxis. Two common psychophysical tools within dQST are *Conditioned Pain Modulation (CPM)* and *Temporal Summation (TS),* which have been linked with mechanisms of descending modulation & ascending facilitation, respectively (Mackey, Dixon, Johnson, & Kong, 2017).

As mentioned within section 1.2.1, pain is a product of the combination of ascending and descending pathways. Those with effective descending modulatory mechanisms can better inhibit the ascending nociceptive signal, therefore reducing pain (Ossipov et al., 2010). CPM is a psychophysical test that is said to be a behavioural proxy for the efficiency of this circuitry, with high CPM being associated with more effective endogenous analgesia mechanisms (Yarnitsky et al., 2012). CPM is developed on the principle that "pain-inhibits-pain" i.e., the experience of pain can be inhibited by inducing pain at a proximally distal anatomical site, for example, via the application of a thermal test stimulus on the leg, and a hot water bath as a conditioning stimulus applied to the arm (Yarnitsky et al., 2008, 2012). Originally, this inhibitory phenomenon was identified in animals, and termed diffuse noxious inhibitory controls (DNIC) (Cadden, Villanueva, Chitour, & Le Bars, 1983; Le Bars, Dickenson, & Besson, 1979).

Tests of TS consist of a participant providing subjective pain ratings to a painful consistent stimulus repeatedly delivered at a high frequency (Rolke et al., 2006). Generically, despite the pain stimuli being of a consistent intensity, the subjective pain ratings of the experience will increase. This has been attributed to a process of *central sensitisation*, whereby the central nervous system engages in a process of wind-up and progresses into a state of high reactivity (D'Mello & Dickenson, 2008). The repeated input of nociceptive input via c-fibres in the periphery appears to

lead to an increased frequency of secondary spinal firing from the dorsal horn, interpreted as an increased intensity of pain. Modern models of chronic pain have hypothesised that central sensitisation serves as a key maintenance factor in this condition (Latremoliere & Woolf, 2009; Woolf, 2004). This is based on the premise that when in a high state of reactivity, the central nervous system can misappropriate the interpretation of signals associated with pain.

Two recognised instances of this misrepresentation of signal are *allodynia* and *hyperalgesia*. Allodynia is the phenomenon whereby a subthreshold peripheral stimulus can be interpreted as being painful (Sandkühler, 2009). For example, a common test for central sensitisation is the brush allodynia test, where a soft paintbrush is stroked across the site of stimulation to test whether the participant correctly interprets the stimulus as non-painful (Maracle et al., 2017). Similarly, hyperalgesia is a product of the amplification of a nociceptive signal so that a suprathreshold stimulus is perceived as being more painful than it usually is (Sandkühler, 2009). A common illustration of hyperalgesia is a sunburn. Before being burnt, a slap to the back may cause a mild, sharp pain which is easily tolerated. However, after sunburn, the intensity of the pain will be substantially increased, both to the site of sunburn itself (primary hyperalgesia) and even to the area around the sunburn (secondary hyperalgesia). Given the examples of allodynia and hyperalgesia, it is likely not surprising that central sensitisation has been found to be linked to acute and chronic pain within animal models (Cook, Woolf, Wall, & Mcmahon, 1987; Woolf & Wall, 1986; Woolf, 1984; Woolf, 1983; Woolf & Salter, 2000), and that abnormalities in the behavioural proxy of TS are associated with a range of detrimental clinical outcomes.

It has been suggested that via the combination of CPM and TS, it is possible for assessments to phenotype participants into profiles of nociceptive processing, based on their underlying mechanisms (Yarnitsky, Granot, & Granovsky, 2014). Yarnitsky proposed that the outcomes from CPM/TS indicate a balance of inhibitory/facilitatory mechanisms, and that this can be used to classify an individual as being pro- (high pain facilitation), eu- (no pain facilitation) or anti-

nociceptive (low pain facilitation). The associative conclusions of this profiling system are that those who are pro-nociceptive are more likely to experience pain sensitivity and low pain modulation, and that these individuals are those at risk of detrimental outcomes for clinical pain. This proposal for nociceptive profiles would provide a method of metapsychophysical assessment, whereby the results from behavioural tests can be combined to stratify individuals into three subsets of pain profile, associated with varying degrees of vulnerability to pain. Recently, validation for this theory was provided indicating that, within a sample of knee osteoarthritis patients, a higher proportion met the criteria for a pro-nociceptive (27%), as opposed to an anti-nociceptive profile (16%) (Bossmann, Brauner, & Horstmann, 2018). However, within this sample, the majority of patients were classified as a eu-nociceptive profile (57%) despite suffering from a chronic pain condition. Therefore, whilst CPM/TS can provide useful information regarding the underlying mechanisms of pain processing, assessments cannot rely on one level of inspection alone, as indicated by the presence of a eu-nociceptive majority within a chronic pain sample. Instead, to truly understand chronic pain, we must ideally evaluate the experience of pain using all levels known to affect pain processing.

1.3.3. Psychology & Personality

For many sufferers, chronic pain is a wholly negative experience characterised by distress, despair and hopelessness (Corbett et al., 2007). This condition is associated with multiple cognitive, emotional, social and attentional components and, therefore, it is not surprising that many psychological variables have already been identified as being associated with chronic pain (Bruce, Thornton, Powell, Johnston, Wells, Heys, Thompson, Smith, et al., 2014). Critically, the representation of chronic pain varies as a function of diagnosis. For example, cancer pain will likely be associated with an increased presence of fear and anxiety to mortality than fibromyalgia, which has no direct medical risk of death. However, the internalised perspective on fibromyalgia, with no known pathological cause or effective treatment, may be viewed differently in comparison to chronic knee pain that is associated with a simpler formal diagnosis and treatment pathway.

Therefore, while psychological factors are incredibly relevant to chronic pain, variability across conditions is a crucial factor to consider when calibrating assessments.

Personality has long been linked to the instantiation, maintenance and experience of pain (Gamsa, 1994). Within the 1800s, pain management started to emerge as a serious medical challenge, and this stimulated an investigation into personality in an attempt to explain pain in the absence of pathology (Tuke, 1884). Within the 20th century, the rise of psychoanalysis introduced a model that via trauma in development, detriments in personality led to emotional disturbance, which stimulated emergent expression via pain (Lesse, 1968; Merskey et al., 2002). This cumulated in the designation of a "pain-prone" personality type, related to a denial of emotions, failure in interpersonal communications and being within a "depressive-spectrum" (Blumer & Heilbronn, 1981). It was presumed that as personality represents a stable trait, the implications of an individual's personality would affect the mechanisms with which a person would respond to pain and manage their condition. However, the concept of a pain-prone personality type was later debunked as the evidence base for personality became more comprehensive, and multiple personality sub-types were associated with chronic pain (Naylor, Boag, & Gustin, 2017). Generally, chronic pain patients display normal patterns of personality, with no systematic variation in personality types (Wade, Dougherty, Hart, & Cook, 1992).

Ultimately, the pursuit of a single pain-prone personality type proved to be a reductionist approach. The main criticisms of this pursuit revolved around the use of cross-sectional designs, preventing the identification of whether the personality factors disposed the individual to pain, or whether the detrimental presence of pain led to the identified personality characteristics (Wachleski et al., 2008). Additionally, the lack of specificity of the identified personality characteristics to chronic pain, as opposed to anxiety (Wachleski et al., 2008), obsessive-compulsive disorder (Cruz-Fuentes, Blas, Gonzalez, Camarena, & Nicolini, 2004) or depression (Smith, Duffy, Stewart, Muir, & Blackwood, 2005), contradicted the concept of these individuals being prone specifically to pain.

Instead, modern approaches target trait-like psychological concepts as being more appropriate for assessment and provide more specificity than broad personality subtypes. While the existence of a pain-prone personality appears to be non-apparent, reoccurring psychological factors (that are often associated with axis 1 personality disorders, such as depression and anxiety) do appear to present as risk factors to the development and maintenance of pain (Gatchel, Polatin, & Kinney, 1995).

For a comprehensive overview of the full range of psychological predictors for pain outcomes, there are a number of high quality reviews that cover this expansive field of research (Bruce, et al., 2014; Thibault et al., 2008). However, specifically, depression and anxiety have consistently been identified as risk factors for the transition from acute to chronic pain (Linton, 2000; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012) as well as being involved in the maintenance of the condition (Gaskin, Greene, Robinson, & Geisser, 1992). Levels of depression have been found to be predictive of the development of lower-back pain, as much as three years after an initial pain-free assessment, with depressed patients being 2.3 times more likely to develop lower-back pain than patients without depression (Jarvik et al., 2005). It is estimated that up to 85% of patients diagnosed with chronic pain also suffer from severe depression (Diamond, 1964), so unsurprisingly the neurobiological & neuroplastic changes associated with these two conditions have a large degree of overlap (Sheng, Liu, Wang, Cui, & Zhang, 2017). These overlaps are known to exist over multiple levels, including similar inflammatory factors and receptor subtype activity changes, but a common theory postulates that each condition also impacts the descending modulatory system (Bair, Robinson, Katon, & Kroenke, 2003). In particular, the modulatory brainstem pathway engaged via the PAG, as well as limbic and cortical regions which co-ordinate affect and attention to peripheral stimuli, contains serotonergic, noradrenergic & opioidergic neurons (Omelchenko & Sesack, 2009; Stahl, 2002). Levels of these neurotransmitters are known to be depleted in depression (Cowen & Browning, 2015; Moret & Briley, 2011), which is a key reason why antidepressants, which increase these neurotransmitters, are used to treat chronic pain (Micó, Ardid, Berrocoso, & Eschalier, 2006).

Psychologically, symptoms of depression are associated with altered cognitive, emotional and attentional states (Fales et al., 2008; Goeleven, De Raedt, Baert, & Koster, 2006; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005). These altered psychological states can also be associated with chronic pain and are valuable for assessment. For instance, distress, depression & fear-avoidance have been shown to be correlated with the transition between acute pain and chronic pain in lower-back pain patients and were identified as the best predictors across 11-identified studies (Linton, 2000). Psychological distress is defined as emotional suffering caused by symptoms of depression and anxiety (Mirowsky & Ross, 2002) and high levels of psychological distress have been associated with unfavourable clinical outcomes in pain management (Pincus et al., 2002). Relatedly, pain catastrophising, a set of negative pain-themed cognitive biases, has also been identified as a predictor variable for poor clinical outcomes and the transition from acute to chronic pain (Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016; Khan et al., 2011; Sullivan et al., 2001; Theunissen et al., 2012). Utilisation of the highly validated Pain Catastrophising Scale (Sullivan, Bishop, & Pivik, 1995) in pain research has revealed that pain catastrophizing, as a trait, is associated with a wealth of negative chronic pain outcomes (Turner, Jensen, Warms, & Cardenas, 2002). It has been proposed that pain catastrophising may be characterised by an attentional processing bias, which exaggerates the experience of sensory and affective pain information (Eccleston, 1994). The detrimental mechanism of action is proposed to orientate around three main concepts; the magnification of the threat of pain, a failure to inhibit pain-related cognitions, with predisposition for ruminative thinking, and a feeling of helplessness in the context of pain (Sullivan et al., 1995).

As a functional antithesis to the detrimental influence of catastrophising, mindfulness is a concept that has been associated with beneficial pain outcomes (Chiesa & Serretti, 2011; Kabat-Zinn, 1982). Mindfulness is an attentional regulatory process, characterised by a present-focused awareness within the moment, in a curious, open and accepting manner (Bishop et al., 2004).

Pertinently, regarding assessment, mindfulness can be viewed as both a state and a trait. Administering mindfulness-based interventions (MBIs) to enhance an individual's capacity for mindfulness (and therefore their state mindfulness), has been associated with increased pain thresholds and reduced negative pain-related biases, such as catastrophising (Turner et al., 2016; Zeidan, Gordon, Merchant, & Goolkasian, 2010; Zeidan, Grant, Brown, McHaffie, & Coghill, 2012). However, when assessing for individual differences in intrinsic variations in pain processing, the use of the Five-Factor Mindfulness Questionnaire (Baer et al., 2008) can quantify an individual's trait mindfulness, even in the absence of any exposure to MBIs. High trait mindfulness has been associated with higher pain thresholds and decreased pain catastrophising (Grant & Rainville, 2009; Mun, Okun, & Karoly, 2014). It has been suggested that this may be achieved via attentional regulation to sensory-discriminative processing, with reduced attention for cognitive reappraisal and rumination (Grant, Courtemanche, & Rainville, 2011; Salomons & Kucyi, 2011). These findings suggest that trait mindfulness would might be a useful assessment measure for evaluating how effective an individual's ability to manage pain.

The prospective capability of psychologically orientated assessment highlights the potential application for identifying intrinsic traits relating to an individual's capability for managing pain. As well as this, psychometrics provide a potential strategy for the stratification of interventions, targeted towards the detrimental influence of specific psychological features. Psychological assessment can also be useful when attempting to predict how well a patient may fare with clinical pain outcomes or understanding why some patient's pathological diagnosis does not match the described symptomology. The way in which psychological factors can influence how we attend, think and feel about pain can have an impact on how pain is managed and modulated. The use of psychometric assessment can illuminate hidden criteria, that may otherwise be missed, which could help us better understand how people are likely to respond to pain.

1.3.4. The Brain

Multiple attributes associated with the brain have been identified that could help identify biomarkers for pain response. These can be acquired via multiple means, including MRI, EEG, transcranial magnetic stimulation (TMS), Magnetoencephalography (MEG) & Positron Emission Topography (PET). The differences in these neuroimaging techniques are associated with a series of strengths and weaknesses when compared to each other, especially regarding spatial and temporal resolution. There is a collection of high-quality reviews of pain biomarkers within EEG (Dos Santos Pinheiro et al., 2016; Leiser, Dunlop, Bowlby, & Devilbiss, 2011), TMS (Barr, Farzan, Davis, Fitzgerald, & Daskalakis, 2013; Nardone et al., 2015; Zaghi, Thiele, Pimentel, Pimentel, & Fregni, 2011) & MEG (Ploner & May, 2018), but for the purposes of this thesis, the focus of the synopsis will be on MRI.

It is evident that nociceptive stimulation consistently elicits BOLD activation within certain areas of the brain (see section 1.2.2), and that the magnitude of this activity covaries with increases in the intensity of the stimulus (Derbyshire et al., 1997). In combination with an increase in popularity of fMRI research and ambitions of an objective measure of pain, this encouraged the pursuit of a neural marker for pain in the human brain. The advantages of such a tool would be numerous. Within the clinic, assessment of pain is still reliant on clear communication, presenting challenges when treating pre-communicative children, patients with no shared language or adults with learning disabilities or degenerative conditions. Within the age of the 'opiate epidemic' (Wilkerson, Kim, Windsor, & Mareiniss, 2016), there are also ongoing concerns of the duplicitous pursuit of opioids and due to the dangers associated with opioid abuse, a corroborative measure is highly desired.

While the motivations for an objective measure of pain are valid, the application of a neural signature of pain is still incomplete. As described in section 1.2.2, the original BOLD signature across the pain matrix is not specific to the experience of pain (Mouraux et al., 2011). Modern analytical methods, namely multi-variate pattern analysis (MVPA), have facilitated the

development of more advanced neural representations of pain. Namely, Tor Wager's neurological signature is more sensitive and specific to physical pain, and has better discriminatory power for noxious stimulation, than other aversive stimuli (Wager et al., 2013). Their approach consisted of using machine learning to identify patterns of activity associated with thermal pain, which were identified across key pain processing regions such as the thalamus, PAG, somatosensory, insula & ACC. The specificity and sensitivity of this machine learning was then tested against warm (non-noxious) stimulation, social pain (via images relating to social rejection) and tested its response to analgesic relief. The resulting findings for this signature were highly promising with a high degree of sensitivity & specificity shown across all comparisons, and at the least, improved upon the original models identified using simple contrast analyses.

While there are benefits to MVPA, many of the original criticisms of such a signature remain. The neurological signature was developed using healthy controls, stimulated in a forced-choice design (on vs off), using peripheral thermal stimulation applied to the same body site. Whether this would possess the ecological validity to transition into the clinic remains unlikely, and the substantial increase in degrees of freedom encountered when adopting this across multiple clinical sites, with multiple chronic pain conditions & the variability inherent within these patients, would be highly challenging. Based on this, an IASP task force investigated the ethical & moral implications behind using brain imaging for pain assessment and concluded that "the use of brain imaging findings to support or dispute a claim of chronic pain- effectively as a pain lie detector- is not warranted" (Davis et al., 2017, p. 1). However, the review also stated that imaging provides a great potential for other clinical advances, such as investigating the neural underpinning of chronic pain and its development, as well as predicting treatment outcomes and the pursuit of personalised pain medicine.

One such approach that uses fMRI effectively for these targets is resting-state fMRI (rs-fMRI) and connectivity analysis. Although evoked-response fMRI can help identify regions that are involved

when experiencing pain, it is less capable of explaining how these regions function within larger networks and allows us to examine participants at rest with no task, to understand aspects about who they are as individuals (Cabral, Kringelbach, & Deco, 2014). Connectivity analysis provides us with more detail on this macro level and reveals how nodes within a network communicate during a task or when at rest (Greicius, Krasnow, Reiss, & Menon, 2003). This approach also enables us to take a neural 'snapshot' of who an individual is at rest, and we can use this to investigate individual differences in connectivity to establish how underlying neural mechanisms may provide innate resilience or sensitivity to the experience of pain (Schmidt-Wilcke et al., 2014; Yu et al., 2014). This approach can address, for example, how chronic pain may develop by examining changes in connectivity before and after the development of chronic pain (Chapman & Vierck, 2017). This is especially useful for chronic postsurgical pain, where the risk for developing chronic pain via surgery is identified and can be predicted, as opposed to conditions such as lower-back pain, where the condition may emerge over the course of years, with no discernible trigger. Rs-fMRI can also be used to predict treatment outcomes, before they've undergone the treatment itself, by comparing baseline pre-treatment connectivity with eventual treatment outcomes, to potentially identify biomarkers for poor outcomes (Tétreault et al., 2016).

Resting state fMRI is an approach that can assess the functional connectivity of spatially distinct regions of the brain (Greicius et al., 2003). This is achieved using spontaneous fluctuations in BOLD response, which is used as a proxy for neural activity within regions (Karl, 1994). Resting state connectivity aims to evaluate how spatially distinct regions may share co-activation patterns in slow oscillatory activity (less than 0.1Hz (Friston, 1994)), thus representing synchronisation and functional connectivity. Similarly, this approach can also identify inverse functional connectivity by identifying regions that are asynchronous, representing more independent functions associated with the two comparative regions. This can provide insight for how brain areas combined to form networks, and how the efficiency of connectivity within networks can function to formulate an experience of pain, or pain modulation (Denk et al., 2014).

While we know that exposure to noxious stimuli elicits a neural response across a number of distinct areas that coalesce to formulate the experience of pain, these areas do not act in isolation of each other (Baliki et al., 2012; Kucyi & Davis, 2015; Napadow et al., 2010). Networks such as the default mode network (DMN), descending pain modulation system (DPMS) and salience network have all been implicated in the chronification of pain and the prediction of treatment response (Apkarian, Baliki, & Farmer, 2013; De Felice et al., 2011; Ren & Dubner, 2002). Therefore, by using connectivity analysis, we can evaluate how these areas are connected to one another, and whether there are systematic associative variations in these connections that facilitate better or worse pain management. For example, chronic pain is associated with deficiencies in descending pain modulation (Davis & Moayedi, 2013; De Felice et al., 2011; Lewis, Rice, & McNair, 2012; Potvin & Marchand, 2016; Yarnitsky et al., 2014) and attentional biases to the sensation of pain (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013; Eccleston, 1994; McCracken, 1997). Resting state can allow us to examine how individual differences in the DMN (attention) or DPMS (modulation) can contribute to the chronification of pain, maintenance of chronic pain or vulnerability to developing this condition in the first place.

This approach can also be used with predictor variables, or individual differences variables, to understand how psychological or behavioural factors can be associated with variations in functional connectivity. This can allow insight for how individual differences may be associated with underlying neural mechanisms, and how these variations in mechanism can provide benefit or detriment to an individual when dealing with future instances of pain. In line with the recommendations of the IASP task force, this approach has great potential for assessment via the identification of robust indicators of pain sensitivity or treatment response. An associative benefit to this approach is that, if a predictor variable, such as a specific psychometric, can predict neural responses that relate to treatment response, then this can allow a non-imaging metric to be used to

predict treatment response. This has crucial clinical implications, as it could potentially identify those at risk of pain while eliminating the need for expensive fMRI scanning.

Based on this premise, a number of potential biomarkers for pain chronification or vulnerability to pain have already been proposed. For instance, it has been found that the DMN is disrupted by chronic pain and it was subsequently proposed that this may contribute to underlying cognitive and behavioural impairments that are associated with chronic pain (Baliki, Geha, Apkarian, & Chialvo, 2008). This DMN disruption has been noted in a wide-range of chronic pain conditions, including diabetic neuropathic pain, migraine, fibromyalgia, lower-back pain and temporomandibular disorder (Cauda et al., 2009; Napadow et al., 2010; Rocca et al., 2010; Tagliazucchi, Balenzuela, Fraiman, & Chialvo, 2010; Weissman-Fogel et al., 2011). To investigate this, a study was completed whereby lower-back pain patients & controls were scanned at baseline and after an intervention aimed at exacerbating the subjective intensity of pain (Loggia et al., 2013). Interestingly, the extent to which the interventions exacerbated their pain was predicted by baseline DMN connectivity & baseline connectivity between the DMN and right insula cortex, a key pain processing region. This is one example of rs-fMRI being used to identify an underlying mechanism associated with chronic pain, but also provides insight for interventional predictions, and may suggest this neural indicator could be applied to stratifying patients towards personalised treatment pathways, especially if a behavioural correlate for the mechanism is uncovered.

Regarding the DMN, it has previously been shown that chronic pain patients are more likely to possess an attentional bias towards pain (Crombez et al., 2013), and that even in healthy controls, this bias is related to the disruptive influence of pain on cognitive performance (Kucyi, Salomons, & Davis, 2016). Empirical literature has highlighted that when individuals are less focused on pain, and when their mind is wandering away from pain, the DMN and DPMS are both engaged (Kucyi, Salomons, & Davis, 2013). Consistent with this, it has also been found that patients with lower-back pain have *less* intra-DMN connectivity than healthy controls, but that this connectivity is

substantially restored after pain relieving acupuncture is administered to the LBP patients (Li et al., 2014). This finding is promising as it suggests that, not only is abnormal DMN connectivity related to the maintenance of a chronic pain condition, but also that reversal of this connectivity is associated with clinical improvements. Being able to track clinical outcomes or the subjective pain experience of a patient may enable us to evaluate treatment outcomes, or better yet, predict the onset of a condition, or recovery from the condition, by imaging the underlying mechanism.

As stated by the IASP taskforce, one of the main objections to using neural signatures to assess the presence of pain is that we cannot be confident in the sensitivity of our tools to be able to appropriately detect it. One reason behind this assertion is that, in their view, we are currently in the "discovery stage" of brain imaging, and our findings do not represent a finished product (Davis, 2019, p. 1). As such, whilst we are beginning to identify potential biomarkers, the ability to apply them predictively is still limited. For example, one promising study has highlighted that functional connectivity between the medial prefrontal cortex and nucleus accumbens was able to predict the transition from acute to chronic backpain (Baliki et al., 2012). It has also been noted that decreased pain sensitivity in experienced Zen-meditators can be predicted by reductions in functional connectivity between the anterior cingulate and DLPFC (Grant et al., 2011), indicating that this reduction in connectivity may be an indicator of a heightened ability to manage pain. Lastly, the response to placebo analgesia has also been predicted separately by functional connectivity between the insula and prefrontal cortices (Hashmi et al., 2013) and connectivity between the medial midfrontal gyrus and the rest of the brain (Tétreault et al., 2016). Whilst these findings are promising, they present a starting-point in the pursuit of clinically applicable predictive assessments for treatment. Understanding how these conditions develop, and who is likely to develop them is crucial for improving our knowledge of chronic pain. However, finding psychological or behavioural correlates of these resting state findings is essential for transitioning towards the clinic and real-world application, where access to MRI is limited and highly expensive.

1.4. Principle Questions

This thesis aims to contribute to the literature examining how psychology influences the way in which pain is modulated and how this may relate to intrinsic variability in processing pain. As reviewed above, pain represents a challenge both within the clinic and within the laboratory. Examples such as Beecher's famous observations of soldiers on the battlefield ascribing no pain to severe injuries (Beecher, 1946) or clinical observations of painful symptomology in the absence of underlying pathology (Brinjikji et al., 2015) serve to demonstrate the importance of psychology in pain processing. The literature highlights that psychological processes are associated with cortical activity which influence the way in which the ascending nociceptive signal can be modulated. We know that stable traits exist which may contribute to how effectively an individual can manage their pain, such as the efficiency of descending modulatory circuitry (as measured by CPM) (Granovsky & Yarnitsky, 2013; Lewis, Rice, et al., 2012; Yarnitsky et al., 2014) and psychological components such as depression or mindfulness (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006; Grant & Rainville, 2009). However, pain still presents a substantial problem for the clinic where variability in pain outcomes still remains a mystery in certain clinical domains (Abbott et al., 2011). While the influence of psychology on pain is growing in the clinic and laboratory, with support from large bodies such as the National Institute of Clinical Excellence (NICE), International Association for the Study of Pain (IASP) and the World Health Organisation (WHO), our understanding of this interaction is still limited. As such, further clinical, psychological and neuroscientific research is required to expand on an area with great potential for tackling one of the largest global health problems in the 21st century.

Do some patients experience severe pain within a medical procedure, while others do not? Are pain management strategies sufficient for managing these patients?

As reviewed above, even without a pathological indicator of injury or damage, subsets of patients will likely still experience pain. This disconnect between symptomology and pathology can present a serious clinical challenge. In chapter 2, we aimed to investigate the emergence of severe pain in a

subset of patients who underwent hysteroscopy; a diagnostic medical procedure described as being associated with no pain or a little discomfort (Appendix C). Within this study, we evaluated subjective ratings of pain within 801 hysteroscopy patients to investigate the emergence of severe pain within a subset of these patients. Within these assessment variables, we analysed whether clinicians were able to accurately estimate the intensity of pain being experienced by their patients. This was of interest because pain management, via the administration of local anaesthetic, was determined based on the clinician's subjective judgement of their patients' pain. Therefore, chapter 2 aimed to investigate the experience of pain within patients after a procedure deemed to elicit low-or-no pain and examined current clinical assessment techniques to understand the implications for pain management. We hypothesised that hysteroscopy would be a procedure associated with a range of pain intensities, and patients who experienced less intense pain during the operation would consider their expectations of the hysteroscopy matched or surpassed.

How is intrinsic trait mindfulness associated with pain, and what is the underlying mechanism?

As described within section 1.3.3, mindfulness-based interventions are associated with beneficial pain processing. But, as well as being conceptualised as a state (via short-term changes), mindfulness can also be viewed as a trait. Within chapter 3, data was collected from 40 healthy controls, who were naïve to mindfulness, meditation and MBIs. We used the Five Factor Mindfulness Questionnaire (FFMQ) to quantify the degree to which they were intrinsically mindful and calculated sensory pain thresholds and pain catastrophising using the Pain Catastrophising Scale (PCS) (Baer et al., 2008; Sullivan et al., 1995). This allowed us to investigate how untrained, trait mindfulness may provide an innate marker of effective pain management, and whether it was able to yield this benefit across sensory and cognitive dimensions of pain. We also completed a rs-fMRI scan to understand how participants resting state connectivity was associated with trait mindfulness, in order to decipher the neurological underpinnings of trait mindfulness at rest and to help clarify how this mechanism may provide a beneficial influence for managing pain. As mindfulness is known to be an attentional regulation process, we used seed-based connectivity

analysis to attempt to evaluate activity of the precuneus, a core node within the DMN. The DMN is an attentionally-relevant resting state network associated with ruminative and self-reflectory processes that represent the anti-thesis for mindfulness. Understanding how attentional regulation may be variably connected with other cortical regions may help explain how trait mindfulness provides a positive influence for the processing of pain. We hypothesised that trait mindfulness would elicit similar pain-related benefits as reported in the interventional mindfulness literature, and that this would be achieved via attentional regulation.

What can individual differences in conditioned pain modulation (CPM) inform us about the underlying connectivity of pain modulation?

CPM is a psychophysical assessment that is viewed as a proxy for the efficiency of an individual's descending pain modulation circuitry (Lewis, Rice, et al., 2012; Yarnitsky et al., 2014). CPM represents a method of "pain inhibits pain", and the higher the CPM score, the greater an individual's ability to modulate a peripheral nociceptive stimulus. CPM has also been utilised as a predictive clinical assessment tool, and poor CPM has been associated with a range of detrimental outcomes across multiple clinical domains, such as surgeries for multiple conditions (Wilder-Smith & Robert-Yap, 2007; Yarnitsky et al., 2008), analgesia efficacy (Yarnitsky et al., 2012), and is also associated with the persistent maintenance of chronic pain conditions (Daenen et al., 2013; Mlekusch et al., 2016). However, it is unclear why this basic psychophysical tool can predict such a range of varied clinical outcomes, and what neural aspects of pain individual differences in CPM may be associated with. Within chapter 4, we targeted our analysis to the PAG, as being a key modulatory region, heavily associated with the descending modulatory pathway that relays signals between the cortex and the brainstem (and ultimately spinal cord). Using rs-fMRI and resting state data from 40 healthy controls, we used seed-based connectivity analysis to target the PAG and understand how functional connectivity between the PAG and the cortex may be associated with individual differences in CPM. We predicted that higher CPM, and therefore more effective pain

modulation, would be associated with heightened integration of the PAG with other regions involved in the processing of pain.

1.5. References

Abbott, C. A., Malik, R. A., Van Ross, E. R. E., Kulkarni, J., & Boulton, A. J. M. (2011). Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care*, *34*(10), 2220–2224. https://doi.org/10.2337/dc11-1108

Adler, G., & Gattaz, W. F. (1993). Pain perception threshold in major depression. *Biological Psychiatry*, *34*(10), 687–689. https://doi.org/10.1016/0006-3223(93)90041-B

Alford, D. P., German, J. S., Samet, J. H., Cheng, D. M., Lloyd-Travaglini, C. A., & Saitz, R. (2016). Primary Care Patients with Drug Use Report Chronic Pain and Self-Medicate with Alcohol and Other Drugs. *Journal of General Internal Medicine*, *31*(5), 486–491. https://doi.org/10.1007/s11606-016-3586-5

Apkarian, A. V., Baliki, M. N., & Farmer, M. A. (2013). Predicting transition to chronic pain. *Current Opinion in Neurology*, *26*(4), 360–367. https://doi.org/10.1097/WCO.0b013e32836336ad

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*(4), 463–484. https://doi.org/10.1016/j.ejpain.2004.11.001

Asmundson, G. J. G., & Katz, J. (2009). Understanding the co-occurrence of anxiety disorders and chronic pain: State-of-the-art. *Depression and Anxiety*, *26*(10), 888–901. https://doi.org/10.1002/da.20600

Baer, R. A., Smith, G., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., … Williams, J. M. G. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment*, *15*(3), 329–342. https://doi.org/10.1177/1073191107313003

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and Pain Comorbidity. *Archives of Internal Medicine*, *163*(20), 2433. https://doi.org/10.1001/archinte.163.20.2433

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics. *Journal of Neuroscience*, *28*(6), 1398–1403. https://doi.org/10.1523/JNEUROSCI.4123-07.2008

Baliki, Marwan N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., … Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience*, *15*(8), 1117–1119. https://doi.org/10.1038/nn.3153

Banks, S. M., & Kerns, R. D. (1996). Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychological Bulletin*, *119*(1), 95–110. https://doi.org/10.1037/0033-2909.119.1.95

Barr, M. S., Farzan, F., Davis, K. D., Fitzgerald, P. B., & Daskalakis, Z. J. (2013). Measuring GAB aergic inhibitory activity with TMS-EEG and its potential clinical application for chronic pain. *Journal of Neuroimmune Pharmacology*, *8*(3), 535–546. https://doi.org/10.1007/s11481-012-9383-y

Beecher, H. K. (1946). Pain in Men Wounded in Battle. *Annals of Surgery*, *123*(1), 96–105. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17858731

Bessou, P., & Perl, E. R. (1969). Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *Journal of Neurophysiology*, *32*(6), 1025–1043. https://doi.org/10.1152/jn.1969.32.6.1025

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., … Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. https://doi.org/10.1093/clipsy/bph077

Blumer, D., & Heilbronn, M. (1981). The pain-prone disorder: A clinical and psychological profile. *Psychosomatics*, *22*(5), 395–397. https://doi.org/10.1016/S0033-3182(81)73509-6

Bossmann, T., Brauner, T., & Horstmann, T. (2018). Differences in pain intensity in anti- and pro-nociceptive pain profile subgroups in patients with knee osteoarthritis. *Pain Management*, *8*(1), 27–36. https://doi.org/10.2217/pmt-2017-0039

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain*, *10*(4), 287–333. https://doi.org/10.1016/j.ejpain.2005.06.009

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., … Jarvik, J. G. (2015). Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology*, *36*(4), 811–816. https://doi.org/10.3174/ajnr.A4173

Bruce, J., Thornton, A. J., Powell, R., Johnston, M., Wells, M., Heys, S. D., … Scott, N. W. (2014). Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain*, *155*(2), 232–243. https://doi.org/10.1016/j.pain.2013.09.028

Bruce, J., Thornton, A. J., Powell, R., Johnston, M., Wells, M., Heys, S. D., … Scott, N. W. (2014). Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain*, *155*(2), 232–243. https://doi.org/10.1016/j.pain.2013.09.028

Bunzli, S., Watkins, R., Smith, A., Schütze, R., & O'Sullivan, P. (2013). Lives on hold: a qualitative synthesis exploring the experience of chronic low-back pain. *The Clinical Journal of Pain*, *29*(10), 907–916. https://doi.org/10.1097/AJP.0b013e31827a6dd8

Burgess, P. R., & Perl, E. R. (1967). Myelinated afferent fibres responding specifically to noxious stimulation of the skin. *The Journal of Physiology*, *190*(3), 541–562. https://doi.org/10.1113/jphysiol.1967.sp008227

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

Cabral, J., Kringelbach, M. L., & Deco, G. (2014). Exploring the network dynamics underlying brain activity during rest. *Progress in Neurobiology*, *114*, 102–131. https://doi.org/10.1016/j.pneurobio.2013.12.005

Cadden, S. W., Villanueva, L., Chitour, D., & Le Bars, D. (1983). Depression of activities of dorsal horn convergent

neurones by propriospinal mechanisms triggered by noxious inputs; comparison with diffuse noxious inhibitory controls (DNIC). *Brain Research*, *275*(1), 1–11. https://doi.org/10.1016/0006-8993(83)90412-2
Campbell, C., & Guy, A. (2007). `Why Can't They Do Anything for a Simple Back Problem?'. *Journal of Health Psychology*, *12*(4), 641–652. https://doi.org/10.1177/1359105307078171
Cauda, F., Sacco, K., Duca, S., Cocito, D., D'Agata, F., Geminiani, G. C., & Canavero, S. (2009). Altered Resting State in Diabetic Neuropathic Pain. *PLoS ONE*, *4*(2), e4542. https://doi.org/10.1371/journal.pone.0004542
Chapman, C. R., & Vierck, C. J. (2017). The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *The Journal of Pain*, *18*(4), 359.e1-359.e38. https://doi.org/10.1016/j.jpain.2016.11.004
Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*, *17*(1), 83–93. https://doi.org/10.1089/acm.2009.0546
Christensen, B. N., & Perl, E. R. (1970). Spinal neurons specifically excited by noxious or thermal stimuli: marginal zone of the dorsal horn. *Journal of Neurophysiology*, *33*(2), 293–307. https://doi.org/10.1152/jn.1970.33.2.293
Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (2017). Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism. *Journal of Neurophysiology*, *82*(4), 1934–1943. https://doi.org/10.1152/jn.1999.82.4.1934
Cohen, S. P. (2005). Sacroiliac joint pain: A comprehensive review of anatomy, diagnosis and treatment. *Anesthesia and Analgesia*, *101*(5), 1440–1453. https://doi.org/10.1213/01.ANE.0000180831.60169.EA
Cook, A. J., Woolf, C. J., Wall, P. D., & Mcmahon, S. B. (1987). Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. *Nature*, *325*(6100), 151–153. https://doi.org/10.1038/325151a0
Coole, C., Drummond, A., Watson, P. J., & Radford, K. (2010). What concerns workers with low back pain? Findings of a qualitative study of patients referred for rehabilitation. *Journal of Occupational Rehabilitation*, *20*(4), 472–480. https://doi.org/10.1007/s10926-010-9237-5
Corbett, M., Foster, N. E., & Ong, B. N. (2007). Living with low back pain-Stories of hope and despair. *Social Science and Medicine*, *65*(8), 1584–1594. https://doi.org/10.1016/j.socscimed.2007.06.008
Coronado, R. A., Kindler, L. L., Valencia, C., & George, S. Z. (2011). Thermal and Pressure Pain Sensitivity in Patients with Unilateral Shoulder Pain: Comparison of Involved and Uninvolved Sides. *Journal of Orthopaedic & Sports Physical Therapy*, *41*(3), 165–173. https://doi.org/10.2519/jospt.2011.3416
Coronado, R. A., Simon, C. B., Valencia, C., & George, S. Z. (2014). Experimental Pain Responses Support Peripheral and Central Sensitization in Patients With Unilateral Shoulder Pain. *The Clinical Journal of Pain*, *30*(2), 143–151. https://doi.org/10.1097/AJP.0b013e318287a2a4
Cousins, M. J., & Lynch, M. E. (2011). The Declaration Montreal: Access to pain management is a fundamental human right. *Pain*, *152*(12), 2673–2674. https://doi.org/10.1016/j.pain.2011.09.012
Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, *14*(2), 158–160. https://doi.org/10.1002/wps.20229
Croft, P., Blyth, F., & van der Windt, D. (2010). The global occurrence of chronic pain: an introduction. In P. Croft, F. Blyth, & D. van der Windt (Eds.), *Chronic Pain Epidemiology from Aetiology to Public Health* (pp. 9–18). Oxford: Oxford University Press.
Croft, P. R., Papageorgiou, A. C., Ferry, S., Thomas, E., Jayson, M. I., & Silman, A. J. (1995). Psychologic distress and low back pain. Evidence from a prospective study in the general population. *Spine*, *20*(24), 2731–2737. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8747252
Crombez, G., Viane, I., Eccleston, C., Devulder, J., & Goubert, L. (2013). Attention to pain and fear of pain in patients with chronic pain. *Journal of Behavioral Medicine*, *36*(4), 371–378. https://doi.org/10.1007/s10865-012-9433-1
Cruz-Almeida, Y., & Fillingim, R. B. (2014). Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management? *Pain Medicine*, *15*(1), 61–72. https://doi.org/10.1111/pme.12230
Cruz-Fuentes, C., Blas, C., Gonzalez, L., Camarena, B., & Nicolini, H. (2004). Severity of obsessive-compulsive symptoms is related to self-directedness character trait in obsessive-compulsive disorder. *CNS Spectrums*, *9*(8), 607–612. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15273653
Cui, M., Feng, Y., Adoo, D. J. M. C., Willis, W. D., McAdoo, D. J., & Willis, W. D. (1999). Periaqueductal Gray Stimulation-Induced Inhibition of Nociceptive Dorsal Horn Neurons in Rats is Associated With the Release of Norepinephrine, Serotonin, and Amino Acids. *The Journal of Pharmacology and Experimental Therapeutics*, *289*(2), 868–876.
D'Mello, R., & Dickenson, A. H. (2008). Spinal cord mechanisms of pain. *British Journal of Anaesthesia*, *101*(1), 8–16. https://doi.org/10.1093/bja/aen088
Daenen, L., Nijs, J., Roussel, N., Wouters, K., Van Loo, M., & Cras, P. (2013). Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: An experimental study. *Clinical Rheumatology*, *32*(1), 23–31. https://doi.org/10.1007/s10067-012-2085-2
Davis, K. D. (2019). Imaging vs quantitative sensory testing to predict chronic pain treatment outcomes. *PAIN*, *160*(5), S59–S65. https://doi.org/10.1097/j.pain.0000000000001479
Davis, K. D., Flor, H., Greely, H. T., Iannetti, G. D., Mackey, S., Ploner, M., … Wager, T. D. (2017). Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nature Reviews Neurology*, *13*(10), 624–638. https://doi.org/10.1038/nrneurol.2017.122
Davis, K. D., & Moayedi, M. (2013). Central mechanisms of pain revealed through functional and structural MRI. *Journal of Neuroimmune Pharmacology*, *8*(3), 518–534. https://doi.org/10.1007/s11481-012-9386-8
De Felice, M., Sanoja, R., Wang, R., Vera-Portocarrero, L., Oyarzo, J., King, T., … Porreca, F. (2011). Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain. *Pain*, *152*(12), 2701–2709. https://doi.org/10.1016/j.pain.2011.06.008
Demyttenaere, K., Bruffaerts, R., Lee, S., Posada-Villa, J., Kovess, V., Angermeyer, M. C., … Von Korff, M. (2007). Mental disorders among persons with chronic back or neck pain: Results from the world mental health surveys.

Pain, *129*(3), 332–342. https://doi.org/10.1016/j.pain.2007.01.022
Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: a neurobiological perspective. *Nature Neuroscience*, *17*(2), 192–200. https://doi.org/10.1038/nn.3628
Derbyshire, S. W. G., Jones, A. K. P., Gyulai, F., Clark, S., Townsend, D., & Firestone, L. L. (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain*, *73*(3), 431–445. https://doi.org/10.1016/S0304-3959(97)00138-3
Diamond, S. (1964). Depressive Headaches. *Headache: The Journal of Head and Face Pain*, *4*(3), 255–260. https://doi.org/10.1111/j.1526-4610.1964.hed0403255.x
Diatchenko, L., Nackley, A. G., Slade, G. D., Fillingim, R. B., & Maixner, W. (2006). Idiopathic pain disorders - Pathways of vulnerability. *Pain*, *123*(3), 226–230. https://doi.org/10.1016/j.pain.2006.04.015
Dickenson, A. H. (2002). Gate control theory of pain stands the test of time. *British Journal of Anaesthesia*, *88*(6), 755–757. https://doi.org/10.1093/bja/88.6.755
Dickenson, J., Berkman, E. T., Arch, J., & Lieberman, M. D. (2013). Neural correlates of focused attention during a brief mindfulness induction. *Social Cognitive and Affective Neuroscience*, *8*(1), 40–47. https://doi.org/10.1093/scan/nss030
Dieppe, P. A., & Lohmander, L. S. (2005). Pathogenesis and management of pain in osteoarthritis. *The Lancet*, *365*(9463), 965–973. https://doi.org/10.1016/S0140-6736(05)71086-2
Dos Santos Pinheiro, E. S., De Queirós, F. C., Montoya, P., Santos, C. L., Do Nascimento, M. A., Ito, C. H., … Baptista, A. F. (2016). Electroencephalographic patterns in chronic pain: A systematic review of the literature. *PLoS ONE*, *11*(2), 1–26. https://doi.org/10.1371/journal.pone.0149085
Dubin, A. E., & Patapoutian, A. (2010). Nociceptors : the sensors of the pain pathway Find the latest version : Review series Nociceptors : the sensors of the pain pathway. *Journal of Clinical Investigation*, *120*(11), 3760–3772. https://doi.org/10.1172/JCI42843.3760
Dunbar, R. I. M., Baron, R., Frangou, A., Pearce, E., van Leeuwen, E. J. C., Stow, J., … van Vugt, M. (2012). Social laughter is correlated with an elevated pain threshold. *Proceedings of the Royal Society B: Biological Sciences*, *279*(1731), 1161–1167. https://doi.org/10.1098/rspb.2011.1373
Eccleston, C. (1994). Chronic pain and attention: A cognitive approach. *British Journal of Clinical Psychology*, *33*(4), 535–547. https://doi.org/10.1111/j.2044-8260.1994.tb01150.x
Edwards, R. R., Dworkin, R. H., Sullivan, M. D., Turk, D. C., & Wasan, A. D. (2016). The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *The Journal of Pain*, *17*(9), T70–T92. https://doi.org/10.1016/j.jpain.2016.01.001
Eisenberger, N. I. (2003). Does Rejection Hurt? An fMRI Study of Social Exclusion. *Science*, *302*(5643), 290–292. https://doi.org/10.1126/science.1089134
Elliott, A. M., Smith, B. H., Penny, K. I., Smith, W. C., & Chambers, W. A. (1999). The epidemiology of chronic pain in the community. *Lancet (London, England)*, *354*(9186), 1248–1252. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10520633
Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. A., Snyder, A. Z., Cohen, J. D., … Sheline, Y. I. (2008). Altered Emotional Interference Processing in Affective and Cognitive-Control Brain Circuitry in Major Depression. *Biological Psychiatry*, *63*(4), 377–384. https://doi.org/10.1016/j.biopsych.2007.06.012
Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*(1–2), 56–78. https://doi.org/10.1002/hbm.460020107
Gamsa, A. (1994). The role of psychological factors in chronic pain. I. A half century of study. *Pain*, *57*(1), 5–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8065796
Gaskin, M. E., Greene, A. F., Robinson, M. E., & Geisser, M. E. (1992). Negative affect and the experience of chronic pain. *Journal of Psychosomatic Research*, *36*(8), 707–713. https://doi.org/10.1016/0022-3999(92)90128-O
Gatchel, R. J., McGeary, D. D., McGeary, C. A., & Lippe, B. (2014). Interdisciplinary chronic pain management: Past, present, and future. *American Psychologist*, *69*(2), 119–130. https://doi.org/10.1037/a0035514
Gatchel, R. J., Polatin, P. B., & Kinney, R. K. (1995). Predicting Outcome of Chronic Back Pain Using Clinical Predictors of Psychopathology: A Prospective Analysis. *Health Psychology*, *14*(5), 415–420. https://doi.org/10.1037/0278-6133.14.5.415
Gauriau, C., & Bernard, J. (2002). Pain pathways and parabrachial circuits in the rat. *Experimental Physiology*, *87*(2), 251–258.
Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. W. (2006). Deficient inhibition of emotional information in depression. *Journal of Affective Disorders*, *93*(1–3), 149–157. https://doi.org/10.1016/j.jad.2006.03.007
Granges, G., & Littlejohn, G. (1993). Pressure pain threshold in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome. *Arthritis & Rheumatism*, *36*(5), 642–646. https://doi.org/10.1002/art.1780360510
Granovsky, Y. (2013). Conditioned Pain Modulation: A Predictor for Development and Treatment of Neuropathic Pain. *Current Pain and Headache Reports*, *17*(9), 361. https://doi.org/10.1007/s11916-013-0361-8
Granovsky, Y., & Yarnitsky, D. (2013). Personalized Pain Medicine: The Clinical Value of Psychophysical Assessment of Pain Modulation Profile. *Rambam Maimonides Medical Journal*, *4*(4), 1–8. https://doi.org/10.5041/RMMJ.10131
Grant, J. A., Courtemanche, J., & Rainville, P. (2011). A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*, *152*(1), 150–156. https://doi.org/10.1016/j.pain.2010.10.006
Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in zen meditators: A cross-sectional study. *Psychosomatic Medicine*, *71*(1), 106–114. https://doi.org/10.1097/PSY.0b013e31818f52ee
Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253–258.

https://doi.org/10.1073/pnas.0135058100
Hadjipavlou, G., Dunckley, P., Behrens, T. E., & Tracey, I. (2006). Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: A diffusion tensor imaging study in healthy controls. *Pain*, *123*(1–2), 169–178. https://doi.org/10.1016/j.pain.2006.02.027
Hamelsky, S. W., & Lipton, R. B. (2006). Psychiatric comorbidity of migraine. *Headache*, *46*(9), 1327–1333. https://doi.org/10.1111/j.1526-4610.2006.00576.x
Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., … Apkarian, A. V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*, *136*(9), 2751–2768. https://doi.org/10.1093/brain/awt211
Heinricher, M. M., Tavares, I., Leith, J. L., & Lumb, B. M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Research Reviews*, *60*(1), 214–225. https://doi.org/10.1016/j.brainresrev.2008.12.009
Helmstetter, F. J., Tershner, S. A., Poore, L. H., & Bellgowan, P. S. F. (1998). Antinociception following opioid stimulation of the basolateral amygdala is expressed through the periaqueductal gray and rostral ventromedial medulla. *Brain Research*, *779*(1–2), 104–118. https://doi.org/10.1016/S0006-8993(97)01104-9
Holloway, I., Sofaer, B., & Walker, J. (2016). The Transition from Well Person to "Pain Afflicted" Patient: The Career of People with Chronic Back Pain. *Illness, Crisis & Loss*, *8*(4), 373–387. https://doi.org/10.1177/105413730000800403
Iannetti, G. D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research*, *205*(1), 1–12. https://doi.org/10.1007/s00221-010-2340-1
Jarvik, J. G., Hollingworth, W., Heagerty, P. J., Haynor, D. R., Boyko, E. J., & Deyo, R. A. (2005). Three-year incidence of low back pain in an initially asymptomatic cohort: Clinical and imaging risk factors. *Spine*, *30*(13), 1541–1548. https://doi.org/10.1097/01.brs.0000167536.60002.87
Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*. https://doi.org/10.1016/0163-8343(82)90026-3
Karl, J. F. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*(1–2), 56–78. Retrieved from http://dx.doi.org/10.1002/hbm.460020107
Katz, J., & Rosenbloom, B. N. (2015). The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management. *Pain Research and Management*, *20*(6), 285–286. https://doi.org/10.1155/2015/865487
Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., … National Comorbidity Survey Replication. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, *289*(23), 3095–3105. https://doi.org/10.1001/jama.289.23.3095
Khan, R. S., Ahmed, K., Blakeway, E., Skapinakis, P., Nihoyannopoulos, L., MacLeod, K., … Athanasiou, T. (2011). Catastrophizing: A predictive factor for postoperative pain. *American Journal of Surgery*, *201*(1), 122–131. https://doi.org/10.1016/j.amjsurg.2010.02.007
Koster, E. H. W., De Raedt, R., Goeleven, E., Franck, E., & Crombez, G. (2005). Mood-congruent attentional bias in dysphoria: Maintained attention to and impaired disengagement from negative information. *Emotion*, *5*(4), 446–455. https://doi.org/10.1037/1528-3542.5.4.446
Krames, E. S., & Olson, K. (1997). Clinical realities and economic considerations: Patient selection in intrathecal therapy. *Journal of Pain and Symptom Management*, *14*(3), S3–S13. https://doi.org/10.1016/S0885-3924(97)00166-8
Kucyi, A, Salomons, T. V, & Davis, K. D. (2013). Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *PNAS*, *110*(46), 18692–18697. https://doi.org/10.1073/pnas.1312902110
Kucyi, Aaron, & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences*, *38*(2), 86–95. https://doi.org/10.1016/j.tins.2014.11.006
Kucyi, Aaron, Salomons, T. V., & Davis, K. D. (2016). Cognitive behavioral training reverses the effect of pain exposure on brain network activity. *Pain*, *157*(9), 1895–1904. https://doi.org/10.1097/j.pain.0000000000000592
Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *The Journal of Pain*, *10*(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012
Le Bars, D., Dickenson, A. H., & Besson, J. M. (1979). Diffuse noxious inhibitory controls. I. Effects on dorsal horn convergent neurons in the rat. II. Lack of effect on nonconvergent neurons, supraspinal involvement and theoretical implications. *Pain*, *6*(3), 305–327. https://doi.org/10.1016/0304-3959(79)90049-6
Legrain, V., Iannetti, G. D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: A salience detection system for the body. *Progress in Neurobiology*, *93*(1), 111–124. https://doi.org/10.1016/j.pneurobio.2010.10.005
Leiser, S. C., Dunlop, J., Bowlby, M. R., & Devilbiss, D. M. (2011). Aligning strategies for using EEG as a surrogate biomarker: A review of preclinical and clinical research. *Biochemical Pharmacology*, *81*(12), 1408–1421. https://doi.org/10.1016/j.bcp.2010.10.002
Lesse, S. (1968). The multivariant masks of depression. *The American Journal of Psychiatry*, *124*(11), 35–40. https://doi.org/10.1176/ajp.124.11S.35
Lewis, G. N., Heales, L., Rice, D. A., Rome, K., & McNair, P. J. (2012). Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*, *17*(2), 98–102. https://doi.org/10.1155/2012/610561
Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2012.07.005
Li, J., Zhang, J. H., Yi, T., Tang, W. J., Wang, S. W., & Dong, J. C. (2014). Acupuncture treatment of chronic low back pain reverses an abnormal brain default mode network in correlation with clinical pain relief. *Acupuncture in Medicine : Journal of the British Medical Acupuncture Society*, *32*(2), 102–108. https://doi.org/10.1136/acupmed-

2013-010423
Linton, S. J. (2000). A review of psychological risk factors in back and neck pain. *Spine*, *25*(9), 1148–1156. https://doi.org/10.1097/00007632-200005010-00017
Loggia, M. L., Kim, J., Gollub, R. L., Vangel, M. G., Kirsch, I., Kong, J., … Napadow, V. (2013). Default mode network connectivity encodes clinical pain: An arterial spin labeling study. *Pain*, *154*(1), 24–33. https://doi.org/10.1016/j.pain.2012.07.029
Lohman, D., Schleifer, R., & Amon, J. J. (2010). Access to pain treatment as a human right. *BMC Medicine*, *8*. https://doi.org/10.1186/1741-7015-8-8
Lovell, G. (1995). The Diagnosis of Chronic Groin Pain in Athletes: A review of 189 cases. *The Australian Journal of Science and Medicine in Sport*, *27*(3), 76–79.
Lynch, M. E., Campbell, F. A., Clark, A. J., Dunbar, M. J., Goldstein, D., Peng, P., … Tupper, H. (2007). Waiting for Treatment for Chronic Pain – a Survey of Existing Benchmarks: Toward Establishing Evidence-Based Benchmarks for Medically Acceptable Waiting Times. *Pain Research and Management*, *12*(4), 245–248. https://doi.org/10.1155/2007/891951
Lynch, M. E., Campbell, F., Clark, A. J., Dunbar, M. J., Goldstein, D., Peng, P., … Tupper, H. (2008). A systematic review of the effect of waiting for treatment for chronic pain. *Pain*, *136*(1), 97–116. https://doi.org/10.1016/j.pain.2007.06.018
Mackey, I. G., Dixon, E. A., Johnson, K., & Kong, J.-T. (2017). Dynamic Quantitative Sensory Testing to Characterize Central Pain Processing. *Journal of Visualized Experiments*, (120), 1–9. https://doi.org/10.3791/54452
Magni, G., Caldieron, C., Rigatti-Luchini, S., & Merskey, H. (1990). Chronic musculoskeletal pain and depressive symptoms in the general population. An analysis of the 1st National Health and Nutrition Examination Survey data. *Pain*, *43*(3), 299–307. https://doi.org/10.1016/0304-3959(90)90027-B
Maher, C., Underwood, M., & Buchbinder, R. (2017). Non-specific low back pain. *The Lancet*, *389*(10070), 736–747. https://doi.org/10.1016/S0140-6736(16)30970-9
Maracle, E. C., Hung, L. Y., Fell, S. I., Osmond, M. R., Brown, S. H. M., & Srbely, J. Z. (2017). A Comparison of the Sensitivity of Brush Allodynia and Semmes–Weinstein Monofilament Testing in the Detection of Allodynia Within Regions of Secondary Hyperalgesia in Humans. *Pain Practice*, *17*(1), 16–24. https://doi.org/10.1111/papr.12418
Marcuzzi, A., Wrigley, P. J., Dean, C. M., Adams, R., & Hush, J. M. (2017). The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. *Pain*, *158*(7), 1217–1223. https://doi.org/10.1097/j.pain.0000000000000901
Masson, E. A., & Boulton, A. J. M. (1991). The Neurometer: Validation and Comparison with Conventional Tests for Diabetic Neuropathy. *Diabetic Medicine*, *8*(S2), S63–S66. https://doi.org/10.1111/j.1464-5491.1991.tb02159.x
May, A. (2009). New insights into headache: An update on functional and structural imaging findings. *Nature Reviews Neurology*, *5*(4), 199–209. https://doi.org/10.1038/nrneurol.2009.28
McCracken, L. M. (1997). "Attention" to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, *28*(2), 271–284. https://doi.org/10.1016/S0005-7894(97)80047-0
McGhie, J., & Grady, K. (2016). Where now for UK chronic pain management services? *British Journal of Anaesthesia*, *116*(2), 159–162. https://doi.org/10.1093/bja/aev447
McGhie, Jon. (2014). Faculty of Pain Medicine: Workforce Update. *Transmitter*, 10–11.
McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain*, *106*(1), 127–133. https://doi.org/10.1016/S0304-3959(03)00301-4
Melzack, R., & Wall, P. (1965). Pain Mechanism: A new Theory. *Science*. https://doi.org/10.1126/science.150.3699.971
Mendell, L. M. (1966). Physiological Properties Projection of the Unmyelinated Spinal Fiber to spinal cord. *Experimental Neurology*, *16*, 316–332.
Mendell, L. M. (2014). Constructing and deconstructing the gate theory of pain. *Pain*, *155*(2), 210–216. https://doi.org/10.1016/j.pain.2013.12.010
Merskey, H., Addison, R. G., Beric, A., Blumberg, H., Bogduk, N., Boivie, J., … Watson, C. P. N. (2002). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Second edition.* (H. Merskey & N. Bogduk, Eds.), *IASP Press* (Second). Seattle, WA: IASP Press. Retrieved from http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf
Micó, J. A., Ardid, D., Berrocoso, E., & Eschalier, A. (2006). Antidepressants and pain. *Trends in Pharmacological Sciences*, *27*(7), 348–354. https://doi.org/10.1016/j.tips.2006.05.004
Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6), 355–474. https://doi.org/10.1016/S0301-0082(02)00009-6
Mirowsky, J., & Ross, C. E. (2002). Measurement for a human science. *Journal of Health and Social Behavior*, *43*(2), 152–170. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12096697
Mlekusch, S., Neziri, A. Y., Limacher, A., Juni, P., Arendt-Nielsen, L., & Curatolo, M. (2016). Conditioned pain modulation in patients with acute and chronic low back pain. *Clinical Journal of Pain*, *32*(2), 116–121. https://doi.org/10.1097/AJP.0000000000000238
Moret, C., & Briley, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment*, *7*(Suppl 1), 9. https://doi.org/10.2147/NDT.S19619
Moulin, D. E., Clark, A. J., Speechley, M., & Morley-Forster, P. K. (2002). Chronic pain in Canada--prevalence, treatment, impact and the role of opioid analgesia. *Pain Research & Management*, *7*(4), 179–184. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36215849
Mouraux, A., Diukova, A., Lee, M. C., Wise, R. G., & Iannetti, G. D. (2011). A multisensory investigation of the functional significance of the "pain matrix." *NeuroImage*, *54*(3), 2237–2249. https://doi.org/10.1016/j.neuroimage.2010.09.084

Mun, C. J., Okun, M. A., & Karoly, P. (2014). Trait mindfulness and catastrophizing as mediators of the association between pain severity and pain-related impairment. *Personality and Individual Differences*, *66*, 68–73. https://doi.org/10.1016/j.paid.2014.03.016
Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis and Rheumatism*, *62*(8), 2545–2555. https://doi.org/10.1002/art.27497
Nardone, R., Höller, Y., Brigo, F., Orioli, A., Tezzon, F., Schwenker, K., … Trinka, E. (2015). Descending motor pathways and cortical physiology after spinal cord injury assessed by transcranial magnetic stimulation: a systematic review. *Brain Research*, *1619*, 139–154. https://doi.org/10.1016/j.brainres.2014.09.036
Naylor, B., Boag, S., & Gustin, S. M. (2017). New evidence for a pain personality? A critical review of the last 120 years of pain and personality. *Scandinavian Journal of Pain*, *17*, 58–67. https://doi.org/10.1016/j.sjpain.2017.07.011
Nisbett, R. E., & Schachter, S. (1966). Cognitive manipulation of pain. *Journal of Experimental Social Psychology*, *2*(3), 227–236. https://doi.org/10.1016/0022-1031(66)90081-3
Omelchenko, N., & Sesack, S. R. (2009). Periaqueductal gray afferents synapse onto dopamine and GABA neurons in the rat ventral tegmental area. *Journal of Neuroscience Research*, *88*(5), NA-NA. https://doi.org/10.1002/jnr.22265
Osborn, M., & Smith, J. A. (1998). The personal experience of chronic benign lower back pain: An interpretative phenomenological analysis. *British Journal of Health Psychology*, *3*(1), 65–83. https://doi.org/10.1111/j.2044-8287.1998.tb00556.x
Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766
Penttinen, J. (1995). Back Pain and Risk of Suicide among Finnish Farmers. *American Journal of Public Health*, *85*(10), 1452–1453.
Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. *Neurophysiologie Clinique = Clinical Neurophysiology*, *30*(5), 263–288. Retrieved from papers://40c68295-5659-4035-8dff-71162e06882b/Paper/p420
Pincus, T., Burton, A. K., Vogel, S., & Field, A. P. (2002). A Systematic Review of Psychological Factors as Predictors of Chronicity/Disability in Prospective Cohorts of Low Back Pain. *Spine*, *27*(5), E109–E120. https://doi.org/10.1097/00007632-200203010-00017
Ploner, M., & May, E. S. (2018). EEG and MEG in pain research – Current state and future perspectives. *Pain*, *159*, 206–2011. https://doi.org/10.1097/j.pain.0000000000001087
Ponirakis, G., Odriozola, M. N., Odriozola, S., Petropoulos, I. N., Azmi, S., Ferdousi, M., … Malik, R. A. (2016). NerveCheck for the Detection of Sensory Loss and Neuropathic Pain in Diabetes. *Diabetes Technology & Therapeutics*, *18*(12), 800–805. https://doi.org/10.1089/dia.2016.0279
Porreca, F., Ossipov, M. H., & Gebhart, G. . (2002). Chronic pain and medullary descending facilitation. *Trends in Neurosciences*, *25*(6), 319–325. https://doi.org/10.1016/S0166-2236(02)02157-4
Potvin, S., & Marchand, S. (2016). Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*, *157*(8), 1704–1710. https://doi.org/10.1097/j.pain.0000000000000573
Price, D. D. (2000). Psychological and Neural Mechanisms of the Affective Dimension of Pain. *Science*, *288*(5472), 1769–1772. https://doi.org/10.1126/science.288.5472.1769
Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, Lawrence, C., LaMantia, A.-S., McNamara, J. O., & Williams, M. S. (2001). *Neuroscience*. Sunderland, MA: Sinauer Associates.
Ren K, & Dubner R. (2002). Descending modulation in persistent pain: an update. *Pain*, *100*, 1–6.
Rey, R. (1998). *The History of Pain*. (J. Cadden & S. W. Cadden, Eds.). Boston: Harvard University Press.
Reynolds, D. . (1969). Surgery in the Rat during Electrical Analgesia Induced by Focal Brain Stimulation. *Science*, *164*(3878), 444–445.
Rocca, M. A., Valsasina, P., Absinta, M., Colombo, B., Barcella, V., Falini, A., … Filippi, M. (2010). Central nervous system dysregulation extends beyond the pain-matrix network in cluster headache. *Cephalalgia*, *30*(11), 1383–1391. https://doi.org/10.1177/0333102410365164
Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R. D., Beyer, A., … Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain*, *123*(3), 231–243. https://doi.org/10.1016/j.pain.2006.01.041
Salomons, T. V., Iannetti, G. D., Liang, M., & Wood, J. N. (2016). The "Pain Matrix" in Pain-Free Individuals. *JAMA Neurology*, *73*(6), 755. https://doi.org/10.1001/jamaneurol.2016.0653
Salomons, T. V, & Kucyi, A. (2011). Does Meditation Reduce Pain through a Unique Neural Mechanism? *Journal of Neuroscience*, *31*(36), 12705–12707. https://doi.org/10.1523/JNEUROSCI.2843-11.2011
Sandkühler, J. (2009). Models and Mechanisms of Hyperalgesia and Allodynia. *Physiological Reviews*, *89*(2), 707–758. https://doi.org/10.1152/physrev.00025.2008
Sayar, K., Arikan, M., & Yontem, T. (2002). Sleep Quality in Chronic Pain Patients. *The Canadian Journal of Psychiatry*, *47*(9), 844–848. https://doi.org/10.1177/070674370204700905
Schmidt-Wilcke, T., Ichesco, E., Hampson, J. P., Kairys, A., Peltier, S., Harte, S., … Harris, R. E. (2014). Resting state connectivity correlates with drug and placebo response in fibromyalgia patients. *NeuroImage: Clinical*, *6*, 252–261. https://doi.org/10.1016/j.nicl.2014.09.007
Schneider, S., Junghaenel, D. U., Keefe, F. J., Schwartz, J. E., Stone, A. A., & Broderick, J. E. (2012). Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: Associations with psychological variables. *Pain*, *153*(4), 813–822. https://doi.org/10.1016/j.pain.2012.01.001
Sevcik, M. A., Jonas, B. M., Lindsay, T. H., Halvorson, K. G., Ghilardi, J. R., Kuskowski, M. A., … Mantyh, P. W. (2006). Endogenous Opioids Inhibit Early-Stage Pancreatic Pain in a Mouse Model of Pancreatic Cancer. *Gastroenterology*, *131*(3), 900–910. https://doi.org/10.1053/j.gastro.2006.06.021

Sheng, J., Liu, S., Wang, Y., Cui, R., & Zhang, X. (2017). The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. *Neural Plasticity*, *2017*. https://doi.org/10.1155/2017/9724371
Sherrington, C. S. (1906). *The integrative action of the nervous system.* New Haven, CT: Yale University Press. https://doi.org/10.1037/13798-000
Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. ., & Frith, C. . (2004). Empathy for Pain Involves the Affective but not Sensory Components of Pain. *Science*, *303*(5661), 1157–1162. https://doi.org/10.1126/science.1093535
Smith, D. J., Duffy, L., Stewart, M. E., Muir, W. J., & Blackwood, D. H. R. (2005). High harm avoidance and low self-directedness in euthymic young adults with recurrent, early-onset depression. *Journal of Affective Disorders*, *87*(1), 83–89. https://doi.org/10.1016/j.jad.2005.03.014
Stahl, S. M. (2002). Does depression hurt? *Journal of Clinical Psychiatry*, *63*(4), 273–274. https://doi.org/10.4088/JCP.v63n0401
Sullivan, M J, Bishop, S., & Pivik, J. (1995). Pain Catastrophizing Scale. *Psychological Assessment, 7*, 524–532. https://doi.org/10.1037/t01304-000
Sullivan, M J, Reesor, K., Mikail, S., & Fisher, R. (1992). The treatment of depression in chronic low back pain: review and recommendations. *Pain*, *50*(1), 5–13. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1387469
Sullivan, Michael J., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *Clinical Journal of Pain*, *17*(1), 52–64. https://doi.org/10.1097/00002508-200103000-00008
Tagliazucchi, E., Balenzuela, P., Fraiman, D., & Chialvo, D. R. (2010). Brain resting state is disrupted in chronic back pain patients. *Neuroscience Letters*, *485*(1), 26–31. https://doi.org/10.1016/j.neulet.2010.08.053
Tétreault, P., Mansour, A., Vachon-Presseau, E., Schnitzer, T. J., Apkarian, A. V., & Baliki, M. N. (2016). Brain Connectivity Predicts Placebo Response across Chronic Pain Clinical Trials. *PLoS Biology*, *14*(10), 1–22. https://doi.org/10.1371/journal.pbio.1002570
Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., & Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. *Clinical Journal of Pain*, *28*(9), 819–841. https://doi.org/10.1097/AJP.0b013e31824549d6
Thibault, P., Loisel, P., Durand, M. J., Catchlove, R., & Sullivan, M. J. L. (2008). Psychological predictors of pain expression and activity intolerance in chronic pain patients. *Pain*, *139*(1), 47–54. https://doi.org/10.1016/j.pain.2008.02.029
Thomas, E., Mottram, S., Peat, G., Wilkie, R., & Croft, P. (2007). The effect of age on the onset of pain interference in a general population of older adults: Prospective findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain*, *129*(1–2), 21–27. https://doi.org/10.1016/j.pain.2006.09.027
Toye, F., & Barker, K. (2010). "Could i be imagining this?" - The dialectic struggles of people with persistent unexplained back pain. *Disability and Rehabilitation*, *32*(21), 1722–1732. https://doi.org/10.3109/09638281003657857
Tracey, I., & Bushnell, M. C. (2009). How Neuroimaging Studies Have Challenged Us to Rethink: Is Chronic Pain a Disease? *Journal of Pain*, *10*(11), 1113–1120. https://doi.org/10.1016/j.jpain.2009.09.001
Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*, *55*(3), 377–391. https://doi.org/10.1016/j.neuron.2007.07.012
Tracey, W. D. (2017). Nociception. *Current Biology*, *27*(4), R129–R133. https://doi.org/10.1016/j.cub.2017.01.037
Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., … Wang, S.-J. (2015). A classification of chronic pain for ICD-11. *PAIN*, *156*(6), 1. https://doi.org/10.1097/j.pain.0000000000000160
Tsou, K., & Jang, C. S. (1964). Studies on the site of analgesic action of morphine by intracerebral microinjection. *Scientia Sinica*, *13*, 1099–1109.
Tu, F. F., As-Sanie, S., & Steege, J. F. (2005). Musculoskeletal causes of chronic pelvic pain: A systematic review of existing therapies: Part II. *Obstetrical and Gynecological Survey*, *60*(7), 474–483. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=40934877%0Ahttp://gw2jh3xr2c.search.serialssolutions.com?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed10&rft.genre=article&rft_id=info:
Tuke, D. (1884). *Illustrations of the Influence of the Mind upon the Body in Health and Disease. Designed to elucidate the action of the imagination* (2nd Ed). Philadelphia: Henry C. Lea Son & Co.
Turk, D. C., Wilson, H. D., & Cahana, A. (2011). Treatment of chronic non-cancer pain. *The Lancet*, *377*(9784), 2226–2235. https://doi.org/10.1016/S0140-6736(11)60402-9
Turner, J. A., Anderson, M. L., Balderson, B. H., Cook, A. J., Sherman, K. J., & Cherkin, D. C. (2016). Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain. *Pain*, *157*(11), 2434–2444. https://doi.org/10.1097/j.pain.0000000000000635
Turner, J. A., Jensen, M. P., Warms, C. A., & Cardenas, D. D. (2002). Catastrophizing is associated with pain intensity , psychological distress , and pain-related disability among individuals with chronic pain after spinal cord injury. *Pain*, *98*, 127–134.
U.S. Bureau of the Census. (1998). *Population Profile of the United States: 1997*. *Current Population Reports*. Washington.
Valeriani, M., Betti, V., Le Pera, D., De Armas, L., Miliucci, R., Restuccia, D., … Aglioti, S. M. (2008). Seeing the pain of others while being in pain: A laser-evoked potentials study. *NeuroImage*, *40*(3), 1419–1428. https://doi.org/10.1016/j.neuroimage.2007.12.056
van Hecke, O., Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. *British Journal of Anaesthesia*, *111*(1), 13–18. https://doi.org/10.1093/bja/aet123
Vasquez, E., & Vanegas, H. (2000). The antinociceptive effect of PAG-microinjected dipyrone in rats is mediated by endogenous opioids of the rostral ventromedial medulla. *Brain Research*, *854*(1–2), 249–252.

https://doi.org/10.1016/S0006-8993(99)02303-3
Wachleski, C., Salum, G. A., Blaya, C., Kipper, L., Paludo, A., Salgado, A. P., & Manfro, G. G. (2008). Harm avoidance and self-directedness as essential features of panic disorder patients. *Comprehensive Psychiatry*, *49*(5), 476–481. https://doi.org/10.1016/j.comppsych.2008.03.003
Wade, J. B., Dougherty, L. M., Hart, R. P., & Cook, D. B. (1992). Patterns of normal personality structure among chronic pain patients. *Pain*, *48*(1), 37–43. https://doi.org/10.1016/0304-3959(92)90129-Y
Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of Medicine*, *368*(15), 1388–1397. https://doi.org/10.1056/nejmoa1204471
Walker, J., Holloway, I., & Sofaer, B. (1999). In the system: The lived experience of chronic back pain from the perspectives of those seeking help from pain clinics. *Pain*, *80*(3), 621–628. https://doi.org/10.1016/S0304-3959(98)00254-1
Waters, A. J., & Lumb, B. M. (1997). Inhibitory effects evoked from both the lateral and ventrolateral periaqueductal grey are selective for the nociceptive responses of rat dorsal horn neurones. *Brain Research*, *752*(1–2), 239–249. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9106463
Weissman-Fogel, I., Moayedi, M., Tenenbaum, H. C., Goldberg, M. B., Freeman, B. V., & Davis, K. D. (2011). Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. *Pain*, *152*(2), 384–396. https://doi.org/10.1016/j.pain.2010.10.046
Westlund, K. N., & Willis Jnr, W. D. (2012). Pain System. In J. K. Mai & G. Paxinos (Eds.), *The Human Nervous System (Third Edition)* (pp. 1144–1186). Academic Press.
White, S., & Seibold, C. (2008). Walk a mile in my shoes: An auto-ethnographic study. *Contemporary Nurse*, *30*(1), 57–68. https://doi.org/10.5172/conu.673.30.1.57
Wilder-Smith, C. H., & Robert-Yap, J. (2007). Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World Journal of Gastroenterology*, *13*(27), 3699–3704. https://doi.org/10.3748/wjg.v13.i27.3699
Wilkerson, R. G., Kim, H. K., Windsor, T. A., & Mareiniss, D. P. (2016). The Opioid Epidemic in the United States. *Emergency Medicine Clinics of North America*, *34*(2), e1–e23. https://doi.org/10.1016/j.emc.2015.11.002
Williams, A. C. D. C. (2016). What can evolutionary theory tell us about chronic pain? *PAIN*, *157*(4), 788–790. https://doi.org/10.1097/j.pain.0000000000000464
Willis, W. D., Zhang, X., Honda, C. N., & Giesler, G. J. (2001). Projections from the marginal zone and deep dorsal horn to the ventrobasal nuclei of the primate thalamus. *Pain*, *92*(1–2), 267–276. https://doi.org/10.1016/S0304-3959(01)00268-8
Woolf, C J, & Wall, P. D. (1986). Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *The Journal of Neuroscience*, *6*(5), 1433–1442. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3711988
Woolf, Clifford J. (1984). Long term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. *Pain*, *18*(4), 325–343. https://doi.org/10.1016/0304-3959(84)90045-9
Woolf, Clifford J. (2004). Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy. *Life Sciences*, *74*(21), 2605–2610. https://doi.org/10.1016/j.lfs.2004.01.003
Woolf, Clifford J., & Ma, Q. (2007). Nociceptors-Noxious Stimulus Detectors. *Neuron*, *55*(3), 353–364. https://doi.org/10.1016/j.neuron.2007.07.016
Woolf, Clifford J. (1983). Evidence for a central component of post-injury pain hypersensitivity. *Nature*, *306*, 686–688.
Woolf, Clifford J, & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science (New York, N.Y.)*, *288*(5472), 1765–1769. Retrieved from http://www.sciencemag.org/cgi/content/abstract/288/5472/1765
Xie, Y. F., Huo, F. Q., & Tang, J. S. (2009). Cerebral cortex modulation of pain. *Acta Pharmacologica Sinica*, *30*(1), 31–41. https://doi.org/10.1038/aps.2008.14
Yang, M. M. H., Hartley, R. L., Leung, A. A., Ronksley, P. E., Jetté, N., Casha, S., & Riva-Cambrin, J. (2019). Preoperative predictors of poor acute postoperative pain control: A systematic review and meta-analysis. *BMJ Open*, *9*(4). https://doi.org/10.1136/bmjopen-2018-025091
Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., … Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033
Yarnitsky, D., Granot, M., & Granovsky, Y. (2014). Pain modulation profile and pain therapy: Between pro- and antinociception. *Pain*, *155*(4), 663–665. https://doi.org/10.1016/j.pain.2013.11.005
Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*, *153*(6), 1193–1198. https://doi.org/10.1016/j.pain.2012.02.021
Yeung, J., Yaksh, T., & Rudy, T. (1977). Concurrent mapping of brain sites for sensitivity to the direct application of morphine and focal electrical stimulation in the production of antinociception in the rat. *Pain*, *4*(1), 23–40.
Yu, R., Gollub, R. L., Spaeth, R., Napadow, V., Wasan, A., & Kong, J. (2014). Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *NeuroImage: Clinical*, *6*, 100–108. https://doi.org/10.1016/j.nicl.2014.08.019
Zaghi, S., Thiele, B., Pimentel, D., Pimentel, T., & Fregni, F. (2011). Assessment and treatment of pain with non-invasive cortical stimulation. *Restorative Neurology and Neuroscience*, *29*(6), 439–451. https://doi.org/10.3233/RNN-2011-0615
Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The Effects of Brief Mindfulness Meditation Training on Experimentally Induced Pain. *Journal of Pain*, *11*(3), 199–209. https://doi.org/10.1016/j.jpain.2009.07.015
Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173.

https://doi.org/10.1016/j.neulet.2012.03.082
Ziegler, D., Mayer, P., & Gries, F. A. (1988). Evaluation of thermal, pain, and vibration sensation thresholds in newly diagnosed type 1 diabetic patients. *Journal of Neurology, Neurosurgery & Psychiatry*, *51*(11), 1420–1424. https://doi.org/10.1136/jnnp.51.11.1420

Chapter 2. Evaluating the clinical assessment of pain during hysteroscopy and the implications for the administration of local anaesthetic

Evaluating the clinical assessment of pain during hysteroscopy and the implications for the administration of local anaesthetic

Richard Harrison[1], Bill Kuteesa[2], Atul Kapila[2], Deepak Ravindran[2], Mark Little[2], Wiebke Gandhi[1], Tim V. Salomons[1,3*],

1. University of Reading, School of Psychology and Clinical Language Sciences, Reading, UK
2. Royal Berkshire NHS Foundation Trust, Reading, UK.
3. Queen's University, Department of Psychology, Kingston, ON, Canada

*Corresponding Author

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2.1 Abstract

Hysteroscopy is a diagnostic medical procedure used to inspect for pathological conditions in the uterine cavity. Multiple sources in the UK describe this procedure as usually being associated with no pain, although this description is being challenge by public campaigns and ex-patients who suggest that hysteroscopy can be intensely painful. To determine whether this procedure can elicit such intense pain, we evaluated surgical data from 804 hysteroscopy patients. We primarily focused on patient's retrospective ratings of intraoperative pain. We also compared these ratings to the clinician's estimates of patient pain, and to the dosage of anaesthetic applied. This was especially relevant as the administration of analgesia is currently based solely upon clinical judgement. We also investigated how the experience of pain may be associated with the patient's evaluation of their expectations for the comfort of the surgery. It was found that hysteroscopy is associated with a wide range of pain intensities (M_{rating}= 3.97, s.d. =2.45), with only a small subset of patients experiencing no pain at all (7.8%). On average, most patients found their comfort to match their expectations, although higher pain experienced during the procedure was associated with a negative evaluation of the procedure regarding their expectations ($R^2(20)$= .32, p<.0001). Interestingly, clinician estimates were inversely correlated with patient pain ratings (rs(714)= -.525, p<.0001). Regarding anaesthetic dose, patients who received the highest dose of analgesia described the most pain. However, clinicians viewed these patients as being in the least pain, potentially indicating an overestimation of the efficacy of the analgesia. These findings indicate that hysteroscopy should be described as potentially causing intense pain in a subset of patients and methods of pain assessment could be applied to test whether it aids clinician judgement for prescribing intraoperative pain relief.

2.2. Introduction

Hysteroscopy is a medical procedure used to inspect for pathological conditions within the uterine cavity. This procedure utilises endoscopy which involves the insertion of a hysteroscope, into the cervix. The hysteroscope contains optical fibres which allow the operator to examine the inner uterine cavity and can also be fitted with operational tools such as electrical loops for operative hysteroscopy when required. Hysteroscopy is a common medical procedure, often used to investigate symptoms such as abnormal bleeding in relation to periods, pelvic pain or difficulty in getting pregnant or to formally diagnose fibroids or polyps. Traditionally, hysteroscopy required the use of general anaesthetic as part of an in-patient care service, although modern hysteroscope design can now facilitate the use of local anaesthetic and an outpatient pathway. There are many advantages associated with this development, including dramatically decreased completion times, no adverse patient symptoms due to general anaesthetic, lower clinical costs & reduced resource utilisation (beds/nursing etc) (Anderson, Walls, & Canelo, 2017; Bajaj, Sethi, Carr, & Knight, 2009; Darwin & Chung, 2013; Marsh, Rogerson, & Duffy, 2006). It's been estimated that within a similar medical procedure, uterine polyp treatment, the transition from in-patient to outpatient pathway could save £9421 per patient (Clark et al., 2015). However, while the pursuit of a streamlined medical service is a crucial requirement for a modern nationalised health service, maintaining high patient satisfaction should continue to remain a high priority.

Within hysteroscopy, the main patient concern of outpatient admission is the risk of pain and discomfort (Marsh et al., 2006), while this risk is obviously abolished via sedation. The amount of pain that occurs in the absence of general anaesthesia, however, is more contentious. Numerous services advertise the procedure as being either pain-free or low pain (Tylko-Hill, 2018), with the clinic identified in this study only advertising the potential for "discomfort and occasional period-like pains during the test" (Appendix C). However, subsets of patients sometimes report experiencing intense or unpleasant pain as a result of the procedure, with one clinic reporting that 17% of patients aborting the procedure due to intolerable pain (Tylko-Hill, 2018). In instances of

severe pain, local anaesthetic can be administered, but this does not always guarantee effective pain management (Meechan, 2017). There are multiple medical complications that can potentially cause pain, including uterine perforation or excessive insufflation leading to risk of serious complications via distension. However, instances of complications occurring during hysteroscopy are reportedly low (0.13%), thus not sufficiently explaining all instances of painful hysteroscopies (Jansen et al., 2000), especially when it has since been reported that up to 25% of women undergoing hysteroscopy across Britain report severe pain (Tylko-Hill, 2018). Clinically, there are methods available to manage and reduce this pain, however due to the reputation of hysteroscopy being a routine procedure, pain management is often not considered to be an area of influence or importance. Preceding 2013, NHS Choices described a hysteroscopy by indicating that "it should not hurt" and that "woman may want to take a pain killer, such as ibuprofen, beforehand". Likewise, a national audit identified multiple institutions providing patient leaflets wherein the risks of severe pain are minimally address or absent (Tylko-Hill, 2018).

In 2013, a Parliamentary initiative helped instigate a campaign to "End barbaric NHS hysteroscopies with inadequate pain relief" (Falkner & Tylko, 2019), with a variety of targets including: 1) All hysteroscopists must have advanced training in pain medicine, 2) Improved communication & information pre-surgically, listing full risks & benefits breakdown, 3) Patients may choose from a range of analgesic options from none, up to general anaesthetic. These changes focus on improving pain management and address pre-surgical knowledge & expectation, which are likely to improve the operative experience for the patient. However, it is still unclear why such a disconnect exists between the clinical view of hysteroscopy as a low-pain procedure, and the reports of frequent severe pain being reported by patients. It is possible that, for some, hysteroscopy is a routine and painless procedure, whilst for others it is one that can elicit severe pain. This may represent a disconnect between how the patient and clinician views the painfulness of the procedure or, alternatively, these perspectives may be congruent and it is simply an inaccurate description being provided via the patient-informatics services, via leaflets or websites, outside of the scope of the direct clinical team. Additionally, in line with the parliamentary

initiative, one critical area may be within the strategies of intraoperative pain management, and whether we are appropriately targeting this towards the patients that are likely to be vulnerable to severe pain.

Therefore, this study will evaluate hysteroscopy outcome data from the Royal Berkshire Hospital's obstetrics & gynaecology department to better understand the experience of pain across all patients who undergo this procedure. Currently, within routine treatment decisions about analgesia dose are made based upon the clinical judgement of the consultant performing the hysteroscopy. Therefore, we will aim to evaluate the strategy for analgesia administration and examine the strategy for pain management regarding the patient's experience of pain and the clinician's perception of this pain. This is the first known study of its kind to use a large sample with both patient and clinician ratings of accounts of the hysteroscopy to empirically investigate this issue. Secondarily, we will also investigate how the pain of the operation influenced patients' interpretation of the procedure and whether the comfort of the hysteroscopy ultimately matched their expectations. Regarding this, we hypothesise that those patients who experienced a pain-free or low-pain hysteroscopy will consider their expectations matched or surpassed, whereas the experience of pain would be detrimental to patient's perspectives on hysteroscopy.

2.3. Methods

2.3.1. Participants

Between 2009 and 2017, data was recorded from 804 hysteroscopy patients (M_{age}= 51.8 years, s.d.=12.17) within the obstetrics and gynaecological department at the Royal Berkshire Hospital.

2.3.2. Materials

Data collection consisted of two separate questionnaires and verbal pain reports from patients. The first questionnaire was a post-operative clinical report including demographics, findings of the

hysteroscopy, any complications encountered during the procedure and how many ampules of anaesthetic was administered (0-3 ampules) (Appendix A). This questionnaire also recorded the clinician's estimate of the intensity of pain experienced during the procedure. This item was record on a 5-point descriptive scale (none; discomfort; mild; moderate; severe). The second questionnaire was completed post-operatively by the patient and consisted of 11-items asking them about their satisfaction with the procedure, such as whether the comfort of the procedure was better or worse than they expected or whether their experience was better or worse than their previous hysteroscopy (Appendix B). The patient also verbally reported the level of pain experienced during surgery, between 0-10, retrospectively after the hysteroscopy, with 0 representing no pain, and 10 corresponding to the most severe pain they have ever experienced.

2.3.3. Rating Procedure

Pain ratings for, both, patients and clinicians were recorded retrospectively after the hysteroscopy. Clinicians ratings were provided immediately after the conclusion of the procedure, on a standardised clinical form (Appendix A). This rating was recorded by circling one entry on a 5-item scale, from none to severe. After the procedure, the patient returned to the waiting room, and was shown a 10-point Likert scale and verbally asked to indicate their level of pain while the hysteroscopy was being performed. Both the patient and clinician remained blinded to the other's rating. After the patient's pain rating has been recorded, a satisfaction questionnaire (Appendix B) was then completed by the patient, to conclude data collection.

2.3.4. Hysteroscopy Procedure

The medical procedure for each patient consisted of a diagnostic hysteroscopy administered as part of an outpatient procedure without the use of general anaesthetic. During the procedure, patients could be administered up to 3 ampules (units) of anaesthetic (a combinative dose of 3% citanest & octapressin) if pain behaviour was observed by the clinician that indicated the presence of pain. During the diagnostic hysteroscopy, the clinician would indicate any instances of abnormal pathology, presence of polyps or scarring. A subset of patients underwent an endometrial biopsy whereby a sample of endometrial tissue would be collected via pipelle (a thin straw-like device

which uses suction to extract a tissue sample). After the completion of the biopsy, the patient was then dressed and returned to a waiting room. During this time, the clinician completed their clinical report, while the patient completed their post-procedure questionnaire and verbally recollected how much pain was experienced during surgery.

2.3.5. Data Analysis

For the purpose of addressing the research questions, analysis was restricted to the responses to four variables; Clinician's retrospective rating of patient pain during the procedure (0-5), patient's retrospective rating of their own pain during the procedure (0-10), number of ampules of anaesthetic applied intra-surgically (0-3 ampules) and whether the comfort of the procedure was better or worse than expected (better/same/worse). To firstly examine the distribution of patient's expectations of comfort reported after the procedure, a chi-square goodness of fit was calculated, with comfort experience as a test statistic across three levels (as expected/better than expected/worse than expected). To understand whether pain experienced during the procedure may predict patient's post-surgical evaluation of whether the procedure met their expectations in terms of comfort, a multinomial logistic regression model was created with patient's retrospective pain rating as a predictor variable and whether the level of comfort experience during surgery was better, same or worse than expected as the outcome variable. To investigate the validity of clinician pain estimates, correlations were completed between these estimates and the patients pain ratings using Spearman's rank-order correlation coefficient. Lastly, to investigate how pain assessment is associated with analgesia administration, correlations were also completed between clinician pain estimates, patient pain ratings and analgesia dose using spearman's rank-order correlation coefficient. Spearman's rank, as a non-parametric statistical test, was used due to its specialisation for ranked ordinal data, and the absence of a pattern of normal distribution in the raw data.

2.4. Results

2.4.1. Patient Expectations & Pain Intensity

On average, patients retrospectively reported their comfort during the hysteroscopy to be as expected (n=190), as opposed to better (n=174) or worse (n=117) and the distribution of responses was found to be significantly different to an equal distribution ($\chi^2(2)= 18.37$, p=.001), indicating that more patients found comfort to be better or equal to their expectations than we would expect by chance. To investigate how a patient's perceived comfort was influenced by pain, their pain ratings were used to predict their evaluated comfort expectations. It was found that patient's retrospective pain ratings significantly predicted whether the comfort of the procedure met their expectations ($R^2(20)= .32$, p=.000103)[1], with higher pain ratings representing a greater likelihood that the patient viewed the comfort during the hysteroscopy to be worse than they had expected.

2.4.2. Pain Assessment & Analgesia Administration

The average retrospective pain rating recorded from patients during their hysteroscopy was 3.97 (s.d.= 2.45; median= 4) on an 11-point scale, with 17.6% of patients reporting a 7 or higher on the pain scale (n=126) and only 7.8% being pain-free (n=64). The clinician's retrospective estimate of the patients pain during surgery was 3.92 (s.d.= 1.00; median= 4), their ratings were considered within a 5-point scale, representing that doctors perceived higher levels of pain in patients than the patients had reported. By way of comparison, patients rated their pain as 36% of the maximum intensity of pain, whereas clinician ratings equate to 78.4%.

Table 1a: *Distribution of clinician pain rating estimates during hysteroscopy, with 1 representing no pain and 5 severe pain*

	1	2	3	4	5
Number of responses	20	64	83	343	211

[1] Due to the use of multinomial logistic regression, the effect size used was Nagelkerke Pseudo-R^2 representing a Cox and Snell R^2 value, adjusted for categorical data.

Table 1b: *Distribution of patient pain ratings during hysteroscopy, with 0 representing no pain and 10 most severe pain they've experienced.*

	0	1	2	3	4	5	6	7	8	9	10
Number of responses	56	77	90	112	80	91	83	64	46	9	7

As reflected via standard deviation, the variation in mean clinician ratings was low with a large proportion of the ratings being provided for the top two ratings (table 1a), as opposed to patient ratings (table 1b). Patient retrospective pain ratings were negatively correlated with the clinician's retrospective estimates of patient's pain ($r_s(714) = -.525$, $p < .001$), indicating that patients who reported experiencing more pain during the hysteroscopy were estimated to be in less pain by clinicians (Figure 1).

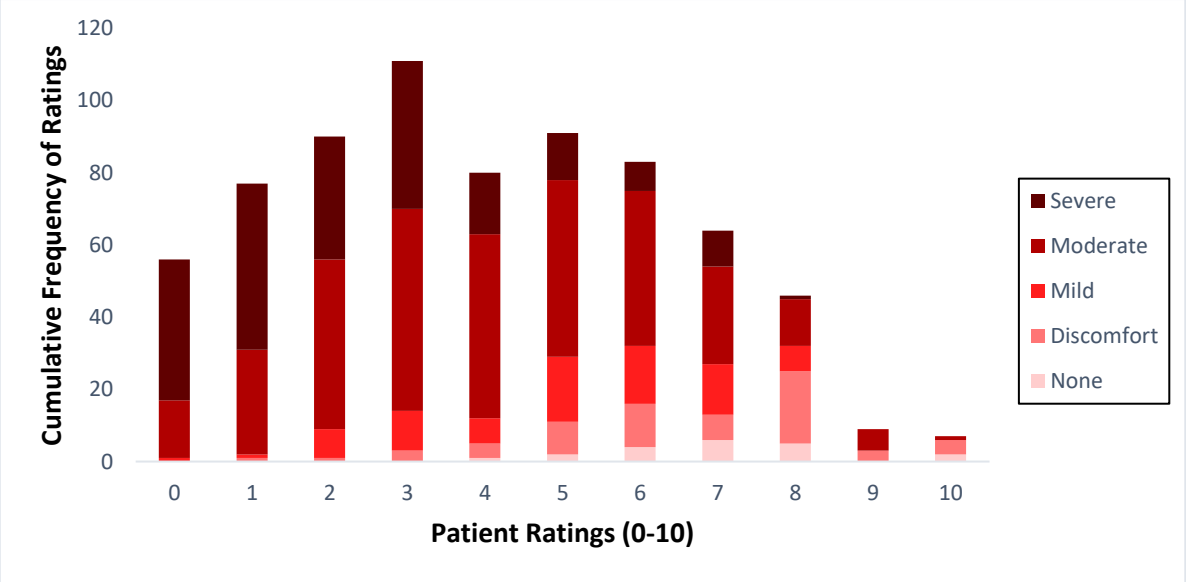


Figure 1: *Association between patient's pain ratings and the estimated rating of the patient's pain provided by the clinician that completed the hysteroscopy. Stacked bars indicate the proportion of clinician ratings for each unit of patient ratings.*

Clinicians retrospective estimates of the overall pain patients experienced during surgery was negatively correlated with anaesthetic dose ($r_s(678) = -.213$, $p < .001$. This indicates that patients who received more ampules of anaesthetic during surgery were perceived by clinicians as having experienced less pain during hysteroscopy (Figure 2). However, patient pain ratings were positively

correlated with anaesthetic dose (rs(673)= .110, p=.007), representing the opposite, that patients who received more ampules of anaesthetic during surgery retrospectively reported having experienced high levels of pain during surgery. Regarding the dispersion of anaesthetic dose, the majority of patients received no anaesthetic (n=328; 40.8%), 235 patients received 1 dose (29.2%), 150 patients received 2 doses (18.7%) and only 14 patients received a maximum dose of 3 ampules (1.7%).

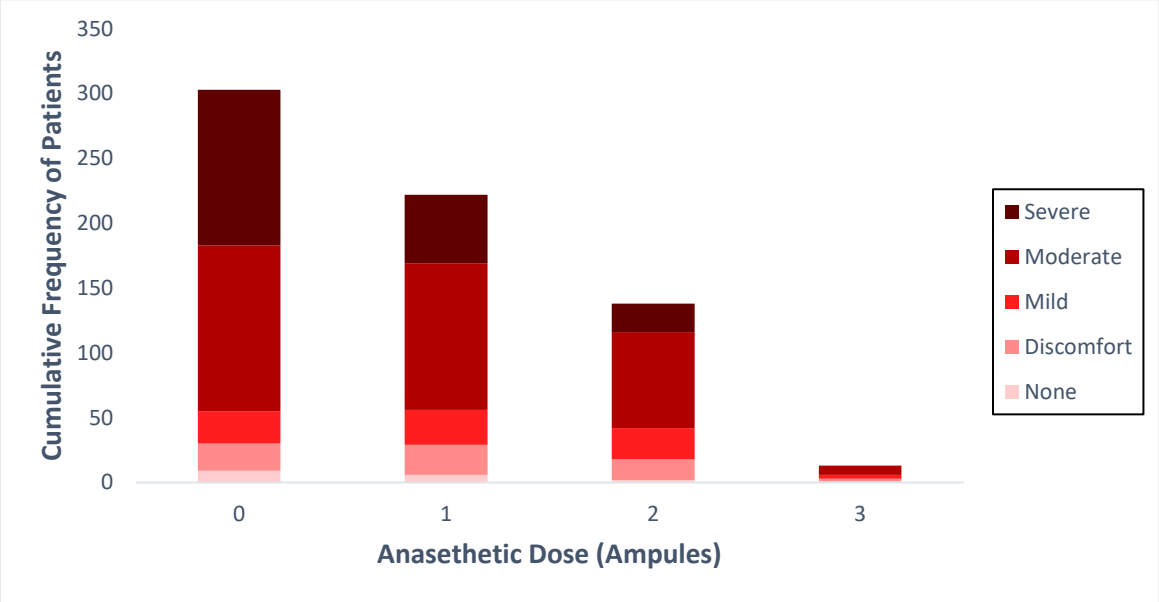


Figure 2: *Estimated clinician pain ratings associated with number of ampules of anaesthetic applied intrasurgically. Stacked bars indicate the proportion of clinician ratings for each unit of administered anaesthetic.*

2.5. Discussion

Hysteroscopies are a common diagnostic & interventional procedure that are now commonly performed as an in-patient procedure, without the need for general anaesthetic. Originally, without general anaesthetic, the procedure was described as eliciting low-pain, or being a pain-free operation. This has been challenged in recent years by governmental and grass-root campaigns, which suggest that, based on multiple case-studies, hysteroscopies can yield significant severity of pain (Tylko-Hill, 2018). This concept has been identified by clinicians within a local

gynaecological department who were anecdotally encountering problematic levels of acute pain during the procedure. To investigate this, we analysed a large sample of hysteroscopy patients who had undergone this procedure where patient and clinician pain ratings were recorded after the procedure, alongside information regarding analgesia administration and patient expectations. Regarding the pain experienced during hysteroscopy, we were able to confirm that, on average, only 7.8% of patients reported being pain-free and that clinicians estimated the pain to be, on average, 3.9 out of 5. Regarding these assessments, clinician ratings had less variation than patients', with the majority of ratings being allocated the top two points on their rating scale and overall ratings were negatively correlated with their patient rating counterparts. Clinicians' pain estimates were also negatively correlated with anaesthetic dose, with higher dose being associated with lower pain estimates. This was the inverse within patients whose ratings were positively correlated with anaesthetic dose. Lastly, the intensity of pain experienced during the procedure significantly predicted the degree to which the comfort of the hysteroscopy met patients' expectations post-operatively. Patients who experienced higher pain were likely to be those who felt the comfort of the procedure was worse than they anticipated.

Ultimately, one conclusion based on our findings is that hysteroscopy should no longer be described as a painless procedure or being a procedure that will elicit low pain. Within this sample, 92.2% of patients reported experiencing pain during the procedure. Additionally, variability of pain ratings across patients was large with a significant subset of patients rating a 7-10 on the pain scale (17.6%). This suggests that more attention is needed to determine why pain may vary, and which patients are likely to be those that experience severe pain during hysteroscopy. In reality, a hysteroscopy patient will likely experience intra-operative pain, and the intensity of this pain can vary across patients. This provides support for recent initiatives launched to raise awareness of the presence of pain within hysteroscopy, who wish to provide more accurate descriptions of the procedure to potential patients. We also noted that when expectations of the comfort of the procedure were not met, this was associated with higher pain during the hysteroscopy. This could potentially lead to reluctance or fear to attend again in the future, which is not ideal due to the

diagnostic potential of the procedure, especially with conditions such as uterine cancer or endometriosis. Although this hypothesis would require empirical follow-up to test, providing better descriptions of the procedure, raising awareness of the risk of pain and improving our assessments to improve our pain management are all strategies raised by the implications of our results which can improve the conduct of hysteroscopies. Scientifically, we also know expectations to be intrinsically linked to the experience of pain with negative expectations facilitating the amplification of pain, whereas positive expectations yield a beneficial modulatory effect (Koyama, McHaffie, Laurienti, & Coghill, 2005; Price, 2000; Robinson, Gagnon, Riley, & Price, 2003). This has even been identified on a neurological level, where expectations can exert a strong influence upon nociceptive processing in the central nervous system and key pain processing regions in the brain (Atlas & Wager, 2012). This indicates that expectations should be suitably managed to achieve the maximal clinical outcomes for our patients. The benefits to an outpatient hysteroscopy procedure, without general anaesthetic, are substantial for patient and clinician alike. However, ensuring that we effectively manage the pain of the operation and maximise the comfort of hysteroscopy patients is an essential requirement in the pursuit of quality duty of care.

As proposed by the campaign to "End barbaric NHS hysteroscopies with inadequate pain relief" (Falkner & Tylko, 2019), the strategies behind pain management are a key target to reduce the instances of intensely painful hysteroscopy. We were interested in whether pain assessment is a suitable starting point for improving clinical pain management. Interestingly, regarding effective assessment of pain, patients' retrospective ratings of pain during surgery were negatively correlated with clinicians' retrospective estimates of patient pain during surgery. This suggests that the patients who were experiencing higher levels of pain, were being viewed as being in less pain than they were. This finding could have special significance due to the administration of local anaesthesia within this clinic being calculated based on clinical judgement and this result could be interpreted that those patients who are in greatest need of analgesia may not have been receiving it. Intuitively, clinicians within this study reported that as the dose of anaesthetic increased, the patient's pain was managed, and their ratings were estimated to decrease, whereas in fact, patients

who received the more analgesia reported higher ratings of pain. However, this interpretation represents the worst-case scenario for the implications of pain management and may be better explained by examining methodological weaknesses in the design. The instructions given when collecting pain ratings from clinicians and patients were vague and asked to "indicate the level of pain experienced during the hysteroscopy". To be able to clarify on this in the future, more consideration should be given to the specificity of the rating instructions and asking everyone to rate the "peak" pain experienced during the procedure could reduce the influence of anaesthetic of the clinician's judgement

Ultimately, it was found that patients who rated higher pain were given more ampules of anaesthetic, and these patients were rated as being in less pain by their clinicians. If the clinicians believed that the anaesthetic was sufficiently managing their patient's pain, they would intuitively lower their pain ratings for these patients, which could explain this deviance in results. It is worth noting, however, that in this instance the patients who received more anaesthetic were still experiencing pain, and the clinicians may have been incorrectly overestimating the effectiveness of the pain management. This overestimation of analgesia efficacy could be a key weakness in hysteroscopy pain management. Clinician decision making towards analgesia is a burgeoning area for research, especially considering the opioid epidemic in North America (Wilkerson, Kim, Windsor, & Mareiniss, 2016). As clinical decisions often require quick, reflexive reactions, they likely rely upon heuristics, and as such, examining biases can be informative when understanding intraoperative pain management (Klein, 2005). It's previously been reported that clinicians can be predisposed to overinflated beliefs of their own clinical skills, which can lead to pain assessment being more focused on their own beliefs, rather than patient statements (Lander, 1990) and can also be erroneously confident regarding the effectiveness of their pain management (Larue, Colleau, Fontaine, & Brasseur, 1995; Weis, Sriwatanakul, Alloza, Weintraub, & Lasagna, 1983).

Additionally, a recent Cochrane review into analgesic pain relief during hysteroscopy reported that, while local anaesthetic does reduce pain scores during the procedure, these changes are minimal and unlikely to be clinically meaningful (Ahmad et al., 2017). This may help explain why patients who received the highest dose of analgesia were associated with lower clinician pain estimates, due to overestimates of the efficacy of anaesthetic, whilst reporting higher pain intensity themselves, due to minimal analgesic relief. One prevalent explanation for poor pain management is a deficiency in clinical pain education (Green, Wheeler, & LaPorte, 2003), which is especially relevant as British medical doctorates lack a pain education specialism ("Specialities," 2018) and the lack of suitable curricula being identified as a barrier to effective pain treatment in the United States (Darnall et al., 2016).

One of the more surprising findings to emerge from the data was the inverse relationship between patient ratings & clinician pain estimates. One explanation for this statistical result is that while patients demonstrated a wide variety of pain reports, clinicians' estimates were biased towards higher pain estimates with 68.9% of reports being restricted to the highest two points on the pain scale. As such, this lack of variability could have led to the emergence of specific incongruence between low pain patients, and high clinician estimates, which may facilitate a negative correlation. As the basis of analgesia administration is primarily founded upon clinical judgement, the inverse relationship between clinician and patients views on pain may facilitate inaccuracies within the prescription of local anaesthetic. These results may indicate that patients who experience low pain intensity during their procedure may be administered unnecessary analgesia, as they are estimated to be in more pain than they actually are. The lack of specificity in clinician estimates could also mean that a subset of patients experiencing severe pain are not being appropriately tagged as such, as may be receiving insufficient pain management. This assertion is supported by findings that, while clinicians estimated that patients who receive higher doses of analgesia were in less pain, this was not replicated in the patient's own pain ratings, with those who received high doses of analgesia experiencing worse pain. Given that only 1.7% of patients received the maximum dose of anaesthetic, it is possible that patients who received two ampules of anaesthetic, in particular, could

have been experiencing severe pain, but were not estimated as such by the clinicians, and therefore did not receive an extra dose of analgesia.

Assessment is one of the most challenging obstacles in pain management. The global body for pain, International Association for the Study of Pain (IASP) have multidimensional pain assessment as being one of the key factors to substantially improve pain treatment worldwide (Merskey et al., 2002). Clinical assessment of pain in others is known to be extremely challenging. It has been proposed that accurate pain assessment is dependent on multi-dimensional evaluation, including psychological, cognitive and social measures (Manias, Botti, & Bucknall, 2002) and should be validated within the patient-sample that are being assessed (Breivik et al., 2008). For example, it has been found that supplementing paracetamol with codeine provides no additional benefit to those undergoing c-section for those with low acute pain at baseline but does provide additional relief for patients with severe baseline pain (Bjune, Stubhaug, Dodgson, & Breivik, 1996). Although it would require empirical follow-up, this could indicate that pre-operative pain ratings (before the insertion of a hysteroscope) may be a useful variable in the consideration of analgesia administration. Fundamentally however, these results alongside the background literature do illustrate the complex challenge that is facing medical professionals when trying to manage pain in the midst of an operation, and supplementing the clinician estimates of pain with auxiliary assessment items is a suitable approach for improving pain management within a procedure likely to be associated with acute pain.

One approach which could benefit patient & clinician alike is to improve the quality of pre-surgical assessments to identify these patients before a hysteroscope is picked up. As an example, within our dataset we found that within the subset of patients who received the highest dose of analgesia, pain ratings were highly varied. This high variance may be a product of the relatively low sample size within this subset, which could in turn be related to the erroneous view of hysteroscopy being a minimally painful procedure, whereby as a result, few patients were given the highest dose at all

(n=14). Clearly however, within this sub-group of patients there were a wide range of pain experiences. This could indicate that some of these patients were experiencing the full benefit of the anaesthetic dose, while others were not receiving pain relief. In this instance, identifying the patients that will not respond to this method of pain management beforehand could increase the clinician's specificity of analgesia use and stratify the patient sample into those whose pain is better managed pharmacologically, and those who may require alternative pain management strategies. It has been previously shown that quantitative sensory testing is one such assessment strategy that could be applied towards predictive pain management. Conditioned pain modulation (CPM) is a psychophysical assessment that is seen as a proxy for effective inhibitory brain mechanisms (Yarnitsky et al., 2008) and represents the degree to which the brain can utilise circuitry associated with modulating pain. Interestingly, CPM has previously been shown to be able to predict the efficacy of analgesia within individuals (Edwards et al., 2016; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). Therefore, the application of CPM before hysteroscopy could help stratify responders and non-responders to intra-surgical analgesia. Whether this assessment tool would be a better predictor of analgesia response than clinical judgement is a valid empirical question worth addressing. However, this strategy to bolster the limited pre-surgical assessment currently in place would provide us with a better impression of who these patients are and could help guide the intra-surgical assessments made by the clinician.

As well as psychophysics, another method to improve the current clinical assessment strategy is psychometrics. Within this sample, psychological concepts were limited to a post-surgical satisfaction questionnaire and were further limited to investigating how their pre-surgical expectations were met after the surgery have concluded. While this is essential for reviewing the quality of care delivered and identifying areas where satisfaction was low, it provides little benefit to the clinician pre-surgically and enhancing their perspective on how their patient is likely to fare. A large proportion of the literature available focuses on predicting chronic post-surgical pain (CPSP), rather than intra-surgical pain, often due to the utilisation of general anaesthetic. Therefore, although these studies have identified that depression, catastrophisation, psychological

distress, sleep quality, expectations, or anxiety (Bruce et al., 2014; Gandhi, Davey, & Mahomed, 2009; Khan et al., 2011; Mamie, 2004; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012) are predictors of CPSP, we cannot be certain that these would also predict sensitivity to pain during an operation. If the development of CPSP and the emergence of intense pain during hysteroscopy emerge as a product of a similar intrinsic quality (e.g. the ability to modulate pain), then we may expect these psychological variables to be equally predictive of both clinical problems. If so, it can be postulated that they would also benefit pre-surgical assessments to predict pain processing during the procedure itself. Support for this approach comes from findings that certain pre-surgical predictors seem to be consistent across surgical models and may be quantifying aspects of pain processing mechanisms which are utilised regardless of a specific medical approach (Masselin-Dubois et al., 2013). As with psychophysics, by incorporating psychometrics into our assessment battery, we may provide our clinicians with a better perspective on their patients, which may be able to improve the accuracy of their intuitions and help provide guidance when making judgments of analgesia administration.

In summary, these findings provide useful insight towards the experience of pain during hysteroscopies. The data also provides support for campaigns aimed at raising awareness of pain within this procedure, with 17.6% of patients reporting a 7 or higher for pain during the procedure and only 7.8% reporting no pain at all. This means that, on average, patients are likely to experience pain during their procedure, and the descriptions provided to our patients should reflect this. These findings also suggest that the pain is likely to be variable across patients, with some experiencing more severe pain than others. Alongside this perspective, we also identified an inverse relationship between patient pain ratings and clinician estimates of the same pain. Considered together, this represents a serious challenge inherent within the assessment of pain. The clinical pain assessment of hysteroscopy is currently not best equipped to be able to assist our clinicians in making accurate estimates of pain, and as such, the prescription of intra-operative anaesthetic, which is currently calibrated based solely on their judgement. We propose that via the application of psychometric & psychophysical assessment, we may be able to identify pre-surgical

predictive markers for individual differences in pain sensitivity, although this is yet to be empirically tested within hysteroscopy and would require follow-up investigation. Transitioning hysteroscopy from an inpatient admittance procedure to outpatient is a beneficial medical development for clinicians and patients alike. However, ensuring that we are sufficiently managing pain within hysteroscopy is a crucial step in being able to facilitate this transition. Fortifying our current clinical assessments to stratify patients into those who are likely to remain pain-free, and those at risk of severe pain, may be one such strategy in being able to meet this step.

2.6. References

Ahmad, G., Saluja, S., Flynn, O. H., Sorrentino, A., Leach, D., & Watson, A. (2017). Pain relief for outpatient hysteroscopy. *Cochrane Database of Systematic Reviews*, (10). https://doi.org/10.1002/14651858.CD007710.pub3.www.cochranelibrary.com

Anderson, T., Walls, M., & Canelo, R. (2017). Day case surgery guidelines. *Surgery*, *35*(2), 85–91. https://doi.org/10.1016/j.mpsur.2016.11.013

Arcidiacono, G. (2009). Statistics Calculator: Linear Regression. Retrieved from http://www.alcula.com/calculators/statistics/linear-regression/

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003

Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*(2), 140–148. https://doi.org/10.1016/j.neulet.2012.03.039

Baer, R. A., Smith, G., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., … Williams, J. M. G. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment*, *15*(3), 329–342. https://doi.org/10.1177/1073191107313003

Baer, R. A., Smith, G. T., Hopkins, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, *13*(1), 27–45. https://doi.org/10.1177/1073191105283504

Bajaj, Y., Sethi, N., Carr, S., & Knight, L. C. (2009). Endoscopic sinus surgery as daycase procedure. *Journal of Laryngology and Otology*, *123*(6), 619–622. https://doi.org/10.1017/S0022215108003332

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics. *Journal of Neuroscience*, *28*(6), 1398–1403. https://doi.org/10.1523/JNEUROSCI.4123-07.2008

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., … Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. https://doi.org/10.1093/clipsy/bph077

Bjune, K., Stubhaug, A., Dodgson, M. S., & Breivik, H. (1996). Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. *Acta Anaesthesiologica Scandinavica*, *40*(4), 399–407. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8738682

Bogdanov, V. B., Viganò, A., Noirhomme, Q., Bogdanova, O. V, Guy, N., Laureys, S., … Schoenen, J. (2015). Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. *Behavioural Brain Research*, *281*, 187–198. https://doi.org/10.1016/j.bbr.2014.11.028

Bohlmeijer, E., ten Klooster, P. M., Fledderus, M., Veehof, M., & Baer, R. (2011). Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment*, *18*(3), 308–320. https://doi.org/10.1177/1073191111408231

Bouhassira, D., Villanueva, L., & Le Bars, D. (1992). Effects of systematic morphine on diffuse noxious inhibitory controls: Role of the periaqueductal grey. *European Journal of Pharmacology*, *216*(2), 149–156. https://doi.org/10.1016/0014-2999(92)90355-8

Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences*, *104*(27), 11483–11488. https://doi.org/10.1073/pnas.0606552104

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Breivik Hals, E. K., … Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia*, *101*(1), 17–24. https://doi.org/10.1093/bja/aen103

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y.-Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences*, *108*(50), 20254–20259. https://doi.org/10.1073/pnas.1112029108

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., … Jarvik, J. G. (2015). Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology*, *36*(4), 811–816. https://doi.org/10.3174/ajnr.A4173

Brooks, J., & Tracey, I. (2005). From nociception to pain perception: Imaging the spinal and supraspinal pathways. *Journal of Anatomy*, *207*(1), 19–33. https://doi.org/10.1111/j.1469-7580.2005.00428.x

Brown, C. A., & Jones, A. K. (2013). Psychobiological correlates of improved mental health in patients with musculoskeletal pain after a mindfulness-based pain management program. *Clinical Journal of Pain*, *29*(3), 233–244. https://doi.org/10.1097/AJP.0b013e31824c5d9f

Bruce, J., Thornton, A. J., Powell, R., Johnston, M., Wells, M., Heys, S. D., … Scott, N. W. (2014).

Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain*, *155*(2), 232–243. https://doi.org/10.1016/j.pain.2013.09.028
Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J.-I., & Carrier, B. (1999). Pain perception: Is there a role for primary somatosensory cortex? *Proceedings of the National Academy of Sciences*, *96*(14), 7705–7709. https://doi.org/10.1073/pnas.96.14.7705
Bushnell, M. Catherine, Čeko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*, *14*(7), 502–511. https://doi.org/10.1038/nrn3516
Cadden, S. W., Villanueva, L., Chitour, D., & Le Bars, D. (1983). Depression of activities of dorsal horn convergent neurones by propriospinal mechanisms triggered by noxious inputs; comparison with diffuse noxious inhibitory controls (DNIC). *Brain Research*, *275*(1), 1–11. https://doi.org/10.1016/0006-8993(83)90412-2
Carmon, A., Mor, J., & Goldberg, J. (1976). Evoked cerebral responses to noxious thermal stimuli in humans. *Experimental Brain Research*, *25*(1), 103–107. https://doi.org/10.1007/BF00237330
Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suárez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex*, *10*(3), 220–242. https://doi.org/10.1093/cercor/10.3.220
Cheriyan, J., & Sheets, P. L. (2018). Altered Excitability and Local Connectivity of mPFC-PAG Neurons in a Mouse Model of Neuropathic Pain. *The Journal of Neuroscience*, *38*(20), 4829–4839. https://doi.org/10.1523/jneurosci.2731-17.2018
Cherkin, D. C., Sherman, K. J., Balderson, B. H., Cook, A. J., Anderson, M. L., Hawkes, R. J., … Turner, J. A. (2016). Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain. *JAMA*, *315*(12), 1240. https://doi.org/10.1001/jama.2016.2323
Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*, *17*(1), 83–93. https://doi.org/10.1089/acm.2009.0546
Christoff, K., Smallwood, J., Smith, R., Gordon, A. M., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, *106*(21), 8719–8724. https://doi.org/10.1073/pnas.0900234106
Clark, T. J., Middleton, L. J., Cooper, N. A., Diwakar, L., Denny, E., Smith, P., … Daniels, J. P. (2015). A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding. *Health Technology Assessment*, *19*(61), 1–194. https://doi.org/10.3310/hta19610
Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999). Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism. *Journal of Neurophysiology*, *82*(4), 1934–1943. https://doi.org/10.1152/jn.1999.82.4.1934
Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., … Ferris, J. L. (2016). Alterations in resting state functional connectivity link mindfulness meditation with reduced interleukin-6: a randomized controlled trial. *Biological Psychiatry*, *80*(1), 53–61. https://doi.org/10.1016/j.biopsych.2016.01.008
Darnall, B. D., Scheman, J., Davin, S., Burns, J. W., Murphy, J. L., Wilson, A. C., … Mackey, S. C. (2016). Pain psychology: A global needs assessment and national call to action. *Pain Medicine (United States)*, *17*(2), 250–263. https://doi.org/10.1093/pm/pnv095
Darwin, L., & Chung, F. (2013). Patient selection for day surgery. *Anaesthesia and Intensive Care Medicine*, *14*(3), 114–118. https://doi.org/10.1016/j.mpaic.2013.01.003
Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: a neurobiological perspective. *Nature Neuroscience*, *17*(2), 192–200. https://doi.org/10.1038/nn.3628
Dickenson, J., Berkman, E. T., Arch, J., & Lieberman, M. D. (2013). Neural correlates of focused attention during a brief mindfulness induction. *Social Cognitive and Affective Neuroscience*, *8*(1), 40–47. https://doi.org/10.1093/scan/nss030
Edwards, R. R., Dolman, A. J., Martel, M. O., Finan, P. H., Lazaridou, A., Cornelius, M., & Wasan, A. D. (2016). Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 284. https://doi.org/10.1186/s12891-016-1124-6
Eippert, F., Bingel, U., Schoell, E. D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia. *Neuron*, *63*(4), 533–543. https://doi.org/10.1016/j.neuron.2009.07.014
Ezra, M., Faull, O. K., Jbabdi, S., & Pattinson, K. T. S. (2015). Connectivity-based segmentation of the periaqueductal gray matter in human with brainstem optimized diffusion MRI. *Human Brain Mapping*, *36*(9), 3459–3471. https://doi.org/10.1002/hbm.22855
Falkner, E., & Tylko, K. (2019). Campaign against painful hysteroscopy: Hysteroscopy without pain.

Retrieved July 3, 2019, from https://www.hysteroscopyaction.org.uk/
Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., Mckeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. https://doi.org/10.1093/scan/nsm030
Faull, O. K., & Pattinson, K. T. S. (2017). The cortical connectivity of the periaqueductal gray and the conditioned response to the threat of breathlessness. *ELife*, *6*, 1–18. https://doi.org/10.7554/eLife.21749
Fillingim, R. B., King, C. D., Currie, T., Riley, J. L., Wong, F., & Mauderli, A. P. (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain*, *143*(3), 172–178. https://doi.org/10.1016/j.pain.2008.12.027
Gandhi, R., Davey, J. R., & Mahomed, N. (2009). Patient Expectations Predict Greater Pain Relief with Joint Arthroplasty. *Journal of Arthroplasty*, *24*(5), 716–721. https://doi.org/10.1016/j.arth.2008.05.016
Gandhi, W., Rosenek, N. R., Harrison, R., & Salomons, T. V. (n.d.). Functional connectivity of the amygdala is linked to individual differences in emotional pain facilitation. *Pain*.
Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: From dipoles to functional significance. *Neurophysiologie Clinique*, *33*(6), 279–292. https://doi.org/10.1016/j.neucli.2003.10.008
Gard, T., Hölzel, B. K., Sack, A. T., Hempel, H., Lazar, S. W., Vaitl, D., & Ott, U. (2012). Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cerebral Cortex*, *22*(11), 2692–2702. https://doi.org/10.1093/cercor/bhr352
Gauriau, C., & Bernard, J. (2002). Pain pathways and parabrachial circuits in the rat. *Experimental Physiology*, *87*(2), 251–258.
Goffaux, P., Redmond, W. J., Rainville, P., & Marchand, S. (2007). Descending analgesia - When the spine echoes what the brain expects. *Pain*, *130*(1–2), 137–143. https://doi.org/10.1016/j.pain.2006.11.011
Granot, M., Weissman-Fogel, I., Crispel, Y., Pud, D., Granovsky, Y., Sprecher, E., & Yarnitsky, D. (2008). Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? *Pain*, *136*(1–2), 142–149. https://doi.org/10.1016/j.pain.2007.06.029
Granovsky, Y. (2013). Conditioned Pain Modulation: A Predictor for Development and Treatment of Neuropathic Pain. *Current Pain and Headache Reports*, *17*(9), 361. https://doi.org/10.1007/s11916-013-0361-8
Granovsky, Y., & Yarnitsky, D. (2013). Personalized Pain Medicine: The Clinical Value of Psychophysical Assessment of Pain Modulation Profile. *Rambam Maimonides Medical Journal*, *4*(4), 1–8. https://doi.org/10.5041/RMMJ.10131
Grant, J. A., Courtemanche, J., Duerden, E. G., Duncan, G. H., & Rainville, P. (2010). Cortical thickness and pain sensitivity in zen meditators. *Emotion*, *10*(1), 43–53. https://doi.org/10.1037/a0018334
Grant, J. A., Courtemanche, J., & Rainville, P. (2011). A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*, *152*(1), 150–156. https://doi.org/10.1016/j.pain.2010.10.006
Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in zen meditators: A cross-sectional study. *Psychosomatic Medicine*, *71*(1), 106–114. https://doi.org/10.1097/PSY.0b013e31818f52ee
Green, C. R., Wheeler, J. R. C., & LaPorte, F. (2003). Clinical decision making in pain management: Contributions of physician and patient characteristics to variations in practice. *Journal of Pain*, *4*(1), 29–39. https://doi.org/10.1054/jpai.2003.5
Grosen, K., Fischer, I. W. D., Olesen, A. E., & Drewes, A. M. (2013). Can quantitative sensory testing predict responses to analgesic treatment? *European Journal of Pain (United Kingdom)*, *17*(9), 1267–1280. https://doi.org/10.1002/j.1532-2149.2013.00330.x
Grosen, Kasper, Vase, L., Pilegaard, H. K., Pfeiffer-Jensen, M., & Drewes, A. M. (2014). Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: A prospective observational cohort study. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0090185
Harper, D. E., Ichesco, E., Schrepf, A., Hampson, J. P., Clauw, D. J., Schmidt-Wilcke, T., … Harte, S. E. (2018). Resting Functional Connectivity of the Periaqueductal Gray Is Associated With Normal Inhibition and Pathological Facilitation in Conditioned Pain Modulation. *Journal of Pain*, *19*(6), 635.e1-635.e15. https://doi.org/10.1016/j.jpain.2018.01.001
Harrison, R., Zeidan, F., Kitsaras, G., Ozcelik, D., & Salomons, T. V. (2019). Trait Mindfulness Is Associated With Lower Pain Reactivity and Connectivity of the Default Mode Network. *Journal of Pain*, *20*(6). https://doi.org/10.1016/j.jpain.2018.10.011
Harvey, W. F., Rones, R., Tao, J., Kong, J., Wolcott, E., Wang, C., … Jorgenson, K. (2018). Altered resting state functional connectivity of the cognitive control network in fibromyalgia and the modulation effect of mind-body intervention. *Brain Imaging and Behavior*, 1–11. https://doi.org/10.1007/s11682-018-9875-3

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage*, *59*(1), 750–760. https://doi.org/10.1016/j.neuroimage.2011.07.008

Hölzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How Does Mindfulness Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural Perspective. *Perspectives on Psychological Science*, *6*(6), 537–559. https://doi.org/10.1177/1745691611419671

Jansen, F. W., Vredevoogd, C. B., van Ulzen, K., Hermans, J., Trimbos, J. B., & Trimbos-Kemper, T. C. (2000). Complications of hysteroscopy: a prospective, multicenter study. *Obstetrics and Gynecology*, *96*(2), 266–270. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10908775

Jenkinson, M. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *Neuroimage*, *17*(2), 825–841. https://doi.org/10.1016/S1053-8119(02)91132-8

Jenkinson, Mark, Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jones, D. H., Kilgour, R. D., & Comtois, A. S. (2007). Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *J Pain*, *8*(8), 650–656. https://doi.org/10.1016/j.jpain.2007.04.003

Julien, N., Goffaux, P., Arsenault, P., & Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*, *114*(1–2), 295–302. https://doi.org/10.1016/j.pain.2004.12.032

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*. https://doi.org/10.1016/0163-8343(82)90026-3

Kam, J. W. Y., & Handy, T. C. (2013). The neurocognitive consequences of the wandering mind: a mechanistic account of sensory-motor decoupling. *Frontiers in Psychology*, *4*(October), 1–13. https://doi.org/10.3389/fpsyg.2013.00725

Khan, R. S., Ahmed, K., Blakeway, E., Skapinakis, P., Nihoyannopoulos, L., MacLeod, K., … Athanasiou, T. (2011). Catastrophizing: A predictive factor for postoperative pain. *American Journal of Surgery*, *201*(1), 122–131. https://doi.org/10.1016/j.amjsurg.2010.02.007

Kiken, L. G., Garland, E. L., Bluth, K., Palsson, O. S., & Gaylord, S. A. (2015). From a state to a trait: Trajectories of state mindfulness in meditation during intervention predict changes in trait mindfulness. *Personality and Individual Differences*, *81*, 41–46. https://doi.org/10.1016/j.paid.2014.12.044

Kingston, J., Chadwick, P., Meron, D., & Skinner, T. C. (2007). A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *Journal of Psychosomatic Research*, *62*(3), 297–300. https://doi.org/10.1016/j.jpsychores.2006.10.007

Klein, J. G. (2005). Five pitfalls in decisions about diagnosis and prescribing. *Bmj*, *330*(7494), 781–783. https://doi.org/10.1136/bmj.330.7494.781

Kong, J., Tu, P. C., Zyloney, C., & Su, T. P. (2010). Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. *Behavioural Brain Research*, *211*(2), 215–219. https://doi.org/10.1016/j.bbr.2010.03.042

Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: Where expectations become reality. *Proceedings of the National Academy of Sciences*, *102*(36), 12950–12955. https://doi.org/10.1073/pnas.0408576102

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced Medial Prefrontal-Default Mode Network Functional Connectivity in Chronic Pain and Its Association with Pain Rumination. *Journal of Neuroscience*, *34*(11), 3969–3975. https://doi.org/10.1523/JNEUROSCI.5055-13.2014

Kucyi, Aaron, & Davis, K. D. (2014). Dynamic functional connectivity of the default mode network tracks daydreaming. *NeuroImage*, *100*, 471–480. https://doi.org/10.1016/j.neuroimage.2014.06.044

Kucyi, Aaron, & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences*, *38*(2), 86–95. https://doi.org/10.1016/j.tins.2014.11.006

Lander, J. (1990). Clinical judgments in pain management. *Pain*, *42*(1), 15–22. https://doi.org/10.1016/0304-3959(90)91086-X

Larue, F., Colleau, S. M., Fontaine, A., & Brasseur, L. (1995). Oncologists and primary care physicians' attitudes toward pain control and morphine prescribing in france. *Cancer*, *76*(11), 2375–2382. https://doi.org/10.1002/1097-0142(19951201)76:11<2375::AID-CNCR2820761129>3.0.CO;2-C

Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., & Arendt-Nielsen, L. (2005). Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*, *115*(3), 410–418. https://doi.org/10.1016/j.pain.2005.03.025

Le Bars, D, Dickenson, A. H., & Besson, J. M. (1979). Diffuse noxious inhibitory controls. I. Effects on

dorsal horn convergent neurons in the rat. II. Lack of effect on nonconvergent neurons, supraspinal involvement and theoretical implications. *Pain*, *6*(3), 305–327. https://doi.org/10.1016/0304-3959(79)90049-6

Le Bars, Daniel, Chitour, D., Kraus, E., Dickenson, A. H., & Besson, J. M. (1981). Effect of naloxone upon diffuse noxious inhibitory controls (DNIC) in the rat. *Brain Research*, *204*(2), 387–402. https://doi.org/10.1016/0006-8993(81)90597-7

Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2012.07.005

Linnman, C., Moulton, E. A., Barmettler, G., Becerra, L., & Borsook, D. (2012). Neuroimaging of the periaqueductal gray: State of the field. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.11.095

Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, *126*(5), 1079–1091. https://doi.org/10.1093/brain/awg102

Ludwig, D. S., & Kabat-Zinn, J. (2008). Mindfulness in Medicine. *JAMA*, *300*(11), 1350. https://doi.org/10.1001/jama.300.11.1350

Lutz, A., McFarlin, D. R., Perlman, D. M., Salomons, T. V., & Davidson, R. J. (2013). Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage*, *64*(1), 538–546. https://doi.org/10.1016/j.neuroimage.2012.09.030

Mamie, C. (2004). Are there reliable predictors of postoperative pain? *Acta Anaesthesiologica Scandinavica*, *48*(2), 234–242. https://doi.org/10.1111/j.0001-5172.2004.00298.x

Manias, E., Botti, M., & Bucknall, T. (2002). Observation of pain assessment and management--the complexities of clinical practice. *Journal of Clinical Nursing*, *11*(6), 724–733. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L35513243%5Cnhttp://pm6mt7vg3j.search.serialssolutions.com?sid=EMBASE&issn=09621067&id=doi:&atitle=Observation+of+pain+assessment+and+management--the+complexities+of+clinical+practic

March, L., Burstein, R., Murray, C., Buchbinder, R., Barendregt, J., Woolf, A., … Hoy, D. (2014). The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(6), 968–974. https://doi.org/10.1136/annrheumdis-2013-204428

Marsh, F. A., Rogerson, L. J., & Duffy, S. R. G. (2006). A randomised controlled trial comparing outpatient versus daycase endometrial polypectomy. *BJOG: An International Journal of Obstetrics and Gynaecology*, *113*(8), 896–901. https://doi.org/10.1111/j.1471-0528.2006.00967.x

Masselin-Dubois, A., Attal, N., Fletcher, D., Jayr, C., Albi, A., Fermanian, J., … Baudic, S. (2013). Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of total knee arthroplasty and breast surgery for cancer. *Journal of Pain*, *14*(8), 854–864. https://doi.org/10.1016/j.jpain.2013.02.013

Mattos Feijó, L., Tarman, G. Z., Fontaine, C., Harrison, R., Johnstone, T., & Salomons, T. (2018). Sex-Specific Effects of Gender Identification on Pain Study Recruitment. *Journal of Pain*, *19*(2). https://doi.org/10.1016/j.jpain.2017.09.009

May, A. (2009). New insights into headache: An update on functional and structural imaging findings. *Nature Reviews Neurology*, *5*(4), 199–209. https://doi.org/10.1038/nrneurol.2009.28

McCracken, L. M., Gauntlett-Gilbert, J., & Vowles, K. E. (2007). The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain*, *131*(1–2), 63–69. https://doi.org/10.1016/j.pain.2006.12.013

Meechan, J. G. (2017). Why Does Local Anaesthesia Not Work Every Time? *Dental Update*, *32*(2), 66–72. https://doi.org/10.12968/denu.2005.32.2.66

Melzack, R., & Wall, P. (1965). Pain Mechanism: A new Theory. *Science*. https://doi.org/10.1126/science.150.3699.971

Merskey, H., Addison, R. G., Beric, A., Blumberg, H., Bogduk, N., Boivie, J., … Watson, C. P. N. (2002). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Second edition.* (H. Merskey & N. Bogduk, Eds.), *IASP Press* (Second). Seattle, WA: IASP Press. Retrieved from http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6), 355–474. https://doi.org/10.1016/S0301-0082(02)00009-6

Morone, N. E., Greco, C. M., Moore, C. G., Rollman, B. L., Lane, B., Morrow, L. A., … Weiner, D. K. (2016). A mind-body program for older adults with chronic low back pain a randomized clinical trial. *JAMA Internal Medicine*, *176*(3), 329. https://doi.org/10.1001/jamainternmed.2015.8033

Morton, C. R., Maisch, B., & Zimmermann, M. (1987). Diffuse noxious inhibitory controls of lumbar spinal neurons involve a supraspinal loop in the cat. *Brain Research*, *410*(2), 347–352. https://doi.org/10.1016/0006-8993(87)90336-2

Mun, C. J., Okun, M. A., & Karoly, P. (2014). Trait mindfulness and catastrophizing as mediators of the association between pain severity and pain-related impairment. *Personality and Individual Differences*,

66, 68–73. https://doi.org/10.1016/j.paid.2014.03.016
O'Brien, A. T., Deitos, A., Triñanes Pego, Y., Fregni, F., & Carrillo-de-la-Peña, M. T. (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *Journal of Pain*. Elsevier Inc. https://doi.org/10.1016/j.jpain.2018.01.010
Olesen, S. S., Brock, C., Krarup, A. L., Funch-Jensen, P., Arendt-Nielsen, L., Wilder-Smith, O. H., & Drewes, A. M. (2010). Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. *Clinical Gastroenterology and Hepatology*, *8*(8), 724–730. https://doi.org/10.1016/j.cgh.2010.03.005
Ong, W.-Y., Stohler, C. S., & Herr, D. R. (2019). Role of the Prefrontal Cortex in Pain Processing. *Molecular Neurobiology*, *56*(2), 1137–1166. https://doi.org/10.1007/s12035-018-1130-9
Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766
Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current Opinion in Supportive and Palliative Care*, *8*(2), 143–151. https://doi.org/10.1097/SPC.0000000000000055
Paul, N. A., Stanton, S. J., Greeson, J. M., Smoski, M. J., & Wang, L. (2013). Psychological and neural mechanisms of trait mindfulness in reducing depression vulnerability. *Social Cognitive and Affective Neuroscience*, *8*(1), 56–64. https://doi.org/10.1093/scan/nss070
Perlman, D. M., Salomons, T. V, Davidson, R. J., & Lutz, A. (2010). Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*, *10*(1), 65–71. https://doi.org/10.1037/a0018440
Petter, M., Chambers, C. T., McGrath, P. J., & Dick, B. D. (2013). The role of trait mindfulness in the pain experience of adolescents. *Journal of Pain*, *14*(12), 1709–1718. https://doi.org/10.1016/j.jpain.2013.08.015
Piche, M., Arsenault, M., & Rainville, P. (2009). Cerebral and Cerebrospinal Processes Underlying Counterirritation Analgesia. *Journal of Neuroscience*, *29*(45), 14236–14246. https://doi.org/10.1523/jneurosci.2341-09.2009
Popescu, A., Leresche, L., Truelove, E. L., & Drangsholt, M. T. (2010). Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. *Pain*, *150*(2), 309–318. https://doi.org/10.1016/j.pain.2010.05.013
Potvin, S., & Marchand, S. (2016). Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*, *157*(8), 1704–1710. https://doi.org/10.1097/j.pain.0000000000000573
Price, D. D. (2000). Psychological and Neural Mechanisms of the Affective Dimension of Pain. *Science*, *288*(5472), 1769–1772. https://doi.org/10.1126/science.288.5472.1769
Price, Donald D., Bush, F. M., Long, S., & Harkins, S. W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*, *56*(2), 217–226. https://doi.org/10.1016/0304-3959(94)90097-3
Price, Donald D., McGrath, P. A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*, *17*(1), 45–56. https://doi.org/10.1016/0304-3959(83)90126-4
Prins, B., Decuypere, A., & Van Damme, S. (2014). Effects of mindfulness and distraction on pain depend upon individual differences in pain catastrophizing: An experimental study. *European Journal of Pain*, *18*(9), 1307–1315. https://doi.org/10.1002/j.1532-2149.2014.491.x
Rabey, M., Poon, C., Wray, J., Thamajaree, C., East, R., & Slater, H. (2015). Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual Therapy*, *20*(6), 763–768. https://doi.org/10.1016/j.math.2015.02.011
Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, *12*(2), 195–204. https://doi.org/10.1016/S0959-4388(02)00313-6
Ram, K. C., Eisenberg, E., Haddad, M., & Pud, D. (2008). Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - New perspective of opioid-induced hyperalgesia. *Pain*, *139*(2), 431–438. https://doi.org/10.1016/j.pain.2008.05.015
Reiner, K., Granot, M., Soffer, E., & Lipsitz, J. D. (2016). A Brief Mindfulness Meditation Training Increases Pain Threshold and Accelerates Modulation of Response to Tonic Pain in an Experimental Study. *Pain Medicine (Malden, Mass.)*, *17*(4), 628–635. https://doi.org/10.1111/pme.12883
Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Medicine*, *14*(2), 230–242. https://doi.org/10.1111/pme.12006
Robinson, M. E., Gagnon, C. M., Riley, J. L., & Price, D. D. (2003). Altering gender role expectations: Effects on pain tolerance, pain threshold, and pain ratings. *Journal of Pain*, *4*(5), 284–288. https://doi.org/10.1016/S1526-5900(03)00559-5

Salomons, T. V, & Kucyi, A. (2011). Does Meditation Reduce Pain through a Unique Neural Mechanism? *Journal of Neuroscience*, *31*(36), 12705–12707. https://doi.org/10.1523/JNEUROSCI.2843-11.2011
Sauer, S., Walach, H., Schmidt, S., Hinterberger, T., Lynch, S., Büssing, A., & Kohls, N. (2013). Assessment of Mindfulness: Review on State of the Art. *Mindfulness*, *4*(1), 3–17. https://doi.org/10.1007/s12671-012-0122-5
Schütze, R., Rees, C., Preece, M., & Schütze, M. (2010). Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*, *148*(1), 120–127. https://doi.org/10.1016/j.pain.2009.10.030
Shapiro, S. L., Brown, K. W., Thoresen, C., & Plante, T. G. (2011). The moderation of Mindfulness-based stress reduction effects by trait mindfulness: Results from a randomized controlled trial. *Journal of Clinical Psychology*, *67*(3), 267–277. https://doi.org/10.1002/jclp.20761
Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences*, *107*(24), 11020–11025. https://doi.org/10.1073/pnas.1000446107
Sheline, Yvette I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106
Silva, C., & McNaughton, N. (2019). Are periaqueductal gray and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review. *Progress in Neurobiology*, *177*(January), 33–72. https://doi.org/10.1016/j.pneurobio.2019.02.001
Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062
Specialities. (2018). Retrieved July 1, 2019, from https://www.medschools.ac.uk/studying-medicine/after-medical-school/specialties
Sprenger, C., Bingel, U., & Büchel, C. (2011). Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain*, *152*(2), 428–439. https://doi.org/10.1016/j.pain.2010.11.018
Sullivan, M. J., Bishop, S., & Pivik, J. (1995). Pain Catastrophizing Scale. *Psychological Assessment*, *7*, 524–532. https://doi.org/10.1037/t01304-000
Taylor, V. A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-vidal, S., … Beauregard, M. (2013). Impact of meditation training on the default mode network during a restful state. *Social Cognitive and Affective Neuroscience*, *8*(1), 4–14. https://doi.org/10.1093/scan/nsr087
Taylor, V. A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., … Beauregard, M. (2011). Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. *NeuroImage*, *57*(4), 1524–1533. https://doi.org/10.1016/j.neuroimage.2011.06.001
Teixeira, E. (2010). The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. *Holistic Nursing Practice*, *24*(5), 277–283. https://doi.org/10.1097/HNP.0b013e3181f1add2
Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., & Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. *Clinical Journal of Pain*, *28*(9), 819–841. https://doi.org/10.1097/AJP.0b013e31824549d6
Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., & Koyama, S. (1991). Chronic Motor Cortex Stimulation for the Treatment of Central Pain, *139*, 137–139. https://doi.org/10.1007/978-3-7091-9160-6_37
Turner, J. A., Anderson, M. L., Balderson, B. H., Cook, A. J., Sherman, K. J., & Cherkin, D. C. (2016). Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain. *Pain*, *157*(11), 2434–2444. https://doi.org/10.1097/j.pain.0000000000000635
Tylko-Hill, K. (2018). *Clinical Audit*. Retrieved from https://www.whatdotheyknow.com/search/Outpatient hysteroscopy/biopsy - RCOG/BSGE 2018/all
Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus Is a Functional Core of the Default-Mode Network. *The Journal of Neuroscience*, *34*(3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014
Valencia, C., Kindler, L. L., Fillingim, R. B., & George, S. Z. (2012). Investigation of central pain processing in shoulder pain: Converging results from 2 musculoskeletal pain models. *Journal of Pain*, *13*(1), 81–89. https://doi.org/10.1016/j.jpain.2011.10.006
Walker B. (2000). The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. *Journal of Spinal Disorders*, *13*(3), 205–217. https://doi.org/10.1097/00002517-200006000-00003
Weis, O. F., Sriwatanakul, K., Alloza, J. L., Weintraub, M., & Lasagna, L. (1983). Attitudes of Patients, Housestaff, and Nurses Toward Postoperative Analgesic Care. *Anesthesia & Analgesia*, *62*(1), 70–74. https://doi.org/10.1213/00000539-198301000-00012
Wilder-Smith, C. H., Schindler, D., Lovblad, K., Redmond, S. M., & Nirkko, A. (2004). Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in

irritable bowel syndrome patient subgroups and healthy controls. *Gut*, *53*(11), 1595–1601. https://doi.org/10.1136/gut.2003.028514
Wilder-Smith, Clive H., & Robert-Yap, J. (2007). Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World Journal of Gastroenterology*, *13*(27), 3699–3704. https://doi.org/10.3748/wjg.v13.i27.3699
Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J., & Arendt-Nielsen, L. (2010). Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: A pilot study. *Journal of Pain and Palliative Care Pharmacotherapy*, *24*(2), 119–128. https://doi.org/10.3109/15360281003706069
Wilkerson, R. G., Kim, H. K., Windsor, T. A., & Mareiniss, D. P. (2016). The Opioid Epidemic in the United States. *Emergency Medicine Clinics of North America*, *34*(2), e1–e23. https://doi.org/10.1016/j.emc.2015.11.002
Willer, J., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain*, *107*(4), 1095–1112. https://doi.org/10.1093/brain/107.4.1095
Xie, Y. F., Huo, F. Q., & Tang, J. S. (2009). Cerebral cortex modulation of pain. *Acta Pharmacologica Sinica*, *30*(1), 31–41. https://doi.org/10.1038/aps.2008.14
Yarkoni, T., Poldrack, R. A. R., Nichols, T. T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. https://doi.org/10.1038/nmeth.1635
Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., … Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033
Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*, *153*(6), 1193–1198. https://doi.org/10.1016/j.pain.2012.02.021
Youssef, A. M., Macefield, V. G., & Henderson, L. A. (2016). Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. *Human Brain Mapping*, *37*(7), 2630–2644. https://doi.org/10.1002/hbm.23199
Zeidan, F. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082
Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The Effects of Brief Mindfulness Meditation Training on Experimentally Induced Pain. *Journal of Pain*, *11*(3), 199–209. https://doi.org/10.1016/j.jpain.2009.07.015
Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082
Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain Mechanisms Supporting the Modulation of Pain by Mindfulness Meditation. *Journal of Neuroscience*, *31*(14), 5540–5548. https://doi.org/10.1523/JNEUROSCI.5791-10.2011
Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation–based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences*, *1373*(1), 114–127. https://doi.org/10.1111/nyas.13153
Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424

2.7. Appendices

2.7.1. Appendix A: Post-surgical Clinician Hysteroscopy Report

OPD Hysteroscopy Proforma

Patient ID sticker

Date:
Hysteroscopist:
Grade:
Referral source:

Age: **LMP:** **Consent obtained: Y / N**

P/Complaint: PMB IMB Heavy P. Irreg P. Lost IUD Fertility Ix Sterilisation request **Cx Smear: …... -ve / +ve**

Past Rx. for this complaint: **PMHx:**

PGHx: **Parity:** **No. of C/S**

Misoprostol/Cervigem Oral/vaginal Dose: ..…… When given: ..…… Mins.

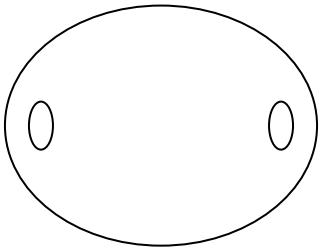
HRT/Contracept: **BMI:**

Hormone duration: **Drugs:**

USS findings:

EE: …….. mm

Hysterosc. procedure: **Hysterosc./Exam findings:**



Bx type: ……

F/Up: **GP** **GOPD** **Uni clin.** **OPH** **Other ……**

***Indication* for OPH, DSU, or GOPD F/up** **……..**

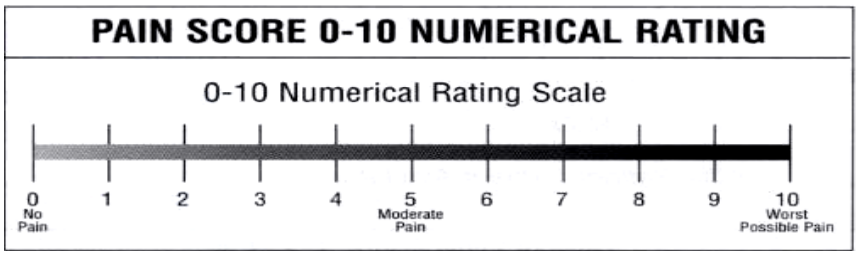
Recommendations:

Adverse events:

(page 2) OPD Hysteroscopy Proforma

Cx Smear score

Venesection score



Dr's Pain Assessment: None Discomfort Mild pain Moderate pain Severe pain

Coding: Diagnostic Therapeutic Mirena inserted Obese /Co-morbid:……..

Detailed Findings:

Uterus: Size: Position: Adnexae:

Cervix: Normal Stenosed Polyp Suspicious lesion

Pre-OPH: Ibuprofen? Paracetamol? When taken?.....Hours ago

Anaesthetic: No/Yes Octapressin …..Ampules

Dilate Cx: No/Yes Hagar…… Difficult/easy Vaginoscopy

View: Good / Unsatisfactory: (Reason)……

Instruments used: Pipelle Scissors Vulsellum Bx forceps Diathermy

Other: ……..…….

Complications: None Bleeding Vasovagal Perforation False passage

Other: ……..…….

Procedure stopped: Cx stenosis Bleeding Pain Complication
Other: ……..……..

2.7.2. Appendix B: Post-surgical Patient Satisfaction Questionnaire

RBH/WBCH Satisfaction Questionnaire

Your Post code ……..…….. Date ……

1. If necessary, would you have hysteroscopy in outpatients again?
Yes definitely Yes probably No definitely Not sure

2. Was the comfort during hysteroscopy more or less than you expected?
More comfortable Less comfortable The same as I expected

3. Were you satisfied with the overall experience during the hysteroscopy?
Very satisfied Satisfied Unsatisfied Very unsatisfied

Is there anything about the hysteroscopy appointment you did ***not*** like? (please list)
1…….
2…….
3…….

4. Would you recommend this hysteroscopy procedure to a friend or relative?
Yes definitely Yes probably No definitely Not sure

5. Were you anxious / nervous about the hysteroscopy before you came today?
Very nervous Slightly nervous Not nervous

6. If you were anxious / nervous about hysteroscopy what were your worries?
1…….
2…….
3…….

7. Have you had a hysteroscopy under general anaesthetic (while asleep) or in outpatients (awake) before today?
Never before General anaesthetic Outpatients Cant remember

8. If you had a hysteroscopy with a general anaesthetic before, how does your experience compare with today's hysteroscopy? Today's hysteroscopy was…..
Better About the same Worse Can't remember

9. If today's hysteroscopy was better or worse than your previous hysteroscopy please explain why below.
…….
…….

10. Did the written hysteroscopy information you received before today make you feel anxious, nervous or scared?
Very anxious Slightly anxious Not at all Did not receive leaflet Did not read it

Were you given the chance to ask any questions during your hysteroscopy appointment?
Yes No Too nervous to ask questions I had no questions

NHS
Royal Berkshire
NHS Foundation Trust

Gynaecology patient information

Having an outpatient hysteroscopy

Introduction

The doctor has advised you to have a hysteroscopy to help find the cause of your problems. This leaflet will answer some of the common questions asked about this procedure before you arrive for your appointment. We will be happy to answer any questions you may have when you visit the clinic.

Feel free to discuss any questions or concerns with your nurse or telephone us on: 0118 322 7181.

What is a hysteroscopy?

Hysteroscopy is the name given to the procedure that allows a doctor to look inside the uterus (womb) using a thin telescope called a hysteroscope. The hysteroscope is gently passed into the vagina and through the cervix (neck of the womb); no external cutting is involved. The hysteroscope is connected to a TV screen so that the inside of the womb can be seen by the doctor and also the patient (if the patient wishes).

Why have I been referred to the outpatient hysteroscopy clinic?

Women are referred to the hysteroscopy clinic to find the cause of their abnormal vaginal bleeding and to decide on treatment. Abnormal vaginal bleeding may take many forms such as:

- Heavy or irregular periods.
- Bleeding in between periods.
- Bleeding after the menopause.

Why outpatient hysteroscopy? What are the benefits?

Hysteroscopy is traditionally carried out when the patient is under general anaesthetic (you are asleep); however, modern thin hysteroscopes now allow this procedure to be performed while you are awake. Being awake for the test carries many patient advantages over general anesthetic:

- Because patients are conscious (awake) throughout the outpatient hysteroscopy test they do not feel drowsy or need a long recovery period when it has finished (unlike general anaesthetic hysteroscopy).

- Patients can drive, go to work, or go home independently, straight after the test. This is not possible after a general anaesthetic.
- The outpatient hysteroscopy appointment lasts for approximately 40 minutes; general anaesthetic hysteroscopy will take the whole day.
- Patients generally need fewer visits to hospital if they have outpatient hysteroscopy.
- There is no need to fast (no food or fluids) before the outpatient test.
- Patients are told what is going on and what can be seen during the outpatient test. Patients can watch the TV screen with the doctor if they wish.
- The outpatient test avoids the risks of general anaesthetic.
- There is less risk of complications during outpatient hysteroscopy.

Before arriving for your appointment

We would advise you to take simple pain relief such as paracetamol or ibuprofen 1-2 hours before your appointment. This is to help reduce any crampy 'period' type pain that you may experience during the procedure.

What does outpatient hysteroscopy involve?

When you attend the hysteroscopy clinic the doctor or specialist nurse will ask you questions about your problems. Following the discussion, you will be asked to remove your lower clothes and wear a hospital gown. A nurse will be with you for the whole of the procedure. She will answer your questions and make you feel comfortable.

Just as happens during a smear test, an instrument is used to examine the vagina and cervix. The cervix is cleaned with cleaning fluid and the thin hysteroscope (a telescope thinner than a pencil) is gently passed through it to look at the endometrium (inner lining of the womb). A small amount of clean water passes through the telescope into the womb so that all of the lining can be seen clearly. The hysteroscope pictures can be seen by the doctor / specialist nurse on a TV screen that you can also see if you wish.

The doctor will sometimes take a tiny sample of tissue (a biopsy), or remove any small polyps from the womb lining , which will be sent for laboratory analysis. The result of this will be sent to your GP. You can get the result from your GP practice approximately 3 weeks after your hysteroscopy appointment.

How long will the outpatient hysteroscopy take?

Most hysteroscopy procedures take less than 5 minutes. The whole appointment takes about 40 minutes.

Is outpatient hysteroscopy painful?

This procedure is not generally painful. Some women experience a little discomfort and occasionally 'period-like' pains during the test. The doctor can apply local anaesthetic to the cervix but this is not usually necessary.

The doctor can stop at any time if the test becomes too uncomfortable.

What are the risks or potential complications of outpatient hysteroscopy?

Outpatient hysteroscopy is a safe procedure but just as with any medical procedure, complications can occur. Fortunately, these are very rare and most occur much less often than if the hysteroscopy is performed under a general anaesthetic.

The potential complications are as follows:

- Infection of the womb or abdomen (tummy) is uncommon and occurs in approximately 1 in 500 outpatient hysteroscopy procedures.
- Inability of the doctor to pass the hysteroscope into the womb. This occurs in about 4 in 100 outpatient hysteroscopy procedures.
- Fainting (Vasovagal) episode occurs in about 1 in every 100 outpatient hysteroscopy procedures.
- Making a hole in the womb is an extremely rare event. It is even rarer to injure other structures within the abdomen (tummy). These include the bladder, bowel or blood vessels. In the rare event of injury to these internal structures, an open abdominal operation would be needed on the same day.
- Heavy bleeding is also a very rare event during this test. Complications such as this, or injury to internal organs occur less than 2 in 1000 outpatient hysteroscopy procedures.

How should I prepare for my outpatient hysteroscopy appointment?

- Eating and drinking: You should eat and drink as normal before your appointment.
- Clothing: As we provide you with a gown, we advise you to come to the clinic in clothes that you find easy to change out of for the test.
- Period: The test is not usually performed when you are having your period but can be done if you have prolonged or continuous bleeding. If the appointment date is on the same day as your expected period date, please call the hospital number on the appointment letter to change your appointment date as soon as possible.
- Sanitary pads: Because some women have a small amount of bleeding after the hysteroscopy we advise you to come with a sanitary pad to use after the test.
- Can I come alone? Although it is reasonable to come to the clinic alone, you may prefer to come with a partner, friend or relative.

- Pregnancy: If you are, or think you may be pregnant, you should not have the hysteroscopy. Please contact the outpatient hysteroscopy clinic (telephone number on back of this leaflet) before your appointment for further advice.

What should I expect following outpatient hysteroscopy appointment?

- Recovery: You can continue doing most normal activities directly after the hysteroscopy.
- Driving / work: You may drive and even return to work on the same day as the test.
- Painkillers: Some women experience period-like pains for a short length of time after the procedure. These are eased with normal painkillers (e.g. Ibuprofen or Paracetamol).
- Bleeding: Some women experience a small amount of vaginal bleeding or discharge following the procedure. This may last up to two weeks. If this becomes heavy or offensive smelling, please contact your GP for further advice. We advise you to use a sanitary pad rather than a tampon for a week after your test.
- Sex: We advise you to avoid sexual intercourse for about a week after the hysteroscopy.

Other sources of information:

- NHS Choices www.nhs.uk
- Visit the Trust website at www.royalberkshire.nhs.uk

Contact us

Appointments Office Tel: 0118 322 7295

Outpatient Hysteroscopy Clinic, Sonning Ward
Royal Berkshire Hospital NHS Foundation Trust
Reading RG1 5AN
Tel: 0118 322 7194

For more information about the Trust, visit our website at www.royalberkshire.nhs.uk

This document can be made available in other languages and formats upon request.

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Chapter 3. Trait mindfulness is associated with lower pain reactivity and connectivity of the default mode network

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Trait mindfulness is associated with lower pain reactivity and connectivity of the default mode network

Richard Harrison[1], Fadel Zeidan[2], George Kitsaras[1], Dila Ozcelik[1], Tim V. Salomons[1,3*]

1. University of Reading, School of Psychology and Clinical Language Sciences, Reading, UK
2. Wake Forest School of Medicine, Winston Salem NC, USA
3. Queen's University, Department of Psychology, Kingston, ON, Canada
*Corresponding Author

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3.1. Abstract

Mindfulness-based training reduces pain in clinical and experimental settings. Evidence suggests these beneficial effects are facilitated via increased focus on the present moment, and reduced emotional enhancement of pain. The majority of the existing literature has focused on mindfulness as a learned skill, and on the neural mechanisms that underlie the acquisition of this skill. It is unknown whether similar mechanisms are associated with trait mindfulness in the absence of training and whether these mechanisms confer the ability to cope with pain. To determine this, we measured trait mindfulness and pain responsivity in 40 healthy volunteers naive to mindfulness meditation. As a feature of interest, we targeted the default mode network (DMN); a network of interacting brain regions associated with processes such as introspective thought, mind-wandering and rumination. As extant studies have implicated the DMN, in the beneficial effects of mindfulness, we examined resting state connectivity of the precuneus, a core DMN node. Higher trait mindfulness was associated with higher pain thresholds ($r=.43$, $p=.007$) and lower pain catastrophising ($r=-.51$, $p<.0001$). Consistent with the neural mechanisms of trained mindfulness, higher trait mindfulness was associated with decreased connectivity between nodes of the DMN. It was also associated with increased connectivity between the DMN and somatosensory cortices. These findings are consistent with processes taught in formal meditation training, namely increased focus on sensory experience and decrease in emotional appraisal processes, indicating that behavioural and neurological mechanisms described in the interventional mindfulness literature also underlie trait mindfulness prior to any formal training.

3.2. Introduction

Mindfulness training reduces pain in clinical and laboratory settings (Cherkin et al., 2016; Kabat-Zinn, 1982; Morone et al., 2016; Reiner, Granot, Soffer, & Lipsitz, 2016; Teixeira, 2010; Zeidan et al., 2011). Similarly, long term meditative practice mitigates sensory (Grant, Courtemanche, Duerden, Duncan, & Rainville, 2010; Grant, Courtemanche, & Rainville, 2011; Grant & Rainville, 2009) and emotional (Brown & Jones, 2013; Gard et al., 2012; Perlman, Salomons, Davidson, & Lutz, 2010) components of pain. Several studies have shown that mindfulness attenuates pain by enhancing attentional focus on the present moment and regulating associated emotional responses (Bishop et al., 2004; Ludwig & Kabat-Zinn, 2008; Salomons & Kucyi, 2011). A growing body of work documents neural activations associated with the effects of mindfulness training on pain. Decreases in pain following mindfulness-based training are frequently associated with greater activation in brain areas associated with sensory and/or salience processing (Gard et al., 2012; Lutz, McFarlin, Perlman, Salomons, & Davidson, 2013; Zeidan et al., 2011), alongside decreases in the prefrontal cortical regions linked to evaluative and/or emotional responses (Hölzel et al., 2011; Zeidan, 2012).

These 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 (Reiner, Tibi, & Lipsitz, 2013; Salomons & Kucyi, 2011; Zeidan & Vago, 2016). Growing evidence demonstrates that training of attentional focus is accompanied by altered activation in areas related to cognitive control and, in particular, brain networks supporting self-referential processing, such as the default mode network (DMN) (Creswell et al., 2016; Kucyi & Davis, 2014; Zeidan, 2012; Zeidan et al., 2011). Trained mindfulness is associated with decreased activation across DMN nodes (including the medial prefrontal cortex (mPFC) and precuneus) following both short term (<1 month) mindfulness-based interventions (Dickenson, Berkman, Arch, & Lieberman, 2013; Farb et al., 2007) and long term meditative practice (Brewer et al., 2011; Taylor et al., 2011). These findings have been interpreted in terms of a top-down control of

ruminative and self-referential processes (Farb et al., 2007; Taylor et al., 2011). In particular, the precuneus has been repeatedly associated with the processes of self-referential processing, autobiographical reflection, self-centred mental imagery and rumination (Cavana & Trimble, 2006; Cooney et al., 2015; Lois & Wessa, 2016; Nejad, Fossati & Lemogne, 2013; Sheline, Price, Yan, & Mintun, 2010) and may represent the most appropriate node within the DMN for investigating trait mindfulness. However, while these associations have been extensively documented in studies of mindfulness training (Zeidan, Grant, Brown, McHaffie, & Coghill, 2012), little is known about the neural mechanism of untrained dispositional mindfulness and its potential role in pain reactivity.

Higher dispositional mindfulness is associated with lower chronic pain severity (McCracken, Gauntlett-Gilbert, & Vowles, 2007; Mun, Okun, & Karoly, 2014; Petter, Chambers, McGrath, & Dick, 2013), lower frequency of rumination (Paul, Stanton, Greeson, Smoski, & Wang, 2013) and lower levels of pain catastrophising (Prins, Decuypere, & Van Damme, 2014). Determining the neural mechanisms that underlie these differences can provide key insight into why some individuals appear to be intrinsically vulnerable to pain while others seem to possess innate protective mechanisms.

Here we investigate whether untrained trait mindfulness is associated with differential responses to pain stimuli prior to any meditative training, and whether these intrinsic differences reflect differential patterns of resting state functional connectivity. Based on previous work (Cavada, Compañy, Tejedor, Cruz-Rizzolo, & Reinoso-Suárez, 2000; Grant & Rainville, 2009; Perlman et al., 2010; Reiner et al., 2013; Zeidan, Gordon, Merchant, & Goolkasian, 2010), we hypothesize that individuals high in trait mindfulness will have higher pain thresholds and lower emotional reactivity to pain. Secondly, consistent with mindfulness training studies, higher trait mindfulness will be associated with lower intrinsic default mode connectivity (Brewer et al., 2011; Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012; Taylor et al., 2013) consistent with a reduced tendency towards ruminative processes (Christoff, Smallwood, Smith, Gordon, & Schooler, 2009).

Finally, individual differences in pain coping behaviour will be associated with higher connectivity between attentional and sensory/salience regions, consistent with elevated attention to the ongoing sensory environment.

3.3. Methods

3.3.1. Participants

Forty healthy study volunteers were recruited from the University of Reading and screened for this present study. Four participants were excluded. One participant was missing questionnaire data and was unable to return to correct this. Two participants were excluded for excessive motion artifacts during resting state based on a cut-off of 2.5mm for peak movement artifacts (7mm & 10mm, respectively) and one participant was excluded because of insufficient scan data quality due to large artifacts which couldn't be corrected and impacted on group analysis. This left a final sample of 36 participants (14 Female; mean age 22.83 years, SD=5.41). Participants were excluded if they had active or historical chronic pain disorder diagnoses, current instances of acute pain (e.g. serious cuts or bruises), current substance abuse or uncorrected visual impairment. All participants also confirmed that they had never practiced mindfulness meditation. All participants provided informed consent prior to the study, and the study was approved by the University of Reading's University Research Ethics Committee.

3.3.2. Materials

3.3.2.1. Thermal Stimulation

Noxious heat stimulation was generated by a MEDOC Pathway system (Medoc Medical Systems, Haifa, Israel) using a 30x30 Peltier thermode, applied to the lower right calf, which was placed into a customised wooden leg rest.

3.3.2.1. Questionnaires

Pain catastrophising was measured using the Pain Catastrophising Scale (PCS) (Sullivan, Bishop, & Pivik, 1995). The scale includes 13 items scored on a 5-point Likert-Type scale (0=not at all, to 4=all of the time). Total scores were used in this study, with higher scores indicating higher catastrophising (Appendix D). Trait Mindfulness was measured using the Five Facet Mindfulness Questionnaire (FFMQ) (Baer, Smith, Hopkins, & Toney, 2006). The scale includes 39 items scored on a 5-point Likert-type scale (1=never or rarely true to 5=very often or always true). Higher scores represent higher levels of mindfulness (Appendix E). The FFMQ is the most widely studied measure of trait mindfulness (Sauer et al., 2013) and possesses good psychometric properties (Baer et al., 2008; Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011).

3.3.3. Design

The current experiment is part of a larger study investigating the link between neural and psychophysical measures and cognitive/emotional modulation of pain, which took place over four sessions, counterbalanced for order of completion. Firstly, participants completed the FFMQ and PCS via a secure third-party website (https://www.surveymonkey.com). After this, they attended the first session, a psychophysical assessment, followed by a neuroimaging session that took place no more than seven days after the initial session. The final two sessions examined cognitive and emotional pain modulation tasks unrelated to this study, which are not described further.

3.3.4. Procedure

3.3.4.1. Pain Threshold Assessment

We used two assessments to measure pain threshold. Both methods utilised a visual analogue scale (VAS) (Price, Bush, Long, & Harkins, 1994), displayed on a laminated A4 piece of paper. The minimum rating of 0 was described as “No pain at all” and the highest anchor of 10 was anchored with “most intense pain imaginable”. To investigate how mindfulness may be associated with the sensory experience of sensory pain, ratings for pain intensity were recorded, rather than pain unpleasantness, which, although tightly coupled, is reported to reflect a more emotive and affective rating of the pain experience (Fields, 1999). The first assessment was via method of limits, starting

at a 32°C baseline rising by 0.5°C /s until the participant indicated that the stimulus was painful. There were 4 trials with an 8s inter-stimulus interval. The average of the final 3 trials was taken as the limits threshold.

In the method of levels design, stimuli were initiated at a 32°C baseline, and increased by 8°/s to a 40°C peak, where it remained for 8s. The participant was primed to indicate on a mouse whether the stimulus was painful. If they indicated "no", the subsequent trial increased by 2°C. If they indicated yes, the temperature decreased at half the interval size and the same pattern continued until 4 reversals of direction had been reached, and which point the programme terminated. The average of the final two trials was used as the individual's levels threshold. The products of each threshold method were highly correlated ($r(37)=.786$, $p<.01$), and the mean of the limits and levels threshold was used as the participant's threshold.

3.3.4.2. Behavioural Data Analysis

Pearson's correlations were used to examine associations between trait mindfulness, pain catastrophising and pain threshold. Significance was set at $p<.05$. All statistical analysis was completed using SPSS. To investigate the specific interaction between these three variables, an additional analysis was performed with pain catastrophising and threshold as independent variables and trait mindfulness as a dependent variable. This was used to examine the differential and combined variance of these variables on mindfulness, to test whether each was significantly predictive of trait mindfulness, or whether the effect is driven by one variable over the other.

3.3.4.3. fMRI Acquisition

Functional images were acquired using a 3T Siemens TRIO MRI scanner with a 32-channel head coil. The MRI session consisted of an initial localiser, followed by a 10-minute resting-state scan. Two runs of an event-related functional task (not described here) were completed, either side of a T1-weighted structural scan. A field map was collected as the last item within the scan protocol. For resting-state, participants were instructed to close their eyes and not to move. The protocol consisted of 30 interleaved 3.5mm sagittal T2* weighted gradient echo echo-planar imaging (EPI)

slices. All functional images were prepared as 4D NIFTI images (TE=28ms, TR=2000ms, flip angle=90°, 1mm interslice gap; 128x128 matrix, field-of-view (FOV)=240mm).

Anatomical images were then acquired within an 8-minute T1-weighted inversion recovery fast gradient echo-high resolution structural scan (176 volumes, TE=2.9ms, TR=2000ms, FA= 90°, voxel size= 1x1x1; 256x256 matrix, FOV=250mm).

3.3.5. fMRI Data Analysis

3.3.5.1. ROI Selection

The precuneus is a core DMN node and an anatomical target for examining DMN processing (Sheline et al., 2009; Utevsky, Smith, & Huettel, 2014). The precuneus has often been associated with processes such as self-referential thinking, rumination and autobiographical reflection (Cavana & Trimble, 2006; Cooney et al., 2015; Lois & Wessa, 2016; Nejad, Fossati & Lemogne, 2013; Sheline, Price, Yan, & Mintun, 2010), and as such is a pertinent seed within the DMN for investigating trait mindfulness. A region within the precuneus cortex was selected for seed-based whole brain connectivity analysis (Sheline, Price, Yan, & Mintun, 2010). For the purpose of preparing this seed region, a 2mm sphere was projected around the co-ordinates supplied (X=-8, Y=-64, Z=18). As there were no hypothesised differences in relation to lateralisation, these seed co-ordinates were bilateralised when creating the seed.

3.3.5.2. Pre-Processing

Analysis was performed using the FSL analysis package (FSL Version 6.00; www.fmrib.ox.ac.uk/fsl), (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). The Brain Extraction Tool (BET) (Smith, 2002) was used for skull stripping. The first 5 volumes were removed to allow for signal equilibration effects. An interleaved slice-timing correction was applied. Data was smoothed with a 5mm full-width half-maximum (FWHM) Gaussian spatial smoothing kernel. MCFLIRT was used for motion correction and data were visually inspected for motion artifacts and registration accuracy (Jenkinson, 2002).

FSL's FAST module (Zhang, Brady, & Smith, 2001) was used to segment grey matter from white matter (WM) and cerebrospinal fluid (CSF). WM and CSF maps were thresholded at 0.99 to minimize overlapping signal from grey matter prior to time series extraction. Time series of WM and CSF were entered into a general linear model along with motion parameters. Residuals from this nuisance analysis were normalised and bandpass filtered (0.1/0.01 Hz) to reduce the influence of low frequency drift (inclusive of scanner drift), and high frequency interference such as cardiac or respiratory confounds.

3.3.5.3. Resting State Analysis

The mean time series of all voxels within the precuneus seed region were extracted and included as a regressor in a whole-brain functional connectivity analysis. Contrast images were then entered into a second higher level analyses in which participant's demeaned FFMQ scores were entered as a regressor. This analysis examined brain regions where connectivity of the precuneus was significantly correlated with trait mindfulness. All fMRI analyses were corrected for multiple comparisons using Gaussian random field theory ($Z<2.3$; $p<.05$).

To ensure that results were not driven by outliers, and to investigate whether connectivity patterns associated with trait mindfulness were also associated with pain reactivity, parameter estimates from regions where functional connectivity with the precuneus was significantly correlated with trait mindfulness were extracted using FEATQuery (Jenkinson et al., 2012), an FSL module used for extracting statistics, such as BOLD activity, from a given image or input. To allow for more anatomically specific inferences, these clusters were constrained using meta-analysis masks generated from the NeuroSynth database (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). In line with our hypotheses that connectivity patterns associated with trait mindfulness would be consistent with a tendency to attend to sensory aspects of pain without emotional evaluation, the map of regions positively correlated with trait mindfulness were masked with a reverse inference mask of the terms "pain" and "painful", while the map of regions negatively associated with trait mindfulness was masked with a mask of the terms "emotion" and "emotional". While these masks are not specific to the named processes, the advantage of this approach is that it constrains findings

to areas known to be relevant to these processes. Although the use of these meta-analysis masks aided inference, results were not dependent on their use, as similar results were obtained from the larger unmasked clusters.

3.4. Results

3.4.1. Mindfulness and Pain

Higher trait mindfulness was significantly associated with higher pain thresholds (r=.43, p=.004) and lower pain catastrophising (r= -.59, p=.0001) (Figure 1). Pain catastrophising and pain threshold were not significantly correlated (r= -.22, p=.103).

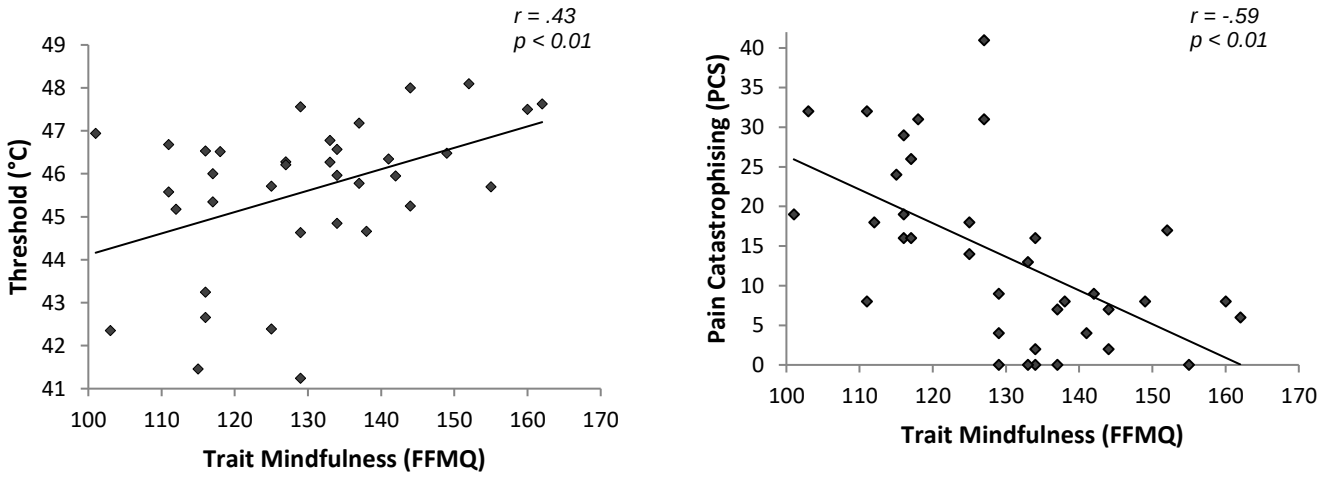

Figure 1. *Association between trait mindfulness and threshold (left) and pain catastrophizing scores*

To examine the overlap in predictive variance, we included both threshold and pain catastrophising in a regression model with FFMQ as dependent measure (Table 1). Whilst otherwise a predictive variable, this allowed the examination of relationship between catastrophising and threshold, and mindfulness. Pain catastrophising & threshold were significantly predictive of trait mindfulness. ($F(2,33)= 12.96$, $p<0.001$). Both variables remained significantly associated with FFMQ within the model.

Table 1. *Statistical output from behavioural regression model investigating the association between pain catastrophising and pain threshold on trait mindfulness*

Variable	Standardised Beta Coefficient	Significance	Zero order correlations	Partial correlations	Part correlations
Pain Catastrophising	-.516	.000	-.585	-.558	-.504
Threshold	.320	.022	.432	.385	.313

3.4.2. Seed-based DMN Connectivity

A thresholded map of precuneus functional connectivity confirmed that the precuneus ROI effectively probed the DMN (Figure 2). There were two significant clusters of activation where precuneus connectivity was positively correlated with trait mindfulness. These included the primary and secondary somatosensory cortices (cluster 1&2; Figure 2 & Table 2), as well as adjacent areas within the precuneus cluster 7).

Table 2. *Statistical peaks in MNI space of clusters associated with FFMQ scores*

Anatomical Region	Brodmann Areas	Direction of correlation	Max Z-Stat	MNI Co-ordinates (mm)		
				X	*Y*	*Z*
1. R. Parietal/ Motor/ Somatosensory Cortex	BA2, BA3a, BA4, BA40	Positive	4.61	32	-18	38
2. L. Parietal/ Motor/ Somatosensory Cortex	BA1, BA2, BA3a, BA4, BA7, BA40	Positive	3.77	-10	-46	52
3. L. Parietal/Somatosensory Cortex	BA1, BA2, BA3a, BA3b, BA4, BA6	Positive	3.28	14	-32	44
4. Medial Prefrontal Cortex/ Perigenual ACC	BA32, BA10	Negative	5.24	-2	44	6
5. L. Superior Frontal Gyrus/Pre-motor	BA6	Negative	4.13	-10	36	54
6. R. Superior Frontal Gyrus/Pre-motor	BA6	Negative	4.2	6	22	66
7. Posterior Cingulate Cortex/Precuenus	BA29	Negative	4.65	-10	-50	26

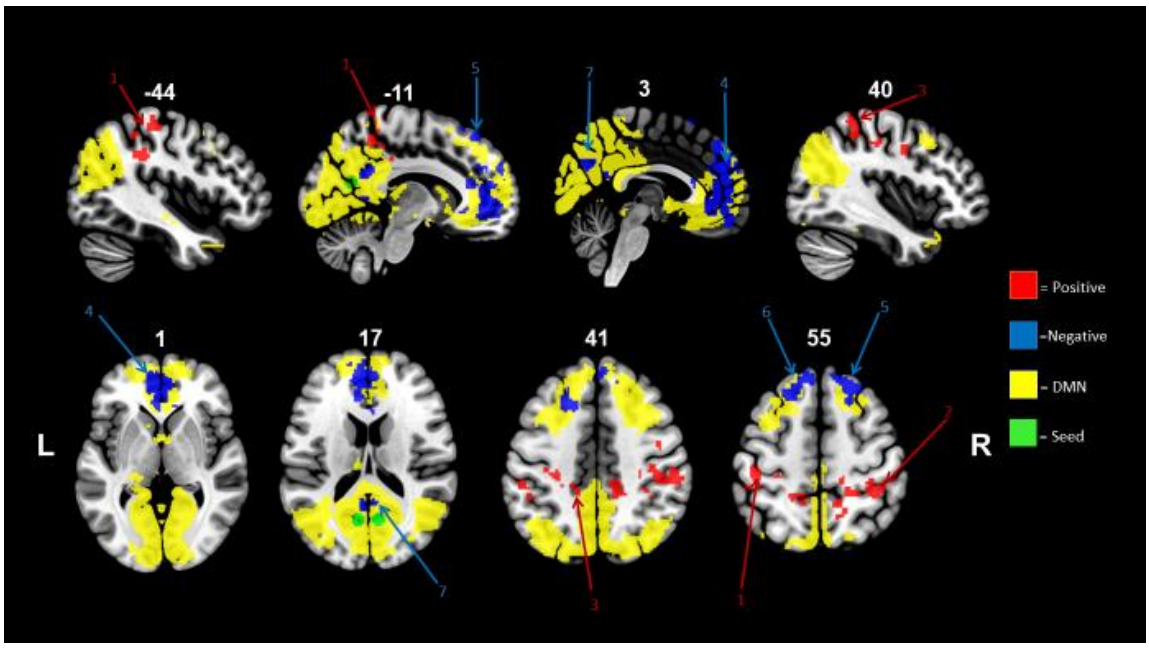

Figure 2. *Isolated clusters (numbered in relation to clusters in table 2) in MNI space positively and negatively correlated with FFMQ scores (thresholded at Z> 2.3, p=.05 corrected). Also displayed are DMN activation (yellow) and precuneus seed region (green). Images displayed according to neurological orientation conventions, with slice numbers*

Due to the bilateral symmetry of the two positively correlated clusters, these were merged to a form a single bilateral cluster for the purpose of extraction. The association between trait mindfulness and connectivity between precuneus and somatosensory cortices (BA1, BA2, BA3) are plotted in Figure 3.

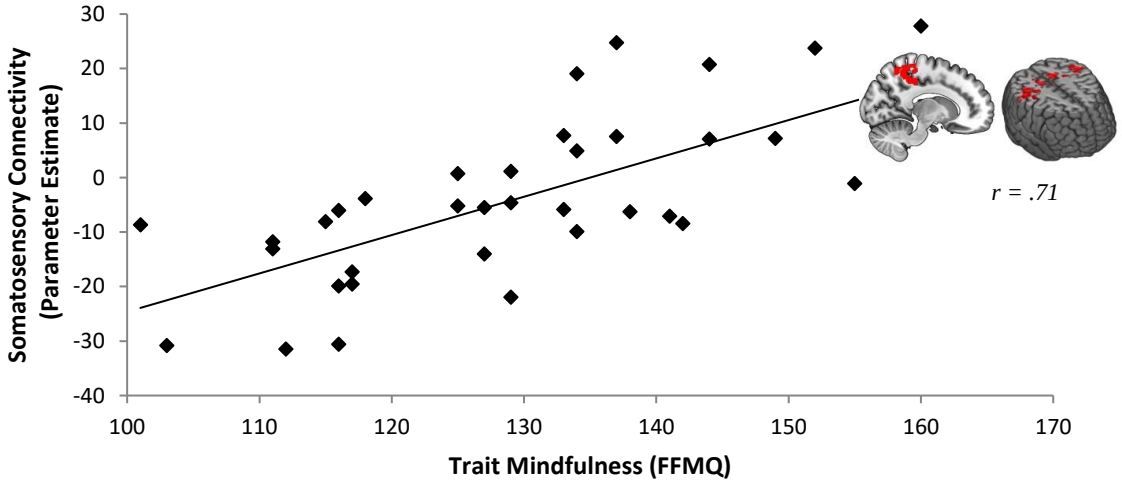

Figure 3. *The relationship between trait mindfulness, and extracted mean time series connectivity values between the precuneus and somatosensory cluster*

There were five clusters where precuneus connectivity was negatively correlated with trait mindfulness, including the medial prefrontal cortex (mPFC; cluster 3), confirming our hypothesis

that trait mindfulness would be associated with reduced connectivity of key DMN nodes. The association between trait mindfulness and connectivity between these DMN nodes is plotted in Figure 4.

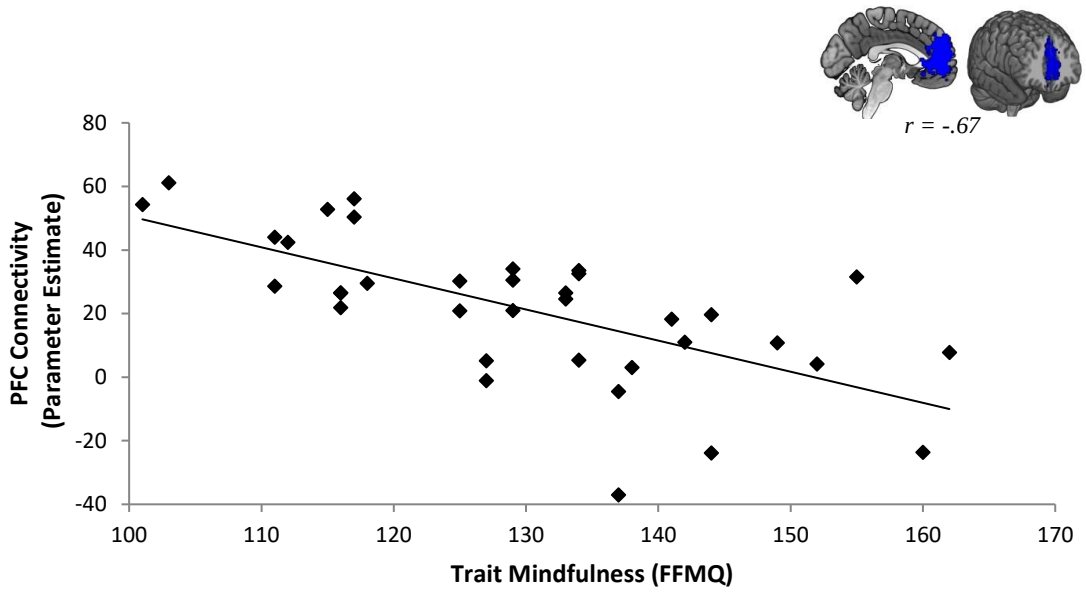

Figure 4. *The relationship between trait mindfulness scores, and extracted mean time series connectivity values between the precuneus and dorsal medial prefrontal cluster*

Connectivity between our precuneus seed and both the somatosensory (Figure 5) and prefrontal clusters (Figure 6) were significantly correlated with pain threshold (r=.46, p=.003; r= -.34, p=.023 respectively) and pain catastrophising (r= .50, p=.001; r= .31, p= .034 respectively).

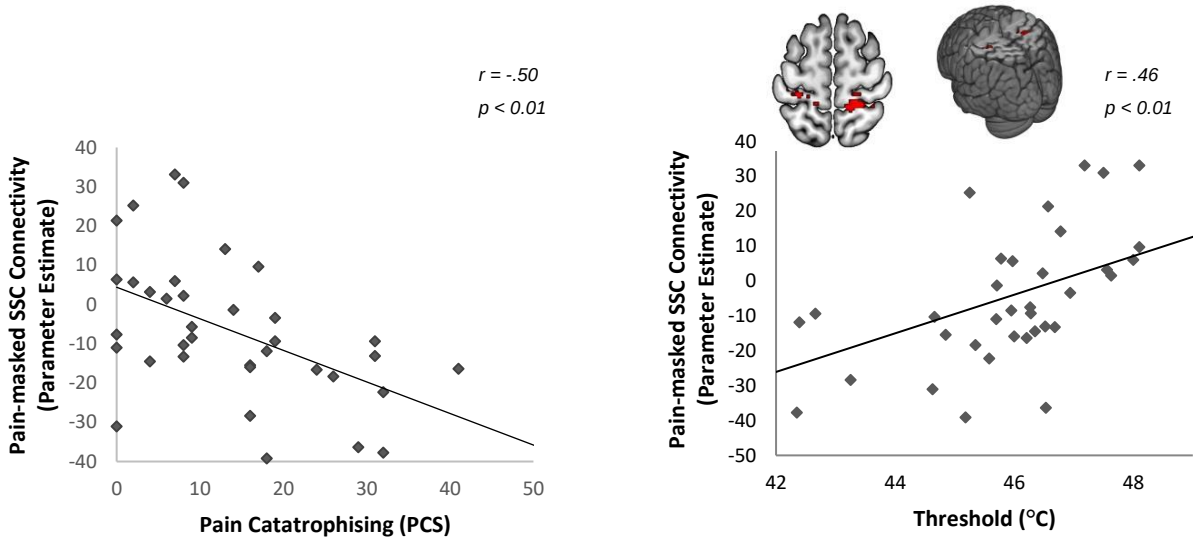

Figure 5. *The relationship between pain catastrophising and stimulus threshold, and extracted mean time series connectivity values between the precuneus and pain-related regions of the bilateral somatosensory cluster*

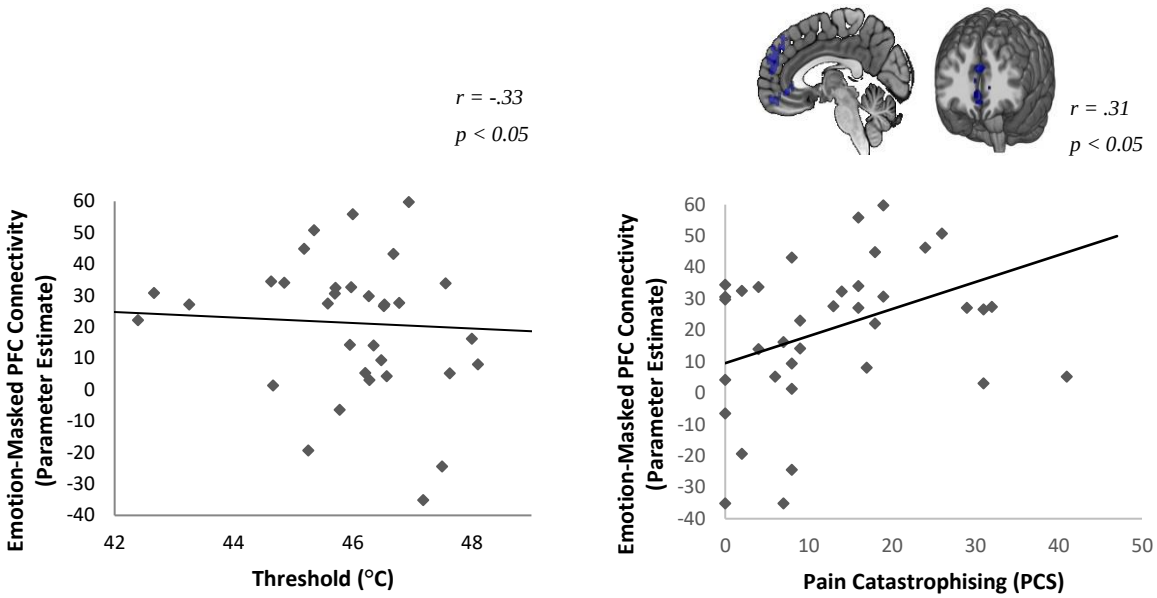

Figure 6. *The relationship between pain catastrophising and stimulus threshold, and extracted mean time series connectivity values between the precuneus and pain-related regions of the prefrontal cortex cluster*

3.5. Discussion

Numerous studies have shown that mindfulness practice attenuates pain (Cherkin et al., 2016; Chiesa & Serretti, 2011; Morone et al., 2016; Reiner et al., 2013; Zeidan et al., 2011) but less is known about whether dispositional mindfulness confers the ability to cope with pain in the absence of training or explicit mindful practice. This study examined the relationship between dispositional mindfulness and pain reactivity, and the neural mechanisms that underlie these relationships. As hypothesised, trait mindfulness was associated with higher pain thresholds and lower pain catastrophising. These findings are similar to observations following increases in mindfulness via training (Kingston, Chadwick, Meron, & Skinner, 2007; Schütze, Rees, Preece, & Schütze, 2010; Turner et al., 2016; Zeidan et al., 2010). Mindfulness based interventions and long term contemplative practice are associated with increases in sensory pain thresholds (Kingston et al., 2007; Reiner et al., 2016; Schütze et al., 2010; Zeidan et al., 2010), as well as decreases in maladaptive pain-related cognitions, such as pain catastrophising (Schütze et al., 2010; Turner et al., 2016). It is worth nothing that pain catastrophising was not significantly correlated with pain threshold. This surprising result may reflect the use of a controlled, experimental pain stimulus, in a

context where participants are reassured that the stimulus presents no threat of damage, and can be stopped immediately at any time. Regardless of the explanation, the fact that trait mindfulness correlates with both variables even though they do not correlate with each other reinforces the assertion that it reflects both sensory and emotional responsivity. This is further supported by the regression model, where both threshold and catastrophising were significantly associated with trait mindfulness, even after accounting for shared variance.

We also found that higher trait mindfulness was associated with stronger functional connectivity of a key default mode network node (precuneus) and somatosensory cortices, as well as weaker connectivity between the precuneus and another DMN node, the medial prefrontal cortex. Previous research has linked meditative practice with deactivation of these DMN nodes (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Brewer et al., 2011; Farb et al., 2007; Taylor et al., 2013). This deactivation is associated with a decreased tendency towards maladaptive cognitive processes like rumination and mind-wandering, where attention is drawn away from the present moment (Baliki, Geha, Apkarian, & Chialvo, 2008; Kucyi et al., 2014; Kucyi & Davis, 2015; Taylor et al., 2013). Our findings suggest that trait mindfulness might function as a marker for these processes, even in the absence of a previous mindfulness-based intervention or long-term meditative practice. Taken together with the positive correlation observed between trait mindfulness and functional connectivity of DMN and somatosensory cortices, these findings are consistent with decoupling of sensory and evaluative processes and with characterisation of mindfulness as "…a state of awareness that attends towards immediate experience and is free of rumination or apprehension" (Bishop et al., 2004). Therefore, this pattern of associative connectivity that has been identified may facilitate the processes that are inherent within the concept of mindfulness. The ability to decouple sensory and evaluative processes and direct your attentional focus more towards the tactile, present-moment experience of a noxious stimulus, rather than a ruminative, or overtly indirect cognitive representation of pain, may underly the beneficial relationship between mindfulness and pain experience.

To investigate whether these patterns of activation characterise pain reactivity, we tested whether connectivity of precuneus with regions associated with, either, sensory/salience processing and emotional or evaluative processes was associated with individuals' sensory and affective pain responses. Consistent with sensory/affective decoupling described in interventional literature (Gard et al., 2012; Grant et al., 2010; Kam & Handy, 2013) we found that connectivity between the precuneus and both somatosensory cortices and mPFC were significantly correlated with pain threshold and pain catastrophising. We have previously proposed that meditative training influences pain perception through a unique neural mechanism, characterized by increased activation of regions associated with sensory/salience-discrimination and decreased activation in areas involved in regions associated with affective/evaluative processing (Salomons & Kucyi, 2011; Zeidan & Vago, 2016), consistent with increased attention to sensory aspects of pain but reduction in negative cognitive and affective responses. Our findings are in line with this proposed mechanism, but with two critical distinctions. First, we observed correlations between pain reactivity and resting state functional connectivity, rather than pain-evoked neural responses. Second, these associations were found in individuals prior to any mindfulness training. Together, these findings suggest that trait mindfulness might function as a marker for dispositional individual differences in the ability to cope with pain and that the mechanism of these individual differences is similar to that observed in individuals with both short- and long-term mindfulness training. It is important to note that independent replication is necessary to more accurately characterize the size and reliability of these effects. Also, the addition of a task-based design would allow us to more directly characterize the specific processes that these patterns of connectivity are engaging in, and how they contribute to the ability to cope with pain.

A dispositional marker of pain reactivity, particularly one like trait mindfulness that does not rely on previous experience with pain (as constructs like pain catastrophising do) could have clinical utility. While the FFMQ does not query pain behaviour, or current mental health symptoms, our

findings suggest that mindfulness could provide information about how individuals cope with pain. As such, it could be used to identify individuals who might benefit from additional pain coping training in the wake of a painful event such as surgery, where poor coping can confer increased risk of developing chronic pain. These data do not speak to whether mindfulness training would be effective in such a setting, to the efficacy of mindfulness interventions more generally or to whether this decoupling process would apply to patients with long-term chronic pain. Instead, we demonstrate that even in the absence of any kind of formal mindfulness training, practice or intervention, trait mindfulness is associated with individual differences in pain responsivity. A critical area for further research is understanding the relationship between trait mindfulness and responsiveness to mindfulness-based interventions. Repeated increases in state mindfulness can lead to increased trait mindfulness (Kiken, Garland, Bluth, Palsson, & Gaylord, 2015), indicating that trait mindfulness is not immutable. It is less clear, however, whether high or low trait mindfulness is associated with optimal response to mindfulness-based interventions. Preliminary research indicates that participants high in trait mindfulness experience greater increases in mindfulness, subjective well-being and empathy in response to a mindfulness intervention, with larger decreases in perceived stress after a year (Shapiro, Brown, Thoresen, & Plante, 2011). The generalizability of these findings to pain responsivity, however, has yet to be investigated.

In summary, this study took a novel approach to studying mindfulness by examining dispositional mindfulness in individuals naïve to mindfulness-based practices or interventions. We demonstrated that even in the absence of any kind of formal mindfulness training, practice or intervention, trait mindfulness is associated with individual differences in pain responsivity, and characteristic patterns of functional connectivity. Mirroring the interventional literature, we found that trait mindfulness was positively associated with pain threshold, and inversely associated with pain catastrophising. Resting state analysis revealed that this pattern of pain reactivity was associated with lower connectivity of the default mode network and greater synchronization of the DMN with somatosensory regions, consistent with a disposition to attend to immediate sensory aspects of experience and disengage from ruminative and evaluative cognitive processes.

3.6. References

Ahmad, G., Saluja, S., Flynn, O. H., Sorrentino, A., Leach, D., & Watson, A. (2017). Pain relief for outpatient hysteroscopy. *Cochrane Database of Systematic Reviews*, (10). https://doi.org/10.1002/14651858.CD007710.pub3.www.cochranelibrary.com

Anderson, T., Walls, M., & Canelo, R. (2017). Day case surgery guidelines. *Surgery*, *35*(2), 85–91. https://doi.org/10.1016/j.mpsur.2016.11.013

Arcidiacono, G. (2009). Statistics Calculator: Linear Regression. Retrieved from http://www.alcula.com/calculators/statistics/linear-regression/

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003

Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*(2), 140–148. https://doi.org/10.1016/j.neulet.2012.03.039

Baer, R. A., Smith, G., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., … Williams, J. M. G. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment*, *15*(3), 329–342. https://doi.org/10.1177/1073191107313003

Baer, R. A., Smith, G. T., Hopkins, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, *13*(1), 27–45. https://doi.org/10.1177/1073191105283504

Bajaj, Y., Sethi, N., Carr, S., & Knight, L. C. (2009). Endoscopic sinus surgery as daycase procedure. *Journal of Laryngology and Otology*, *123*(6), 619–622. https://doi.org/10.1017/S0022215108003332

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics. *Journal of Neuroscience*, *28*(6), 1398–1403. https://doi.org/10.1523/JNEUROSCI.4123-07.2008

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., … Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. https://doi.org/10.1093/clipsy/bph077

Bjune, K., Stubhaug, A., Dodgson, M. S., & Breivik, H. (1996). Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. *Acta Anaesthesiologica Scandinavica*, *40*(4), 399–407. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8738682

Bogdanov, V. B., Viganò, A., Noirhomme, Q., Bogdanova, O. V, Guy, N., Laureys, S., … Schoenen, J. (2015). Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. *Behavioural Brain Research*, *281*, 187–198. https://doi.org/10.1016/j.bbr.2014.11.028

Bohlmeijer, E., ten Klooster, P. M., Fledderus, M., Veehof, M., & Baer, R. (2011). Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment*, *18*(3), 308–320. https://doi.org/10.1177/1073191111408231

Bouhassira, D., Villanueva, L., & Le Bars, D. (1992). Effects of systematic morphine on diffuse noxious inhibitory controls: Role of the periaqueductal grey. *European Journal of Pharmacology*, *216*(2), 149–156. https://doi.org/10.1016/0014-2999(92)90355-8

Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences*, *104*(27), 11483–11488. https://doi.org/10.1073/pnas.0606552104

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Breivik Hals, E. K., … Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia*, *101*(1), 17–24. https://doi.org/10.1093/bja/aen103

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y.-Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences*, *108*(50), 20254–20259. https://doi.org/10.1073/pnas.1112029108

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., … Jarvik, J. G. (2015). Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology*, *36*(4), 811–816. https://doi.org/10.3174/ajnr.A4173

Brooks, J., & Tracey, I. (2005). From nociception to pain perception: Imaging the spinal and supraspinal pathways. *Journal of Anatomy*, *207*(1), 19–33. https://doi.org/10.1111/j.1469-7580.2005.00428.x

Brown, C. A., & Jones, A. K. (2013). Psychobiological correlates of improved mental health in patients with

musculoskeletal pain after a mindfulness-based pain management program. *Clinical Journal of Pain*, *29*(3), 233–244. https://doi.org/10.1097/AJP.0b013e31824c5d9f

Bruce, J., Thornton, A. J., Powell, R., Johnston, M., Wells, M., Heys, S. D., … Scott, N. W. (2014). Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain*, *155*(2), 232–243. https://doi.org/10.1016/j.pain.2013.09.028

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J.-I., & Carrier, B. (1999). Pain perception: Is there a role for primary somatosensory cortex? *Proceedings of the National Academy of Sciences*, *96*(14), 7705–7709. https://doi.org/10.1073/pnas.96.14.7705

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

Cadden, S. W., Villanueva, L., Chitour, D., & Le Bars, D. (1983). Depression of activities of dorsal horn convergent neurones by propriospinal mechanisms triggered by noxious inputs; comparison with diffuse noxious inhibitory controls (DNIC). *Brain Research*, *275*(1), 1–11. https://doi.org/10.1016/0006-8993(83)90412-2

Carmon, A., Mor, J., & Goldberg, J. (1976). Evoked cerebral responses to noxious thermal stimuli in humans. *Experimental Brain Research*, *25*(1), 103–107. https://doi.org/10.1007/BF00237330

Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suárez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex*, *10*(3), 220–242. https://doi.org/10.1093/cercor/10.3.220

Cavana, A.E., Trimble, M.R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*,129, 564-583. doi:10.1093/brain/awl004.

Cheriyan, J., & Sheets, P. L. (2018). Altered Excitability and Local Connectivity of mPFC-PAG Neurons in a Mouse Model of Neuropathic Pain. *The Journal of Neuroscience*, *38*(20), 4829–4839. https://doi.org/10.1523/jneurosci.2731-17.2018

Cherkin, D. C., Sherman, K. J., Balderson, B. H., Cook, A. J., Anderson, M. L., Hawkes, R. J., … Turner, J. A. (2016). Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain. *JAMA*, *315*(12), 1240. https://doi.org/10.1001/jama.2016.2323

Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*, *17*(1), 83–93. https://doi.org/10.1089/acm.2009.0546

Christoff, K., Smallwood, J., Smith, R., Gordon, A. M., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, *106*(21), 8719–8724. https://doi.org/10.1073/pnas.0900234106

Clark, T. J., Middleton, L. J., Cooper, N. A., Diwakar, L., Denny, E., Smith, P., … Daniels, J. P. (2015). A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding. *Health Technology Assessment*, *19*(61), 1–194. https://doi.org/10.3310/hta19610

Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999). Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism. *Journal of Neurophysiology*, *82*(4), 1934–1943. https://doi.org/10.1152/jn.1999.82.4.1934

Cooney, R.E., Joormann, J., Eugene, F., Dennis, E.L., Gotlib, I.H. (2010). Neural correlates of rumination in depression. *Cogn Affect Behav Neurosci.* 10*(4)*,470-478. doi:10.3758/CABN.10.4.470.

Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., … Ferris, J. L. (2016). Alterations in resting state functional connectivity link mindfulness meditation with reduced interleukin-6: a randomized controlled trial. *Biological Psychiatry*, *80*(1), 53–61. https://doi.org/10.1016/j.biopsych.2016.01.008

Darnall, B. D., Scheman, J., Davin, S., Burns, J. W., Murphy, J. L., Wilson, A. C., … Mackey, S. C. (2016). Pain psychology: A global needs assessment and national call to action. *Pain Medicine (United States)*, *17*(2), 250–263. https://doi.org/10.1093/pm/pnv095

Darwin, L., & Chung, F. (2013). Patient selection for day surgery. *Anaesthesia and Intensive Care Medicine*, *14*(3), 114–118. https://doi.org/10.1016/j.mpaic.2013.01.003

Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: a neurobiological perspective. *Nature Neuroscience*, *17*(2), 192–200. https://doi.org/10.1038/nn.3628

Dickenson, J., Berkman, E. T., Arch, J., & Lieberman, M. D. (2013). Neural correlates of focused attention during a brief mindfulness induction. *Social Cognitive and Affective Neuroscience*, *8*(1), 40–47. https://doi.org/10.1093/scan/nss030

Edwards, R. R., Dolman, A. J., Martel, M. O., Finan, P. H., Lazaridou, A., Cornelius, M., & Wasan, A. D. (2016). Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 284.

https://doi.org/10.1186/s12891-016-1124-6
Eippert, F., Bingel, U., Schoell, E. D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia. *Neuron*, *63*(4), 533–543. https://doi.org/10.1016/j.neuron.2009.07.014
Ezra, M., Faull, O. K., Jbabdi, S., & Pattinson, K. T. S. (2015). Connectivity-based segmentation of the periaqueductal gray matter in human with brainstem optimized diffusion MRI. *Human Brain Mapping*, *36*(9), 3459–3471. https://doi.org/10.1002/hbm.22855
Falkner, E., & Tylko, K. (2019). Campaign against painful hysteroscopy: Hysteroscopy without pain. Retrieved July 3, 2019, from https://www.hysteroscopyaction.org.uk/
Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., Mckeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. https://doi.org/10.1093/scan/nsm030
Faull, O. K., & Pattinson, K. T. S. (2017). The cortical connectivity of the periaqueductal gray and the conditioned response to the threat of breathlessness. *ELife*, *6*, 1–18. https://doi.org/10.7554/eLife.21749
Fillingim, R. B., King, C. D., Currie, T., Riley, J. L., Wong, F., & Mauderli, A. P. (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain*, *143*(3), 172–178. https://doi.org/10.1016/j.pain.2008.12.027
Gandhi, R., Davey, J. R., & Mahomed, N. (2009). Patient Expectations Predict Greater Pain Relief with Joint Arthroplasty. *Journal of Arthroplasty*, *24*(5), 716–721. https://doi.org/10.1016/j.arth.2008.05.016
Gandhi, W., Rosenek, N. R., Harrison, R., & Salomons, T. V. (n.d.). Functional connectivity of the amygdala is linked to individual differences in emotional pain facilitation. *Pain*.
Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: From dipoles to functional significance. *Neurophysiologie Clinique*, *33*(6), 279–292. https://doi.org/10.1016/j.neucli.2003.10.008
Gard, T., Hölzel, B. K., Sack, A. T., Hempel, H., Lazar, S. W., Vaitl, D., & Ott, U. (2012). Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cerebral Cortex*, *22*(11), 2692–2702. https://doi.org/10.1093/cercor/bhr352
Gauriau, C., & Bernard, J. (2002). Pain pathways and parabrachial circuits in the rat. *Experimental Physiology*, *87*(2), 251–258.
Goffaux, P., Redmond, W. J., Rainville, P., & Marchand, S. (2007). Descending analgesia - When the spine echoes what the brain expects. *Pain*, *130*(1–2), 137–143. https://doi.org/10.1016/j.pain.2006.11.011
Granot, M., Weissman-Fogel, I., Crispel, Y., Pud, D., Granovsky, Y., Sprecher, E., & Yarnitsky, D. (2008). Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? *Pain*, *136*(1–2), 142–149. https://doi.org/10.1016/j.pain.2007.06.029
Granovsky, Y. (2013). Conditioned Pain Modulation: A Predictor for Development and Treatment of Neuropathic Pain. *Current Pain and Headache Reports*, *17*(9), 361. https://doi.org/10.1007/s11916-013-0361-8
Granovsky, Y., & Yarnitsky, D. (2013). Personalized Pain Medicine: The Clinical Value of Psychophysical Assessment of Pain Modulation Profile. *Rambam Maimonides Medical Journal*, *4*(4), 1–8. https://doi.org/10.5041/RMMJ.10131
Grant, J. A., Courtemanche, J., Duerden, E. G., Duncan, G. H., & Rainville, P. (2010). Cortical thickness and pain sensitivity in zen meditators. *Emotion*, *10*(1), 43–53. https://doi.org/10.1037/a0018334
Grant, J. A., Courtemanche, J., & Rainville, P. (2011). A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*, *152*(1), 150–156. https://doi.org/10.1016/j.pain.2010.10.006
Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in zen meditators: A cross-sectional study. *Psychosomatic Medicine*, *71*(1), 106–114. https://doi.org/10.1097/PSY.0b013e31818f52ee
Green, C. R., Wheeler, J. R. C., & LaPorte, F. (2003). Clinical decision making in pain management: Contributions of physician and patient characteristics to variations in practice. *Journal of Pain*, *4*(1), 29–39. https://doi.org/10.1054/jpai.2003.5
Grosen, K., Fischer, I. W. D., Olesen, A. E., & Drewes, A. M. (2013). Can quantitative sensory testing predict responses to analgesic treatment? *European Journal of Pain (United Kingdom)*, *17*(9), 1267–1280. https://doi.org/10.1002/j.1532-2149.2013.00330.x
Grosen, Kasper, Vase, L., Pilegaard, H. K., Pfeiffer-Jensen, M., & Drewes, A. M. (2014). Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: A prospective observational cohort study. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0090185
Harper, D. E., Ichesco, E., Schrepf, A., Hampson, J. P., Clauw, D. J., Schmidt-Wilcke, T., … Harte, S. E. (2018). Resting Functional Connectivity of the Periaqueductal Gray Is Associated With Normal

Inhibition and Pathological Facilitation in Conditioned Pain Modulation. *Journal of Pain*, *19*(6), 635.e1-635.e15. https://doi.org/10.1016/j.jpain.2018.01.001
Harrison, R., Zeidan, F., Kitsaras, G., Ozcelik, D., & Salomons, T. V. (2019). Trait Mindfulness Is Associated With Lower Pain Reactivity and Connectivity of the Default Mode Network. *Journal of Pain*, *20*(6). https://doi.org/10.1016/j.jpain.2018.10.011
Harvey, W. F., Rones, R., Tao, J., Kong, J., Wolcott, E., Wang, C., … Jorgenson, K. (2018). Altered resting state functional connectivity of the cognitive control network in fibromyalgia and the modulation effect of mind-body intervention. *Brain Imaging and Behavior*, 1–11. https://doi.org/10.1007/s11682-018-9875-3
Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage*, *59*(1), 750–760. https://doi.org/10.1016/j.neuroimage.2011.07.008
Hölzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How Does Mindfulness Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural Perspective. *Perspectives on Psychological Science*, *6*(6), 537–559. https://doi.org/10.1177/1745691611419671
Jansen, F. W., Vredevoogd, C. B., van Ulzen, K., Hermans, J., Trimbos, J. B., & Trimbos-Kemper, T. C. (2000). Complications of hysteroscopy: a prospective, multicenter study. *Obstetrics and Gynecology*, *96*(2), 266–270. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10908775
Jenkinson, M. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *Neuroimage*, *17*(2), 825–841. https://doi.org/10.1016/S1053-8119(02)91132-8
Jenkinson, Mark, Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015
Jones, D. H., Kilgour, R. D., & Comtois, A. S. (2007). Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *J Pain*, *8*(8), 650–656. https://doi.org/10.1016/j.jpain.2007.04.003
Julien, N., Goffaux, P., Arsenault, P., & Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*, *114*(1–2), 295–302. https://doi.org/10.1016/j.pain.2004.12.032
Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*. https://doi.org/10.1016/0163-8343(82)90026-3
Kam, J. W. Y., & Handy, T. C. (2013). The neurocognitive consequences of the wandering mind: a mechanistic account of sensory-motor decoupling. *Frontiers in Psychology*, *4*(October), 1–13. https://doi.org/10.3389/fpsyg.2013.00725
Khan, R. S., Ahmed, K., Blakeway, E., Skapinakis, P., Nihoyannopoulos, L., MacLeod, K., … Athanasiou, T. (2011). Catastrophizing: A predictive factor for postoperative pain. *American Journal of Surgery*, *201*(1), 122–131. https://doi.org/10.1016/j.amjsurg.2010.02.007
Kiken, L. G., Garland, E. L., Bluth, K., Palsson, O. S., & Gaylord, S. A. (2015). From a state to a trait: Trajectories of state mindfulness in meditation during intervention predict changes in trait mindfulness. *Personality and Individual Differences*, *81*, 41–46. https://doi.org/10.1016/j.paid.2014.12.044
Kingston, J., Chadwick, P., Meron, D., & Skinner, T. C. (2007). A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *Journal of Psychosomatic Research*, *62*(3), 297–300. https://doi.org/10.1016/j.jpsychores.2006.10.007
Klein, J. G. (2005). Five pitfalls in decisions about diagnosis and prescribing. *Bmj*, *330*(7494), 781–783. https://doi.org/10.1136/bmj.330.7494.781
Kong, J., Tu, P. C., Zyloney, C., & Su, T. P. (2010). Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. *Behavioural Brain Research*, *211*(2), 215–219. https://doi.org/10.1016/j.bbr.2010.03.042
Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: Where expectations become reality. *Proceedings of the National Academy of Sciences*, *102*(36), 12950–12955. https://doi.org/10.1073/pnas.0408576102
Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced Medial Prefrontal-Default Mode Network Functional Connectivity in Chronic Pain and Its Association with Pain Rumination. *Journal of Neuroscience*, *34*(11), 3969–3975. https://doi.org/10.1523/JNEUROSCI.5055-13.2014
Kucyi, Aaron, & Davis, K. D. (2014). Dynamic functional connectivity of the default mode network tracks daydreaming. *NeuroImage*, *100*, 471–480. https://doi.org/10.1016/j.neuroimage.2014.06.044
Kucyi, Aaron, & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences*, *38*(2), 86–

95. https://doi.org/10.1016/j.tins.2014.11.006
Lander, J. (1990). Clinical judgments in pain management. *Pain*, *42*(1), 15–22. https://doi.org/10.1016/0304-3959(90)91086-X
Larue, F., Colleau, S. M., Fontaine, A., & Brasseur, L. (1995). Oncologists and primary care physicians' attitudes toward pain control and morphine prescribing in france. *Cancer*, *76*(11), 2375–2382. https://doi.org/10.1002/1097-0142(19951201)76:11<2375::AID-CNCR2820761129>3.0.CO;2-C
Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., & Arendt-Nielsen, L. (2005). Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*, *115*(3), 410–418. https://doi.org/10.1016/j.pain.2005.03.025
Le Bars, D, Dickenson, A. H., & Besson, J. M. (1979). Diffuse noxious inhibitory controls. I. Effects on dorsal horn convergent neurons in the rat. II. Lack of effect on nonconvergent neurons, supraspinal involvement and theoretical implications. *Pain*, *6*(3), 305–327. https://doi.org/10.1016/0304-3959(79)90049-6
Le Bars, Daniel, Chitour, D., Kraus, E., Dickenson, A. H., & Besson, J. M. (1981). Effect of naloxone upon diffuse noxious inhibitory controls (DNIC) in the rat. *Brain Research*, *204*(2), 387–402. https://doi.org/10.1016/0006-8993(81)90597-7
Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2012.07.005
Linnman, C., Moulton, E. A., Barmettler, G., Becerra, L., & Borsook, D. (2012). Neuroimaging of the periaqueductal gray: State of the field. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.11.095
Lois, G., Wessa, M. (2016). Differential association of default mode network connectivity and rumination in healthy individuals and remitted MDD patients. *Social Cognitive and Affective Neuroscience*. 11*(11)*, 1792-1801. Doi: 10.1093/scan/nsw085
Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, *126*(5), 1079–1091. https://doi.org/10.1093/brain/awg102
Ludwig, D. S., & Kabat-Zinn, J. (2008). Mindfulness in Medicine. *JAMA*, *300*(11), 1350. https://doi.org/10.1001/jama.300.11.1350
Lutz, A., McFarlin, D. R., Perlman, D. M., Salomons, T. V., & Davidson, R. J. (2013). Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage*, *64*(1), 538–546. https://doi.org/10.1016/j.neuroimage.2012.09.030
Mamie, C. (2004). Are there reliable predictors of postoperative pain? *Acta Anaesthesiologica Scandinavica*, *48*(2), 234–242. https://doi.org/10.1111/j.0001-5172.2004.00298.x
Manias, E., Botti, M., & Bucknall, T. (2002). Observation of pain assessment and management--the complexities of clinical practice. *Journal of Clinical Nursing*, *11*(6), 724–733. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L35513243%5Cnhttp://pm6mt7vg3j.search.serialssolutions.com?sid=EMBASE&issn=09621067&id=doi:&atitle=Observation+of+pain+assessment+and+management--the+complexities+of+clinical+practic
March, L., Burstein, R., Murray, C., Buchbinder, R., Barendregt, J., Woolf, A., … Hoy, D. (2014). The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(6), 968–974. https://doi.org/10.1136/annrheumdis-2013-204428
Marsh, F. A., Rogerson, L. J., & Duffy, S. R. G. (2006). A randomised controlled trial comparing outpatient versus daycase endometrial polypectomy. *BJOG: An International Journal of Obstetrics and Gynaecology*, *113*(8), 896–901. https://doi.org/10.1111/j.1471-0528.2006.00967.x
Masselin-Dubois, A., Attal, N., Fletcher, D., Jayr, C., Albi, A., Fermanian, J., … Baudic, S. (2013). Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of total knee arthroplasty and breast surgery for cancer. *Journal of Pain*, *14*(8), 854–864. https://doi.org/10.1016/j.jpain.2013.02.013
Mattos Feijó, L., Tarman, G. Z., Fontaine, C., Harrison, R., Johnstone, T., & Salomons, T. (2018). Sex-Specific Effects of Gender Identification on Pain Study Recruitment. *Journal of Pain*, *19*(2). https://doi.org/10.1016/j.jpain.2017.09.009
May, A. (2009). New insights into headache: An update on functional and structural imaging findings. *Nature Reviews Neurology*, *5*(4), 199–209. https://doi.org/10.1038/nrneurol.2009.28
McCracken, L. M., Gauntlett-Gilbert, J., & Vowles, K. E. (2007). The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain*, *131*(1–2), 63–69. https://doi.org/10.1016/j.pain.2006.12.013
Meechan, J. G. (2017). Why Does Local Anaesthesia Not Work Every Time? *Dental Update*, *32*(2), 66–72. https://doi.org/10.12968/denu.2005.32.2.66
Melzack, R., & Wall, P. (1965). Pain Mechanism: A new Theory. *Science*. https://doi.org/10.1126/science.150.3699.971

Merskey, H., Addison, R. G., Beric, A., Blumberg, H., Bogduk, N., Boivie, J., … Watson, C. P. N. (2002). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Second edition.* (H. Merskey & N. Bogduk, Eds.), *IASP Press* (Second). Seattle, WA: IASP Press. Retrieved from http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6), 355–474. https://doi.org/10.1016/S0301-0082(02)00009-6

Morone, N. E., Greco, C. M., Moore, C. G., Rollman, B. L., Lane, B., Morrow, L. A., … Weiner, D. K. (2016). A mind-body program for older adults with chronic low back pain a randomized clinical trial. *JAMA Internal Medicine*, *176*(3), 329. https://doi.org/10.1001/jamainternmed.2015.8033

Morton, C. R., Maisch, B., & Zimmermann, M. (1987). Diffuse noxious inhibitory controls of lumbar spinal neurons involve a supraspinal loop in the cat. *Brain Research*, *410*(2), 347–352. https://doi.org/10.1016/0006-8993(87)90336-2

Mun, C. J., Okun, M. A., & Karoly, P. (2014). Trait mindfulness and catastrophizing as mediators of the association between pain severity and pain-related impairment. *Personality and Individual Differences*, *66*, 68–73. https://doi.org/10.1016/j.paid.2014.03.016

Nejad, A.B., Fossati, P., Lemogne, C. Self-referential processing, rumination and cortical midline structures in major depression. *Frontiers in Human Neuroscience,* 7, 666. Doi: 10.3389/fnhum.2013.00666

O'Brien, A. T., Deitos, A., Triñanes Pego, Y., Fregni, F., & Carrillo-de-la-Peña, M. T. (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *Journal of Pain*. Elsevier Inc. https://doi.org/10.1016/j.jpain.2018.01.010

Olesen, S. S., Brock, C., Krarup, A. L., Funch-Jensen, P., Arendt-Nielsen, L., Wilder-Smith, O. H., & Drewes, A. M. (2010). Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. *Clinical Gastroenterology and Hepatology*, *8*(8), 724–730. https://doi.org/10.1016/j.cgh.2010.03.005

Ong, W.-Y., Stohler, C. S., & Herr, D. R. (2019). Role of the Prefrontal Cortex in Pain Processing. *Molecular Neurobiology*, *56*(2), 1137–1166. https://doi.org/10.1007/s12035-018-1130-9

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766

Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current Opinion in Supportive and Palliative Care*, *8*(2), 143–151. https://doi.org/10.1097/SPC.0000000000000055

Paul, N. A., Stanton, S. J., Greeson, J. M., Smoski, M. J., & Wang, L. (2013). Psychological and neural mechanisms of trait mindfulness in reducing depression vulnerability. *Social Cognitive and Affective Neuroscience*, *8*(1), 56–64. https://doi.org/10.1093/scan/nss070

Perlman, D. M., Salomons, T. V, Davidson, R. J., & Lutz, A. (2010). Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*, *10*(1), 65–71. https://doi.org/10.1037/a0018440

Petter, M., Chambers, C. T., McGrath, P. J., & Dick, B. D. (2013). The role of trait mindfulness in the pain experience of adolescents. *Journal of Pain*, *14*(12), 1709–1718. https://doi.org/10.1016/j.jpain.2013.08.015

Piche, M., Arsenault, M., & Rainville, P. (2009). Cerebral and Cerebrospinal Processes Underlying Counterirritation Analgesia. *Journal of Neuroscience*, *29*(45), 14236–14246. https://doi.org/10.1523/jneurosci.2341-09.2009

Popescu, A., Leresche, L., Truelove, E. L., & Drangsholt, M. T. (2010). Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. *Pain*, *150*(2), 309–318. https://doi.org/10.1016/j.pain.2010.05.013

Potvin, S., & Marchand, S. (2016). Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*, *157*(8), 1704–1710. https://doi.org/10.1097/j.pain.0000000000000573

Price, D. D. (2000). Psychological and Neural Mechanisms of the Affective Dimension of Pain. *Science*, *288*(5472), 1769–1772. https://doi.org/10.1126/science.288.5472.1769

Price, Donald D., Bush, F. M., Long, S., & Harkins, S. W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*, *56*(2), 217–226. https://doi.org/10.1016/0304-3959(94)90097-3

Price, Donald D., McGrath, P. A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*, *17*(1), 45–56. https://doi.org/10.1016/0304-3959(83)90126-4

Prins, B., Decuypere, A., & Van Damme, S. (2014). Effects of mindfulness and distraction on pain depend upon individual differences in pain catastrophizing: An experimental study. *European Journal of Pain*, *18*(9), 1307–1315. https://doi.org/10.1002/j.1532-2149.2014.491.x

Rabey, M., Poon, C., Wray, J., Thamajaree, C., East, R., & Slater, H. (2015). Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual Therapy*, *20*(6), 763–768. https://doi.org/10.1016/j.math.2015.02.011

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, *12*(2), 195–204. https://doi.org/10.1016/S0959-4388(02)00313-6

Ram, K. C., Eisenberg, E., Haddad, M., & Pud, D. (2008). Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - New perspective of opioid-induced hyperalgesia. *Pain*, *139*(2), 431–438. https://doi.org/10.1016/j.pain.2008.05.015

Reiner, K., Granot, M., Soffer, E., & Lipsitz, J. D. (2016). A Brief Mindfulness Meditation Training Increases Pain Threshold and Accelerates Modulation of Response to Tonic Pain in an Experimental Study. *Pain Medicine (Malden, Mass.)*, *17*(4), 628–635. https://doi.org/10.1111/pme.12883

Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Medicine*, *14*(2), 230–242. https://doi.org/10.1111/pme.12006

Robinson, M. E., Gagnon, C. M., Riley, J. L., & Price, D. D. (2003). Altering gender role expectations: Effects on pain tolerance, pain threshold, and pain ratings. *Journal of Pain*, *4*(5), 284–288. https://doi.org/10.1016/S1526-5900(03)00559-5

Salomons, T. V, & Kucyi, A. (2011). Does Meditation Reduce Pain through a Unique Neural Mechanism? *Journal of Neuroscience*, *31*(36), 12705–12707. https://doi.org/10.1523/JNEUROSCI.2843-11.2011

Sauer, S., Walach, H., Schmidt, S., Hinterberger, T., Lynch, S., Büssing, A., & Kohls, N. (2013). Assessment of Mindfulness: Review on State of the Art. *Mindfulness*, *4*(1), 3–17. https://doi.org/10.1007/s12671-012-0122-5

Schütze, R., Rees, C., Preece, M., & Schütze, M. (2010). Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*, *148*(1), 120–127. https://doi.org/10.1016/j.pain.2009.10.030

Shapiro, S. L., Brown, K. W., Thoresen, C., & Plante, T. G. (2011). The moderation of Mindfulness-based stress reduction effects by trait mindfulness: Results from a randomized controlled trial. *Journal of Clinical Psychology*, *67*(3), 267–277. https://doi.org/10.1002/jclp.20761

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences*, *107*(24), 11020–11025. https://doi.org/10.1073/pnas.1000446107

Sheline, Yvette I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106

Silva, C., & McNaughton, N. (2019). Are periaqueductal gray and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review. *Progress in Neurobiology*, *177*(January), 33–72. https://doi.org/10.1016/j.pneurobio.2019.02.001

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Specialities. (2018). Retrieved July 1, 2019, from https://www.medschools.ac.uk/studying-medicine/after-medical-school/specialties

Sprenger, C., Bingel, U., & Büchel, C. (2011). Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain*, *152*(2), 428–439. https://doi.org/10.1016/j.pain.2010.11.018

Sullivan, M. J., Bishop, S., & Pivik, J. (1995). Pain Catastrophizing Scale. *Psychological Assessment*, *7*, 524–532. https://doi.org/10.1037/t01304-000

Taylor, V. A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-vidal, S., … Beauregard, M. (2013). Impact of meditation training on the default mode network during a restful state. *Social Cognitive and Affective Neuroscience*, *8*(1), 4–14. https://doi.org/10.1093/scan/nsr087

Taylor, V. A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., … Beauregard, M. (2011). Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. *NeuroImage*, *57*(4), 1524–1533. https://doi.org/10.1016/j.neuroimage.2011.06.001

Teixeira, E. (2010). The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. *Holistic Nursing Practice*, *24*(5), 277–283. https://doi.org/10.1097/HNP.0b013e3181f1add2

Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., & Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. *Clinical Journal of Pain*, *28*(9), 819–841. https://doi.org/10.1097/AJP.0b013e31824549d6

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., & Koyama, S. (1991). Chronic Motor Cortex Stimulation for the Treatment of Central Pain, *139*, 137–139. https://doi.org/10.1007/978-3-7091-9160-6_37

Turner, J. A., Anderson, M. L., Balderson, B. H., Cook, A. J., Sherman, K. J., & Cherkin, D. C. (2016).

Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain. *Pain*, *157*(11), 2434–2444. https://doi.org/10.1097/j.pain.0000000000000635
Tylko-Hill, K. (2018). *Clinical Audit*. Retrieved from https://www.whatdotheyknow.com/search/Outpatient hysteroscopy/biopsy - RCOG/BSGE 2018/all
Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus Is a Functional Core of the Default-Mode Network. *The Journal of Neuroscience*, *34*(3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014
Valencia, C., Kindler, L. L., Fillingim, R. B., & George, S. Z. (2012). Investigation of central pain processing in shoulder pain: Converging results from 2 musculoskeletal pain models. *Journal of Pain*, *13*(1), 81–89. https://doi.org/10.1016/j.jpain.2011.10.006
Walker B. (2000). The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. *Journal of Spinal Disorders*, *13*(3), 205–217. https://doi.org/10.1097/00002517-200006000-00003
Weis, O. F., Sriwatanakul, K., Alloza, J. L., Weintraub, M., & Lasagna, L. (1983). Attitudes of Patients, Housestaff, and Nurses Toward Postoperative Analgesic Care. *Anesthesia & Analgesia*, *62*(1), 70–74. https://doi.org/10.1213/00000539-198301000-00012
Wilder-Smith, C. H., Schindler, D., Lovblad, K., Redmond, S. M., & Nirkko, A. (2004). Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut*, *53*(11), 1595–1601. https://doi.org/10.1136/gut.2003.028514
Wilder-Smith, Clive H., & Robert-Yap, J. (2007). Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World Journal of Gastroenterology*, *13*(27), 3699–3704. https://doi.org/10.3748/wjg.v13.i27.3699
Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J., & Arendt-Nielsen, L. (2010). Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: A pilot study. *Journal of Pain and Palliative Care Pharmacotherapy*, *24*(2), 119–128. https://doi.org/10.3109/15360281003706069
Wilkerson, R. G., Kim, H. K., Windsor, T. A., & Mareiniss, D. P. (2016). The Opioid Epidemic in the United States. *Emergency Medicine Clinics of North America*, *34*(2), e1–e23. https://doi.org/10.1016/j.emc.2015.11.002
Willer, J., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain*, *107*(4), 1095–1112. https://doi.org/10.1093/brain/107.4.1095
Xie, Y. F., Huo, F. Q., & Tang, J. S. (2009). Cerebral cortex modulation of pain. *Acta Pharmacologica Sinica*, *30*(1), 31–41. https://doi.org/10.1038/aps.2008.14
Yarkoni, T., Poldrack, R. A. R., Nichols, T. T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. https://doi.org/10.1038/nmeth.1635
Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., … Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033
Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*, *153*(6), 1193–1198. https://doi.org/10.1016/j.pain.2012.02.021
Youssef, A. M., Macefield, V. G., & Henderson, L. A. (2016). Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. *Human Brain Mapping*, *37*(7), 2630–2644. https://doi.org/10.1002/hbm.23199
Zeidan, F. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082
Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The Effects of Brief Mindfulness Meditation Training on Experimentally Induced Pain. *Journal of Pain*, *11*(3), 199–209. https://doi.org/10.1016/j.jpain.2009.07.015
Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082
Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain Mechanisms Supporting the Modulation of Pain by Mindfulness Meditation. *Journal of Neuroscience*, *31*(14), 5540–5548. https://doi.org/10.1523/JNEUROSCI.5791-10.2011
Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation–based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences*, *1373*(1), 114–127. https://doi.org/10.1111/nyas.13153
Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical*

Imaging, *20*(1), 45–57. https://doi.org/10.1109/42.906424

3.7. Appendices

3.71. Appendix D: Five-Factor Mindfulness Questionnaire

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

3.7.2. Appendix E: Pain Catastrophising Scale

PCS-EN

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

…Total

Updated 11/11

Chapter 4. Conditioned Pain Modulation (CPM) is associated with heightened connectivity between the periaqueductal grey (PAG) and the descending pain modulation network.

Conditioned Pain Modulation (CPM) is associated with heightened connectivity between the periaqueductal grey (PAG) and the descending pain modulation network.

Richard Harrison[1], Wiebke Gandhi[1], Tim V. Salomons[1,2*],

1. University of Reading, School of Psychology and Clinical Language Sciences, Reading, UK
2. Queen's University, Department of Psychology, Kingston, ON, Canada
   *Corresponding Author

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4.1. Abstract

Chronic pain is a challenging condition to assess and treat in the clinic. Within chronic lower-back pain, some symptomatic patients present no pathological cause, while asymptomatic patients can demonstrate substantial spinal damage. Ultimately, it appears that concerning chronic pain, some people are vulnerable to the experience of pain. Conditioned Pain Modulation (CPM) is a psychophysical assessment that is known to be a proxy for the efficiency of an individual's descending pain modulation circuitry. Less efficient CPM has been associated with higher incidences of chronic postsurgical pain, lower analgesia efficacy and the presence of chronic pain conditions. By viewing CPM as an individual differences measure, we can help to understand how some people appear to possess an innate ability to manage pain. We were interested in how CPM may be associated with the neural networks underlying pain processing and modulation. To determine this, we measured CPM and collected resting state data for 40 healthy controls. We targeted our investigations of resting state connectivity to the periaqueductal grey (PAG), a region known to be important in the modulation of pain. Higher CPM, represent more efficient modulation, was associated with increased connectivity between the PAG and the somatosensory, premotor, motor and dorsolateral prefrontal cortices. All clusters identified in the connectivity analysis are areas known to be involved in processing pain. These findings suggest that those with higher CPM appear to have more integration between the processing of pain, and the PAG, which is actively involved in the modulating a noxious stimulus. This may represent a neural indicator for effective pain modulation, with this more integrated mechanism underlying individual differences in CPM, which has previously been associated with beneficial clinical outcomes for pain.

4.2. Introduction

Original Cartesian models of pain posited that there was a direct relationship between noxious input, and the perceived level of pain. In the wake of Melzack & Wall's Gate Theory of Pain (Melzack & Wall, 1965), we have learned that pain is not just a reflection of injury, but can be up- or down- regulated endogenously on the basis of various contextual factors (Ossipov, Morimura, & Porreca, 2014; Rainville, 2002). The traditional medical approach of matching injury to symptomology (and vice versa) appears increasingly inappropriate within chronic pain diagnostics. For example, chronic lower-back pain (LBP) is likely to affect up to two-thirds of people across their life-span (Walker, 2000) and is the leading cause of pain-related disability worldwide (March et al., 2014), but is poorly linked to peripheral pathology, with spinal degeneration being present in a large proportion of asymptomatic patients, and pain often present without pathology (Brinjikji et al., 2015). The "variable link" between pain and peripheral pathology necessitates study of why some patients with sub-diagnostic pathology are vulnerable to chronic pain, while others appear to be more resilient.

One approach to understanding this vulnerability is to assess the efficiency of an individual's endogenous modulatory mechanisms. One psychophysical paradigm that has been used to do this is Conditioned Pain Modulation (CPM; Yarnitsky et al., 2008). This paradigm is used to test a specific mechanism in humans, based on a similar mechanism originally identified in animals (Le Bars, Dickenson, & Besson, 1979; Le Bars, Chitour, Kraus, Dickenson, & Besson, 1981) and termed diffuse noxious inhibitory control (DNIC). DNIC is based on the premise that "pain experienced in one part of the body is inhibited by the application of a noxious stimulus to another part of the body. This mechanism utilises a spinobulbospinal loop whereby processes within the brain can influence the inhibition of a noxious stimuli in the dorsal horn (Le Bars et al., 1979). Originally, it was discovered that CPM can be used to predict the development of chronic post-surgical pain (CPSP) in thoracotomy patients (Yarnitsky et al., 2008). From here, less efficient CPM has since been associated with a range of chronic pain conditions (Arendt-Nielsen et al.,

2010; Fillingim et al., 2009; Lewis, Rice, & McNair, 2012; O'Brien, Deitos, Triñanes Pego, Fregni, & Carrillo-de-la-Peña, 2018; Rabey et al., 2015; Valencia, Kindler, Fillingim, & George, 2012) and post-surgical outcomes (Wilder-Smith, Schreyer, Scheffer, & Arendt-Nielsen, 2010; Yarnitsky et al., 2008), as well being able to predict the efficacy of analgesics for treating pain symptoms (Edwards et al., 2016; Grosen, Fischer, Olesen, & Drewes, 2013; Yarnitsky et al., 2012). Although the clinical predictive utility of CPM is promising, the underlying neural mechanism that facilitates these clinical outcomes regarding pain is still unclear. By improving our understanding of the individual differences in CPM, we could elucidate how this psychophysical assessment tool is associated with such a wide range of clinical outcomes and how this be associated with the efficiency of an individual's descending modulatory system.

Specifically, early developmental work on DNIC was completed using animals and provided a good foundation of research into the underlying spinal mechanisms of this effect (Cadden, Villanueva, Chitour, & Le Bars, 1983; Le Bars et al., 1979; Morton, Maisch, & Zimmermann, 1987; Willer, Roby, & Le Bars, 1984). However, when investigating CPM in humans, the specifics of how cortical input & psychological processes influence this mechanism remain unclear. In event-related designs, the associative decrease in pain ratings, via concurrent stimulation from test and conditioning stimuli, is paralleled with decreased BOLD responses in key pain processing regions, such as the thalamus, somatosensory cortex and dorsolateral prefrontal cortex (dlPFC) (Goffaux, Redmond, Rainville, & Marchand, 2007; Piche, Arsenault, & Rainville, 2009; Wilder-Smith, Schindler, Lovblad, Redmond, & Nirkko, 2004) with an enhanced BOLD response identified within the anterior cingulate cortex (ACC) (Sprenger, Bingel, & Büchel, 2011). This may indicate that the mechanism underlying CPM utilises a process whereby modulatory regions are engaged to decrease the activation of regions which are actively involved in the processing of the noxious signal. When conceptualising a perspective on individual differences in CPM, a primary target for evaluating intrinsic ability to modulate pain could therefore be a region associated with this ability to modulate the activity of pain processing areas.

The mechanism of DNIC, alongside models of supraspinal endogenous pain modulation, specify regions within the brainstem to be critical in descendingly modulating pain via dorsal horn inhibition (Brooks & Tracey, 2005; Millan, 2002; Ossipov et al., 2014). The periaqueductal grey (PAG) is one brainstem region known to be involved within the mechanism of CPM (Bouhassira, Villanueva, & Le Bars, 1992; Le Bars et al., 1981; Sprenger et al., 2011), capable of endogenously modulating spinal cord input (Brooks & Tracey, 2005; Gauriau & Bernard, 2002; Ong, Stohler, & Herr, 2019; Xie, Huo, & Tang, 2009) and is a key node within the descending pain modulation network (May, 2009; Millan, 2002; Ossipov et al., 2014). Importantly, while the descending properties of the PAG are pertinent to how our participants modulate pain, we know that the PAG is bidirectionally connected to cortical regions, including the dlPFC, amygdala, anterior cingulate and insula cortices, thalamus, precuneus & primary visual cortices (Faull & Pattinson, 2017; Kong, Tu, Zyloney, & Su, 2010) and that input from the cortex influences how the PAG modulates the ascending nociceptive signal (Xie et al., 2009). To appropriately investigate intrinsic variation in pain modulation, and how this is associated with CPM, the use of rs-fMRI allows us to examine individuals at rest, with no added confound of explicit task-related instructions, and an a-priori seed selection allows us to target the scope of our analysis to a modulatory region. Investigating how CPM is associated with connectivity between the PAG (a key modulatory region) and the cortex may help elucidate how individual differences in the intrinsic ability to modulate pain are associated with pain modulation and how this is associated with resting patterns of functional connectivity.

This current study aims to use rs-fMRI with healthy controls to analyse how the intrinsic connectivity of a key modulatory brain region, the PAG, is related to individual differences in supraspinal mechanisms of pain modulation. We predict that CPM will be associated with higher connectivity between PAG and regions within the descending modulatory pain network.

4.3. Methods

4.3.1. Participants

This study utilises the same sample as described in chapter 3. Therefore, 40 healthy individuals were recruited and screened. Three participants were excluded (3 could not tolerate the conditioning stimulus within the CPM paradigm, 2 had excessive motion artifacts during resting state (>2.5mm)), leaving a final sample of 35 participants (14 Female; M_{age}=22.83 years, SD=5.53). Participants were recruited from the University of Reading and were excluded if they had active or historical chronic pain disorder diagnoses, current substance abuse, uncorrected visual defects or left-hand dominance. All participants provided informed consent prior to the study, and the study was approved by the University of Reading's University Research Ethics Committee (UREC).

4.3.2. Materials

4.3.2.1. Pain Stimulation

Noxious heat stimulation was administered via a MEDOC Pathway system (Medoc Medical Systems, Ramat Yishai, Israel) with a 30x30 Peltier thermode applied to the lower right calf, which was placed into a custom-made wooden leg rest. The leg was chosen due to recommendations from the standardised methodology for CPM (Yarnitsky et al., 2014), as well as practical considerations such as the use of a custom-made leg rest and the application of thermal stimulation in the MRI being better suited for leg, rather than arm. The test stimulus was calibrated to represent a 6/10 pain intensity rating for each participant (see below for calibration method). The conditioning stimulus was elicited by a Julubo TW20 water bath set at 46.5°C.

4.3.3. Design

This experiment was completed as part of a larger 4-session study. One session was a psychophysical assessment, a separate neuroimaging session was completed no more than seven days after this initial session. Lastly, two sessions consisting of cognitive and emotional pain modulation tasks (not described here) were run. Within the neuroimaging session, an rs-fMRI scan was run immediately after an initial localiser. Additionally, four runs of an event-related functional

task (not described here) were completed, with a T1-weighted structural scan placed halfway between. This dataset has previously been analysed and findings regarding trait mindfulness (Harrison, Zeidan, Kitsaras, Ozcelik, & Salomons, 2019), emotional modulation of pain (Gandhi, Rosenek, Harrison, & Salomons, 2019) and the influence of gender role on study recruitment bias (Mattos Feijó et al., 2018) are reported elsewhere.

4.3.4. Procedure

4.3.4.1. Pain Threshold Assessment

To calibrate each participant's pain threshold for noxious heat stimulation, we used a combination of two separate techniques. Both methods utilised the same visual analogue scale (VAS) (Price, McGrath, Rafii, & Buckingham, 1983). The minimum rating of 0 was described as "No pain at all", while the highest rating of 10 was anchored with "most intense pain imaginable", and the scale was displayed to the participant using a piece of laminated A4 paper. Pain intensity was chosen, rather than unpleasantness, in line with recommendations for standardised practice of CPM (Yarnitsky et al., 2014). The premise underlying CPM is that the intensity of a noxious stimulus can be reduced via the application of a distal noxious stimulus applied elsewhere. As such, implications for pain unpleasantness are not a central concept within this experimental paradigm. The first assessment was via method of limits, starting at a 32°C baseline rising by 0.5°C/s until the participant indicated that the stimulus was painful. There were 4 trials with an 8s inter-stimulus interval. The average of the final 3 trials was taken as the *limits threshold*.

The second measure used followed a method of levels design. Stimuli began at a 32°C baseline and increased by 8°/s to a 40°C peak, where it remained for 8s. The participant was provided a mouse to indicate whether the stimulus was painful. An indication of "no", led to the subsequent trial being increased by 2°C. If they indicated yes, the temperature decreased at half the interval size and the same pattern continued until 4 reversals of direction had been reached. The average of the final two trials was recorded as the individual's *levels threshold*. The participant's threshold was calculated via the average of the limits and levels threshold.

4.3.4.2. Temperature Calibration

To calibrate the CPM test stimulus, the next stage of the assessment consisted of a ranged-temperature stimulus response curve. A total of nine ranges were available, with median points between 42.5-46.5°C (at 0.5°C intervals). Each range consisted of eight different temperatures. Temperature were separated by 0.75°C, with four temperatures above the median point and three below (i.e. Mid-2.25°C, Mid-1.50°C, Mid-0.75°C, Mid, Mid+0.75°C, Mid+1.50°C, Mid+2.25°C, Mid+3°C). After the calibration of pain threshold, the median-point closest to this threshold was selected and this range was used for the participant's stimulus response curve. Each temperature within the range was presented three times, equalling a total of 24 stimuli. Participants were told to rate the intensity of each stimulus using the same 0-10 VAS scale as before. The stimuli were presented for 8 seconds, after which a rating was collected. Each temperature was separated by an inter-stimulus duration of 20 seconds to limit the influence of habituation or sensitisation on the proceeding stimuli.

Once all ratings had been recorded, the pairings of temperature and pain ratings was entered into an online linear regression calculator (Arcidiacono, 2009). The model generated from the stimulus response curve data allowed us to interpolate which temperature best matched each participant's indicated 6 out of 10, based on their pain ratings to all temperatures within their range.

4.3.4.3. Conditioned Pain Modulation

Our CPM paradigm was based on previously published material (Granot et al., 2008; Yarnitsky et al., 2008, 2012). This method uses the Peltier thermode as a test stimulus, with a warm water (46.5°) bath as a conditioning stimulus. The interpolated temperature for the participant's 6/10 was designated as the test stimulus. The first trial consisted of the test stimulus in isolation for 30 seconds, with a total of 3 pain intensity ratings provided by the participant at 10s intervals. The second trial started with the participant submerging their left hand into the water bath where they provided 3 ratings of the pain intensity of the conditioning stimulus at 10s intervals. Once these 30 seconds had elapsed, the participant continued to keep their hand in the water bath, while the test stimulus was administered for another 30 seconds. The participant provided three more test

stimulus pain intensity ratings at equal 10s intervals. Finally, the participant provided a conditioning stimulus pain rating once the test stimulus has ended. CPM is calculated as a difference between the test stimulus rating in isolation and the test stimulus ratings during submersion in the water bath. A positive CPM score represents better inhibition.

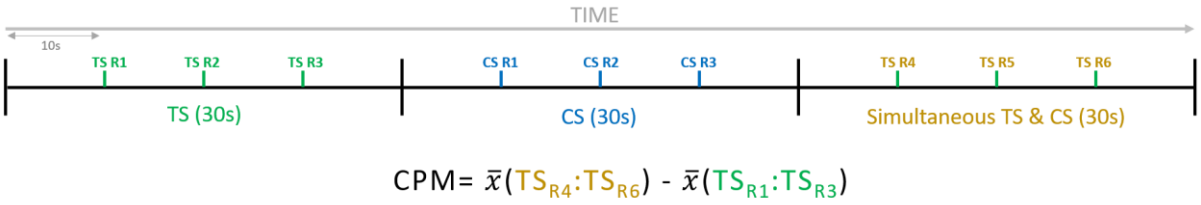

Figure 1: *Method for calculating CPM scores. TS= Test Stimulus, CS= Conditioning Stimulus; R= Rating*

4.3.4.4. fMRI Acquisition

Brain images were acquired using a 3T Siemens (Siemens, Erlangen, Germany) TRIO MRI scanner with a 32-channel head coil. For the 10-minute resting-state scan, participants were instructed to keep their eyes closed. The protocol consisted of 30 interleaved 3.5mm sagittal T2* weighted gradient echo echo-planar imaging (EPI) slices (TE=28ms, TR= 2000ms, flip angle (FA)= 90°, 1mm interslice gap; 128x128 matrix, field-of-view (FOV)= 240mm). Consequently, 300 volumes were acquired and then prepared as 4D NIFTI images Structural images were then acquired within an 8-minute T1-weighted inversion recovery fast gradient echo-high resolution structural scan (176 volumes, TE=2.9ms, TR=2000ms, FA= 90°, voxel size= 1x1x1; 256x256 matrix, FOV=250mm).

4.3.5. fMRI Data Analysis

4.3.5.1. ROI Selection

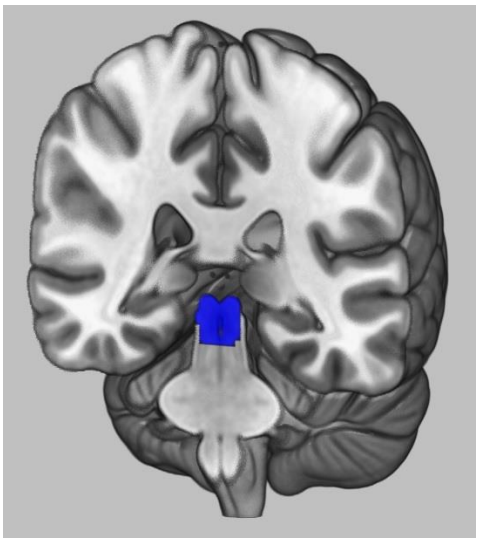

Figure 2: *Hand-drawn Periaqueductal Grey ROI (red) (Y=-32, X=0, Z=-10)*

For the purpose of preparing this seed region, our PAG seed was hand-drawn onto the MNI template in the grey matter surrounding the cerebral aqueduct within the tegmentum of the midbrain, which coalesces with the area previously described and reported for the human PAG (Ezra, Faull, Jbabdi, & Pattinson, 2015). The PAG was chosen due to its prominent role in the descending modulation of pain (Denk, McMahon, & Tracey, 2014; Eippert et al., 2009; Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012).

4.3.5.2. Pre-Processing

Analysis was performed using the FSL analysis package (FSL Version 6.00; www.fmrib.ox.ac.uk/fsl), (Jenkinson et al., 2012). The Brain Extraction Tool (BET) (Smith, 2002) was used for skull stripping. The first 5 volumes were removed to allow for signal equilibration effects. An interleaved slice-timing correction was applied. Data was smoothed with a 5mm full-width half-maximum (FWHM) Gaussian spatial smoothing kernel. MCFLIRT was used for motion correction (Jenkinson, 2002) and data were visually inspected for motion artifacts and to confirm registration accuracy.

To isolate a grey matter mask, grey matter was segmented from white matter (WM) and cerebrospinal fluid (CSF) using FSL's FAST module (Zhang et al., 2001). To minimize overlapping signal from grey matter prior to time series extraction, WM and CSF maps were thresholded at 0.99. Time series of WM and CSF were added to a general linear model (GLM) along with motion parameters. Residuals from this nuisance analysis were normalised and bandpass filtered (0.1/0.01 Hz) to reduce the influence of low frequency drift (inclusive of scanner drift), and high frequency interference such as cardiac or respiratory confounds.

4.3.5.3. Resting State Analysis

The mean timeseries of all voxels within our PAG seed were extracted and included as a regressor in a whole-brain functional connectivity analysis. Contrast images were then entered into a second higher level analysis with participant's demeaned CPM scores entered as a regressor. This analysis sought regions where connectivity with the PAG was significantly associated with CPM. All fMRI analyses were corrected for multiple comparisons using Gaussian random field theory ($Z>2.3$; $p<0.05$). For the purposes of graphical presentation of our results, parameter estimates from regions where functional connectivity with the PAG was significantly correlated with CPM were extracted using FEATQuery.

4.4. Results

4.4.1. Conditioned Pain Modulation

Participants rated the pain intensity of the thermode in isolation to be 5.93 (s.d.=1.49) and the bath in isolation at 4.80 (s.d.=2.17). When combined with a conditioning stimulus, the rating for the thermode decreased to 4.27 (s.d.=2.0) indicating a significant reduction of 1.65 (s.d.=1.38) in pain intensity ($t(33)=6.97$, $p=.011$). Each individual's difference score was used as their CPM score.

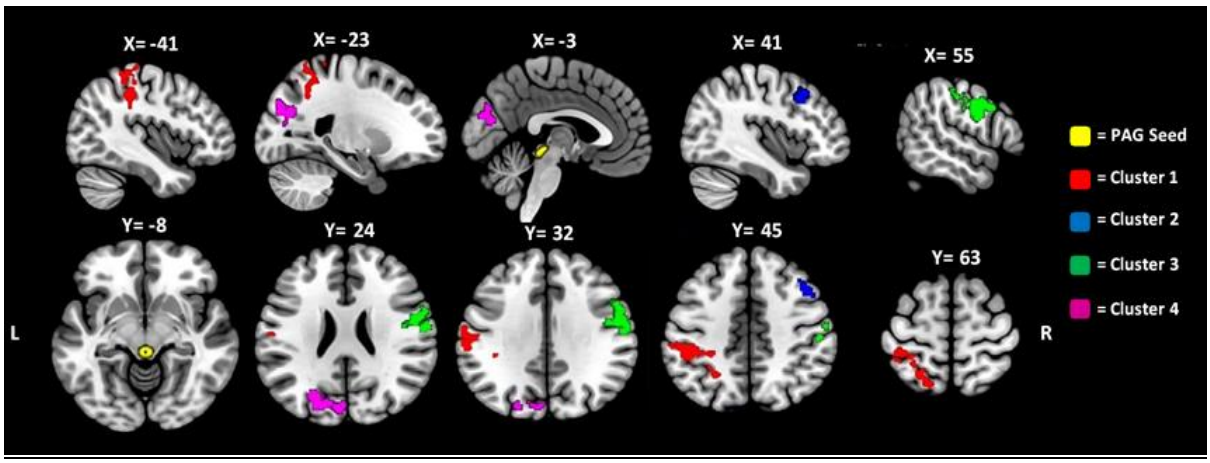

Figure 3: *Isolated clusters (numbered in relation to clusters in table 1) in MNI space positively correlated with CPM (thresholded at Z>2.3, p<.05). Clusters in legend relate to co-ordinates displayed in Table 1 (below).*

4.4.2. Resting-state connectivity & CPM

In total, there were four clusters of activation where connectivity with the PAG was positively correlated with participants' CPM scores (figure 3 & table 1). These included the bilateral primary & secondary somatosensory clusters (clusters 1&3), as well as the right motor & premotor cortices (cluster 3) and the right dorsolateral prefrontal cortex (cluster 2).

Table 1: *Statistical peaks in MNI space associated with positive connectivity to the PAG and CPM scores. Co-ordinates provided at site of maximum Z-stat.*

Anatomical Brain region	**Brodmann Areas**	**MNI coordinates**			**Max Z-Stat**
		X	Y	Z	
1. Somatosensory cortex 1 (S1) & 2 (S2), Inferior Parietal & Anterior Intraparietal Sulcus (aIPS)	BA1, BA2, BA3b	-44	-34	44	4.46
2. Dorsolateral Prefrontal Cortex (dlPFC)	BA44, BA46	44	20	42	4.53
3. Primary motor & premotor cortices, S1 & S2	BA3a,BA3b,BA4a, BA4p, BA6	56	-2	30	4.22
4. Visual cortex, V1 & Superior Parietal	BA17 & BA18	-22	-82	30	3.48

The association between CPM and all four extracted clusters is plotted in Figure 4. Due to the presence of a single outlier that scored highly on CPM, all correlations were re-tested with the anomaly excluded, and all correlations remained significant.

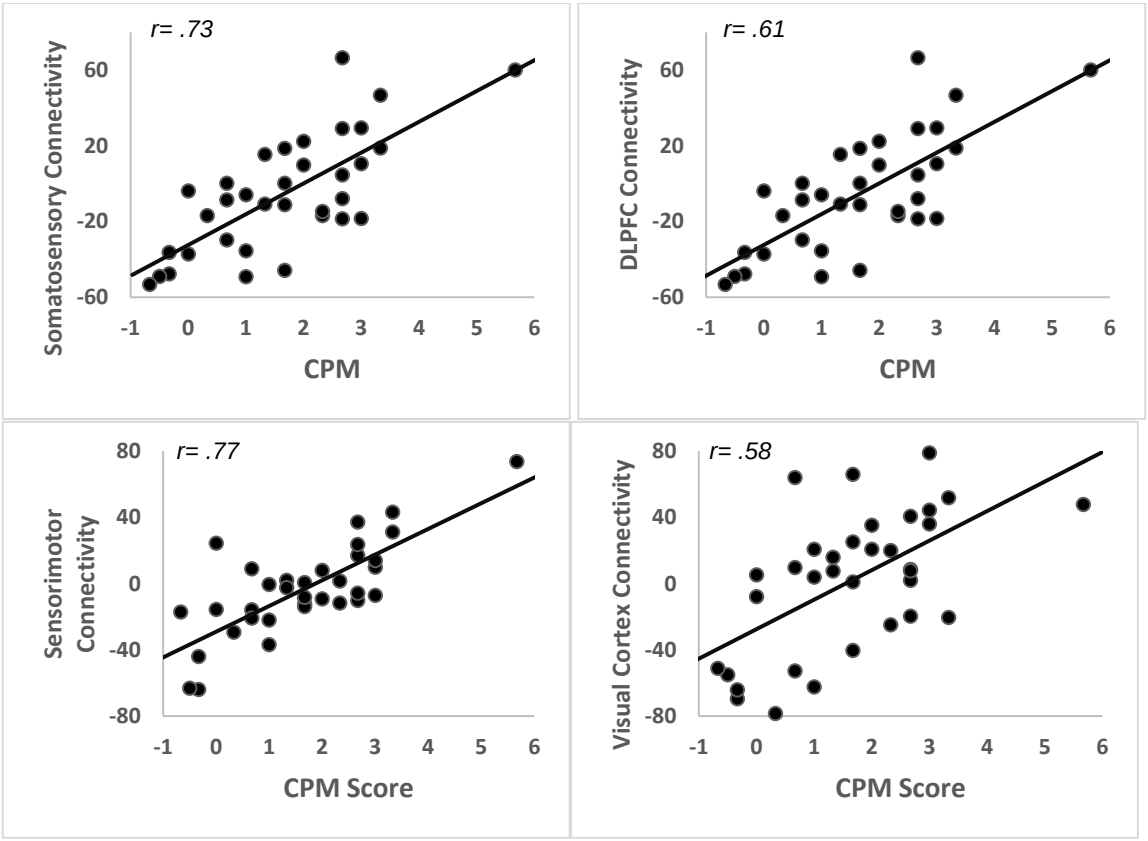

Figure 4: *Connectivity of the PAG and all extracted clusters correlated with CPM scores (p<.001). Y-axis units are parameter estimates of connectivity; higher CPM score represents more efficient modulation. Figures are graphical representation of cluster 1 (top-left), cluster 2 (top-right), cluster 3 (bottom-left) and cluster 4 (bottom-right) in table 1.*

4.5. Discussion

Conditioned pain modulation (CPM) is a quantitative sensory testing technique using a "pain inhibits pain" paradigm, involving simultaneous noxious stimulation applied to peripherally distinct locations on the body. Exposure to a noxious conditioning stimulus in the design often leads to a reduction in the perceived painfulness of a noxious test stimulus. CPM has also been used as a predictive assessment for post-surgical outcomes, analgesic efficiency and the risk of developing neuropathic pain (Edwards et al., 2016; Granovsky, 2013; Yarnitsky et al., 2008, 2012), suggesting that it can be used as a clinically meaningful measure of the efficiency of an

individual's descending modulatory circuitry (Yarnitsky et al., 2008). The method of CPM is said to be related to DNIC, a process of modulation in the dorsal horn via regions in the brainstem. However, the neural basis underlying individual differences in CPM, or why CPM appears to serve as a proxy for more effective pain management, is still unclear. This study investigated intrinsic resting state connectivity in healthy controls and how connectivity of the PAG (a key pain modulatory region) was associated with CPM. As hypothesised, we found that CPM was associated with heightened integration of the PAG and pain processing regions. Specifically, higher CPM score was associated with higher connectivity between the PAG and the somatosensory cortices, premotor and motor cortices and the dorsolateral prefrontal cortex (dlPFC); all regions associated with descending pain modulation network (Denk et al., 2014; Millan, 2002; Ossipov, Dussor, & Porreca, 2010) and the processing of pain (Brooks & Tracey, 2005; Carmon, Mor, & Goldberg, 1976; Garcia-Larrea, Frot, & Valeriani, 2003). Based on this, our findings indicate that those with higher CPM have stronger functional connections within the descending pain modulation network. The synchronicity of BOLD response between the PAG and pain processing regions identified within this finding may indicate that these spatially distal regions are functioning more cohesively in those participants within higher CPM scores. This functional connectivity may be one of the aspects that facilitates more effective modulation of pain processing in these individuals, which reflect their higher CPM scores, and possibly their exposure to pain in the real-world outside of the laboratory.

These findings suggest that individuals who are efficient modulators have greater functional connectivity between the PAG, and regions involved in processing pain. The PAG is known to be a key region in the modulation of pain (Ossipov et al., 2014) and the cortex and PAG have a bidirectional relationship which can affect the modulatory process itself (Cheriyan & Sheets, 2018; Xie et al., 2009). The PAG has previously been shown to be functionally connected with the dorsolateral prefrontal, motor and somatosensory cortices at rest (Faull & Pattinson, 2017), with each of these known to be involved in the processing of pain. The somatosensory cortex has been implicated in the sensory aspects of pain, such as localisation and discrimination, and is known to

be highly modulated by attentional and cognitive processes (Bushnell et al., 1999; Jones, Kilgour, & Comtois, 2007). The dlPFC has been shown to exert control over pain perception, by modulating regions involved in attention towards pain (Lorenz, Minoshima, & Casey, 2003). Lastly, the motor cortex is known to process the intensity of a painful stimulus, and via transcranial magnetic stimulation, stimulation of the motor cortex can alleviate pain in chronic pain patients (Coghill, Sang, Maisog, & Iadarola, 1999; Tsubokawa, Katayama, Yamamoto, Hirayama, & Koyama, 1991). Taken together, and our results may indicate that when functional connectivity between these regions and the PAG is better synchronised, people are able to more effectively modulate their pain. This influence is likely to be bidirectional, as the PAG not only modulates the ascending signal at the level of the spinal cord, but also is involved in preparing the body to deal with noxious stimuli (Silva & McNaughton, 2019). This may involve communication with sensory, cognitive and motor areas, better enabling the individual to attend to the stimuli itself.

While comparable literature is sparse, our findings do partially complement previous findings using similar approaches. CPM score has previously been shown to be associated with higher resting connectivity between the PAG and cortical pain processing regions, the insula & anterior cingulate cortex (Harper et al., 2018). Although our findings did not unanimously coalesce with this study, in particular regarding the specific cortical regions identified, it is worth nothing that key differences may exist in the methodology of each study. Harper et al's study consisted of all female participants, with only 12 healthy controls in total. This was complicated further by a lack of inhibitory CPM effect being identified within healthy controls, with no significant reduction of the test stimulus elicited by exposure to the conditioning stimulus. This may potentially be due to CPM being less efficient in females than males (Popescu, Leresche, Truelove, & Drangsholt, 2010). Additionally, this study was completed using a different CPM methodology (mechanical vs thermal stimuli), which could contribute to the variation in specific cortical regions identified. Lastly, functional connectivity between the PAG and cortical regions was only identified when patients and healthy controls were analysed together. This is an important analytical feature because this study reported that patients and controls demonstrated variations in PAG connectivity, as well as

differences in grey matter density of the PAG, which was lower within chronic pain patients than controls. Therefore, one another potential cause for the discrepancies between the specific pain-processing regions identified across studies may be due, in part, to variations in the modulatory mechanisms underlying healthy controls and chronic pain patients. This is especially true regarding fibromyalgia, which is frequently associated with inefficient, or non-existent, CPM (Julien, Goffaux, Arsenault, & Marchand, 2005; Lautenbacher, Kunz, Strate, Nielsen, & Arendt-Nielsen, 2005; Potvin & Marchand, 2016). When analysed together as a group, these differences may coalesce, which could explain the variation in results between our study using solely healthy controls. This is an important distinction when investigating how CPM may relate to intrinsic ability to manage pain in healthy individuals who are not experiencing chronic pain, although it is promising that the results between both studies report a similar mechanism.

While rs-fMRI cannot provide any additional information about the real-time mechanisms underlying CPM, a strength of this approach is that we can use CPM as a proxy for efficient pain modulation to investigate individual differences in the intrinsic ability to modulate pain. The benefit of using a sample of healthy controls is that this may allow us to identify neural mechanisms associated with effective pain management , as a product of efficiency of their modulatory circuitry, and could provide insight into why some individuals can appear predisposed towards chronic pain conditions. Contrastingly, the challenges of imaging CPM with an event-related design are substantial. Typically, the standardised methodological approaches for testing CPM use equipment that is restrictive or unusable in an MRI environment (e.g. water baths, thermal stimulators, metallic algometers etc). Moreover, the combinative stimulation of test & conditioning stimulus can make isolating the pure influence of modulation difficult.

Promisingly, our findings do also complement the limited evidence available regarding the neural mechanism underlying the process of CPM itself. Within the available literature, it's been found that during concurrent conditioning & test stimuli presentation, the dorsolateral prefrontal,

premotor and primary and secondary somatosensory cortices show reductions in BOLD response in parallel to reductions in pain intensity elicited by the CPM effect (Bogdanov et al., 2015; Goffaux et al., 2007; Piche et al., 2009; Sprenger et al., 2011; Wilder-Smith et al., 2004; Youssef, Macefield, & Henderson, 2016). This informs us that the regions identified within our findings are known to associated with pain processing and are pertinent to CPM. Ideally, these imaging strategies could be combined to benefit from the strengths of each approach. For example, comparing patterns of neural activity in healthy controls while completing a pain task, and then following up by investigating whether resting connectivity between these regions varies as a function of a variable associated with beneficial pain responses (such as CPM). This allows for an a-priori mask from one analysis to be utilised in another to inform about pain processing mechanisms, as well as intrinsic neural connectivity, thus improving a design using two imaging pathways.

Importantly, across both event-related and rs-fMRI designs, it appears that connectivity between pain modulatory regions, and pain processing regions is a feature of CPM. Our findings suggest that by using CPM as an individual difference variable, we can view this connectivity as a potential feature of effective pain modulation and beneficial pain responses. This could help us to understand why CPM has been identified as a potential predictive assessment across a variety of medical domains and clinical outcomes, ranging from the development of CPSP in thoracotomy patients, to the efficacy of non-steroidal anti-inflammatory drugs (NSAIDS) for osteoarthritis of the knee. By using CPM as an individual difference variable, we may be gaining an understanding of whether a person is likely to be able to effectively manage their pain in the future, as a feature of their ability to modulate nociceptive signals. This relative efficiency in the descending pain modulation network may help elaborate on the implications for CPM across the breadth of medical disciplines reported in the literature (Granovsky & Yarnitsky, 2013; Ram, Eisenberg, Haddad, & Pud, 2008; Wilder-Smith & Robert-Yap, 2007; Yarnitsky et al., 2012) and provide insight into why multiple chronic pain conditions are associated with deficiencies in CPM (Lewis et al., 2012). Individuals

with higher CPM (more efficient modulatory circuitry) have an increased integration of pain processing regions in the cortex and the PAG.

Previous literature has indicated that pain modulation may be associated with increased activity in modulatory regions alongside decreased activity in regions processing the noxious signal. It's possible that those who lack this function will not experience the reduction in processing of nociception and may be more impacted by their pain as a result. Ultimately, chronic pain is thought to be a condition partly maintained via deficiencies in descending modulation (Bushnell, Čeko, & Low, 2013; Olesen et al., 2010; Ossipov et al., 2014) and the variations in PAG connectivity and grey matter density may contribute to this lack of modulatory capacity. As our findings suggest that healthy controls with greater functional connectivity of the PAG to key pain processing regions are associated with more effective pain modulation, this provides support for the importance of PAG connectivity when evaluating effective pain modulation and may represent a predictive indicator of ability to effectively manage pain.

One question for future research into individual differences in CPM is whether we can intervene with our patients to modify this neural mechanism. While an increase in CPM score presents little benefit to a chronic pain patient, if this in fact indicates that the improvement correlates with an enhancement of functional connectivity in pain modulation, this may facilitate a beneficial associative effect on managing pain clinically. The recent development in pre-clinical pain assessments has helped develop measures which can be used to identify patients at high-risk of poor outcomes, and the application of these stands to improve the efficacy of our clinical assessments. However, the next step that is currently lacking empirical support is what to do once we've identified these patients. For example, if we stratify a group of high-risk patients before elective surgery, how do we reduce this risk to ensure our patients can still undergo the surgery and experience positive clinical outcomes? For example, it's been found in fibromyalgia patients that a mindfulness-based intervention enhances functional connectivity between the medial prefrontal

cortex and PAG, which are similar to the clusters identified within our study associated with better CPM (Harvey et al., 2018). Although in need of empirical investigation, it would be pertinent to explore whether the enhancement of functional connectivity in this case was also associated with improvements in CPM. If so, this may represent a potential approach to improve the CPM of high-risk pre-surgical patients, and to observe whether this would reduce the incidence of chronic post-surgical pain as a result.

4.6. References

Ahmad, G., Saluja, S., Flynn, O. H., Sorrentino, A., Leach, D., & Watson, A. (2017). Pain relief for outpatient hysteroscopy. *Cochrane Database of Systematic Reviews*, (10). https://doi.org/10.1002/14651858.CD007710.pub3.www.cochranelibrary.com

Anderson, T., Walls, M., & Canelo, R. (2017). Day case surgery guidelines. *Surgery*, *35*(2), 85–91. https://doi.org/10.1016/j.mpsur.2016.11.013

Arcidiacono, G. (2009). Statistics Calculator: Linear Regression. Retrieved from http://www.alcula.com/calculators/statistics/linear-regression/

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003

Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*(2), 140–148. https://doi.org/10.1016/j.neulet.2012.03.039

Baer, R. A., Smith, G., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., … Williams, J. M. G. (2008). Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment*, *15*(3), 329–342. https://doi.org/10.1177/1073191107313003

Baer, R. A., Smith, G. T., Hopkins, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, *13*(1), 27–45. https://doi.org/10.1177/1073191105283504

Bajaj, Y., Sethi, N., Carr, S., & Knight, L. C. (2009). Endoscopic sinus surgery as daycase procedure. *Journal of Laryngology and Otology*, *123*(6), 619–622. https://doi.org/10.1017/S0022215108003332

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics. *Journal of Neuroscience*, *28*(6), 1398–1403. https://doi.org/10.1523/JNEUROSCI.4123-07.2008

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., … Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. https://doi.org/10.1093/clipsy/bph077

Bjune, K., Stubhaug, A., Dodgson, M. S., & Breivik, H. (1996). Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section. Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. *Acta Anaesthesiologica Scandinavica*, *40*(4), 399–407. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8738682

Bogdanov, V. B., Viganò, A., Noirhomme, Q., Bogdanova, O. V, Guy, N., Laureys, S., … Schoenen, J. (2015). Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. *Behavioural Brain Research*, *281*, 187–198. https://doi.org/10.1016/j.bbr.2014.11.028

Bohlmeijer, E., ten Klooster, P. M., Fledderus, M., Veehof, M., & Baer, R. (2011). Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment*, *18*(3), 308–320. https://doi.org/10.1177/1073191111408231

Bouhassira, D., Villanueva, L., & Le Bars, D. (1992). Effects of systematic morphine on diffuse noxious inhibitory controls: Role of the periaqueductal grey. *European Journal of Pharmacology*, *216*(2), 149–156. https://doi.org/10.1016/0014-2999(92)90355-8

Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences*, *104*(27), 11483–11488. https://doi.org/10.1073/pnas.0606552104

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Breivik Hals, E. K., … Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia*, *101*(1), 17–24. https://doi.org/10.1093/bja/aen103

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y.-Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences*, *108*(50), 20254–20259. https://doi.org/10.1073/pnas.1112029108

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., … Jarvik, J. G. (2015). Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology*, *36*(4), 811–816. https://doi.org/10.3174/ajnr.A4173

Brooks, J., & Tracey, I. (2005). From nociception to pain perception: Imaging the spinal and supraspinal pathways. *Journal of Anatomy*, *207*(1), 19–33. https://doi.org/10.1111/j.1469-7580.2005.00428.x

Brown, C. A., & Jones, A. K. (2013). Psychobiological correlates of improved mental health in patients with

musculoskeletal pain after a mindfulness-based pain management program. *Clinical Journal of Pain*, *29*(3), 233–244. https://doi.org/10.1097/AJP.0b013e31824c5d9f

Bruce, J., Thornton, A. J., Powell, R., Johnston, M., Wells, M., Heys, S. D., … Scott, N. W. (2014). Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain*, *155*(2), 232–243. https://doi.org/10.1016/j.pain.2013.09.028

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J.-I., & Carrier, B. (1999). Pain perception: Is there a role for primary somatosensory cortex? *Proceedings of the National Academy of Sciences*, *96*(14), 7705–7709. https://doi.org/10.1073/pnas.96.14.7705

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

Cadden, S. W., Villanueva, L., Chitour, D., & Le Bars, D. (1983). Depression of activities of dorsal horn convergent neurones by propriospinal mechanisms triggered by noxious inputs; comparison with diffuse noxious inhibitory controls (DNIC). *Brain Research*, *275*(1), 1–11. https://doi.org/10.1016/0006-8993(83)90412-2

Carmon, A., Mor, J., & Goldberg, J. (1976). Evoked cerebral responses to noxious thermal stimuli in humans. *Experimental Brain Research*, *25*(1), 103–107. https://doi.org/10.1007/BF00237330

Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suárez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex*, *10*(3), 220–242. https://doi.org/10.1093/cercor/10.3.220

Cheriyan, J., & Sheets, P. L. (2018). Altered Excitability and Local Connectivity of mPFC-PAG Neurons in a Mouse Model of Neuropathic Pain. *The Journal of Neuroscience*, *38*(20), 4829–4839. https://doi.org/10.1523/jneurosci.2731-17.2018

Cherkin, D. C., Sherman, K. J., Balderson, B. H., Cook, A. J., Anderson, M. L., Hawkes, R. J., … Turner, J. A. (2016). Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain. *JAMA*, *315*(12), 1240. https://doi.org/10.1001/jama.2016.2323

Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*, *17*(1), 83–93. https://doi.org/10.1089/acm.2009.0546

Christoff, K., Smallwood, J., Smith, R., Gordon, A. M., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, *106*(21), 8719–8724. https://doi.org/10.1073/pnas.0900234106

Clark, T. J., Middleton, L. J., Cooper, N. A., Diwakar, L., Denny, E., Smith, P., … Daniels, J. P. (2015). A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding. *Health Technology Assessment*, *19*(61), 1–194. https://doi.org/10.3310/hta19610

Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999). Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism. *Journal of Neurophysiology*, *82*(4), 1934–1943. https://doi.org/10.1152/jn.1999.82.4.1934

Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., … Ferris, J. L. (2016). Alterations in resting state functional connectivity link mindfulness meditation with reduced interleukin-6: a randomized controlled trial. *Biological Psychiatry*, *80*(1), 53–61. https://doi.org/10.1016/j.biopsych.2016.01.008

Darnall, B. D., Scheman, J., Davin, S., Burns, J. W., Murphy, J. L., Wilson, A. C., … Mackey, S. C. (2016). Pain psychology: A global needs assessment and national call to action. *Pain Medicine (United States)*, *17*(2), 250–263. https://doi.org/10.1093/pm/pnv095

Darwin, L., & Chung, F. (2013). Patient selection for day surgery. *Anaesthesia and Intensive Care Medicine*, *14*(3), 114–118. https://doi.org/10.1016/j.mpaic.2013.01.003

Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: a neurobiological perspective. *Nature Neuroscience*, *17*(2), 192–200. https://doi.org/10.1038/nn.3628

Dickenson, J., Berkman, E. T., Arch, J., & Lieberman, M. D. (2013). Neural correlates of focused attention during a brief mindfulness induction. *Social Cognitive and Affective Neuroscience*, *8*(1), 40–47. https://doi.org/10.1093/scan/nss030

Edwards, R. R., Dolman, A. J., Martel, M. O., Finan, P. H., Lazaridou, A., Cornelius, M., & Wasan, A. D. (2016). Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 284. https://doi.org/10.1186/s12891-016-1124-6

Eippert, F., Bingel, U., Schoell, E. D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia. *Neuron*, *63*(4), 533–543. https://doi.org/10.1016/j.neuron.2009.07.014

Ezra, M., Faull, O. K., Jbabdi, S., & Pattinson, K. T. S. (2015). Connectivity-based segmentation of the periaqueductal gray matter in human with brainstem optimized diffusion MRI. *Human Brain Mapping*, *36*(9), 3459–3471. https://doi.org/10.1002/hbm.22855

Falkner, E., & Tylko, K. (2019). Campaign against painful hysteroscopy: Hysteroscopy without pain. Retrieved July 3, 2019, from https://www.hysteroscopyaction.org.uk/

Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., Mckeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, *2*(4), 313–322. https://doi.org/10.1093/scan/nsm030

Faull, O. K., & Pattinson, K. T. S. (2017). The cortical connectivity of the periaqueductal gray and the conditioned response to the threat of breathlessness. *ELife*, *6*, 1–18. https://doi.org/10.7554/eLife.21749

Fields, H.L. (1999). Pain: An unpleasant topic. *Pain*, 8, 61-69. Doi: 10.1016/s0304-3959(99)00139-6

Fillingim, R. B., King, C. D., Currie, T., Riley, J. L., Wong, F., & Mauderli, A. P. (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain*, *143*(3), 172–178. https://doi.org/10.1016/j.pain.2008.12.027

Gandhi, R., Davey, J. R., & Mahomed, N. (2009). Patient Expectations Predict Greater Pain Relief with Joint Arthroplasty. *Journal of Arthroplasty*, *24*(5), 716–721. https://doi.org/10.1016/j.arth.2008.05.016

Gandhi, W., Rosenek, N. R., Harrison, R., & Salomons, T. V. (2019). Functional connectivity of the amygdala is linked to individual differences in emotional pain facilitation. *Pain*. 10. Doi: 10.1097/j.pain.0000000000001714

Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: From dipoles to functional significance. *Neurophysiologie Clinique*, *33*(6), 279–292. https://doi.org/10.1016/j.neucli.2003.10.008

Gard, T., Hölzel, B. K., Sack, A. T., Hempel, H., Lazar, S. W., Vaitl, D., & Ott, U. (2012). Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cerebral Cortex*, *22*(11), 2692–2702. https://doi.org/10.1093/cercor/bhr352

Gauriau, C., & Bernard, J. (2002). Pain pathways and parabrachial circuits in the rat. *Experimental Physiology*, *87*(2), 251–258.

Goffaux, P., Redmond, W. J., Rainville, P., & Marchand, S. (2007). Descending analgesia - When the spine echoes what the brain expects. *Pain*, *130*(1–2), 137–143. https://doi.org/10.1016/j.pain.2006.11.011

Granot, M., Weissman-Fogel, I., Crispel, Y., Pud, D., Granovsky, Y., Sprecher, E., & Yarnitsky, D. (2008). Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? *Pain*, *136*(1–2), 142–149. https://doi.org/10.1016/j.pain.2007.06.029

Granovsky, Y. (2013). Conditioned Pain Modulation: A Predictor for Development and Treatment of Neuropathic Pain. *Current Pain and Headache Reports*, *17*(9), 361. https://doi.org/10.1007/s11916-013-0361-8

Granovsky, Y., & Yarnitsky, D. (2013). Personalized Pain Medicine: The Clinical Value of Psychophysical Assessment of Pain Modulation Profile. *Rambam Maimonides Medical Journal*, *4*(4), 1–8. https://doi.org/10.5041/RMMJ.10131

Grant, J. A., Courtemanche, J., Duerden, E. G., Duncan, G. H., & Rainville, P. (2010). Cortical thickness and pain sensitivity in zen meditators. *Emotion*, *10*(1), 43–53. https://doi.org/10.1037/a0018334

Grant, J. A., Courtemanche, J., & Rainville, P. (2011). A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*, *152*(1), 150–156. https://doi.org/10.1016/j.pain.2010.10.006

Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in zen meditators: A cross-sectional study. *Psychosomatic Medicine*, *71*(1), 106–114. https://doi.org/10.1097/PSY.0b013e31818f52ee

Green, C. R., Wheeler, J. R. C., & LaPorte, F. (2003). Clinical decision making in pain management: Contributions of physician and patient characteristics to variations in practice. *Journal of Pain*, *4*(1), 29–39. https://doi.org/10.1054/jpai.2003.5

Grosen, K., Fischer, I. W. D., Olesen, A. E., & Drewes, A. M. (2013). Can quantitative sensory testing predict responses to analgesic treatment? *European Journal of Pain (United Kingdom)*, *17*(9), 1267–1280. https://doi.org/10.1002/j.1532-2149.2013.00330.x

Grosen, Kasper, Vase, L., Pilegaard, H. K., Pfeiffer-Jensen, M., & Drewes, A. M. (2014). Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: A prospective observational cohort study. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0090185

Harper, D. E., Ichesco, E., Schrepf, A., Hampson, J. P., Clauw, D. J., Schmidt-Wilcke, T., … Harte, S. E. (2018). Resting Functional Connectivity of the Periaqueductal Gray Is Associated With Normal Inhibition and Pathological Facilitation in Conditioned Pain Modulation. *Journal of Pain*, *19*(6), 635.e1-635.e15. https://doi.org/10.1016/j.jpain.2018.01.001

Harrison, R., Zeidan, F., Kitsaras, G., Ozcelik, D., & Salomons, T. V. (2019). Trait Mindfulness Is Associated With Lower Pain Reactivity and Connectivity of the Default Mode Network. *Journal of Pain*, *20*(6). https://doi.org/10.1016/j.jpain.2018.10.011

Harvey, W. F., Rones, R., Tao, J., Kong, J., Wolcott, E., Wang, C., … Jorgenson, K. (2018). Altered resting state functional connectivity of the cognitive control network in fibromyalgia and the modulation effect of mind-body intervention. *Brain Imaging and Behavior*, 1–11. https://doi.org/10.1007/s11682-018-9875-3

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage*, *59*(1), 750–760. https://doi.org/10.1016/j.neuroimage.2011.07.008

Hölzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How Does Mindfulness Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural Perspective. *Perspectives on Psychological Science*, *6*(6), 537–559. https://doi.org/10.1177/1745691611419671

Jansen, F. W., Vredevoogd, C. B., van Ulzen, K., Hermans, J., Trimbos, J. B., & Trimbos-Kemper, T. C. (2000). Complications of hysteroscopy: a prospective, multicenter study. *Obstetrics and Gynecology*, *96*(2), 266–270. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10908775

Jenkinson, M. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *Neuroimage*, *17*(2), 825–841. https://doi.org/10.1016/S1053-8119(02)91132-8

Jenkinson, Mark, Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jones, D. H., Kilgour, R. D., & Comtois, A. S. (2007). Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *J Pain*, *8*(8), 650–656. https://doi.org/10.1016/j.jpain.2007.04.003

Julien, N., Goffaux, P., Arsenault, P., & Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*, *114*(1–2), 295–302. https://doi.org/10.1016/j.pain.2004.12.032

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*. https://doi.org/10.1016/0163-8343(82)90026-3

Kam, J. W. Y., & Handy, T. C. (2013). The neurocognitive consequences of the wandering mind: a mechanistic account of sensory-motor decoupling. *Frontiers in Psychology*, *4*(October), 1–13. https://doi.org/10.3389/fpsyg.2013.00725

Khan, R. S., Ahmed, K., Blakeway, E., Skapinakis, P., Nihoyannopoulos, L., MacLeod, K., … Athanasiou, T. (2011). Catastrophizing: A predictive factor for postoperative pain. *American Journal of Surgery*, *201*(1), 122–131. https://doi.org/10.1016/j.amjsurg.2010.02.007

Kiken, L. G., Garland, E. L., Bluth, K., Palsson, O. S., & Gaylord, S. A. (2015). From a state to a trait: Trajectories of state mindfulness in meditation during intervention predict changes in trait mindfulness. *Personality and Individual Differences*, *81*, 41–46. https://doi.org/10.1016/j.paid.2014.12.044

Kingston, J., Chadwick, P., Meron, D., & Skinner, T. C. (2007). A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *Journal of Psychosomatic Research*, *62*(3), 297–300. https://doi.org/10.1016/j.jpsychores.2006.10.007

Klein, J. G. (2005). Five pitfalls in decisions about diagnosis and prescribing. *Bmj*, *330*(7494), 781–783. https://doi.org/10.1136/bmj.330.7494.781

Kong, J., Tu, P. C., Zyloney, C., & Su, T. P. (2010). Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. *Behavioural Brain Research*, *211*(2), 215–219. https://doi.org/10.1016/j.bbr.2010.03.042

Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: Where expectations become reality. *Proceedings of the National Academy of Sciences*, *102*(36), 12950–12955. https://doi.org/10.1073/pnas.0408576102

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced Medial Prefrontal-Default Mode Network Functional Connectivity in Chronic Pain and Its Association with Pain Rumination. *Journal of Neuroscience*, *34*(11), 3969–3975. https://doi.org/10.1523/JNEUROSCI.5055-13.2014

Kucyi, Aaron, & Davis, K. D. (2014). Dynamic functional connectivity of the default mode network tracks daydreaming. *NeuroImage*, *100*, 471–480. https://doi.org/10.1016/j.neuroimage.2014.06.044

Kucyi, Aaron, & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences*, *38*(2), 86–95. https://doi.org/10.1016/j.tins.2014.11.006

Lander, J. (1990). Clinical judgments in pain management. *Pain*, *42*(1), 15–22. https://doi.org/10.1016/0304-

3959(90)91086-X
Larue, F., Colleau, S. M., Fontaine, A., & Brasseur, L. (1995). Oncologists and primary care physicians' attitudes toward pain control and morphine prescribing in france. *Cancer*, *76*(11), 2375–2382. https://doi.org/10.1002/1097-0142(19951201)76:11<2375::AID-CNCR2820761129>3.0.CO;2-C
Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., & Arendt-Nielsen, L. (2005). Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*, *115*(3), 410–418. https://doi.org/10.1016/j.pain.2005.03.025
Le Bars, D, Dickenson, A. H., & Besson, J. M. (1979). Diffuse noxious inhibitory controls. I. Effects on dorsal horn convergent neurons in the rat. II. Lack of effect on nonconvergent neurons, supraspinal involvement and theoretical implications. *Pain*, *6*(3), 305–327. https://doi.org/10.1016/0304-3959(79)90049-6
Le Bars, Daniel, Chitour, D., Kraus, E., Dickenson, A. H., & Besson, J. M. (1981). Effect of naloxone upon diffuse noxious inhibitory controls (DNIC) in the rat. *Brain Research*, *204*(2), 387–402. https://doi.org/10.1016/0006-8993(81)90597-7
Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2012.07.005
Linnman, C., Moulton, E. A., Barmettler, G., Becerra, L., & Borsook, D. (2012). Neuroimaging of the periaqueductal gray: State of the field. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.11.095
Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, *126*(5), 1079–1091. https://doi.org/10.1093/brain/awg102
Ludwig, D. S., & Kabat-Zinn, J. (2008). Mindfulness in Medicine. *JAMA*, *300*(11), 1350. https://doi.org/10.1001/jama.300.11.1350
Lutz, A., McFarlin, D. R., Perlman, D. M., Salomons, T. V., & Davidson, R. J. (2013). Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage*, *64*(1), 538–546. https://doi.org/10.1016/j.neuroimage.2012.09.030
Mamie, C. (2004). Are there reliable predictors of postoperative pain? *Acta Anaesthesiologica Scandinavica*, *48*(2), 234–242. https://doi.org/10.1111/j.0001-5172.2004.00298.x
Manias, E., Botti, M., & Bucknall, T. (2002). Observation of pain assessment and management--the complexities of clinical practice. *Journal of Clinical Nursing*, *11*(6), 724–733. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L35513243%5Cnhttp://pm6mt7vg3j.search.serialssolutions.com?sid=EMBASE&issn=09621067&id=doi:&atitle=Observation+of+pain+assessment+and+management--the+complexities+of+clinical+practic
March, L., Burstein, R., Murray, C., Buchbinder, R., Barendregt, J., Woolf, A., … Hoy, D. (2014). The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(6), 968–974. https://doi.org/10.1136/annrheumdis-2013-204428
Marsh, F. A., Rogerson, L. J., & Duffy, S. R. G. (2006). A randomised controlled trial comparing outpatient versus daycase endometrial polypectomy. *BJOG: An International Journal of Obstetrics and Gynaecology*, *113*(8), 896–901. https://doi.org/10.1111/j.1471-0528.2006.00967.x
Masselin-Dubois, A., Attal, N., Fletcher, D., Jayr, C., Albi, A., Fermanian, J., … Baudic, S. (2013). Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of total knee arthroplasty and breast surgery for cancer. *Journal of Pain*, *14*(8), 854–864. https://doi.org/10.1016/j.jpain.2013.02.013
Mattos Feijó, L., Tarman, G. Z., Fontaine, C., Harrison, R., Johnstone, T., & Salomons, T. (2018). Sex-Specific Effects of Gender Identification on Pain Study Recruitment. *Journal of Pain*, *19*(2). https://doi.org/10.1016/j.jpain.2017.09.009
May, A. (2009). New insights into headache: An update on functional and structural imaging findings. *Nature Reviews Neurology*, *5*(4), 199–209. https://doi.org/10.1038/nrneurol.2009.28
McCracken, L. M., Gauntlett-Gilbert, J., & Vowles, K. E. (2007). The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain*, *131*(1–2), 63–69. https://doi.org/10.1016/j.pain.2006.12.013
Meechan, J. G. (2017). Why Does Local Anaesthesia Not Work Every Time? *Dental Update*, *32*(2), 66–72. https://doi.org/10.12968/denu.2005.32.2.66
Melzack, R., & Wall, P. (1965). Pain Mechanism: A new Theory. *Science*. https://doi.org/10.1126/science.150.3699.971
Merskey, H., Addison, R. G., Beric, A., Blumberg, H., Bogduk, N., Boivie, J., … Watson, C. P. N. (2002). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Second edition.* (H. Merskey & N. Bogduk, Eds.), *IASP Press* (Second). Seattle, WA: IASP Press. Retrieved from http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6), 355–474. https://doi.org/10.1016/S0301-0082(02)00009-6

Morone, N. E., Greco, C. M., Moore, C. G., Rollman, B. L., Lane, B., Morrow, L. A., … Weiner, D. K. (2016). A mind-body program for older adults with chronic low back pain a randomized clinical trial. *JAMA Internal Medicine*, *176*(3), 329. https://doi.org/10.1001/jamainternmed.2015.8033

Morton, C. R., Maisch, B., & Zimmermann, M. (1987). Diffuse noxious inhibitory controls of lumbar spinal neurons involve a supraspinal loop in the cat. *Brain Research*, *410*(2), 347–352. https://doi.org/10.1016/0006-8993(87)90336-2

Mun, C. J., Okun, M. A., & Karoly, P. (2014). Trait mindfulness and catastrophizing as mediators of the association between pain severity and pain-related impairment. *Personality and Individual Differences*, *66*, 68–73. https://doi.org/10.1016/j.paid.2014.03.016

O'Brien, A. T., Deitos, A., Triñanes Pego, Y., Fregni, F., & Carrillo-de-la-Peña, M. T. (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *Journal of Pain*. Elsevier Inc. https://doi.org/10.1016/j.jpain.2018.01.010

Olesen, S. S., Brock, C., Krarup, A. L., Funch-Jensen, P., Arendt-Nielsen, L., Wilder-Smith, O. H., & Drewes, A. M. (2010). Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. *Clinical Gastroenterology and Hepatology*, *8*(8), 724–730. https://doi.org/10.1016/j.cgh.2010.03.005

Ong, W.-Y., Stohler, C. S., & Herr, D. R. (2019). Role of the Prefrontal Cortex in Pain Processing. *Molecular Neurobiology*, *56*(2), 1137–1166. https://doi.org/10.1007/s12035-018-1130-9

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766

Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current Opinion in Supportive and Palliative Care*, *8*(2), 143–151. https://doi.org/10.1097/SPC.0000000000000055

Paul, N. A., Stanton, S. J., Greeson, J. M., Smoski, M. J., & Wang, L. (2013). Psychological and neural mechanisms of trait mindfulness in reducing depression vulnerability. *Social Cognitive and Affective Neuroscience*, *8*(1), 56–64. https://doi.org/10.1093/scan/nss070

Perlman, D. M., Salomons, T. V, Davidson, R. J., & Lutz, A. (2010). Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*, *10*(1), 65–71. https://doi.org/10.1037/a0018440

Petter, M., Chambers, C. T., McGrath, P. J., & Dick, B. D. (2013). The role of trait mindfulness in the pain experience of adolescents. *Journal of Pain*, *14*(12), 1709–1718. https://doi.org/10.1016/j.jpain.2013.08.015

Piche, M., Arsenault, M., & Rainville, P. (2009). Cerebral and Cerebrospinal Processes Underlying Counterirritation Analgesia. *Journal of Neuroscience*, *29*(45), 14236–14246. https://doi.org/10.1523/jneurosci.2341-09.2009

Popescu, A., Leresche, L., Truelove, E. L., & Drangsholt, M. T. (2010). Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. *Pain*, *150*(2), 309–318. https://doi.org/10.1016/j.pain.2010.05.013

Potvin, S., & Marchand, S. (2016). Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*, *157*(8), 1704–1710. https://doi.org/10.1097/j.pain.0000000000000573

Price, D. D. (2000). Psychological and Neural Mechanisms of the Affective Dimension of Pain. *Science*, *288*(5472), 1769–1772. https://doi.org/10.1126/science.288.5472.1769

Price, Donald D., Bush, F. M., Long, S., & Harkins, S. W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*, *56*(2), 217–226. https://doi.org/10.1016/0304-3959(94)90097-3

Price, Donald D., McGrath, P. A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*, *17*(1), 45–56. https://doi.org/10.1016/0304-3959(83)90126-4

Prins, B., Decuypere, A., & Van Damme, S. (2014). Effects of mindfulness and distraction on pain depend upon individual differences in pain catastrophizing: An experimental study. *European Journal of Pain*, *18*(9), 1307–1315. https://doi.org/10.1002/j.1532-2149.2014.491.x

Rabey, M., Poon, C., Wray, J., Thamajaree, C., East, R., & Slater, H. (2015). Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual Therapy*, *20*(6), 763–768. https://doi.org/10.1016/j.math.2015.02.011

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, *12*(2), 195–204. https://doi.org/10.1016/S0959-4388(02)00313-6

Ram, K. C., Eisenberg, E., Haddad, M., & Pud, D. (2008). Oral opioid use alters DNIC but not cold pain

perception in patients with chronic pain - New perspective of opioid-induced hyperalgesia. *Pain*, *139*(2), 431–438. https://doi.org/10.1016/j.pain.2008.05.015
Reiner, K., Granot, M., Soffer, E., & Lipsitz, J. D. (2016). A Brief Mindfulness Meditation Training Increases Pain Threshold and Accelerates Modulation of Response to Tonic Pain in an Experimental Study. *Pain Medicine (Malden, Mass.)*, *17*(4), 628–635. https://doi.org/10.1111/pme.12883
Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Medicine*, *14*(2), 230–242. https://doi.org/10.1111/pme.12006
Robinson, M. E., Gagnon, C. M., Riley, J. L., & Price, D. D. (2003). Altering gender role expectations: Effects on pain tolerance, pain threshold, and pain ratings. *Journal of Pain*, *4*(5), 284–288. https://doi.org/10.1016/S1526-5900(03)00559-5
Salomons, T. V, & Kucyi, A. (2011). Does Meditation Reduce Pain through a Unique Neural Mechanism? *Journal of Neuroscience*, *31*(36), 12705–12707. https://doi.org/10.1523/JNEUROSCI.2843-11.2011
Sauer, S., Walach, H., Schmidt, S., Hinterberger, T., Lynch, S., Büssing, A., & Kohls, N. (2013). Assessment of Mindfulness: Review on State of the Art. *Mindfulness*, *4*(1), 3–17. https://doi.org/10.1007/s12671-012-0122-5
Schütze, R., Rees, C., Preece, M., & Schütze, M. (2010). Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*, *148*(1), 120–127. https://doi.org/10.1016/j.pain.2009.10.030
Shapiro, S. L., Brown, K. W., Thoresen, C., & Plante, T. G. (2011). The moderation of Mindfulness-based stress reduction effects by trait mindfulness: Results from a randomized controlled trial. *Journal of Clinical Psychology*, *67*(3), 267–277. https://doi.org/10.1002/jclp.20761
Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences*, *107*(24), 11020–11025. https://doi.org/10.1073/pnas.1000446107
Sheline, Yvette I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106
Silva, C., & McNaughton, N. (2019). Are periaqueductal gray and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review. *Progress in Neurobiology*, *177*(January), 33–72. https://doi.org/10.1016/j.pneurobio.2019.02.001
Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062
Specialities. (2018). Retrieved July 1, 2019, from https://www.medschools.ac.uk/studying-medicine/after-medical-school/specialties
Sprenger, C., Bingel, U., & Büchel, C. (2011). Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain*, *152*(2), 428–439. https://doi.org/10.1016/j.pain.2010.11.018
Sullivan, M. J., Bishop, S., & Pivik, J. (1995). Pain Catastrophizing Scale. *Psychological Assessment*, *7*, 524–532. https://doi.org/10.1037/t01304-000
Taylor, V. A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-vidal, S., … Beauregard, M. (2013). Impact of meditation training on the default mode network during a restful state. *Social Cognitive and Affective Neuroscience*, *8*(1), 4–14. https://doi.org/10.1093/scan/nsr087
Taylor, V. A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., … Beauregard, M. (2011). Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. *NeuroImage*, *57*(4), 1524–1533. https://doi.org/10.1016/j.neuroimage.2011.06.001
Teixeira, E. (2010). The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. *Holistic Nursing Practice*, *24*(5), 277–283. https://doi.org/10.1097/HNP.0b013e3181f1add2
Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., & Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. *Clinical Journal of Pain*, *28*(9), 819–841. https://doi.org/10.1097/AJP.0b013e31824549d6
Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., & Koyama, S. (1991). Chronic Motor Cortex Stimulation for the Treatment of Central Pain, *139*, 137–139. https://doi.org/10.1007/978-3-7091-9160-6_37
Turner, J. A., Anderson, M. L., Balderson, B. H., Cook, A. J., Sherman, K. J., & Cherkin, D. C. (2016). Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain. *Pain*, *157*(11), 2434–2444. https://doi.org/10.1097/j.pain.0000000000000635
Tylko-Hill, K. (2018). *Clinical Audit*. Retrieved from https://www.whatdotheyknow.com/search/Outpatient hysteroscopy/biopsy - RCOG/BSGE 2018/all
Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus Is a Functional Core of the Default-Mode Network. *The Journal of Neuroscience*, *34*(3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014

Valencia, C., Kindler, L. L., Fillingim, R. B., & George, S. Z. (2012). Investigation of central pain processing in shoulder pain: Converging results from 2 musculoskeletal pain models. *Journal of Pain*, *13*(1), 81–89. https://doi.org/10.1016/j.jpain.2011.10.006

Walker B. (2000). The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. *Journal of Spinal Disorders*, *13*(3), 205–217. https://doi.org/10.1097/00002517-200006000-00003

Weis, O. F., Sriwatanakul, K., Alloza, J. L., Weintraub, M., & Lasagna, L. (1983). Attitudes of Patients, Housestaff, and Nurses Toward Postoperative Analgesic Care. *Anesthesia & Analgesia*, *62*(1), 70–74. https://doi.org/10.1213/00000539-198301000-00012

Wilder-Smith, C. H., Schindler, D., Lovblad, K., Redmond, S. M., & Nirkko, A. (2004). Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut*, *53*(11), 1595–1601. https://doi.org/10.1136/gut.2003.028514

Wilder-Smith, Clive H., & Robert-Yap, J. (2007). Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World Journal of Gastroenterology*, *13*(27), 3699–3704. https://doi.org/10.3748/wjg.v13.i27.3699

Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J., & Arendt-Nielsen, L. (2010). Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: A pilot study. *Journal of Pain and Palliative Care Pharmacotherapy*, *24*(2), 119–128. https://doi.org/10.3109/15360281003706069

Wilkerson, R. G., Kim, H. K., Windsor, T. A., & Mareiniss, D. P. (2016). The Opioid Epidemic in the United States. *Emergency Medicine Clinics of North America*, *34*(2), e1–e23. https://doi.org/10.1016/j.emc.2015.11.002

Willer, J., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain*, *107*(4), 1095–1112. https://doi.org/10.1093/brain/107.4.1095

Xie, Y. F., Huo, F. Q., & Tang, J. S. (2009). Cerebral cortex modulation of pain. *Acta Pharmacologica Sinica*, *30*(1), 31–41. https://doi.org/10.1038/aps.2008.14

Yarkoni, T., Poldrack, R. A. R., Nichols, T. T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. https://doi.org/10.1038/nmeth.1635

Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., … Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033

Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*, *153*(6), 1193–1198. https://doi.org/10.1016/j.pain.2012.02.021

Youssef, A. M., Macefield, V. G., & Henderson, L. A. (2016). Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. *Human Brain Mapping*, *37*(7), 2630–2644. https://doi.org/10.1002/hbm.23199

Zeidan, F. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082

Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The Effects of Brief Mindfulness Meditation Training on Experimentally Induced Pain. *Journal of Pain*, *11*(3), 199–209. https://doi.org/10.1016/j.jpain.2009.07.015

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, *520*(2), 165–173. https://doi.org/10.1016/j.neulet.2012.03.082

Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain Mechanisms Supporting the Modulation of Pain by Mindfulness Meditation. *Journal of Neuroscience*, *31*(14), 5540–5548. https://doi.org/10.1523/JNEUROSCI.5791-10.2011

Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation–based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences*, *1373*(1), 114–127. https://doi.org/10.1111/nyas.13153

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424

Chapter 5. General Discussion

5.1. Overview of Results

The overall aim of this thesis was to investigate individual differences in pain and expand on the literature examining how intrinsic psychological processes can influence the way we modulate pain. As reviewed in section 1.2, the mechanisms of pain modulation have received a great deal of research interest over the last couple of decades. However, how innate individual differences in psychology may inherently predispose people to degrees of vulnerability to future instances of pain is still an area of great importance, with limited empirical basis. To address the problems outlined, three studies were conducted. This general discussion will review the findings, before considering the strengths and limitations, theoretical and practical implications as well as future directions for this area of research.

5.1.1. Chapter 2: Evaluating the clinical assessment of pain during hysteroscopy and the implications for the administration of local anaesthetic

Chapter 2 aimed to investigate the scope of the problem of pain vulnerability within the real-world, by examining a surgical procedure that was associated with a wide range of variability in its perceived painfulness. Hysteroscopy is described as a low-pain medical procedure (Appendix C) but has attracted public attention due to the emergence of patients who reported experiencing severe and, sometimes, excruciating pain (Tylko-Hill, 2018). We analysed pain reports across a large clinical sample that had undergone hysteroscopy to investigate the patterns in pain intensity associated with this procedure. We also compared patient reported pain scores to clinical estimates of their patients pain during the operation. Lastly, we investigated how patient's expectations were shaped as a result of the pain that they experienced during their hysteroscopy. We hypothesised that hysteroscopy would be a procedure associated with a range of pain intensities, and patients who experienced less intense pain during the operation would consider their expectations of the hysteroscopy matched or surpassed.

Our results suggest that hysteroscopy is not a low-pain procedure, and for some patients the pain elicited is severe. This could indicate the presence of individual differences across the patient sample that allowed some to experience a pain-free hysteroscopy, whilst others may possess vulnerabilities that predisposes them to a risk of intense pain. Interestingly, we also noted that clinician estimates of pain were inversely correlated with the patient's own views of their pain. This had special significance as, within this clinic, the quantity of analgesia administered was decided based upon clinical judgement. Based upon this, it was noticed that within the patients who received the highest dose of anaesthetic, the clinician pain estimates were the lowest, whereas the patient pain ratings were the highest. This may indicate that these patients were the ones who were most vulnerable to pain, and that, despite the clinical view that anaesthetic was decreasing their pain, their pain was not being managed appropriately.

5.1.2. Chapter 3: Trait mindfulness is associated with lower pain reactivity and connectivity of the default mode network

In attempting to understand how these individual differences may manifest, and how they may relate to the mechanisms with which pain is modulated in the brain, chapters 3 and 4 both investigated psychological concepts related to pain perception, and the association with underlying neural resting state connectivity. Within chapter 3, we investigated trait mindfulness as a concept that may facilitate resilience towards the experience of pain. Mindfulness has previously been shown to be a useful intervention for pain management and is associated with beneficial experimental and clinical pain outcomes (Cherkin et al., 2016; Kabat-Zinn, 1982; Morone et al., 2016; Reiner, Granot, Soffer, & Lipsitz, 2016; Teixeira, 2010; Zeidan et al., 2011). However, by investigating mindfulness as a trait, and not a state, we aimed to understand how intrinsic mindfulness, in the absence of exposure to mindfulness-based interventions, may provide an innate benefit to processing sensory and cognitive dimensions of pain. We hypothesised that trait mindfulness would elicit similar pain-related benefits as reported in the interventional mindfulness literature, and that this would be achieved via attentional regulation. As such, we also investigated

how mindfulness could influence pain via variations in how attention is processed in the brain, and specifically within the default mode network, using the precuneus as a seed. We found that trait mindfulness provides a psychological influence towards the processing of cognitive and sensory dimensions of pain. We also identified that trait mindfulness was associated with variations in functional connectivity between regions associated with attentional processes (precuneus), and cognitive (prefrontal cortex) and sensory processes (somatosensory cortices). Based upon findings within interventional literature, it was concluded that trait mindfulness involves an attentional regulation which involves heightened awareness of sensory elements within the environment, with decreased ruminative reappraisal. This functional disconnect between attentional focus on cognitive and sensory aspects may be beneficial in reducing negative cognitive biases, such as catastrophising, and that by evaluating a nociceptive stimulus as more of a simple sensory experience, it may make the experience of pain less emotionally aversive and more tolerable.

5.1.3. Chapter 4: Conditioned Pain Modulation (CPM) is associated with heightened connectivity between the periaqueductal grey (PAG) and the descending pain modulation network.

In chapter 4, we investigated a psychophysical assessment tool, CPM. This quantitative sensory testing (QST) assessment is described as a proxy for the efficiency of an individual's descending modulation circuitry (Yarnitsky et al., 2008) and has been associated with a range of beneficial clinical outcomes (Edwards et al., 2016; Granovsky & Yarnitsky, 2013; Yarnitsky, Granot, & Granovsky, 2014; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). As CPM has been shown to provide resilience to pain across a wide range of medical domains, we investigated it as an innate individual difference's marker and examined how it related to underlying neural mechanisms of pain modulation. A key pain modulatory region is the PAG, which is involved in processing the descending and ascending pain signal and is connected to regions in the cortex associated with the processing of pain (Brooks & Tracey, 2005; Millan, 2002; Ossipov, Morimura, & Porreca, 2014). We predicted that higher CPM, and therefore more effective pain modulation, would be associated with heightened integration of the PAG with other regions

involved in the processing of pain. We found that better CPM was associated with increased connectivity between the PAG and the somatosensory, premotor, motor and dorsolateral prefrontal cortices (dlPFC); all regions involved in processing pain (Brooks & Tracey, 2005; Carmon, Mor, & Goldberg, 1976; Garcia-Larrea, Frot, & Valeriani, 2003). We concluded that CPM is likely to be a suitable marker for beneficial pain response, and that as an assessment, it may serve to quantify the efficacy of an individual's ability to modulate pain. Our results indicated that heightened integration of pain processing regions with a key modulatory region may facilitate more effective modulation of pain, which may in turn, may benefit an individual when dealing with pain in the real world.

5.1.4. Consolidating results between Chapters 3 and 4

As both studies across these chapters utilised regressors that can serve as individual differences markers, and used resting-state functional magnetic resonance imaging (rs-fMRI), they each provide useful information towards innate beneficial influences regarding the experience of pain. As described in section 1.2, pain is a multi-faceted experience, involving multiple levels of processing which coalesce to form an amalgam experience. The way in which we attend to our own body state, as well as elements within our environment can shape the way in which we experience pain, as described when discussing mindfulness in chapter 3. Beecher's classic observations of soldiers in the battlefield not noticing severe injuries until they were out of danger demonstrates the powerful influence of environmental context on pain (Beecher, 1946). Relatedly, the active influence of modulatory regions within our brain to tone-down the nociceptive signal is likely to be a core evolutionary function, allowing an organism to adhere to the premise of fight-or-flight, despite potential grievous injury.

Taken in concert, chapters 3 and 4 provide us with an interesting basis for examining these examples of intrinsic influences of pain processing. The former may suggest that individuals who are dispositionally mindful, in relation to their personality and who they are as people, are likely to

be able to better manage their pain. Importantly, this is not solely in relation to the sensory experience of a pain stimulus, but also regarding negative cognitive biases that relate to pain; trait mindfulness provides a protective influence against both sensory and cognitive dimensions of pain experience. When examining how our participants brains "ticked over" at rest, we were able to extract an interesting underlying mechanism beneath this attentional concept. Participants who were more mindful were associated with an increased connectivity between an attentional node and the somatosensory cortex, perhaps indicating they are better equipped to relay and attend to the tactile experience of their environment. Additionally, they were associated with decreased connectivity between the same node and the medial prefrontal cortex (mPFC); an area previously associated with reappraisal and rumination (amongst a swathe of other processes) (Fuster, 2008). This may relate to the "present-moment-ness" of a mindful individual, existing within a moment and being aware of it, rather than being consumed by over-evaluation, apprehension or rumination.

Interestingly, in chapter 4, the prefrontal cortex was also identified within another mechanism of pain, namely that of pain modulation, associated with individual differences in CPM. As a simple psychophysical assessment, CPM is described as a proxy for the efficiency of descending modulatory circuitry (Yarnitsky, 2008). Regarding the evolutionary basis above, this would be a representation of the basal ability of a brain to influence the ascending signal from the periphery. The more effective this system is, the better able a person may be at disregarding or persisting despite the presence of a painful experience. Within this context, it is easier to understand how CPM is associated with a range of beneficial clinical outcomes and is not limited to any one specific clinical domain. Our findings highlighted that higher CPM was associated with a general increase in connectivity within the descending pain modulation system (DPMS). The integration this modulatory mechanism appears to benefit individuals when completing a CPM assessment, but may equally benefit them in everyday domains of their life.

Within chapter 3, we found that lower connectivity between the mPFC and precuneus may facilitate beneficial pain responses, potentially as a product of decreased attention towards cognitive reappraisals. Within chapter 4, we found that higher connectivity between the dlPFC and PAG may facilitate more efficient pain modulation, by integrating a pain processing region with one that actively modulates noxious ascending signals. Crucially, the prefrontal cortex has been associated with a colossal range of cognitive, emotional and affective processes (Fuster, 2008). Therefore, the variations in function between the mPFC and dlPFC are likely to be substantial. Subsequently, the evidence within chapters 3 and 4 may in fact represent two distinct mechanisms that each provide a beneficial influence for processing pain. In the case of chapter 3, the mechanism represents variations in attentional regulation, that may benefit an individual's ability to process and manage pain. More specifically, connectivity of the PFC to an attentional seed (precuneus) was theorised to represent a reduced tendency towards ruminative or apprehensive thought. Whereas in chapter 4, the mechanism involving the PAG may be a feature of regulating the combination of ascending and descending signals, with the PFC connectivity indicating more efficient integration of pain processing (PFC) and pain modulating (PAG) regions. Clearly, the processes underlying activity within these distinct regions of the PFC are likely to serve different functions, but it does inform us of the importance of the PFC when evaluating neural mechanisms associated with pain, and represents that these two results may serve as two distinct indicators of effective pain management. Each neural mechanism could be trait-like psychobehavioural markers which benefit an individual, both in the lab and the real-world. These studies have each provided insight towards how individual differences in trait mindfulness and CPM are represented within the brain and provide potential insights to two different neural mechanisms that are associated with more effective mechanisms for managing pain.

Regarding comparisons between the concepts described within chapters 3 and 4 directly, the empirical basis underlying mindfulness and CPM is still limited. One strength of evaluating these distinct psychological concepts within the same sample of participants, is we can make direct comparisons between these two variables in the same people. Interestingly, CPM and FFMQ scores

did not correlate within our sample (R(36)=-.209, p=.11), with only the subscale of Mindful awareness nearing significance (R(36)=-.229, p=.089). This finding is supported in the literature which indicates that mindfulness may reduce pain via a unique mechanism (Zeidan et al., 2012), which is not mediated by endogenous opioids (Zeidan et al., 2016), unlike the proposed endogenous inhibitory pain pathways which underlying CPM (Lewis et al., 2012; Yarnitsky, 2015).

Therefore, the mechanisms identified within chapters 3 and 4 within this body of work may reflect two unique processes that facilitate a beneficial response to pain. Within this perspective, mindfulness is associated with a functional disconnect attentional processing of sensory and cognitive information. Regarding pain, this allows an individual to attend to the tactile experience of a noxious stimulus, with a reduced tendency towards affective reappraisal, rumination or apprehension of the stimulus itself. This attentional mindset may benefit an individual when managing pain by facilitating a more accurate interpretation of the stimulus, without negative emotional or cognitive biases influencing their processing of the pain. However, the mechanism identified within chapter 4 is perhaps indicative of the process of pain modulation, rather than the interpretation and processing of a noxious stimulus in isolation. The functional connectivity of the PAG with regions known to be involved in processing pain may indicate that this individual's modulatory circuitry is more cohesive and integrated, which allows for more effective endogenous modulation of the noxious signal, via descending modulatory circuitry. This interpretation would indicate that trait mindfulness and CPM may both provide a beneficial influence to an individual when managing pain, but that they are not necessarily associated with one another and are associated with unique mechanisms. Whether mindfulness and CPM elicit a combined effective, which coalesce would be a valid follow-up empirical question, that would require additional experimentation to examine.

5.2. Clinical Considerations

Chapter 2 examined hysteroscopy patients, and their experience of undergoing a procedure that is described as low-pain or pain-free. The primary clinical implication from this study is that hysteroscopy should no longer be described as such. Streamlining and cost-cutting are compulsory ventures within a 21st century National Health Service (NHS) and one targeted strategy to accomplish this is the transition from in-patient procedures into an outpatient pathway (Department of Health, 2000). However, whilst this is a vital pragmatic goal, it is crucial that patients are fully informed about the risks of adverse effects from the procedure and the potential for severe pain is one such risk. The campaign to "end barbaric NHS hysteroscopies, with inadequate pain relief" is a movement dedicated to raising awareness of this risk, and our data provides support for their campaign. One consideration should be to update the leaflets informing patients about the risks of hysteroscopy within an outpatient pathway. The benefits of avoiding general anaesthetic and an overnight stay are aptly described (Anderson, Walls, & Canelo, 2017; Bajaj, Sethi, Carr, & Knight, 2009; Darwin & Chung, 2013; Marsh, Rogerson, & Duffy, 2006), however with our result of just over 17% of patients reporting a 7 or higher on an 11-point scale, the description of the pain being akin to "discomfort" or "period-like" are not supported by the data. Similarly, within this description the requirement for analgesia is underplayed. Within the data, over half of patients received at least one ampule of anaesthetic, whereas the clinic's leaflet states that "local anaesthetic [can be applied] to the cervix, although this is not usually necessary" (Appendix C, p. 3). Ensuring that an accurate portrayal of the procedure is provided to the patients could help ensure expectations and intraoperative anxiety is managed as best possible, but also fulfils ethical and moral obligations to ensure patients can make a fully informed decision for their health.

As well as improving descriptions of the procedure, there are potential avenues available for improving pain management during the procedure. Chapter 2 identified two concerns regarding the clinicians estimates of their patients' pain. Firstly, the estimates were very limited in their variability suggesting a lack of specificity or accuracy regarding the range of pain experienced

across all patients. Secondly, the clinician's estimates were inversely correlated with the patient's own ratings. Specific discussions of what this is likely to entail are detailed in chapter 2, but regarding the implications, this may suggest that the clinician's assessment needs support and corroboration. Accurate pain assessment is one of the most difficult challenges facing clinicians and this challenge is likely to be even greater when having to assess during a precise medical procedure, with a time pressure upon their decision. However, when evaluating the evidence from this dataset, it is clear that some patients are vulnerable and experience intense pain, whereas others experience no discomfort or pain at all. Consequently, it would likely be beneficial to create and implement predictive assessment measures, delivered pre-surgically that are capable of stratifying patients into high or low risk pain categories. Based on the findings within this thesis, two candidates for such assessments are CPM and trait mindfulness measures, which may allow for the categorisation of patients into high-end and low-end subgroups. Within the context of hysteroscopy, the low-end subgroup would be more at risk of pain and extra care could be provided pre-surgically (expectation monitoring, information, anxiety management etc), as well as helping inform the operator of the likely requirement for pain management intraoperatively. Whilst this suggestion is outside the scope of this dataset, it is a valid hypothesis for empirical follow-up.

Fundamentally, the scope of this clinical collaboration was targeted towards investigating the presence of severe pain within a subset of hysteroscopy patients. The motivation behind this investigation was strongly supported by the clinicians involved, as they were anecdotally struggling to understand or manage the pain in these patients. One further implication of our evidence is that the clinical team would likely benefit from specific pain management education as a part of their clinical training. As described in section 1.1, pain in a medical setting is becoming one of the core clinical challenges of the 21st century. Pain can be difficult to assess, treat and explain. Pain can also vary across time and individuals, as can the efficacy of analgesia designed to manage it. As such, the lack of pain management as a specialism within the medical training pathway will likely need addressing as we continue to struggle with pain in the clinic.

Whilst this represents an implication too ambitious for this body of work, one related suggestion would be to enhance clinical decision making, especially regarding the efficacy of analgesia for managing acute pain. As described, patients who received the highest dose of analgesia were those who experienced the most pain but were estimated to be in the least pain by their clinicians. This likely represents an overestimation of the efficacy of the analgesia, or even their own pain management abilities, which have previously been identified as chronic biases within clinicians (Lander, 1990; Larue, Colleau, Fontaine, & Brasseur, 1995). In fact, it has been reported that the actual reduction of pain scores via local anaesthetic during hysteroscopy is minimal and unlikely to be clinically meaningful (Ahmad et al., 2017). By normalising the actual effect of local anaesthetic on intraoperative pain, we may better focus the attention of the clinicians within a stressful environment by educating them that intense pain can still persist, even during maximal pharmacological pain management and alternative strategies or approaches will be required to manage the pain of these most vulnerable patients.

5.3. Strengths and Limitations

5.3.1. Clinical Dataset

To our knowledge, the dataset described within chapter 2 is the first of its kind to, not only, investigate the experience of pain within outpatient hysteroscopy, but also to compare the ratings provided by patients to the equivalent estimate of pain from their clinician. The implications of this study provide much needed empirical support to ongoing public campaigns of the presence of pain during this procedure and will also provide insight towards the clinicians themselves regarding strategies for improving pain management. Forming a body of work across clinical and laboratory domains facilitates the uptake of modern research innovations into a real-world environment which may benefit from them. For example, within this study, it was identified that the current pain assessment employed within hysteroscopy may place too much emphasis on the importance of a

clinicians estimate, whereas chapters 3 and 4 may propose suitable individual differences measures, with empirical basis, that could potentially aid medical professionals in the clinic. Whilst this is a research question that would require empirical investigation to confirm, the potential for this approach was only made apparent by the completion of these studies.

However, regarding the clinical dataset itself, there are limitations to the methodological design of the experiment which restricted the scope of our conclusions. Whilst we have identified that a subset of patients will likely experience severe pain during hysteroscopy, the lack of pre-surgical psychometrics hampered our ability to predict which patients these are likely to be. Therefore, the conclusions of chapter 2 remain that some patients are likely to experience substantial pain during this procedure, however, we are currently unable to predict who these are likely to be until the pain emerges. Currently, the presurgical assessment for hysteroscopy at the Royal Berkshire Hospital is limited to purely medical information. The addition of relevant psychometrics within this assessment, such as measures of state anxiety, sleep quality or pain catastrophising could help pre-emptively predict those who are most vulnerable to the experience of pain, before the initiation of the procedure. However, whilst these psychological concepts have previously been linked to surgical outcomes (Cremeans-Smith, Millington, Sledjeski, Greene, & Delahanty, 2006; Granot & Ferber, 2016; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012), these findings are restricted to post-operative pain, rather than intra-operative pain. As many studies investigating pre-surgical predictions focus on major surgeries that require general anaesthetic, there is a dearth of literature examining the emergence of intrasurgical pain. Therefore, whilst it is unclear whether psychometrics would be able to assist clinicians in identifying high-risk patients, this represents a research venture with great potential and a key clinical need.

Moreover, the methods underlying the collection of patient pain ratings and clinician pain estimates have flaws which undermine the ability to make assured conclusions regarding our results. From an initial perspective, the existence of an inverse relationship between these two variables appears

illogical. There is little intuition associated with the concept that clinicians systematically rate high-pain patients as being in no/little pain and vice versa. Upon further investigation, it was concluded that this was likely the product of clinicians administering maximal analgesia to those who they felt were in the most pain, but alongside an overconfidence in the management of pain, these patients were concluded to be in low pain, as a result of the anaesthetic. This narrative is founded upon the evidence but requires a degree of supposition to fulfil a logical standpoint and is likely a feature of inefficient methodological design. Firstly, the instructions provided alongside the collection of ratings and estimates were minimal and unguided. The clinician was given no instructions or framing and was given a choice of five verbal indicators under the heading of "Dr's Pain Assessment" (Appendix A). The patient was asked for their rating verbally and asked to rate "the level of pain experienced during the surgery". One simple alteration to this design, that would likely help account for the influence of analgesia, is for both clinicians and patients to be asked to rate their peak/highest pain rating experienced during the surgery. This would allow us to strengthen the scope of our conclusions, as we can be assured that they are rating pain using similar framing, whereas in this dataset, our interpretation indicates that patients were rating the peak pain, whilst clinicians were estimating an approximation of the average pain, taking into account the effect of the anaesthetic.

Relatedly, although studies comparing pain ratings across visual and numeric rating scales report similarity of inter-scale ratings, they are often subject of a degree of variance (DeLoach, Higgins, Caplan, & Stiff, 1998; Hjermstad et al., 2011). Importantly, these studies uniformly compare these two scales with the same degree of sensitivity, for example, two 11-point scales, rather than a 5-point scale vs a 11-point scale. Therefore, whilst the literature suggests the use of the two scales is likely to be similar, the utilisation of varying sensitivity across the scales reduces the certainty with which we can be confident in their direct comparison. Follow-up investigation into this area should standardise the instructions and rating scales used across both the clinician and patient and indicates the importance of having multidisciplinary work, whereby clinicians and researchers collaborate to conduct high quality research.

Lastly, it is unclear what influence retrospection would have on the decision-making of the pain ratings in this study. Rather than taking ratings during the procedure, this study elected to collect the pain ratings as soon as possible after the completion of the hysteroscopy. Interestingly, studies examining retrospective vs real-time pain ratings during surgery have found substantial variation in the pain that was remembered by patients during surgical procedures. For instance, patients undergoing colonoscopy and lithotripsy procedures recorded their pain in real-time, as well as providing a retrospective rating after the operation (Ntomaris & Bakirtzis, 2015). It was found that retrospective ratings were subject to bias and were generally correlated with the peak intensity of pain in their real-time ratings, as well as indicating a recency bias towards the final 3 minutes of the operation. The implications of this reaffirm the importance of calibrating standardised instructions for pain rating collection, as the variation will only likely confound the results if one rating is focused on peak intensity, and the other not. If clinicians and patients are each asked to retrospectively rate/estimate the peak intensity of pain experienced during the procedure, the literature seems to confirm that this judgement is likely to be reliable.

Alternatively, the modelling of real-time pain ratings would provide interesting and accurate insight towards the progression of pain throughout the procedure. This would also facilitate inspection of the effect of anaesthetic administration on pain ratings, at the moment that it is applied. However, the acquisition of real-time ratings would increase the burden upon clinicians in an environment that is already stressful. The practical requirements of high intensity data recording during the medical procedure would likely require additional staffing, and as such, the utilisation of retrospective ratings, alongside standardised instructions, is likely to be the most appropriate methodological improvement for this study.

5.3.2. Resting State and Functional Connectivity

Event-related fMRI designs are well-equipped to derive knowledge regarding specific functions of regions associated with a participant's response to a stimulus. However, when examining

individual differences, rs-fMRI is a powerful tool which can monitor intrinsic fluctuations in BOLD signal in a participant at rest, with no task or agenda. By utilising this approach, rs-fMRI can be used to estimate the functional architecture of an individual's brain. By applying connectivity analysis to rs-fMRI, an experimenter can then compare across a sample to identify idiosyncrasies in the connectivity between regions that are associated with variables or conditions of interest. Furthermore, by applying a seed-choice to this connectivity analysis, researchers can specify the scope of their analysis and apply this towards an a-priori hypothesis; for example, using the PAG to specify a hypothesis towards the modulation of pain.

There are multiple strengths associated with the use of rs-fMRI. The characteristic resting state networks (RSNs), such as the default mode network (DMN), sensorimotor network or salience network (Beckmann, Deluca, Devlin, & Smith, 2005) have been shown to be consistent across participants, sessions and even non-human primates or small mammals (Damoiseaux et al., 2006; Hutchison et al., 2011; Lu et al., 2012). This confirms that the recorded fluctuations in BOLD response do not represent random fluctuations, and that there is characteristic structure to brain connectivity at rest. The investigation of variations in these consistent networks has provided a useful tool for learning more about clinical conditions, whereby the resting state connectivity of patients can be compared to controls (Zhang & Raichle, 2010). An added benefit of rs-fMRI within the clinical domain is that the circumvention of a task-based design facilitates the participation of all types of patients and people, regardless of cognitive, verbal or physical function. Regarding the pursuit of developmental models, for example the transition towards chronic pain, this would allow the modelling of children and adolescents which can often be challenging or burdensome within task-based designs, but provides vital insight towards how this transition can manifest itself neurologically. Given this, as well as the increasing access to imaging tools and the non-invasive nature of fMRI, it is likely not surprising that the application of rs-fMRI has been growing in popularity within both clinical and research environments over the past two decades (Lv et al., 2018).

However, the development of rs-fMRI techniques, as well as its increase in popularity, has seen a similar rise in criticisms of the approach which must be taken into consideration. From a methodological perspective, the detrimental influence of movement and physiological artifacts has been targeted as a core vulnerability within the design. Tellingly, it has been reported that not only can participant movement create spurious functional connectivity correlations, but these correlations can be systematic with longer-distance correlations being weakened and shorter-distance ones being strengthened (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Worryingly, these artifacts cannot be corrected by current pre-processing movement correction techniques; once the data has been collected, the influence of movement is locked into the data. Head movement has long been targeted as a core concern within the acquisition of fMRI data (Johnstone et al., 2006; Karl, 1994), with movement as small as 0.5mm being able to bias correlation estimates (O'Connor & Zeffiro, 2019; Parkes, Fulcher, Yücel, & Fornito, 2018). The acquisition within fMRI requires a high degree of spatial accuracy, as well as the maintenance of specific temporal magnetic gradients. As the scale of this accuracy is in the realm of milliseconds and millimetres, the movement of a head can shift the brain in space, and disrupt magnetic gradients (and ultimately, the resulting BOLD output). These influences are not limited to simple movement of the head and can also emerge as a feature of non-neuronal physiological movement such as respiration and cardiac activity (Murphy, Birn, & Bandettini, 2013). As these influences often fluctuate within a repetitive and frequent synchronicity (i.e. heartbeat), these can be very challenging to control for in pre-processing and to distinguish from the oscillatory patterns within the fMRI time-course. These features are also likely to vary across clinical patients and healthy controls, raising concerns about rs-fMRI designs such as these (Griffanti et al., 2016).

To date, there are several options available for managing motion-related artifacts, although none of them have been found to wholly effective (Parkes et al., 2018). However, some papers have proposed new guidelines for processing the data, which can provide maximal confidence in the conclusions of rs-fMRI (Brahms & Wardrip, 2013; Murphy et al., 2013; Smitha et al., 2017). These can often be grouped into two categories; 1) External physiology measurements during acquisition

and 2) Use of data-based post-acquisition clean-up. Unfortunately, regarding chapters 3 and 4 within this body of work, the former was not possible as physiological data was not acquired during the collection of resting state. This criticism is notably influential within chapter 4 which utilised a brainstem seed (PAG) as the brainstem is more susceptible to breathing and cardiac movements than the cortex (Brooks, Faull, Pattinson, & Jenkinson, 2013). Within our lab, this correction has since been made and physiological data collection has been applied to future research projects, but consideration should be given towards the implications of movement artifacts on our findings.

While connectivity analysis is a useful analytical tool for evaluating resting state data, it is important to note the limitations for the implications of the results. Regarding chapter 4, the data supports a conclusion that activity in the PAG was more synchronised with activation in other pain processing regions in participants with higher CPM scores. This provides us with a degree of insight about how functional connected, yet anatomically distal, regions may operate more cohesively, and be associated with a beneficial response. For example, the functional connectivity of the PAG with pain processing regions may bely a more synchronised network of pain processing and modulation, which facilitates more effective CPM. However, based on this premise alone, we are unable to conclude a temporal relationship between these identified clusters and our seed, ergo, whether the PAG is operating more efficiently as part of a top-down process, as opposed to disseminating more efficiently into the cortex. To be able to address this, analytical tools such as dynamic causal modelling (DCM) would be an appropriate strategy to target this research question (Friston, Kahan, Biswal, & Razi, 2014). To further investigate the relationship of the PAG within descending pain modulation, as associated with CPM, the use of DCM could help elaborate on the nature of this relationship. For example, it would help to understand whether the PAG is receiving more synchronised input from the somatosensory cortex to facilitate modulation, or alternatively, whether the modulation is benefited from efficient detailing of the ascending signal, from the PAG to the somatosensory cortex. Ultimately, the result could indicate that the integration is benefiting

the relationship between these areas bidirectionally, but the use of a different analytical tool could help elaborate on this empirical question.

5.3.3. Conditioned Pain Modulation

One of the conclusions raised from the results of chapter 2 is that clinical assessments could benefit from more comprehensive assessments which may help identify, pre-surgically, those at risk of pain sensitivity. CPM is one such assessment, and chapter 4 is able to corroborate this assertion, by indicating that individuals with better CPM are associated with heightened integration of pain processing and modulation regions. As described in section 1.3.2, CPM has already been identified as a useful pre-surgical assessment, associated with outcomes related to surgery (Landau et al., 2010; Wilder-Smith, Schreyer, Scheffer, & Arendt-Nielsen, 2010; Yarnitsky et al., 2008), analgesia efficacy (Edwards et al., 2016; Grosen, Fischer, Olesen, & Drewes, 2013; David Yarnitsky et al., 2012) and the maintenance of chronic pain conditions (Arendt-Nielsen et al., 2010; Lewis, Rice, & McNair, 2012; O'Brien, Deitos, Triñanes Pego, Fregni, & Carrillo-de-la-Peña, 2018; Rabey et al., 2015). However, criticisms are beginning to emerge regarding its reliability and replicability which require addressing to enhance the efficacy of these assessments. Inter-rater reliability has been found to fluctuate wildly, with interclass correlation coefficients (ICCs) reported between 0.10-0.76 (Bossmann et al., 2016). As such, understanding the basis of this lack of reliability is crucial, especially if the ultimate goal is clinical application, where it could be expected that a selection of different healthcare professionals will be required to assess patients. Test-retest reliability has also shown to fluctuate within the literature, with ICCs ranging from 0.34 to 0.69 (Cathcart, Winefield, Rolan, & Lushington, 2009; Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016; Lewis, Heales, Rice, Rome, & McNair, 2012; Wilson, Carvalho, Granot, & Landau, 2013).

Two main proposals have been suggested to attempt to explain this variability. The first is that when assessing CPM with a short time interval, the reliability appears to be high, whereas this decreases as the interval between tests gets longer (Gehling et al., 2016). The second is that, despite

CPMs growing popularity and literature base, the standardisation of the methodology is still lacking, with a variety of test or conditioning stimuli employed interchangeably. One specific issue with the methodology, is that the original publication which first identified the predictive capabilities of CPM adopted a standardised procedure involving thermal test and conditioning stimuli (as used within this current body of work) (Yarnitsky et al., 2008). These seminal findings motivated a swell of research, using the same method, which were vital for the development of our understanding regarding CPM as a clinical assessment (Moont, Crispel, Lev, Pud, & Yarnitsky, 2011; Moont, Pud, Sprecher, Sharvit, & Yarnitsky, 2010; Nir, Yarnitsky, Honigman, & Granot, 2012; Yarnitsky et al., 2012). Since then, work has been completed investigating the influences of stimulus medium on reliability and the combination of two heat stimuli was associated with the lowest test-retest reliability (ICC= 0.34-0.39; (Granovsky, Miller-Barmak, Goldstein, Sprecher, & Yarnitsky, 2016; Wilson et al., 2013)), indicative of a classification of poor reliability (Koo & Li, 2016). To counter this, a CPM consensus meeting was held at a meeting of the European Pain Federation (EFIC), where principles for a standardised methodology were proposed, in order to promote reliable application of this tool (Yarnitsky et al., 2015).

Based upon these reviews, there are several steps that can be taken to increase the reliability of a CPM paradigm, especially if applied to a clinical environment. Firstly, as stability of the CPM effect appears to weaken with time, assessments should be completed within a consistent and short time frame of the procedure or invention they are required for. Within chapter 4, the duration between the sensory pain assessment and MRI was kept to a maximum of 7 days, and this consistent and short interval may have benefited the implications of our results. Secondly, new studies should consider adopting the EFIC standardised guidelines for CPM by adopting the use of mechanical and thermal test stimuli, cold-water conditioning stimuli and the repetition of each test stimuli twice with a 10-minute inter-stimulus interval. Lastly, whilst the variation in inter-rater reliability is so high, it is unclear how much of an influence this would represent if the initial two corrections were made to the design. However, until further empirical work is completed to

elaborate on this relationship, an ideal CPM design would utilise the same experimenter across the timeline of a trial or experiment.

5.4. Broader Implications and Future Directions

5.4.1. Enhancing clinical pain assessment

As described within sections 1.2 and 1.4, clinical pain assessment embodies a core medical challenge and the development of multi-faceted assessments are likely to be a suitable strategy for improving our current techniques. This thesis represents part of a larger body of work developing such an assessment battery, termed the Modulatory Capacity Assessment Battery (MCAB) (See Appendix F for overview).

Chapters 3 and 4 both provide initial empirical basis for the inclusion of CPM, trait mindfulness, pain thresholds, pain catastrophising and resting state within the MCAB. An empirical investigation on emotional modulation and associations with resting-state connectivity of amygdala has also been published using this data, to provide support for the use of this in understanding individual differences in emotional regulation and pain., (Gandhi, Rosenek, Harrison, & Salomons, 2019) . Additionally, data has already been published on how gender roles, as measured using the Bem Sex-Role Inventory (Bem, 1977), may introduce a recruitment bias in experimental studies, with an underrepresentation of males who identify with traditional feminine traits (Mattos Feijó et al., 2018). Lastly, the MCAB is currently part of a large-scale project examining whether responses of healthy controls to cognitive interventions can be predicted via our assessment, and whether we can find neural predictors of sensitisation to pain. This is an essential translational project that will help us understand how the MCAB functions predictively regarding psychological interventions and would represent an important steppingstone towards clinical application.

Although, further work is required to fully validate the battery towards an application within a clinical setting, the sensory and psychometric component is already being utilised within an experimental clinical trial investigating a new form of embolization surgery for treating knee osteoarthritis (Harrison, Little, Gandhi, Kapila, & Salomons, in prep). The initial findings reported in chapters 3 and 4 provide a positive start in the validation of this multi-faceted assessment, and due to their neuroscientific component, have potentially identified distinct mechanisms of effective pain management, specifically regarding pain modulation. The completion of the embolization study will hopefully provide clinical insight towards the development of chronic postsurgical pain, and ultimately, the MCAB can be used to bolster routine clinical assessments.

5.4.2. Mindfulness and pain

As concluded from the findings in chapter 3, trait mindfulness may represent a beneficial psychological trait for managing pain. Mindfulness-based interventions (MBIs) have also been shown to be an effective strategy for improving pain outcomes in the clinic (Kabat-Zinn, 1982; Morone et al., 2016). However, within a recent trial examining feasibility, tolerability and acceptability of MBIS, it was reported that 22% of patients attended under half of the sessions for mindfulness meditation (Day et al., 2018). While ratios of dropout, acceptability and attendance were acceptable, the suitability of MBIs for all patients is not comprehensive. Overall, those who adhere to a programme within MBIs are likely to experience benefits regarding pain intensity, depression, physical function and pain interference (de Jong et al., 2018; Kabat-Zinn, 2003; Williams, Eccleston, & Morley, 2012). However, like with all psychological interventions, MBIs are not suitable or acceptable for every patient and not all those that complete MBIs experience pain relief (Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016; Williams et al., 2012). Developing processes to stratify patients based on suitability for the intervention would be of benefit to health care providers and, most importantly, the patients themselves.

One research question that this perspective raises, is whether the neural mechanism identified within chapter 3 provides any insight towards suitability for MBIs. These participants were naïve to

MBIs and meditation, yet those with higher trait mindfulness were associated with variations in connectivity which may relate to the way they attend to sensory and cognitive information. Therefore, theoretically, are these individuals likely to not gain further benefit for the attentional training within MBIs (as they already have this attentional regulatory focus)? Alternatively, is the ability to functionally disconnect attentional focus to sensory and cognitive stimuli a prerequisite for adhering to the training of MBIs? Will those that lack this mechanism struggle to adapt to this attentional disconnect?

One key benefit of using rs-fMRI as in chapter 3, is that it allows us to investigate individual differences and to associate our observations with a behavioural marker. Within a clinical setting, it is wildly unrealistic to propose assessment that requires access to MRI and the training to evaluate resting state connectivity. However, findings from chapter 3 suggest that scores on the Five-Factor Mindfulness Questionnaire (FFMQ) are associated with this neural mindfulness mechanism, and as such, pre-clinical assessments could be completed using the FFMQ. Based on this, an interesting follow-up to chapter 3 would be to investigate whether trait mindfulness serves as a useful predictor for outcomes, feasibility and acceptability to MBIs in the clinic. Additionally, we could investigate this mechanism further by utilising pre/post rs-fMRI resting to understand if this pattern of neural connectivity can be altered via exposure to MBIs. For example, will those that are low in trait mindfulness, wherein this mechanism is less pronounced, be able to enhance their attentional focus and alter the underlying neural processes? If so, are those who are high in trait mindfulness able to further enhance this attentional regulation and further depolarise the functional disconnect of attentional regulation of sensory and cognitive information?

5.4.3. Evaluating outpatient surgeries

As described in chapter 2, increasing pressure on resources within the NHS will necessitate the translation of more surgical procedure from in-patient to outpatient pathways. The ability to make this transition is a positive indicator of technological and medical advances that facilitate the

avoidance of general anaesthetic. However, evidence from chapter 2 indicates that caution should be taken and that we need to consider the experience of patients within this decision. The first clear implication of this evidence is that hysteroscopy cannot be described as uniformly associated with no pain, or even low pain; outcomes are varied, and a subset of patients will likely experience severe pain. This study provides support for the campaign to "end barbaric NHS hysteroscopies, with inadequate pain relief" (Falkner & Tylko, 2019) by suggesting that patients should be warned of the risk of severe pain and that improvements to intraoperative pain management are required to curtail the risk and incidence of such pain.

However, while outside the scope of chapter 2, these findings do have broader implications regarding other surgeries which are transitioning away from general anaesthetic to outpatient pathways. Through the development of flexible, non-metallic surgical instruments, many types of surgery or diagnostics are now possible without the need for sedation (Bailey et al., 2019). Alongside a target that 75% of elective surgeries in the UK should be completed via outpatient pathway (Department of Health, 2000), this will lead to an emerging reliance upon local anaesthetic and, as such, pain management will become a critical area of importance.

Procedures such as cystoscopy (diagnosis via insertion into the urethra), carotid endarterectomy (removal of plague via insertion into the neck) and laparoscopic cholecystectomy (removal of gallbladder via keyhole surgery) all no longer require sedation, but are associated with a risk of intraoperative pain (Bailey et al., 2019; Calleary, Masood, Van-Mallaerts, & Barua, 2007; Luchetti, Canella, Zoppi, & Massei, 2008; McCutcheon, Orme, Scott, Davies, & McGlade, 2006). One follow-up experiment that emerged from the findings of chapter 2 is whether it could be predicted which of the patients are those that are likely to experience severe pain during the procedure. However, another related question is whether the risk factors that predispose hysteroscopy patients to the experience of severe pain during the procedure would also predispose them to pain within other surgical procedures. As described in chapter 4, CPM is a psychophysical assessment that

quantifies the efficiency of modulatory circuitry in the brain, hence, it can be utilised across a variety of medical domains and is not specific to a type of procedure. Whether we could develop a similar assessment for intra-operative pain and apply it across multiple outpatient procedures is a valid scientific question worth addressing.

5.5. Conclusions

The body of work contained within this thesis aimed to expand on the available literature regarding psychological variables associated with the concept of innate ability to manage pain, and how this relates to underlying neural mechanisms. Firstly, we investigated hysteroscopy, a medical procedure described as being associated with low pain, or no pain at all (Appendix C). This assertion has been queried by clinical collaborators, as well as public campaigns (Falkner & Tylko, 2019). We investigated outcome data from the Royal Berkshire Hospital's gynaecological department, and found that hysteroscopy was, in fact, associated with a range of varying pain intensities, with a minority of patients experiencing no pain. Interestingly, clinical estimates of pain were inversely correlated with patient pain ratings, which was a result of special significance, as decisions regarding analgesic dose during routine care in this clinic are made based on clinical judgement alone. Our results concluded that the advertisement of hysteroscopy should include sufficient warning of the risks of intraoperative pain and that improvements should be made to the way pain is managed intra-operatively. This is especially important given the potential presence of clinical overconfidence in the efficacy of anaesthetic for pain management.

One of the conclusions from this study was that a pre-surgical assessment for individual differences may help identify patients who are likely to be vulnerable to the experience pain. In chapters 3 and 4, we examined two such individual measures associated with effective pain management. In chapter 3, we examined trait mindfulness in healthy controls who were naïve to mindfulness. Our results indicated that even with this naivety, intrinsic mindfulness provides a similar beneficial

influence regarding cognitive and sensory dimensions of pain as observed in studies investigating MBIs and pain outcomes. Trait mindfulness was also associated with heightened connectivity between a seed associated with self-referential and attentional processing and the somatosensory cortex and decreased connectivity between the same seed and the prefrontal cortex. The beneficial pain response may emerge via a functional disconnect of attentional regulation between sensory and cognitive features of pain, which enables a more present-focussed, active processing of the noxious stimulus with a reduced tendency towards ruminative reappraisal.

In chapter 4, CPM was examined, a psychophysical assessment that is described as a proxy for the efficiency of descending pain modulation circuitry in the brain. CPM has previously been associated with beneficial clinical pain outcomes and may represent an intrinsic beneficial influence for pain, via the ability to modulate the ascending noxious stimulus. Our data shows that those with higher CPM were associated with heightened connectivity between a key pain modulatory region, and multiple areas of the brain known to be associated with the processing of pain. This integration of pain processing regions, with a region involved in modulating the nociceptive signal, may enable more efficient pain modulation, which could provide a protective influence when dealing with pain in the real-world.

Based on our findings, future research should investigate the prediction of intraoperative pain within medical procedures performed under local anaesthetic. Regarding hysteroscopy, the way in which the procedure is described should be changed to inform of the risk of severe pain. The inclusion of predictive measures may facilitate improved intraoperative pain management and could potentially help stratify patients into risk categories. Empirically, the identification of two distinct mechanisms that appear to provide intrinsic benefit for managing pain is promising. However, investigating how to best manage these patients still requires further work. For example, follow-up studies should examine whether trait mindfulness can be used as a behavioural marker for treatment suitability, and whether there are implications for the use of MBIs in the clinic. This

type of improvement would potential help clinical teams manage the on-going challenge of pain treatment, but importantly, could also help chronic pain patients find a suitable treatment quicker, and help them deal with the burdensome implications of a life with pain.

5.6. References

Ahmad, G., Saluja, S., Flynn, O. H., Sorrentino, A., Leach, D., & Watson, A. (2017). Pain relief for outpatient hysteroscopy. *Cochrane Database of Systematic Reviews*, (10). https://doi.org/10.1002/14651858.CD007710.pub3.www.cochranelibrary.com

Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003

Bailey, C. R., Ahuja, M., Bartholomew, K., Bew, S., Forbes, L., Lipp, A., … Stocker, M. (2019). Guidelines for day-case surgery 2019. *Anaesthesia*, *74*(6), 778–792. https://doi.org/10.1111/anae.14639

Beckmann, C. F., Deluca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society*, *360*(May), 1001–1013. https://doi.org/10.1098/rstb.2005.1634

Beecher, H. K. (1946). Pain in Men Wounded in Battle. *Annals of Surgery*, *123*(1), 96–105. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17858731

Bem, S. (1977). The measurement of psychological androgyny: an extended replication. *Journal of Clinical Psychology*, *33*(4), 1009–1013. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/925154

Bossmann, T., Brauner, T., Lowak, H., Anton, F., Forster, C., & Horstmann, T. (2016). Reliability of conditioned pain modulation for the assessment of endogenous pain control pathways. *Neurology, Psychiatry and Brain Research*, *22*(3–4), 155–161. https://doi.org/10.1016/j.npbr.2016.09.001

Brahms, L., & Wardrip, P. S. (2013). Making With Young Learners : An Introduction. *American Journal of Neuroradiology*, *9*(5), 6–9. https://doi.org/10.3174/ajnr.A3263.Resting

Brooks, J., Faull, O. K., Pattinson, K. T. S., & Jenkinson, M. (2013). Physiological Noise in Brainstem fMRI. *Frontiers in Human Neuroscience*, *7*(October), 1–13. https://doi.org/10.3389/fnhum.2013.00623

Brooks, J., & Tracey, I. (2005). From nociception to pain perception: Imaging the spinal and supraspinal pathways. *Journal of Anatomy*, *207*(1), 19–33. https://doi.org/10.1111/j.1469-7580.2005.00428.x

Calleary, J. G., Masood, J., Van-Mallaerts, R., & Barua, J. M. (2007). Nitrous Oxide Inhalation to Improve Patient Acceptance and Reduce Procedure Related Pain of Flexible Cystoscopy for Men Younger Than 55 Years. *Journal of Urology*, *178*(1), 184–188. https://doi.org/10.1016/j.juro.2007.03.036

Cathcart, S., Winefield, A. H., Rolan, P., & Lushington, K. (2009). Reliability of Temporal Summation and Diffuse Noxious Inhibitory Control. *Pain Research and Management*, *14*(6), 433–438. https://doi.org/10.1155/2009/523098

Cremeans-Smith, J. K., Millington, K., Sledjeski, E., Greene, K., & Delahanty, D. L. (2006). Sleep Disruptions Mediate the Relationship Between Early Postoperative Pain and Later Functioning Following Total Knee Replacement Surgery. *Journal of Behavioral Medicine*, *29*(2), 215–222. https://doi.org/10.1007/s10865-005-9045-0

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853. https://doi.org/10.1073/pnas.0601417103

Day, M. A., Ward, L. C., Ehde, D. M., Thorn, B. E., Burns, J., Barnier, A., … Jensen, M. P. (2018). A Pilot Randomized Controlled Trial Comparing Mindfulness Meditation, Cognitive Therapy, and Mindfulness-Based Cognitive Therapy for Chronic Low Back Pain. *Pain Medicine*, *00*(0), 1–15. https://doi.org/10.1093/pm/pny273

de Jong, M., Peeters, F., Gard, T., Ashih, H., Doorley, J., Walker, R., … Mischoulon, D. (2018). A Randomized Controlled Pilot Study on Mindfulness-Based Cognitive Therapy for Unipolar Depression in Patients With Chronic Pain. *The Journal of Clinical Psychiatry*, *79*(1), 26–34. https://doi.org/10.4088/JCP.15m10160

DeLoach, L. J., Higgins, M. S., Caplan, A. B., & Stiff, J. L. (1998). The Visual Analog Scale in the Immediate Postoperative Period. *Anesthesia & Analgesia*, *86*(1), 102–106. https://doi.org/10.1097/00000539-199801000-00020

Department of Health. (2000). *The NHS Plan 2000*. London, UK. Retrieved from http://pns.dgs.pt/files/2010/03/pnsuk1.pdf

Edwards, R. R., Dolman, A. J., Martel, M. O., Finan, P. H., Lazaridou, A., Cornelius, M., & Wasan, A. D. (2016). Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 284. https://doi.org/10.1186/s12891-016-1124-6

Friston, K. J., Kahan, J., Biswal, B., & Razi, A. (2014). A DCM for resting state fMRI. *NeuroImage*, *94*, 396–407. https://doi.org/10.1016/j.neuroimage.2013.12.009

Fuster, J. (2008). *The Prefrontal Cortex*. (J. Fuster, Ed.) (4th ed.). Cambridge, MA: Academic Press.

Gandhi, W., Rosenek, N. R., Harrison, R., & Salomons, T. V. (2019). Functional connectivity of the amygdala is linked to individual differences in emotional pain facilitation. *Pain*. 10. Doi: 10.1097/j.pain.0000000000001714

Gehling, J., Mainka, T., Vollert, J., Pogatzki-Zahn, E. M., Maier, C., & Enax-Krumova, E. K. (2016). Short-term test-retest-reliability of conditioned pain modulation using the cold-heat-pain method in healthy subjects and its correlation to parameters of standardized quantitative sensory testing. *BMC Neurology*, *16*(1), 125. https://doi.org/10.1186/s12883-016-0650-z

Granot, M., & Ferber, S. G. (2016). The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *The Clinical Journal of Pain*, *21*(5), 439–445. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16093750

Granovsky, Y., Miller-Barmak, A., Goldstein, O., Sprecher, E., & Yarnitsky, D. (2016). CPM test-retest reliability: "standard" vs "single test-stimulus" protocols. *Pain Medicine (United States)*, *17*(3), 521–529. https://doi.org/10.1111/pme.12868

Granovsky, Y., & Yarnitsky, D. (2013). Personalized Pain Medicine: The Clinical Value of Psychophysical Assessment of Pain Modulation Profile. *Rambam Maimonides Medical Journal*, *4*(4), 1–8. https://doi.org/10.5041/RMMJ.10131

Griffanti, L., Rolinski, M., Szewczyk-Krolikowski, K., Menke, R. A., Filippini, N., Zamboni, G., … Mackay, C. E. (2016). Challenges in the reproducibility of clinical studies with resting state fMRI: An example in early Parkinson's disease. *NeuroImage*, *124*, 704–713. https://doi.org/10.1016/j.neuroimage.2015.09.021

Grosen, K., Fischer, I. W. D., Olesen, A. E., & Drewes, A. M. (2013). Can quantitative sensory testing predict responses to analgesic treatment? *European Journal of Pain (United Kingdom)*, *17*(9), 1267–1280. https://doi.org/10.1002/j.1532-2149.2013.00330.x

Harrison, R., Little, M., Gandhi, W., Kapila, A., & Salomons, T. V. (n.d.). Pre-surgical predictors of clinical outcome in embolization, a novel method for the treatment of knee osteroarthritis. *In Prep.*

Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., … Kaasa, S. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management*, *41*(6), 1073–1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016

Hutchison, R. M., Leung, L. S., Mirsattari, S. M., Gati, J. S., Menon, R. S., & Everling, S. (2011). Resting-state networks in the macaque at 7T. *NeuroImage*, *56*(3), 1546–1555. https://doi.org/10.1016/j.neuroimage.2011.02.063

Johnstone, T., Ores Walsh, K. S., Greischar, L. L., Alexander, A. L., Fox, A. S., Davidson, R. J., & Oakes, T. R. (2006). Motion correction and the use of motion covariates in multiple-subject fMRI analysis. *Human Brain Mapping*, *27*(10), 779–788. https://doi.org/10.1002/hbm.20219

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*. https://doi.org/10.1016/0163-8343(82)90026-3

Kabat-Zinn, J. (2003). Mindfulness-based interventions in context: Past, present, and future. *Clinical Psychology: Science and Practice*, *10*(2), 144–156. https://doi.org/10.1093/clipsy/bpg016

Karl, J. F. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*(1–2), 56–78. Retrieved from http://dx.doi.org/10.1002/hbm.460020107

Kennedy, D. L., Kemp, H. I., Ridout, D., Yarnitsky, D., & Rice, A. S. C. (2016). Reliability of conditioned pain modulation. *Pain*, *157*(11), 2410–2419. https://doi.org/10.1097/j.pain.0000000000000689

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, *15*(2), 155–163. https://doi.org/10.1016/j.jcm.2016.02.012

Landau, R., Kraft, J. C., Flint, L. Y., Carvalho, B., Richebé, P., Cardoso, M., … Cahana, A. (2010). An Experimental Paradigm for the Prediction of Post-Operative Pain (PPOP). *Journal of Visualized Experiments*, (35), 3–7. https://doi.org/10.3791/1671

Lander, J. (1990). Fallacies and phobias about addiction and pain. *Addiction*, *85*(6), 803–809. https://doi.org/10.1111/j.1360-0443.1990.tb01693.x

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International affective picture system (IAPS): Technical manual and affective ratings. *NIMH Center for the Study of Emotion and Attention*, 39–58.

Larue, F., Colleau, S. M., Fontaine, A., & Brasseur, L. (1995). Oncologists and primary care physicians' attitudes toward pain control and morphine prescribing in france. *Cancer*, *76*(11), 2375–2382. https://doi.org/10.1002/1097-0142(19951201)76:11<2375::AID-CNCR2820761129>3.0.CO;2-C

Lewis, G. N., Heales, L., Rice, D. A., Rome, K., & McNair, P. J. (2012). Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*, *17*(2), 98–102. https://doi.org/10.1155/2012/610561

Lewis, G. N., Rice, D. A., & McNair, P. J. (2012). Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2012.07.005

Lu, H., Zou, Q., Gu, H., Raichle, M. E., Stein, E. A., & Yang, Y. (2012). Rat brains also have a default mode network. *Proceedings of the National Academy of Sciences*, *109*(10), 3979–3984. https://doi.org/10.1073/pnas.1200506109

Luchetti, M., Canella, M., Zoppi, M., & Massei, R. (2008). Comparison of Regional Anesthesia Versus Combined Regional and General Anesthesia for Elective Carotid Endarterectomy: A Small Exploratory Study. *Regional Anesthesia and Pain Medicine*, *33*(4), 340–345. https://doi.org/10.1016/j.rapm.2008.01.013

Lv, H., Wang, Z., Tong, E., Williams, L. M., Zaharchuk, G., Zeineh, M., … Wintermark, M. (2018). Resting-state functional MRI: Everything that nonexperts have always wanted to know. *American Journal of Neuroradiology*, *39*(8), 1390–1399. https://doi.org/10.3174/ajnr.A5527

Mattos Feijó, L., Tarman, G. Z., Fontaine, C., Harrison, R., Johnstone, T., & Salomons, T. (2018). Sex-Specific Effects of Gender Identification on Pain Study Recruitment. *Journal of Pain*, *19*(2). https://doi.org/10.1016/j.jpain.2017.09.009

McCutcheon, C. A., Orme, R. M., Scott, D. A., Davies, M. J., & McGlade, D. P. (2006). A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anesthesia. *Anesthesia and Analgesia*, *102*(3), 668–675. https://doi.org/10.1213/01.ane.0000197777.62397.d5

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, *66*(6), 355–474. https://doi.org/10.1016/S0301-0082(02)00009-6

Morone, N. E., Greco, C. M., Moore, C. G., Rollman, B. L., Lane, B., Morrow, L. A., … Weiner, D. K. (2016). A mind-body program for older adults with chronic low back pain a randomized clinical trial. *JAMA Internal Medicine*, *176*(3), 329. https://doi.org/10.1001/jamainternmed.2015.8033

Murphy, K., Birn, R. M., & Bandettini, P. A. (2013). Resting-state fMRI confounds and cleanup. *NeuroImage*, *80*, 349–359. https://doi.org/10.1016/j.neuroimage.2013.04.001

Ntomaris, A. V., & Bakirtzis, A. G. (2015). Stochastic day-ahead scheduling of thermal and hybrid units in insular power

systems with high wind penetration. *2015 IEEE Eindhoven PowerTech, PowerTech 2015*, *66*, 3–8. https://doi.org/10.1109/PTC.2015.7232658
O'Brien, A. T., Deitos, A., Triñanes Pego, Y., Fregni, F., & Carrillo-de-la-Peña, M. T. (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *Journal of Pain*. Elsevier Inc. https://doi.org/10.1016/j.jpain.2018.01.010
O'Connor, E. E., & Zeffiro, T. A. (2019). Why is clinical fMRI in a resting state? *Frontiers in Neurology*, *10*(APR), 1–8. https://doi.org/10.3389/fneur.2019.00420
Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current Opinion in Supportive and Palliative Care*, *8*(2), 143–151. https://doi.org/10.1097/SPC.0000000000000055
Parkes, L., Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*, *171*(December 2017), 415–436. https://doi.org/10.1016/j.neuroimage.2017.12.073
Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018
Pron, G., Bennett, J., Common, A., Wall, J., Asch, M., & Sniderman, K. (2003). The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. *Fertility and Sterility*, *79*(1), 120–127. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12524074
Rabey, M., Poon, C., Wray, J., Thamajaree, C., East, R., & Slater, H. (2015). Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual Therapy*, *20*(6), 763–768. https://doi.org/10.1016/j.math.2015.02.011
Smitha, K. A., Akhil Raja, K., Arun, K. M., Rajesh, P. G., Thomas, B., Kapilamoorthy, T. R., & Kesavadas, C. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *Neuroradiology Journal*, *30*(4), 305–317. https://doi.org/10.1177/1971400917697342
Theunissen, M., Peters, M. L., Bruce, J., Gramke, H. F., & Marcus, M. A. (2012). Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. *Clinical Journal of Pain*, *28*(9), 819–841. https://doi.org/10.1097/AJP.0b013e31824549d6
Veehof, M. M., Trompetter, H. R., Bohlmeijer, E. T., & Schreurs, K. M. G. (2016). Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cognitive Behaviour Therapy*, *45*(1), 5–31. https://doi.org/10.1080/16506073.2015.1098724
Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J., & Arendt-Nielsen, L. (2010). Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: A pilot study. *Journal of Pain and Palliative Care Pharmacotherapy*, *24*(2), 119–128. https://doi.org/10.3109/15360281003706069
Williams, A., Eccleston, C., & Morley, S. (2012). Psychological therapies for the management of chronic pain (excluding headache) in adults. *The Cochrane Database of Systematic Reviews*, (11), 1–83. https://doi.org/10.1002/14651858.CD007407.pub3.www.cochranelibrary.com
Wilson, H., Carvalho, B., Granot, M., & Landau, R. (2013). Temporal stability of conditioned pain modulation in healthy women over four menstrual cycles at the follicular and luteal phases. *Pain*, *154*(12), 2633–2638. https://doi.org/10.1016/j.pain.2013.06.038
Yarnitsky, D. (2015). Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain*, 156, 24-31. Doi: 10.1097/01.j.pain.0000460343.46847.58.
Yarnitsky, D., Bouhassira, D., Drewes, A. M., Fillingim, R. B., Granot, M., Hansson, P., … Wilder-Smith, O. H. G. (2015). Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain*, *19*(6), 805–806. https://doi.org/10.1002/ejp.605
Yarnitsky, David, Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., … Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*, *138*(1), 22–28. https://doi.org/10.1016/j.pain.2007.10.033
Yarnitsky, David, Granot, M., & Granovsky, Y. (2014). Pain modulation profile and pain therapy: Between pro- and antinociception. *Pain*, *155*(4), 663–665. https://doi.org/10.1016/j.pain.2013.11.005
Yarnitsky, David, Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*, *153*(6), 1193–1198. https://doi.org/10.1016/j.pain.2012.02.021
Zeidan, F., Grant, J.A., Brown, C.A., McHaffie, J.G., Coghill, R.C. (2012). Mindfulness meditation-related pain relief: Evidecne for unique brain mechanisms in the regulation of pain. *Neuroscience Letters*, 520(*2)*, 165-173. Doi: 10.1016/j.neulet.2012.03.082
Zeidan, F., Adler-Neal, A.L., Wells, R.E., Stagnaro, E., May, L.M., Eisenach, J.C., McHaffie, J.G., Coghil, R.C. (2016). Mindfulness-meditation-based pain relief is not mediated by endogenous opioids. *The Journal of Neuroscience,* 36*(11)*,3391-3397. Doi: 10.1523/JNEUROSCI.4328-15.2016
Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature Reviews Neurology*, *6*(1), 15–28. https://doi.org/10.1038/nrneurol.2009.198

6. Appendices

Appendix F: Overview of the Modulatory Assessment Capacity Battery (MCAB)

The MCAB consists of four-sessions, alongside the administration of psychometrics, and attempts to quantify multiple aspects of an individual's ability to process and modulate pain. The timeline of the MCAB is standardised and presented below (Figure 1).

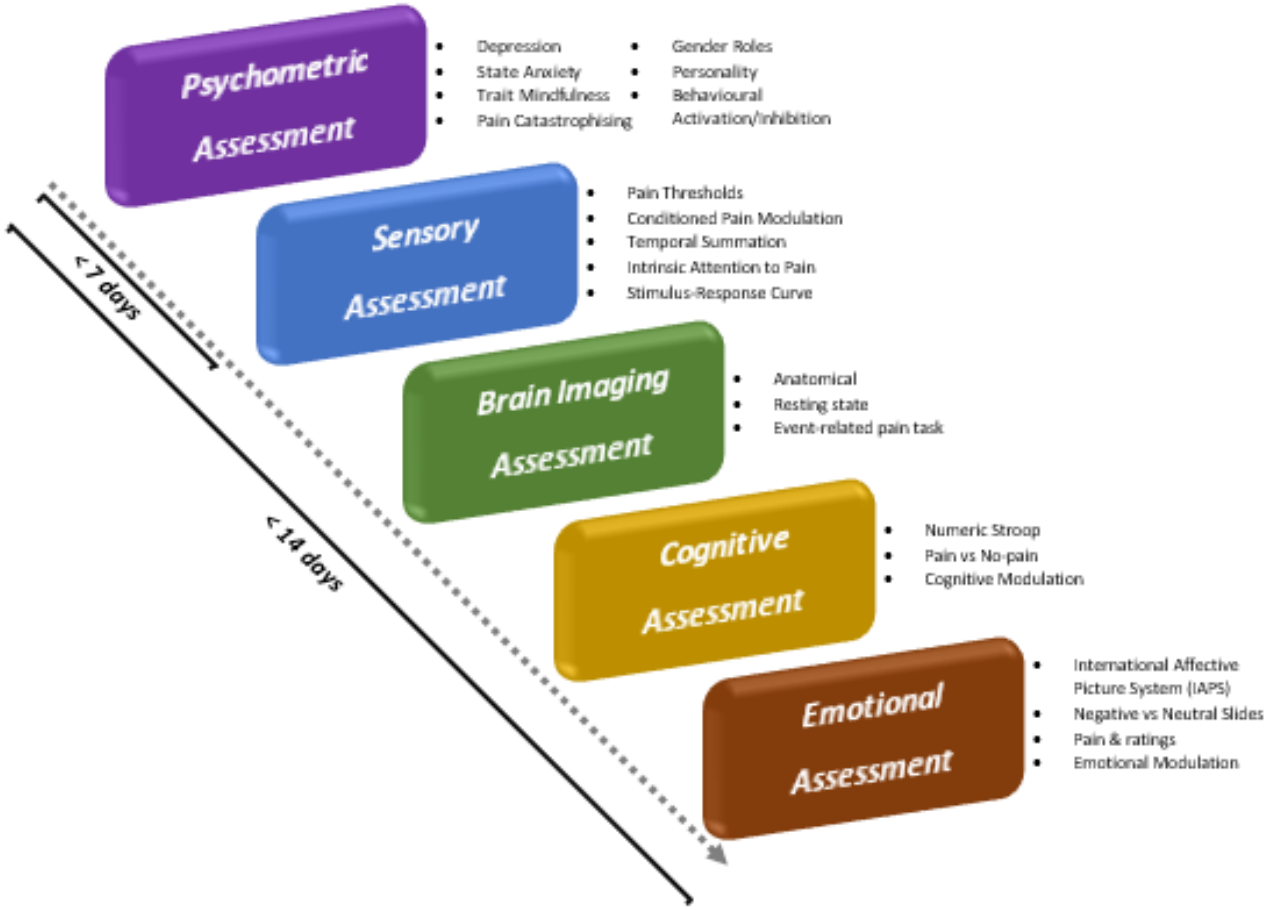

Figure 1*. Graphical representation of the timeline and content for the Modulatory Capacity Assessment Battery (MCAB), with multiple session breakdown.*

The foundation for the MCAB is based upon the initial sensory assessment, during which multiple psychophysical tests are completed to calibrate an individual's pain profile. This pain profile contains information about a participant's pain threshold, as well as the degree of thermal heat that

elicits a suitable intensity of pain (usually 6/10 on a numeric rating scale) for use in future tasks. One such task is within the brain imaging session that occurs no more than 1 week after the sensory assessment. During this task, the participant is administered a range of temperatures around their threshold and is asked to provide ratings for pain intensity and sensation for each temperature. The aim of this task is to investigate pain processing mechanisms within participants and to understand how variations in these neural mechanisms may be associated with individual differences in pain processing taken from other components of the MCAB. Within the imaging session, this is also where resting state data is collected, as well as a detailed T1 anatomical scan.

After the fMRI session, the participant completes an emotional and cognitive assessment, dependent upon a counterbalanced order. The cognitive assessment consists of a numeric Stroop task (Figure 2), whereby the inhibition of a distractor digit is required to provide the correct answer.

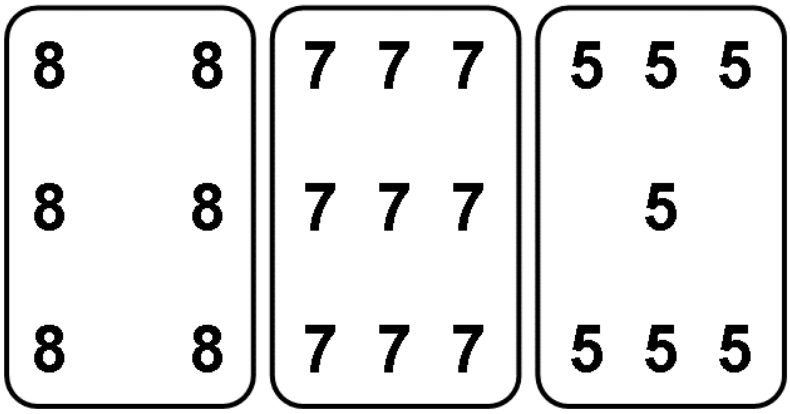

Figure 2*. Numeric Stroop task within the cognitive modulation session of the MCAB. The participant is asked to respond with the highest number of digits across any of the three cards. Within this image, 7 is the distractor number, and the participant is required to answer 9 (the number of digits on the middle card).*

The participant completes a series of trials, with half including the administration of a painful stimulus. The difference between pain and no-pain conditions, regarding accuracy and reaction-time, provide a metric for the efficiency of their cognitive modulatory ability. For the emotional

assessment, participants are asked to view a collection of negative and neutral images from the International Affective Picture System (IAPS; (Lang, Bradley, & Cuthbert, 1997)). During presentation of these images, the participant is administered a painful stimulus and then asked to rate the intensity and unpleasantness of the stimulus. The difference between a participant's ratings within neutral and negative conditions provide an estimate of how emotions influence their perception of pain. Lastly, throughout the duration of the MCAB, a participant completes a series of questionnaires (Figure 1), aimed at quantifying aspects of their psychology which may influence their mechanisms of pain processing and modulation.