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The Psychology of Anxiety & Pain in Fibromyalgia

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THE PSYCHOLOGY OF ANXIETY & PAIN IN FIBROMYALGIA

by

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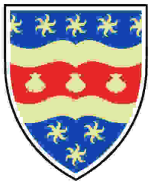

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Author Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

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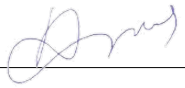
Signed: 

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The Psychology of Anxiety & Pain in Fibromyalgia

Anna Kharko

UNDERSTANDING pain is integral to understanding fibromyalgia, a chronic musculoskeletal pain condition of undetermined aetiology, and for which no single successful medical therapy exists. Most of what is known about fibromyalgia pain comes from psychophysical research of central sensitisation, a phenomenon of abnormally amplified pain following disruptions in the central nervous system. Anxiety has been long theorised to mediate this centralised pain, but its contribution is yet to be characterised.

This thesis presents a multimodal investigation of pain perception under different manifestations of anxiety in both fibromyalgia-diagnosed and pain-free cohorts.

Chapter 3 presented the findings from the first study in the series of PhD research, in which a novel method for gathering pain ratings was tested. Continuous pain report allowed for the extraction of novel measures, which characterised the unique properties of pain processing in fibromyalgia.

Chapter 4 described a study with pain-free participants, in which, for the first time, continuous pain ratings were combined with concurrent modulation and report of experimentally maintained acute anxiety. Results indicated that anxiety evoked through the 7.5% CO_2 Model is associated with an overall decrease of reported pain but not with individual measures, extracted from the pain response.

Chapter 5 further adopted the successful pain and anxiety experimental paradigm and tested its feasibility with fibromyalgia-diagnosed participants. The limited success of the study discouraged further use of the CO_2 Model with that patient population but highlighted the significance of anxiety for that condition.

The final chapter, Chapter 6, explored the role of anxiety under a different taxonomy, as sustained psychological distress evoked by the COVID-19 pandemic. In an observational study, it was revealed that fluctuations in sustained anxiety are mirrored by changes in reported pain intensity.

Together, the findings support that the study of anxiety advances the understanding of fibromyalgia pain processing, and argue for the continued research of both their momentary and long-term interaction for the comprehensive understanding of their relationship.

Keywords: *fibromyalgia, acute pain, chronic pain, acute anxiety, 7.5% CO_2, sustained anxiety, COVID-19*

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Introduction

The wind was not the beginning.
There are neither beginnings nor endings to the Wheel of Time.
But it was a beginning.
*– **Robert Jordan, The Wheel of Time***

M starts her morning with a slow and painful rise from bed. Her arms ache, her legs feel stiff and heavy, her back hasn't stopped hurting all night. She takes a handful of pills and makes breakfast for her family while she waits for the medication to kick in. In her words, the pills "take the edge off the pain". Later, she drives her daughter to school and then goes to work. At work, she can't shake off this nagging feeling that she had forgotten something. Then she remembers; she was supposed to attend a meeting but had already missed it. Yet again she must email her manager to apologise and reschedule. The worry and embarrassment set off a range of new pains and aches so she takes the stronger pills, hoping they will help her focus on her work. They don't but she continues. In the evening, even breathing feels painful and she goes to bed early. The next morning comes and it starts with a slow and painful rise from bed.

This is not an imaginary scenario, M is real and this is her everyday. It is also the Groundhog day for almost 2.8 million patients in the UK who live with fibromyalgia (Jones et al., 2015). Fibromyalgia is not curable. When a cure is not available, management becomes the sole goal. Quality of life is intimately connected with successful symptoms management. For fibromyalgia, chronic

pain is on the forefront.

Great efforts have been dedicated to alleviating anything presumed to exacerbate fibromyalgia pain. In the clinical-psychological approach, depression has been the main target. It is understandable, depressive symptoms will be diagnosed in up to 68% of fibromyalgia patients during their lifetime (Fietta et al., 2007). Then there is anxiety, which has a similar prevalence: 60% are found to exhibit behaviour aligning with clinical diagnosis (Buskila and Cohen, 2007). However, while depression has been well-researched and is readily treated, anxiety is yet to receive the same attention. This is concerning, particularly because patients identify "emotional distress" and "worrying" as leading factors preceding worsening of their pain (Bennett et al., 2007). If the focus of current psychophysiologic research is aiding patients in managing their pain, anxiety must receive due attention.

In this thesis, I studied anxiety and pain processing in fibromyalgia-diagnosed and healthy participants. My main question was: what is the contribution of anxiety to pain perception? I derived from this main question several aims to explore the topic, employing a variety of innovative experimental and observational approaches.

Chapter 1

Literature Review

What's past is prologue,
*—- **William Shakespeare, The Tempest***

ANY chronic pain is trying on the individual who must live with it. Fibromyalgia, however, is a particularly hard condition due to the poor understanding of its symptoms. This impacts upon its long-term management. A rigorous investigation of the contribution of anxiety to the experience of pain must be grounded in a thorough consideration of key concepts. In this chapter, I describe what fibromyalgia is and what challenges it presents to patients and experts. I discuss theory of anxiety and how it is connected to pain perception. In the end, I present the most recent findings on the relationship between anxiety and pain processing in fibromyalgia, emphasising unexplored questions.

1.1 Fibromyalgia

Fibromyalgia (FM) is a chronic widespread pain condition, diagnosed in 2 – 10 % of the general population (Walitt et al., 2015a; Wolfe et al., 1995; McBeth and Jones, 2007; Queiroz, 2013), with females historically being three times more likely to receive the diagnosis (Clauw, 2014). Patients with FM experience a considerable number of medically unexplained symptoms, rendering not only

diagnosis but long-term symptom management challenging.

1.1.1 Symptomatology

Cardinal Symptoms

The most well-known FM symptom is the chronic, widespread, nonspecific **pain**, described by patients as predominantly emerging in deep tissue such as muscles (Clauw, 2014) but also joints and ligaments (Leavitt et al., 1986). The pain cannot be linked to structural damage (Häuser et al., 2009b). A variety of descriptors appear to be applicable to FM pain: it can range from "tender" and "aching" to "burning" and "stabbing" (Clauw, 2014; Söderberg and Norberg, 1995). This variability in description demonstrates an important quality of FM pain, and that it is unique both to the individual and the moment, continuously fluctuating in intensity seemingly unprovoked. It is not localised in any one body area nor is it unilateral; however, one body side is commonly reported as being more affected than the other. In that, it resembles rheumatic conditions, such as rheumatoid arthritis (RA) (Leavitt et al., 1986).

Another core FM symptom is **chronically disturbed sleep**. This may include: difficulty in falling asleep (insomnia) or remaining asleep (fragmented sleep); high arousal during sleep (vigilance) (Harding, 1998; Roizenblatt et al., 2001); prolonged phase of superficial sleep, as evident in the alhpa intrusions of non-REM sleep (Roizenblatt et al., 2001); and most commonly, non-restorative sleep ending with severe muscle stiffness in the morning (Arnold et al., 2019). Sleep disordered breathing is also prevalent in FM patients. Up to 70% of patients are diagnosed with obstructive sleep apnea (Roizenblatt et al., 2001). Restless leg syndrome is less common (up to 30%) but it is a leading complaint for poor sleep in FM (Stehlik et al., 2014).

Considering the poor course of sleep, it is unsurprising that the next most reported concern for patients is chronic **fatigue**. It is described as extreme tiredness, which cannot be relieved by rest nor diminished by typically prescribed medication (Guymer and Clauw, 2002; van Houdenhove and Egle, 2004). Chornic fatigue is pervasive in FM, with an estimated 80% of patients meeting the diagnostic criteria for chronic fatigue syndrome (CFS) (Mease, 2005). Fatigue also interacts with other FM symptoms. It has been found to have a mediational role in the dysfunctional cycle between non-restorative sleep, fatigue and heightened pain (Zautra et al., 2007).

The last cardinal symptom is mental fog, an informal term, popularised by patients and adopted by researchers to denote a constellation of **mild cognitive impairment** symptoms (Kravitz and Katz, 2015). These include hypervigilance (González et al., 2010), poor visuospatial working memory (Pidal-Miranda et al., 2018), poor long-term memory retrieval (Grisart et al., 2002), and reduced information processing speed (Bar-On Kalfon et al., 2016).

While these symptoms are central to FM, they do not exhaust the long list of clinical manifestations associated with the syndrome. FM patients are so heterogeneous as a group, that this heterogeneity has become key to differentiating it from other chronic musculoskeletal pain conditions (Arnold et al., 2019; Gostine et al., 2018). Diffused chronic pain, non-restorative sleep, fatigue and dyscognition are the hallmark somatic symptoms of FM but there are more.

Somatic Symptoms

In truth, the pool of somatic symptoms is so diverse yet so consistent that some experts consider FM a *functional somatic syndrome* (Mayou, 2002). 'Functional somatic' refers to the disturbance in bodily functioning and avoids assumption

of the origin of such disturbance. While the term is met with resistance both by researchers and patients due to the agnosticism of symptoms origin, it does highlight the complexity of FM symptomatology. Apart from the mentioned, common somatic symptoms in FM include: irritable bowel (Kurland et al., 2006), vertigo (Koca et al., 2018), paresthesia (both as 'pins and needles' and numbness) (Hawkins, 2013), muscle weakness (Arnold et al., 2011), muscle spasms (Bennett et al., 2007), tinnitus (Bayazıt et al., 2002), and impaired thermoregulation (Pardo et al., 2019). One common diagnostic tool for FM lists 56 somatic symptoms (Wolfe et al., 2010), none of which are clinically unique (Silverman et al., 2010), leaving syndrome definition a topic of heated debates for the medical community (e.g., Cohen, 2017). In contrast, some great strides have been made in recent years in psychophysiology.

Psychophysiologic Symptoms

One of the most well-researched aspects of FM is the generalised hyperexcitability to sensory stimuli. This includes an amplified perception of both innocuous sensations such as light, sound or smell (Wilbarger and Cook, 2011; Ten Brink et al., 2020), as well as of noxious stimuli (Petzke et al., 2003). The exaggerated pain response is termed **hyperalgesia**. In FM it occurs at sites without tissue damage (Banic et al., 2004), unlike in neuropathy. It is observable through self-reported pain ratings, which are heightened in patients unlike their pain-free counterparts (Meeus and Nijs, 2007). Hyperalgesia of pain has been observed across all stimulation modalities: heat and cold (Gibson et al., 1994; Stevens et al., 2000), muscle and bone pressure (Mikkelsson et al., 1992), and electrical stimulation (Banic et al., 2004). Imoprtantly, hyperalgesia has also been confirmed through neurophysiologic measurements of nociceptive response (Desmeules et al., 2003). Lowered pain tolerance is also frequently

detected in FM and has been ascribed to hyperalgesia (Gracely et al., 2003).

Another prominent psychophysiologic marker of FM is **allodynia**, the perception of an innocuous sensation as noxious. It is evident in the lowered intensity threshold necessary to evoke a painful response (Cervero, 2009). Some evidence exists to suggest that in FM allodynia may be stress-modulated (Crettaz et al., 2013), but at the very least it is considered to reflect pathology in the plasticity of the central nervous system (CNS) (Meeus and Nijs, 2007).

By far the most well-researched physiologic symptoms of FM is **wind-up (WU)**, which is the frequency-dependent increase in the excitability of dorsal horn neurons at spinal level (Price et al., 1977). WU is a CNS mechanism that is triggered by repetitive stimulation of C-fibre nociceptors, for example through mechanical pricking or electrical stimulation, which gradually elicits a higher number of action potentials per stimulus (Gebhart and Schmidt, 2013). The resulting sensation is regarded as painful and its magnitude has been postulated to reflect endogenous pain modulation (Gracely et al., 2003). The measurement of WU can be used as an informative tool. Comparison between pain-free individuals and patients with some primary musculoskeletal diagnoses finds an augmented WU in the latter, suggesting a deficiency of central pain mechanisms (Latremoliere and Woolf, 2009). The same has been observed in FM.

WU has been central to FM as it has furthered the understanding of the syndrome's pain aetiology. It has allowed differentiating FM from other chronic pain conditions such as neuropathy by demonstrating that the origin of the dysfunctional pain processing is not in the periphery Nielsen and Henriksson (2007). A phenomenon directly related to WU has allowed quantifying the hyperalgesia and allodynia in self-reported pain. It is called temporal summation (TS) and is considered the behavioural equivalent of WU (McMahon et al., 2013). In

a similar fashion, TS is evident through the increase of pain ratings to objectively unchanged noxious stimulation (McMahon et al., 2013). To understand research on WU and TS in FM, an overview of the current leading theories of FM pain aetiology is necessary.

1.1.2 Aetiology

The described hyperexcitability phenomena have been interpreted as indicative of *central sensitisation*, a term which denotes the presumed origin of FM chronic pain: the CNS. Sensitisation to a prolonged noxious stimulus is normal (Nielsen and Henriksson, 2007). It is the pathological expression of central sensitisation that is considered the driving force for the FM chronic pain. In that context, central sensitisation is the augmented synaptic efficacy of dorsal horn neurons, which produces pain hypersensitivity, lasting beyond the conditioning stimuli (Woolf, 2011). Unlike WU, in central sensitisation the resulting hyperexcitebility maintains an amplified perception of the peripheral input. This means that the arising sensory response is no longer reflective of the noxious stimuli but is instead a product of the CNS (Latremoliere and Woolf, 2009). Further, in central sensitisation, the presence of the noxious stimulus is not necessary to maintain the painful experience (Woolf, 2011). These conclusions were not always agreed upon and became a major breakthrough for those clinical conditions, where chronic pain was observed beyond the timeline of supposed tissue restoration (Woolf, 2011). The redefined view of pain transformed how prominent musculoskeletal conditions are viewed, including FM.

Early evidence supporting that FM is a syndrome of central sensitisation came from Gibson et al. (1994) and Lorenz et al. (1996), who observed allodynia and hyperalgesia through self-reported pain ratings and amplified evoked potentials. However, the most convincing support comes from a series of studies started

Table 1.1: Research on Enhanced Temporal Summation (+TS) in Fibromyalgia

No evidence for +TS (n = 1)	**Inconclusive Evidence** (n = 7)	**Evidence for +TS** (n = 9)
Lim et al. (2016)	Staud et al. (2005)	Staud et al. (2001)
	Staud et al. (2008)	Price et al. (2002)
	Desmeules et al. (2003)	Staud et al. (2003a,b)
	Staud et al. (2014)	Staud et al. (2007a)
	Coppieters et al. (2015)	Klauenberg et al. (2008)
	Schreiber et al. (2017)	Craggs et al. (2012)
	Potvin et al. (2012)	Kim et al. (2015)
		Hilgenberg-Sydney et al. (2016)

in 2001 by Staud et al.. In them, FM patients regularly appear to produce increased TS of pain ratings, higher than that observed in healthy controls, thus indicating deficient pain inhibition (Price et al., 2002; Staud et al., 2003a,b). An independent meta-analysis has largely supported that conclusion but has pointed to some methodological concerns (O'Brien et al., 2018). In fact, a closer look at the literature reveals a high number of incongcruent findings. While some studies have found definitively that TS was enhanced in the clinical samples when compared to controls (see Table 1.1), others, who experimented with nociceptive protocols, have found that elevated TS was largely dependant on the testing paradigm. Several factors may be at play, such as the operational definition of TS or the choice of noxious stimulation. An in-depth discussion of this will follow in Chapter 3.

Although research on WU and TS have supported the notion that central sensitisation is the main mechanism that sustains pain chronicity in FM, the question of what sets off the dysfunction remains unanswered. Several theories exist, stemming from findings of various deficiencies or abnormalities in patients. Such is the theory about **substance P**, a neuropeptide involved in the

regulation and transmission of nociception (Harrison and Geppetti, 2001). It has been found to be elevated in FM (Russell et al., 1994), unlike in CFS, a symptomatologically similar condition, often conflated with FM in clinical practice (Evengard et al., 1998). Another popular theory is that of **aberrant regional cerebral blood flow** based on the observations of decreased flow to the thalamus (Kwiatek et al., 2000), as well as the bilateral dorsolateral prefrontal cortex (Johansson et al., 1995), among other cortical structures (Guedj et al., 2008). Here, as noted by Mease (2005), it is however unclear how these alterations enable FM chronic pain. One long-standing theory that does provide a mechanistic framework is the theory of dysfunctional reactivity of the stress response system.

Pathological Stress Response System Theory

When an individual is exposed to a stressor a complex reaction is triggered by the stress response system (see Figure 1.1). It comprises of the neuroendocrine system hypothalamic–pituitary–adrenal axis (HPA axis) and the autonomic nervous system (ANS). Together they launch a coordinated chain reaction of physiological changes to provide a merited response to the stressor.

The HPA axis comprises of the hypothalamus, the pituitary gland and adrenal glands. Each organ of the network secrets a hormone, thus offsetting a multifactorial response to a stressor, which may range from an aversive stimulus such as pain to cardiovascularly challenging stimuli such as physical strain (Van de Kar and Blair, 1999). Starting with the hypothalamus, which releases corticotropin-releasing hormone (CRH) as the first response of the HPA axis to a perceived or real stressor. The anterior pituitary gland, stimulated by CRH, secrets adrenocorticotropic hormone (ACTH), which in turn promotes the release of cortisol by the adrenal cortex. Importantly, the HPA axis is not unidi-

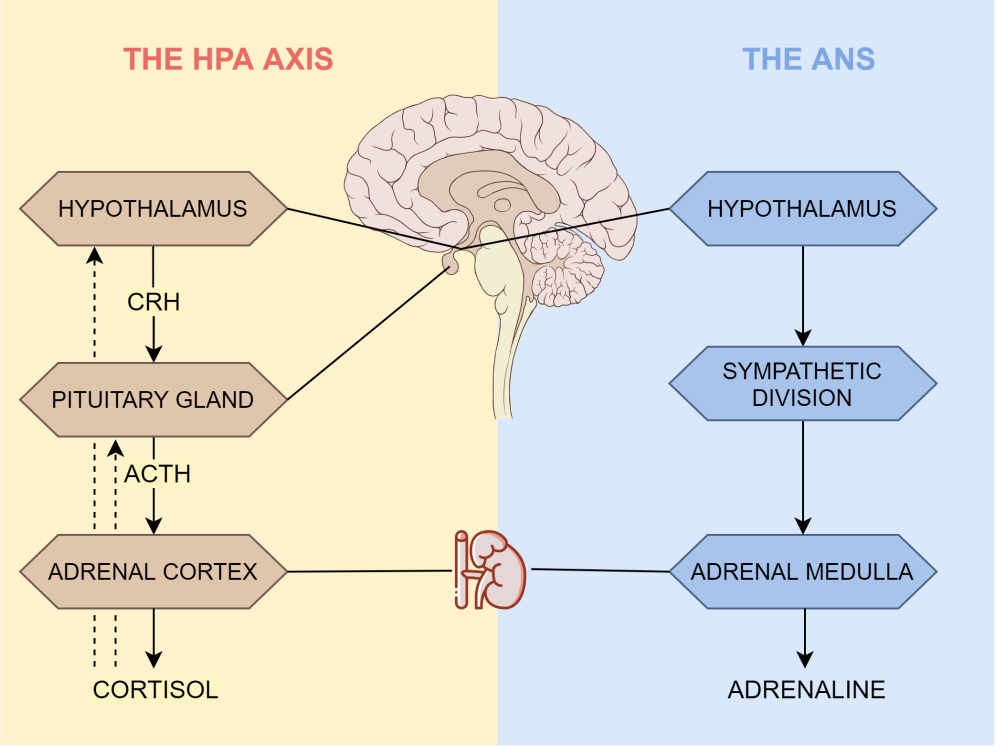

Figure 1.1: The Stress Response System. *HPA axis* – The hypothalamic–pituitary–adrenal axis; *CRH* – corticotropin-releasing hormone; *ACTH* – adrenocorticotropic hormone; *ANS* – the autonomic nervous system. Saggital view of the brain created by Patrick J. Lynch, medical illustrator, under CC BY 2.5 license, Wikimedia Commons. Adrenal gland illustration made by Smashicons, Flaticon.

rectional. The increase in cortisol sends inhibitory signals to the hypothalamus and the pituitary gland to decrease their hormones production. Cortisol is vital to daily functioning, and when produced abnormally, it has been linked to widespread inflammation (Hannibal and Bishop, 2014), fatigue (Powell et al., 2013), and disrupted sleeping cycle (Payne, 2004).

The ANS similarly engages several reactions following exposure to a stressor. It includes the activation of the sympathetic nervous system (responsible for the 'fight or flight' response) and the inhibition of the parasympathetic nervous system (responsible for the 'rest and digest' response). The ANS controls the

secretion of both cortisol and adrenaline by the adrenal glands, which have broad effects on the cardiovascular, respiratory and gastrointestinal systems. These effects are stressor-dependent thus they are maintained to some degree during prolonged stress exposure (Ziegler, 2004).

There are several factors pointing to insufficiencies of the stress response system in FM. In research on the HPA axis, FM patients have been found to exhibit mild hypocortisolism (low cortisol production levels) in response to an acute stressor (Wingenfeld et al., 2008), also observed in daily urinary free cortisol values (Crofford et al., 1994). Other detected abnormalities in HPA axis have also been confirmed to be functional and not structural, primarily related to the hypothalamus (Holtorf, 2007). Similar pathological functioning has been found in studies on the ANS. For instance, FM patients have been observed to have poor nocturnal heart rate variability, which is an indicator of ongoing hyperactivity of the cardiac rhythm, similarly to the hyperactivity present during stress (Martinez-Lavin, 2007). These clinical assessments of the ANS have led some to term FM a sympathetically-maintained pain syndrome (Martinez-Lavin, 2007).

The abnormal stress response in FM has been postulated to produce hyperalgesia and allodynia through long-term changes in muscle nociceptors (Crettaz et al., 2013), though others argue a direct stress-pain route (Bansevicius, 2001). In terms of central sensitisation, it is also highly debated whether the disrupted stress response elicits it (Wood, 2004) or stems from it (Nielsen and Henriksson, 2007). Some research suggests that early life traumatic experience such as psychological or physical trauma coincides with onset of chronic pain (Cedraschi et al., 2013). Nonetheless, almost uniformly experts agree that the presence of abnormal stress reactivity is a key characteristic of the syn-

drome profile (van Houdenhove and Egle, 2004). Still, it has not made FM diagnosis easier.

1.1.3 Diagnosis

The topic of diagnosis may be a conversation starter for patients but it has become a point of contention for clinicians. Surprisingly, the vast inconsistency of medically unexplained symptoms is only partially responsible for this. FM has been stumping the medical community from as early as the 18th century when it was referred to as *non-deforming musculoskeletal rheumatism* (Block, 1993). Later, in an attempt to differentiate it from other painful musculoskeletal conditions, the term *fibrositis* was coined (Gowers, 1904). The new name came with a new theory that FM stems from muscular inflammation. A very prominent study at the time even supported that notion by reporting supposed evidence for biological deformations (Kelly, 1946; Stockman, 1904). We now know that no such process is detectable (Elert et al., 1992; Bengtsson, 2002; Yunus et al., 1989; Yunus and Kalyan-Raman, 1989); however, for a long time clinicians attempted to diagnose the condition looking for this non-existing deformity. The attitude toward the condition further deteriorated during the World War II when army clinicians presented with chronic pain and what they then called *shell shock*, linked both together in claiming that the widespread pain is driven by profound psychological distress. That is when a new name emerged: *psychogenic rheumatism* (Halliday, 1937a,b). No real progress was made in terms of defining and diagnosing FM until the colossal efforts of several prominent researchers (for an engrossing historical review see Inanici and Yunus, 2004).

In the Past

FM, as we know it today, was conceptualised by Smythe (1972), whose work prepared the foundation for the first widely accepted diagnostic tools. At the same time, the syndrome received its current name thanks to Hench (1976). The new name came with reignited medical and research interests. Wide recognition of the condition was still challenged by the lack of an exclusive and definitive diagnosis. In response to that, Yunus et al. (1981) created the first clinical protocol, which allowed to not only diagnose FM based on previously compiled symptom pool but to also exclude similar overlapping conditions. Then in 1990, the American College of Rheumatology compiled its own list of criteria, which integrated physical examination with patient history. As the lead investigator later noted, the American College of Rheumatology Criteria for Fibromyalgia from 1990 (ACR'90) was only ever intended as a research tool to confirm the diagnosis in an experimental setting. However, likely the physical aspect of the protocol made it familiar to clinicians and solidified FM as a real, diagnosable condition (Staud et al., 2010). ACR'90 required the continuous presence of widespread non-specific pain simultaneously in several bodily areas: left and right side of the body, pain above and below the waist (Wolfe et al., 1990). It also required the researcher, and as it later became the physician, to apply moderate pressure on 18 predetermined points across the body (see Figure 1.2). These were called tender points, following historical naming convention, and were chosen as the supposedly optimal points to examine FM allodynia.

ACR'90 reduced diagnostic times and even allowed to quantify the severity of FM but it also introduced new problems. The palpating approach depended on patient's rating of the sensation as painful. This inadvertently created bias:

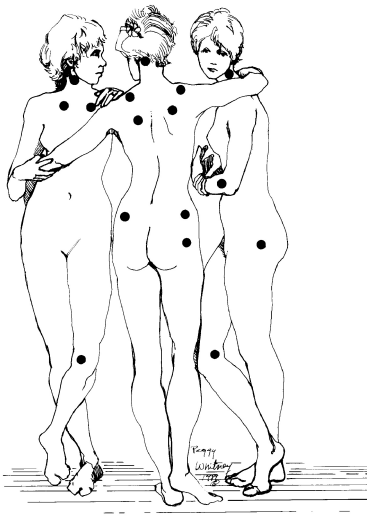

Figure 1.2: The Fibromyalgia tender points depicted on the Three Graces. Adapted from Wolfe (1990).

males were far less likely to report such pressure as painful (Yunus et al., 2000). Male patients were thus underdiagnosed, by some estimates bringing the ratio to as little as 1:12 males to females (Jones et al., 2015). To this day, FM is widely considered a female-predominant condition, stigmatising its diagnosis and treatment in males (Muraleetharan et al., 2018). Perhaps most strikingly, tender points are not unique to FM, rendering them futile in differential diagnosis (Cohen, 2017). The ACR'90 also did not assess the presence of other cardinal symptoms, such as disrupted sleep and cognitive dysfunction (Wolfe et al., 2010). The quality of the assessment also depended on the physician, who had the choice of administering the pressure manually or through a dolorimeter. Ultimately, it was never intended as a clinical diagnostic tool but was adopted as such out of necessity. The scope of what it could tell a physician about the patient's well-being was limited and yet again, doubts over the existence of FM were cast.

Present

At present, FM diagnosis remains a challenge but significant improvements have been made. The adoption of the American College of Rheumatology Criteria for Fibromyalgia from 2010 (ACR'10) and the American College of Rheumatology Criteria for Fibromyalgia from 2016 (ACR'16) has reconceptualised the core description of FM. Instead of physical examination of tender points, the patient's account of recently experienced pain, fatigue, non-restorative sleep and "fibrofog" are central. Appropriate laboratory tests are administered to exclude similarly presenting conditions, e.g. hypothyroidism or a rheumatic disease (Arnold et al., 2019; Arnold and Clauw, 2017). Importantly, the history of disease progression and management up to that point are key. As noted by an expert committee in one study (Häuser et al., 2009b), the steadiness of various somatic symptoms, the lack of typical response to medication and the influence of psychosocial stressors on the worsening of symptoms, are all strong indicators of FM. Despite the expert agreement on the importance of the relationship between mental and physical well-being in FM, treatment strategies do not necessarily reflect that.

1.1.4 Treatment

An effective long-term treatment plan for FM is alike to a white-whale hunt. The large volatile symptomatology pool renders a standardised treatment approach unfeasible. Instead, management of core patient complaints is advised (Peterson, 2005). For pain these can be **pharmacological therapies** that either inhibit facilitatory neurotransmitters: gabapentinoids, e.g. gabapentin, pregabalin (Häuser et al., 2009a); or promote inhibitory neurotransmitters: selective serotonin reuptake inhibitors (SSRIs), e.g. sertraline, fluoxetine (Walitt et al., 2015b; Arnold et al., 2002), serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g.

duloxetine, milnacipran (Welsch et al., 2018) or tricyclic antidepressants (Arnold et al., 2000). Other medication such as opioids are commonly prescribed despite the low clinical significance (Painter and Crofford, 2013). Some research even suggests that they can worsen hyperalgesia in FM (Fitzcharles et al., 2011). Easily available analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids have not been found effective for most users (Okifuji et al., 2016). Muscle relaxants (e.g. cyclobenzaprine) are also common with some promising results (Tofferi et al., 2004). No single drug provides sustainable long-term effective analgesia, resulting in dose escalation and regular adjustments of drug combination (Wolfe et al., 2013). To note, some medication elicit complex side effects, enabling further medication prescription.

To avoid these complications, **non-pharmacological therapies** are also typically advised for pain management. These include pain education (Van Oosterwijck et al., 2013), cognitive-behavioural therapy (Bernardy et al., 2010), or low intensity exercise such as aquatic exercise or Tai Chi (Häuser et al., 2010a). Psychology-based interventions show some long-term benefits (Thieme and Gracely, 2009); however, meta-analyses of randomised-controlled studies fail to find consistent improvements (Hassett and Gevirtz, 2009). Behavioural interventions are further met with resistance from patients. This is in part due to the limited benefits and high costs (Briones-Vozmediano et al., 2013) but also due to fears over stigmatisation ((Peterson, 2005), see Section 1.2.1). A recent review of treatment guidelines for FM found that behavioural interventions with adjunctive pharmacological therapies yield the most benefits for the patient (Kia and Choy, 2017).

Still, an expert agreement is lacking in regards to pain management in FM.

A recent review of international guidelines found that suggested patient care protocol is skewed by the speciality of the advising experts (e.g. rheumatologist vs psychiatrist) (Häuser et al., 2010b). Different specialists offer different strategies to the patient; however, referral to these specialists is only initiated in pressing circumstances, such as uncertainty of diagnosis or profound psychiatric disturbance (Clauw, 2014). This is of high importance since attendance to non-pain complaints has been found to benefit chronic pain management (Sancassiani et al., 2017). For this reason, alternative treatment options are continuously trialled.

A recent survey found that most patients feel that they lack control over their healthcare plan (Briones-Vozmediano et al., 2013) and report high dissatisfaction over their inability to settle on one effective therapeutic approach (Valentini et al., 2020). These are only some of the many challenges faced by FM patients.

1.2 Challenges in Fibromyalgia

1.2.1 Patient Perspective

"It is all in your head!"

The complex history of defining FM is reflected in the persisting scepticism towards the syndrome. Receiving the diagnosis is hindered by ongoing stigmatisation. FM is highly comorbid with Axis I diagnoses (Uguz et al., 2010), for example with depression. Depending on the measurement approach, it is observed in 14 – 65 % of patients (Kurland et al., 2006; Løge-Hagen et al., 2019; Uguz et al., 2010). It is true that somatisation of depression exists; however, research has decisively dismissed that FM is a depressive syndrome (Ahles et al., 1987). Still, the notion that FM is a clinical manifestation of an underlying

psychiatric issue maintains (Abeles et al., 2007). This attitude is even seen outside of the expert community, in the family members of FM patients (Juuso et al., 2011).

As a result, many FM sufferers distance themselves from discussions of their mental health, even when seeking healthcare support (Kool et al., 2009).

Patient Disregard

A closely related problem is disregard for the patient's account of their own condition. Due to the medically unexplained basis of their symptoms, FM patients are often dismissed as malingering (Belenguer-Prieto et al., 2013). In fact, common tools aimed at detecting illness simulation overdiagnose such in FM (Palmer et al., 2013). Some researchers have even proposed that ceasing discussions about the condition in medical and social settings will dematerialise it similarly to 'hysteria' or 'Gulf War syndrome' (Hazemeijer, 2003). This dangerous narrative discounts patients' expertise of their own condition, which is well-documented to negatively affect healthcare outcomes (Bieber et al., 2006).

Invalidating the knowledge of FM patients on their condition is in direct opposition to the patient-governed treatment approach that is advised by experts (Peterson, 2005).

Poor Prognosis

Since no cure for FM exist, long-term symptom management following patient preferences is the single most important healthcare aim (Daraz et al., 2011). Management of pain and prevention of flare-ups is a central request in the doctor's office (Pastor-Mira et al., 2019). Traditional pharmacological therapy for chronic pain yields mixed results (Rossy et al., 1999), as no single medication appears to have long-term benefits (Kia and Choy, 2017). This is further com-

plicated by the variance of symptomatology due to age and diagnosis duration (Cronan et al., 2002). Together, these factors developed a sense of anxiety over future self-autonomy (Raymond and Brown, 2000).

Patients are thus continuously seeking out new treatment strategies (Valentini et al., 2020).

1.2.2 Expert Perspective

Poor Patient Rapport

Challenges in FM are recognised by experts as well. Just as patients, clinicians describe the doctor-patient relationship as poor (Åsbring and Närvänen, 2003). It is unsurprising. Rheumatologists report frustration over continuously returning patients (Crofford and Clauw, 2002), with some avoiding working with them altogether (Wolfe et al., 1997). This is concerning because poor rapport is related to poor prognosis (Bieber et al., 2006). With the shift from *'doctor's notes are absolute'* to shared decision-making between patient and doctor, conditions with medically unexplained symptoms introduce discord to that relationship. For example, Dobkin et al. (2003) found that physicians regularly underestimated the satisfaction of FM patients with their visit.

Medical professionals need guidance on how to attend to their FM patients.

Poor Understanding of the Condition

In the medical community, it is regarded that only rheumatologists possess sufficient knowledge to diagnose and research the syndrome. But even they point to insufficient training (Briones-Vozmediano et al., 2013). This is concerning, as FM is very prevalent: it is estimated that in the UK alone 2.8 million individuals hold the diagnosis (Jones et al., 2015). In comparison, RA, which is another chronic musculoskeletal condition affecting a similar demographic, is

estimated to in 400,000 of the UK population (Siebert et al., 2016). Nonetheless, compared to RA, a much higher rate of discordance is observed between FM patients and their therapists (Hidding et al., 1994). Part of the issue may be due to limited training. Doctors themselves agree that further education on FM is necessary (Briones-Vozmediano et al., 2013). Research has shown the benefits of such. For example, Potts and Silverman (1990) point out that physicians, who endorsed new research-based treatment options and focused on patient mental health, had better-adjusted patients.

Medical professionals need guidance on what to focus on when treating FM patients.

High Rate of Comorbidities

Lastly, a major challenge in FM is the high rate of comorbid conditions (Wolfe et al., 1997). The variability of concurrent ailments hinders the treatment of FM itself as every new complaint is attributed to it (Bass and Henderson, 2014). Some conditions are particularly prevalent, such as disorders of mental health. It is well-established that psychological well-being is linked to chronic pain (Turk and Monarch, 2002). In FM, emotional dysregulation has been documented but perhaps in an attempt to avoid previously stigmatised view that FM is of psychiatric origin, it is cautiously approached (Cohen, 2017). By far, the most commonly research aspect of mental health in FM is depression. This is likely because outside of FM the impact of depression on chronic pain is well-understood (Bair et al., 2003; Fishbain et al., 1997).

However, what about other mental health states? Upon closer investigation, FM sufferers persistently cite "emotional distress", "worrying", and "stress" as leading triggers for pain (Bennett et al., 2007). These descriptors closely follow

the concept of anxiety. Further, it has been demonstrated that anxiety contributes to FM pain independently from depression (Kurtze et al., 1998; Kurtze and Svebak, 2001).

Due to historical focus on depression, however, research on ***how*** *anxiety contributes to FM pain has been sparse. In the context of the described challenges, a deeper understanding must be developed for the potential benefit of managing FM symptoms.*

1.3 Anxiety

Before discussing what is known about anxiety in FM, key concepts and theories about anxiety itself must be discussed.

1.3.1 What is Anxiety?

Anxiety is a multidimensional construct, associated with a range of psychophysiological, behavioural, and clinical states. Some consider anxiety a product of evolutionary adaptation, designed to guide us through uncertainty, and an inherent coping mechanism for facing aversive events (Maner, 2009). Others, follow a more fine-grained approach and distinguish between different modalities of anxiety based on its expression, e.g. phasic or stable (Spielberger, 2013). One thing is certain, anxiety is the presence of high arousal and negative affect, which may or may not be linked to a direct aversive stimulus (Woo, 2010).

There are many theories that deconstruct this definition of anxiety in accordance with their research context. For example, some advocate for a distinction between anxiety and fear (Grillon and Baas, 2003), while others use the terms anxiety, fear and stress interchangeably. In this section, I will discuss those theorised dimensions of anxiety that are relevant to the contents of the thesis,

giving a nod to related concepts where appropriate but without their in-depth review.

Dispositional & Acute Anxiety

One of the most long-lived taxonomies of anxiety is that of the state vs trait framework (Spielberger, 2013). In it, anxiety is divided based on its presumed origin. Primarily, state anxiety is described as a mood state that is transient and reactive to context, while trait anxiety is a person's disposition or personality characteristic that is relatively stable Eysenck (2010). Further applications of the framework, however, have expanded the definitions, reflecting the mountainous research on it. Broadly, state anxiety is the acute experience of high arousal, marked by distinct psychological and physiological changes, which are in response to perceived imminent or diffused danger. Trait anxiety encompasses not only the personality trait but the general disposition and attitude that acts as a baseline for the response toward an aversive event. For these reasons, state anxiety is synonymous with acute, transient or momentary anxiety, and trait anxiety is interchangeable with general and dispositional anxiety.

The trait vs state dichotomy has been successfully adopted in the field of cognition, where anxiety is commonly explained as an attentional control mechanism (Eysenck et al., 2007). Notably, most research has focused on dispositional anxiety and not state since the latter is challenging to *evoke* experimentally. Traditional approaches to inducing acute anxiety include imagining a stressful event or its reenactment with confidants, Pavlovian conditioning, or unpredictable administration of noxious stimulation (Grillon, 2007), the latter of which raises some ethical concerns. Almost all of these methods rely on participant compliance and do not produce stable effects (further discussion in Chapter 4). Respectable progress has been made though in the development of robust

anxiogenic methods, one of which will be presented in Chapter 2.

In contrast, *measurement* of acute and dispositional anxiety has been more successful. Subjective measures of both include self-report questionnaires (Julian, 2011): Hamilton Test for Depression & Anxiety (Zigmond and Snaith, 1983), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1999), State–Trait Inventory for Cognitive and Somatic Anxiety (STICSA) (Roberts, 2013). Objective markers include physiological measures such as heart rate, blood pressure, respiratory rate, diaphoresis, cortisol levels, pupil dilation and even acoustic perception (Mattys et al., 2013).

Clinical Anxiety

Apart from having an anxious disposition or state, one can experience clinically significant levels of anxiety. These refer to psychiatric conditions that are divergent from a personality trait or a temporary state but not independent of them (Cisler et al., 2010). Generalised anxiety disorder (GAD), for instance, can not only increase vulnerability to dispositional anxiety but prolong state anxiety (Newman et al., 2013).

Compared to other psychiatric diagnoses, for example, mood disorders such as major depressive disorder or bipolar disorder, anxiety diagnoses have the highest lifetime rate of 5.7% – 16.6% in the general population (Newman et al., 2013; Somers et al., 2006). The range shifts depending on specific diagnosis. The most widespread is GAD with an estimated lifetime rate of 6.2%, followed by any specific phobia – 4.9%, social phobia – 2.5%, post-traumatic stress disorder (PTSD) – 2.1%, and panic disorder (PD) – 1.2% (Somers et al., 2006). Despite different prevalences, all anxiety disorders have high familial aggregation risks (Hettema et al., 2001)

Any anxiety disorder can have a considerable impact on the individual. In otherwise healthy populations, clinical anxiety is associated with reduced quality of life, irrespective of a particular diagnosis (Olatunji et al., 2007). Furthermore, anxiety disorders are highly comorbid with other clinical states, particularly chronic pain (Hooten, 2016), in which it is associated with meaningful changes in physical well-being (further discussed in Section 1.3.2).

In anxiety research, the presence or severity of a given anxiety diagnosis is measured mainly through disorder-specific scales. For GAD, these could be the GAD-IV Scale (Newman et al., 2002) or the GAD-7 Scale (Spitzer et al., 2006). Still, generalised tools aimed at detection of any anxiety disorders are also popular and particularly useful for detection of undiagnosed comorbidities. The most popular such scale is the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998), which provides reliable measures of clinical diagnoses in a research environment.

Sustained Anxiety

Separating an inherent anxiety characteristic from the momentary experience of anxiety is the most widely accepted approach to researching anxiety. However, it is not necessarily the best one. As Moser et al. (2011) explained in their study on anxiety and coronary heart disease, in itself state anxiety is transient and when measured at one time point, the experience of it is affected by the context. For example, in one instance, reported state anxiety may be found to correlate with hypertension but in another, the individual may employ better coping mechanisms and thus their acute anxiety subsides. This is a normal variance but it complicates the study of state anxiety. Singular measurements of an acute sate not only do not generalise well but are also not representative of how we experience anxiety.

Anxiety can occur acutely but it can also persist. Research on risks associated with the development of coronary heart disease has long acknowledged the detrimental effects of such anxiety (Paterniti Sabrina et al., 2001). Beyond one's disposition, a person can experience periods of sustained or persistent anxiety. Alike to state, sustained anxiety encompasses the behavioural and physiological reactions to a stressor. Unlike the state, it persists while the anxiogenic event is psychologically or physically distant (Davis et al., 2010), with no present cue (Hasler et al., 2007) but still continues to have an impact, consistent with that from negative affect (Lee et al., 2015). In a laboratory setting the event could be the promise of a noxious electric shock (Grillon, 2008) or an innocuous airblast to the eye (Grillon et al., 2004), in naturalistic setting – a pandemic. Sustained anxiety is measured through scales typically used for state anxiety (Bayrampour et al., 2015) or through those that assess anxiety over long periods of time, such as the Profile of Mood States Short Form which covers week-long periods (Armer et al., 2018).

An argument for sustained anxiety being different from its transient counterpart has also been made in neuropsychopharmacology (Grillon et al., 2006), for instance, by Davis et al. (2010), who proposed a working model of acute vs sustained anxiety. To note, their research adopts a different nomenclature that was alluded to at the start of the section. In it, acute anxiety is referred to as fear, while sustained anxiety as anxiety. To complicate matters further, elsewhere, sustained anxiety is sometimes referred to as sustained or contextual fear. The naming convention (anxiety vs fear) relies on nuanced differentiation between the two, which is a highly debated topic (Grillon, 2007). It is acknowledged but avoided in the present work for the sake of brevity and consistency.

Finally, sustained anxiety is different from clinical manifestations of anxiety, in

which an exaggerated anxious response maintains as a result of a chronic pathological mechanism. For example, in PD the recurrence of panic attacks is the hallmark presentation of clinical anxiety, but a diagnosed individual can still experience sustained anxiety due to apprehensive anticipation of panic attacks (Grillon, 2002, 2007).

1.3.2 Anxiety & Pain

The view that the magnitude of reported pain must be proportionate to an objective lesion is outdated. Today, we accept that pain is a private experience, shaped by psychosocial and environmental factors in addition to possible biological processes such as tissue damage (Raja et al., 2020). This is known as the biopsychosocial model of pain (Gatchel et al., 2007). An essential part of the psychological component are affective states, one of which is anxiety. Anxiety, be it as a state/trait construct or a psychiatric disorder is widely accepted as one of the most common concomitants to pain (McMahon et al., 2013), though no such consensus is observed when discussing the direction of the relationship between the two. Whether anxiety is associated with increased or decreased pain is a broad topic for debate (Lumley et al., 2011).

Anxiety & Acute Pain

When considering acute pain, the answer is not straightforward. In pain-free individuals, experimentally evoked **state anxiety** appears to increase self-reported pain, but this depends on the method of induction. Some studies have found that acute anxiety evoked through pain-related or unrelated instructions leads to higher pain ratings than non-anxiogenic control instructions (Cornwall and Donderi, 1988; Al Absi and Rokke, 1991), implying the causal strength of acute distress.

The effect, however, seems to be more nuanced upon further investigation. Manipulating attention alongside state anxiety may modulate the painful response. This has been demonstrated in paradigms where the magnitude of state anxiety is manipulated: low vs high (Arntz et al., 1991), or source: relevant vs irrelevant to pain (Arntz et al., 1994).

Research into **dispositional anxiety** suggests a different picture. Generally, individuals with a low anxiety trait report less pain than individuals with a high trait, both in settings distracting from pain or such that do not (James and Hardardottir, 2002). Still, there appears to be a limit to how much general disposition affects acute pain. Trait anxiety does not negate the effects of state anxiety, on the contrary, it can enhance them (Tang and Gibson, 2005).

The induction method itself is of a decisive role. For example, anxiety evoked by cognitive stress following a complex mental math task can decrease subsequently rated pain (Hoeger Bement et al., 2010), while non-manipulated, naturally occurring state anxiety before a painful task is associated with enhanced pain sensitivity and temporal summation (Robinson, 2010). The latter finding agrees with research carried out in emergency hospital visits where it is found that state anxiety predicts the level intensity of the acute pain that warranted the visit (Kapoor et al., 2016). The discrepancy may be explained by the nature of anxiogenesis. Traditional approaches to anxiety induction produce time-unstable effects and largely depend on compliance resulting in a high non-response rate (Grillon, 2007).

In contrast, **clinical anxiety** is easier to study due to no necessity to manipulate its levels. Here, research is uniform: increased pain is more commonly reported by individuals with anxiety diagnoses, e.g. GAD or PD (Fleming and Volcheck, 2015), than by those without one.

Lastly, **sustained anxiety** is less well-researched in humans but in rodents it has been linked to increased pain sensitivity. Sustained anxiety, evoked by daily water avoidance stress paradigm, has been found to induce hyperalgesia in rodents (Lee et al., 2015).

Anxiety & Chronic Pain

Considering the discussion so far, the intuitive assumption about the relationship between anxiety and chronic pain may be that the former perpetuates the latter. As before, research is not uniform in supporting this notion.

Acute bouts of anxiety have been linked to increased self-rated chronic pain, independently of other psychological states (Lerman et al., 2015). In chronic migraine, time-series analysis has found that stress reliably predicts migraine attacks (Hashizume et al., 2008; Wacogne et al., 2003). For some conditions, changes in **state anxiety** are canonically linked to chronic pain flare-ups. This is particularly true for orofacial conditions such as temporomandibular disorder (Monteiro et al., 2011).

The effects of state anxiety are not as simple in experimental settings. In tension-type headache, an anxious state induced by an hour-long mentally taxing task that typically provokes a headache flare-up, has not been observed to exacerbate TS of pain ratings (Cathcart et al., 2010). This is a prominent example of the nuanced impact of anxiety in chronic pain conditions.

In studies on **trait anxiety**, not only has heightened anxious disposition been documented, it has also been found to be associated with higher self-assessed chronic pain (Gaskin et al., 1992). This is true for patients diagnosed with osteoarthritis (Cottam et al., 2016), chronic low back pain (Eccleston et al., 2001), and chronic pelvic pain (Kaya et al., 2006).

Beyond increased dispositional anxiety, clinically significant levels of anxiety are also common in chronic pain. Generally, a lifetime diagnosis of any **anxiety disorder** is predicted in 7 – 28% of chronic pain patients (McMahon et al., 2013), though this range changes depending on the diagnosis. For example, in chronic musculoskeletal pain conditions, the instance of any anxiety diagnosis is 17%, while in chronic low back pain it escalates to 29% (Asmundson and Katz, 2009).

Further, clinical anxiety has broad health-related consequences for chronic pain sufferers, beyond what is observed in acute pain. The presence of phobic conditions such as kinesiophobia, the fear of movement causing pain or injury, is associated with decreased range of said movement in chronic low back pain patients (Lumley et al., 2011). The literature is rich with examples of the positive relationship between clinical anxiety and chronic pain report but its review is necessarily curated in the present discussion.

Instead, it is important to recognise that such findings are unsurprising as they are predicted by the biopsychosocial perspective on chronic pain (see Figure 1.3). In it, anxiety is acknowledged as a key psychological mechanism that perpetuates pain chronicity (Michaelides and Zis, 2019). Failure to recognise anxiety as a component of one's pain experience would be a failure to understand the dynamic changes in chronic pain (Adams and Turk, 2018). For FM, it would also mean a failure to understand the condition itself (Meeus and Nijs, 2007).

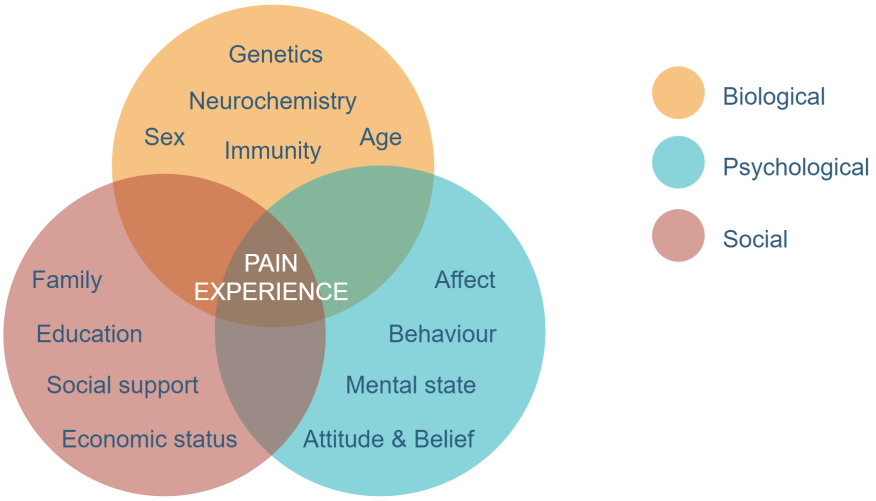

Figure 1.3: The Biopsychosocial Model of Chronic pain.

1.4 Anxiety & Fibromyalgia

1.4.1 Clinical Anxiety

As with other chronic pain conditions, a similar trend for an increased prevalence of **anxiety disorders** is observed in FM patients compared to healthy populations. Depending on the tool (diagnostic or research), we find different rates of clinical anxiety. Structured interviews for DSM Axis I diagnoses find a frequency of 26 – 35% (Epstein et al., 1999; Hudson et al., 1985; Thieme et al., 2004; Uguz et al., 2010), which is comparable to self-assessed prevalence of 38% (Bennett et al., 2007). Whether anxiety disorders are more common in FM than other painful musculoskeletal conditions is not clear. Compared to RA, FM patients have been found to have a higher rate of anxiety disorders (Sayar et al., 2004; Uveges et al., 1990), but this difference disappears during blind clinical interviews (Ahles et al., 1991). In fact, among other medically unexplained chronic pain conditions, FM does not stand out as the most highly comorbid with anxiety (Henningsen et al., 2003). This further suggests that though mental health diagnosis is concurrent to FM, it is not a defining part of

the syndrome profile.

Nonetheless, various anxiety-based disorders have been linked to the severity of FM symptomatology. For example, both fatigue and muscle tension, which translate into pain, increase with comorbid anxiety diagnosis (van Houdenhove and Egle, 2004). However, as noted, clinical anxiety is observed in approximated a third of the patient population. Thus, other dimensions of anxiety, such as trait and state, and their relation to FM must be considered.

1.4.2 Dispositional & Acute Anxiety

One of the earliest studies that compared **dispositional anxiety** between FM and healthy cohorts had failed to find significantly greater levels in the former (Clark et al., 1985). This is in contrast with another study from that time, by Yunus et al. (1991), who found that self-reported depression, anxiety, and stress were elevated in FM. Although influential to this day, both studies are hard to interpret since they relied on pre-ACR'90 definition of FM.

Post-1991, research has reported elevated dispositional anxiety when comparing FM patients to matched controls (Çeliker et al., 1997), and more, the presence of such was found to be significantly associated with pain (Kurtze and Svebak, 2001; Martinez et al., 1995). FM patients appear to experience higher levels of dispositional anxiety than individuals with chronic lower back pain (Giesecke et al., 2004) or complex regional pain syndrome (Verbunt et al., 2008). In one study (Sayar et al., 2004), blinded categorisation based on trait anxiety correctly determined whether patients had FM or RA. Interestingly, when comparing the trait in other functional conditions, FM does not surpass irritable bowel syndrome (IBS) or CFS (Janssens et al., 2015). Still, unlike with clinical anxiety, there is a strong suggestion that dispositional anxiety is higher

in FM than other medically-explained chronic pain conditions.

Beyond mere presence, there is some evidence for the positive relationship between dispositional anxiety and FM pain. Kurtze and Svebak (2001) demonstrated that trait anxiety is positively correlated with historically reported pain independently of depression. The positive association may even be stronger in FM than other comparable chronic pain conditions, such as neuropathy Gormsen et al. (2010). However, this relationship has not maintained when considering trait anxiety and acute pain. In a key study by Jensen et al. (2010), it was found that trait anxiety is not associated with pain perception of experimental pain. This raises the question: how exactly does anxiety aggravate FM pain?

One way to explore the problem is through research of **state anxiety**. Despite the routine study of the state alongside the trait (due to shared measurement tools), only a few studies have explored the former in FM. The role of transient anxiety has been addressed through observational or cross-sectional studies, where it was largely a self-standing outcome variable (e.g. Amutio et al., 2015) or measured concurrently to pain but not jointly analysed (e.g. Field et al. (2003); Matarán-Peñarrocha et al. (2011).

Some studies have attempted to investigate base rates of state anxiety in FMs compared to other populations. For example, White et al. (2002) measured acute anxiety in both FM patients and healthy controls and failed to find a difference. This is replicated by Chalaye et al. (2014), which did observe an increase in patients, but it also failed to reach significance. Compared to other chronic pain diagnoses, state anxiety has been found to be lower in FM than RA (Celiker and Borman, 2001), but the same as work-related chronic low back pain Hallberg and Carlsson (1998). Neither independent measures of state anxiety nor base rate analyses enable further discussion of the role of acute anxiety in

FM.

Only a few studies have attempted to research what is the meaningful contribution of state anxiety to pain processing in FM. That has been done with both inherent chronic pain and experimentally induced acute pain, and results are again divergent.

One early study failed to find any significant association between acute anxiety and FM pain (Çeliker et al., 1997), but later investigations on both adult (Ernberg et al., 2000) and juvenile participants (King et al., 2017) did find a positive trend. Similar discordance is observed in the consensus on the relationship between state anxiety and experimental acute pain. Two studies, which explored the matter using pressure pain found no association with state anxiety (Bement et al., 2011; King et al., 2017). One study did find that acute anxiety reported prior to pain induction does predict ratings of pressure pain (Arnold et al., 2008a); however, that was not reconfirmed in another study with pneumatic pain (Jensen et al., 2010). In all four studies, state anxiety was measured at a single time point, it was not maintained or otherwise controlled for. This observational approach hinders the interpretation of how the magnitude of state anxiety relates to concurrently experienced acute pain.

To the best of knowledge, the only study that has manipulated state anxiety was carried out by Crettaz et al. (2013) and it deserved an in-depth look. In it, FM-diagnosed and control participants took part in a paradigm known as the trier social stress test. The paradigm requires the participants to perform challenging mental maths test followed by a panel interview. The test has an extensive preparation phase to ensure that participants are fully engaged with the tasks. Following anxiogenesis, Crettaz et al. applied painful stimuli of various modalities to test how the evoked anxiety affects pain threshold, pain tol-

erance and TS. While the authors concluded that the FM cohort experienced stress-induced allodynia, as suggested by the lowered pain thresholds, group responses to the anxiety manipulation challenge this conclusion. Unlike the patients, the control participants were *least* anxious during the stress test. This is in direct opposition to what the authors expected: an increase during the stress test, as compared to baseline. There are further discrepancies that question the validity of the reached interpretation but these will be addressed in detail in Chapter 5. Here, it is sufficient to note that pain and anxiety were not concurrently measured, thus strongly limiting any understanding of the produced anxiogenic effects on acute pain.

Research into the fine temporal relationship between state anxiety and FM pain leaves several questions unanswered. How does, for example, acute anxiety affect the development of temporal summation or WU in FM? Or why are cross-sectional studies showing a reducing effect of anxiety while observational studies suggest the opposite? The current state of research does not answer them. Addressing these questions is key for the comprehensive understanding of the role of anxiety in FM. The current state of research, however, simply does not allow to begin attempting to answer them.

1.4.3 Sustained Anxiety

Lastly, research on **sustained anxiety** in FM is also limited. Of all anxiety dimensions, this has been investigated the least, possibly due to the novelty of the field. Only one study has explored how does anxiety maintain beyond the momentary experience interact with pain in FM. Ironically, it is an old longitudinal study from 1992 by Hazlett and Haynes. There, daily fluctuations of anxiety were recorded alongside daily FM pain, fatigue and muscle stiffness. Sustained anxiety was defined through a questionnaire designed to measure daily stress.

FM pain was found to be mediated by the number of daily stressors: the more items were reported as anxiogenic during the day, the higher the reported pain was. Albeit encouraging, just as with other discussed research directions, much remains to be explored for a confident interpretation of the relationship between persisting anxiety and FM pain.

1.4.4 Significance of Anxiety & Fibromyalgia Research

An investigation of concurrently experienced anxiety and pain will not merely fill a knowledge gap in FM literature. It may also have a meaningful impact by addressing the central challenges experienced by patients and experts.

A rigid belief in the aetiological role of psychiatric disturbances in FM still persists (Hazemeijer, 2003), causing patients to denounce mental health considerations in the discussion of their condition (see "It's all in your head"). This is concerning, particularly because we do know that anxiety can worsen FM pain (see Anxiety & Fibromyalgia). That narrative also invalidates the voice of those patients, who as experts of their condition, recognise the impact of anxiety on their health (Bennett et al., 2007) and seek appropriate help (see Patient Disregard and Poor Prognosis).

By studying how anxiety and pain develop concurrently in the presence of FM, the key concerns of FM clinicians and researchers will also be addressed. Among many psychological factors that may undermine the physical well-being of chronic pain sufferers, anxiety is a known contender (see Anxiety & Chronic Pain). Nonetheless, anxiety management has not been established as part of FM management plan. This is evident in the treatment recommendations of a lead expert in FM, who has stated that patients should foremost receive support with their cardinal complaints and only be referred to a psychiatrist or psycholo-

gist in the case of suspicion of "significant comorbid psychiatric issues" (Clauw 2014, p.1550). The discrepancy between research and practice hinder the work of medical professionals, who admit the need for help in better understanding of their patients (see Poor Patient Rapport and Poor Understanding of the Condition). In comparison, the same is not true for depression, which is similarly highly comorbid with FM (High Rate of Comorbidities). Anxiety must be studied because it contributes qualitatively differently to FM (Kurtze et al., 1998). One possibility for the poor translation to clinical practice is that most research has relied on cross-sectional surveys or on subjective patient recall (see Anxiety & Fibromyalgia). An experimental investigation should be used to examine how anxiety contributes to pain perception. Further, such investigation must employ the most-well researched in FM central sensitisation phenomenon, TS.

1.5 Research Objectives & Hypotheses

After reviewing the literature on anxiety and pain processing in FM, several significant knowledge gaps were identified. These formed the basis for the thesis research aims and hypotheses. The overarching goal was to expound the contribution of acute and sustained anxiety to the experience of acute and inherent FM pain. It was broken down into three research objectives and general hypotheses.

I. Temporal Summation for the Study of Central Sensitisation in Fibromyalgia

Central sensitisation has been proposed as the key mechanism driving FM pain (Staud, 2002; Cohen, 2017; Arnold et al., 2016). The assertion has been largely based on research of TS, the psychological counterpart of WU, which has been found to be augmented in FM patients (Staud et al., 2001). A closer

inspection of the literature, however, finds that the acclaimed abnormal increase has not been reliably achieved (Lim et al., 2016). One possibility for why that is the case is the methodological approach chosen for the definition and measurement of TS. Studies that have adopted testing paradigms divergent from the seminal work, have failed to find FM-dependant abnormal TS. Further research employing novel methodology has been requested to investigate the literature discrepancy (O'Brien et al., 2018). Thus, the first aim of the thesis was to test whether continuous pain ratings, an established method for collection pain report, are suitable for the study of TS in FM. If compatible, the next aim was to analyse whether an enhanced TS is observed in patients compared to pain-free controls.

1. *It was predicted that continuously rated pain will reveal amplified TS in FM, as defined through new temporally sensitive measures of TS.*

II. Experimentally-induced Acute Anxiety & Temporal Summation

Research on mediators of pain perception in FM has pointed to anxiety as a key modulator of both acute and chronic pain (Eich, 2000; Thieme et al., 2015; Arnold et al., 2008a). Despite the causal link identified by patients (Bennett et al., 2007), research has not yet provided conclusive support for such an effect (Jensen et al., 2010). This is also true for the key marker of central sensitisation, TS, which had not been studied in the context of concurrently maintained acute anxiety. To address this, an experimental manipulation of anxiety was necessary. This was done by employing the CO_2 Model, a robust method of anxiogenesis, in two experimental phases. In the first, the aim was to test the CO_2 Model with the previously established pain testing protocol. The application of the CO_2 Model in pain research was novel and had not been

previously paired with continuous pain report. The development of TS in the presence of CO_2-induced anxiety had also not been investigated. For these reasons, the first phase included only healthy participants. Upon successful methodological integration, the procedure was then repeated in the second phase, with FM patients.

2 *It was predicted that not only the CO_2 Model would be successfully incorporated in the continuous pain testing protocol, but that the experimentally evoked anxiety would modulate TS. This was expected to be true both for pain-free participants in the first phase and the FM patients in the second.*

III. Sustained Anxiety & Chronic Pain

Finally, for a comprehensive investigation of the impact of anxiety on pain in FM, it was necessary to observe their relationship beyond minute intervals under experimental conditions. This could be done through research on sustained anxiety, or anxiety that maintains beyond the introduction of an anxiogenic source. Such persisting anxiety has been found to have a broad effect on the physical well-being (Paterniti Sabrina et al., 2001). In FM research, daily fluctuations of sustained anxiety have been observed to correlate with respective changes in chronic pain, but that only been investigated in one study by Hazlett and Haynes (1992). There, the definition of anxiety and the limited sample pool prevented from concluding whether the observed positive trend between sustained anxiety and FM pain was meaningful. For this reason, we conducted a study focused on anxiety elicited by the coronavirus disease 2019 (COVID-19) pandemic. Our goal was to observe how the presence of sustained anxiety contributes to the magnitude of reported FM pain.

3 *It was predicted that unlike experimentally induced anxiety, an increase*

in daily reported sustained anxiety will be mirrored by a comparable increase in self-rated FM pain, thus demonstrating the multifaceted impact of anxiety on FM.

1.6 Chapters Overview

The research objectives were explored in a series of studies, each addressing a portion of the research question, building upon preceding findings. All studies but one have been published as preprints. The contents of the chapters are as follows:

Chapter 2 The second chapter introduces the general methods used across the series of studies. Where methods deviated from the ones described, additional information will be provided in that chapter.

Chapter 3 The first experiment is described in Chapter 3. The aim of the study was to trial the application of continuous pain ratings for the measurement of the fine temporal changes of acute pain in the pain profile of FM patients and matched pain-free controls.

Chapter 4 Following the successful trial of the continuous pain ratings, the next study tested integration of acute pain with concurrently maintained and measured acute anxiety. Chapter 4 presents the study with pain-free participants only, with whom this novel approach was first carried out.

Chapter 5 Once the baseline interaction between pain and anxiety measures was established in healthy controls, the next study replicated the paradigm with FM-diagnosed participants. Chapter 5 described that feasibility study.

Chapter 6 The final experimental chapter reports the results from a study, which tested the role of sustained anxiety evoked by the COVID-19 pandemic in the direction of FM chronic pain.

Chapter 7 The last chapter of the thesis concludes by summarising key findings and highlighting further research directions.

Chapter 2

General Methods

I have never tried that before, so I think I should definitely be able to do that.
—- ***Astrid Lindgren, Pippi Longstocking***

GENERAL methods, equipment, analyses as well as the rationale for choosing them are described in this chapter.

2.1 Participants

Both FM and healthy participants were recruited. The study aim and design dictated which population was tested.

2.1.1 Fibromyalgia Patients

The target clinical population were adults, diagnosed with FM and no other chronic nor acute pain condition. While both are common in FM (Arnold et al., 2019), including such would prevent attributing any observed effects to the diagnosis of interest. In order to determine individual eligibility, participants were screened according to several requirements.

Inclusion Criteria

There were two main sources of strict inclusion criteria: manufacturer's safety guidelines for Transcutaenous Electrical Stimulation (TES) and the Laboratory

for Respiratory Experimental Designs (Lab RED) Safety Protocol for the application of the CO_2 Model (see Table 2.1). An additional criteria set, the NHS shielded list (see Appendix A), was only applied to the final online study. Both the main and additional criteria were checked via an online screening form, within two weeks of testing.

The Lab RED Safety Protocol listed additional in-session exclusion criteria, all of which were not possible to check beforehand. Failure to meet any of them immediately terminated study progression. These were: a) failure to pass the short M.I.N.I. (see Appendix B); b) blood pressure outside of the 90/60 - 140/90 mmHg range; and c) heart rate outside of 60 – 100 bpm range.

The short M.I.N.I. was used to assess the possible presence of an undiagnosed psychiatric condition. It comprised of six sections for the condition depression, mania, PTSD, GAD, obsessive-compulsive disorder (OCD), and addiction. This short version of the form was provided by the Bristol Tobacco and Alcohol Research Group (Bristol TARG), University of Bristol, which pioneered the use of the CO_2 Model in psychology research. The short M.I.N.I. has been successfully applied for screening in previous research (Attwood et al., 2015).

Recruitment & Reimbursement

For in-person testing, FM participants were recruited through the School of Psychology Participation Pool, University of Plymouth, and through advertisement in the local patient support group in Plymouth, UK. For online research, the survey was shared through social media (Facebook, Twitter, Instagram), as well as through two national charities: Pain UK and Fibromyalgia Action UK. Eligible participants were invited within two weeks of screening and non-eligible participants were notified within the same timescale.

Table 2.1: General Inclusion Criteria

Guideline	Criterion
TES	1) No diagnosis of a CNS condition.
	2) No peripheral neuropathy.
	3) No diagnosed/suspected epilepsy, experience of convulsion/seizure, or family history of epilepsy.
	4) Unexplained syncope.
	5) Not potentially/currently pregnant or breastfeeding.
	6) No pacemaker, implantable device, shunts or stents in body.
	7) No tattoo or abrasions on site of stimulation.
	8) No alcohol or caffeine 24 hrs prior to testing.
	9) No over the counter medication on the day of testing.
CO_2 Model	1) At least 18 years old at time of screening.
	2) No diagnosis of a psychiatric condition.
	3) Not potentially/currently pregnant or breastfeeding.
	4) No long-term condition, apart from FM in the clinical sample.
	5) No prescribed medication a month prior to testing.
	6) No illicit drug intake a month prior to testing.
	7) Not currently smoking or vaping.
	8) No high daily consumption of caffeine (> 8 cups per day) and not xanthine-based drinks 24 hrs prior to testing.
	9) No alcohol dependency, defined as > 35 units/week (females) and > 50 units/week (males), and no alcohol 24 hrs prior to testing.
	10) Participant-calculated BMI outside of 18 - 30 range.

Note: *TES* – transcutaneous electrical stimulation; *CNS* – central nervous system; *FM* – fibromyalgia; *BMI* — body mass index.

Participants who attended the study were reimbursed proportionally at the rate of £4 per half an hour.

2.1.2 Healthy Participants

Healthy participants were recruited for two purposes. First, as matched healhy controls (HCs) for the clinical sample, and second, as a target sample in pilot testing.

Inclusion Criteria

The inclusion criteria for the HCs were the same as described in Table 2.1, with the exception of necessity for FM diagnosis. When matched, HCs were selected based on age, gender, and handedness.

Recruitment & Reimbursement

Healthy participants were similarly recruited through the School of Psychology Participation Pool, University of Plymouth, university mailing list, and advertisement at local social media pages on Facebook. As with patients, HCs were notified of their eligibility within two weeks of screening and invited to partake, if appropriate.

Participants who attended the study were reimbursed proportionally at the rate of £4 per half an hour.

2.2 Pain

The main outcome in all studies was self-rating of pain intensity. Both acute pain, evoked through experimental manipulation, and chronic pain, evoked by FM, were investigated.

2.2.1 Experimental Pain

There are a variety of nociceptive methods that can be used to deliver noxious stimuli, each creating a qualitatively different painful sensation. The research

carried out as part of this PhD adopted only one: TES. It was chosen for its well-researched methodology for TS elicitation (Arendt-Nielsen et al., 1994, 2000), as well as the relatively low intrusiveness, which would allow for continuous pain report. The following section describes the TES protocol, as well as what measurements of pain were gathered.

Induction

Stimulation Protocol. Electrical stimulation was delivered via constant current stimulator DS7AH Digitimer (Digitimer Ltd., UK). The equipment was semi-automatically operated by the researcher. The researcher was always responsible for the manual adjustment of the output intensity. During static quantitative sensory testing (QST), the researcher also delivered the stimuli at a self-maintained frequency. During dynamic QST, the stimulator was controlled jointly by computer software and an Arduino Genuino (Arduino Inc.) to deliver pulses at 2.5 Hz. The digimeter was set to output a single-square wave pulse of 500ms duration. Maximum voltage for the output was set at 400V for all participants.

Stimulation Site. TES was delivered to the skin over the sural nerve over the tendo-Achilles. This area was chosen to minimise contraction of muscle tissue, which is particularly tender in FM. Only one leg was stimulated throughout the experimental session, thus the body side was counterbalanced between participants. To deliver the stimuli, two disposable self-adhesive disk electrodes, 2 cm in diameter, were positioned with an inter-electrode distance of 3 cm. They were placed on an area free of skin abrasions, tattoos or hair. To ensure high conduction, the skin was prepared with an abrasive gel and cleaned with 70% isopropyl alcohol wipes. Impedance was checked by D175 impedance meter (Digimeter Ltd., United Kingdom) and was maintained below 50 ohm.

Psychophysical Testing. To determine the intensity of TES, static psychophysical testing was carried out. Three measures were collected: sensory threshold (STHR), pain threshold (PTHR), and pain tolerance (PTOL). STHR was defined as the mA, at which the participant felt any sensation for the first time during the stimulation. PTHR was defined as the mA, at which the participant reported the stimulation as minimally painful. PTOL was defined as the mA, at which the participant was no longer able to tolerate the stimulation. Participants were questioned on what sensation they were experiencing during each measure to ensure correct instructions comprehension.

Psychophysical testing was repeated three times. Each cycle of psychophysical testing began with the current intensity set at 0 mA. The current was then increased in steps of 0.1 mA by the same researcher. To prevent any adaptation, pulses were delivered at 1-second intervals. The maximal threshold for the current intensity was preset at 40 mA. If PTOL was not established prior to that value, the stimulation increase was stopped. If any more cycles were left, the testing was restarted. If at no point the PTOL value was < 40mA, it was deemed that the participant's tolerance level was beyond the acceptable value for the experiment and that participant was excluded.

Using PTHR and PTOL, participant's pain range (PRAN) was derived. It was calculated as PTOL - PTHR = PRAN.

Stimulation Conditions. For dynamic QST, several stimulation conditions were used, each set at a different intensity level. They were: 10%, 20%, 30%, 40% , 50% and 60% of the PRAN value. Each condition was calculated as PTHR + (PRAN x %/100). Stimulation frequency was adjusted to 2.5H to evoke TS.

Pain Rating Task

Pain ratings were collected in blocks of stimulation. Depending on the study (Chapters 3, 4 or 5), a stimulation block was between 45 – 60 s long and was repeated two or three times. The blocks were always randomised and had a short break between them. In some studies (Chapters 4 and 5), the participant completed a short anxiety rating task during that break. Otherwise, the experimenter used it as an opportunity to check on the participant and the electrodes.

During a block, the participant's task was to continuously rate the evoked painful sensation. If the participant had other pain, as it was the case with FM patients, they were instructed to ignore during the ratings. To provide a pain rating, participants used a proprietary response box mounted with a rotary dial with a hard start and end.

Measurement

A horizontal 101-point pain visual analogue scale (pVAS) was used to report pain intensity. On it, '0' was marked as *'no pain'*, '1' – *'least pain'* and '100' – *'worst possible pain'*. As a block began and with it stimulation, participants were instructed to continuously provide a rating. This meant that no single value could be extracted from the pVAS. Instead, the position of the pVAS marker was recorded every 50ms. This allowed for the plotting of the pain ratings as a single pain response line. This pain response was then broken into time periods, as depicted in Figure 2.1.

The first is the **TS Period** where a rapid incline of pain ratings was expected. Based on the applied stimulation protocol (Arendt-Nielsen et al., 1994), TS was defined as the first 15s of the pain response. Several key variables were extracted from this period to characterise TS. These included: the point at which

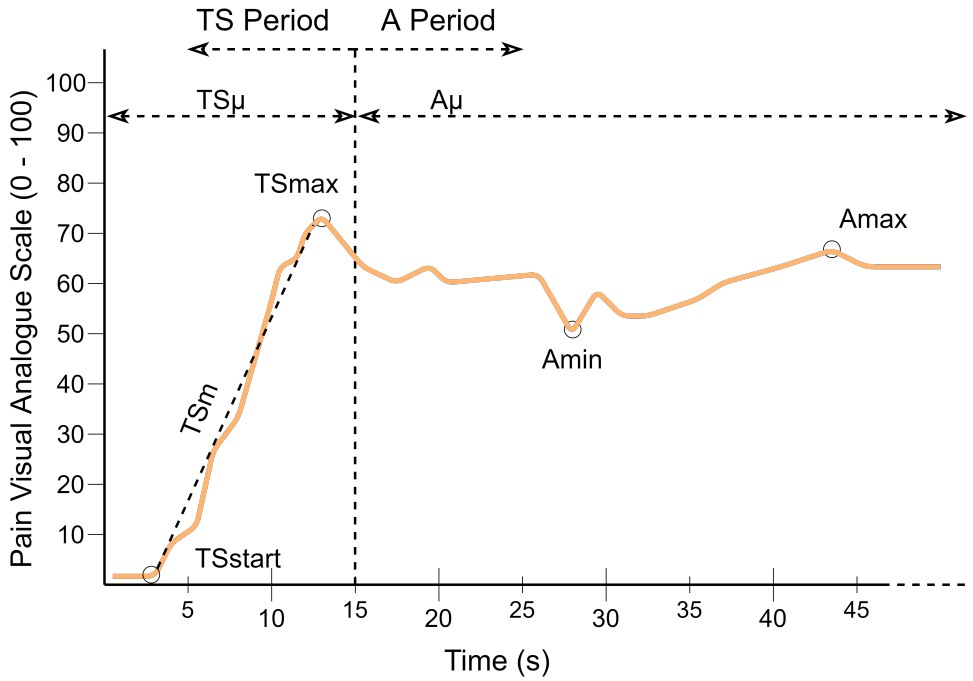

Figure 2.1: A prototypical continuous pain response. TS – temporal summation; *TSμ* – average pain rating during TS; *TSmax* – maximal pain rating during TS; *TSstart* – the first pain rating > 0; *TSm* – slope between TSstart and TSmax; *A* – adaptation; *Aμ* – average pain rating during adaptation; *Amin* – minimal pain rating during adaptation; *Amax* – maximal pain rating during adaptation.

the pain response was first rated above 0 (TSstart), the value of the maximal rating during the TS Period (TSmax-v), the time of the maximal rating during the TS Period (TSmax-t), the slope between TSstart and TSmax (TSslope), and the average pain rating during the TS period (TSμ). Time was only extracted when it was part of the study aim.

Following TS was the adaptation period (**A Period**). Adaptation was chosen as a term to reflect that participants may sensitise or habituate to the painful stimulation. Predicting which occurred was not part of any study hypothesis so a neutral label was decided upon. Similarly to TS, several time points were extracted: the minimal rating during the A period (Amin), the value of the maximal rating during the A Period (Amax-v), the time of the maximal rating during the

A Period (Amax-t), and the average pain rating during the A period (Aμ). As before, time was only extracted when it aligned with study aims.

2.2.2 Chronic Pain

Definition

Only chronic pain related to FM was studied. It was measured both as participant characteristic as well as an outcome variable.

Measurement

Participant Characteristic. To confirm the presence or absence of an FM diagnosis, as well as to determine its severity, several forms were administered to both participant cohorts. The ACR'90, as well as ACR'10 were used to confirm the diagnosis and characterise pain severity in the week preceding testing (Wolfe et al., 1990, 2010). While the ACR'90 is outdated in clinical practice, it is still commonly used in research. The Revised Fibromyalgia Impact Questionnaire (FIQ-R) was administered exclusively to patients to assess the impact of FM on daily functioning (Bennett et al., 2009). Both patients and matched controls completed the Short Form McGill Pain Questionnaire (SF-MPQ) to further characterise any pain experienced in the week prior to testing Melzack (1987).

Outcome. Changes in chronic FM pain were the subject of investigation in the final study on COVID-19 anxiety (Chapter 6). In it, FM participants repeatedly rated their anxiety and pain over several days. To align the ratings of chronic pain with those of anxiety, a horizontal visual analogue scale (VAS) was used. Similarly to the previously described pVAS, the daily FM pVAS was a horizontal 101-point scale ranging from '0' – *'no pain'*, '1' – *'least pain'* to '100' – *'worst possible pain'*. Unlike the experimental pVAS, participants provided only one daily rating of their chronic pain. Specifically, they were asked to rate the over-

all intensity of the FM pain experienced that day (*'How was your pain overall today?'*).

2.3 Anxiety

The contribution of anxiety to the experience of pain was the central focus of several studies. Depending on the research objective, either acute or sustained anxiety was studied; however, dispositional anxiety was also measured as a participant characteristic.

2.3.1 Acute Anxiety

Acute anxiety was evoked in two studies (Chapters 4 and 5), where its contribution to the temporal development of pain was researched in pain-free and FM cohorts.

Induction

Acute anxiety was evoked using an established human experimental model of anxiety, the CO_2 Model. It involves the continuous inspiration of an air mixture with elevated levels of carbon dioxide (CO_2), usually between 5% to 8% for adult testing (Bailey et al., 2011a). This results in the temporary inhalation-dependent accumulation of CO_2 in the blood, or hypercapnia. It, in turn, induces respiratory distress, which is marked by *hyperpnea*, laboured breathing, or *tachypnea*, fast and shallow breathing (Patrick and Howard, 1972; Stegen et al., 1998; Roberson-Nay et al., 2017). Beyond respiration, cardiovascular changes such as tachycardia, elevated heart rate, and hypertension, elevated blood pressure, both of which are also dependant on continued engagement with the challenge. Together, the resulting physiological state not only closely mirrors naturally occurring acute bout of anxiety but is also interpreted as anx-

ious (Bailey et al., 2005).

In our research, the CO_2 Model was applied following a strict protocol, aimed at both maintaining acute anxiety while preventing an adverse reaction to the manipulation. Participants inhaled two mixtures. The anxiogenic one: 7.5% CO_2/21% O_2/ 71.5% N_2; and medical air, which acted as a control: 0.04% CO_2/21% O_2/ 78% N_2. To inhale the mixtures, participants wore an appropriately sized sterilised face mask (7450 Series V2, Hans Rudolph Ltd.), which was affixed to the head using the corresponding headgear (Hans Rudolph Ltd.), and equipped with two-way non-rebreathing valves (Hans Rudolph Ltd.) to isolate inspiratory and expiratory flows. Gas mixtures were delivered first to a 10 L Douglas bag and then to the face mask through UVA tubing. Expired air was released into the ambient air of a well-ventilated room.

Prior to inhalation, participants were briefed about what could be reasonably expected during the procedure, as well as the safety precautions undertaken to minimise discomfort. When the inhalation began, heart rate and blood pressure were recorded to ensure that the cardiovascular measures are within the acceptable range. An increase in both is typical for the CO_2 inhalation (Roberson-Nay et al., 2017) but it should not exceed the accepted range of 60 to 100 bpm for heart rate and 90/60 to 140/90 mmHg for systolic blood pressure (SYS) and diastolic blood pressure (DIA). If cardiovascular readings were acceptable, the inhalation continued, otherwise the inhalation was terminated. The researcher was aware of which mixture was being delivered, unlike the participant, resulting in a single-blinded delivery. Inhalation of both the hypercapnic mixture and the control was up to 15 min and followed by at least a 20 min break. Upon completion of both inhalations and both breaks, participants were thoroughly debriefed and their cardiovascular measures were recorded for a final time.

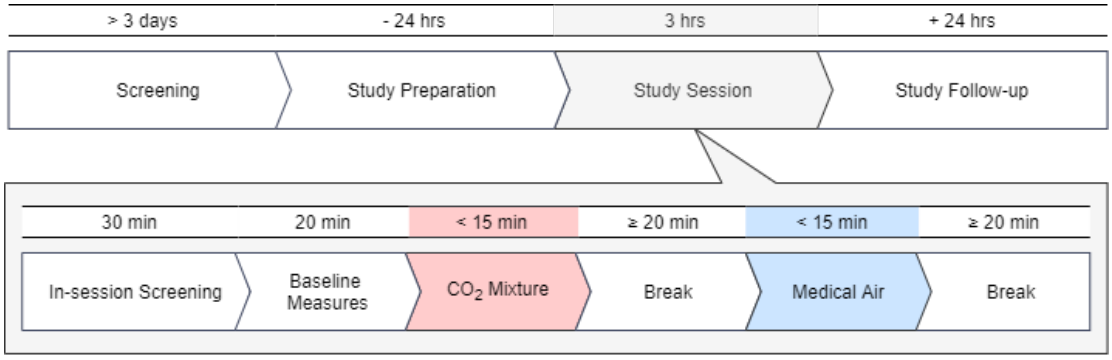

Figure 2.2: The CO_2 Model timeline.

A follow-up phone interview was scheduled 24 hrs after the study, to ensure that no carry-over effects were observed. This was particularly important for the study involving FM participants. The timeline of the procedure is depicted graphically in Figure 2.2. The testing protocol was guided by the Lab RED Safety Report and was approved by the School of Psychology, University of Plymouth, Ethics Committee (18/19-1044).

Measurement

Self-report Measures. These were the primary measures for acute anxiety. Two tools were used. The first one was a vertical 101-point anxiety visual analogue scale (aVAS), ranging from '0' – *'no anxiety'* through '1' – *'least anxiety'* to '100' – *'worst possible anxiety'*, with a major tick at every tenth mark. Participants always rated their present anxiety by answering the question *'How anxious do you feel right now?'*. Once the participant provided the rating, the scale disappeared and was replaced by a pVAS. To avoid confusion both aVAS and pVAS were clearly labelled. In the CO_2 paradigm, aVAS was presented during inhalation before each block of continuous pVAS ratings, resulting in 12 single aVAS ratings. Thanks to its intuitive design, the aVAS allowed for the repeated reassessment of anxiety. This is unlike previous studies where anxiety was measured post-inhalation. To indicate their anxiety level on aVAS, participants

used the proprietary response box previously described in Section 2.2.1.

The second self-report measure was the state version of the State–Trait Inventory for Cognitive and Somatic Anxiety (S-STICSA). It is comprised of 21 statement describing signs of anxiety: 11 statements presented somatic symptoms of anxiety and 10 presented cognitive symptoms. The S-STICSA was completed 4 times: once immediately after each inhalation while recalling the state during that inhalation (using modified instructions *'How did you feel during the inhalation?'*), and once at the end of each break while considering the current state at that time (using original instructions *'How do you feel right now?'*). Due to time constraints imposed by the maximal time allowed for the hypercapnic inhalation, it was not feasible to administer S-STICSA during the inhalation. While this approach is susceptible to memory decay, it is commonly used elsewhere in the literature (Attwood et al., 2014; Bailey et al., 2005).

Physiological Measures. Acute anxiety was further characterised through physiological measures. Blood pressure (BP) and heart rate (HR) were measured to confirm the effects of the anxiogenic mixture (Bailey et al., 2007). An increase in SYS, DIA, and HR during the CO_2 mixture but not medical air indicated successful anxiety induction. The cardiovascular measures further allowed to assess independently of participant the intensity of the evoked anxiogenic effect. Lastly, as discussed, the measures were used to ensure the comfort and well-being of the participant. If the measures were outside the predetermined limits, participation was discontinued as per Lab RED protocol to prevent an adverse event. For these purposes, BP and HR were collected several times over the course of the experiment (see Figure 2.3).

30 min	20 min	< 15 min	≥ 20 min	< 15 min	≥ 20 min
In-session Screening	Baseline Measures	CO_2 Mixture	Break	Medical Air	Break
MINI	T-STICSA S-STICSA aVAS	aVAS x12	S-STICSA x2 aVAS	aVAS x12	S-STICSA x2 aVAS

(a) Self-report Measures

SYS DIA HR	SYS DIA HR	SYS DIA HR	SYS DIA HR	SYS DIA HR	SYS DIA HR

(b) Physiological Measures

Figure 2.3: The schedule for anxiety measures acquisition during the CO_2 Model. a) Self-report Measures: *MINI* – Mini-International Neuropsychiatric Interview; *T-/S-STICSA* – the trait/state version of the State-Trait Inventory for Cognitive and Somatic Anxiety; *aVAS* – anxiety visual analogue scale. b) Physiological Measures: *SYS* – systolic blood pressure; *DIA* – diastolic blood pressure; *HR* – heart rate.

2.3.2 Sustained Anxiety

To gain a balanced understanding of the contribution of anxiety to FM pain, an extension beyond laboratory-induced pain was necessary. This was achieved by studying anxiety evoked by the COVID-19 pandemic (thereafter COVID-19 anxiety).

Definition

International research on the COVID-19 pandemic found that mental well-being deteriorated with the progression of lockdown measures. Several studies measured COVID-19 anxiety but no single definition has been agreed on. For this reason, a literature search was performed. At the time it was still a novel topic, thus an additional consultation with the local patient group was carried out to compile a comprehensive list of the most commonly reported sources of pandemic anxiety. Table 2.2 lists the identified anxiety sources and broadly defines

them.

Measurement

Just as with defining anxiety, there was no single accepted method of measuring it. Thus, I applied the established approach of measuring anxiety through a horizontal 101-point VAS. It was identical to aVAS in numbering and labelling but differed in the posed question. Participants provided single daily ratings instead of several. Further, when rating their COVID-19 anxiety, participants were asked to separately consider each anxiety source and rate it accordingly (e.g. *'How anxious were you today about yourself contracting COVID-19?'*). This means that there was no single COVID-19 aVAS but instead multiple ones. Although more labour-intensive, this detailed approach allowed to separately assess the anxiety evoked by each aspect of the pandemic.

None of the individual pandemic anxiety sources, however, sufficiently represented COVID-19 anxiety. For this reason, an average rating of all source ratings was calculated as a global measurement of COVID-19 anxiety, creating the COVID-19 aVASμ. It is important to note that this average rating *did not* include sources that were rated at '0'. This was favoured for several reasons. First, prior to rating a sources of COVID-19 anxiety, participants were asked whether they experienced such anxiety at the time of measurement. If they answered negatively, the aVAS did not appear and the source was automatically rated at '0'. Second, it was observed that the identification of sources as anxious was homogeneous within participants and dependant on the time of testing. That is, some participants would never report anxiety about a certain source (e.g. "*Home loss/eviction*"), perhaps reflecting that this was an issue not applicable to them. Further, some anxiety sources became less prominent with the course of the pandemic. This was particularly true for '*Access to essential*

Table 2.2: Sources of anxiety related to the COVID-19 (C-19) pandemic.

Anxiety Source	**Study**	**Defined as anxiety about ...**
Oneself contracting C-19	Casagrande et al. (2020) McElroy et al. (2020) Roy et al. (2020)	... contracting COVID-19 by the individual.
Household member contracting C-19	(Shanafelt et al., 2020)	... members from the individual's household contracting COVID-19.
Family member contracting C-19	(Islam et al., 2020) (Petzold et al., 2020)	... the individual's family members contracting COVID-19.
Work/Education issues	Kleinberg et al. (2020) (van der Velden et al., 2020)	... work or education issues caused by the pandemic.
Loss of employment	(Shevlin et al., 2020) (Wilson et al., 2020)	... potential or actual loss of employment as a result of the pandemic.
Financial hardship	Casagrande et al. (2020) Kleinberg et al. (2020) Shahabi et al. (2020) Milne et al. (2020)	... financial hardship as a result of the pandemic.
Home loss/eviction	–	... losing or leaving house of residence due to the pandemic.
Access to medication	(Sorokin et al., 2020)	... accessing medication due to the pandemic.
Access to medical help	–	... accessing help from medical professionals due to the pandemic.
Access to essential supplies	(Roy et al., 2020)	... access to supplies such as food and household items during the pandemic.
Isolation	(Usher et al., 2020) (Boyraz et al., 2020)	... isolation due to pandemic safety measures.
Delayed/Cancelled travel plans	–	... changes or cancellations of travel plans due to the pandemic.
Impact on personal relationships	–	... the impact of the pandemic on friendships, family, or romantic relationships.
Other reason	–	... another reason related to the pandemic, not covered by the other categories.

supplies', which likely reflected the decrease in panic-buying and resumption of normal work of food services in the UK. For these reasons, COVID-19 aVASμ was calculated only using the anxiety source ratings above 0.

2.3.3 Dispositional Anxiety

As discussed in the literature review, the experience of acute anxiety is affected by its general, dispositional counterpart. While anxiety as a trait was not part of the central investigation, measuring it to characterise our participant sample was beneficial. This was done for all studies that investigated anxiety (Chapters 4, 5, and 6).

Measurement

Dispositional anxiety was measured through the trait version of the State–Trait Inventory for Cognitive and Somatic Anxiety (T-STICSA). It would only be delivered once, either on the day of testing in the experimental studies (Chapters 4, 5) or during the first daily survey in the observational study (Chapter 6).

2.4 Analysis

All analysis was carried out in `R Studio` (v 1.2.5). Due to the different sets of measurements between studies, detailed analytical approach will not be discussed in this section. Instead, the general approach and reasoning for it will be presented.

2.4.1 Sample Size

Sample size estimation was driven by two factors. Foremost, by consulting with previously published research. If effect sizes were reported, those were used in power estimation. For all studies, the aim was to achieve a power of $\geq$80% for the main effects. However, none of the studies presented in the thesis was

a direct replication of a previously reported design, thus that approach was not optimal. Following a protocol described elsewhere (Green and MacLeod, 2016), sample size estimations were carried out for an effect of $n = .3$. To do so, model simulations were the preferred method for power analysis. These were carried out using the `simr` (v 1.0.5) package with the following parameters: 200 simulations, Kenward-Roger approximation for each fixed covariate.

2.4.2 Main Analysis

While the combination of variables varied greatly between studies, the relationship of central interest was that between FM diagnosis, pain, and anxiety (where appropriate). To distil the contribution of these predictors to pain, be it acute or chronic, mixed-effects modelling was used. This method improves on traditional ANOVAs by allowing for variables to be input as fixed or random covariates, as well as on regression by controlling for mediating and confounding effects. In all studies, the outcome variable for the analysis was a pain measure (e.g. pVAS); however, the predictor variables, or covariates, differed between studies, depending on the research question. Each study chapter details what measures were used and why.

Both traditional frequentist analysis and Bayesian inference were adopted. In frequentist analysis, mixed-effects models (MEMs) were built through `lme4` (v 1.1). The package does not normally produce significance values, thus these were separately computed through the typically adopted package `lmerTest` (v 3.1). Bayesian analysis was used to verify the frequentist model estimates. This was achieved by inputting the same model formula in `rstanarm` (v 1.18.2) and visualising the model in `shinystan` (v 2.5.0), to ensure that the parameters of the model are adequate.

While mixed-effects modelling is more flexible than traditional regression, the output greatly depends on the user. The biggest caveat is the choice of the best MEM, which may skew the end results in any direction. To prevent biased selection, the process was guided by several widely-accepted principles:

1. A base model (H_0) that comprised of by-participant intercept only was created to assess whether a model of interest (H_1) outperforms it.

2. A model of interest could include several key covariates (fixed or random) that are theoretically assumed to predict the outcome variable (Baayen et al., 2008; Blackwell et al., 2006).

3. To find the optimal model of interest, several model formulas with sensibly added covariates were compiled until a maximal model is created (Barr et al., 2013).

4. Once all models have been created, these are compared between each other based on Akaike information criterion (AIC) or Bayesian information criterion (BIC) (Vrieze, 2012), as well as on χ^2 when fixed effects are the same. BIC-derived Bayes Factor (BF) was further used as a complementary method for best model assessment.

5. Select few models would stand out from this comparison. If a parsimonious model (i.e. one missing some non-key covariates) was found superior, it was chosen over the maximal to avoid Type II error in small samples (Bates et al., 2018).

6. Model formula, its performance over base mode and detailed estimates were reported only for the best MEM.

2.4.3 Figures

Figures were created in `RStudio` (v 1.0.153) using the package `ggplot` (v 3.3.2) and the open-access online tools `sankeymatic.com` and `draw.io`.

Chapter 3

Temporal Summation in Fibromyalgia: Continuous Pain Ratings & TES

Of pain you could wish only one thing: that it should stop.
*– **George Orwell, 1984***

THE first study aimed to establish what, if any, differences exist between fibromyalgia patients and matched healthy controls in the continuous self-report of pain intensity. This approach would allow observing the development of temporal summation, which has previously been suggested as a hallmark indicator of deficient endogenous pain modulation in fibromyalgia. If successful, the testing paradigm adopted here would serve as a basis four further study of the contribution of acute anxiety to the acute pain response in fibromyalgia.

3.1 Introductory Commentary

It is not coincidental that TS assumed central position in FM and other chronic pain research. TS is a dynamic QST paradigm, used to quantify endogenous facilitatory processes (Arendt-Nielsen et al., 1994). Alongside of static

QST, which includes innocuous stimulus detection, pain threshold and pain tolerance, TS can alert of atypical somatosensory processing, though without pointing to the precise source of the dysfunction (Fillingim et al., 1999). In chronic pain, TS is a clinically-relevant measure. Cruz-Almeida and Fillingim (2014) list four benefits of adopting QST measures, including: to differentiate between chronic pain and healthy individuals, to forecast the development or severity of chronic pain, as well as to assess or predict chronic pain during treatment. The last application of QST is the most relevant to FM research and it is based on the observation that comparable pain modulatory mechanisms are involved in both acute pain perception during QST and chronic pain (Goodin et al., 2014). Because of that, TS is suitable for the experimental investigation of biopsychosocial determinants involved in pain perception (Cruz-Almeida and Fillingim, 2014). Several studies have thus experimented with TS in FM.

The investigation of TS in FM patients was developed by Staud et al. who began this line of research in 2001. It was then that Staud et al. (2001) systematically described the exaggerated pain response during dynamic QST. In their seminal paper, they found that not only were singular pain stimuli rated as higher by FM participants but that this hyperalgesic effect persisted after a train of stimuli. The increased pain rating after prolonged stimulation is expected due to TS but it was markedly higher in the FM group than the control. Consecutive investigations largely replicated the observation of hyperalgesia and expanded on it. In 2003a, Staud et al. found that painful aftersensations following noxious stimulation are prolonged in FM patients beyond the typical period observed in controls. Further, lower stimulation intensity was required to maintain these sensations in FM patients (Craggs et al., 2012). At least some of these altered characteristics of TS were attributed to altered primary somatosensory con-

nectivity (Kim et al., 2015; Lim et al., 2016) and enhanced dorsal horn activity (Bosma et al., 2016).

Notably, results have not been uniform. Upon closer inspection of reported findings, it becomes evident that not all studies have found a uniquely elevated TS in FM patient. The possible reasons for that point to some shortcomings in the field.

What is missing in Research on Temporal Summation in Fibromyalgia?

Though research on TS in FM has been promising, particularly because robust measures of pain modulatory mechanisms are theorised as beneficial in healthcare (Grosen et al., 2013), a definitive difference has not always been achieved. Understanding *why* is crucial for the subsequent study of factors that shape pain perception in the presence of FM. There may be several reasons.

First, the modality of noxious stimulation. Depending on the method, different nociceptors will be predominantly excited and thus different painful sensation will arise. For example, a focused mechanical pressure would primarily engage the myelinated A-δ fibres, while distributed mechanical pressure would mainly engage the unmyelinated C-fibres (Treede et al., 2002). While TS can be evoked using both methods in pain-free participants (Arendt-Nielsen and Yarnitsky, 2009), the presence of centrally modulated chronic pain may mediate the process differently in both instances. In research on TS and FM, all pain modalities have been researched with *thermal stimulation* being the most common. 12 studies have applied thermal stimuli (heat or cold), of which 9 (75 %) found greater TS in patients (Staud, 2002; Price et al., 2002; Staud et al., 2003c,a, 2004, 2007b, 2008; Klauenberg et al., 2008; Craggs et al., 2012). 3 (25 %) produced mixed results where the effect was not conclusively estab-

lished across all measures (Staud et al., 2005; Potvin et al., 2012; Staud et al., 2014). Six studies applied *mechanical pressure* and four (67%) observed increased TS in the FM group(Hilgenberg-Sydney et al., 2016; Kim et al., 2015; Klauenberg et al., 2008; Staud et al., 2003a), as opposed to two (23%) that did not (Coppieters et al., 2015; Meeus and Nijs, 2007).

Far less popular have been electrical stimulation and ischaemic pain. Only one study used *electrical stimulation* (intracutaneous) to compare and it failed to find enhanced TS in patients (Lim et al., 2016). One study applied *ischaemic pain* and it also did not reliably produce TS in either cohort (Schreiber et al., 2017). It appears that the studies which applied painful heat stimuli were the most successful in observing greater TS in FM patients. It is not clear as to why electrical stimulation has not been more readily adopted, since the protocols for eliciting TS are widely-accepted as reliable (Nie et al., 2005).

Second and related to that, the operational definition of TS varies greatly between studies. While stimulation protocols for dynamic TS are fairly uniform due to the rigorous prerequisites necessary for the elicitation of TS (Arendt-Nielsen and Yarnitsky, 2009; Eckert et al., 2017; Kong et al., 2013), the operational definitions are more liberal. Defining TS is ultimately determined by the stimulation method, which has led to several distinct measurement approaches. For example, in different years TS has been defined as the last or the highest pain rating following a train of stimulation (Staud et al., 2001, 2003c, 2007a), as the difference between first and last (or highest, whichever is higher) pain rating in a series of painful stimuli (Staud et al., 2014; Lim et al., 2016), or as the difference between the average pain ratings for an "initial" and "later" pain rating periods (Kim et al., 2015; Potvin et al., 2012). The last study, the one by Potvin et al. (2012), is particularly interesting as they gathered continuous pain ratings

but did not utilise their temporal property in the definition of TS. Arguably, a comprehensive evaluation of TS should include both measures of magnitude and time.

Third and last, the overwhelming majority of findings have been generated by two research groups, who consistently adopted similar testing protocols. In fact, this was cited as the leading criticism in a recent meta-analysis by O'Brien et al. (2018). Continued replication of the established TS effects through varied methodology is needed to strengthen the understanding of how pain is modulated in the presence of FM.

A Modern Solution: Continuous Pain Ratings

As alluded to, some stagnation is present in research on TS in FM. Due to the limited methodology, it is unclear whether facilitated TS, a key marker of central sensitisation, is a prominent feature of the syndrome or a product of a particular testing paradigm. This is concerning not only for the field but also from a clinical perspective, where QST is increasingly being progressed for the benefit of chronic pain assessment (Fillingim and Lautenbacher, 2004). In Section 1.2. Challenges in Fibromyalgia, it became evident that accurate and reliable tools are lacking in the arsenal of healthcare specialists tasked with attending to FM patients. It is these theoretical and practical concerns that inspired the search for innovative methods of pain assessment.

Continuous record of pain is not novel but rather a well-recognised and established method for increasing the quality of pain data collection (Boormans et al., 2009). As the name suggests, it involves continuously recording pain ratings for a period of time, during which the participant is asked to constantly reassess their pain. The sampling rate can be as small as necessary for the precise reg-

istry of time-sensitive fluctuations. In comparison, the currently conventional approach is to gather single pain ratings at key time points, predetermined as relevant. Commonly, this also involves rating a painful sensation retrospectively, after the period of stimulation has ended (e.g. *"What was the highest pain rating during the stimulation"* or *"How would you rate the pain overall?"*). As explained by Wijk et al. (2013), strong effect of memory should be expected when using such approach. Adopting continuous pain ratings does not mean that traditional measures of TS will be inaccessible. Let us consider, for example, the studies where the maximal pain rating after a period of stimulation was used (Staud et al., 2008). Instead of collecting singular ratings at times of anticipated increase, we can continuously monitor the ratings for that same time period and extract the maximal value. This data-driven approach creates two new research directions for the study of TS in FM.

Foremost, it would allow examining a so-far overlooked aspect of TS: when does TS happen in FM? This is well-researched in WU, both in pain-free and in clinical cohorts (Arendt-Nielsen et al., 1994), undoubtedly due to the reliance on measurement of physiological events. This has not been directly addressed in TS yet. It is possible that where no augmented TS in FM patients has been found, it was measured either too early or too late to capture peak increase. It is also viable that the common approach of quantifying TS through a start-to-peak ratio is distorted by the inherently present FM hyperalgesia, which has been demonstrated to produce an amplifying pain effect, independent of that of repeated stimulation (Magerl et al., 1998). Alternatively, it may be that it is the time of peak TS and not its actual magnitude that is uniquely different in FM. This is also yet to be researched.

Second, due to the previous limited number of observations, it is unclear whether

increased pain ratings in the period of TS persist into the period of adaptation. Do FM patients continue to reaching higher peak pain ratings than their pain-free counterparts, thus indicating failure to habituate? If so, that would be another indication of deficient endogenous pain modulation in FM. Or do patients report an overall reduction in pain, as it has been observed in studies on healthy participants (Edwards and Fillingim, 2001)? Analysis of this later period may further characterise pain processing in FM.

Significance of Present Study

To summarise, there are many indications that in FM patients TS is indicative of atypical pain facilitation. The failure to observe discernible enhancement may be due to continued reliance on the same stimulation protocols or due to measurement and definition of TS. Continuous record of self-reported pain intensity may counter the latter by providing high temporal resolution. The study described in this chapter thus gathered continuous pain ratings alongside tonic electrical painful stimulation in an attempt to observe whether TS is enhanced in FM. The goal was not to merely replicate an effect but to establish a new testing paradigm, suitable for future study of modulating psychological factors.

In alignment with the planned thesis aims, this study will:

- Attempt to replicate the finding of abnormally enhanced TS in FM patients. This will be done through a comparison with pain-free matched controls, who will undergo the same QST protocol.
- Gather continuous pain measurements, as opposed to single pain ratings, to enhance the temporal resolution of the data. Through this, the temporally sensitive measures of both TS and the following it adaptation period will be captured.

- Extract both the magnitude and the time of key time points, where applicable. This continuous collection of pain ratings will allow to study and compare the pain profile of patients and controls in a new dimension.

3.2 Manuscript

The work presented in this chapter was published as a 'green' article on medRxiv with the title 'Continuous pain report demonstrates time delay of pain ratings in Fibromyalgia'. The full citation of the article is as follows:

Kharko, A. Y., Hall, S. D., Furlong, P. L., & Roser M.E. (2021) Continuous pain report demonstrates time delay of pain ratings in Fibromyalgia. *medRxiv*, https://doi.org/10.1101/2020.12.28.20248780

3.2.1 Abstract

***Background**: Enhanced temporal summation (TS), measured through self-reported pain ratings, has been interpreted as indicative of central sensitisation in fibromyalgia. Greater TS in patients, however, has not been universally observed. It is also unclear whether increased pain report maintains beyond the TS period.*

***Methods**: In this study, we measured TS through continuously reported pain ratings. Fibromyalgia-diagnosed patients (n = 17) and matched pain-free controls (n = 13) rated painful transcutaneous electrical stimulation of various intensity levels in 18 one-minute-long blocks. Pain was rated on a 101-point visual analogue scale. The resulting continuous response was divided into TS (< 15s) and adaptation (15 — 60s) periods. Average pain values were extracted for each period alongside the timing of key events such as maximal pain ratings. The difference in temporal summation and adaptation measures between*

fibromyalgia and control participants was analysed using mixed-effects modelling.

***Results**: The average pain ratings for TS and adaptation periods were not significantly associated with fibromyalgia diagnosis but were with stimulation intensity. The same was true for the magnitude of the maximal rating during TS and the slope leading to that peak rating. The presence of fibromyalgia, however, did predict the time of the maximal TS rating, as well as the value and the time of the maximal adaptation rating.*

***Conclusions**: Our study did not find homogeneously increased TS pain ratings. Instead, by utilising continuous pain data we demonstrate for the first time that the time of TS peak rating, as well as the magnitude and time of adaptation peak rating are linked to fibromyalgia diagnosis.*

3.2.2 INTRODUCTION

Fibromyalgia (FM) is a chronic widespread pain condition of unknown aetiology, associated with disrupted sleep, fatigue and mild cognitive disturbances; resulting in high emotional burden (Clauw, 2014). The high prevalence, 2% to 5% of the population (Queiroz, 2013), and limited long-term success of symptom management (Häuser et al., 2014), has put pressure on understanding the mechanisms that underlie pain processing in FM. Allodynia and hyperalgesia, the key markers of FM pain (Sluka and Clauw, 2016), have been attributed to abnormal pain facilitation in the central nervous system (CNS) (Meeus and Nijs, 2007) a phenomenon known as central sensitisation. In psychophysical research, it has been studied through temporal summation (TS).

TS is the increase in reported pain in response to unremitting stimulation at a fixed frequency (Arendt-Nielsen et al., 2000). It is considered the behavioural

counterpart of wind-up (WU), a central spinal mechanism where an increased excitation of dorsal horn neurons is observed following repeated engagement of C-fibres (Gebhart and Schmidt, 2013). While TS and WU are part of healthy nociception, both have been reported to be augmented in chronic pain conditions, such as FM (Staud, 2012).

The majority of observations on TS in FM come from a series of studies began by Staud and Price (Staud et al., 2001). They have reported that FM patients require less stimulation intensity than pain-free controls to produce similar TS pain ratings (Staud et al., 2003a). Further, maintenance of TS required less stimulation in the FM cohort than control (Staud et al., 2004). Importantly, this pattern of increased TS in FM has been demonstrated across several stimulation modalities (Graven-Nielsen et al., 2000; Staud et al., 2003a, 2014).

Greater TS in FM, however, is not a universally-observed phenomenon. Several studies report mixed results, in which increased TS in patients was contingent on stimulation location or modality (for review see O'Brien et al. 2018. One study failed to find any deviancy in the clinical cohort (Lim et al., 2016). Part of this literature heterogeneity may stem from varying methods of TS elicitation and measurement. The conventional approach dictates deriving a measure based on comparison between a single pain rating and a later rating following repeated stimulation at a frequency that evokes TS (Lim et al., 2016; Staud et al., 2001). Such a low rate of pain sampling provides a coarse measure of the temporal aspect of TS and does not show whether the enhanced pain perception maintains beyond the period of TS. It has also been noted TS is likley only the initial phase of the pain response (Graven-Nielsen et al., 2000) and the following period, here termed adaptation, could also be used as a behavioural marker of WU but has not yet been adopted in FM.

The conventional approach has limited utility. Firstly, the use of singular pain ratings does not capture the possible development of pain perception across a fixed interval. Secondly, the reporting of a single value from a point in time is likely subject to high measurement error and individual variation. Thirdly, the serial processes of summation and adaptation are likely to be conflated by use of a fixed measurement point and the temporal envelope of these processes overlooked.

Here, we describe the collection of continuous pain ratings, to address the limitations of single fixed pain reports. Continuous pain ratings, concurrent to stimulation, have been found to reliably reflect acute pain perception (Boormans et al., 2009; Wijk et al., 2013). In FM research, one study used continuous pain report but did not analyse the time property of the gathered pain data (Potvin et al., 2012). The extraction of key timepoints from TS and adaptation for comprehensive analysis of acute pain processing in the presence of FM is yet to be done.

To address this, we carried out a study with FM patients and pain-free controls using transcutaneous electrical stimulation (TES), a well-established method for eliciting TS (Arendt-Nielsen et al., 1995). We applied tonic single-pulse TES at individual-derived intensity levels and asked participants to rate their pain continuously on an automated visual analogue scale (VAS). We anticipated that time, a new property of the extracted data, will be the key measure to characterise TS in FM.

3.2.3 METHODS

Participants

Participants were recruited on the basis of several strict eligibility criteria (see Table 3.1). Ethical permission was granted by the School of Psychology, University of Plymouth (17/18-890).

Psychological Testing

Presence or absence of FM was confirmed on the day of testing through the American College of Rheumatology Criteria from 1990, ACR '90, and 2010, ACR '10 (Wolfe et al., 1990, 2010). The latter were scored considering the redactions from 2016 (Wolfe et al., 2016). Recent pain history was assessed through the Short-Form McGill Pain Questionnaire, SF-MPQ (Melzack, 1987).

Psychophysical Testing

All psychophysical testing was performed on the skin over the sural nerve at lateral border of tendo-Achilles. The testing setup can be seen in Figure 3.1. Body side was counterbalanced between participants. The area was to be free of skin damage, tattoos, and hair. Prior to placing electrodes, the stimulation site was cleaned with an abrasive gel followed by 70% isopropyl alcohol. Two disposable 2 cm self-adhesive disk electrodes were then positioned with inter-electrode distance of 3 cm. Impedance was checked by D175 impedance meter (Digimeter Ltd., United Kingdom) and was maintained below 50 kohm.

Stimulation Parameters. Stimulation was delivered by a constant current stimulator DS7AH Digitimer (Digitimer Ltd., UK). The equipment was operated semi-automatically by the same experimenter: a computer maintained the frequency while the experimenter adjusted the intensity. Stimulation was a single-

Table 3.1: Eligibility Requirements for Participation

All Participants	
(a) Age	18 to 60 years
(b) No diagnosis of a CNS condition *	2) Including infections (e.g. meningitis), inflammatory diseases (e.g. multiple sclerosis), genetic conditions (e.g. Huntington's diseases), neurological conditions (e.g. autism), neurode-generative disorders (e.g. Parkinson's disease), or cancer.
(c) No diagnosis of a rheumatoid condition	E.g. lupus, rheumatoid arthritis, osteoarthritis.
(d) No acute pain at time of testing	E.g. temporary pain from mechanical trauma.
(e) No contradiction for receiving TES as dictated by equipment manufacturer.	E.g. unexplained fainting spells, familial history of epilepsy or diagnosis of epilepsy, heart conditions, shunts, stents, or implantable devices.
(f) No intake of gabapentinoids or prescribed analgesics in the month preceding testing.	Incidental intake of mild analgesics such as paracetamol or ibuprofen was allowed.
(g) No caffeine and alcohol 24hrs prior to testing.	-
FM Patients	
(a) A formal diagnosis of FM	Either by general practitioner or a rheumatologist.
(b) No other chronic pain condition.	E.g. chronic nonspecific low back pain.
HC Participants	
(a) No diagnosis of any chronic pain condition	-
(b) Match an FM participant.	By gender, age, ethnicity, site of stimulation and time of the day testing slot.

CNS – central nervous system, FM – fibromyalgia, HC – healthy control.
* Apart from FM diagnosis for patients.

square wave pulse of 500ms duration, with maximum of 400V for the output.

Psychophysical Measures. To derive participant-specific stimulation levels,

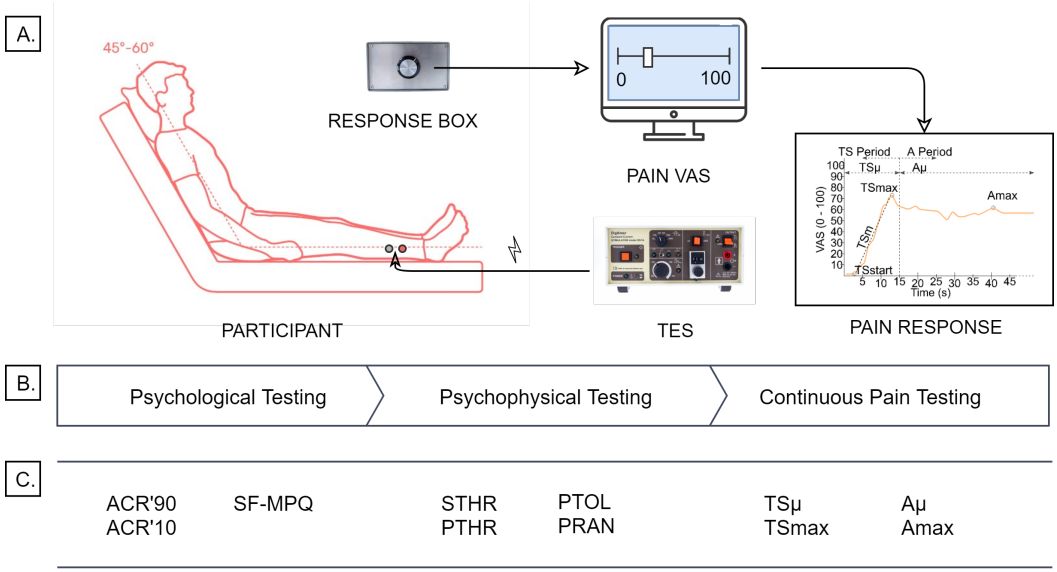

Figure 3.1: A. Equipment setup; B. Study stages; C. Acquired measures at each study stage.

VAS — visual analogue scale; *TES* — transcutaneous electrical stimulator; *ACR'90/'10* -– American College of Rheumatology Criteria for fibromyalgia diagnosis from 1990 and 2010; *SF-MPQ* -– Short-Form McGill Pain Questionnaire; *STHR* — sensory threshold; *PTHR* -– pain threshold; *PTOL* — pain tolerance; *PRAN* — pain range; *TS/Aμ* — average pain rating during temporal summation/adaptation; *TS/Amax* -– maximal pain rating during TS/A.

Stimulator image is supplied by manufacturer (Digitimer Ltd., UK) and sitting position image from Dimensions.Guide. Reproduced from respective sources with permission.

static quantitative sensory testing (QST) was first performed. Three psychophysical measures were collected: sensory threshold (STHR), pain threshold (PTHR), and pain tolerance (PTOL). ISD was the first instance of any sensation at the site of stimulation. PTHR was the first instance of stimulation being perceived as painful. PTOL was the first instance of participant indicating that they no longer wish to experience the next stimulation level increase. At each point, participants described the sensation to ensure understanding of instructions. Static QST was performed three times and each measure was defined as the average from these.

At the start of stimulation, the current was set at 0 mA and then increases in 0.1 mA increments. Stimulation was delivered manually by experimenter at an approximate interval of 1 s to prevent adaptation. Maximal current intensity was predetermined to be 40 mA. If PTOL was not established prior to that, the stimulation was stopped. If more runs were left, the procedure was restarted. If during all runs the limit was reached, it was deemed that a participant's pain tolerance was not established, and they were excluded from further participation.

At the end of the procedure a secondary psychophysical measure was derived: pain range (PRAN), which was determined as the difference between pain threshold and tolerance (PTOL – PTHR = PR).

Continuous Pain Testing

Stimulation Conditions. There were six stimulation levels 10%PRAN, 20%PRAN, 30%PRAN, 40%PRAN, 50%PRAN, and 60%PRAN, calculated as PTHR + (PRAN x %/100). Each stimulation intensity was delivered three times, resulting in 18 experimental blocks, presented in a computer-randomised order. Short breaks (no more than 1 min) were available between each block, with mandatory longer breaks after the 6th and 12th blocks (no more than 5 min).

Stimulation Parameters. During continuous pain testing, stimulation protocol was adjusted to elicit TS. The current remained as single-wave pulses with 500ms duration and up to 50 V. Instead of manual stimuli delivery, a computer maintained a 2.5 Hz frequency. Current intensity was dictated by stimulation condition and was thus always within acceptable to the participant range. The experimenter was responsible for the manual adjustment of intensity and did so before each block, without the awareness of the participant.

Continuous Pain Rating. To continuously reassess pain, a pain visual analogue scale (VAS) was used. The scale ranged from '0' to '100', with major ticks at every tenth mark. On the scale '0' was no pain, '1' was minimal pain, and '100' was the worst pain imaginable. Participants were instructed to constantly rate the experienced pain for the duration of the stimulation block. If other pain was present, which was the case for the clinical cohort, participants were to exclude it from the rating.

The rating was provided using a proprietary response device fitted with an Arduino Genuino (Arduino LLC) and a rotary button. By adjusting the rotation of the button, participants adjusted a sliding marker on the VAS. It is the position of that marker that was constantly resampled every 200 ms.

Analysis

Analysis was carried out in RStudio (v. 1.0.136).

Participant characteristics were summarised through average values and standard deviation (*SD*). Group differences were assessed through separate Student's t-tests (two-tailed, with post-hoc Bonferroni correction) where appropriate.

Psychological Testing. Cumulative and subsection questionnaire scores were summarised as average values and SD. Student's t-test (two-tailed) was used to compare cohorts on all forms.

Psychophysical Testing. STHR, PTHR and PTOL were calculated as the mean of each of the three recorded measurements. The average of each values was compared between groups through a Student's t-test (two-tailed, with post-hoc Bonferroni correction). Group level mean, SD, and range were used to describe psychophysical values. The same procedure was repeated for stimu-

lation conditions.

Continuous Pain Testing. To assess whether the presence of FM diagnosis was related to increased average and continuous pain ratings, key events and timepoints were extracted from the data for analysis. Figure 3.1, panel A) shows a prototypical pain response with measures of interest. First the response was broken into period of TS (0 to 15 s) and period of adaptation (15 s to 60 s). An average pain rating was calculated for each period (**TS**μ and **A**μ) to assess the overall pain rating for that period. Then maximal pain ratings were then extracted for each period (TSmax and Amax). Both value and time were recorded for each, resulting in the variables **TSmax-v**, **TSmax-t**, **Amax-v**, **Amax-t**. Lastly, for the TS period we calculated the slope from start of response to TSmax (**TSm**) to quantify the time needed to reach maximal rating during TS.

To analyse what factors predict the measures we used mixed-effect modelling. Separate models were created for each of the seven outcome variables. Predictors' inclusion was predetermined based on relevancy to hypotheses. *Group* (FM vs HC) was entered as a fixed factor to determine whether the presence of a diagnosis is associated with an increase in pain measures. *Stimulation* (stimulation intensity in mA) was entered as a fixed factor to account for the mediating effects of stimulation intensity. And finally, *Participant* was entered as a random effect, to account for individual variance.

Model syntax was guided by protocol described elsewhere (Brysbaert and Stevens, 2018; Matuschek et al., 2017), suitable for minimising Type I error in small samples. Sample size was estimated through power simulations following an established method (Green and MacLeod, 2016). A Kenward-Roger approximation was calculated for each fixed covariate, with the goal of observing $\geq$ 80% power for effect size .5.

3.2.4 RESULTS

33 participants met all eligibility requirements. Three participants from the control cohort were unable to complete the experiment due to failure to establish PTOL, thus leaving a sample of 30 participants. 17 were FM participants and 13 were pain-free controls.

Participants & Psychological Testing

All participants were Caucasian females. No significant differences were found between samples on individual characteristics (see Table 3.2). Psychological testing did find that the FM sample experienced more pain due to their condition in the week preceding testing.

Psychophysical Testing

No significant group differences were observed for STHR and PTHR (see Table 3.3). Both PTOL and PRAN were significantly higher in the clinical sample, just as all stimulation levels.

Continuous Pain Testing

The best mixed-fixed effects model for all measures had the following formula:

$$Group + Stimulation + (1 + Stimulation|Participant) \tag{3.1}$$

A full model summary can be found in Supplementary Material 1. Analysis of **TS**μ showed that it is significantly associated with Stimulation (*Coeff.* = 5.56, *SE* = 6.52, t = 7.14, $p < .001$) but not Group (*Coeff.* = 10.64, *SE* = 6.52, t = 1.63, p = .110), indicating that an increase in stimulus intensity was reflected in the average rating for the period, unlike the presence of diagnosis. Marginal

Table 3.2: Descriptive Statistics for Participants Samples & Psychological Testing

	Mean (SD)		*p-value*
	FM	***HC***	
Age (*n years*)	33.35 (11.9)	35.7 (12.84)	.941
Education (*n years*)	17.88 (2.23)	18.46 (2.3)	.492
Marital Status (*n married*) [a]	9 (53%)	4 (31%)	-
FM diagnosis duration (*years*)	3.63 (3.13)	-	-
FM symptoms duration (*years*)	10.04 (7.98)	-	-
Medication in the last 30 day [a]	17 (100%)	4 (31%)	-
Analgesics [a,b]	12 (71%)	3 (18%)	-
Anticonvulsants [a]	1 (6%)	-	-
Antidepressants [a]	10 (59%)	1 (8%)	-
ACR'90			
Widespread Pain	7.76 (.75)	.15 (.38)	<.001 ***
Tender Points	14.24 (2.49)	.31 (.63)	<.001 ***
ACR'10			
Widespread Pain Index	13.88 (3.18)	1.54 (1.44)	<.001 ***
Somatic Symptoms Severity	7.65 (1.58)	1.92 (2.22)	<.001 ***
Other Somatic Symptoms	2.06 (.56)	1.08 (.64)	<.001 ***
SF-MPQ			
Pain Descriptors	24.77 (7.4)	2.85 (2.61)	<.001 ***
Visual Analog Scale	6.65 (1.37)	1.15 (.8)	<.001 ***
Present Pain Intensity	3 (1.23)	-	-

SD -– standard deviation, *FM* – fibromyalgia group, *HC* – healthy control group. P-values were calculated using Student's t-test. Post-hoc Bonferroni correction indicated corrected p-value of $\leq$ .006.
[a] Number and percentage calculated.
[b] Analgesics included mild over the counter analgesics and mild opioids.
*** Statistically significant.

means estimated based on that model show a trend for increased pain rating in FM group (see Table 3.4). This trend, however, was not statistically significant, a pattern that was repeated in the subsequent analyses of TS pain measures.

The magnitude of the maximal TS pain rating (**TSmax.v**) was similarly predicted by Stimulation (*Coeff.* = 7.81, *SE* = 1.08, t = 7.22, $p < .001$) but not the Group

Table 3.3: Average Values (mA) for Psychophysical Measures Stimulation Levels

	FM		***HC***		*p-value*
	Mean (SD)	*Range*	*Mean (SD)*	*Range*	
STHR	1.38 (0.49)	.73 – 2.3	1.5 (0.33)	1 – 1.97	.427
PTHR	4.71 (2.83)	1.97 – 13.17	6.57 (3.62)	2.43 – 13.9	.124
PTOL	11.82 (7.85)	5.3 – 34.33	22.14 (9.75)	9.33 – 38.9	.003 ***
PRAN	7.11 (5.7)	2.53 – 24.5	15.57 (8.22)	5.6 – 27.5	.002 ***
10% PRAN	5.42 (3.23)	2.3 – 14.69	8.13 (3.89)	3.12 – 16.37	.047
20% PRAN	6.13 (3.67)	2.7 – 16.22	9.68 (4.32)	3.81 – 18.87	.022
30% PRAN	6.84 (4.15)	3 – 17.75	11.24 (4.84)	4.5 – 21.37	.008
40% PRAN	7.55 (4.65)	3.3 – 19.63	12.8 (5.44)	5.19 – 23.87	.006
50% PRAN	8.27 (5.16)	3.7 – 22.08	14.35 (6.09)	5.88 – 26.37	.006
60%PRAN	8.98 (5.69)	4 – 24.53	15.91 (6.78)	6.57 – 28.87	.005 ***

SD -– standard deviation, *FM* – fibromyalgia group, *HC* – healthy control group, *STHR* — sensory threshold, *PTHR* — pain threshold, *PTOL* — pain tolerance, *PRAN* — pain range. P-values were calculated using Student's t-test. Post-hoc Bonferroni correction indicated corrected p-value of $\leq$ .005.
*** Statistically significant.

(*Coeff.* = 14.03, *SE* = 9.53, *t* = 1.47, *p* = .152). The time when the maximal rating was made (**TSmax.t**), however, was significantly associated both with Stimulation (*Coeff.* = .51, *SE* = .09, *t* = 5.46, *p* < .001) and Group (*Coeff.* = 3.17, *SE* = 1.23, *t* = 2.58, *p* = .016). Increase in stimulation slightly increased the time to the peak rating. Separately, belonging to the FM cohort was associated with an additional almost 3 s delay (see Table 3.4).

The slope from the start of the response to the maximal pain rating (**TSm**) was not related to Stimulation (*Coeff.* = .14, *SE* = .08, *t* = 1.8, *p* = .089) or Group (*Coeff.* = .41, *SE* = .98, *t* = .42, *p* = .681), suggesting that the slope did not differ on basis of stimulus intensity nor the presence of FM diagnosis.

The average pain rating during the period of adaptation (**A**μ) significantly increased with Stimulation (*Coeff.* =8.15, *SE* = .98, *t* = 8.29, *p* < .001) but not

Table 3.4: Estimated Marginal Means.

Group	EMM	SE	95% CI	
			Lower	Upper
TSμ				
HC	24.12	(6.49)	11.03	37.22
FM	34.76	(5.86)	22.94	46.59
TSmax.v				
HC	36.47	(9.61)	17.09	55.86
FM	50.51	(8.69)	32.98	68.03
TSmax.t *				
HC	7.38	(.98)	5.39	9.37
FM	10.56	(.91)	8.72	12.39
TSm				
HC	6.36	(.79)	4.74	7.97
FM	6.76	(.71)	5.32	8.2
Aμ				
HC	30.48	(9.61)	11.05	49.91
FM	50.52	(8.6)	33.15	67.88
Amax.v *				
HC	29.25	(9.3)	10.39	48.12
FM	59.05	(8.32)	42.22	75.88
Amax.t *				
HC	24.33	(3.31)	17.58	31.07
FM	36.81	(3.05)	30.66	42.97

SD -– standard deviation, *FM* – fibromyalgia group, *HC* – healthy control group. *EMM* — estimated marginal means, *SE* -– standard error, *CI* — confidence interval. P-values were calculated using Student's t-test.

Group (*Coeff.* = 20.04, *SE* = 10.6, t = 1.89, p = .069). As with TS, the trend exhibited by FM patients for higher average pain rating for the period did not reach statistical significance.

In contrast, the maximal rating made during adaptation (**Amax.v**) was sensitive to both stimulation and presence of diagnosis. An increase of Stimulation intensity was associated with an increase of reported pain (*Coeff.* = 7.96, *SE* = .97, t = 8.23, $p < .001$). The FM Group additionally produced significantly higher maximal pain ratings during adaptation (*Coeff.* = 29.8, *SE* = 10.87, t = 2.74, p = .011). The same was true for the time the peak rating was made

(**Amax.t**). Increased Stimulation (*Coeff.* = 1.26, *SE* = .37, *t* = 3.41, *p* = .006) and belonging to the FM group (*Coeff.* = 12.49, *SE* = 4.1, *t* = 3.04, *p* = .005) predicted a delay in reaching that maximal rating.

3.2.5 DISCUSSION

Despite a large body of research reporting augmented TS in FM (O'Brien et al., 2018), several studies have failed to consistently achieve the same results (Lim et al., 2016; Potvin et al., 2012; Staud et al., 2008). To address this discrepancy, we adopted a different pain measurement approach, in which pain perception was assessed through continuously gathered pain ratings. Using it, we were able to analyse not only the value of a given pain rating but also the time it was made.

We found that FM was significantly associated with delays in reaching peak pain ratings during the periods of TS and adaptation. In contrast, only the magnitude of the maximal peak rating during adaptation differed significantly between cohorts. The value of the peak TS rating was not significantly associated with diagnosis, and neither was the slope to that peak. Average pain rating during TS and adaptation were also not found to be significantly different between participant groups. The best mixed-effects model for each measure included stimulation intensity as a factor. Apart from the TS slope, all measures were found to be predicted by it. An increase in stimulus intensity was mirrored by an increase in average pain ratings during TS and adaptation, as well as magnitude and time of maximal ratings. Together, the findings show that continuous pain report not only enabled the extraction of a new variable property but that it was this temporal property that was consistently associated with the presence of FM diagnosis.

Although using the maximal pain rating in response to TS eliciting stimulation has been the conventional approach to characterising central sensitisation in FM (Staud et al., 2001), our study suggests that this may be only one of several markers of deficient pain modulation. In previous studies, pain ratings were collected at predetermined timepoints following a prolonged stimulation needed to elicit TS (Staud et al., 2001). This both limited the measurement window and the number of observations. In our study, we purposefully extended the pain rating collection time. This gave us sufficient time to measure the TS part of the response, as well as to observe how participants adapt to pain post-TS. Let us consider both in succession. First, the extended record enabled the flexible extraction of maximal TS rating. We propose that it was this key change that allowed us to observe significant group differences in the TS period. It may be that previous research, which was not successful in finding augmented TS, measured peak TS rating too early, as our results indicate that FM patients were slow in reaching their peak rating. That delay is of particular importance when considered together with analysis of the later adaptation period.

Extending data collection past the TS period was the second major advancement of our study. The conventional focus on TS as a method of quantifying centrally dysregulated pain modulation in FM had demotivated further inspection into how participants adapt to prolonged pain. This is different to studies where aftersensations to TS-inducing pain stimulation were studied (Banic et al., 2004). Here, we were interested to observe whether FM participants continue to rate their pain increasingly high, thus indicating sensitisation, or whether they would slowly begin to habituate to it, evident in reduced pain ratings. The finding that maximal adaptation rating was not only higher but reached later by the FM group suggests that these participants continued to

sensitise to the stimulation. The yet again delayed peak further supports the idea of disrupted pain inhibition under FM (Sluka and Clauw, 2016).

Our study also agreed with previous research that hyperalgesia is integral to the FM pain profile (Nielsen and Henriksson, 2007). We chose to apply individually-derived stimulation conditions in order to demonstrate the differences in sensitivity between the participant cohorts. Despite the stimulation levels being calculated so that comparable pain ratings are be observed between participants, this was not found. For example, the 10% PRAN condition should have elicited pain ratings around the 10th mark on the VAS, regardless of which group the participant belonged to. As could be seen in Figure 3.2, however, patients consistently provided ratings higher than their pain-free counterparts. Further, the average stimulation values were lower in the FM group, yet they still rated the evoked pain as higher than the control. Together, this pattern of results suggests that hyperalgesia, a key marker of central sensitisation, is present in FM.

It is interesting that HC participants produced consistently lower ratings than those expected for the respective stimulation condition. Perhaps the trend is partially attributable to habituation. The ability to adjust to continuous mild nociceptive input is part of the CNS regulatory mechanisms. The failure to see a similar effect in FM participants further supports the theory of the CNS origin of the syndrome (Nielsen and Henriksson, 2007).

Limitations & Future Directions

Unlike other studies (Staud et al., 2005), we only examined continuous pain report in response to TES. Research has shown that a comprehensive pain profile can only be achieved when testing pain perception through multiple stim-

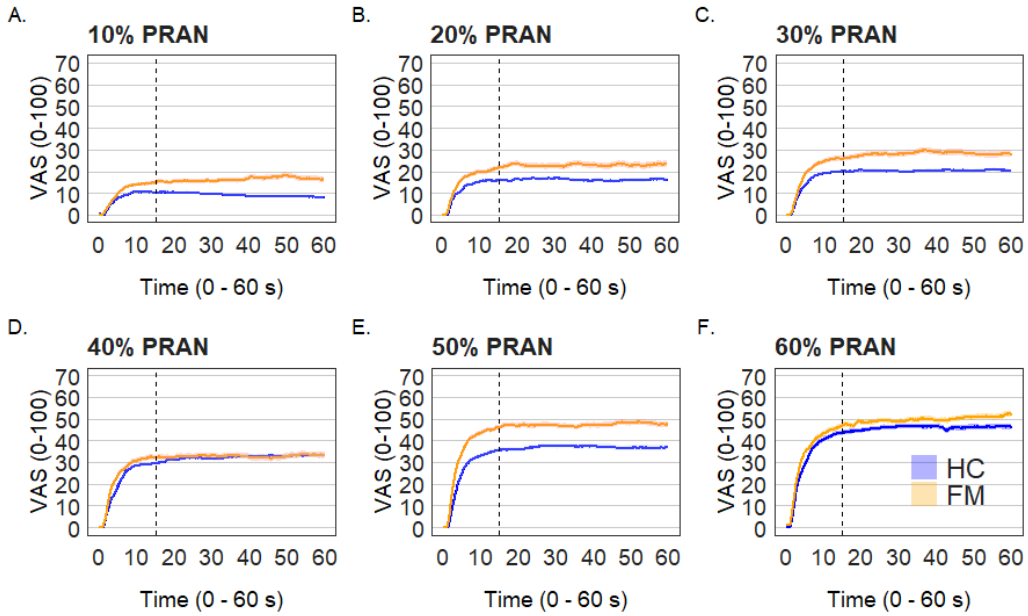

Figure 3.2: Average Trajectory of Continuous Pain Ratings per Stimulation Condition.

VAS – visual analogue scale; *PRAN* – pain range; HC – healthy control; FM – fibromyalgia.

ulus modalities (Hastie et al., 2005). In FM, employing a multidimensional pain testing protocol with continuous pain ratings would further clarify the role of time in the augmented development of TS and adaptation. Further, the focus of the current study were only behavioural markers of central sensitisation. It remains unclear how does the subjective pain report connect to the physiological response. Although, TS and adaptation are assumed to reflect underlying WU (Graven-Nielsen et al., 2000), psychological modulators such as stress have been theorised to mediate self-reported pain at the supraspinal level (Crettaz et al., 2013). Concurrent measurement of both TS and WU (unlike the measurement of TS only in this study) is not only plausible due to the common stimulation protocol but would also be useful in the clarification of their relationship and allow for further investigation of psychological mediating factors. Lastly, while the benefits of individually derived stimulation levels were evident,

they do complicate data interpretation. Here we calculated stimulation conditions using an individual's pain range, which led us to deliver vastly different stimulation between cohorts. The alternative approach where predetermined values are used may be adopted instead.

Conclusion

Continuous pain ratings of TES were simple to implement while rich in produced data. The newly extracted time property of the maximal pain ratings made during TS and adaptation were found to be reliable measures of differentiation between FM-diagnosed and pain-free cohorts. Analysis of the later pain response period, adaptation, was also beneficial for the characterisation of central sensitisation in FM and should be analysed alongside TS in future investigations.

3.3 Concluding Commentary

Summary

This chapter presented the first study of PhD research, which investigated pain processing in FM. The main goals included establishing whether TS, measured through continuous pain ratings, is augmented in patients unlike in matched controls. The new pain measurement approach leads to two novel findings.

First, continuous pain ratings enabled the *flexible* extraction of key pain measures. For example, instead of predetermining when does a maximal rating occur in temporal summation period (TS Period) (Staud et al., 2005), its value and associated time were extracted. It was thanks to this open approach that we did find an indication of augmented in FM-diagnosed patients. None of the other TS measures was significantly different between the cohorts. This in-

cluded the magnitude of maximal rating (TSmax-v), the slope to maximal rating (TSslope), and the overall average rating for the period (TSμ). It must be noted that the trend for increased pain rating in the presence of FM diagnosis was evident in all these measures. The failure to reach significance may be due to the insufficient number of control participants.

Further, the application of continuous pain report allowed us to calculate a new measure of TS, TSslope. It was included as a way to quantify the rate of increase to the maximal rating during the TS Period (TSmax), similarly to previous research, but it did not demonstrate any significant group differences.

Second, the continued pain collection beyond the window for TS was productive. While the average rating for adaptation period (A Period) did not reveal a group difference, both the time and the value of the peak rating did (Amax-t and Amax-v). FM patients were slower to reach their pain rating maximum but when they did, it was higher than the one observed in their pain-free counterparts. We interpret this as another indicator of augmented pain perception related to FM.

Discussion of Key Findings

Taken together the novel findings strengthen the argument for using continuous pain ratings in the study of both TS and adaptation in FM. The only other study that had a comparable pain collection paradigm was that by Potvin et al. (2012). In it, the the presence of FM was significantly associated with enhanced TS, but only in a subset of patients who received weaker stimuli. Comparison between Potvin et al.'s findings and ours is challenging due to the different pain modalities (thermal vs electrical stimulation), as well as the vastly distinct operational definitions of TS. Still, the common use of continuous pain report justifies a cur-

sory discussion. Potvin et al. (2012) applied heat stimulation at an individual's pain tolerance level over 2 min. They predicted that TS would occur at the end of that period. Thus, they defined TS as the difference between the average pain rating for last 15 s and the average pain rating between 15 - 30 s. In our study, we used several measures to characterise TS with a focus on extracting the temporal property of key pain response events. We argue that this new variable property is more suitable for the characterisation of central sensitisation when applying TES and should be considered further. We acknowledge there are different approaches to analysing continuous pain data and some may be more appropriate than others considering practical restrictions of the chosen stimulation method. Nonetheless, continuous pain rating can enable time-sensitive dissemination of acute pain report.

One of the key findings from this investigation is the delay in the clinical cohort of both TS and adaptation peak pain ratings. The significant time delay of peak rating is particularly meaningful in the context of the previous comparable study by Lim et al. (2016), which used intracutaneous electrical stimulation. There, TS was defined as the pain rating of a train of five 1 ms stimuli at intensity set as 100% of individual PTHR. While the rating of the train of stimuli was higher than the rating of a single stimulus, thus indicating TS, that increase was not greater in patients than control. Considering our results of the significant group effect on the timing of TS maximal rating, it may be that Lim et al. did not achieve a group effect due to short stimulation duration. As noted by experts in noxious electrical stimulation elsewhere Arendt-Nielsen et al. (2000), TS is a product of the right combination of sampling frequency and stimulation intensity. An increased stimulation duration is necessary to comprehensively observe WU and from it TS (Arendt-Nielsen and Yarnitsky, 2009). We thus conclude our

current pain testing protocol may be more suitable for the study of TS through electrical stimulation.

Lastly, in all our analyses we repeatedly found a significant effect of stimulation. While this is not a novel observation, it does facilitate the question of whether previous reports which found increased TS in FM were aided by their choice of stimulation protocol. To remind, in our study we applied TES at individually-derived levels. Their magnitude was greatly affected by participant tolerance. As shown in Table 3.3, the clinical cohort had on average much lower pain tolerance. While the applied stimulation levels were sufficient to facilitate varying degrees of painful response, they may not have been strong enough to produce a significant difference when comparing to controls. To paraphrase, the pain-free group received stimulation at a significantly higher intensity. If patients had received stimulation at the same levels as controls, an even higher increase across pain measures could be reasonably expected, in line with previous studies. Here, objectively same stimuli were avoided both for ethical and practical reasons, the latter of which included the aim to adopt previously trialled testing protocols (Banic et al., 2004; Lim et al., 2016).

Conclusion

Results from this chapter encourage the further study of acute pain perception through continuous pain report at individually determined stimulation intensity. Both pain-free and chronic pain patients tolerated well the tonic painful stimulation and were able to continuously reassess their pain. The novel observations that arose from the analysis of the time of peak ratings point to a new research direction in the general field of TS. Ratings from both TS and adaptation periods pointed to key measures of differentiation between patients and controls, further strengthening the necessity of adopting continuous pain ratings. Next, the

success of the testing paradigm poses two questions. First, whether it works with concurrent modulation of anxiety, and second, whether it similarly affects TS and adaptation measures. These questions will be addressed sequentially in the next two chapters.

Chapter 4

Effects of 7.5% CO_2 Inhalation on Pain-free Pain in Healthy Participants

Man is not worried by real problems
so much as by his imagined anxieties about real problems.
*– **Epictetus***

FOLLOWING the successful adoption of continuous pain ratings for the study of temporal summation in fibromyalgia-diagnosed patients and healthy controls, the next step was to integrate it with an anxiogenic intervention. This was a key study that determined the feasibility of concurrent induction and measurement of experimental pain and experimental anxiety.

4.1 Introductory Commentary

The previous study contributed to the bank of evidence supporting the significance of TS in understanding FM's pain profile. It also ratified continuous pain ratings as a robust method for the measurement of TS by preserving the fine temporal fluctuations otherwise lost in traditional approaches. Following the preset thesis goals, the next step would be to evaluate the contribution of acute anxiety in the modulation of TS. A novel methodological approach had to be

adopted to fulfil this purpose, hence, this phase was investigated in two studies. The first study tested the concurrent genesis of pain and anxiety in pain-free adults, and the second one replicated the paradigm in FM patients. This chapter describes the foremost study.

As previously discussed in Section 1.3.2, studies that have investigated the relationship between acute anxiety and acute pain have produced varied results. Early research found that induced anxiety increased ratings of experimental pain when compared to no anxiety manipulation (Cornwall and Donderi, 1988). Such an increase was modulated to a degree by the relevancy of the induced anxiety, i.e. whether anxiety was induced through warnings about the severity of an upcoming pain task, or an irrelevant set of instructions (Al Absi and Rokke, 1991). However, other research has failed to observe such an increase, regardless of anxiogensis method's relevance to the pain task (Arntz et al., 1991, 1994). Later studies do not achieve homogeneous results either. Carter et al. (2002), Hoeger Bement et al. (2010), Rhudy and Williams (2005), and Tang and Gibson (2005) found a positive trend between heightened state anxiety and reported pain, but Wiech and Tracey (2009), and Rhudy and Meagher (2003) reported the opposite: pain ratings reduced with the increase of state anxiety. Although seemingly paradoxical, the latter is a well-known phenomenon termed *stress-induced analgesia*. It has been extensively demonstrated in animal studies, where the presence of an acute stressor elicits production of endogenous opioids, which in turn inhibit typical nociceptive responses such as the withdrawal reflex (Gamble and Milne, 1990; Mischler et al., 1996; Otsuguro et al., 2007). To understand how the framework of stress-induced analgesia explains some of the pain-anxiety research, a closer look at the anxiety induction process itself is required.

What is Missing in Anxiety & Pain Research?

Unlike other psychological factors such as attention or belief, which are common psychological processes in pain modulation research, studies on experimental anxiety are less prevalent and have produced conflicting findings. This may be due to several factors. First, there appears to be little standardisation of the anxiety induction protocols. Some popular methods include the performance of complex mental maths task or staged public speaking (Grillon et al., 2019). There are, however, many variations to their execution, which hinders study comparison and generalisation (Allen et al., 2016). Another popular method is the elicitation of a startle response by an unpredictable delivery schedule of electric shocks (Kaye et al., 2016). While the unpredictable shock paradgm is considered reliable, it is also believed to be strongly modulated by individual traits (Vaidyanathan et al., 2009), which may confound the inivestigation of anxiety. Second, it is highly questionable how effective these methods have been. Unless some degree of deception is used, participants are aware of the purpose of the task, which may either greatly diminish or on the contrary increase the resulting anxiety (Broadbent et al., 2019). Further, conventionally anxiogenic induction precedes the task which it is intended to influence. As mentioned, in some studies anxiety is induced through a promise of a very painful stimulus (Grillon et al., 2004) or a promise of assessment of intellectual capabilities by testing arithmetic skills (Lyons and Beilock, 2012). In both instances, the anxiety induction is not carried out concurrently to the pain task, and what ultimately is being measured are the *carryover effects* from anxiogenesis. Arguably, these are less potent and less reliable in the study of acute anxiety. Third and most important, state anxiety produced by scenario- or imagination-based tasks may be morphologically dissimilar to the naturally

occurring one due to the time-variant potency. As explained by Grillon et al. (2019), a human experimental model of anxiety must produce such an effect that will allow for the unversal testing of basic behaviour and higher-order cognitive abilities.

A Human Experimental Model of Anxiety

For these reasons, an alternative method has been gaining popularity in the study of experimental anxiety in Psychology. It is the CO_2 Challenge or Model, which involves the continuous inhalation of a hypercapnic mixture, an air mixture with elevated levels of CO_2, compared to that found in ambient air. The Model has a long history in respiratory research, where the produced effects have been extensively studied (Alexander et al., 1955; Stegen et al., 1998; Graeff et al., 2003; Pappens et al., 2012; Dyer et al., 2020). In Psychology, the CO_2 Model has been popularised by Bailey et al. (2005), who described a standardised protocol for anxiety induction. The structured approach allowed to study the resulting psychophysical and behavioural changes for a sustained period of time, in a manner that is conventional to experimental Psychology. Notably, the arousal elicited during the CO_2 Challenge strongly resembles that observed during an acute bout of anxiety, as judged both by objective measures and by the participants themselves (Bailey et al., 2005). These qualities earned it the title of a human experimental model of anxiety (Bailey et al., 2011a). The model has even enabled clinical research to study the efficacy of anxiety-reducing medication (Bailey et al., 2009, 2011b). For pain research, one of the biggest strengths of the model is the time-stable anxiogenesis, driven by the simple act of continuous inspiration of the anxiogenic mixture. Such setup allows for both acute anxiety and acute pain to be tested simultaneously. For this reason, this method was chosen over traditional anxiogenesis approaches.

Research on CO_2 Model & Pain

Despite its long and successful history, the CO_2 Model, as described by Bailey et al. (2005), has been scarcely applied to pain research. One of the earliest experiments is that by Stokes et al. (1948), who found that the inspiration of 5% – 7.5% CO_2 mixture increased the pain threshold to thermal noxious stimulation. The analgesic effect was categorically contributed to the mixture and not changes in skin conductance or altered peripheral perception following cardiovascular changes. Elsewhere, the inhalation of 5% or 15% CO_2 mixtures, has been found to coincide with a reduction of pain ratings, with the analgesic effects being more pronounced in the higher concentration condition (Vowles et al., 2006). The same pattern has been observed in experimentation with thermal pain but not mechanical pressure or electrical stimulation (Grönroos and Pertovaara, 1994). Apart from subjective measures of pain, psychophysiologic measures of nociception have also been studied under the CO_2 Model. In striking contrast to self-reported pain, the nociceptive withdrawal reflex does not appear to be inhibited by the hypercapnic inhalation (Grönroos and Pertovaara, 1994; Morélot-Panzini et al., 2014). Interestingly, none of the listed studies analysed evoked anxiety in relation tothe self-reported pain ratings. This is not true for another variation of the CO_2 challenge, where the goal is to induce painful dyspnoea. There, when participants give stressful descriptions of the evoked dyspnoea, these correlated with reduced nociceptive withdrawal reflex (Morélot-Panzini et al., 2007). This prompts the question: is it the subjective experience of the arousal elicited by the hypercapnic mixture, and not the hypercapnic inhalation itself, that reduces the pain response?

The question has not been directly addressed. Research so far has either assessed subjective ratings of pain by comparing them between conditions:

hypercapnic vs air (Morélot-Panzini et al., 2014), or has tested the nociceptive withdrawal reflex, also between conditions (Grönroos and Pertovaara, 1994). Where ratings of aversion or stress were gathered, these were not analysed in relation to pain (Vowles et al., 2006). To reiterate, so far any effect on pain or nociception had been directly attributed to the hypercapnic manipulation and only indirectly to the evoked stressful state.

Further, the discordance of effects produced by the CO_2 Model is also unclear: why is pain inhibited, as evident in the reduced subjective ratings, but nociception remains unchanged, as evident in the largely preserved nociceptive withdrawal reflex. The theoretical framework proposed by research on stress-induced analgesia provides a potential explanation. As described by Butler and Finn (2009), major differences are observed between animal and human studies, even when using comparable paradigms. For example, a typical experimental protocol includes an erratic administration of electric shocks as an aversive stimulus and a startle reflex as a pain response. This can be performed both with rats and humans, with analgesia being observed in animals (e.g. rats Otsuguro et al., 2007. But in humans, the opposite has been achieved: an increased startle, indicating stress-induced-hyperalgesia (Ploghaus et al., 2001). According to Butler and Finn (2009) the difference may be due to the expectations and interpretations that humans assign to the stressful stimulus, such as anxiety or fear.

Perhaps it is the involvement of these supraspinal CNS processes that accounts for part of the dissonance between the behavioural and physiologic measures of pain. In the context of the CO_2 model, this is likely the evoked anxious state. One way to directly address the psychophysiologic divide is by employing dynamic QST and studying TS. As previously discussed, TS is considered the

psychological counterpart of WU. Analysing it under the effects of the CO_2 Model would serve two purposes. First, it will aid the question of what drives the reduced behavioural response in the CO_2 Model: the hypercapnic mixture or the concurrent feelings of anxiety. Second, it will lay the foundation for studying the effects of anxiety in chronic pain conditions, where TS is commonly used as a marker of deficient central pain processing.

Significance of Present Study

To summarise, several significant gaps have been identified in the literature on acute anxiety and pain. To the best of current knowledge, there has been no investigation of concurrently evoked acute anxiety and pain, even in CO_2 Model research. Despite the promising results elsewhere, there is a lack of direct evidence for the analgesic properties of CO_2-induced anxiety. Lastly, the dissidence between the effects of CO_2 inhalation on pain and nociception raises the question of *how* self-reported pain is reduced in the presence of retained nociception. Addressing these questions aligns with the broad aims of the thesis.

In this study, I will:

- Test the integration of concurrent anxiety induction and pain induction. Based on similar research (Morélot-Panzini et al., 2014), it is expected to be successful, thus serving as a basis for consequent application with chronic pain patients.
- Test the feasibility of continuously rating both pain and anxiety during acute respiratory anxiety. Furthering previous work, the study will take advantage of the parallel administration of anxiogenic and noxious stimuli for their combined analysis.

- Observe the development of TS under acute anxiety. Few studies have experimentally manipulated anxiety and pain and none have explored TS. It is predicted that unlike studies on static nociceptive responses (Morélot-Panzini et al., 2014), TS will be suppressed during the anxiogenic inhalation, thus demonstrating stress-induced analgesia.

4.2 Manuscript

The work presented in this chapter was published as a 'green' article on bioRxiv with the title 'The role of anxiety in the perception of pain: Exploring the cumulative & temporal mechanisms of hypercapnic analgesia.' The full citation is as follows:

> Kharko, A. Y., Hansford, K. J., Klein, F. B., Furlong, P. L., Hall, S. D., Roser M.E. (2020) The role of anxiety in the perception of pain: Exploring the cumulative & temporal mechanisms of hypercapnic analgesia. *BioRxiv*, https://doi.org/10.1101/2020.10.30.357061

4.2.1 Abstract

Background: *Anxiety, evoked by continuous inspiration of a 5 – 8% CO2 mixture, has been found to have an analgesic effect on self-reported pain. The precise mechanism whereby this effect obtains remains unknown.*

Methods: *The present study tested whether temporal summation, the psychological counterpart of wind-up, is involved in hypercapnic analgesia. 21 healthy participants received painful transcutaneous electrical stimuli of varied intensity, during continuous inhalation of 7.5% CO2 mixture and medical air, presented in a single-blinded counterbalanced order. Continuous pain ratings were acquired*

to measure the temporal development of the pain response. Several points and events of interest that characterise the pain response profile were extracted from the continuous data.

Results: *Mixed-effects modelling demonstrated a reduction of all pain measures during inspiration of the anxiogenic mixture, but not air. This was accompanied by an increase in the psychological and physiological measures of anxiety. Analyses of the characteristic measures of temporal summation suggested that the hypercapnic mixture has an analgesic property evident from the start of the pain response. The same was true for the remainder of the response, the adaptation period, where pain ratings were also inhibited. Anxiety was found to be a mediating factor for summative pain ratings but not the temporally sensitive TS measures, suggesting an overall, cumulative effect.*

Conclusions: *The findings provide an explanation for the previously observed low self-reported pain during the inhalation of an anxiogenic hypercapnic mixture.*

4.2.2 INTRODUCTION

In psychopharmacology, the 5 - 10% carbon dioxide (CO_2) model is an established human experimental model of anxiety (Bailey et al., 2011a). It requires the participant to continuously breathe in the CO_2 mixture, which elicits a range of stable physiological symptoms of anxiety including hypercapnia, hypertension, tachycardia and diaphoresis (Pappens et al., 2012; Poma et al., 2005; Tominaga et al., 1976; Woods et al., 1988). Psychological and behavioural markers of anxiety are also observed, including increased ratings and attribution of negative affect, poor emotion recognition, and impaired information processing (Attwood et al., 2017; Cooper et al., 2013; Easey et al., 2018).

In pain research, as early as 1948, CO_2-evoked hypercapnia has been found to elevate pain threshold (Stokes et al., 1948). More recently, studies have demonstrated a dose-dependent decrease in self-reported pain intensity during the administration of thermal (Grönroos and Pertovaara, 1994) and mechanical pain (Vowles et al., 2006). While CO_2 inspiration appears to have an analgesic effect, electrophysiologic data does not definitively support this. The inhalation of a hypercapnic mixture has been found to produces an anti-nociceptive effect characterised by preserved nociceptive flexion reflex (Morélot-Panzini et al., 2014).

The decrease in self-reported pain, despite the persistent nociceptive reflex, has suggested that CO_2-mediated analgesia is preserved at a supraspinal level (Grönroos and Pertovaara, 1994); however, this has not yet been explicitly tested. One way to do so is by examining temporal summation (TS); the escalation of consecutive pain ratings in response to continuous stimulation of constant intensity at a critical frequency, within the first seconds of the painful input (Price et al., 1977). TS is the behavioural counterpart of wind-up; a central nervous system (CNS) measured increase in excitability of dorsal-horn neurons during nociceptive stimulation. While the CO_2 model has been used to study spinal nociception, it has not yet been applied to TS.

Further, since TS originates from self-report, is likely to be affected by the subjective experience of the hypercapnic inhalation. Previous research has found a complex aversive response to pain and/or CO_2-induced fear (Vowles et al., 2006). However, the anxiogenic effects of the inhalation and the temporal development of acute pain concurrent to CO_2-induced anxiety have not been directly investigated.

Here, we address the questions using a robust continuous pain-measurement

approach (Wijk et al., 2013), to capture the influence of the hypercapnic mixture on TS of pain and self-reported acute anxiety. We recorded the moment-to-moment changes in continuous pain ratings of painful transcutaneous electrical stimulation (TES), during inspiration of a 7.5% CO_2 mixture (anxiogenic condition) and medical air (control condition).

Consistent with previous reports, we hypothesised that summative pain ratings would be lower in the anxiogenic than the control inhalation. Utilising the continuous pain data, we next hypothesised that key measures extracted from the TS period would also reveal an analgesic effect of the CO_2 inhalation. In particular, TS rate would be slower (reduced TS slope) and reaching a lower maximum (reduced TS peak). Further, the pain ratings in the period following TS will remain reduced in the CO_2 condition. Lastly, we predicted that the lowered pain measurements will be associated with heightened anxiety.

4.2.3 METHODS

Participants & Screening

An extensive screening process was completed to minimise the risk of adverse reaction to the experimental process. Consequently, the participant group satisfied the following criteria: participants were 18 to 60 years of age; with a healthy BMI (18 – 30); were not pregnant (confirmed or suspected) or breast-feeding. Participants had no diagnosis of a concurrent chronic or acute condition; no medical issues relating to respiratory or cardiovascular systems; had no Axis I or Axis II diagnoses; and reported no acute pain at the time of testing. Participants were non-smokers (including vaping); had no current or history of substance abuse, including illicit drugs intake, alcohol abuse (> 35 units/week for females), and no excess caffeine consumption (> 8 cups/day). Participants

had taken no medication in the past month, other than contraceptive pills, topical creams or incidental use of over the counter mild analgesics and antihistamines. In compliance with the guidelines set by the manufacturer of the stimulation equipment, participants had no pacemakers, shunts, stents or metal in the body, and no skin abrasions on the site of TES.

In preparation to testing, participants were required to discontinue alcohol consumption 24 hrs prior to the study and xanthine-based beverages on the day of the study. Final eligibility was confirmed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Blood pressure (BP) and heart rate (HR) were monitored throughout the study, to ensure they remained within an acceptable range, as determined by the UK National Health Service (NHS) guidelines (BP range 90/60 - 140/90 mmHg; HR 60 - 100 bpm). Variance outside of these ranges would result in termination of the experiment.

Following screening, the participant group consisted of twenty-six adult females. Participant data, including age, ethnicity, height, weight, and BMI were recorded for further analysis. Participants were invited to a single testing session. Collected data was anonymised. Ethical approval (Ref. Number 18/19–1044) was obtained from the School of Psychology, Faculty of Health Ethics Committee at the University of Plymouth, UK. Informed written consent was obtained on the day of testing.

Pain History

Data from this study will also be used to inform the development of a further implementation of the CO_2 model in clinical pain populations. Therefore, additional data related to fibromyalgia (FM) were recorded but not reported here. These included the American College of Rheumatology Criteria from 1990,

ACR '90 (Wolfe et al., 1990) and from 2010, ACR '10 (Wolfe et al., 2010), considering the redactions from 2016 (Wolfe et al., 2016). Recent pain history was also assessed through the Short-Form McGill Pain Questionnaire, SF-MPQ (Melzack, 1987).

T*ES Stimulation & Pain Rating*

All psychophysical testing was performed by the same experimenter. Throughout the process participants were seated in a reclining chair in a semi-Fowler's position.

Stimulation Site. Stimulation site was the skin over the sural nerve at lateral border of the tendo-Achilles. Body side was counterbalanced between participants and stimulation site was confirmed to be free from hair and skin trauma. The site was prepared with an abrasive gel and cleaned with isopropyl alcohol prior to electrode placement. Two disposable self-adhesive disk electrodes, 2 cm in diameter, were positioned with inter-electrode distance of 3 cm. Electrical stimulation was delivered by a constant current stimulator DS7A Digitimer (Digitimer Ltd., UK). During acquisition of psychophysical measures, the equipment was manually operated by the experimenter.

Psychophysical Measures. Three psychophysical measures were collected to characterise individual pain profiles and calculate stimulation levels: sensory threshold (STHR), pain threshold (PTHR), and maximum tolerance (MTOL). STHR was the current amplitude at which the participant first felt a sensation at the site of stimulation. PTHR was the amplitude at which the participant perceived the stimulation as minimally painful. MTOL was the amplitude at which the participant was unwilling to experience a further stimulation intensity increase. Pain range (PRAN) was then determined as the difference be-

tween MTOL and PTHR (PRAN = MTOL – PTHR). Participants were asked to describe the sensation at each measure to ensure correct interpretation of instructions. Current amplitudes were identified using a staircasing approach, with pulses delivered at 1Hz, with increments of 0.1mA. A maximal acceptable current of 40mA was pre-defined for safety. Psychophysical measures were acquired three times and their mean value was used to determine the stimulation levels used during the pain rating task.

Stimulation Parameters. There were six experimental stimulation levels (SLs) in ten-percent increments (10-60%), calculated as:

SL = PTHR + (PRAN x %/100)

Experimental stimuli were single square-wave pulses with a pulse-width of 500ms, delivered at 2.5Hz. Stimuli were delivered at each of the stimulation levels in 45-second blocks, in a pseudo-randomised order. Each condition was repeated twice, producing a total of 12 experimental blocks. Stimulation was delivered semi-automatically using a computer, with manual adjustment of intensity between blocks.

Pain Ratings. Once the psychophysical measures and stimulation levels were determined, the participant was introduced to the pain rating task. A trial run of two blocks was carried out without anxiety induction.

A pain visual analogue scale (pVAS) was used to continuously measure pain ratings on a scale of 0 to 100, delineated with ticks at tenth intervals, where ‘0’ represented lack of pain, ‘1’ was the minimal sensation of pain, and ‘100’ was the worst pain imaginable. The rating was provided using a custom-build response box fitted with a rotary potentiometer button. Participants continuously rated the stimulation for the duration of the block, with values being recorded

every 50 ms using an Arduino Genuino (Arduino LLC).

4.2.4 CO_2 Model & Anxiety Testing

Gas Mixtures. Two gas mixtures were used in the experiment. The anxiogenic mixture contained elevated CO_2 (7.5% CO_2/21% O_2/ 71.5% N_2). The control mixture was Medical Air (0.04% CO_2/21% O_2/ 78% N_2). Gas cylinders were connected to a 10 L Douglas Bag and delivered to participants via a sterilised reusable face mask (7450 Series V2, Hans Rudolph Ltd). Inspiratory and expiratory flows were isolated using two-way non-rebreathing valves (Hans Rudolph Ltd). Delivery order of gas mixtures was randomised, single-blinded for safety purposes and counterbalanced between participants.

Anxiety Measures. Several measures of anxiety were collected. Participants completed the Trait version of the State-Trait Inventory for Cognitive and Somatic Anxiety, STICSA-T (Grös et al., 2007), prior to psychophysical testing to measure dispositional anxiety. Changes in state anxiety were measured throughout the study, using the State version of STICSA, STICSA-S (Grös et al., 2007), BP, HR, as well as an anxiety VAS (aVAS). aVAS was also a 101-point scale ranging from '0' – no anxiety, through '1' – least anxiety, to '100' – worst anxiety imaginable. Anxiety measures were delivered at key points during the study. STICSA-S was administered five times: prior to psychophysical testing, immediately following each inhalation session, and following each post-inhalation break. BP and HR were also recorded at five intervals: prior to psychophysical testing, two-minutes into each inhalation, and following each post-inhalation break. Twenty-seven individual aVAS ratings were recorded: prior to psychophysical testing and during each inhalation at the start of each stimulation block (12 blocks during each inhalation or 24 blocks in total), as well as at the end of each post-inhalation break.

4.2.5 *Procedure*

Participants first completed pain history and anxiety scales, followed by psychophysical testing and a pain rating practice run. After familiarisation with the task and safety briefing, participants were connected to the respiratory equipment. An initial two-minute idle inhalation, followed by BP and HR measurement, was used to confirm that participants' cardiovascular measures were within the acceptable range. Eligible participants continued to the testing session, which comprised of the first up to 15-min gas inhalation (CO_2 mixture or Medical Air), followed by a mandatory 20-min break, then second up to 15-min gas inhalation (CO_2 mixture or Medical Air), then final mandatory break. Participants were debriefed and reimbursed upon study termination. The experimental procedure is visualised in Figure 4.1.

4.2.6 *Analysis*

All analysis was carried out using RStudio v1.0.153 (RStudio Inc). Descriptive statistics for the sample, questionnaire scores, psychophysical measures, and stimulation levels were summarised as: mean values (μ) or count (n) and standard deviation (*SD*) or percentage (%); as appropriate. Mixed-effects modelling was used to determine the factors that affected a given outcome variable. Each model contained two fixed effects - Mixture (CO_2 Mixture or Medical Air), and Stimulation (SL10%, 20%, 30%, 40%, 50% or 60%). There were several possible random effects: Participant, and the anxiety measures aVAS, STICSA-S, HR, systolic BP (SYS), and diastolic BP (DIA). Model selection was theory-driven (Barr et al., 2013), toward a parsimonious formula (Bates et al., 2018), that minimises Type I error in small samples (Brysbaert and Stevens, 2018; Matuschek et al., 2017). The observed power for each appropriate model was assessed using Kenward-Roger approximation. Hypothesis testing was achieved

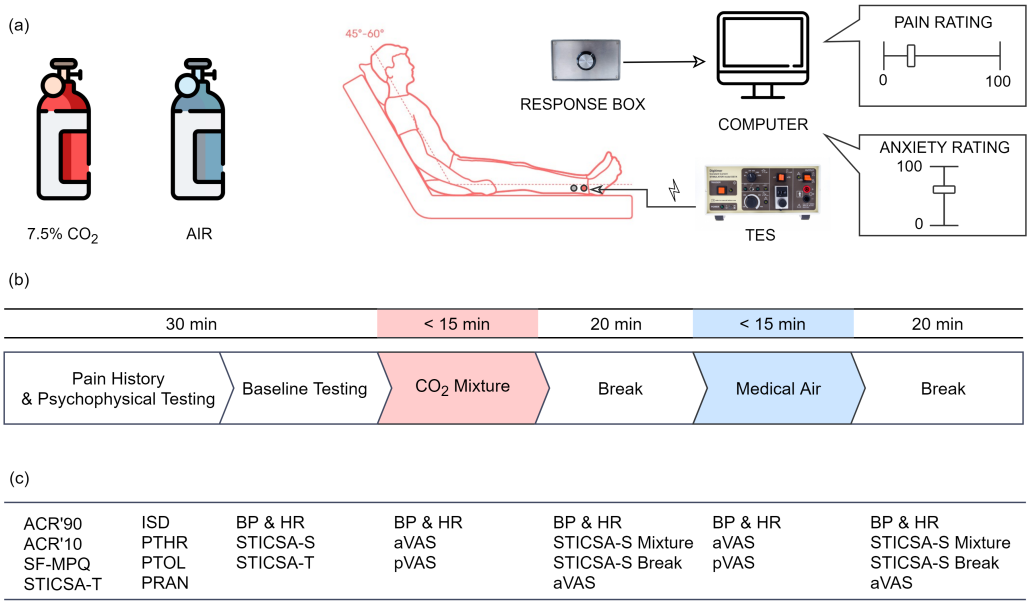

Figure 4.1: (a) The equipment setup, (b) The study stages, (c) Acquired measures.

TES: transcutaneous electrical stimulator; ACR'90/'10: American College of Rheumatology Questionnaire from 1990/2010; SF-MPQ: Short Form McGill Pain Questionnaire; STICSA-S/T: State-Trait Inventory for Cognitive and Somatic Anxiety - State / Trait Version; STHR: sensory threshold; PTHR: pain threshold; MTOL: maximum tolerance; PRAN: pain range; BP: blood pressure; HR: heart rate; a/pVAS: anxiety/pain visual analogue scale.

Stimulator image is supplied by manufacturer (Digitimer Ltd., UK), cylinder icons are sourced from FlatIcon, and sitting position image from Dimensions.Guide. Reproduced from respective sources with permission.

by comparison to a null model (by-participant intercept only), based on Bayes Factor (BF), likelihood-ratio testing (χ^2), and p-values. The final model statistics were: estimated μ and coefficient, *SD* and standard error (*SE*), reported alongside Bayesian estimated μ and coefficient, *SD*, and credible intervals. Bayesian analysis was carried out using weakly informed priors (Muth et al., 2018).

Average Pain Ratings. In our first hypothesis we predicted that summative pain ratings would be lower in the anxiogenic than the control inhalation. This was tested by comparison of the mean pain ratings per block (pVASμ) and per

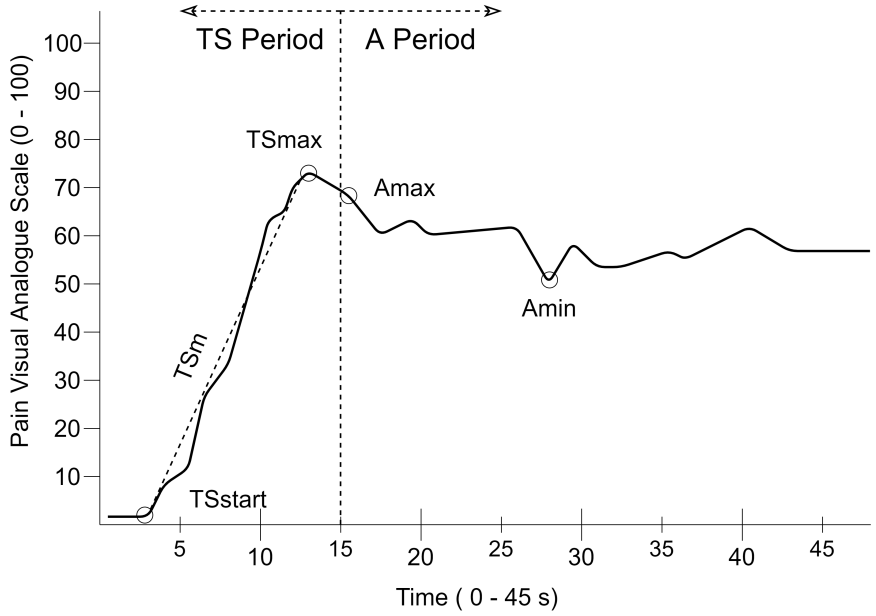

Figure 4.2: The prototypical continuous pain rating response is broken into two periods with several measures of interest.

TS Period: temporal summation period; A Period: adaptation period; TSstart: the start of the response; TSmax: the maximal rating made during TS; TSm: the slope calculated between the start of the response and the maximal TS value; Amin: the minimal value; Amax: the maximal value were recorded.

period. The continuous pain response was broken into two periods. At the start of a response block we expected to observe a period of rapid incline of pain ratings. We termed this portion of the pain response the TS Period. Taking into account the stimulation protocol (Arendt-Nielsen et al., 2000), the length of the TS Period was predetermined to span the initial 15 s. A measure of mean pain rating during the TS period (TSμ) was calculated alongside with the averaged pVAS rating for the time interval between 15 s - 45 ms called a period of adaptation, or A Period (Aμ). A prototypical response with the described periods could be seen in Figure 4.2

Continuous Pain Ratings. Our second hypothesis predicted that key measures extracted from the TS Period will be reduced during the CO_2 inhalation.

This was tested through comparison of the peak and the slope of the pVAS during TS. The peak (TSmax) was the maximal pVAS rating during TS, and the slope (TSm) was computed by fitting a line between the first pain rating (TSstart) to TSmax.

In our third hypothesis, we predicted that the CO_2 mixture will continue to lead to reduced pain ratings in the A Period. Here we computed two measures to capture the pVAS response: maximal (Amax) and minimal (Amin) pVAS ratings.

Anxiety Measures. In the last hypothesis we stated that increased anxiety will be associated lowered pain measurements. To test this we first confirmed that the CO_2 model was successful, by analysing whether the CO_2 inhalation significantly increased the psychological (aVAS, STICSA-S) and physiological (HR, DIA, SYS) measures of acute anxiety. This was determined using separate mixed-effects models. The inclusion of fixed and random effects following the same approach as previously described, with the addition of pVASμ as a random effect to account for the potential interaction of pain and anxiety. To test whether the elevated acute anxiety is associated with reduced pain measurements, the above mentioned anxiety measures were included as potential random effects as previously described.

Data relevant to the hypotheses are stored on Open Science Framework: https://osf.io/ds4e3/?view_only=07d2a59bd8a54685ac44700bc910947d.

4.2.7 RESULTS

Participants Data, Pain History, & Psychophysical Testing

Five of the 26 participants did not complete the 7.5% CO_2 inhalation, providing a final sample of 21 females. Their demographic data, cumulative scores on pain history questionnaires and average psychophysical measures are sum-

Table 4.1: Descriptive statistics for demographics, pain history, and psychophysical measures.

	μ or **n**	(***SD***) **or %**
Age (n years)	25	(7.27)
Ethnicity [a]		
Asian British	1	5%
Black British	1	5%
White British	18	85%
White Other	1	5%
STICSA-T	26.76	(5.52)
Cognitive Anxiety	13.33	(3.45)
Somatic Anxiety	13.43	(2.6)
SF-MPQ		
Pain Descriptors (0 - 45)	2.14	(2.15)
Visual Analogue Scale (0 - 10)	1.05	(.93)
STHR (mA)	1.30	(.42)
PTHR (mA)	6.56	(3.57)
MTOL (mA)	14.62	(7.57)
PRAN (mA)	8.06	(6.83)

Note: μ - average value, n – count, *SD* – standard deviation, % - percentage.
[a] Items, for which n and % were calculated.

marised in Table 4.1.

Pain Ratings

Average Pain Ratings. The best mixed-effects model for each average pain measure had the same fixed and random effects but differed in performance over baseline model (see Table 4.2).

The best model for pVASμ found that it decreased during the CO_2 Mixture (*Coeff.* = -3.68, *SE* = 1.23, *t* = 3.01, *p* = .003) but significantly increased with each Stimulation level. Variance in the pVAS was explained by individual variability, Participant (σ^2 = 180.5, *SD* = 13.43), and individual anxiety rating, aVAS (σ^2 = 55.4, *SD* = 7.44). pVASμ ratings per stimulation level and inhalation are

Table 4.2: Descriptive statistics for demographics, pain history, and psychophysical measures.

Variable	Model Formula	χ^2	*p*	BF
Average Pain Ratings				
pVASμ	~ Mixture + Stimulation + (1 | Participant/aVAS)	254.28	< .001	1.68 x 10^{50}
TSμ	~ Mixture + Stimulation + (1 | Participant/aVAS)	227.74	< .001	8.42 x 10^{43}
Aμ	~ Mixture + Stimulation + (1 | Participant/aVAS)	249.19	< .001	2.99 x 10^{49}
Continuous Pain Ratings				
TSmax	~ Mixture + Stimulation + (1 | Participant)	234.49	< .001	6.48 x 10^{42}
TSm	~ Mixture + Stimulation + (1 | Participant)	19.48	< .001	0.1
Amax	~ Mixture + Stimulation + (1 | Participant)	250.45	< .001	1.9 x 10^{46}
Amin	~ Mixture + Stimulation + (1 | Participant/aVAS)	249.19	< .001	3 x 10^{49}

Note: pVASμ: average pain rating for the whole response; TSμ: average pain rating for the period of temporal summation; Aμ: average pain rating for the period of adaptation. The choice of best model was design-driven with the goal of reaching a formula with a parsimonious number of factors. Each model was compared to a baseline model based on likelihood-ratio testing (χ^2) and BIC-derived Bayes Factor (BF).

summarised in Table 4.3.

The same was true for TSμ and Aμ. TSμ was reduced during the CO_2 Mixture (*Coeff.* = -2.9, *SE* = 1.07, *t* = 2.72, *p* = .007) but significantly increased with each increase of Stimulation intensity. Participants (σ^2 = 106.39, *SD* = 10.31) and their anxiety rating, aVAS (σ^2 = 64.06, *SD* = 8), accounted for large proportion of the variance in TSμ. Similarly, the CO_2 Mixture led to a decrease in Aμ (*Coeff.* = -4.11, *SE* = 1.36, *t* = 3.02, *p* < .01) while increase of Stimulation lead to an increase in Aμ, when considering the variance explained by Participants (σ^2 = 236.63, *SD* = 15.38) and their anxiety rating, aVAS (σ^2 = 51.64, *SD* = 7.19). Full model statistics can be viewed online in Supplemental Material 1.

Continuous Pain Ratings. The best mixed-effects models for continuous pain data differed in random effects (see Table 4.2). Detailed statistics for each model can be found online in Supplemental Material 2.

Table 4.3: Average stimulation levels and pain ratings per inhalation.

Stimulation	μ	*(SD)*	**CO_2 Mixture**		**Medical Air**	
			μ	*(SD)*	μ	*(SD)*
SL 10%	7.36	(3.61)	16.59	(13.86)	18.87	(16.52)
SL 20%	8.17	(3.77)	22.27	(15.73)	26.14	(17.95)
SL 30%	8.97	(4.04)	28.29	(18.41)	25.36	(19.29)
SL 40%	9.78	(4.40)	37.35	(20.8)	39.51	(18.44)
SL 50%	10.59	(4.83)	40.14	(18.15)	41.13	(20.39)
SL 60%	11.39	(5.32)	44.63	(21.34)	52.14	(22.46)

Note: SL: stimulation level, calculated as a percentage of an individual's pain range added to the individual's pain threshold. Descriptive statistics include μ: average value, and SD: standard deviation.

Mixed-effect modelling found that TSmax was lower during the inhalation of the CO¬2 Mixture (*Coeff.* = -4.56, *SE* = 1.21, *t* = 3.78, *p* = .001), increased with each Stimulation increase, with large portion of the rating explained by individual variability, Participant (σ^2 = 217.4, *SD* = 14.74). aVAS was not found to significantly improve the model unlike it did in the summative pain measures analysis. TSm was also decreased during the CO¬2 Mixture (*Coeff.* = -1.37, *SE* = .51, *t* = 2.71, *p* = .007), but significantly increased in the stronger intensity stimulation conditions SL 40%, SL 50%, SL 60% compared to the reference category SL10%, when accounting for Participant variability (σ^2 = 4.12, *SD* = 2.03). As with TSmax, the model for TSm that included anxiety was not superior.

Analysis of the A Period found similar effects of the anxiogenic manipulation and the painful stimulation. The CO_2 Mixture lowered Amax (*Coeff.* = -3.92, *SE* = 1.28, *t* = 3.06, *p* = .002) while all Stimulation levels significantly increased it. Participant variability further explained Amax (σ^2 = 234.6, *SD* = 15.32). For Amin, the CO_2 Mixture also further reduced the rating (*Coeff.* = -4.11, *SE* = 1.36, *t* = 3.02, *p* = .003), while Stimulation had an increasing effect. Unlike

Amax, Participant (σ^2 = 236.63, *SD* = 15.38) was not the only random effect accounting for the variance in Amin. The individually reported anxiety, aVAS was also contributing to the rating (σ^2 = 51.64, *SD* = 7.19).

Anxiety Testing

Both psychological measures (aVAS, STICSA-S) and physiological markers (HR, DIA, SYS) of acute anxiety were significantly increased during the inspiration of the CO_2 mixture, compare to that of medical air. The variability of STICSA-S and cardiovascular values through the progression of the experiment can be seen in Figure 4.3.

Mixed-effects modelling found that all of the best models for anxiety measures shared the same formula: $\sim$ Mixture + (1 | Participant). The best models always included Mixture as a fixed effect, Participant as a random effect and never Stimulation as a fixed effect. The latter was due to Stimulation never being a significant predictor for any of the anxiety outcome variables. pVASμ, which was an additional optional random effect for these analyses, was never found to explain variance in of the anxiety measures.

The best model for aVAS found that the CO_2 Mixture significantly increased the rating (*Coeff.* = 16.26, *SE* = .94, *t* = 17.33, $p < .001$) when taking into account Participants (σ^2 = 124.8, *SD* = 11.17), Intercept (*Coeff.* = 8.75, *SE* = 2.53, *t* = .346, $p = .002$), χ^2 = 233.98, $p < .001$, BF = 4.13 x 10^{50}. The same was true for STICSA-S which increased during the CO_2 Mixture (*Coeff.* = 8.62, *SE* = 0.20, *t* = 42.82, $p < .001$), after taking into account variance explained by Participants (σ^2 = 28.80, *SD* = 5.37), Intercept (*Coeff.* = 25.95, *SE* = 1.18, *t* = 22, $p < .001$), χ^2 = 757.26, $p < .001$, BF = 1.22 x 10^{163}.

The cardiovascular measures followed the same pattern of increase. SYS was

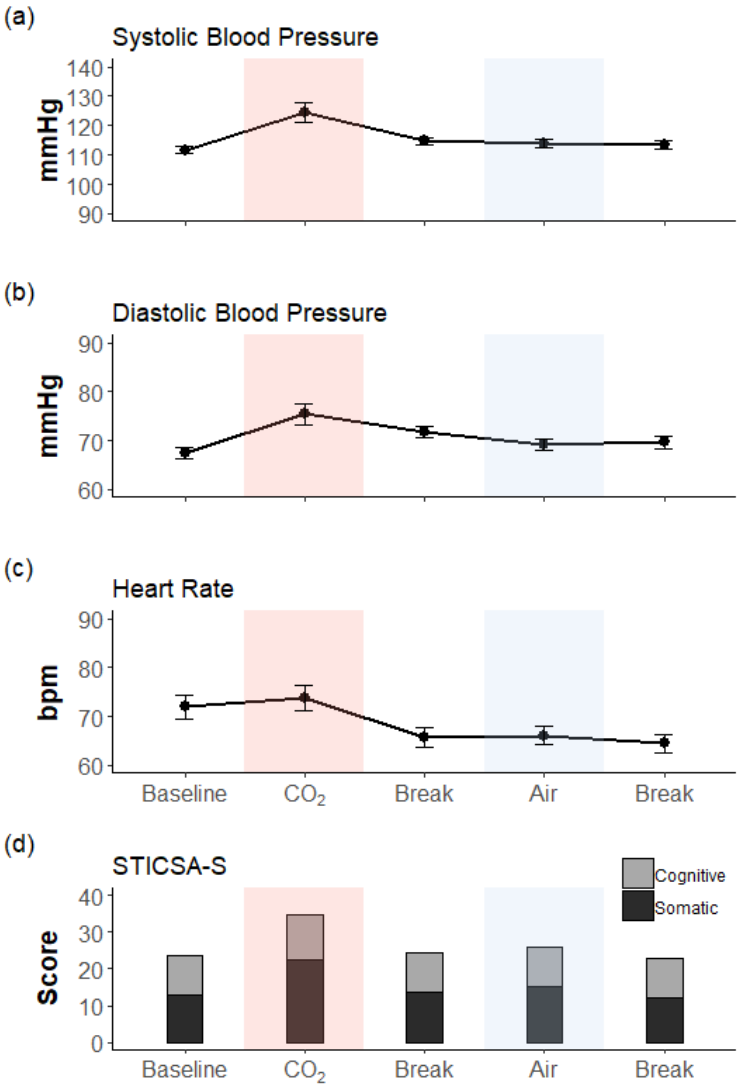

Figure 4.3: (a) On the average systolic blood pressure plot the y-axis shows the acceptable range from 90 to 140 mmHg. (b) On the average diastolic blood pressure plot the y-axis shows the acceptable range from 60 to 90 mmHg. (c) On the average heart rate plot the y-axis shows acceptable range. (d) On the y axis is the total score for STICSA-S: State-Trait Inventory for Cognitive and Somatic Anxiety – State Version. The total score is composed of the cognitive and somatic components of the inventory.

For all subsections, on the x-axis are plotted the study stages: Baseline: beginning of the study; CO_2: the CO_2 Inhalation; Break: the break after the CO_2 Inhalation/Air; Air: the Air Inhalation. Error bars are standard error.

significantly higher during the CO_2 Mixture (*Coeff.* = 16.14, *SE* = 0.46, *t* = 35.32, $p < .001$), when accounting for participants' variance (σ^2 = 51.75, *SD* = 7.19), Intercept (*Coeff.* = 113.91, *SE* = 1.6, *t* = 71.1, $p < .001$), χ^2 = 616.41, $p < .001$, BF = 3.17 x 10^{132}. As was DIA in the CO_2 Mixture (*Coeff.* = 10.91, *SE* = 0.37, *t* = 29.74, $p < .001$), after accounting for Participants variance (σ^2 = 23.12, *SD* = 4.81), Intercept (*Coeff.* = 69.24, *SE* = 1.08, *t* = 64.1, $p < .001$), χ^2 = 502.63, $p < .001$, BF = 6.22 x 10^{107}; and HR in the CO_2 Mixture (*Coeff.* = 11.43, *SE* = .39, *t* = 29, $p < .001$), Participants' variance (σ^2 = 80.95, *SD* = 9), Intercept (*Coeff.* = 66.14, *SE* = 1.98, *t* = 33.4, $p < .001$), χ^2 = 487.08, $p < .001$, BF = 2.61 x 10^{104}.

4.2.8 DISCUSSION

The present study investigated the effects of an established CO_2 experimental anxiety model on self-reported pain ratings using TES. We confirmed that increased state anxiety was elicited by the model, as previously reported. The addition of continuous pain ratings, using the pVAS approach, enabled high temporal-resolution characterisation of the emerging pain response alongside measures of anxiety. Analysis of continuous measures compared to cumulative measures revealed inconsistent effects of CO_2-induced anxiety.

Consistent with previous observations, analysis of cumulative measures found that average pain ratings per block (pVASμ) are reduced in the anxiogenic condition compared to control, but increase with stimulation intensity. The same was true for the average ratings per TS Period and A Period (TSμ and Aμ). Mixed-effects modelling confirmed that the best model for prediction of all three averaged pain ratings included the aVAS, but not the anxiety questionnaire (STICSA-S), nor the cardiovascular values (SYS BP, DIA BP, HR). It is reasonable to suggest that this reflects a greater level of accuracy in the aVAS

compared to other measures. Practical constraints on the timely completion of STICSA-S during the experiment likely had an impact on the utility of the resulting scores, as a consequence of changing conditions (during or after inhalation) and memory bias (Mitte, 2008). The use of aVAS enabled measurement of acute anxiety at regular intervals throughout inhalation, thus capturing the its fluctuation. Similar limitations are also present for cardiovascular measures, as BP and HR are highly time-variable, with possible adaptations to the respiratory challenge (Bailey et al., 2011b). Continuous monitoring is advisable to improve the value of these measures as a counterpart to anxiety measures.

An important focus of this study, was the temporal variation in the TS period and testing the hypotheses that continuous self-report of pain would reveal changes during the anxiogenic inhalation, compared to control. We found that the maximal pain rating from the period, TSmax, was lower during the CO_2 mixture compared to medical air. An increase in TES current amplitude, unsurprisingly, resulted in an increase in TSmax. However, these measures were not found to be explained by any of the anxiety measures, including aVAS, in the best mixed-effects model. This suggests that, in the early phase the pain response is less influenced or driven by an anxiety/emotional response. Importantly, this observation is distinctly different from the summative pain measurement, which shows a stronger association.

Furthermore, analysis of the rate of incline leading to TSmax, the slope of TS (TSm), confirmed an expected increase in slope with current amplitude (see Figure 4.4). Comparison between mixtures, revealed a reduction in the slope during the anxiogenic inhalation. As with TSmax, anxiety measures were not a predictive factor in the best mixed-effects model for TSm. Taken together, this suggests that anxiety is not a definitive driver of pain summation in the early

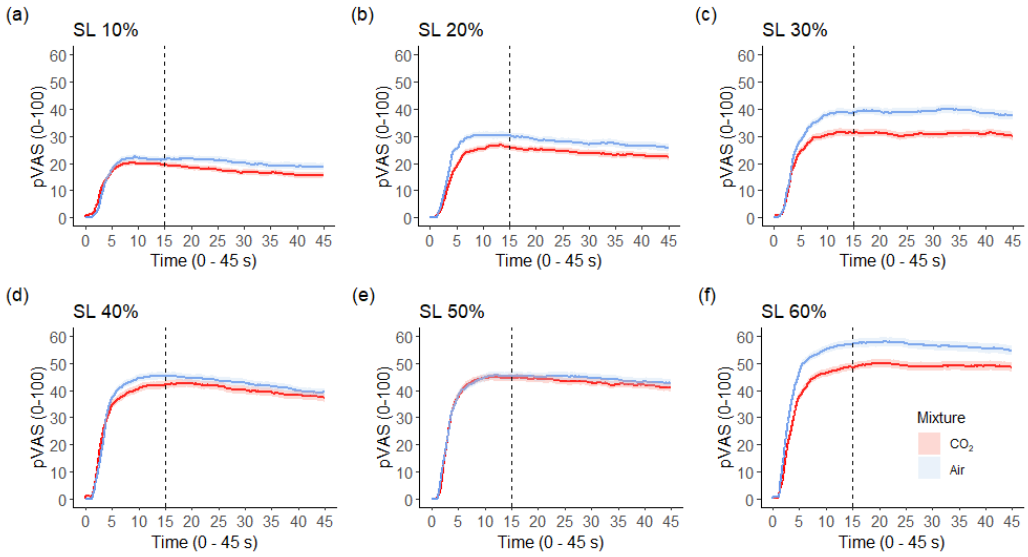

Figure 4.4: Average Pain Responses per Stimulation Level. Time in seconds is plotted on the x-axis and pain rating on visual analogue scale is plotted on the y-axis. Red line represents average response during the 7.5% CO_2 mixture and blue line - during medical air. The grey area above and below the line represents 95% confidence intervals.

SL: Stimulation level.

phase of the pain report.

Given the observed association between anxiety and pain in summative measurements, this raises two possible explanations for this relationship. Firstly, it is possible that anxiety only plays a role in the interpretation of intense sensory stimuli following a sustained period, longer than the TS window. Secondly, that anxiety is perpetuated by the painful sensory stimulus, rather than being a preceding factor. The latter was tested by including pVASμ in the analyses of anxiety measures. It was found, however, that the summative pain rating did not explain any of the variance in the anxiety scores. We postulate that while a reciprocal relationship between the states of anxiety and pain exist, as suggested in similar research (Vowles et al., 2006). In our study reported pain was not universally associated with reported anxiety.

Our observations of the longer, post-TS A period, confirmed similar effects of mixture and stimulus intensity. However, individual variance was a more influential factor in the mixed effects model. This was confirmed in the analysis of the Aμ and was consistent in both Amax and Amin. Increased inter-participant variance was not unexpected, as individual variability, including age, gender, or previous experience of pain are influential of adaption to continuous pain stimulation (Cooper et al., 2013). Contrary to other continuous pain measures, analysis of Amin included aVAS in the best model. This is challenging to interpret as the range for Amin value was very large within and between participants, reflecting the variability of adaptation one may experience. We propose that the minimal rating is similar to the summative ratings in that it is sensitive to the influence of the experienced anxiety in addition to the hypercapnic inhalation. Further investigation, however, is necessary to verify that this is a reproducible effect.

While a linear relationship did not transpire between pain ratings and concurrently reported anxiety ratings, all anxiety measures, both psychological and physiological, displayed a significant increase during the anxiogenic manipulation, unlike the control inhalation of air or breaks. This increase in anxiety was independent of the TES and as mentioned above, the associated pVASμ. However, it is worth noting that the use of the CO_2 model, and the associated screening procedure, incur a level of preselection that may influence participant characteristics. While the CO_2 model has a lower rate of non-responders than conventional psychological methods of anxiety induction, a higher rate of drop-outs is observed. This appears to be associated with higher trait and baseline negative affectivity (Stegen et al., 1998), which may lead to premature termination of the experiment. Future work, which aims to research this relationship

or would like to increase their retention rate, could use a lower concentration of CO_2, e.g. a 5% concentration.

The central observation in this study is that the reduction in the early stage pain response, was not found to be best described by associated increase in the anxiety level. While the 7.5% CO_2 model is a robust model of anxiety and its increase was observed here, our results indicate that CO_2-induced anxiety is not necessarily related to reported pain. In contrast, the presence of the anxiogenic mixture alone was a definitive predictor of the reduction. While our study provides further evidence for lower pain ratings during hypercapnia, it remains unclear what property of the inhalation triggers this effect.

In previously reported animal models, the analgesic property of the CO_2 inhalation has been attributed to the adenosine receptors at the spinal level (Otsuguro et al., 2007). However, in human research the delivery of a hypercapnic mixture does not certainly lead to a reduction in static nociceptive responses as measured through the spinal nociceptive reflex (Morélot-Panzini et al., 2014). The answer to why TS measures were found reduced in our study may be sourced from related literature on dyspnoea induced via inspiratory threshold loading. Such paradigm has been found to reliably inhibit the reflex (Morélot-Panzini et al., 2007). Specifically, the reduced nociceptive flexion reflex was found to be associated with both measured and self-rated respiratory stress; the reflex remained low while the respiratory challenge was described as strenuous and distressing. In our study we may not have established a linear relationship between reported anxiety and TS measures, but the anxiogenic effect evoked by the hypercapnic inhalation may still have mediated the pain measures.

Conclusions

Temporal summation, the psychological equivalent of the physiological wind-up, was inhibited during the inspiration of a 7.5% CO_2 mixture. Our data further evidence the value of continuous self-reported pain measures and suggest that they should be adopted to improve the accuracy of future research on acute experimental pain, particularly where temporal profiles of pain could be clinical applied (Staud et al., 2007a).

Finally, we demonstrate an important distinction between the early and late stages of acute pain experience, which suggests a more complex relationship between the concurrence of pain and anxiety. Observed reductions in pain ratings with the 7.5% CO_2 model, which is an established model of anxiety, suggests that further research is required to disentangle the direct physiological effect of this model from the anxiety-related impact on pain.

4.3 Concluding Commentary

Summary

This chapter presented the first of two studies on experimentally-evoked acute anxiety and pain. It had several goals, aimed at determining the prospect and usefulness of applying the paradigm with patients for the study of acute pain processing under chronic pain.

The preset objectives were achieved. Namely, to test whether continuous evocation of anxiety alongside pain is tolerable to participants. Previous research promised success; however, research was scarce and the experimental paradigm was to be implemented for the first time in the School of Psychology, University of Plymouth. We had no previous experience with running such

demanding paradigms on participants, thus prior to using the CO_2 Model with FM-diagnosed patients, the protocol was tested with healthy participants. Doing so ensured that the Model produced results in line with what is typically expected of it, as well as it allowed us to gather baseline measures of a typical pain response under CO_2-anxiety.

The study established that the integration of the CO_2 Model with continuous painful electrical stimulation is not only possible but facilitates the collection of high-definition data. Participants readily rated the magnitude of their present anxiety between the blocks of continuous pain report. This approach not only enabled continuous reassessment of participant's state but importantly it strengthened any findings of the relationship between acute anxiety and acute pain due to both ratings being recorded during the anxiogenic manipulation and not after.

The last aim was to observe the development of TS under the pressures elicited by the CO_2 Model. This served two purposes. First, it would aid the understanding of why pain but not nociception had been previously found to be inhibited during the inhalation of elevated CO_2 mixture. Second and most important, it was a measure of key relevance to acute pain processing in FM. The study provided a good basis for addressing both aims.

Discussion of Key Findings

The central finding from this study was the distinct contributions of the hypercapnic mixture and self-reported anxiety on self-reported pain. When continuous pain ratings were transformed into summative, both the CO_2 inhalation and the concurrently reported anxiety were associated with reduced pain measures. This was true for the average rating for the whole response, as well as when the average ratings were calculated separately for TS Period and A Period. Such

reduction of subjective pain ratings during the hypercapnic inhalation is similar to that reported by Stokes et al. (1948) or by Grönroos and Pertovaara (1994). However, our findings extend the previous literature by demonstrating the significant contribution of hypercapnic anxiety. They demonstrate for the first time that part of the subjectively reported analgesic effect *does* depending on the individually experienced acute anxiety.

This is not true for the continuous pain rating data. Key measures of TS were found to be best predicted by a simple model that includes only the type of inhaled mixture. Subjectively rated anxiety was not necessary for the explanation of the reduced TS measures. Why that is the case, is challenging to hypothesise in the context of no other comparable literature. From a technical point of view, it is possible that since the hypercapnic inhalation manipulates both anxiety and pain reports, its mediating effects mask any additional properties of anxiety in the analysis (Morélot-Panzini et al., 2007). Simply put, the hypercapnic mixture, which is already associated with anxiogenesis, carries most of the analgesic effect. From a theoretical point of view, it may be that anxiogenic effects are not possible to detect at the level of singular temporally fine fluctuations. Instead, the effect may be apparent on a larger, summative level. Not to be overlooked as well is that the concurrently reported anxiety was only registered between pain response blocks. If it was measured continuously alongside pain ratings, a greater degree of association may have been observed. Perhaps through measures of skin conductance as an indicator of diaphoresis, which reliably reflects changes in arousal (Poma et al., 2005). Nonetheless, for the broader purposes of this series of studies, the current experimental paradigm was suitable for the study of acute anxiety and chronic pain.

Conclusion

The research in this chapter demonstrated the potential of the CO_2 Model for the study of acute pain self-report. In pain-free individuals, it allows discerning between the analgesic properties of the hypercapnic mixture and those of the evoked acute anxiety. Whether these effects will preserve in chronic pain individuals is next to be determined.

Chapter 5

Effects of 7.5% CO_2 Inhalation on Self-reported Pain in Fibromyalgia

There was only one catch and that was Catch-22, which specified that a concern for one's own safety in the face of dangers that were real and immediate was the process of a rational mind. Orr was crazy and could be grounded. All he had to do was ask; and as soon as he did, he would no longer be crazy and would have to fly more missions. Orr would be crazy to fly more missions and sane if he didn't, but if he was sane, he had to fly them. If he flew them, he was crazy and didn't have to; but if he didn't want to, he was sane and had to.

— ***Joseph Heller, Catch-22***

AFTER determining the typical anxiety and pain responses during the CO_2 Model in pain-free participants, the next step was to apply the paradigm with the chronic pain cohort. The initial plans for replication of the successful dual anxiety-pain protocol were hindered by practical constraints. This chapter argues the significance of such investigation in fibromyalgia and presents the results from a feasibility study.

5.1 Introductory Commentary

In the first study chapter, analysis of continuous pain report pointed to differences in acute pain processing between FM patients and pain-free individuals.

The chronic pain cohort produced reached higher pain ratings than the controls, even when receiving objectively weaker painful stimulation. Research had suggested that such hyperalgesic response, although inherent to FM, may be centrally mediated by negative affect processes such as anxiety (Edwards et al., 2006). However, few attempts had been made to confirm or disprove this in an experimental setting (Staud et al., 2003c), and none with analysis of TS. To address this gap, the experiment from the second study chapter trialed continuous pain ratings with continuous pain induction in pain-free participants. It was found that the anxiogenic condition elicited through the CO_2 Model led to an increase in anxiety but a decrease in pain. After establishing this baseline effect, the Model can be applied with FM-diagnosed participants to test how the presence of chronic pain interacts with acute anxiety and pain.

The CO_2 Model in Clinical Populations

In clinical research, several patients populations have been investigated through the CO_2 Model. Predominantly, these have been patients with anxiety disorders such as PD, GAD, or PTSD (Amaral et al., 2013; Colasanti et al., 2012; Muhtz et al., 2011), or mood disorders such as major depression (Gorman et al., 2001). As a human experimental model of anxiety, the paradigm has been used to test anxiolytic properties of common medication in such patients (Bailey et al., 2011b), as well as psychological interventions in healthy cohorts (Ainsworth et al., 2015). Patients with chronically recurrent pain have also been tested but not commonly.

Beitman et al. (1992) studied the reactivity of patients, diagnosed with PD with or without chronic chest pain, to paniconergic version of the CO_2 Model. They found that those with chronic pain exhibited higher anxiety at baseline readings. In another study, by Nillni et al. (2016), females with confirmed premen-

strual syndrome (PMS) reported more panic-like sensations following 10% CO_2 inhalation when tested during the premenstrual phase than those without the syndrome. According to Dickerson et al. (2003), PMS includes psychological symptoms such as increased negative affect (anxious or depressive state) alongside of physical symptoms (muscle hyperalgesia or localised pain). Both PMS and PD can be associated with recurring chronic pain but are not predominantly painful conditions in a manner that FM is. However, the application of the model is needed in prototypical chronic pain conditions, as it can aid the understanding of how the pain experience is modulated by anxiety. As discussed in Section 1.4 on anxiety research in FM, this is also meaningful for FM sufferers, where the detrimental effects of state anxiety have been implied but not supported.

What is Missing in Research on Acute Anxiety & Fibromyalgia?

Studies, which analysed the impact of state anxiety in FM, have failed to reach an agreement. Focusing on research where patients were tasked with rating experimentally evoked pain, non-manipulated acute anxiety has not been established as a pain modulating factor. Jensen et al. (2010), for instance, did not observe any significant relationship between state anxiety measured prior to pressure pain sensitivity testing. Another study with a similar QST protocol achieved the same results with juvenile FM patients (King et al., 2017). There, acute anxiety reported prior to pressure pain assessment was not associated with an increase or decrease in the latter. In contrast, a study by Arnold et al. (2008a) did find that non-manipulated state anxiety predicted pain ratings of noxious pressure stimulation. Arguably, measuring acute anxiety prior to and not concurrently with the pain task does not allow for drawing conclusions about their interactive effects. For this reason, it is challenging to address the source

of discrepancy in the literature.

Only one study manipulated state anxiety in FM patients and it observed, what authors concluded was, stress-induced hyperalgesia (Crettaz et al., 2013). A closer inspection of the experimental protocol is necessary in order to interpret their findings. Crettaz et al. tested the effects of experimentally induced stress on pain in FM-diagnosed and pain-free participants. Stress, or acute anxiety, was elicited through the Trier Social Stress Test, where a participant receives instructions for 10 minutes, then delivers a speech in front of an expert panel for 5 minutes and finishes by performing a challenging arithmetic task for another 5 minutes (Allen et al., 2016). State anxiety was measured an hour before the anxiogenic task, during the task and 90 minutes after the end of the task. Pain was assessed at similar timepoints through cold, heat, mechanic and pressure static QST (detection and pain thresholds), as well as through dynamic QST. The latter was TS ratio, calculated as the average pain rating of five trains of pinprick stimuli divided by the average pain rating of five single pinprick stimuli. Crucial to note, it is not clear at which phase during the anxiety task were anxiety and pain measures acquired. Further, some descriptions even suggest pain was measured after the anxiety task.

The results of the study are similarly conflicting. In the FM cohort, cold and pressure pain threshold were lowest during anxiogenesis, when compared with the other time points, indicating an increased sensitivity to the painful stimulus uniquely during heightened anxiety. No such trend was observed for heat and mechanic pain threshold, nor TS ratio. At a glance, these results suggest that stress-induced *hyperalgesia* was achieved, albeit only in some pain modalities. The results from the pain-free cohort, however, hinder this straightforward interpretation. The authors predicted that healthy controls would experience stress-

induced *analgesia* during the anxiety task and across stimuli. Interestingly, this expectation did not actualise. A trend for decreased heat pain threshold was found during anxiogenesis, though not significant. Of the other pain measures, some thresholds showed a similar sign of hyperalgesia, but none were significantly different between timepoints. Though it is lucrative to conclude that the different effects of anxiogenesis depended on group belonging, it is not possible to do so, since no between-group analysis was conducted. Instead, the anxiogenic manipulation will be considered.

Despite its popularity, the Trier Social Stress Test has been found to produce short-lived arousal of varying intensity Allen et al. (2016). The failure to produce an analgesic effect in the healthy group may indicate that the manipulation was not successful. This is supported by the informal comparison of anxiety ratings at baseline and anxiogenesis. In healthy participants, self-rated anxiety drastically decreased between the two measures, while in patients, it slightly increased. This pattern goes against expected effects from the Trier Social Stress Test and fortifies the case for adopting a more robust anxiety model such as the CO_2 Model.

Significance of Experimental Anxiety Research for Fibromyalgia

The application of the CO_2 Model in FM-diagnosed participants is ambitious, given the limited pool of studies that applied it with chronic pain cohorts, but necessary. Various theoretical frameworks have pointed to anxiety as a key psychological mechanism involved in the chronicity of FM pain (Houdenhove and Luyten, 2006). In Section 1.1.2 on aetiology of FM, for example, we discussed neuroendocrine research, which has observed markers of recurrent stress in FM diagnosed individuals (Martinez-Lavin, 2007). It remained, however, unclear how that chronic stress relates to centrally-augmented pain per-

ception. Some explanations have been offered from a psychological perspective.

On the basis of the biopsychosocial model of chronic pain (Turk and Monarch, 2002), Eich (2000) has pointed to emotional distress as a core psychological factor that may serve as one of three purposes in FM. First, it may be a predisposing factor that sets off FM. In support of this, Eich points to research that has established the high incidence of traumatic events in the formative years of many FM sufferers (for review see Häuser et al. 2011). Second, psychological stress may be a trigger for the onset of an acute pain bout. This is indeed a common observation among patients, who note that a stressful event can precede pain flare-up. Third and last, Eich (2000) postulated that emotional distress can act as a chronification mechanism, which maintains pain independently of its initial source. Among the cited examples of which psychological processes are likely to be involved in this, Eich directly suggests anxiety. It is this last proposed role of stress in FM that is of direct relevance to anxiety and central sensitisation research. It still, however, remains unclear how anxiety interacts with pain modulation in FM.

A comprehensive explanation has been offered by Meeus and Nijs (2007), who directly links anxiety to pain pathophysiology. They noted that research has often suggested a disrupted "top-down" endogenous pain modulation. This has been shown, for example, in studies on diffuse noxious inhibitory control (DNIC), a paradigm, in which a pain response to a target painful stimulus is modulated by another spatially distant noxious stimulus (Le Bars et al., 1979; McMahon et al., 2013). Importantly, the DNIC pain modulation network is not continuously engaged (Rygh et al., 2002) but is instead sensitive to changes in psychological and emotional equilibrium (Brosschot, 2002). In FM, Staud et al.

(2003b) has found that DNIC is augmented in female patients, as evident in the elevated TS of secondary pain signalling poor pain inhibition. Their paradigm, however, involved modulation of attention and not of an emotional state. Moreover, a direct experimental investigation of how negative affect interacts with the development of first pain TS, a key central sensitisation marker, is still needed.

The fact that the current most promising tool for understanding pain processing in FM has not been observed in the presence of anxiety greatly hinders discussion of the role of the latter in the condition. Addressing this using a human experimental model of anxiety will directly address theoretical predictions. Interestingly, one study did measure state anxiety prior to testing TS but did not analyse the relationship between the two (Staud et al., 2008). It was reported that the anxiety score was used to compare patients and healthy controls, thus ensuring they are reasonably matched at baseline.

Significance of Present Study

To summarise, the contribution of acute anxiety to acute pain perception is underresearched in FM. Where attempts have been made, the preferred approach has been to measure non-manipulated state anxiety at a time point preceding the pain perception task. One study that did evoke heightened state anxiety, used a common anxiogenesis method, which has been criticised for the reliability of its produced effects Crettaz et al. (2013). Further, no study has jointly analysed the effects of diagnosisa and anxiety on TS, thus impeding the understadning of the mechanisms by which pain ratings are modulated by chronic pain and acute anxiety. Addressing these literature gaps will test central assumptions made by several theoretical frameworks about the role of negative affect in FM hyperalgesia.

In line with the thesis aims, the study in this chapter will:

- Trial the feasibility of anxiogenesis through the CO_2 Model in patients diagnosed with FM. It was expected that a select number of patients, who meet strict screening requirements, would be able to tolerate the procedure.
- Compare the development of continuous pain ratings under acute anxiety between FM-diagnosed and matched diagnosis-free participants. It was predicted that pain measures in the FM cohort would be lower during the anxiogenic inhalation, similarly to the previous study.

5.2 Feasibility Study

5.2.1 Abstract

***Background**: Anxiety has been posited as key modulator of pain processing in fibromyalgia. Research on acute anxiety has provided inconclusive support for that.*

***Objective**: To test whether the CO_2 challenge, a robust human experimental model of anxiety, is feasible as experimental acute anxiogenesis method in fibromyalgia for the concurrent study of pain.*

***Methods**: A feasibility study was carried out following an established testing protocol. Acute anxiety was evoked through the CO_2 challenge where participant continuously inspired 7.5% CO_2 mixture (anxiogenic condition) and Medical air (control condition). Pain was elicited through transcutaneous electrical stimulation, delivered in 12 blocks of constant stimulation. During each block participants continuously rated their pain on a horizontal visual analogue scale, VAS (0 – 100). Before each block participants rated their anxiety on a vertical*

VAS (0 – 100). Anxiety was further reassessed during the study through cardiovascular measures and an anxiety questionnaire. To assess feasibility, we considered recruitment capability, suitability of outcome measures and study procedures. We also assessed the required resources and provided exemplary data.

***Results**: 395 fibromyalgia-diagnosed participants completed the screening questionnaire. Of them, 3% (n = 10) met all eligibility requirements and were invited to the study. Four participated in the experiment and one completed it fully. Key factors determining completion were the recruitment of eligible participants, meeting in-study eligibility checks, and tolerance of the anxiogenic manipulation.*

***Conclusions**: While the 7.5% CO_2 challenge was successfully combined with pain induction in one participant, procedural changes must be implemented for a higher retention rate.*

5.2.2 INTRODUCTION

Research on the contribution of anxiety to pain processing in the presence of *central nervous system* (CNS) maintained chronic pain is regularly recommended (Sayar et al., 2004) but rarely carried out. This is particularly true for the prototypical central sensitization syndrome *fibromyalgia* (FM), a chronic musculoskeletal widespread pain condition, with heterogeneous symptomatology of unknown aetiology (Sluka and Clauw, 2016). Research in this area has been mostly observational, focused on establishing the presence of clinical levels of anxiety (e.g., generalized anxiety disorder) or isolated measurements of trait anxiety (Henningsen et al., 2003). The relationship between state anxiety and pain perception is yet to be confirmed, despite indications of a strong

association between affective state and the experience of pain.

FM appears to be particularly susceptible to emotional distress (Houdenhove and Luyten, 2006). Anxiety diagnosis is present in up to 60% of patients in their lifetime (Buskila and Cohen, 2007). Importantly, anxiety is reported by patients as a causal factor preceding the onset of symptom flare-up (Bennett et al., 2007) particularly pain (Cavalli et al., 2020). To date, research has not reliably reported an anxiety-dependent increase in pain severity in FM. This limitation is likely due to the feasibility of reliably studying the influence of temporal fluctuations in acute anxiety on symptomatic severity in FM. Studies in this area have predominantly measured non-manipulated state anxiety prior to experimental pain stimulation Thieme et al. (2015); Jensen et al. (2010).

One study that did manipulate anxiety is that by (Crettaz et al., 2013). They delivered the trier social stress test to both FM and pain-free cohorts. In it, participants performed technically challenging tasks in front of an interview panel, before providing pain responses to thermal, mechanical and pressure stimuli. In FM participants, only cold and mechanical pain thresholds significantly decreased during anxiogenesis, suggesting anxiety-induced hyperalgesia. However, no change in temporal summation (TS) was observed. TS is a behavioural marker of central sensitization where self-reported pain increases following repetitive pain induction (Sluka and Clauw, 2016). An augmented TS would imply stress-induced hyperalgesia (Crettaz et al., 2013). Its absence is challenging to interpret due to disparate effects of the applied anxiety method. Group differences were observed during the stress test, with pain-free participant rating their anxiety as lower than baseline during anxiogenesis, in contrast to FM participants. This variance highlights both the limited predictability of behavioural anxiogenic models and the heterogeneity of this patient cohort.

The uncertainty surrounding efficacy of anxiogenic models challenges the study of experimental anxiety in CNS chronic pain. However, a robust method has recently been established. The *carbon dioxide* (CO_2) challenge, in which participants inhale a 5 – 8% CO_2 mixture, evokes mild but stable respiratory stress, tachycardia and diaphoresis (Roberson-Nay et al., 2017). These physiological changes are comparable to those observed in acute anxiety and are reported as anxious (Bailey et al., 2005). In pain-free participants, a 7.5% CO_2–induced anxiety appears to decrease self-reported pain (Kharko et al., 2020b). More generally, the CO_2 challenge has been successfully adopted in clinical research, predominantly with anxiety diagnoses patients (Amaral et al., 2013) but is yet to be applied to chronic pain patients.

Objectives

To determine the feasibility of applying the 7.5% CO_2 challenge as an experimental manipulation of anxiety, alongside nociceptive stimulation in FM participants.

5.2.3 METHODS

Participants

The target population was fibromyalgia-diagnosed adults, aged between 18 to 55 years, and who met the prerequisite requirements introduced by the CO_2 challenge and *transcutaneous electrical stimulation*, TES (see Supplementary Material 1). Recruitment was carried out online through a screening questionnaire, which included demographic information, medical history, and medication intake in the last month. Eligible participants were contacted to confirm their responses and to invite them to participate. Study received ethical approval from the School of Psychology Ethical Comittee, University of Plymouth

(18/19-1118).

Testing protocol

The full testing protocol, described in previously published research (Kharko et al., 2020b), consisted of three phases. *Phase 1* applied in-study screening and psychological testing, where FM and pain in the preceding week were assessed through the *American College of Rheumatology Criteria* (ACR'90 and ACR'16), the *Revised Fibromyalgia Impact Questionnaire* (FIQ-R) and the *Short Form McGill Pain Questionnaire* (SF-MPQ).

Phase 2 applied psychophysical testing using TES. Static *quantitative sensory testing* (QST), was used to determine: *stimulus detection threshold* (STHR), *pain threshold* (PTHR), *pain tolerance* (PTOL) and *pain range* (PRAN). TES was delivered by the same researcher as 500ms-wide single pulses to the skin over the sural nerve, using a staircase paradigm with 0.1mA increments and a mean value obtained from three repetitions.

Phase 3 included the *anxiogenic model and pain testing*. Participants received 12 blocks of 1-minute stimulation at one of six intensity levels, ranging from 10-60% PRAN. Participants continuously rated the delivered pain on a horizontal *visual analogue scale*, VAS (0 – "no pain" to 100 – "worst pain imaginable"). This was the primary pain outcome measure.

Using a single-blinded, repeated-measures design, participants consecutively received anxiogenic air mixture CO_2 (7.5% CO_2 / 21% O_2 / 71.5% N_2) and a control air mixture (0.04% CO_2 / 21% O_2 / 78% N_2). Only the participant was blinded to the mixture for safety purposes. Anxiety was rated during both conditions before each block on a vertical VAS (0 – "no anxiety" to 100 – "worst anxiety imaginable"), providing 12 ratings per condition. This was the primary

anxiety outcome measure. Additional outcome measures included cardiovascular measures, including: *systolic* (SYS) and *diastolic* (DIA) blood pressure, and *heart rate* (HR) and *State-Trait Inventory for Cognitive and Somatic Anxiety* (STICSA), which were recorded at five fixed timepoints across the experiment: baseline, during inhalations and post-inhalations. Post-inhalation measures were used to ensure return to baseline and the rest were included in analysis.

Feasibility Assessment

Feasibility of the study protocol was assessed through five objectives outlined in previously published research (Orsmond and Cohn, 2015). This included the evaluation of: recruitment, data measures, acceptability of study procedure, required resources, and preliminary data.

5.2.4 RESULTS

Participants Testing Protocol

395 participants expressed interest in the study by completing the screening questionnaire (see Figure 5.1). Of these respondents, 3% (n = 10) satisfied all eligibility requirements and were invited to partake. Following invitation, 6 did not respond and four attended the study. One of the remaining four was withdrawn during in-study screening (Phase 1) due to elevated baseline cardiovascular measures. Two of the remaining three withdrew themselves during Phase 3 where anxiety and pain were tested, due to inability to tolerate of the anxiogenic CO_2 mixture. The remaining one participant completed all study phases.

Demographic and psychological testing data for the FM participant are reported in Table 5.1. There, it is compared to a previously tested matched pain-free

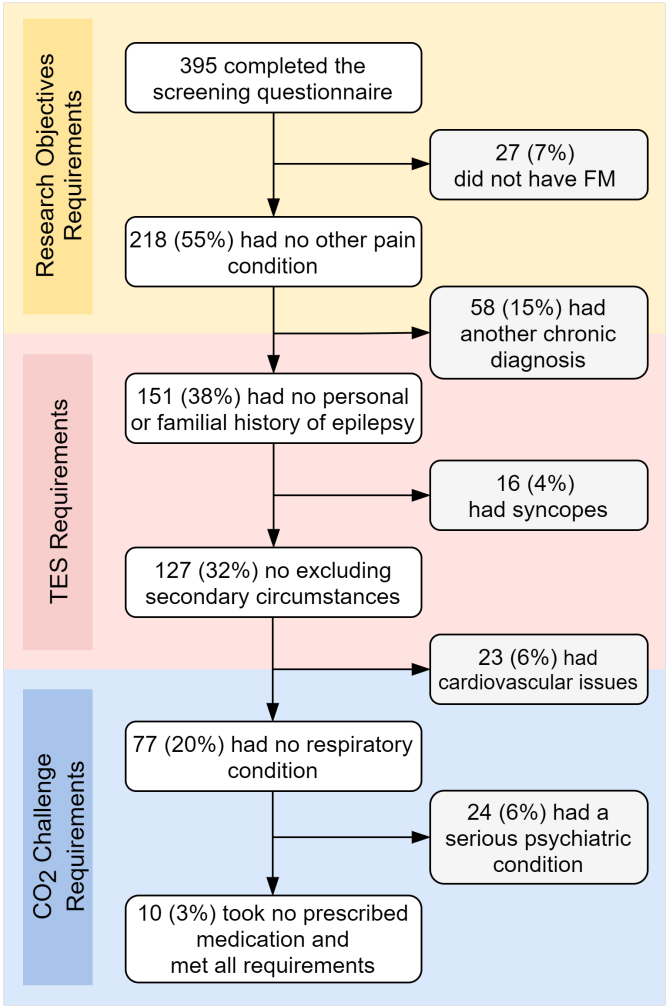

Figure 5.1: Major eligibility requirements during recruitment. *FM* -– fibromyalgia, *CNS* -– central nervous system, *TES* -– transcutaneous electrical stimulation, CO_2 — carbon dioxide. Detailed requirements can be found in Supplementary Material 1.

control (selected based on closest age), as part of the feasibility assessment of preliminary data.

Preliminary data from Phase 3, anxiety and pain induction, are in Table 5.2.

Feasibility Assessment

Observations for each of the five feasibility objectives are summarized in Table 5.3.

Table 5.1: Preliminary Data for Phases 1 & 2: Psychological Psychophysical Testing

Measure	***FM Participant***	***Control Participant***
Demographics		
Age	25	26
Gender	Female	Female
Ethnicity	Caucasian	Caucasian
Fibromyalgia diagnosis (n years)	.6	-
Fibromyalgia symptoms (n years)	8.5	-
Baseline & Psychological Testing		
ACR'90	Pass	Fail
ACR'10	Pass	Fail
FIQ-R (total score)	54.5	-
SF-MPQ		
Pain Descriptors	16	0
Visual Analogue Scale (0 - 10)	6	0
Present Pain Intensity (0 - 5)	1	0
STICSA-T (total score)	40	22
Psychophysical Testing		
STHR (mA)	1.30	.97
PTHR (mA)	4.10	2.97
MTOL (mA)	18.67	13.37
PRAN (mA)	14.57	10.40

FM -– fibromyalgia; *ACR'90 / '10* — American College of Rheumatology Criteria for fibromyalgia diagnosis from 1990 and 2010; *FIQ-R* — the revised Fibromyalgia Impact Questionnaire; SF-MPQ — the short form McGill Pain Questionnaire; *STICSA-T* — the trait version of the State Trait Inventory for Cognitive and Somatic Anxiety; *STHR* — sensory threshold; *PTHR* — pain threshold; *MTOL* — main tolerance; *PRAN* -– pain range.

5.2.5 DISCUSSION

The main aim of this study was to determine the feasibility of applying the CO_2 challenge as an experimental manipulation of acute anxiety, for the modulation of nociceptive perception in FM participants. In summary, based upon the observation that only one of the 10 eligible participants were willing and able to complete the study and although completion is possible, the feasibility of the

Table 5.2: Preliminary Data for Phase 3: Anxiety Pain Induction

Measure	***FM Participant***			***Control Participant***		
	Baseline	7.5% CO_2	Medical Air	Baseline	7.5% CO_2	Medical Air
SYS/DIA (mmHg)	96/69	117/78	100/68	107/64	126/84	104/63
HR (bpm)	74	86	77	63	81	62
STICSA-S	26	30	23	21	37	22
Anxiety VAS *						
10%PRAN	-	10.41	.1	-	44.33	8.11
20%PRAN	-	12.37	0	-	37.93	13.59
30%PRAN	-	7.58	.15	-	40.03	1.96
40%PRAN	-	7.14	0	-	53.27	3.28
50%PRAN	-	10.75	0	-	43.84	9.19
60%PRAN	-	13	0	-	47.12	4.59
Pain VAS *						
10%PRAN	-	5.36	7.38	-	15.19	9.16
20%PRAN	-	4.06	8.21	-	14.71	13.92
30%PRAN	-	16.36	8.89	-	31.44	40.26
40%PRAN	-	22.16	26.44	-	49.99	62.02
50%PRAN	-	41.82	50.82	-	45.10	74.39
60%PRAN	-	33.87	50.15	-	67.17	69.94

FM — fibromyalgia; *SYS/DIA BP* — systolic and diastolic blood pressure; *HR* — heartrate; *STICSA-S* -– the state version of the State Trait Inventory for Cognitive and Somatic Anxiety; *VAS* -– visual analogue scale; *PRAN* — pain range.
* Average values per stimulation condition.

current design for this application is limited.

FM is a prototypical central sensitization syndrome, in which there is a strong likelihood that the experience of pain is modulated by internal affective state (Houdenhove and Luyten, 2006; Gormsen et al., 2010). In particular, it is probable that an increase in anxiety augments the perception of pain amplitude and/or impairs internal suppression mechanisms. Previous research to test the relationship between pain and anxiety in FM have proven inconclusive (Thieme et al., 2015; Crettaz et al., 2013). In the present study, we attempted to mitigate

some of the variability and uncertainty associated with the use of experiential anxiety manipulation approaches, by using a highly reliable physiological anxiogenic model (Roberson-Nay et al., 2017; Bailey et al., 2005).

It is important to note that this feasibility study is a replication of an experimental procedure previously used with a pain-free cohort (Kharko et al., 2020b). In the previous study significant increase in anxiety was associated with a decrease of reported pain. Here, we expected to see a similar anxiety increase anxiety but no necessarily a reduction, given the implicated role of acute anxiety for FM (Crettaz et al., 2013). The low attrition rate leaves that prediction untested but preliminary data provides a first look at possible data trends.

It is also notable that the CO_2 model has been successfully applied to the investigation of anxiety and depressive disorders (Amaral et al., 2013; Gorman et al., 2001). We believe the limited feasibility of the current design is a reflection of the probable central role of anxiety in FM alongside the limited understanding of the complex relationship between anxiety and chronic pain in this patient group. We thus carefully consider the feasibility of recruitment and execution of the three study phases.

While high interest was observed during recruitment, as indicated by the number of participants who completed screening ($n = 395$), only a small portion met all eligibility requirements. Key challenges were posed by the high rate of comorbidity ($n = 208$) with other primary pain conditions (e.g. migraine or arthritis) and other long-term conditions (e.g. thyroid condition or lupus), as well as by the high incidence ($n = 47$) of chronic cardiovascular (e.g. high/low blood pressure or abnormal heart rate) and respiratory issues (e.g. asthma). Even after elimination of these conditions and additional extenuating secondary circumstances (e.g. pregnancy or current smoker), further 43 respondents reported

Table 5.3: Feasibility Assessment

Objective	Observation	Recommendation
1. Recruitment	Only a small percentage of screened participants met all eligibility criteria.	Recruitment should not be expected to yield a high number of eligible participants due to the combined demands posed by the equipment. To maintain confidence in the study, participants should be invited first to familiarize themselves with the laboratory.
2. Data	The selected outcomes for anxiety and pain measurement were intuitive to the participant and informative to the researcher.	The chosen outcomes should be considered in future investigations.
3. Study Procedure	Participants tolerated well psychophysical testing and pain induction. The 7.5% CO_2 inhalation, however, was challenging for them. Two participants dropped out during the anxiogenic condition, despite acceptable cardiovascular readings.	Prior to testing, anxiogenic effects introduced by the equipment should be minimized. This could be done by showing a short informative video of a participant completing the CO_2 inhalation. A weaker mixture (e.g. 5%) should also be considered to produce milder but still stable effects.
4. Resources	Time, necessary to find eligible participants, was the second challenge to study progress. Recruitment was carried out for 3 months with active advertisement to the local community, which yielded a high response rate but a low retention rate.	Sufficient time and trained team members should be dedicated to the study. Both recruitment and familiarization of participants would require increased involvement of the research staff to ensure participants are comfortable with and interested in the study.
5. Preliminary Data	Data collection was hindered by the intolerance of the anxiogenic condition. Still, the participant that did complete the full study produced data aligned to expectations.	No recommendations could be reasonably made due to the limited preliminary data.

undergoing FM- associated pharmacological treatment. This led to 10 eligible participants, of which 6 did not respond to the invitation to in-person testing. This reduction in willingness to participate in-person, where efforts were made to accommodate engagement, is an indication that the details of the study were a discouraging factor.

Of the participants who attended, 1 was withdrawn in Phase 1 during in-study screening of cardiovascular measures. The other 3 participants passed screening and completed the psychological testing. In Phase 2 we did not have a drop in the attrition rate indicating that the demands associated with static QST are acceptable to this patient group. This was expected as previous research with similar testing protocols also did not see a detrimental impact of the procedure (Banic et al., 2004). Phase 3 is when we observed further participants exclusion. There, 2 participants withdrew during the CO_2 inhalation, suggesting that the induced anxiety induced by the experimental manipulation was not tolerable. While great care was taken to control the anxiety inducing nature of the respiratory challenge through familiarization, as well as the detailed briefing aimed to reduce any additional anxiogenic effects related to the laboratory environment, the capacity for heightened arousal remains. This had not posed issues for previous control study (Kharko et al., 2020b) but this is a central consideration for FM research. The withdrawal on commencement of the CO_2 inhalation, is evidence of the limited feasibility of this experimental model for the exploration of FM patients.

The complete dataset collected from the one remaining participant were consistent with the previous observations in the control participants (Kharko et al., 2020b). The continuous reassessment of both pain and anxiety on their respective VAS was not only attainable for the participant, but also produced

anticipated results. Self-reported anxiety amplified exclusively during axiogenesis, while pain ratings increased with pain stimulation level. This encourages future use of similar outcome measures in the study of concurrent acute anxiety and pain with chronic pain participants. It is worth noting that this participant was a psychology student at the University. Therefore, it is likely that this participant has developed coping strategies that enable them to engage more readily in social and interpersonal situations. The laboratory setting is likely to be more familiar and therefore less anxiety-inducing and are likely to have a better understanding and greater acceptance of anxiety in their experiences.

Recommendations

Based upon these observations and recommendation made in Table 5.2, we suggest the following. First, sufficient time and resources should be allocated to recruitment to yield the necessary sample size. Where an eligible participant is identified, great care should be taken when inviting them to the study. An introduction to the experimental paradigm at the recruitment stage, whereby participants are familiarized with the environment and approach, is likely to improve interest in attendance. Second, contextual anxiogenic effects arising from the laboratory environment should be controlled for. It may be necessary to include a video to demonstrate an exemplar participant completing the study. Third, the use of the lower 5% CO_2 concentration mixture should be considered to minimize the evoked feelings of anxiety alongside of the amplitude of the cardiovascular change.

Conclusion

While there are apparent limitations to the feasibility of the CO_2 challenge with FM participants, alternative methods should be pursued. The poor compliance

with the respiratory challenge reinforces the likely role of anxiety in FM and highlights the continued need for research into acute anxiety in this group. In the broader context of experimental anxiety in chronic pain research, proposed recommendations should be considered to assess whether testing of similar patient groups is feasible.

5.3 Concluding Commentary

Summary

Despite the limited acquired data, the feasibility assessment in this study allows us to make several informed conclusions. First, the safety requirements arising from the electrical stimulation equipment and the CO_2 model vastly limited the pool of eligible participants. This, in turn, increased the amount of time and personnel resources necessary to run the study. Recruitment required extensive advertisement and continuous screening, which was not substantiated by the number of eligible participants. Second, although the study procedure incorporated elements that were found to be acceptable by participants in the preceding studies, the core experimental anxiety manipulation was not well tolerated. Third, despite these challenges, the data collected from the single FM participant was encouraging. The acquired outcome measures followed an anticipated pattern, indicating the successful integration of experimental anxiogenesis and pain induction, as well as the suitability of the chosen measures.

Discussion of Key Findings

The poor reception of the CO_2 paradigm necessities further discussion. Of the three participants that successfully initiated the anxiogenic inhalation, two expressed their wish to terminate the procedure. Notably, this was done after the obligatory adjustment period where the participant breathes in the mixture

for two minutes, followed by cardiovascular reading. Both participants produced an acceptable reading and continued to the anxiety and pain rating task. It was then that they judged the sensations as intolerable and terminated the inhalation. This is notable because it suggests a degree of dissonance between the private experience of anxiety with its objective markers.

Further, the low tolerance observed in the preliminary data prompts consultation with the literature, upon which we based our study. As mentioned, the CO_2 model has been widely used in patients with mental health diagnoses. For example, Gorman et al. (2001) carried out a large study with various patient groups, including those diagnosed with depression and PD. Their anxiogenesis protocol is similar to ours and has been found to be well-tolerated in other research involving adolescents with anxiety diagnoses (Pine et al., 1998). This inspired confidence that replication of the paradigm with FM would be feasible. The respiratory anxiety with the added burden of FM, however, likely trounced the tolerance of our participants. It is evident that FM patients and patients with anxiety diagnoses are qualitatively different, even if the presence of elevated anxiety is a common denominator. Further research on understanding the relationship between anxiety and FM is needed.

Another key observation from the feasibility assessment concerns one participant, who attended the study but did not proceed past Phase 1. They were discontinued by the researcher because of their elevated blood pressure at baseline (above 140/90 mmHg). The participant reported to be unaware of a chronic cardiovascular condition, so prior screening was not able to filter them out. A consultation with the literature finds that such an occurrence is not unexpected. On the contrary, research has found that FM individuals may be at risk of cardiovascular disease more often than their healthy counterparts (Acosta-

Manzano et al., 2017). Others have found that some FM sufferers are more likely to experience enhanced cardiovascular activity at rest, suggesting that at least for a portion of this patient population elevated blood pressure or heart rate may be typical (Furlan et al., 2005). Beyond FM, the presence of chronic pain is associated with an increased instance of cardiovascular disease, as suggested by a recent meta-analysis (Fayaz et al., 2016). This further solidifies the recommendation for careful consideration before deciding on the CO_2 Model as the anxiogenesis method with chronic pain patients.

The limited eligible pool of participants calls for a separate discussion. The participants that pass all screening phases are not prototypical of their patient group. FM participants are well-known for their heterogeneous and ever variant pool of symptoms. While anxiety is supposed by patients to trigger these symptom changes (Bennett et al., 2007), it leads to a Catch-22, where the presence of these symptoms does not allow for the study of FM. Other chronic pain conditions that are known for similarly diverse health profile are also likely to yield a modest number of eligible participants. In contrast, simpler conditions such as non-specific chronic low back pain may be good candidates for the adoption of CO_2 paradigm.

Lastly, an informal inspection of the preliminary data suggests that the anxiety manipulation produced such results in the FM participant that are comparable to the previously observed in (Kharko et al., 2020b) the study. That is, both self-reported measures of anxiety and physiological markers increased uniquely during the anxiogenic inhalation. Investigation of the pain profile, however, is not appropriate due to the present sample size.

Conclusion

To summarise, the theoretical benefits of experimentally manipulating acute anxiety are present both for FM research and the broader literature of chronic pain. Whether the CO_2-induced respiratory anxiety is suitable for that, however, is open to discussion. The poor attrition rate paired with high resources demands point to such a study requiring collaborative effort and possibly readjustment of the CO_2 protocol. A change in strategy is thus warranted to continue the investigation of the role of anxiety in FM.

Chapter 6

Sustained Anxiety & Fibromyalgia Pain during the COVID-19 Pandemic

Forces beyond your control can take away everything you possess except one thing, your freedom to choose how you will respond to the situation.
*– **Viktor Frankl***

THIS chapter presents the last study carried out as part of the PhD research. It explored the relationship between sustained anxiety evoked by the COVID-19 pandemic and fibromyalgia chronic pain. Unlike previous investigations, this study has a broader focus of observing the persisting effects of elevated anxiety on fibromyalgia pain.

6.1 Introductory Commentary

The case study on CO_2-induced anxiety in FM-diagnosed individuals found that the 7.5% Model is not well-tolerated by the limited in size eligible patient group. While preliminary data suggested that the FM participants experienced anxiogenic and hypercapnic analgesic effects comparable to the healthy con-

trol, no formal analysis could be carried out and thus no conclusions could be reached. These practical constraints discouraged further experimentation with anxiety induction as part of the PhD. The question, however, remained: how are changes in anxiety reflected in the pain perception of FM patients? This could be addressed through an alternative research strategy. (Un)fortunately, such an opportunity presented itself.

As explained in Section 1.3.1 What is Anxiety, dividing anxiety into clinical or state/trait taxonomies is not the field's modus operandi. Experts elsewhere acknowledge that acute anxiety can maintain beyond the concurrent presentation of a stressor and produce long-lasting effects. Canonical examples come from research on risks associated with the development of chronic cardiovascular conditions (Paterniti Sabrina et al., 2001), for which sustained anxiety has been identified as a key factor. Importantly, here we distinguish between persisting elevated anxiety and clinical presentations of anxiety such as GAD or phobic diagnoses. This differentiation is particularly relevant to FM sufferers, where only a portion of patients have been diagnosed with an anxiety disorder (Thieme and Gracely, 2009) but many more report recurrent episodes of elevated anxiety. These can be related to concerns over worsening physical health and with it personal autonomy (Galvez-Sánchez et al., 2019) or employment security (Kivimaki et al., 2004; Löfgren et al., 2006; Sallinen et al., 2012). While in a pain-free person persisting anxiety may have general negative effects on physical well-being, the impact on FM patients is likely to produce qualitatively different consequences. Little research has been undertaken to address this possibility.

It appears that most research on anxiety in FM has traditionally focused on two properties: how many patients have been diagnosed with an anxiety disorder

and how many patients possess an anxious trait. Both questions are epidemiological in nature, providing little more than highlighting the necessity to attend to anxiety in that patient group. The few studies that have investigated the impact of inherently present or momentary anxiety on pain suggest a detrimental link between the two. Still, as seen in previous research (Crettaz et al., 2013) and in our (Chapter 5, manipulating anxiety in FM patients is challenging. A strategic change of the investigative approach is needed.

Sustained Anxiety & Fibromyalgia

Studying naturally occurring sustained anxiety may be the solution to continuing research on the relationship between impacted mental health and FM pain. Since it is an emerging direction in anxiety research, it is unsurprising that even less research exists involving FM patients. In fact, to the best of current knowledge, only one study has done so, though it was not carried out under the convention "sustained anxiety" due to year of publication.

Hazlett and Haynes (1992) examined daily changes in self-assessed FM pain and sustained anxiety. For the duration of 30 days, patients rated the severity of their pain, alongside of other cardinal FM symptoms, on a VAS. Sustained anxiety was measured through the Daily Stressor Inventory (Brantley et al., 1987), which presents participants with 54 statements containig stressors, likely to be experienced in a day-to-day routine (e.g. *"Heard some bad news"* or *"Performed poorly at task"*). The authors also measured cognitive rumination, a cognitive process marked by the uncontrolled, recurrent focus on negative thoughts and events. Cognitive rumination is most well associated with depression (Robinson and Alloy, 2003) but also with anxious conditions (Fresco et al., 2002; Mellings and Alden, 2000). Hazlett and Haynes (1992) found that in some participants the strongest predictor of daily FM pain was

actually rumination and only in a minority it was the aggregate sustained anxiety score. Here, it must be brought to attention that preceding day distress was analysed in place of same-day distress. That decision was motivated by similar research at the time, which found that the presence of elevated stress in the days leading to a migraine attack is a reliable predictor of such an attack (Köhler and Haimerl, 1990). This approach, however, does not translate well to Hazlett and Haynes's FM. Arguably, fluctuations of daily pain levels are better studied through concurrent daily measures of anxiety. This and other concerns motivate further consideration of sustained anxiety research in FM.

What is missing in Research on Sustained Anxiety & Fibromyalgia?

With only one study that has examined persisting non-clinical anxiety, it is not possible to conclude how impactful its presence is on FM pain. Further investigation is necessary but not necessarily replicating Hazlett and Haynes's approach. Several critical issues must be noted.

Foremost, the way in which sustained anxiety was defined and measured. In that study, it was operationalised through the Daily Stressor Inventory, which was, by author's admission, designed to capture typical daily stressors and exclude significant life-changing events (Brantley et al., 1987). This greatly limits the scope of the measured anxiety to mundane stressors. Apart from being restrictive, however, the scale includes seven items, which overlap with typical FM symptoms and common flare-up triggers. These are *"Unable to complete a task"* (restricted mobility due to FM pain and fatigue), *"Had your sleep disturbed"* (disturbed sleeping pattern due to FM), *"Forgot something"* (fibrofog), *"Feared illness/pregnancy"* (anxiety over FM), *"Experienced illness/physical discomfort"* (FM pain), *"Bad weather"* (a well-known trigger for FM), *"Failed to understand something"* (fibrofog). This overlap undermines the inventory, which

no longer exclusively assessed daily sustained stress, but was partially confounded by the natural fluctuation of the syndrome. Particularly in the analysis of association between stress score and rating of cardinal FM symptoms (including pain), this may have introduced multicollinearity. A more focused definition of sustained anxiety is needed.

Related to that, research elsewhere typically precisely defines the source of sustained anxiety. For example, one large area of research is that of antenatal anxiety, which is defined as sustained anxiety evoked by concerns over pregnancy progression or childbirth (Bayrampour et al., 2015; Dole et al., 2003). Such sustained anxiety has been studied in correlation with premature birth rate (Glynn et al., 2008; Reck et al., 2013) and infant pathology (Austin and Leader, 2000; Staneva et al., 2015). Another example of sustained anxiety is work-related anxiety and its mediating influence on the occurence of non-fatal myocardial infarctions (Chandola et al., 2008; Li et al., 2015). A comparable concentrated approach should be adopted with FM patients. The question of which anxiogenic topic to select was resolved in March of 2020.

COVID-19 Pandemic Anxiety

The emergence and rapid spread of the novel coronavirus, COVID-19, introduced a 'new normal' to almost every country around the globe. By the end of 2020, only a select few island nations in the South Pacific remained free of COVID-19. In all other countries, restrictions at an individual, commercial and governmental levels have been introduced in an attempt to slow down transmission rates. In the living memory of the majority, these would be the most momentous life changes at such magnitude since World War II. Isolation in lockdown, increasing unemployment rates, delayed healthcare and increasing concerns over the well-being of the most vulnerable had become new, persist-

ing sources of distress. Unanimously, the research community began referring to this as COVID-19 pandemic anxiety, or COVID-19 anxiety.

Initial studies on the impact of that new anxiety came from China, where one of the first surveyed populations were medical professionals (Lu et al., 2020). Staff not only experienced profound levels of distress but they attriuted it to the pandemic (Zhu et al., 2020). Soon after, surveys of hospital patients and otherwise healthy individuals also began reporting high levels of anxiety related to the unravelling health crisis (Li et al., 2020b,a; Zhang and Ma, 2020). During the course of the pandemic, surely moving across borders, reports of elevated anxiety related to COVID-19 were coming from surveys of the general population in India (Roy et al., 2020), Italy (Casagrande et al., 2020), the US (Sher, 2020) and the UK (Jia et al., 2020) among others. This had prompted several calls to focus research not only on the impacts of the pandemic on mental health but also on the consequences of this quickly deteriorating mental health (Holmes et al., 2020).

Particular concerns were raised over the mental health of the most vulnerable members of society. In the UK, individuals with some chronic conditions (see Appendix A) were even instructed to *shield*, or isolate completely for up to 8 weeks, to avoid life-threatening health complications. Most chronic pain patients, including those with FM, did not fit into that list on the sole basis of their chronic pain. Still, since FM sufferers experience life-long pain and concomitant impacted mental and physical well-being, we were concerned over the potential impact of the pandemic on them. At the time when the study presented in this chapter was carried out, no study selectively examined what well-being changes were FM-diagnosed individual undergoing. Recently, however, one research team did call for attention to that patient group.

In a letter to the editor, Cavalli et al. (2020) report that over two-thirds of their FM patients experienced worsening of symptoms compared to pre-pandemic times, with the two most cited reasons for that being reduced physical activity and an increase in anxiety. Both of these were attributed to the nation-wide lockdown, which has also been pointed to as a symptom trigger by another study (Salaffi et al., 2020). There, patients similarly reported general deterioration in their condition during lockdown, but particularly when considering pain. This trend of worsening of chronic pain is in agreement with surveys of chronic pain patients as a whole (Kleinberg et al., 2020). Importantly, neither Cavalli et al. (2020) nor Salaffi et al. (2020) directly analysed the relationship between the decreased mental health and physical well-being. Moreover, they did not directly assess what had evoked anxiety. They also did not define what the stressors, or anxiety sources, were beyond lockdown. Further, what aspects of lockdown were anxiogenic? Were these anxiogenesis sources continuously evoking feelings of anxiety? If so, patients may be still experiencing sustained anxiety. If so, is the elevation in FM pain related to that sustained anxiety? These are key questions, which need to be addressed to better understand COVID-19 anxiety and the reported pain increase during the pandemic.

Significance of Present Study

In summary, the study of the effects of elevated anxiety on FM is needed by not easily achieved through experimental manipulation of acute anxiety. Instead, the experimental approach could be supplanted by the observation of naturally present sustained anxiety. Previous research that had done so found some support for a positive relationship between daily minor stressors and FM pain (Hazlett and Haynes, 1992). The methodological constraints, however, limit the impact of their findings and call for a new focused investigation of sus-

tained anxiety tied to a measurable anxiogenesis source. As indicated elsewhere (Cavalli et al., 2020; Salaffi et al., 2020), the unfortunate presence of the COVID-19 pandemic provides just that.

In line with the final thesis objectives, this last study will:

- Investigate whether FM-diagnosed patients are experiencing sustained anxiety related to the COVID-19 pandemic. It was expected that several sources would be established. These would not only pertain to various aspects of the pandemic but would also evoke varying levels of anxiety.
- Analyse whether changes in sustained COVID-19 pandemic anxiety are mirrored by changes in FM chronic pain. To study this, an aggregate anxiety score was calculated as a measure of all COVID-19 anxiety. It was predicted that an increase of FM pain would be predicted by an increase in COVID-19 anxiety.

6.2 Manuscript

The work presented in this chapter was published as a 'green' article on medArxiv with the title 'The Anxiety and Pain of Fibromyalgia Patients during the COVID-19 Pandemic'. The full citation of the article is as follows:

> Kharko, A. Y., Hansford, K. J., Furlong, P. L., Hall, S. D., Roser M.E. (2020) The Anxiety and Pain of Fibromyalgia Patients during the COVID-19 Pandemic. *medRxiv* https://doi.org/10.1101/2020.11.24.20188011

6.2.1 Abstract

***Background**: Early research on the impact of the COVID-19 pandemic found persistent related anxiety in the general population. We hypothesised that this*

anxiety will be associated with increased pain in chronic pain patients diagnosed with fibromyalgia (FM).

***Methods**: To study this, we carried out a 10-day online survey with 58 female participants, diagnosed with FM and no other pain condition. We identified which aspects of the COVID-19 pandemic evoked anxiety. We then asked participants to provide daily ratings of both anxiety and pain on 101-point visual analogue scales (VAS). Key participant characteristics were included as mediators in a mixed-effects analysis, where the primary outcome was pain VAS.*

***Results**: We found that participants were most often anxious about "impact on relationships", "a family member contracting COVID-19", and "financial hardships", but on average rated "financial hardship", "access to medication", and "home loss/eviction" as evoking the strongest anxiety. Mixed-effects modelling showed that an increase in pain was significantly associated with an increase in anxiety when taking into account individual variance and daily caffeine intake. Age and intake of some mild analgesics were also linked to stronger pain.*

***Conclusion**: Our results extend the initial findings from the literature about the effects of COVID-19 pandemic on chronic pain sufferers. We found that not only is pandemic anxiety in FM patients present, but it is associated with amplified self-assessed chronic pain.*

6.2.2 INTRODUCTION

In March 2020, Italy was the first European country to impose a nation-wide lockdown; restricting the behavioural freedom of its citizens in an attempt to control the spread of COVID-19. This step was soon followed by countries worldwide. The global consequences of the evolving circumstances were quickly apparent, with observed changes in behaviour, produced by contextual uncer-

tainty (Shigemura et al., 2020). While the momentous impact of these changes have been widely posited, the negative impact of individual lived experiences on mental and physical wellbeing remains to be fully characterised.

Early research from China indicated significant decline in mental well-being, observed both in front-line healthcare workers (Li et al., 2020a; Pappa et al., 2020) and the general population (Xiao et al., 2020). In the UK, when asked to describe their sentiment toward the pandemic, 55% of 2,500 pooled participants indicated high levels of anxiety (Kleinberg et al., 2020). The general consensus of the healthcare sector worldwide is that investigation of mental and physical well-being in the most vulnerable must follow. Here we propose to address this in a specific patient group, diagnosed with fibromyalgia (FM).

FM is a chronic musculoskeletal pain condition, accompanied by fatigue, non-restorative sleep, and multiple comorbidities; common amongst which are anxiety disorders (Arnold et al., 2019). Generalised anxiety disorder alone is observed in 30% of FM sufferers (Gracely et al., 2012), but 60% exhibit symptoms consistent with diagnosis (Janssens et al., 2015). Despite the prevalence, anxiety in FM, is still poorly researched, compared to depression, which is indicated in 60% of patients (Walitt et al., 2015a). This gap in literature is of particular importance since many patients believe distress is a key factor in the worsening of their pain (Bennett et al., 2007). Despite the increased base rate of anxiety, and patient reports of a causal link to pain, international guidelines make no specific recommendations on anxiety management in FM (Kia and Choy, 2017). The implications for the treatment gap that arise as a result, are likely to be compounded by the increase in the anxiogenic conditions during the current pandemic.

Recent research on chronic pain patients found an increase in pain during the

pandemic; a rise attributed to lockdown and not the concurrently amplified anxiety (Fallon et al., 2020). These findings, however, are based on cross-sectional investigations that do not capture the high variability of anxiety and chronic pain. As recommended in a recent study, repeated assessment of both is necessary to study their relationship during the pandemic (Kleinberg et al., 2020).

To address these concerns, we conducted a 10-day survey of FM-diagnosed participants, with two aims. First, to determine which aspects of the pandemic were sources of anxiety in FM. Our next and primary aim was to determine the association between COVID-19 anxiety and FM pain.

We hypothesised that there will be several sources of anxiety for FM patients, each associated with different levels of anxiogenesis but contraction of the virus being the most prominent. We further hypothesised that an increase in COVID-19 anxiety will be associated with concurrently reported increase in pain.

6.2.3 METHODS

Participants

The target population for the survey were adults, aged 18 to 60 years, diagnosed with FM for at least 6 months and no other pain condition. Participants were not recruited with COVID-19 relevant underlying health conditions, as reflected by placement on the NHS, UK Shielded Patient List. Participants were not recruited if taking gabapentinoids or hormone replacement therapy, both of which significantly mediate either pain or anxiety. Further screening was guided by the recently published diagnostic guidelines (Arnold et al., 2019). We included physical conditions that are commonly concurrent to fibromyalgia, if these were not associated with chronic pain. Mental health conditions classified under Axis I of Diagnostic and Statistical Manual of Mental Disorders, 5th

Edition (DSM-5) were also accepted.

Screening Survey

To find eligible participants, a screening survey was launched online on Qualtrics (Qualtrics, Provo, UT). Its distribution began in May 2020 and involved circulation across various social media platforms and email newsletters of several FM charities and patient-lead support communities. The screening survey had the following sections.

Participant Characteristics. Year of birth, gender, ethnicity, country of residence, marital status, weight, height, typical daily caffeine consumption and weekly alcohol consumption were recorded. Participants' status as key workers or caregivers was recorded with details of circumstance (i.e. job or who they are caring for).

Medical History Medication. The Generalised Anxiety Disorder, Depression and PTSD sections from the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998)were delivered online to account for the lack of a formal Axis I diagnosis in some participants. A researcher reviewed the answers to calculate scores for the PTSD, GAD, and depression, as most relevant to the study sections. As part of medical history, participants confirmed details of their FM diagnosis (e.g. year, diagnosis route). Participants also answered a series of questions to eliminate the possibility of excluding secondary circumstances (ESCs) that may indicate an undiagnosed chronic condition (e.g. convulsions/seizures). Based on COVID-19 advice from the NHS at the time of screening pregnancy was also considered ESC.

Medication intake in the last 30 days was recorded to identify participants, who qualify as a shielded person but failed to select a relevant option (e.g. asthma

inhaler).

Experience with Pandemic Anxiety. Participants were screened for possible COVID-19, based upon the cardinal symptoms, identified by the NHS. Any participant reporting positively were excluded from participation.

Participants were then asked whether they had experienced anxiety that is related to the COVID-19 pandemic. Respondents were to select as many as applicable from 14 possible categories (see Supporting Information 1). The categories were predetermined by the research team based on recent publications and conversations with stakeholders). Any category that was not selected was to be removed from the daily surveys. All categories were selected; thus, none were discarded.

First Daily Survey

Pain History General Anxiety. The first daily survey acquired baseline measures of participant's recent pain history and dispositional anxiety. The presence of FM symptoms was reconfirmed though the American College of Rheumatology Criteria, ACR, (Wolfe et al., 2010, 2016). Impact of FM on daily functioning was measured through the Revised Fibromyalgia Impact Questionnaire, FIQ-R (Bennett et al., 2009), and on overall pain through the Short Form McGill Pain Questionnaire, MPQ-SF (Melzack, 1987). To assess dispositional anxiety, we used the trait version of the State-Trait Inventory for Cognitive and Somatic Anxiety, STICSA-T (Grös et al., 2007).

Daily Caffeine, Alcohol, Medication. Several mediators of pain and anxiety were expected. First is caffeine, which may perpetuate anxiety (Nardi et al., 2009), but is also considered an adjuvant analgesic (Sawynok, 2011). Alcohol is also a known pain mediator. A curvilinear relationship is observed between

chronic pain and the consumption of alcohol (see Zale et al. 2015 for a review). Lastly, our target population was expected to take a variety of medication. To measure, and ultimately control for, these variables, we recorded daily the intake of caffeine (in mg), alcohol (in units), and medication (see Analysis).

Daily Anxiety Pain. Daily ratings of anxiety and pain were the primary variables. To measure anxiety, participants first identified the pandemic-related sources of anxiety relevant to that day. Only then they provided anxiety ratings for the selected sources on a 101-point visual analogue scale (aVAS). If an anxiety source was skipped, that source was automatically recorded as '0' – no anxiety. Pain was similarly recorded on a 101-point visual analogue scale (pVAS). For both scales '0' represented no anxiety/pain, '1' was minimal anxiety/pain and '100' was the worst possible anxiety/pain.

Daily Survey 2 – 10

The same surveys were completed for 9 more consecutive days, omitting the pain history and general anxiety questionnaires.

Procedure

The study was carried out in May and June 2020. Eligible participants completed the first of the 10-days survey within two weeks of passing screening. This resulted in multiple waves of participants with various start times. The daily survey was circulated at 4 PM local time to the participant, followed by a reminder at 8 PM and 10 AM the next day. Participants were given up to 24 hrs after the initial email for survey completion. Answers beyond the time limit were considered as missed. Participants were allowed to miss up to two surveys to achieve a sample completion rate no lower than 80%.

The study was granted ethical permission by the ethical board in the Faculty

of Health at the University of Plymouth and conformed to the Declaration of Helsinki. All data was stored anonymously. Informed consent was gathered during screening and each daily survey. Debrief was provided upon study completion. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Analysis

Following our aims, we first established whether FM patients experienced anxiety related to the pandemic by asking participants to select and rate applicable sources of anxiety on each daily survey. Mean (μ) and standard deviation (*SD*) were calculated for the provided ratings, ignoring those that were automatically zeroed.

We then investigated the relationship of the experienced COVID-19 anxiety with FM pain. Experienced COVID-19 anxiety was defined as the daily average anxiety rating, or aVASμ. It was calculated using only the provided anxiety ratings from the selected anxiety sources. Sources that were not selected by the participant as anxious received an automatic rating of 0 and were thus not contributing aVASμ. This focused approach allowed us to align anxiety ratings between participants with considerably different numbers of selected sources. More importantly, it is the aggregate score that encapsulates COVID-19 pandemic anxiety as a whole and not the separate categories, which capture only individual aspects of that anxiety. FM pain was defined directly through the pVAS rating.

We hypothesised that pVAS would increase with the increase of aVASμ. However, we also expected confounding factors so we utilised mixed-effects modelling. pVAS was the outcome variable. To determine a model of best fit, the

following covariates were possible: aVASμ, participant (*Participant*), participant's age (*Age*), participant status as key worker (*Key Worker*) or caregiver (*Caregiver*), daily caffeine (*Caffeine*), and daily alcohol (*Alcohol*). We also created a categorical variable that denotes the presence of a concurrent medical diagnosis (*Comorbidity*). It was data-driven and resulted in the following levels: no comorbidity, anxiety/fear disorder, depression, allergy, and thyroid condition. Daily medication vastly varied between participants to be added as a single covariate. We thus created separate categorical covariates for medication that was present in at least 10% of the total number of daily surveys (excluding supplements and nutraceuticals). The following covariates emerged: over the counter analgesics (*OTCs*), non-steroidal anti-inflammatory drugs (*NSAIDs*), opioids (*Opioids*), tricyclic antidepressants (*TCAs*), and SSRIs (*SSRIs*). Date of survey completion was not used as a factor in analysis since data was not balanced in respect to calendar date.

Analysis was carried out in `R Studio` (v 1.2.5). Power analysis was carried through simulations (n = 200) in `simr` (v 0.4), where Kenward-Roger approximation was calculated for each fixed covariate to reach effect size d = .3 at 80% (Green and MacLeod, 2016; Matuschek et al., 2017). A Kenward-Roger approximation was calculated for each fixed covariate. For hypothesis testing, models were compared through likelihood-ratio testing and Bayes factor against a baseline model consisting of participant-only intercept. The best model was chosen based on fit assessed through Bayesian modelling, following analysis protocol described elsewhere (Muth et al., 2018), as well as BIC and AIC. Finally, the predictions of the best fit model generated by `lme4` (v 1.1.21) were confirmed through Bayesian credible intervals from `rstanarm` (v 2.18.2).

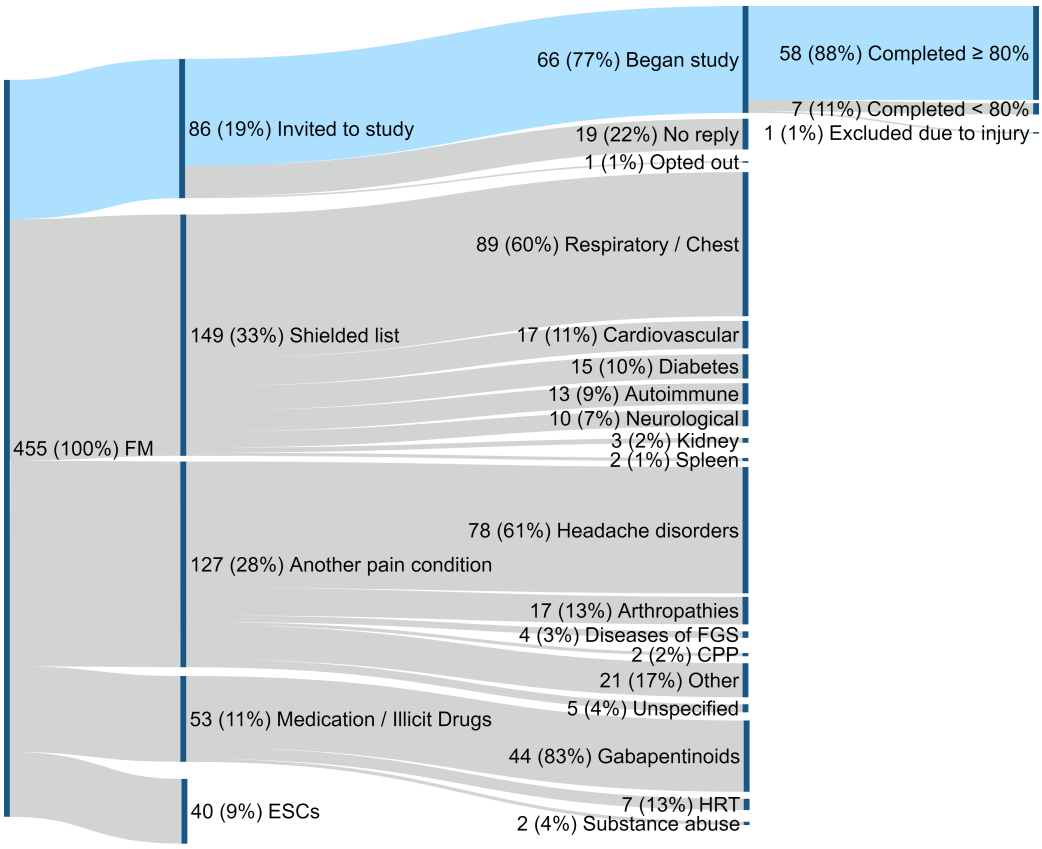

Figure 6.1: Participant recruitment diagram. Participants were excluded based on the following criteria (in order): 1) presence of fibromyalgia (FM) diagnosis; 2) presence of conditions from the shielded list; 3) presence of another pain condition, e.g. diseases of the female genital system (FGS) or chronic primary pain condition (CPP); 4) intake of medication such as gabapentinoids, hormone replacement therapy (HRT), or illicit drugs; and lastly 5) presence of excluding secondary circumstances (ECSs). Each node is labelled with number of participants (n), percent from total screened sample (%) and reason for inclusion/exclusion.

6.2.4 RESULTS

Out of 455 screened participants, 397 (87%) were excluded due to various reasons (see Figure 6.1). Of those who qualified, 58 completed 80% of the surveys and their data were analysed.

Participant characteristics can be found in Table 6.1.

Comorbidities, medication intake, and questionnaire scores of the final sample are summarised in Table 6.2.

Due to 4 missed daily surveys, the final dataset comprised of 576 daily surveys. In total participants made 1,600 ratings across all anxiety sources. However, the anxiety source 'other', which contained participant-entered reasons was highly heterogeneous and commonly unrelated to the pandemic. For this reason, it was removed from analysis leaving 1,548 anxiety ratings. On average participants chose 2.79 (*SD* = 2.27) sources per day out of the remaining 13. Figure 6.2 shows the anxiety sources ordered by mean rating in a descending order, with the researcher-calculated cumulative rating aVASμ on top.

After we determined the different sources of anxiety related to the pandemic, we analysed the relationship between experienced anxiety and FM pain. Plotting the anxiety and pain ratings on a scatterplot (see Figure 6.3) suggests that a positive trend does exist between the two.

Mixed-effects modelling showed that the best fit model had the following formula:

$$\begin{aligned} pVAS_{\mathrm{pd}} &= \beta_0 + P_{0\mathrm{p}} + Caffeine_{0\mathrm{c}} + \\ &+ \beta_1 aVAS_{\mathrm{d}} + \beta_1 OTC_{\mathrm{d}} + \beta_1 NSAID_{\mathrm{d}} + \beta_1 Opioid_{\mathrm{d}} + \beta_1 Age_{\mathrm{d}} + \varepsilon_{\mathrm{i}} \\ p &= 1, 2, ..., 58 \\ d &= 1, 2, ..., 10 \end{aligned} \tag{6.1}$$

The best fit model significantly differed from the baseline model, χ^2 = 94.16, p < .001, BF = 1.04 x10^{14}. It contained several covariates that were significantly linked to pain (see Table 6.3). As predicted, the model showed that higher self-assessed FM pain (pVAS) was significantly associated with increased daily

Table 6.1: Sample Characteristics

	μ or **n**	**(SD) or %**
Gender (n female) [a]	58	100%
Age (n years)	40.29	(10.98)
Ethnicity [a]		
Black / African / Caribbean	1	2%
Caucasian	56	96%
Hispanic	1	2%
Weight (kg)	82.92	(23.67)
Height (cm)	166	(0.7)
BMI	30.16	(8.07)
Country of Residence [a]		
Canada	1	2%
Spain	1	2%
UK	52	89%
USA	4	7%
Marital Status [a]		
Civil Partnership	26	45%
Separated / Divorced	10	17%
Single	20	35%
Widowed	2	3%
Key worker (n yes) [a]	22	38%
Caregiver (n yes) [a]	16	28%
Fibromyalgia (ICD-11 MG30.01)		
Diagnosis duration (n years)	3.86	(3.79)
Symptoms duration (n years)	9.15	(7.37)

μ - average value, n – count, *SD* – standard deviation, % - percentage.
[a] Items, for which n and % were calculated.

anxiety (aVASμ). Further, respondents who took OTCs and NSAIDs reported more pain than those who did not. This difference was mirrored in patients who took opioids but the association failed to reach significance. Intake of TCAs

was not part of the best fit model, possibly due to the lower number of observations. OTC analgesics (17%), NSAIDs (17%), and opioids (22%) accounted for a large portion of total medication intake, while TCAs were present in only 10% of the measurements. In contrast, SSRIs were common (21%) but still were not part of the best fit model.

Age was also significantly allied to pain: the older a participant was, the higher their reported pain was. Variance in pain was attributed to individual differences between participants and the daily amount of caffeine. Models including presence of comorbid conditions and daily alcohol intake were not superior.

6.2.5 DISCUSSION

The present study investigated the effects of the COVID-19 pandemic on the well-being of FM patients. We determined which aspects of living during the pandemic are anxiogenic to FM patients and assessed daily fluctuation in self-reported pain. We found that although respondents differed in sources of anxiety day-to-day and between each other, the resulting incline in anxiety ratings was reflected in ratings of chronic pain.

On the basis of discussions with stakeholders, we expected, that as a health-compromised group, our respondents would be most concerned with health-related issues: *"oneself contracting COVID-19"*, *"access to medication"*, and *"access to medical professionals"*. Instead, our findings on anxiety sources agree with recently published surveys of the general population (Kleinberg et al., 2020; Shahabi et al., 2020). On average FM patients rated "financial hardship", "access to medication", and "home loss/eviction" as the most anxiogenic. Similar concerns with economic security have been observed in both vulnerable and general populations (Kleinberg et al., 2020; McElroy et al., 2020). In that, FM respondents appear homogenous with their healthy counterparts. However, FM patients were least anxious about *"oneself contracting COVID-19"*, *"delayed travel plans"* and *"access to essentials"*. The former has been reported as both the

Table 6.2: Medical Comorbidities, Medication Intake and Questionnaires.

	μ or **n**	**(SD) or %**
Medical Comorbidities (present in n participants) [a]	28	48%
Unspecified Allergy (ICD-11 n)	7	12%
Allergic rhinitis due to pollen (ICD-11 CA08.00)	5	8%
Anxiety/fear-related disorder (ICD-11 6B00 – 6B0Y)	2	3%
Obsessive-compulsive disorder (ICD-11 6B20)	1	2%
Panic attacks (ICD-11 MB23.H)	10	17%
Depressive disorder (ICD-11 6A71)	2	3%
Hypothyroidism (ICD-11 5A00)	5	8%
Postviral fatigue syndrome (ICD-11 8E49)	4	7%
White coat hypertension (ICD-11 MC80.00)	1	2%
Medication Medication (taken by n participants in the last month) [a]	54	93%
Analgesics (non-prescribed)	21	36%
Beta-blockers	2	3%
Antihistamines	10	17%
Benzodiazepines	1	2%
IBS Medication / PPIs	8	14%
Muscle relaxants	2	3%
NSAIDs	20	35%
TCAs	13	22%
Thyroid Medication	6	10%
SNRIs	4	7%
SSRIs	12	20%
Supplement / Nutraceuticals	19	33%
Other [a]	15	26%
ACR (n met criteria)	58	100%
FIQ-R	57.58	(16.95)
SF-MPQ		

Pain Descriptors (0 - 45)	20.36	(7.09)
Sensory	15.74	(5.65)
Affective	4.62	(2.31)
Visual Analogue Scale (0 - 10)	6.39	(1.72)
Present Pain Intensity (0 - 5)	3.03	(.65)
Trait STICSA	48.76	(12.7)
Cognitive Anxiety	24.19	(7.32)
Somatic Anxiety	24.57	(6.64)
M.I.N.I [a]		
Depression (n meet criteria)	33	57%
PTSD (n meet criteria)	24	41%
Anxiety (n meet criteria)	51	88%

IBS – irritable bowel syndrome; PPIs – proton-pump inhibitors; NSAIDs - non-steroidal anti-inflammatory drugs; TCAs – tricyclic antidepressants; SNRIs – serotonin–norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors; ACR – American College of Rheumatology Criteria for Fibromyalgia; FIQ-R – Revised Fibromyalgia Impact Questionnaire; SF-MPQ – Short-form McGill Pain Questionnaire; STICSA – State-Trait Inventory for Cognitive and Somatic Anxiety; M.I.N.I. – Mini-International Neuropsychiatric Interview; PTSD – post-traumatic stress disorder.

μ - average value, n – count, *SD* – standard deviation, % - percentage.

[a] Items, for which n and % were calculated.

most prevalent and the strongest anxiety source (Kleinberg et al., 2020). It is unclear as to why FM respondents rated disease contraction so low. It is possible that as self-identified vulnerable group participants took measures they perceived to sufficiently reduce their risk of contracting COVID-19. Importantly, the highest rated anxiety sources were not necessarily the most reported.

Most often, FM patients pointed to *"impact on relationships"*, *"family contracting COVID-19"*, and *"financial hardship"* as evoking anxiety. Fear over potentially negative effects

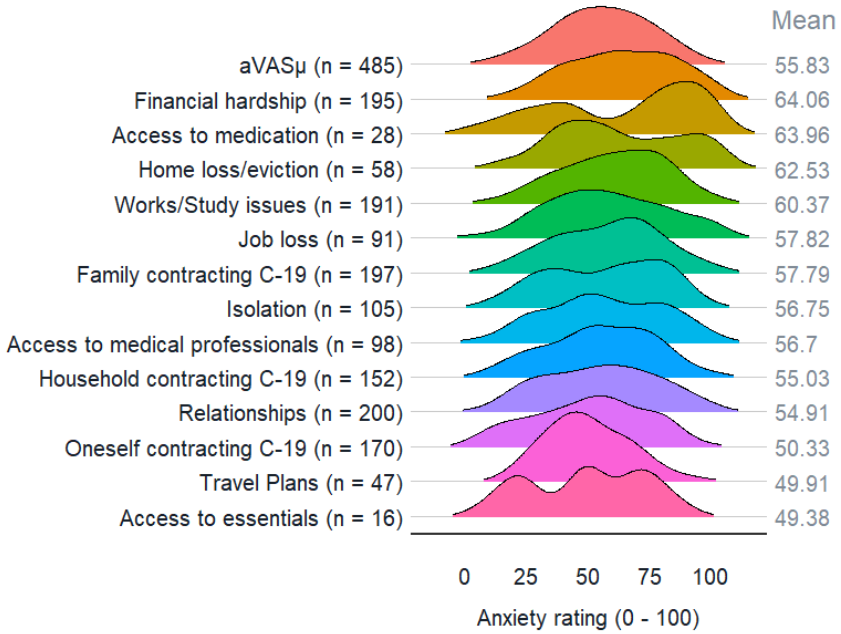

Figure 6.2: Distribution of anxiety ratings per source. The first row of the half-violin plot shows the distribution of the daily average anxiety ratings (aVASμ). Subsequent rows show the distribution of ratings per anxiety source, ordered by highest rated on average to the lowest. The number of times an anxiety source was selected (across all daily surveys) is shown in brackets. The average anxiety rating per source is shown on the right of each distribution.

of long-term quarantine on interpersonal relationships has been predicted in the literature (Schimmenti and Starcevic, 2020), as has concern over family members contraction risk rather than oneself (Wang et al., 2020). The high prevalence of financial anxiety fortifies it as a central concern for FM patients. Economic downfall is expected to maintain for years to come (Baldwin, 2020), which raises the question whether it will remain anxiogenic for chronic pain patients. Pre-pandemic up to 46% of FM sufferers reported job loss due to health complications (Al-Allaf, 2007). Redundancy during the pandemic may mean that such individuals will struggle with finding new employment due to the work restrictions imposed by FM (Bossema et al., 2012). Further, worsening of socio-economic status will likely put FM individuals in a higher risk for contracting COVID-19 (Patel et al., 2020), thus this group of patients should become focus of attention for policymakers. In contrast, FM patients pointed the least times

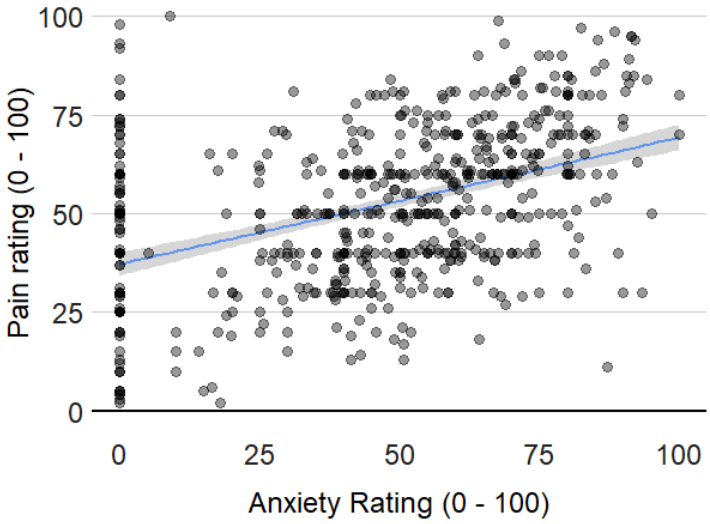

Figure 6.3: Scatterplot of anxiety and pain ratings. The daily anxiety rating (aVASμ) is plotted on the x-axis and the daily rating of fibromyalgia pain (pVAS) is on the y-axis. The regression line is a function of x y, the shaded area represents the standard error around it.

to *"delayed/cancelled travel plans"*, *"access to medication"*, and *"access to essentials"* as anxiogenic. Even though this is also in agreement with cited research, our findings cover only the early phase of the COVID-19 pandemic (i.e. the "first wave"). Easing of travel restrictions may introduce new stressors as it was seen in Wuhan, China (Ma et al., 2020). At present, we found that participants who utilised the comments box at the end of the daily surveys welcomed some easing of the travel rules:

> *" . . . The PMs [Prime Minister's] update has been great as it means we could have some family over and it looks like our caravan holiday in August will go ahead, finally something to look forward to."*

An in-depth qualitative analysis of these comments is a topic of another publication (in preparation). We did observe a reduction in some anxiety ratings coinciding with easing of restrictions in the UK (see Supporting Information 2).

The central finding that emerged during analysis was the positive relationship between anxiety and pain ratings. Our model predicts that for each 10 points of increase on aVAS scale, FM respondents will experience a 2-point increase in pVAS. Although this

increase is small, particularly when compared to the increase associated with intake of OTC and NSAIDs, it is significant. While FM patients experience psychosomatic symptoms, the pain chronicity is not given rise to by a psychogenic mechanism (Pikoff, 2010). Thus, daily psychological fluctuations cannot be presumed as leading determinant of FM pain. For as long as the origin of this pain remains unknown, factors mediating it are actively sought by patients and researchers. The increase of pVAS ratings observed during OTC and NSAID analgesics is indicative of patient behaviour. Both are part of self-management plan for many FM patients despite inconclusive clinically significant benefits (Derry et al., 2017; Rocha et al., 2020). We therefore interpret our findings as indicative of intake of these analgesics in the presence of heightened pain.

Another important finding is that apart from age, no other participant characteristic was found to significantly improve the best fit regression model. A plausible explanation for that is the scope of measured participant qualities was not sufficient. Presence of mental distress or a clinical diagnosis of anxiety have been linked to poor quality of life and pain in FM, unlike comparable pain conditions (Gormsen et al., 2010). In our sample, only 3% participants had an anxiety as a diagnosis but 88% had an indication of general anxiety as measured through MINI.

The finding that the pandemic is not only conducive to heightened anxiety but that the resulting emotional distress is reflected in FM pain, has several implications. Foremost, it confirms the previously raised concerns that the “new normal” introduced by the pandemic may qualitatively differently impact vulnerable populations. Second, it highlights the relationship between mental and physical wellbeing in FM pain. Evidence-based international guidelines suggest that treatments target foremost patient-reported complaints (Clauw, 2014; Häuser et al., 2010b). Psychiatric evaluation is instead undertaken upon request. This practice is in contrast with research where presence of psychological distress has been linked to disease progression (Marcus, 2009). Our findings support that literature and evidence the necessity to address anxiety in FM

Table 6.3: Best Fit Model Statistics.

	Traditional Analysis			Bayesian Analysis			
	Coeff.	***(SE)***	***t-value***	***Coeff.***	***(SD)***	***CI***	
						2.5%	***97.5%***
Fixed Effect							
Intercept	18.74	(5.87)	3.19 **	18.65	(5.95)	7.34	30.54
aVAS	.21	(.03)	7.27 ***	.2	(.03)	.15	.26
OTCs Intake	7.7	(2.18)	3.53 ***	7.71	(2.23)	(2.23)	12.07
NSAIDs Intake	8.01	(2.16)	3.71 ***	7.94	(2.2)	(2.2)	12.29
Opioids Intake	4.4	(2.32)	1.9 [a]	4.39	(2.36)	(2.36)	8.96
Age	0.5	(.14)	3.68 ***	.5	(.14)	(.14)	.78
	σ^2	***(SD)***					
Random Effects							
Participant	1.1	(10.49)					
Caffeine Intake (mg)	1.49	(.01)					
Residual	1.82	(13.50)					

In frequentist analysis, the linear mixed model was fit by maximum likelihood and t-tests were calculated automatically using Satterthwaite approximations to degrees of freedom. In Bayesian analysis, weakly informed priors were used to estimate parameters.

aVAS — anxiety visual analogue scale rating, *OTCs* — over the counter analgesics, *NSAIDs* — non-steroid anti-inflammatory drugs, *Coeff.* -– predicted value for coefficient, σ^2 — estimated variance, *SE/SD* – estimated standard error/deviation, *CI* – credible interval.

*** $p < .001$, ** $p < .01$, * $p < .05$, [a] $p = .058$

during the pandemic. Cognitive and behavioural interventions, however, are often dismissed by FM patients as indicated by low treatment adherence (Dobkin et al., 2006). Further, such therapies may not be viable during a pandemic. New alternative options are needed to aid mental health in patients for the benefit of their chronic pain. One promising direction are open-label placebos, which combine the traditional administration of a placebo pill with an informative narrative (Locher et al., 2017). Such placebos have been found to improve psychological symptoms and with them chronic physical complaints (Carvalho et al., 2016; Kelley et al., 2012; Sandler and Bodfish, 2008).

Lastly, we identified several limitations of our study. The primary focus of our research

was the experience of pain in the presence of COVID-19 anxiety. Pain, however, is only one of the cardinal FM symptoms. Sleep disturbances and fatigue are both most reported concerns for FM (Arnold et al., 2008b), as well as both are acutely sensitive to stressors (Affleck et al., 1996). There has been a decline in the quality of sleep in the general population (Casagrande et al., 2020). If the regression is similar in FM, it may have profound consequences for pain (Affleck et al., 1996). Future investigations should therefore integrate daily evaluations of fatigue and sleep alongside of assessments of COVID-19 anxiety. Another constraint of our work was that the survey was carried out during the early phase of the pandemic, when anxiety was at its highest. Observing pain during time of relative normality as well as during reverting of lockdown would be advantageous for the understanding of long-term development of COVID-19 anxiety in the presence of chronic pain.

Conclusion

Our study found that FM pain increased with COVID-19 anxiety during the pandemic. This relationship was mediated by individual differences and intake of certain medication, such as OTC analgesics and NSAIDs, together with caffeine consumption. These findings indicate that mental health decline as a result of the COVID-19 pandemic coincides with worsening of the physical wellbeing in chronic pain sufferers. Further research is necessary to broaden the understanding of how other key FM symptoms, fatigue and sleep disturbances, are impacted during the pandemic.

6.3 Concluding Commentary

Summary

To summarise, the final study of the thesis documented the daily relationship between sustained anxiety and FM pain. This broad perspective contrasts with the preceding reported studies, where instead fine-grained differences in the temporal relationship between anxiety and pain were studied. Here, we demonstrated how persisting anxiety

contributed to the experience of chronic FM pain.

Sustained anxiety, defined as the everyday anxiety evoked by the COVID-19 pandemic, was found to significantly predict an increase in the average daily rated FM pain. The daily COVID-19 anxiety was an aggregate measure of all reported anxiety ratings for that day. Such an approach allowed to equate the data since participants varied not only in the selected numbers of anxiety sources between each other but within themselves too.

An inspection of the times each source was selected found that some were far more prevalent than others. For example, participants most often pointed to *"impact on relationships"* as anxiogenic and least often to *"access to essentials"*. The times an anxiety category was selected did not necessarily linearly relate to the magnitude of the produced anxiety. For instance, the most common category *"impact on relationships"* produced one of the lowest average anxiety ratings (m = 54.91). In contrast, *"financial hardship"*, another commonly selected category, had the highest average anxiety rating of 64.06, and was notably higher than the lowest rated source *"access to essentials"* (m = 49.38).

Together, the presence of anxiety in relation to various aspects of living during the COVID-19 pandemic and the paired increase of pain alongside of that anxiety, suggest that FM patients do experience worsening of their pain in the presence of sustained elevated distress.

Discussion of Key Findings

The central finding of this work was not that COVID-19 anxiety was present in FM patients; this was reasonably expected based on similar recent research (Cavalli et al., 2020). It is that its presence had a tangible impact on their condition. While an increase in COVID-19 anxiety predicted a proportionally smaller increase in pain, the importance of this factor cannot be underestimated. As explained by Pastor-Mira et al. (2019), the health equilibrium of patients with FM is supported by the concurrent balance of their

mental health. This does not mean that psychological distress is responsible for the chronic FM pain, but that it is an influencing factor. Simply put, declined mental well-being may mean worsening of pain but the absence of mental distress does not mean the absence of pain. In this study, we see support for both of these points. Not only did pain increase with anxiety, but patients also continued to report various levels of pain when COVID-19 anxiety was reported as absent. This can be plainly seen in Figure 6.3, where null anxiety ratings purposefully were not omitted. While without them the trend between anxiety and pain may prove to be steeper, it may suggest a false narrative, in which anxiety appeared to determine the direction of pain magnitude.

The next crucial observation was about the nature of the COVID-19 anxiety itself. As explained, the composite score was necessary for comparative reasons. Further consideration, however, is needed of the individual anxiety categories. In Chapter 2, Section 2.3.2 Sustained Anxiety explained how categories were predominantly based on pandemic anxiogenesis sources, identified in the literature at that point. The present study combined all of them under the umbrella COVID-19 anxiety in an attempt to fully characterise the sustained pandemic distress. This was both a strength and a weakness of this study's methodology. It was a marked improvement on previous investigations, which only recorded the presence of elevated anxiety without specifying the cause (Kleinberg et al., 2020). It was also an advance on those studies that established the causes, but not the magnitude of the corresponding anxiety (Jia et al., 2020). In this study, we flexibly recorded what elicited anxiety in our participants and to what extent. The frailty of our method still is the preselection of possible anxiety categories.

Participants were faced with a choice of 14 categories, one of which was a free-text option *"other"*. It was included to capture other aspects of the pandemic that we did not foresee. Unfortunately, not only were the self-entered descriptions commonly irrelevant to the COVID-19 pandemic, the remaining were unique to participants and vastly different from each other. Informal inductive qualitative analysis suggested that at least one category may have been included. That was the concern over children, be it their

health, education or childcare arrangements. Although it was infrequently entered, it is possible that, if otherwise included as a permanent category, more participants would have selected it. This leads to an obvious conclusion: the generation of anxiogenic categories should *also* be patient-generated. In a post-hoc fashion, we are in the process of performing a proper qualitative analysis on the topic, using the free-text comments left by participants.

The last implication of this study is on the theoretical benefits of studying COVID-19 anxiety in FM. As discussed in the introductory commentary of this chapter, the typical approach to studying sustained anxiety is by choosing a prominent, specific anxiogenesis source, which may present tangible issues to the participant (e.g. fear of birth complications in pregnant women). The challenge in that is how to find a substantial number of participants unified in their source of anxiety. Particularly with FM patients, who are a highly heterogeneous group. One anxiogenic topic previously identified in the literature is employee retention (Al-Allaf, 2007; Kivimaki et al., 2004; Löfgren et al., 2006) and it may warrant a further investigation.

Finally, the COVID-19 pandemic offered an unexpected boost to research on sustained anxiety. It is not known whether stress related to the pandemic is on a decline or whether it is location-specific. For this reason, a replication of the study would not only enrich the literature on sustained anxiety but will also assess the longevity of COVID-19 anxiety in FM patients. Such replication is planned.

Conclusion

In conclusion, the contribution of anxiety to FM pain is evident on a larger scale. Unlike the previous experimental study, where there was an indication that acute anxiety may be related to inhibited pain report, here, daily rated anxiety promoted pain increase. Thus, the measurement of naturally present, sustained anxiety presented another research dimension in the investigation of anxiety and pain in FM.

Chapter 7

General Discussion

How lucky am I to have something that makes saying goodbye so hard.
– Not A.A. Milne, Not the Complete Tales of Winnie-the-Pooh

THE general aim of the thesis was to explore the relationship between anxiety and pain in fibromyalgia-diagnosed individuals. It was broken into several aims, each exploring a different research question using innovative experimental or observational methods. In the final chapter of the thesis, I summarise the key findings, as well as suggest future research directions taking into account the achieved results and experienced challenges.

7.1 Main Findings

7.1.1 Continuous Pain Ratings & Central Sensitisation

The first experimental chapter, Chapter 3, tested whether continuous pain ratings could be adopted in place of the conventional pain collection methods to study behavioural markers of central sensitisation. These included both TS, the elevation of pain ratings in response to constant invariable painful stimulation, and adaptation, the processes of habituation or sensitisation to the prolonged stimulation. Two key observations were made. First, continuous reassessment of experimental pain was intuitive and acceptable to both pain-free and chronic pain participants, who readily updated their ratings throughout stimulation. This is particularly important for the clinical cohort where con-

cerns over their tolerance of the procedure are always present.

Second, continuous pain data collection did not produce a pattern of pain ratings conflicting with previous reports. On the contrary, it furthered the existing literature by enabling the highly precise extraction of canonical pain rating measures, such as peak or slope to peak. More importantly, extraction of these variables was data-driven instead of at times predetermined by the researcher or methodology. Thanks to this, time became a property of the acquired data, thus allowing to analyse not only *what* peak the pain ratings reached but also *when*.

7.1.2 Central Sensitisation in Fibromyalgia

The previously not researched time property was found to be a key measure that differentiates between FM-diagnosed and pain-free individuals. The chronic pain cohort was significantly slower to report their highest pain both during TS and adaptation. Paired with the trend for FM patients to produce higher maximal ratings, the findings fortify that continuous pain report accurately detect deficient pain modulation in FM. Observations are consistent with predictions of pain behaviour in the presence of central sensitisation and further reaffirms FM as a central sensitisation syndrome. Beyond theoretical implications, the significant delay in reaching peak ratings motivates a reappraisal of previous research that failed to observe augmented TS in FM.

The predetermined window for gathering TS pain ratings may have been of insufficient length. In studies, where TS was defined as the mean or highest pain rating of a train of stimulation versus that of a single stimulus, pain measurement may have been too short. Further, limiting pain report only to the period of TS has also prevented the characterisation of central sensitisation through measures of adaptation. As it was found, the deficient pain modulation associated with FM continues to be evident beyond TS, which has been predicted by the literature (Graven-Nielsen et al., 2000). Future research should thus extend their pain measurement window, if not adopt continuous pain ratings altogether.

7.1.3 Effects of Hypercapnic Inhalation on Acute Pain in Pain-free Participants

Chapter 4 demonstrated that the inhalation of a hypercapnic mixture alone is associated with significant reductions of pain measures. When painful TES is applied during inhalation of a mixture with elevated levels of CO_2, the amplitude of continuous pain ratings is suppressed from the start. The maximal ratings during TS Period, as well as the slope leading to that peak, are lower than measurements obtained during normocapnic inhalation. These findings reflected the preceding literature, indicating that the analgesic effects of the CO_2 Model are reproducible across pain modalities.

7.1.4 Effects of Experimental Anxiety on Acute Pain in Pain-free Participants

The same chapter analysed the effects of CO_2-induced anxiety on TS. Acute anxiety was measured through self-report as well as physiologic readings of the cardiovascular system. Only ratings of anxiety made during the hypercapnic inhalation were significantly associated with a reduction in TS. Importantly, the effect was not uniform as it was with hypercapnic manipulation. Higher self-assessed anxiety was linked to lower summative pain ratings, both for the whole pain response, as well as separately for the periods of TS and adaptation. The rate of increase of pain ratings during TS was not influenced by acute anxiety, though it was by the type of inhaled mixture, as well as the maximal points during TS and adaptation. This does not necessarily suggest that experienced anxiety is irrelevant to the development of TS. It may be that the re-measurement of anxiety was not frequent enough, or that the presence of the inhalation type in the analysis is masking the effect of individual anxiety ratings. The uncertainty in interpretation warrants continued testing. The main investigative purpose, however, was achieved: to obtain baseline effects of CO_2-induced anxiety on pain processing in pain-free individuals. These results were thus promising for subsequent comparisons with chronic pain participants.

7.1.5 Response to the CO_2 Model in Fibromyalgia

Chapter 5 presented the study, in which the feasibility of applying the established anxiety and pain testing protocol with FM-diagnosed patients was tested. The small pool of eligible participants and the even smaller number of those who took part greatly limited the investigation. In the end, preliminary data was gathered only from one FM participant. Further three participants attended the study but did not complete it. The reasons for their suspension during the experimental session conduced several key observations about the feasibility of using the CO_2 Model in chronic pain research. First, the evoked respiratory distress may not be suitable for all chronic pain conditions due to the evocation of respiratory distress. The somatic changes associated with the 7.5% CO_2 inhalation may be too strong for individuals with somatically heterogeneous diagnoses, such as FM. Second, the anxiogenic paradigm allows only participants with healthy cardiovascular readings to be tested, which may have been an underestimated challenge. Research elsewhere suggests that chronic pain may be associated with chronic abnormal resting-state sympathetic activity (Bruehl and Chung, 2004). Third and last, the preliminary data showed that the CO_2 Model evoked such anxiety and pain changes that resemble those observed in the previous study (Kharko et al., 2020b). While possible, it is not suitable to compare both cohorts due to limited sample size. Together, the results from this study pointed to many challenges in applying the CO_2 Model with FM participants but also provided informed insight on its possible application with other chronic pain conditions.

7.1.6 Sustained Anxiety & Fibromyalgia Pain

The final study in Chapter 6 examined the relationship between anxiety and FM pain from a broader perspective. Instead of reporting both in a condensed time period, patients were tasked with rating their daily experiences. Further, instead of evoking anxiety in patients, we measured the one introduced by the COVID-19 pandemic. Not only was this sustained anxiety prevalent in the patient population, but it was also

associated with changes in their physical well-being. An increase in daily self-rated COVID-19 anxiety was mirrored by an increase in FM pain. This was the first study to demonstrate how FM sufferers are impacted by changes in mental health, triggered by the pandemic. It was also the first to explicitly test the effects of sustained anxiety on FM patients, highlighting again the multifaceted impact of anxiety on FM.

7.2 Methodological Considerations

In the investigations of experimental anxiety and pain, one of the central methodological constraints was discovered in the study with FM-diagnosed cohort (Chapter 5). While the CO_2 Model has been used to study anxiety in a variety of clinical settings, its adoption in pain research remains limited. This is even more so true for chronic pain research. The endeavour of applying the model with a sample of FM patients was enthusiastic given the time and resource constraints imposed by the PhD. Exclusion criteria greatly limited the pool of participants, suggesting that future recruitment should be done through a collaboration with a local pain management service. It should also be considered whether lowering the CO_2 concentration would be beneficial for the in-study attrition rate when working with chronic pain participants.

Another major consideration that has not been discussed but should be mentioned is the target patient population. The approach in all presented study has been to strictly select only those patients that have been diagnosed exclusively with FM and no other chronic pain condition that is associated with chronic pain. This decision was purposeful. Not only did it ensure that any observed outcome effect could be reasonably attributed to the presence of diagnosis, but it also reduced the target sample size. Where studies had recruited participants with multiple pain comorbidities, these additional diagnoses had been factored in the analysis. To do the same here, an additional number of participants would have to be recruited for an adequately powered study. It should also be noted that for a condition such as FM, recruiting participants with *only* FM means seeking out participants that are possibly not representative of their cohort.

Apart from expanding the eligible target population, several new research directions could be explored.

7.3 Future Directions

Can continuous pain report aid diagnosis differentiation?

The findings from this work point to several research avenues. First is the adoption of continuous pain ratings for the study of pain processing in FM. One recurring suggestion that has been voiced since the first studies by Staud et al. is that dynamic QST may aid diagnosis of FM (Arendt-Nielsen and Yarnitsky, 2009; Pavlaković and Petzke, 2010). Such recommendations reside on the presumption that the temporal profile of pain in FM is uniquely different from other musculoskeletal pain conditions. Whether or not that is the case, could be addressed in future research. Based on our findings (Kharko et al., 2021), continuous pain ratings would be particularly useful in such investigations due to the temporal sensitivity they provide, as well as the informative depth of the acquired data.

Can the CO_2 Model be adjusted for chronic pain research?

Another direction is exploring the modification of the GAD CO_2 Model for compatibility with chronic pain patients. The model may be useful for testing anxiolytics as effective pain management in chronic pain. As mentioned in Chapter 2, in the absence of long-term effective pain management strategies the focus shifts to adjuvant treatment of factors that perpetuate pain. One way to test the potential of anxiolytics is by using the less potent but still stable version of the model, where a lower concentration of CO_2 is delivered. The protocol of gas delivery may also be modified so that a participant receives a practice inhalation of the CO_2 mixture, followed by a mandatory break before commencing the experiment. This will allow for the experimenter to observe vital physiological values and for the chronic pain patient to become accustomed to the sensations. Such an approach poses the risk of minimising the anxiogenic effect

but may greatly improve the in-study retention rate. Alternatively, a series of studies could explore the option of testing chronic pain patients while they continue their regular medication schedule. The studies described in this thesis adhered to a strict safety protocol, which excluded participants ingesting *any* prescribed medication. Including participants who ingest certain classes of medication will allow testing their contribution to acute anxiety management and potential analgesic effects.

Response to the CO_2 Model: informative in itself?

Beyond technical adjustment of the CO_2 Model, a more substantial change in research question may be needed. Characterisation of what makes a participant more likely to tolerate the evoked respiratory distress as well as what makes them less resilient is a question in its own merit. It could be expanded to comparative studies with multiple patient groups. For instance, how do central chronic pain patients differ from patients diagnosed with peripheral neuropathy? How do chronic pain patients compare to pain-free patients with anxiety or depressive diagnoses? Such comparisons would allow to better characterise what, if anything, is unique to chronic pain sufferers in experiencing anxiety.

What else can we learn about fibromyalgia during the COVID-19 pandemic?

The findings in the final chapter, Chapter 6, highlighted the importance of considering FM pain in the context of persisting anxiety. Foremost, the anxiogenic effects of the pandemic should be studied again. It is not clear whether the same sources of anxiety continue to elicit feelings of worry in FM participants, or if new categories have been introduced (e.g. vaccination against COVID-19). Additionally, apart from having pain as an outcome, expanding the list of collected outcome variables may be also beneficial. Sleep, for example, is acutely sensitive to the presence of anxiety, and poor sleep is known to be detrimental to FM symptoms. During the COVID-19 pandemic the combined effect of sustained anxiety and sleep quality may be more pertinent to FM pain than anxiety alone. Causal modelling of the relationship between COVID-19 anx-

iety, sleep and pain should thus be considered. At the time of writing, a plan exists to address this via a study that replicates and extends the original survey (Kharko et al., 2020a).

7.4 Concluding Remarks

The studies from this PhD research highlighted the multifaceted contribution of anxiety to pain perception in both pain-free and FM-diagnosed individuals. Using a robust pain measurement approach with a reliable human experimental model of anxiety we demonstrated the temporally fine relationship between evoked pain and anxiety. While the application of this paradigm did not yield expected results when delivered to FM patients, the model remains promising for other clinical investigations. The research series also explored FM pain in the presence of sustained anxiety caused by the COVID-19 pandemic. The finding that such anxiety is not only present but produced meaningful changes in reported pain encourages further attention to anxiety as part of care for this patient group.

Together, the work presented in this thesis strongly advocates for continued theoretical and practical investigations of mechanisms of anxiety for the benefit of FM sufferers.

Abbreviations

A Period adaptation period

Aμ the average pain rating during the A period

ACR'10 American College of Rheumatology Criteria for Fibromyalgia from 2010

ACR'16 American College of Rheumatology Criteria for Fibromyalgia from 2016

ACR'90 American College of Rheumatology Criteria for Fibromyalgia from 1990

ACTH adrenocorticotropic hormone

AIC Akaike information criterion

Amax-t the time of the maximal rating during the A Period

Amax-v the value of the maximal rating during the A Period

Amin the minimal rating during the A period

ANS autonomic nervous system

aVAS anxiety visual analogue scale

BF Bayes Factor

BIC Bayesian information criterion

BP blood pressure

Bristol TARG Bristol Tobacco and Alcohol Research Group

CFS chronic fatigue syndrome

CNS central nervous system

COVID-19 coronavirus disease 2019

CRH corticotropin-releasing hormone

DIA diastolic blood pressure

DNIC diffuse noxious inhibitory control

FIQ-R the Revised Fibromyalgia Impact Questionnaire

FM Fibromyalgia

GAD generalised anxiety disorder

HCs healhy controls

HPA axis hypothalamic–pituitary–adrenal axis

HR heart rate

IBS irritable bowel syndrome

Lab RED Laboratory for Respiratory Experimental Designs

M.I.N.I. Mini-International Neuropsychiatric Interview

MEM mixed-effects model

NSAIDs nonsteroidal anti-inflammatory drugs

OCD obsessive-compulsive disorder

PD panic disorder

PMS premenstrual syndrome

PRAN pain range

PTHR pain threshold

PTOL pain tolerance

PTSD post-traumatic stress disorder

pVAS pain visual analogue scale

QST quantitative sensory testing

RA rheumatoid arthritis

S-STICSA state version of the State–Trait Inventory for Cognitive and Somatic Anxiety

SF-MPQ Short Form McGill Pain Questionnaire

SNRIs serotonin-norepinephrine reuptake inhibitors

SSRIs selective serotonin reuptake inhibitors

STAI State-Trait Anxiety Inventory

STHR sensory threshold

STICSA State–Trait Inventory for Cognitive and Somatic Anxiety

SYS systolic blood pressure

T-STICSA trait version of the State–Trait Inventory for Cognitive and Somatic Anxiety

TES Transcutaenous Electrical Stimulation

TS temporal summation

TS Period temporal summation period

TSμ the average pain rating during the TS period

TSmax the maximal rating during the TS Period

TSmax-t the time of the maximal rating during the TS Period

TSmax-v the value of the maximal rating during the TS Period

TSslope the slope between TSstart and TSmax

TSstart the point at which the pain response was first rated above 0

VAS visual analogue scale

WU wind-up

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Appendix A

NHS Shielded List

At the time of screening (April 2020), the NHS Shielded List included the following categories:

A) Chronic (long term) respiratory diseases, such as asthma, chronic obstructive pulmonary disease, emphysema or bronchitis.

B) Chronic heart disease, such as heart failure.

C) Chronic kidney disease.

D) Chronic liver disease, such as hepatitis.

E) Chronic neurological conditions, such as Parkinson's disease, motor neurone disease, multiple sclerosis, a learning disability or cerebral palsy.

F) Diabetes.

G) Problems with your spleen - for example sickle cell disease or if you have had your spleen removed.

H) A weakened immune system as the result of conditions such as HIV and AIDS, or medicines such as steroid tablets or chemotherapy.

I) Being seriously overweight (BMI of 40 or above). [1]

J) People who have received an organ transplant and remain on ongoing immunosuppression medication.

K) People with cancer who are undergoing active chemotherapy or radiotherapy.

L) People with cancers of the blood or bone marrow such as leukaemia who are at any stage of treatment.

M) People with severe chest conditions such as cystic fibrosis or severe asthma.

[1] Not used as an exclusion criterion.

N) People with severe diseases of body systems, such as severe kidney disease.

Appendix B

Mini-International Neuropsychiatric Interview

The short M.I.N.I., curated by Bristol TARG, contained several short sections. Participants answered with 'Yes' or 'No'. Affirmative answers to target questions required either follow-up questioning or immediate exclusion from participation.

I) **DEPRESSION**

i) Have you been consistently depressed or down, most of the day, nearly every day, for the past 2 weeks?

ii) In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?

iii) Have you felt sad, low or depressed most of the time in the last 2 years? [1]

iv) Did you *ever* make a suicide attempt? [2]

II) **MANIA**

i) Have you *ever* had a period of time when you were feeling 'up' or 'high' or so full of energy or so full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do no consider times when you were intoxicated or on drugs or alcohol.)

ii) Are you currently feeling 'up' or 'high' or full of energy? (By 'up' or 'high' I mean: having elated mood; increased energy; needing less sleep, having rapid thoughts, being full of ideas, having an increase in productivity, motivation, creativity, or impulsive behaviour.)

[1] Follow-up questioning.
[2] Immediate exclusion.

iii) Have you *ever* been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed you have been more irritable or over-reacted, compared to other people, even in situations that you felt it was justified? [1]

iv) Are you currently feeling persistently irritable? [1]

III) **PTSD**

i) Have you *ever* experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? (Examples of traumatic events include: serious accidents, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, fire, discovering a body, sudden death of someone closed to you, war, or natural disaster.) [1]

ii) Did you respond with intense fear, helplessness or horror?

iii) During the past month, have you re-experienced the event in a distressing way (such as dreams, intense recollections, flashbacks or physical reactions)? [2]

IV) **ANXIETY**

i) Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way? [1]

ii) If 'Yes', did the spell peak within 10 minutes?

iii) Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a queue, when you are alone away from home or alone at home, or when crossing a bridge, travelling in a bus, train or car? [1]

iv) In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public alone or with others, writing while someone watches, or being in social situations. [1]

v) Have you worried excessively or been anxious about several things over the past 6 months? [1]

vi) If 'Yes', are these worries present most days? [2]

V) **OCD**

i) In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, hoarding, collecting, or religion. [2]

VI) **ADDICTION**

i) In the past 12 months, have you had 3 or more alcoholic drinks within a 3 hr period on 3 or more occasions? [1]

ii) Have you *ever* got in trouble by the use of alcohol and/or have you ever been tackled by someone about your drinking behaviour? [1]

iii) In the past 12 months, did you take any of these drugs more than once, to get high, to feel better, or to change your mood? [1]

i. **Stimulants**: amphetamine, speed, crystal meth, diet pills, Dexedrine, Ritalin, 'rush'.

ii. **Cocaine**: snorting, IV, freebase, crack, speedball.

iii. **Narcotics**: heroin, morphine, opium, Dilaudid, Demerol, methadone, codeine, Percodan, Darvon.

iv. **Hallucinogens**: LSD (acid), mescaline, PCP ('angel dust'), 'mushrooms', XTC, MDA, MDMA, peyotem, psilocybin, STP. Inhalants: glue, ethylchloride, laughing gas, amyl-/butyl nitraat ('poppers')

v. **Inhalants**: glue, ethylchloride, laughing gas, amyl-/butyl nitraat ('poppers').

vi. **Marijuana**: hashish, THC, weed, 'pot', 'grass', 'reefer'.

vii. **Tranquilizers**: Quaalude, seconda ('redd'), Valium, Xanax, Librium, ativan, dalmane, lacion, barbiturates, Miltown.

viii. **Other**: steroids, nonprescription sleep/diet pills, GHB, antihistamines, others.