Innovative Mixed Methods for Assessing Chronic Pain in Adolescents and Adults



Claire Elizabeth Lunde
St Peter's College

A thesis submitted for the degree of
Doctor of Philosophy (DPhil) in Women's & Reproductive Health

Trinity Term 2023

Abstract

Innovative Mixed Methods for Assessing Chronic Pain in Adolescents and Adults
A thesis submitted for the degree of Doctor of Philosophy, Trinity Term 2023
Claire Elizabeth Lunde
St Peters College

Chronic pain is a global concern that profoundly impacts the lives of millions, particularly among adolescent and young adult females. This doctoral thesis explores the intricate interplay between life experiences, emotional well-being, and the physiological ramifications of pain. While numerous conditions contribute to chronic pain in women, this thesis focuses specifically on two prevalent conditions: primary dysmenorrhea and endometriosis. By delving into these specific conditions, I aim to deepen understanding and enhance the care provided to women suffering from primary dysmenorrhea or endometriosis-related pain—both of which can be debilitating and regrettably remain without a cure.

The innovative nature of my approach integrates mixed methods and cutting-edge technology to study pain in adolescent and adult women. By amalgamating diverse research approaches and incorporating advanced techniques such as functional near-infrared spectroscopy and offset analgesia, which have not previously been applied to young women with dysmenorrhea or endometriosis, I introduce pioneering methods to pain assessment. This may mark a significant stride forward in the field with the potential to yield novel insights for understanding and managing pain in this population.

Chapter Two underscores the necessity for further exploration and suggests that females may exhibit distinct responses to experimental pain during different phases of their menstrual cycle. Chapter Three presents a comprehensive mixed-method cross-sectional study examining the intricate relationships between dysmenorrhea, endometriosis-related pain, pain inhibition, functional connectivity, pain catastrophising, resiliency, and adverse childhood experiences among young adults. Finally, Chapter Four reports longitudinal data collected at three-time points, assessing the stability of pain catastrophizing from ages 12 to 16 and exploring whether elevated pain catastrophising at age 12 predicts the development of generalised chronic pain and dysmenorrhea in female adolescents.

The findings show the critical role of considering adverse childhood experiences and altered functional connectivity in diagnosing and treating dysmenorrhea and endometriosis-related pain, as these factors may exacerbate and perpetuate pain into adulthood. While this area of research is still in its nascent stages, the ability to manipulate these factors may hold potential as a causal influence on pain experiences. The results also highlight the significance of pain catastrophizing in these populations. However, caution should be exercised when applying these findings in pain-free populations. Although pain catastrophizing is easy to measure in the lab, it may hold different clinical relevance for predicting pain in healthy individuals. Therefore, it is recommended that the clinical use of pain catastrophizing as a predictive tool be approached with discretion, particularly in pain-free populations.

Synthesizing the insights from these chapters provides a holistic understanding: chronic pain in women is a multifaceted phenomenon shaped by a convergence of biological, environmental, psychological, and social factors. This knowledge paves the way for future research and interventions targeting specific neuro-biopsychosocial model elements to enhance well-being and alleviate the burden of chronic pain in women.

.

Acknowledgements

First, I would like to express my sincere gratitude to Dr Christine Sieberg, my primary supervisor, for her untiring support and encouragement throughout my DPhil studies. Dr Sieberg has been an exceptional mentor from the very beginning, allowing me the freedom to explore my interests and pursue my own projects. Her insightful and timely advice has been invaluable in navigating the challenges of my DPhil studies, and her warm encouragement has always given me the confidence to push through difficult times. I feel fortunate to have had her as my advisor, mentor, and friend.

I am grateful for the guidance and support of my co-advisors, Dr Andrea Reinecke and Professor Elaine Fox. Through their insightful feedback and encouragement, they have played a critical role in shaping my academic and personal growth. Their advice has pushed me to explore new avenues of research, think more deeply about the implications of my work, and communicate my ideas with greater clarity and impact. I will always be appreciative of their contributions to my academic success.

I have been privileged to travel worldwide and build collaborations during my studies. I am grateful to those who have helped me along the way, including but not limited to Professor David Borsook, Dr Ziyan Wu, Dr Edina Szabo, Dr Danijela Serbic, Dr Danielle Perro, and Dr Stacey Missmer. Their invaluable mentorship and cherished friendships have been instrumental in shaping my academic and personal growth.

I have never wavered in my desire to become a scientist. Many people have supported me in making this possible, including my grandparents, Pauline and Harry Coveny, the first to encourage my love of learning. My brother Alex Badley was the sole reason I attended university after high school. My adopted families, English, Moses, and Cosentino provided love and support when I needed it most. My in-laws, Bonnie and Greg Wiese always offered love and comfort, especially when I was homesick. Their love and encouragement have been a source of strength for me, and I am truly fortunate to have them as my family.

Last but definitely not least, I owe the deepest gratitude to my beloved husband, David Wiese. David - you are the anchor that grounds me in the turbulent waters of life. I cannot thank you enough for your unflinching support and belief in me, even during my toughest moments. Thank you for celebrating every paper I have written, every grant submitted, and every poster presented. Your persistent pride in my achievements has been a constant source of strength and inspiration, fuelling my drive to push beyond my limits and reach for the stars. Thank you for being my rock, best friend, and life partner.

Declaration

This thesis comprises work by Claire Elizabeth Lunde for the degree of Doctor of Philosophy from the University of Oxford. Chapters 2 and 3 involved recruitment and data collection at Boston Children's Hospital, where Ms Lunde was based at the time. The study presented in Chapter 4 was conducted in and around Oxford. All research in this thesis was conducted under the leadership of Ms Lunde.

COVID-19 Impact Statement

I would like to explain how the COVID-19 pandemic significantly affected my doctoral research and academic journey. The unprecedented global health crisis, which emerged in early 2020, brought about numerous challenges and adjustments to the course of my DPhil work.

The COVID-19 pandemic necessitated a dramatic shift in the location of my work. Before the pandemic, my research primarily occurred within the campus of Boston Children's Hospital and research facilities. However, I had to adapt to remote work from home in response to lockdowns and safety protocols. Additionally, I was placed in Boston (early 2021) to complete experiments delayed by COVID-19. This transition introduced new challenges related to access to resources, laboratory equipment, face-to-face interactions with colleagues and advisors, and, most significantly, finances.

The pandemic led to the reconsideration and adjustment of my research projects. Certain experiments and fieldwork that were originally planned became unfeasible due to restrictions on travel and laboratory access. As a result, I had to pivot towards projects that could be conducted remotely or within the limited resources available locally. This change in research focus required flexibility and adaptability, leading to exploring alternative avenues for data collection and analysis.

COVID-19 restrictions hindered engaging in in-person conferences, workshops, and collaborative research opportunities. Networking, which is a vital aspect of academic growth, became challenging during this period. Instead, I had to embrace virtual conferences and online collaboration tools to stay connected with peers and experts in my field. While these platforms were valuable, they could not fully replicate the experience of in-person interactions.

Lastly, the pandemic's toll on mental and emotional well-being cannot be underestimated. The stress and uncertainty surrounding the health crisis notably impacted my productivity and motivation. Balancing research responsibilities with personal concerns and anxieties became a daily challenge, underscoring the importance of self-care and mental health support.

Despite these challenges, the experience of navigating my DPhil work during the COVID-19 pandemic has reinforced my resilience, adaptability, and determination. It has also highlighted the importance of interdisciplinary collaboration and innovative research approaches in times of crisis. As we gradually emerge from the pandemic and prepare for future pandemics or crises, I am committed to leveraging the lessons learned during this period to contribute meaningfully to the academic community and society as a whole.

Contents

Chapter 1 Introduction 7
1.0 Overview 7
1.1 Chronic Pain 8
1.2 Chronic Pain in Women 10
1.3 Chronic Pain in Adolescent Girls 15
1.4 Neuro-biopsychosocial Model: An Interdisciplinary and Mixed Method Research Approach 16
1.5 Key Hypotheses 28
1.6 Empirical Studies Guiding Hypotheses 30
1.7 Summary 39

Chapter 2 Experimental Pain and the Menstrual Cycle 41
2.0 Overview 41
2.1 Introduction 42
2.2 Scoping Review 45
2.3 Pilot Study 52
2.4 Discussion 61

Chapter 3 The Pain-Brain Connection: Insights into the Complexities of Dysmenorrhea and Endometriosis 65
3.0 Overview 65
3.1 Introduction 66
3.2 Methods 69
3.3 Results 88
3.4 Conclusion 114
3.5 Discussion 117

Chapter 4 Assessing the Stability of Pain Catastrophising in a Longitudinal Community Sample of Adolescents: Can it Predict Chronic Pain and Dysmenorrhea? 120
4.0 Overview 120
4.1 Introduction 121
4.2 Methods 125
4.3 Results 132
4.4 Conclusions 153
4.5 Discussion 156

Chapter 5 Discussion 160
5.0 Overview 160
5.1 Summary of Results 160
5.2 Clinical Relevance 165
5.3 Strengths and Weaknesses 168
5.4 Future Directions 171
5.5 Potential Implications of This Research 173
5.6 Concluding Remarks 174

References 176

Appendices 199
Appendix A - Acronyms in Alphabetical Order 199
Appendix B - Academic Achievements and Contributions 200
Appendix C - Chapter 2 Scoping Review Results 205

Chapter 1
Introduction

"Courage is like — it's a habitus, a habit, a virtue: you get it by courageous acts. It's like you learn to swim by swimming. You learn courage by couraging."

Dr Marie Maynard Daly

First Black woman awarded PhD in Chemistry in the US & scientist dedicated to increasing the enrolment of minority students in graduate science programs.

1.0 Overview

This thesis investigates the complex interactions between life experiences during development (*e.g.,* childhood trauma, stress, positive experiences), emotional functioning (*e.g.,* resiliency, pain catastrophising), and biological consequences of pain (*e.g.,* endogenous pain inhibition, brain alterations). These themes relate to dysmenorrhea and endometriosis-related pain's development, maintenance, and exacerbation.[1–5] I hypothesise that combining these themes is key to developing preventive and early interventions for the millions of adolescent and adult women suffering from pain, specifically dysmenorrhea and endometriosis-related pain.

My thesis title suggests “innovative mixed methods” to assess pain in adolescents and adults. The innovative nature of my approach lies in integrating mixed methods and applying new technology in studying pain in females, specifically. By combining different research approaches and incorporating advanced techniques such as functional near-infrared spectroscopy (fNIRS) and offset analgesia (OA), which have not been previously applied to young women with dysmenorrhea or endometriosis, I am introducing new and cutting-edge methods to pain assessment. This combination represents a significant advancement in the field and has the potential to contribute novel findings to the understanding and management of pain in this population.

1.1 Chronic Pain

Chronic pain affects 35–51% of adults in the UK.[6] According to the International Association for the Study of Pain's latest definition as of July 2020,[7,] pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Furthermore, pain is classified as chronic when it persists for three months or longer.[8] The aetiology of chronic pain involves a complex interplay of neurological, biological, psychological, and social factors.[9] Additionally, life experiences and contextual elements, such as stress levels, availability of social support, and access to healthcare, have demonstrated their influence on the experience of chronic pain.[5,10,11] Within this thesis, the definition above of pain and the broader framework of a neuro-biopsychosocial model serves as the guiding foundation.

There are different ways to categorise chronic pain, but one common approach is classifying pain based on its underlying causes or mechanisms[5] (Table 1). These categories are not mutually exclusive, and many people with chronic pain may experience a combination of the different types of pain.[5] Understanding these classifications is crucial for effective pain management and treatment.

Table 1. Definitions of the Pain Types

Type of Pain	**Definition**
Nociceptive pain	Pain from activated nociceptors which are specialised nerve fibres that respond to harmful or potentially harmful stimuli (*e.g.,* heat, cold, pressure). Typically described as sharp, aching, or throbbing. Often localised to a specific area of the body (*e.g.,* pain from an injury, surgery, arthritis).
Neuropathic pain	Pain from damage or dysfunction in the nervous system, such as from nerve compression, injury, or disease (*e.g.,* diabetic neuropathy, shingles, or spinal cord injury). Typically described as burning, shooting, or stabbing, and can be associated with tingling, numbness, or weakness.
Inflammatory pain	Pain from the activation of the immune system and the release of inflammatory molecules, such as cytokines, in response to tissue damage or infection (*e.g.,* rheumatoid arthritis or inflammatory bowel disease). Typically described as aching or throbbing, and is often accompanied by redness, swelling, and heat.
Nocioplastic pain	Pain from abnormal processing of pain signals within the nervous system, rather than from ongoing tissue damage or inflammation. It is a relatively new term used to describe pain that does not have a clear underlying cause, as traditional diagnostic methods may not reveal any specific injury or pathology. The term "nocioplastic" combines nociceptive and plasticity.
Functional pain	Pain with no clear underlying cause or pathology but is instead related to alterations in the way the nervous system processes pain signals (*e.g.,* fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome). Typically described as aching, burning, or cramping, and can be associated with fatigue, sleep disturbances, or mood changes.
Mixed pain	Pain from a combination of nociceptive and neuropathic pain mechanisms. Arises from conditions that affect both the tissues and nerves (*e.g.,* arthritis, cancer, diabetes, endometriosis).

Clinical classifications of pain offer several advantages.[12,13] Firstly, they enable tailored treatment approaches by guiding healthcare professionals in selecting appropriate interventions based on the underlying pain mechanisms. This customisation can lead to more effective pain management. Secondly, these classifications facilitate targeted research into pain mechanisms, fostering the development of new medications and therapies specifically designed for each type of pain. Lastly, standardised classifications enhance communication among healthcare professionals, ensuring a common language for discussing and documenting pain-related issues.

However, there are notable disadvantages to clinical classifications of pain.[12,13] Pain often arises from a complex interplay of multiple mechanisms, challenging strict categorisation and potentially

oversimplifying. Additionally, pain perception is highly subjective, and a patient's experience may not neatly fit into a single category, leading to possible misdiagnosis and ineffective treatment.

Clinical classifications of pain provide a valuable framework for understanding the diverse mechanisms underlying different types of pain, aiding in diagnosis and treatment. An optimal approach to pain management often necessitates a holistic consideration of both mechanistic aspects and the unique experiences of individual patients.

1.2 Chronic Pain in Women

There are unique challenges for women with chronic pain, such as undefined sex differences in pain, higher incidence of painful conditions, and bias in the treatment of women's pain.[14] By including these challenges in research, we may gain valuable insights into the complex interplay of biological, psychological, and social factors contributing to this phenomenon.

To begin, we know that sex differences in pain sensitivity exist, however, the underlying mechanisms driving these sex differences are not fully understood.[15] Males and females have exhibited varying perceptions of pain and differences in sensitivity to exogenous analgesics, with females generally exhibiting a greater pain sensitivity than males.[16] This has been shown in experimental and clinical settings, as well as for acute and chronic pain conditions.[17] Pain experience and sensitivity differences appear more consistent and robust in clinical than laboratory settings.[18] Several factors have been hypothesised to contribute to this disparity, including genetics, psychological and psychosocial factors, and hormonal fluctuations during the menstrual cycle.[16,17,19]

Additionally, females have a higher incidence of several painful conditions, such as migraine[20] and fibromyalgia.[21] Numerous acute and chronic pain conditions are female-specific, such as dysmenorrhea.[15,22] Many of these conditions have been shown to vary in symptom severity across menstrual cycle phases.[23–27] Pain symptoms appear to be most severe at times of low or rapidly falling

estrogen levels, with estrogen levels rising during the mid-follicular phase and then dropping abruptly after ovulation.[16,19,27,28]

Moreover, the normalisation of menstrual phase pain (MPP) by women, society, and healthcare professionals has contributed to the lack of knowledge, education, and causes.[29] Many people assume that pain during menstruation is natural and inevitable, leading to a culture of silence and normalisation of MPP.[30] This lack of research and understanding among healthcare professionals can result in delays in diagnosis and treatment, with women being dismissed or not taken seriously when they report their symptoms. Addressing these societal and healthcare-related issues is crucial to improving MPP care and management.

1.2.1 Dysmenorrhea and Endometriosis

Although many conditions significantly contribute to chronic pain in women, this thesis specifically delves into two prevalent conditions, primary dysmenorrhea and endometriosis. By examining these specific conditions, I aim to enhance understanding and improve the care provided to women suffering from primary dysmenorrhea or endometriosis-related symptoms, as both can be debilitating and, unfortunately, are incurable.[31–33]

The terms "endometriosis-related pain" and "endometriosis-related dysmenorrhea" are often used interchangeably, as both terms generally describe the pain associated with endometriosis. However, endometriosis-related dysmenorrhea refers to the MPP experienced by individuals with endometriosis. The term "endometriosis-related pain" is a broader term encompassing pain experienced caused by endometriosis throughout the menstrual cycle, as opposed to specifically pain during menstruation.

Primary and secondary dysmenorrhea are the two main types of dysmenorrhea, and they differ in their underlying causes and symptoms. Primary dysmenorrhea is the most prevalent and occurs without a known underlying cause.[33] The prevalence varies between 16% - 91% in women of reproductive age, with 2% - 29% reporting severe pain.[34] The pain typically begins within six to twelve months from

menarche,[33] and is characterised by painful cramps originating from the uterus during menstruation caused by increased prostaglandin production and uterine contractions.[35] The pain is usually located in the lower abdomen or back and may be accompanied by other symptoms such as nausea, vomiting, and diarrhoea. [36] Primary dysmenorrhea can significantly impair quality of life by interfering with daily activities, including school, work, and social life.[34,37,38] It can also impair mental health, including depression and anxiety.[39,40] On the other hand, secondary dysmenorrhea is similar, but is MPP caused by a known underlying medical condition such as endometriosis.[36]

Endometriosis affects approximately 1 in 10 women of reproductive age,[41] 25–50% of women with infertility,[42,43] and 25–70% of women with chronic pelvic pain or secondary dysmenorrhea.[44,45] The condition has been shown to negatively affect reproductive health and the infiltrated organs.[46] In addition, endometriosis may indirectly negatively affect the central nervous system (CNS),[47,48] cognitive and personality factors,[49] psychological functioning,[50,51] respiration,[52] cardiovascular health,[53] digestive functions,[54] sexual function,[55] employment,[56–58] education,[59,60] and lifestyle.[50,61]

Endometriosis is characterised by endometrial glands and stroma outside the uterine cavity.[62] The exact cause of endometriosis is unknown, but it is believed to involve a complex interplay between genetic, hormonal, and immune system factors.[63] Leading theories on the cause suggest the estrogen hormone plays a role in the development and progression of endometriosis, as well as in the associated pain and inflammation.[64]

The primary symptom of endometriosis is pelvic pain.[65] However, there is a wide range of symptom presentations, with 23% of those with endometriosis presenting as asymptomatic.[66] Endometriosis lesions are an incidental finding in 7–10 % of abdominal and pelvic surgeries.[67] Unfortunately, women wait an average of 7-12 years from symptom onset to receive a diagnosis of endometriosis.[68] Of the patients who do undergo laparoscopic surgery to remove the endometriosis lesions that could be causing pain, up to 30% of women report no postoperative improvement in pain, and the degree of

short-term pain improvement among the remaining patients varies.[69] Classification and endometriosis staging systems have not been clinically helpful regarding pain level or chronicity.[70]

Despite its high prevalence and negative effects, little is known about the pathophysiology underlying the development and persistence of endometriosis-related pain. More recent research models of endometriosis-related pain hypothesised it to be mixed pain arising from a combination of inflammatory, neuropathic, nociceptive, and functional pain mechanisms.[48]

Endometriosis often leads to inflammation, scarring, and the development of adhesions, which can exert pressure on nerves, resulting in both neuropathic and inflammatory pain.[71] Endometrial tissue may grow on the nerves supplying the pelvis, leading to irritation and pain. Several studies have indicated that women experiencing endometriosis-related pain may exhibit elevated levels of inflammatory markers, such as cytokines and chemokines, compared to women without endometriosis or those with other gynaecological conditions. [72] However, the extent and duration of inflammation are believed to vary between endometriosis and dysmenorrhea due to their distinct underlying mechanisms.[73]

Moreover, endometriosis can also give rise to nociceptive pain, which arises from abnormal tissue growth resulting in bleeding, inflammation, and lesion formation.[44] Nociceptors that are activated in response to physical damage or inflammation send signals to the brain, which are interpreted as pain. Furthermore, endometriosis adhesions can cause nerve sensitisation, leading to pain that is disproportionate to the amount of endometrial tissue present.[74] Finally, functional pain is not clearly associated with any identifiable cause or underlying pathology but rather linked to changes in how the CNS processes pain signals.[48] Taken together, this suggests that untreated endometriosis-related pain may involve multiple types of pain.

The complex nature of both dysmenorrhea and endometriosis-related pain poses treatment, diagnosis, and research challenges. These conditions often necessitate a combination of treatments that target

various pain mechanisms, emphasising the importance of further investigation into the underlying mechanisms contributing to these conditions.[33,37,44,75–77] Similarly, to address endometriosis and dysmenorrhea as a public health concern, a multifaceted approach encompassing education, early diagnosis and management, and policies promoting menstrual health and overall well-being for women suffering from these conditions is needed.

1.2.1.1 Diagnosis and Treatment

If dysmenorrhea or endometriosis are left untreated, these conditions can lead to infertility and other serious health complications.[41] The diagnosis strategies for endometriosis and dysmenorrhea include ultrasound, magnetic resonance imaging (MRI), laparoscopy, and hysteroscopy.[36,78] Endometriosis can be challenging to diagnose as its symptoms can be similar to those of other conditions. Its severity does not necessarily correlate with the extent of endometrial tissue present in the body.[31] However, there are several methods available to diagnose endometriosis.[67] These include assessing a patient's medical history, family history of endometriosis, symptoms, and menstrual cycle. Additionally, an ultrasound exam can detect endometrial tissue growths or cysts, although it is not always reliable in detecting all cases of endometriosis.

The most definitive diagnostic method for endometriosis is laparoscopic surgery.[79] If endometriosis is detected, it may be removed and/or biopsied to confirm endometriosis. Surgery may be recommended if severe symptoms do not respond to other treatments.[80] The surgical options include laparoscopy, which can be used to diagnose and treat endometriosis, and laparotomy, which is a more invasive surgical procedure. Although less common, the surgical options for dysmenorrhea include an endometrial ablation (destroy the lining of the uterus), an endometrial resection (remove the lining of the uterus), or a hysterectomy (removal of the uterus).[79]

Treatment options are often tailored to the individual's symptoms, the severity of pain, and reproductive goals.[43,62,81] Over-the-counter nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen can help reduce MPP and inflammation.[82–84] Prescription pain medications such as opioids may also be used for severe pain,[85] but are ineffective in treating long-term pain. Despite this evidence, 24% of obstetricians/gynaecologists continue prescribing opioids for endometriosis-related pain.[85,86] This has led to women with endometriosis reporting a four times greater risk of chronic opioid use than women without endometriosis.[87] Hormonal therapies are a mainstay of endometriosis treatment, which suppress the production of estrogen and can help to reduce pain and slow the growth of endometrial tissue.[63] Some individuals may also find pain relief from complementary therapies such as acupuncture, massage, dietary changes, vitamins, exercise, heat, and massage.[76,88] As described above, unfortunately, there is no cure for either condition with existing treatments aimed at managing symptoms and improving quality of life.

1.3 Chronic Pain in Adolescent Girls

Prevalence rates of chronic pain in children and adolescents are less established than in adults. Current epidemiological studies indicate a prevalence of chronic and recurrent pain in 15-30% of children, with 8% reporting severe and frequent pain.[89–91] Generally, pain prevalence rates were higher in females and increased with age and lower socioeconomic status (SES) for most pain types.[92] Several factors contribute to the development of chronic pain in this population, including biological, psychological, and social factors.[2,93–95]

Chronic pain may have more severe adverse effects on the lives of adolescent females.[89,96] It may result in limitations in physical activities, decreased participation in school or social activities, disrupted sleep patterns, mood disturbances, decreased quality of life, and impaired academic performance. It can also lead to feelings of frustration, isolation, and hopelessness. The results from adult studies are often translated to describe adolescent models, but conceptual models specific to adolescent endometriosis-related pain are needed.[97] Additionally, early identification and management

of chronic pain in adolescent females are crucial to addressing their needs and preventing them from becoming adults with chronic pain.[96]

1.3.1 Dysmenorrhea and Endometriosis in Adolescents

Endometriosis in adolescents, typically identified as the developmental stage of symptom onset,[98] may present with several clinical and pathological differences that are not observed in adulthood.[97] Research has shown that the younger the woman at symptom onset, the longer the duration until a diagnosis is made,[99] and a diagnosis under the age of 25 years is associated with a significantly worse quality of life.[100]

Adolescents require unique considerations for treatment approaches, as it presents particular challenges in terms of diagnosis, variable presentation and symptoms, and choice of treatment.[101] The same is true for dysmenorrhea as it is a common problem affecting many adolescents.[102–104] Approximately 50% of adolescent females are estimated to experience some degree of dysmenorrhea, with approximately 10% experiencing severe symptoms that interfere with their daily activities.[102] The reduced quality of life in young patients, the possibility of progression that could endanger reproductive organs, and the considerable life-course impact attributed to dysmenorrhea and endometriosis-related pain are evidence of the need for advocating for increased awareness among adolescents and understanding of the impact of events during the developmental stages.[105]

1.4 Neuro-biopsychosocial Model: An Interdisciplinary and Mixed Method Research Approach

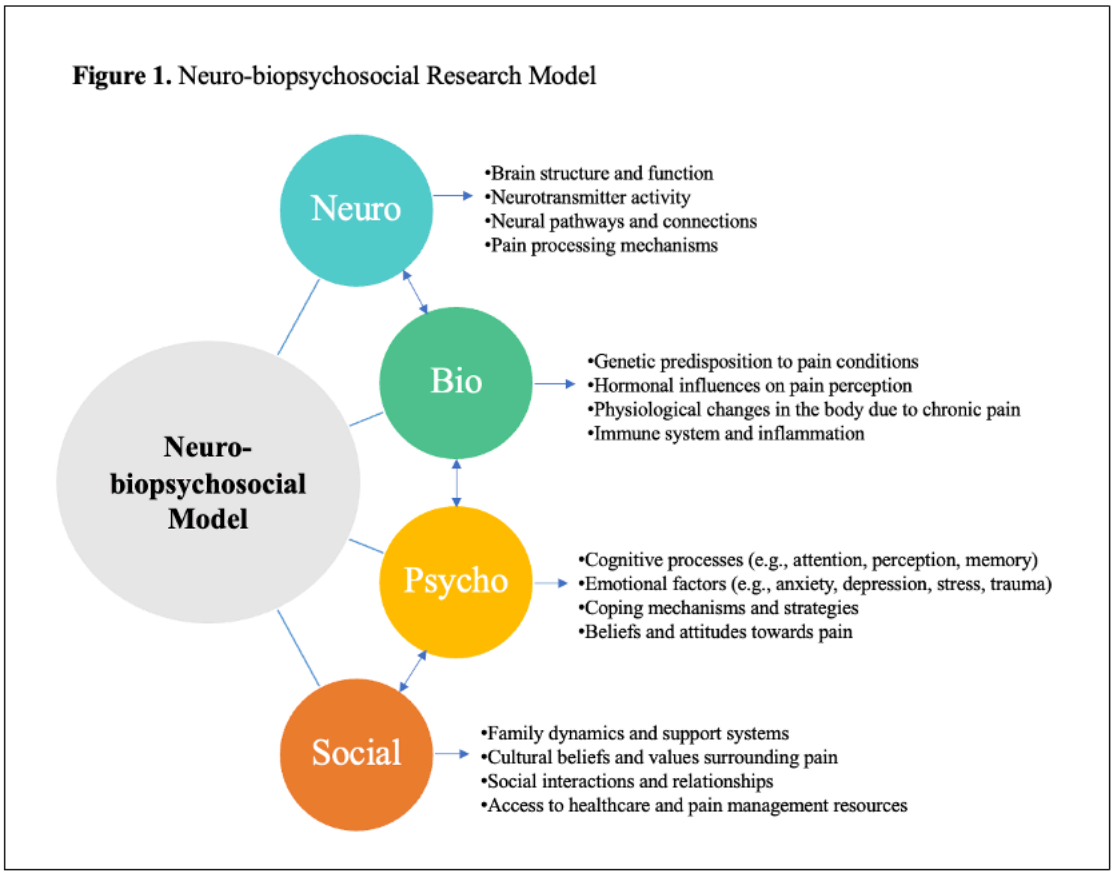
A neuro-biopsychosocial model for research assesses health as not simply the absence of disease or illness but as the interplay between neurological, biological, psychological, and social factors in the pain experiences.[1,106] A mixed method and interdisciplinary approach may offer a comprehensive understanding of the interplay between factors influencing chronic pain in young individuals.

An interdisciplinary approach draws upon multiple fields, in this case, psychology, neuroscience, and public health, to provide a nuanced understanding of chronic pain in young individuals. Neuroscience

insights contribute to understanding the biological foundations of pain, while self-report measures shed light on psychosocial factors. This approach may enhance our understanding of the factors exacerbating or maintaining pain in women by leveraging the strengths of different research methods and disciplines.

Combining quantitative and qualitative data collection methods can capture a holistic perspective of the pain experience in adolescent and young adult women. Various techniques were used to objectively measure chronic pain's neurological and biological consequences, including quantitative sensory testing (QST), offset analgesia (OA), hormone testing, and two neuroimaging techniques. Additionally, several self-report questionnaires were used to gain insight into the subjective aspects of pain, including emotional and social factors.

The neuro-biopsychosocial model employed in this thesis considers health as the interplay between neurological, biological, psychological, and social factors in pain experiences (Figure 1). Mixed methods may be the most comprehensive approach for informing treatment recommendations for adolescents and adults with dysmenorrhea or endometriosis-related pain who may not respond to current medical therapies. The findings from this thesis hold potential for developing more effective treatment strategies.



1.4.1 Methods for the Neuro-biopsychosocial Model Used within Thesis

A multimodal approach that combines multiple measures is often used to assess pain in clinical research to capture the complex and multidimensional nature of pain experiences. Table 2 describes the common methods for assessing pain in clinical research, which also will provide context as to why my thesis title suggests "innovative mixed methods" to assess pain in adolescents and adults. The innovative nature of this approach lies in integrating mixed methods and applying technology in studying pain in adolescent and adult women. By combining different research approaches and incorporating advanced techniques such as fNIRS and OA, which have not been previously applied to young women with dysmenorrhea or endometriosis, I am introducing new and cutting-edge methods to pain assessment. This combination represents a significant advancement in the field and has the potential to contribute novel findings to the understanding and management of pain in this population.

Table 2. Overview of Pain Assessment Methods Clinical Research

Method	Definition
Self-report Measures	Measures that rely on individuals reporting their own pain experiences. Examples include self-report questionnaires or rating pain intensity on a scale from 0-10.
Observer Rating	Measures that rely on observations made by a researcher, such as using a series of faces to help individuals rate their pain intensity.
Physiological Measures	Measures that assess physiological responses to pain, such as heart rate, blood pressure, and skin conductance. Useful for assessing pain in individuals with difficulty communicating their pain experiences, such as infants or individuals with cognitive impairment.
Imaging Techniques	Measures that use neuroimaging techniques such as MRI or fNIRS to assess changes in brain activity associated with pain. Useful for studying the neural mechanisms underlying pain.
Quantitative Sensory Testing (QST)	A standardised approach that uses a battery of sensory tests to assess different aspects of pain perception, such as thermal, mechanical, or electrical stimulation.
Offset Analgesia (OA)	Measures a relatively small decrease in the intensity of a painful stimulus that produces a disproportionately large decrease in pain perception.
Conditioned Pain Modulation	Measures the perception of pain is modulated or suppressed by the application of a second painful stimulus in a different part of the body.
Abbreviations: QST, quantitative sensory testing; OA, offset analgesia; MRI, magnetic resonance imaging fNIRS, functional near-infrared spectroscopy	

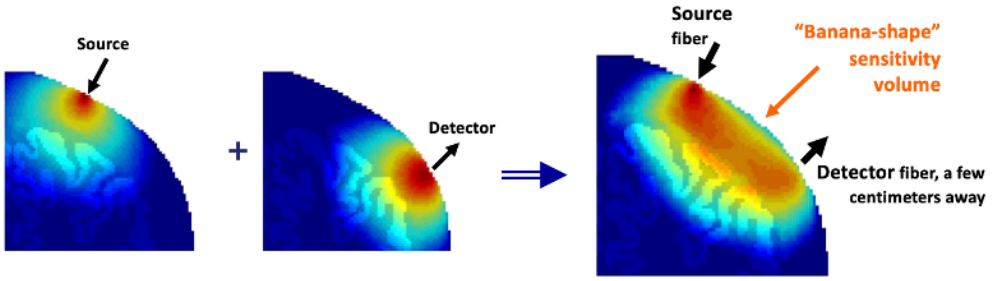
1.4.1.1 Imaging Techniques

MRI and functional MRI (fMRI) are non-invasive imaging techniques that use strong magnetic fields and radio waves to create detailed images of the human body, particularly the brain. MRI produces images by aligning the protons in the body with a strong magnetic field.[107] The protons are then briefly excited with a radiofrequency pulse, which causes them to emit a detectable signal to create the images. fMRI is a specialised form of MRI that measures changes in blood flow in the brain as an indicator of neural activity.[107] When a particular brain area becomes active, blood flow to that area increases in oxygen. This increased blood oxygen level dependent (BOLD) can be detected by fMRI and used to create a map of brain activity.[108]

fNIRS is a non-invasive neuroimaging method that employs near-infrared light to measure cortical hemodynamic changes.[109] It uses sources and detectors to transmit and detect light, respectively. The sources typically use light-emitting diodes to emit near-infrared light into the scalp. The detectors are

typically photodiodes that measure the light transmitted through the scalp and skull and reach the brain (Figure 2).[109]

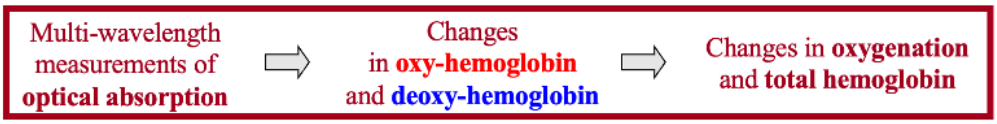
Figure 2. Mechanisms for Sources and Detectors to Measure Blood Flow and Oxygenation in the Brain[a]



[a] Figure adapted from Boston University fNIRS Course

The sources and detectors are placed on the scalp in a specific configuration, designed to measure changes in blood flow and oxygenation in specific brain regions. The near-infrared light penetrates the superficial layers (the skin and the skull) to then reach the cortex. Throughout the travel within the tissue, chromophores mostly absorb light, namely oxygenated haemoglobin (HbO) and deoxygenated haemoglobin (HbR). The amount of absorption is determined by the concentration of HbR and HbO in the blood, which changes as blood flow and oxygenation change in response to brain activity (Figure 3).

Figure 3. Workflow of fNIRS Data Collection



The data from the detectors are then processed using the modified Beer-Lambert law (MBLL) (Equation 1), which is the basis of continuous-wave near-infrared tissue spectroscopy.[109] By using

two wavelengths of near-infrared light, 690 and 830 nm, and the detecting variation of light attenuation at the detector, changes in HbO and HbR can be identified and analysed.

Equation 1. Modified Beer-Lambert Law

$$\Delta OD(\lambda_1) = (\varepsilon^{\lambda 1}{}_{HbR}\,\Delta[HbR] + \varepsilon^{\lambda 1}{}_{HbO}\,\Delta[HbO]) \times L_{eff} \times B_{vol}$$

$$\Delta OD(\lambda_2) = (\varepsilon^{\lambda 2}{}_{HbR}\,\Delta[HbR] + \varepsilon^{\lambda 2}{}_{HbO}\,\Delta[HbO]) \times L_{eff} \times B_{vol}$$

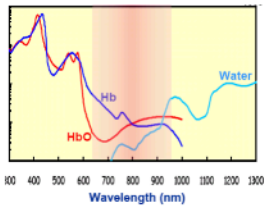
Change in intensity

Chromophore extinction coefficient at each wavelength

Changes in concentration

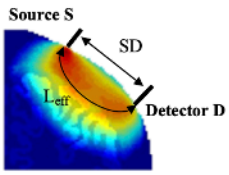
L_{eff} = SD x DPF

Measured



?

Unknown



The few risks associated with the fNIRS testing may include the participant experiencing mild discomfort to their scalp from wearing a tight cap (similar to a swim cap) shown in Figure 4, or they may experience skin irritation. The sensors used in fNIRS can sometimes irritate the skin, typically only if the participant has sensitive skin or if the sensors are worn for longer than required.

Figure 4. fNIRS Cap Worn by Participants



Blue optodes are detectors and red optodes are sources.

Functional connectivity is the statistical correlation or temporal coherence between different brain regions or networks. It measures the synchronised activity and communication between brain areas and provides insights into the brain's functional organisation.[110–113] The fNIRS sensors and detectors previously described are placed on the scalp over the regions of interest to measure functional connectivity. fNIRS uses two main approaches to measure functional connectivity: correlation-based and seed-based.[112] The correlation-based measures the temporal correlation between the hemodynamic responses of different brain regions. By examining the similarity in the time course of oxygenation changes, it can infer the functional connection between those regions. Statistical techniques such as correlation analysis or coherence analysis are employed to quantify the strength of connectivity. The seed-based approach used in this thesis is a specific brain region chosen as a "seed" region of interest (ROI), and the connectivity between this seed ROI and other brain regions is examined. The oxygenation data from the seed ROI are used as a reference, and correlations with other brain regions are calculated to determine the connectivity strength.

Neuroimaging techniques such as electroencephalography, fMRI, and fNIRS have revolutionised the study of chronic pain by providing valuable insights into the brain's response to pain. Each method has unique strengths and limitations, summarised in Table 3. We can better understand the complex neural mechanisms underlying chronic pain by leveraging these complementary approaches. fMRI with QST was used in Chapter 2 and fNIRS with OA was used in Chapter 3. Electroencephalography was included in Table 3 because it is often compared to fMRI and fNIRS.

Table 3. Comparison of Common Neuroimaging Techniques such as EEG, fMRI, and fNIRS

Factor	EEG	fMRI	fNIRS
Temporal Resolution	High (sampling rate of100-2000 Hz)	Low (sampling rate of 1-10 Hz)	Low (sampling rate of 1-10 Hz)
Spatial Resolution	Low	High (resolution of around 1 mm or less)	Low
Measuring Brain Activity	Directly	Indirectly (BOLD response)	Indirectly (BOLD response)
Level of Expertise Needed	Some training	Extensive training	Extensive training

Cost	Highly accessible	Requires extensive funding	Mostly accessible
Portability	Fully and semi-portable options available	Not portable	Fully and semi-portable options available
Abbreviations. EEG, electroencephalography; Hz, Hertz; BOLD, Blood Oxygen Level Dependent			

Pain processing, pain modulation, and pain inhibition are distinct but interconnected concepts related to the perception and regulation of pain.[114] Pain processing is the overall neural process of detecting and interpreting pain signals. Pain modulation involves the regulation of pain signals through various mechanisms and brain regions. Pain inhibition specifically refers to suppressing or reducing pain signals, decreasing pain perception or intensity. Pain modulation can include both pain inhibition and other processes that may enhance or alter pain perception.

1.4.1.2 Quantitative Sensory Testing (QST)

QST assesses responses to standardised noxious stimuli in a controlled laboratory setting.[115] This method has been used frequently and in diverse clinical settings due to its ability to quantify pain perception, variability in pain sensitivity, and pain modulation as putative phenotypic contributors to the risk for the development of chronic pain.[116–118] QST highlights the role of biological factors, such as altered sensory thresholds, aberrant nerve function, and neuroplastic changes, in contributing to pain experiences. By quantifying sensory responses, QST provides objective measures of the biological aspects of pain.

A standardised QST protocol was developed by the German Research Network on Neuropathic Pain.[119] This standard protocol uses various test stimuli to assess responses to noxious and non-noxious stimuli. These include stimuli that detect cool and warmth detection, hot and cold pain thresholds, pressure pain thresholds, touch and vibration detection and thresholds for pinprick and blunt pressures. These test stimuli activate different types of nerve fibres, including Aδ nerve fibres Aβ nerve fibres, and C fibres (most common), which transmit signals to the spinal cord and brain.[120] Chapter 2 used one component of the QST protocol, thermal pain.

Thermal pain can stimulate both Aδ and C fibres. Aδ fibres are thinly myelinated and have a small diameter.[121] They transmit fast, sharp pain fibres to respond to noxious thermal stimuli such as sudden heat or cold.[120] C fibres, on the other hand, are unmyelinated and have a slower conduction velocity. They transmit slower, duller, and longer-lasting pain signals in response to noxious thermal stimuli such as sustained heat or cold.[122] QST can assess the threshold for both types of thermal pain by applying different temperatures to the skin and measuring the responses from Aδ and C fibres. However, when the stimulus decreases even slightly, the pain perception reduces significantly. By measuring the thresholds, thermal QST can provide information about the function of the sensory nerves that transmit pain signals and help diagnose and monitor conditions related to pain perception.

1.4.1.3 Pain Inhibition and Offset Analgesia (OA)

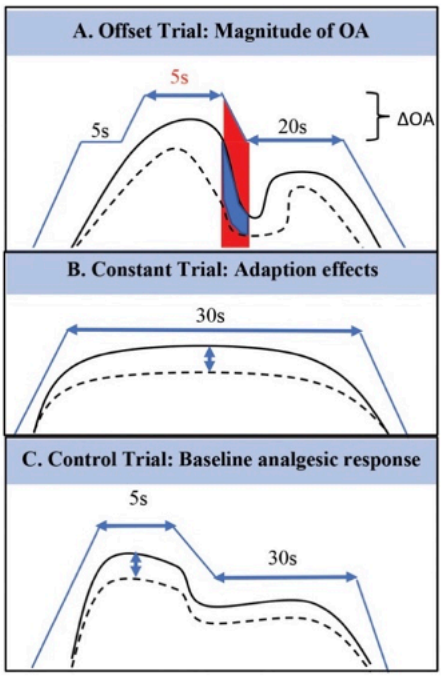
Pain inhibition is a neurobiological process that helps to modulate the perception of pain[123] using different neural circuits and pathways in the brain that work together to diminish or block the transmission of pain signals. For OA, Aδ fibres are primarily involved in the initial perception of intense pain due to a noxious stimulus. This suggests that Aδ fibres' response to temperature changes plays a role in OA.[121] There are several different mechanisms of pain inhibition, including descending pain modulation, where signals from the brainstem and higher brain centres can modulate the activity of spinal neurons that transmit pain signals, and endogenous pain control systems, which release natural pain-relieving chemicals (such as endorphins) that can inhibit the transmission of pain signals.[124]

Dysfunctions in pain inhibition processes have been implicated in several different pain conditions, including fibromyalgia, irritable bowel syndrome, temporomandibular disorder, osteoarthritis, chronic pancreatitis and rheumatoid arthritis, and post-surgical pain.[124] As a damaged pain inhibition process is thought to contribute to the increased sensitivity to pain seen in these conditions, this information is important in this patient population as it may influence treatment plans. Altered pain inhibition can also impact brain functional connectivity, with studies suggesting that it can lead to changes in the

activity of brain regions involved in pain processing, such as the prefrontal cortex.[125,126] These changes can impact how the brain processes and modulates pain signals, leading to increased sensitivity to pain and alterations in pain perception.

OA paradigms are one method for examining the biological mechanisms involved in pain modulation. OA measures a relatively small decrease in the intensity of a painful stimulus, producing a disproportionately large decrease in pain perception. The full three-block OA paradigm is shown in Figure 5. The offset trial (Figure 5A) consists of noxious thermal stimuli for 5 seconds, with a slight increase in temperature (typically 1°C) for 5 seconds, and ending with a decrease in 1°C for 20 seconds. The redline for the offset trial highlights where the OA occurs: a small decrease in temperature during noxious thermal stimulation, leading to a disproportionately large reduction in pain perception. The constant trial (Figure 5B) consists of 30 seconds at 20°C below the noxious stimulus temperature used during the offset trial. The constant trial is used to reduce adaption effects during the study visit. The control trial (Figure 5C) consists of 5 seconds at the noxious stimulus temperature and then 30 seconds at room temperature (typically 32°C). The control trial is used to assess a baseline analgesic response. This OA paradigm captures endogenous pain inhibition and is associated with decreased brain activation of the descending pain modulatory and reward systems in patients with chronic pain.

Figure 5. OA Paradigm Including Three Trials: Offset, Constant, and Control[a]



[a] Figure adapted from Lunde et al 2020. The x-axis represents time (seconds), with the y-axis representing temperature (Celsius). The redline for the offset trial highlights where the OA occurs: a small decrease in temperature during noxious thermal stimulation, leading to a disproportionately large reduction in pain perception.

An attenuated response to the OA task would suggest a dysfunction in the brain's ability to inhibit pain signals, which can lead to an increase in the perception of pain intensity.[127] Some studies have suggested that individuals with chronic pain may have impaired OA response, which may contribute to their ongoing pain.[128] It is also thought to be associated with changes in the activity of pain-modulating circuits in the brain, including the descending pain modulation system. An altered pain inhibition response can also be a useful marker for the effectiveness of pain management interventions, as it reflects the brain's response to pain modulation techniques.[129,130]

Another common but different method for assessing pain inhibition is conditioned pain modulation. Similar to the reason for introducing electroencephalography, conditioned pain modulation is often compared to OA. Conditioned pain modulation is a phenomenon in which applying a painful stimulus to another part of the body reduces pain perception in one part of the body.[131] In other words, the

body's own pain regulatory system is activated in response to a painful stimulus, reducing pain perception in other parts of the body. It is thought to be mediated by the release of endogenous opioids, such as beta-endorphin, which act on pain receptors in the spinal cord and brain to reduce pain perception.[132] Similar to OA, some studies have suggested that individuals with chronic pain may have impaired conditioned pain modulation function, contributing to their ongoing pain.[132]

Although it has been proposed that central and peripheral mechanisms mediate both OA and conditioned pain modulation,[132] OA seems to be related to increased activation in brain regions involved in pain inhibition. In contrast, conditioned pain modulation induces activity reduction in regions connected to afferent nociceptive processing, which might implicate more brain-derived pain modulation during OA.[133] OA is increasingly used to measure endogenous pain inhibition because, compared to CPM, it applies a noxious stimulus that evokes only moderate pain, and the duration of the painful stimulus often takes less time. Thus, the OA task may be more suitable for patients, particularly adolescents and young adults.[132]

In addition, OA responses are unaffected by centrally-acting drugs, while in some studies, conditioned pain modulation effects appear to diminish considerably after taking these medications.[132] OA occurs predominantly by an opioid-independent mechanism which emphasises the role of other neurotransmitters involved in the modulation of pain measured by this paradigm.[134] Several studies have reported that OA responses could not be modified in patients with chronic pain by analgesics such as ketamine,[135] morphine vs placebo,[135] nonsteroidal anti-inflammatory agents and acetaminophen,[136] tapentadol,[137] and hydromorphone.[138]

In summary, pain inhibition mechanisms may be compromised in individuals with chronic pain leading to increased pain sensitivity or amplified pain perception, but it has not been studied in people with dysmenorrhea or endometriosis-related pain. OA and CPM are common methods for assessing pain inhibition, but only OA was used in Chapter 3. An attenuated response to an OA test would

suggest a dysfunction in the brain's ability to inhibit pain signals, which can lead to an increase in the perception of pain intensity.

1.4.1.4 Hormone Testing

Sex hormones are known to significantly influence the experience and perception of pain.[139] The effects of sex hormones on sensory perception have been demonstrated for over 90 years,[140,141] yet the direction of the effects remains a mystery as several studies have reported conflicting results. By examining hormone levels, we may gain valuable insights into the underlying mechanisms contributing to pain perception and the potential role of hormones in modulating pain sensitivity.

Sex hormones, such as estradiol and progesterone, exhibit dynamic fluctuations throughout the menstrual cycle, pregnancy, and menopause. These hormonal changes have been associated with alterations in pain sensitivity and the prevalence of pain conditions.[142,143] For example, studies have demonstrated that changes in estradiol levels influence pain processing pathways and can affect pain thresholds and responses.[144] Progesterone, on the other hand, has been implicated in pain modulation, with evidence suggesting its analgesic properties in certain contexts.[145]

By analysing sex hormone levels in the context of pain, we can gain a deeper understanding of the intricate interactions between hormones and pain pathways. This knowledge contributes to unravelling the biological mechanisms underlying pain modulation, highlighting the potential therapeutic implications of hormone-based interventions for pain management. Furthermore, incorporating sex hormone assessment into the neuro-biopsychosocial model allows for a more comprehensive examination of the multifaceted nature of pain experiences. By considering biological factors, such as sex hormone fluctuations, alongside psychological, social, and life experiences, a holistic understanding of pain and its impact on individuals may develop.

1.5 Key Hypotheses

Taken together, we can draw five hypotheses from the neuro-biopsychosocial model for chronic pain, specifically, dysmenorrhea and endometriosis-related pain. In the next section of this introduction, I will summarise empirical studies that have guided these hypotheses. My research delves into various aspects of pain, including biological, psychological, and emotional factors, offering a comprehensive approach to understanding and managing pain in females with dysmenorrhea or endometriosis-related pain.

Thesis Overview:

- Investigating the intricate connections between life experiences, emotional well-being, and the biological effects of pain in dysmenorrhea and endometriosis-related pain.
- Introducing innovative methods for pain assessment in adolescent girls and adult women with dysmenorrhea and endometriosis-related pain.
- Psychological factors, including pain catastrophizing, anxiety, and depression, play a crucial role in pain perception and developing chronic pain in adolescents.

Chapter 2 Hypotheses:

- Fluctuations in sex hormones during the menstrual cycle significantly impact pain perception.
- Estrogen modulates heat pain sensitivity, and its interaction with the central nervous system alters pain perception.

Chapter 3 Hypotheses:

- Dysmenorrhea and endometriosis-related pain affect functional connectivity of the brain's regions involved in pain processing, amplified by adverse psychological and psychosocial factors.
- Altered endogenous pain inhibition mechanisms in women with dysmenorrhea and endometriosis-related pain contribute to pain chronification.

Chapter 4 Hypotheses:

- Pain catastrophizing scores may decrease with age in adolescent males and females.
- Elevated pain catastrophizing at an earlier age may predict chronic pain, and specifically dysmenorrhea in females, in subsequent years.
- Positive childhood experiences may build resiliency to pain and stress.

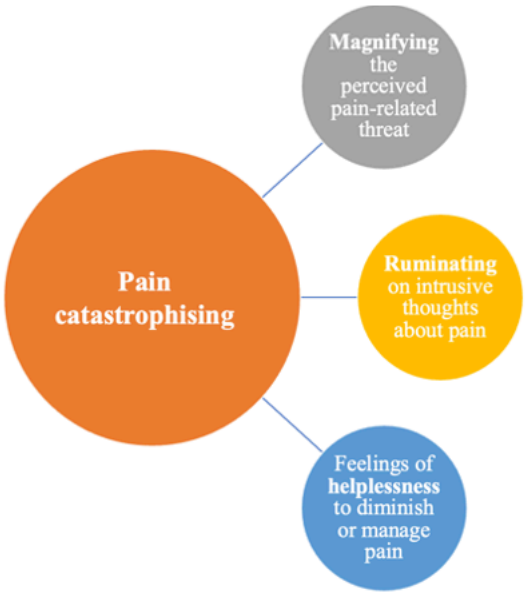
1.6 Empirical Studies Guiding Hypotheses

1.6.1 Psychological Factors Contributing to the Pain

Pain is not solely a sensory experience but also a subjective and multifaceted phenomenon influenced by psychological factors.[146] Within this thesis, pain catastrophising, anxiety, and depression, in participants with and without chronic pain, were assessed.

Pain catastrophising refers to an exaggerated and negative pattern of thoughts and emotions related to actual or anticipated pain.[147,148] For example, individuals may have thoughts like "*This pain will never go away*," "*I can't bear this*," or "*I'll never be able to enjoy the things I love again*." Pain catastrophising has been strongly linked to adverse outcomes in various pain conditions across genders and ages.[149–152] People who catastrophise about their pain often experience higher levels of distress, disability, and impairment in their daily activities.[147,153–157] Three key elements contributing to pain catastrophising (Figure 6) include rumination on intrusive pain-related thoughts, magnifying the perceived pain-related threat, and feelings of helplessness in managing or reducing pain symptoms.[151]

Figure 6. Pain Catastrophising and Three Subscales



Studies have established a strong association between pain catastrophising and poor prognosis in individuals experiencing gynaecological pain. [158,159] These studies have revealed that higher pain catastrophising levels tend to correlate with chronic pain and negatively impact long-term outcomes. For individuals with endometriosis-related pain, higher levels of pain catastrophising have been shown to reduce their health-related quality of life, regardless of the severity of pain experienced and other potential factors that might confound the relationship. [160] These findings suggest that the cognitive and emotional factors associated with pain catastrophising can significantly impact the well-being and functional abilities of individuals suffering from gynaecological pain conditions, particularly those with endometriosis. When considering that pain catastrophising is treatable,[152,161,162] this evidence suggests that further exploring the relationship and underlying mechanisms of pain catastrophising and endometriosis-related pain is crucial for improving treatment outcomes.[158,159] By understanding the role of pain catastrophising, healthcare professionals can develop more targeted and effective interventions to address the unique needs of these individuals and improve their overall pain management and quality of life.

Pain catastrophising has been proposed as a distinctive "brain state" characterised by specific neural mechanisms that differ from other constructs associated with pain disability, such as depression and anxiety.[163] Research has demonstrated that pain catastrophising can influence the functioning of brain regions involved in pain processing and regulation, thereby increasing pain sensitivity and intensity.[164–170] For instance, individuals who engage in pain catastrophising exhibit heightened activity in pain-processing regions like the somatosensory cortex, which contributes to an enhanced perception of pain sensitivity.[171]

Moreover, pain catastrophising is associated with reduced activity in pain-inhibiting brain regions, such as the prefrontal cortex.[152,172,173] This diminished activity makes it more challenging for individuals to regulate pain and decrease pain sensitivity. Additionally, studies have revealed altered connectivity between different brain regions involved in pain processing and regulation among individuals who engage in pain catastrophising. These alterations lead to an amplification of pain processing and ultimately result in greater pain sensitivity.

The theory of pain catastrophising has been subject to some controversy and debate. While many researchers and clinicians view pain catastrophising as an important predictor of pain severity and disability,[151,152,174] others have raised concerns about what is actually measured when using pain catastrophising self-report questionnaires. One of the main criticisms of pain catastrophising is that it may be too narrowly focused on negative thoughts and emotions and may overlook the potential positive coping strategies individuals use to manage pain.[175] This may lead to an overly pessimistic view of the potential for recovery and resilience.

In mine and Dr Sieberg's recently published Pain-Stress Model,[176] we argue that some stress may be protective against pain. Similarly, some pain catastrophising may be normal and protective against pain. Some researchers argue that it is expected to experience pain catastrophising to some degree and

may be an adaptive response to painful experiences.[177,178] By pathologising pain catastrophising, we may inadvertently stigmatise and marginalise individuals who experience pain.

Aside from the theory, the term "pain catastrophising" has also been controversial in pain research and clinical practice.[179] The term may be stigmatising and pathologising, leading to a narrow and negative view of individuals who experience pain. The word “catastrophise” could imply that individuals who experience pain are overreacting or exaggerating their pain experiences, which may contribute to a sense of blame or shame. Considering women are less likely to have their pain believed in a clinical setting,[180,181] using the term “catastrophising” in women's health may be particularly harmful. The term may not accurately capture the complexity of pain experiences and may overlook the social and cultural factors contributing to pain and suffering.

Despite these criticisms, pain catastrophising is thought to be an important predictor of pain severity and disability and is a target for interventions treating chronic pain. Identifying and addressing pain catastrophising may help individuals develop more adaptive and effective coping strategies to improve their quality of life and functioning. Proponents of the term suggest it provides a useful framework for understanding the cognitive and emotional factors that can exacerbate pain experiences and impair functioning.[175] By identifying and addressing pain catastrophising, we can develop more effective treatments targeting specific psychological mechanisms contributing to pain and disability. Overall, the controversy surrounding the use of the term "pain catastrophising" reflects ongoing debates in the field of pain research and clinical practice about how best to understand and treat pain experiences. While some may prefer alternative or more inclusive terms, the concept of pain catastrophising remains an important area of investigation and intervention for many individuals with pain.

Anxiety is a complex and multifaceted psychological condition that is characterised by excessive and persistent worry, fear, or unease.[182] It is a normal and adaptive response to stress or threatening situations, helping individuals prepare for and cope with potential dangers. Depression, similar to

anxiety, involves persistent sadness, hopelessness, and a loss of interest or pleasure in activities.[182] However, when anxiety and depression become chronic, overwhelming, and interfere with daily functioning, it may be classified as a disorder.

Several research studies have focused on depression and anxiety and their relationship to general chronic pain, as well as specifically endometriosis-related pain and dysmenorrhea.[39,40,183–186] While the exact mechanisms underlying this relationship are not fully understood, studies have consistently shown that individuals with endometriosis are more likely to experience both depression and anxiety disorders than those without the condition. The CNS, including the brain and spinal cord, may play a role in the relationship between anxiety and endometriosis-related pain.[44,48,74,187] Alterations in pain processing pathways and increased sensitivity to pain signals have been observed in individuals with endometriosis. Additionally, chronic pain, uncertainty about the disease, and the impact on quality of life can increase anxiety levels. On the other hand, anxiety may exacerbate pain perception.[10,176,188]

1.6.2 Psychosocial Factors Contributing to the Pain

Social support networks, interpersonal relationships, cultural values, and access to healthcare services all contribute to the social context in which pain is experienced and managed.[189] The social dimension of pain is essential for developing holistic interventions that address the individual within their social environments, [10,176,190–196] such as adverse childhood, adverse recent, positive childhood, and positive recent experiences.

The terminology surrounding adverse childhood experiences can vary, with trauma, stress, and maltreatment each holding distinct meanings.[197] Trauma refers to emotionally distressing events that overwhelm coping abilities, leading to feelings of helplessness, terror, and horror. Examples include physical or sexual abuse, natural disasters, or witnessing violence or death. In contrast, stress encompasses physical, emotional, and psychological responses to challenging or threatening situations, often related to work, school, relationships, or finances. It can be acute, occurring in the short-term, or chronic, persisting over an extended period. Maltreatment is a broader term that

encompasses trauma and stress, encompassing any form of abuse, neglect, or harm inflicted on an individual, typically by a caregiver or someone in a position of power. This may involve physical, sexual, or emotional abuse, neglect, or exploitation.

For accurate reporting and meaningful comparisons, precise language is crucial in trauma and stress research. Some researchers propose using "adverse childhood experiences" as an umbrella term for childhood trauma or stress.[198–202] Careful selection of terminology ensures accurate interpretation of research findings and enables comparisons across studies. Moreover, it is essential to approach individuals who have experienced trauma, stress, or maltreatment with sensitivity, using language that is respectful and free of stigmatisation.

Research has identified a connection between a history of such as physical and psychological adverse childhood experiences, and the development of chronic pain later in life.[203–206] Prolonged activation of a sensitised stress response to pain or non-pain-related stressors, especially during the formative years of brain development, may initiate or worsen pain symptoms. Additionally, these experiences can induce physical changes in pain-processing systems, such as increased inflammation, hypothalamic-pituitary-adrenal axis alterations, and nervous system changes.[207]

Moreover, a history of adverse childhood experiences may contribute to developing psychological conditions such as depression and anxiety, which have been linked to heightened pain sensitivity and poorer pain management outcomes. Adverse childhood experiences can also trigger an inflammatory response in the body,[208] which is believed to play a role in developing and maintaining conditions like endometriosis. Increased inflammation can exacerbate pain symptoms and contribute to their persistence. Additionally, physical and psychological adverse recent experiences can lead to anxiety, depression, or post-traumatic stress disorder, all of which can influence the perception and experience of pain.[209] Emotional distress can intensify pain severity, increase pain-related disability, and disrupt coping mechanisms.

Only six studies have examined the relationship between adverse childhood experiences and endometriosis,[210–215] as well as one recent review of the literature published in June 2023.[216] Out of the six studies examining the link between adverse childhood experiences and endometriosis, four found a connection while two did not. Notably, three of the positive studies relied on self-reported endometriosis diagnoses, and the fourth included women with a medical office diagnosis, though without confirmation through surgery or histology. In contrast, the two negative studies used visually confirmed endometriosis lesions, regardless of surgical indications or symptoms.

Therefore, the findings indicate that adverse childhood experiences are associated with pelvic pain when there is a related but mostly unverified diagnosis or label of endometriosis. This means women reporting pelvic pain symptoms and a doctor mentioning the diagnosis and/or a surgical confirmation. However, there was no association between adverse childhood experiences and surgically visible endometriosis lesions, regardless of clinical presentation. Thus, the reported association seems to be driven by pain rather than by visible lesions. This aligns with findings in other pain conditions where adverse childhood experiences are linked to chronic pain.[200,217–219]

Various mechanisms have been proposed to explain the connection between childhood adversity and the development of chronic pain. These mechanisms include psychological and social factors and biological factors such as neuroendocrine alteration, immune dysregulation, genetic damage, and modifications in nociceptive processing.[193,206,220] These factors collectively contribute to an increased vulnerability to pain sensitivity. Investigating the specifics of the underlying biological mechanisms maintaining endometriosis-related pain would provide insight into how adverse childhood experiences impact or possibly exacerbate pain.

Positive childhood experiences are events, situations, or moments that bring individuals joy, fulfilment, and happiness. Positive childhood experiences are important social factors that can influence the development and well-being of individuals across the lifespan, as well as their chronic pain experience.[221] Understanding these factors and their impact is essential for promoting healthy

development and mitigating the negative effects of adversity. Similarly, positive recent experiences can impact pain outcomes by distracting from pain, enhancing emotional well-being, reducing stress, promoting relaxation, and fostering optimism and self-efficacy. These factors can contribute to improved pain management, decreased pain perception, and an overall better quality of life for individuals experiencing pain.[176]

These four variables, adverse childhood, adverse recent, positive childhood, and positive recent experiences, play a role in shaping resiliency, which, in turn, influences the experience of chronic pain.[222,223] Resilience is generally defined as the ability to adapt and rebound in the face of adversity or stress. Key components of resilience include cognitive flexibility, emotional regulation, social support, positive self-concept, and effective coping strategies.[224,225] In the context of chronic pain, resilience refers to an individual's capacity to maintain well-being, cope effectively, and adjust to the challenges associated with living with persistent pain.[222]

Research has revealed that resilience is shaped not only by individual differences like genetics and personality traits but also by life factors such as childhood experiences, social support networks, and access to resources and opportunities.[225,226] Resilience can be nurtured and strengthened through psychotherapy, mindfulness-based practices, and social support programs.[227] Recognising the mechanisms behind resilience is crucial for improving mental health outcomes and promoting resilience throughout one's lifespan, as it is a critical component often excluded in chronic pain and stress/trauma research.

1.6.3 Neuro Impact on the Pain

Pain activates descending pain modulation pathways, triggering the release of endogenous opioids and other neuromodulators that attenuate pain signals.[124] Pain perception involves a distributed network of brain regions, including the somatosensory and prefrontal cortices, which integrate nociceptive signals, modulate emotional and cognitive responses to pain, and contribute to the overall pain experience. However, chronic pain significantly affects both brain structure and functional

connectivity. [171] Studies have revealed volume, thickness, and connectivity alterations of these key brain regions, disrupting neural networks associated with pain processing and affecting overall brain function. [195,228] Furthermore, chronic pain has been found to impact cognitive functions such as memory, attention, and executive function. Psychological and psychosocial factors like pain catastrophising, anxiety, depression, and chronic stress or childhood trauma have been associated with changes in brain regions, particularly the prefrontal cortex, which plays a crucial role in pain processing and modulation.[229–232]

Research on primary dysmenorrhea has shown structural and functional alterations in brain regions involved in pain processing, such as the anterior cingulate cortex and insula. [233] These alterations affect volume, cortical thickness, neuronal connectivity, and connectivity within pain, sensory processing, emotional regulation, and cognitive control networks. Consequently, women with dysmenorrhea may experience increased activation of pain-related brain regions, contributing to heightened pain sensitivity.

Similarly, pain modulation processes can be disrupted in individuals with endometriosis, contributing to persistent and intractable pain. Although research on endometriosis-related pain is limited, neuroimaging studies have provided valuable insights. Pilot studies have revealed alterations in brain regions associated with pain modulation, including the anterior cingulate cortex, insula, prefrontal cortex, somatosensory cortex, and thalamus.[234–236] These regions have also been implicated in other chronic pain conditions.

Although limited, neuroimaging studies exploring endometriosis-related pain have yielded valuable insights. Pilot studies suggest that the maintenance and chronicity of endometriosis-related pain involve changes in brain regions associated with pain modulation, such as the anterior cingulate cortex, insula, prefrontal cortex, somatosensory cortex, and thalamus.[234–236] These regions are implicated in various chronic pain conditions, suggesting a potential neurobiological basis for endometriosis-related pain.

Interestingly, there is a lack of neuroimaging studies using task-based assessments to examine dysmenorrhea and endometriosis-related pain, despite the extensive literature on using such assessments in chronic pain and stress research.[125,237] Additionally, investigating brain changes in patients with endometriosis, considering psychological and psychosocial factors, may aid in developing personalised pain profiles and identifying relevant treatment subgroups.[238] Extrapolating from chronic pain research, disruptions in functional connectivity that affect pain processing and perception can be expected in individuals with dysmenorrhea and endometriosis-related pain.

Similarly, studies of endometriosis-related pain as a centrally mediating phenomenon are lacking. In 2020, I co-authored a commentary that provided the justification and rationale for using OA to study endometriosis-related pain.[129] Using an OA task in patients with endometriosis may provide insight into neural mechanisms contributing to pain maintenance. It may also capture those at risk for the transition to chronic pelvic pain, provide a metric for developing future centrally mediated treatment options for this population, and elucidate the brain changes resulting in resistance to treatment and pain chronification. As more recent findings have suggested,[47] the central effects of endometriosis-related pain should be further explored, and using OA could provide insight into the underlying neural mechanisms related to the persistent pain.

1.7 Summary

The research presented in this introduction section makes a case for the importance of the intricate relationships between adverse life experiences during development, emotional functioning, and biological consequences of pain, all of which contribute to the development and maintenance of chronic pain. Manipulating these factors may have a causal influence on pain experiences, but research in this area is still in its infancy. Each of the three experimental studies investigates at least two of the four components of the neuro-biopsychosocial model (Table 4).

Table 4. Components of the Neuro-biopsychosocial Model Investigated in Experimental Studies

Chapter	Neuro	Bio	Psycho	Social
Two	[1] fMRI [2] QST	[1] Hormone testing [2] QST	N/A	N/A
Three	[1] fNIRS [2] OA	[1] OA	[1] Pain catastrophising [2] Resiliency	[1] Adverse childhood experiences [2] Adverse recent experiences
Four	N/A	N/A	[1] Pain catastrophising [2] Resiliency [3] Depression [4] Anxiety	[1] Adverse childhood experiences [2] Positive recent experiences

Abbreviations. N/A, not applicable; MRI, magnetic resonance imaging; QST, quantitative sensory testing

The three experimental chapters address distinct but related scientific gaps. Each employs a unique methodology and examines a different population, assessing the relationship between chronic pain using a neuro-biopsychosocial model (summarised in Table 5).

Table 5. Summary of the Three Experimental Studies Included in this Thesis

Chapter	Study Design	Population Studied	Gap in Research Addressed
Ch 2	Scoping review & pilot longitudinal (two time points)	Pain-free female young adults	Relationship between experimental pain and hormonal fluctuations during menstrual cycle.
Ch 3	Cross-sectional	Dysmenorrhea, endometriosis & pain-free female young adults	Impact of brain alterations, pain inhibition, and psych variables on dysmenorrhea and endometriosis-related pain.
Ch 4	Longitudinal (three time points)	Unspecified chronic pain, dysmenorrhea, & pain-free adolescent males & females	Pain catastrophising during adolescence as method for predicting unspecified chronic pain and dysmenorrhea development.

Chapter 2

Experimental Pain and the Menstrual Cycle

"The most dangerous phrase in any language is, 'We've always done it this way.'"

Professor Grace Brewster Hopper

Trailblazer in computer programming, software development, and implementation of programming languages.

2.0 Overview

Chapter 2 presents a scoping review of the literature on the relationship between menstrual cycle hormonal fluctuations and experimental pain, as well as pilot neuroimaging results. This topic and data inspired my research on women's pain during my DPhil.

Early on in my studies, I had the opportunity to meet with Dr Pamela Stratton, a highly regarded gynaecologist and surgeon with extensive experience in women's health research. She was a frontrunner in challenging the conventional perspective that endometriosis lesions cause pain. Dr Stratton's ground breaking work on chronic pelvic pain associated with endometriosis challenged conventional thinking and led to innovative treatments using selective estrogen receptor modulators

and botulinum toxin.[239] However, despite her achievements, she made a striking observation during our meeting:

"We fundamentally do not know how females process pain."

Hearing these words changed my perspective on researching women experiencing pain, specifically how I wanted to study endometriosis-related pain.

Additionally, I had the opportunity to analyse pilot mixed-method cross-sectional data of pain-free females to continue my investigation of experimental pain and the menstrual cycle. The study aimed to determine the impact of normal hormonal fluctuations during the menstrual cycle on thermal pain sensitivity. The pilot study's protocol was not registered or published.

For the scoping review, I was the only person to review the screen the titles and abstracts of all articles retrieved in the initial search, and full-text articles were obtained for studies that met the inclusion criteria. Data were extracted from each article using a standardised form that included information on study design, sample characteristics, measurement tools, and key findings.

My responsibilities for the pilot study included data processing and analysis using various statistical tools and techniques. This involved cleaning and organising the data, conducting descriptive and inferential analyses, and presenting the findings clearly and concisely at national and international conferences.

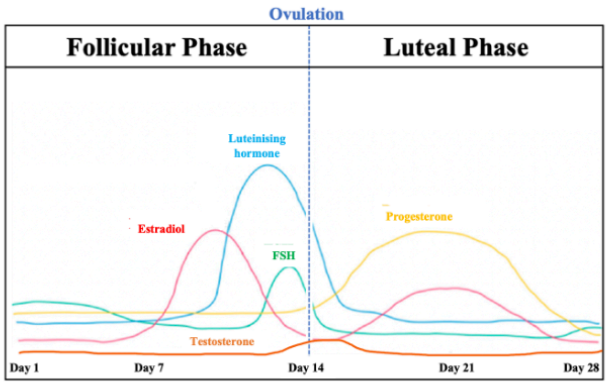
2.1 Introduction

Normal hormone fluctuations during the menstrual cycle have been suggested to impact various physiological processes, including pain perception and sensitivity.[18,143,240] However, the literature on this topic has been characterised by significant debate and controversy for over 90 years.[140,141,] But what is a "normal menstrual cycle"?

2.1.1 Defining Normal Menstrual Cycle Hormonal Fluctuations

Throughout the menstrual cycle, several hormonal fluctuations occur.[241] The three main hormones involved are estrogen, progesterone, and testosterone, which are produced by the ovaries. In the follicular phase (typically days 1-14), estrogen levels gradually increase, stimulating the growth of the uterine lining and the development of follicles in the ovaries. Around day 14, a luteinising hormone (LH) surge triggers ovulation, releasing an egg from the ovary. In the luteal phase (typically days 15-28), progesterone levels increase, preparing the uterus for the possible implantation of a fertilised egg. If implantation does not occur, estrogen and progesterone levels drop, leading to the shedding of the uterine lining and the onset of menstruation. Testosterone levels fluctuate throughout the menstrual cycle, with the highest levels occurring during the pre-ovulatory phase (often around day 12 to 14 of a 28-day cycle) and the lowest levels occurring during the luteal phase (around day 20 to 22 of a 28-day cycle). However, these fluctuations are relatively small compared to the larger fluctuations of estrogen and progesterone during the menstrual cycle (Figure 7).

Figure 7. Normal Menstrual Cycle Hormonal Fluctuations[a]



[a] Figure adapted from PMID: 36768188.
Abbreviations. FSH, follicle-stimulating hormone

Abnormal menstrual cycle hormonal fluctuations can occur due to various factors, including hormonal imbalances, response to some medication, and certain medical conditions. Endometriosis is a condition that can cause hormonal imbalances that disrupt normal menstrual cycle hormonal fluctuations.[242] Women with endometriosis may sometimes experience heavy or prolonged menstrual bleeding, irregular periods, or spotting between periods. On the other hand, it is also hypothesised that the hormonal fluctuations that occur during the menstrual cycle can stimulate the growth of

endometrial tissue outside the uterus, leading to inflammation, pain, and other symptoms.[243] Not all women with abnormal menstrual cycles have endometriosis, and not all women with endometriosis have abnormal menstrual cycles.

Estrogen has been hypothesised to modulate pain sensitivity and regulate the pain response in males and females.[144] One possible mechanism for this effect is that estrogen interacts with the CNS to alter pain perception. Studies have shown that estrogen can affect the activity of pain-modulating circuits in the CNS, such as the endogenous opioid system and the descending pain control system.[244] Specifically, estrogen has been shown to increase the release of endogenous opioids and enhance the activity of the descending pain control system. However, whether estrogen increases or decreases thermal experimental pain sensitivity is unknown.

There are nine published reviews examining the relationship between experimental pain and the menstrual cycle, spanning from 1999 to 2023.[18,143,240,245–250] The most recent review focused on the role of sex hormones in pain-related conditions by briefly highlighting the role of hormones in the experience of experimental, acute, and chronic pain.[246] These reviews consistently highlight the inconclusive nature of the relationship between pain sensitivity and the menstrual cycle. Fluctuations in estrogen and testosterone levels are believed to contribute to these differences, with estrogen associated with increased sensitivity and testosterone linked to decreased sensitivity. The variability in study methodologies, sample characteristics, phase verification, and underpowered samples makes it challenging to establish consistent relationships between the menstrual cycle and experimental pain responses. Consequently, the reviews emphasise the need for further research to explore the impact of hormonal modulation of pain and to improve pain management strategies.

The scoping review presented in this chapter differs from the nine published reviews as it specifically assesses the limitations of previous studies and proposed ideas for future directions and provides a clearer and more comprehensive understanding of this complex topic. This information may also suggest when to recruit chronic pain and pain-free participants for future studies. As our

understanding of chronic pain mechanisms and the factors influencing hormonal fluctuations in the menstrual cycle advances, there is a pressing need for a comprehensive and updated review of the existing knowledge.

2.2 Scoping Review

This scoping review aimed to identify areas of agreement and disagreement in the literature and highlight gaps in knowledge that need to be addressed through further research. It also aimed to critically evaluate the existing methods and tools for measuring pain perception and sensitivity during the menstrual cycle and identify their strengths and limitations. Using the results from the literature, recommendations for future research in this area and inform participant recruitment for future studies, are provided. Ultimately, this review will contribute to a better understanding of the relationship between menstrual cycle phases and experimental pain sensitivity, which can inform future experimental pain studies for women.

2.2.1 Methods

Three electronic databases were searched: PubMed, PsychINFO, and Google Scholar. The search was not limited to articles published between a specific time, but all articles were limited to being published in English. The following keywords were used in combination: menstrual cycle, hormonal fluctuations, pain sensitivity, experimental pain, and QST. The search began in January 2023, and the last search was conducted in April 2023. The reference lists of relevant articles were also screened for additional studies.

Studies were included if they were empirical studies published in peer-reviewed journals, focused on the menstrual cycle and any type of experimental pain, and reported quantitative or qualitative data related to the research question. Data were extracted from each article using a standardised form that included information on the year published, sample characteristics, hormone measurement tools, and key findings.

2.2.2 Results

The results are presented in Table 6, Appendix D. A total of 79 studies were identified to fit the inclusion criteria during the initial screening of titles and abstracts. In the second screening, which included reviewing the full article, 37 articles were identified to fit the inclusion criteria.[141,251–286] The sample characteristics, pain and hormone measurement tools, and key findings for each study are described.

2.2.2.1 Sample Characteristics

The sample characteristics of the 37 studies included in the scoping review varied across different populations, and careful consideration of these characteristics is important for generalising the findings (Table 7). The diversity in sample characteristics highlights the need to consider these factors when interpreting and generalising the findings from the included studies.

Table 7. Varied Study Characteristics of Included Studies

Study Characteristics	Percentage/Number of Studies
Sample Size Range	5 to 66 participants
Studies with ≤20 participants per group	60%
Studies on participants without pain	76%
Studies on individuals with chronic pain	27%
Studies on participants with premenstrual syndrome	1%
Studies on participants using oral contraceptives without chronic pain	11%
Studies on participants using non-oral contraceptives without chronic pain	8%
Studies on participants with chronic pain using oral contraceptives	5%
Studies on participants with chronic pain using non-oral contraceptives	5%
Studies with mixed samples of chronic and non-pain individuals	1 study
Studies focusing on pain-free participants during surgery	1 study

2.2.2.2 Menstrual Phase Validation

In the reviewed studies, multiple methods were used to collect data on the menstrual cycle. These methods encompassed self-report measures,[141,253,274,279–282,284,286] basal body temperature and diary recordings,[252,259,283] blood testing for estradiol and progesterone, LH

testing,[251,258,259,263,265,266,270,273,275,276,280,283,285] pelvic ultrasonographic screening,[277] and saliva testing for hormone levels.[261,262,264,266] These diverse methods were chosen to assess various aspects of the menstrual cycle, including hormone levels, ovulation, and different menstrual phases (Table 8).

Table 8. Varied Methods for Menstrual Phase Validation

Menstrual Phase Validation Method	Percentage/Number of Studies
Self-report measures	31%
Basal body temperature and diary recordings	5%
Blood testing for estradiol and progesterone	27%
LH testing	27%
Pelvic ultrasonographic screening	1 study
Saliva testing for hormone levels	8%

Abbreviations. LH, luteinising hormone

2.2.2.3 Pain Assessment

Several types of pain stimuli were used in the studies, including thermal pain stimuli (cold and heat), pressure pain stimuli, electrical pain stimuli, tactile pain stimuli, used nociceptive flexion reflex, condition pain modulation, and OA (Table 9). The key findings are summarised in Table 10.

Table 9 Varied methods of Pain Assessment

Pain Assessment Type	Percentage of Studies
Thermal pain stimuli (cold and heat)	51%
Pressure pain stimuli	35%
Electrical pain stimuli	24%
Tactile pain stimuli	1%
Nociceptive flexion reflex	1%
Condition pain modulation	1%
Offset analgesia	1%

Table 10. Scoping Review Key Findings by Pain Stimulus

Pain Stimulus	Key Findings
Cold	Mixed results - increased sensitivity after menstruation - peak sensitivity during the follicular phase - decreased sensitivity during the luteal phase
Heat	Mixed results - decreased sensitivity during the luteal phase - increased sensitivity after menstruation - highest sensitivity ovulatory phase 63% of the studies found no significant differences in sensitivity across menstrual phases.
Electric shock	Mixed results - increased sensitivity during the luteal and follicular phases - higher pain responses in chronic pain participants during the luteal phase 67% of studies found no significant differences in sensitivity across menstrual phases.
Pressure	Mixed results - increased sensitivity after menstruation - peaked during the luteal phase - ovulatory phase as the time of highest sensitivity, - highest intensity of pressure pain during the menstrual and mid-luteal phases - lowest intensity during the ovulatory and late luteal phases - increased sensitivity during the follicular phase in normally menstruating females but not in women taking oral contraceptives. - increased pressure pain during menstrual and decreased pain during follicular phases, but only among women taking oral contraceptives - sensitivity to pressure pain during the menstrual and late luteal phases - higher sensitivity was observed during the premenstrual and intermenstrual phases 29% of studies found no significant differences in sensitivity across menstrual phases.
Ischemic pain	Mixed results - highest pain intensity during the menstrual and mid-luteal phases - lowest intensity during the ovulatory and late luteal phases. - decreased ischemic pain sensitivity during the mid-follicular phase - increased sensitivity during the luteal phase. - increased sensitivity during the luteal phase but only among chronic pain patients. 56% of studies found no significant differences in ischemic pain sensitivity across menstrual phases.
Tactile sensitivity	No significant differences in pain sensitivity across menstrual phases.
Nociceptive flexion reflex	Mixed results - increased sensitivity during the follicular phase - estradiol was associated with weaker emotional modulation of nociceptive pain. 33% of studies found no significant differences in ischemic pain sensitivity across menstrual phases.
Venipuncture	Increased sensitivity during the luteal phase
CPM	No significant differences in pain sensitivity across menstrual phases.
OA	No significant differences in pain sensitivity across menstrual phases.

Table 10. Scoping Review Key Findings by Pain Stimulus

Pain Stimulus	Key Findings

Abbreviations. CPM, conditioned pain modulation; OA, offset analgesia

2.2.3 Conclusions

The current scoping review revealed that the relationship between menstrual cycle hormones and experimental pain sensitivity is unclear and may be influenced by various factors. Among these factors is the type of pain stimulus employed, location tested on the body, definition of menstrual phases, and method for confirming menstrual phases. Thus, the present findings suggest that controlling for the menstrual cycle should be essential in pain research studies until sufficient evidence suggests otherwise. By doing so, we better understand how hormonal fluctuations impact pain, we may avoid potential confounding effects of menstrual cycle hormones on experimental pain results, and we may advance our understanding of pain mechanisms. However, it is important to acknowledge that the quantity and precision of data collected varied across the studies, and the reliability of the specific measures employed differed. For example, only 40% of the included studies had more than 20 participants. It is diffiduclt to draw conclusions from the scoping review as there were several types of pain assessed, several types of cycle tracking used, and low-powered sample sizes.

2.3.3.1 Recommendations for Pain Researchers

Based on these review results, I recommend the following to improve our general understanding of the impact of hormonal fluctuations on pain perception: standardization of methods, inclusion of hormonal profiles, sample diversity, inclusion of psychological and social factors, and large samples sizes.

Given the mixed results in many of the studies reviewed, it is essential to standardise research methods and data collection protocols to reduce variability. This includes consistent measurement of menstrual phases, pain stimuli, and pain sensitivity assessment tools. Incorporate hormonal profiling

in research to better understand the relationship between specific hormones (e.g., estradiol) and pain sensitivity. This can help elucidate the underlying mechanisms. Additionally, longitudinal studies may aid in tracking changes in pain sensitivity within individuals across multiple menstrual cycles (e.g. menstrual, follicular, ovulation, and luteal phases). This may provide more robust insights into how pain sensitivity fluctuates. Similarly, if we ensure that research samples are diverse, including women with and without chronic pain conditions, different age groups, and variations in hormonal status (e.g., oral contraceptive users vs. non-users) we may gain a more comprehensive understanding. Lastly, I recommend including the influence of psychological factors (e.g., stress, mood) on pain sensitivity during menstrual phases in these investigations.

2.3.3.2 Clinical Applications

Clinicians should consider menstrual phase-related pain sensitivity when developing pain management plans for female patients. This may involve adjusting medication dosages or therapies during certain menstrual phases. It could also benefit patients to explore the potential use of hormonal interventions, such as hormone replacement therapy or hormonal contraceptives, in managing pain conditions, particularly for women with chronic pain. Additionally, if we are able to educate female patients about the potential variations in pain sensitivity across menstrual phases. This can help them better manage their pain and understand why pain levels may fluctuate. Lastly, if we encourage a multidisciplinary approach to pain management, involving pain specialists, gynaecologists, and psychologists, we address both physical and psychological aspects of pain during different menstrual phases.

2.3.3.3 Addressing Inconsistencies and Future Directions for My Research

To address much of the inconsistencies within the results of the scoping review, a next step could include conducting meta-analyses to synthesize existing research and identify overarching trends or patterns in pain sensitivity across menstrual phases. Additionally, it will address the potential issue of publication bias, where studies with significant findings are more likely to be published.

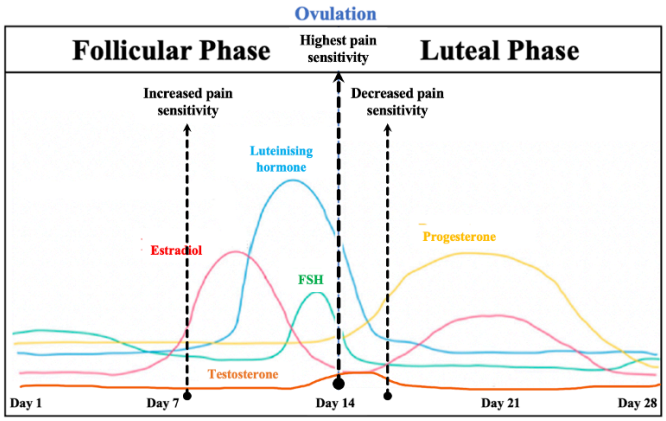
Future directions for this research include exploring the role of genetic and epigenetic factors in pain sensitivity across menstrual phases, as these factors may interact with hormonal fluctuations. Using neuroimaging techniques to investigate the neural mechanisms underlying menstrual phase-related pain sensitivity. This could provide insights into brain regions involved in pain modulation. Additionally, I plan to incorporate patient-reported outcomes, such as pain diaries and quality of life assessments, in both research and clinical practice to capture the subjective experience of pain.

In summary, addressing the complexities of pain sensitivity across menstrual phases requires continued research efforts, standardized methodologies, and a holistic approach in clinical practice. It's crucial to recognize that pain perception is influenced by a combination of biological, hormonal, psychological, and genetic factors, and a comprehensive understanding of these factors will lead to more effective pain management strategies for women.

2.2.4 Next Step – Experimental Pilot Study

Within this thesis, there is a particular focus on heat pain, which was employed in the forthcoming pilot study (Chapter 2) and OA, which was used in the second experiment (Chapter 3). The scoping review findings indicated decreased sensitivity during the luteal phase, increased sensitivity after menstruation, and the highest sensitivity during the ovulatory phase (Figure 8). However, five studies found no significant differences in sensitivity across menstrual phases. This valuable information assists in determining the appropriate timing for participant recruitment in the heat pain and OA studies, as well as guiding the selection of pertinent questions pertaining to their menstrual cycles.

Figure 8. Scoping Review Findings for Thermal Experimental Pain Used to Inform Chapter 3 Participant Recruitment[a]



[a] Figure adapted from PMID: 36768188.
Abbreviations. FSH, follicle-stimulating hormone

2.3 Pilot Study

This study, led by Principal Investigator Professor David Borsook, aimed to investigate the impact of hormonal changes during the menstrual cycle on pain thresholds and CNS network activation in healthy young adult females.

The scoping review showed that experimental pain is commonly evaluated using various QST measures. As described in Chapter 1, QST assesses sensory thresholds for different types of pain with specific fibre functions, such as touch, vibration, and hot and cold temperature sensations.[119] One specific aspect often examined to understand neuropathic pain mechanisms is heat hyperalgesia.[287] By assessing the response to thermal stimuli in a pain-free sample, we can gain insights into the pathophysiological mechanisms underlying pain in patients and the influence of the menstrual cycle.

2.3.1 Objectives and Hypotheses

Females were hypothesised to show decreased heat pain thresholds (increased pain sensitivity) and significantly different CNS network activation in the mid-follicular phase (characterised by higher estrogen level) compared to the mid-luteal phase.[247] Estrogen was hypothesised to modulate pain sensitivity and regulate the pain response as it may affect the activity of pain-modulating circuits in

the CNS, such as the endogenous opioid system and the descending pain control system.[244] Fluctuations in estrogen and testosterone levels are believed to contribute to these differences, with estrogen associated with increased sensitivity and testosterone linked to decreased sensitivity.

2.3.2 Methods

Institutional Ethics Review Boards approved this study for research at Massachusetts General Hospital and Harvard Medical School, and all participants provided informed consent.

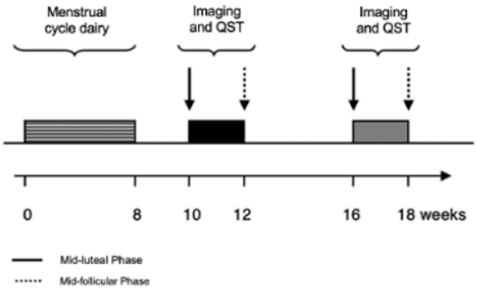
2.3.2.1 Participant Selection

Participants underwent screening for diagnosed medical conditions. Those who had taken hormone-based medication or opioids within the last three months were excluded. A total of ten right-handed females of reproductive age (mean age of 22.4 years, SD = 2.6 years, range = 21-38 years) were recruited for the study.

2.3.2.2 Phase Verification

To ensure participants were in the respective menstrual cycle phase on the day of testing (Figure 9), they monitored their menstrual cycle for two months using a self-report diary. On the study day, participants provided a negative pregnancy test and a blood sample for testing estradiol and progesterone levels. The Massachusetts General Hospital laboratory reference ranges for serum estradiol were the following: Follicular: 20-350 pg/mL; Ovulatory: 150-750 pg/mL; Luteal: 30-450 pg/mL. The reference ranges for serum progesterone were the following: Follicular = 0.057 - 0.893 ng/mL; Ovulatory = 0.121 - 12.0 ng/mL; Luteal = 1.83 - 23.9 ng/mL. These levels align with the literature describing mid-follicular and mid-luteal phase levels.[288]

Figure 9. Hormonal Testing for Pilot Study Phase Verification

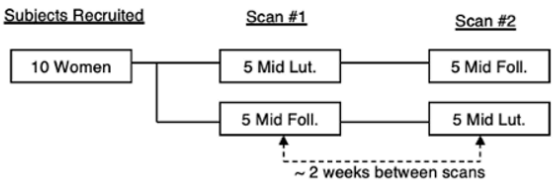


Abbreviations. QST, quantitative sensory testing

2.3.2.3 Experimental Design

Each participant underwent fMRI twice, approximately two weeks apart, within two days of their mid-luteal and mid-follicular phases (Figure 10) to compare CNS activation.

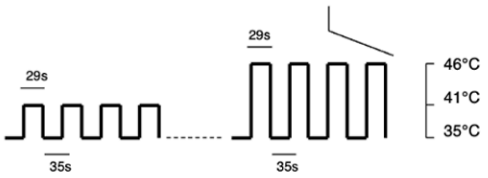
Figure 10. Experimental Design of Participant Recruitment



Participants underwent an MRI twice in a cross-over design. 10 participants were tested during their mid-follicular (days 6-8) and mid-luteal phases (days 20-23).

Thermal testing on the dorsum of the participants' left hand was administered during the MRI brain scan. A Medoc peltier thermode (3 x 3 cm) and a Medoc TSA-II Quantitative Neurosensory Analyzer were used to deliver a non-noxious stimulus (41°C) and a noxious stimulus (46°C) (Figure 11). The experimental paradigm consisted of alternating epochs of a baseline temperature of 35°C for 35 seconds and a test stimulus of 41 or 46°C for 29 seconds, each presented four times for both temperatures.

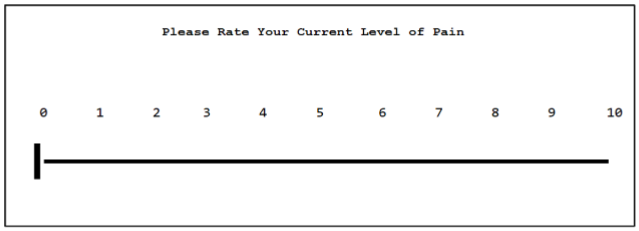
Figure 11. Experimental Thermal Design



Thermal paradigm used during MRI. Pain scores were reported after each heat epoch, providing four for each condition (41C and 46C) and each menstrual phase.
Abbreviation. S, seconds

Pain intensity was rated immediately after each temperature presentation using the Numeric Rating Scale (NRS) for standardised pain intensity assessment with 0 representing "no pain" and 10 representing "worst pain imaginable" (Figure 12). Scores are then grouped into three categories: mild: 1–3; moderate: 4–6; severe: 7–10.

Figure 12. Visual Analogue Scale Presented as the Numerical Rating Scale (NRS).



Zero represents "no pain", and 10 represents "worst pain imaginable". Scores are grouped into three categories: mild pain: 1–3; moderate pain: 4–6; severe pain: 7–10.

2.3.2.4 MRI Data Acquisition

Participants were scanned using a 1.5 Tesla Signa LX 8.2 General Electric Scanner, employing asymmetric spin echo-planar imaging with a repetition time/echo time of 2.5/0.07s and an in-plane resolution of 3.125mm.

2.3.2.5 Statistical Analyses

Data analysis was conducted using FMRI Expert Analysis Tool Version 5.98, a part of FSL's Functional MRI of the Brain Analysis Group at the University of Oxford FMRIB's Software Library - www.fmrib.ox.ac.uk/fsl). The scans were initially motion corrected, spatially smoothed (Gaussian kernel, FWHM 6mm), and corrected for session-specific intensity differences. Time-series analysis was performed using FMRIB's Improved Linear Model with local autocorrelation correction.[289,290]

A regressor was created to model the thermodynamic response to the thermal stimuli, using box-car functions with ramps (4 seconds) between baseline and target temperatures. The first two principal components of the motion parameters were included as covariates of no interest. Following subject-specific analysis, the results were registered to the Montreal Neurological Institute standard 152 atlas before being combined with group analyses.

Registration to the Montreal Neurological Institute standard atlas involved a two-step normalisation process using FMRIB's Linear Image Registration Tool. Firstly, each session's mean echo-planar Imaging image was registered to the subject's high-resolution anatomical scan (12 degrees of freedom; non-brain signal removal was performed using Brain Extraction Tool on anatomical images). Next, the high-resolution anatomical scan was registered to the standard Montreal Neurological Institute 152 atlas (12 degrees of freedom). The resulting registration matrices were combined and applied to the individual Brain Extraction Tool images with trilinear interpolation. The registered, individual results were combined in a higher-level group analysis using (FMRIB's Local Analysis of Mixed Effects).[291,292]

FMRIB's Local Analysis of Mixed Effects was also employed for within-group higher-level analyses to identify significantly activated and deactivated regions in the mid-follicular and mid-luteal groups. The within-group analyses considered results statistically significant if they reached a corrected probability value of 0.05. Between-group higher-level analyses were conducted to determine regions significantly different between the two groups. Due to the low statistical power associated with this type of analysis, a less stringent height threshold of uncorrected probability value 0.001 was

combined with a minimum cluster extent (>10 voxels) to define statistical significance for between-group comparisons. The results were tabulated based on statistical value, region, and Montreal Neurological Institute coordinates.

The within-group higher-level analyses were summarised according to large brain regions, including the frontal, parietal, and temporal lobes and the limbic and sub-lobar regions. These regions were defined using the Talairach Daemon database with the Wake Forest University Pickatlas software. The total number of significantly activated voxels within these large regions was counted for each group (mid-follicular vs. mid-luteal), with only voxels overlapping for all subjects included in voxel counts.

2.3.3 Results

The study included ten females, with a mean age of 22.4 years (SD = 2.6 years; range = 21-38 years). All subjects met the criteria for hormonal levels (mean ± SD). Estradiol mid-follicular phase = 79.5 ± 65.1 pg/mL; Progesterone mid-follicular phase = 0.3 ± 0.3 ng/mL; Estradiol mid-luteal phase = 161.6 ± 51.8 pg/L; Progesterone mid-luteal phase = 4.2 ± 3.6 ng/mL.

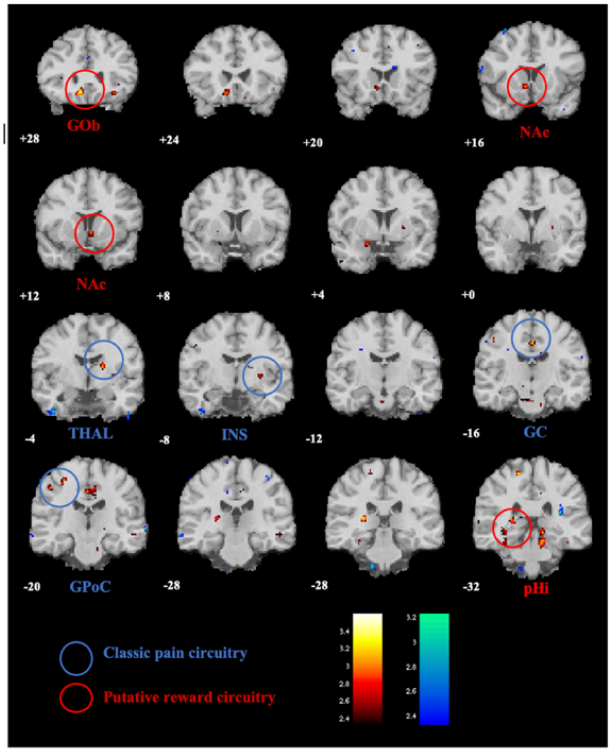
During the mid-luteal phase, eight participants reported an average pain score of less than 0.5 (on a scale of 0-10) for the non-noxious stimuli (41°C). There were no significant differences in NRS pain scores between the mid-follicular and mid-luteal groups ($p > 0.05$). Two participants reported an average of 3.0 on the NRS. For the noxious stimuli (46°C), two participants rated the pain as mild (average of 3.0), three participants reported moderate pain (average of 5.8), and five participants rated the pain as severe (average of 9.2). During the mid-luteal phase, ten participants reported mild pain during the non-noxious stimuli (average of 0.5). In contrast, for the noxious stimuli, two participants rated the pain as mild (average of 3.5), four participants reported moderate pain (average of 5.1), and four participants rated the pain as severe (average of 9.7).

For the mid-follicular group, an artefact was identified via visual inspection of the residuals. The artifact's timeseries and spatial distribution were identified using independent components analysis of the averaged mid-follicular data. The time course of the artefact was included as a further covariate of no interest in the model for the mid-follicular subjects only.

Both the mid-luteal and mid-follicular groups demonstrated activation in bilateral insula (Z = 4.62 [48, 22, 4]) and the anterior cingulate gyrus (Z = 4.86 [2, -6, 52]). Other activations of interest, including the orbitofrontal gyrus (Z = 4.21 [20, 26, -6]), posterior cingulate (Z = 4.07 [2, -22, 28]), postcentral gyrus (Z = 3.62 [22, -36, 64]), and periaqueductal grey area (Z = 4.4 [8, -26, -12]), almost reached the statistical threshold. The significant activation area for the mid-luteal group was larger than that observed in the mid-follicular phase. The mid-follicular activation comprised 203 voxels, whereas the mid-luteal activation encompassed 808 voxels.

The within-group higher-level analyses were summarised based on large brain regions. Figure 13 illustrates the median number of activated and deactivated voxels for five large brain regions in each phase. The mid-follicular group demonstrated a smaller total activation area than the mid-luteal phase in all areas except the temporal lobe. The mid-luteal group exhibited a larger activation area than the mid-follicular group, which included the superior temporal gyrus and the frontal operculum, both of which showed strong activation during the mid-luteal phase.

Figure 13. Significant Activations Differences Between Mid-Luteal and Mid-Follicular Phases



Red circles represent regions related to the reward system. Activations in the orbitofrontal gyrus (GOb), nucleus accumbens (NAc), and parahippocampus (pHi) decreased during the mid-follicular phase compared to the mid-luteal phase. Blue circles represent brain regions related to pain processing. Activations in the insula (INS), thalamus (THAL), cingulate gyrus (GC), and postcentral gyrus (GPoC) were increased in the mid-luteal phase compared to the mid-follicular phase.

2.3.4 Conclusion

In summary, the study's findings did not align with the hypothesis that females would display reduced heat pain thresholds, indicating heightened pain sensitivity during the mid-follicular phase compared to the mid-luteal phase; thus, the null hypothesis was not rejected. However, the results supported the second hypothesis, positing a significant difference in CNS network activation between the mid-follicular phase (marked by higher estrogen levels) and the mid-luteal phase. Consequently, the null hypothesis was rejected. The regions that were highly activated in mid-follicular females, compared to mid-luteal females, included the frontal operculum, orbitofrontal gyrus, nucleus accumbens, pre- and post-central gyrus, secondary somatosensory area, and the cerebellum.

The present study builds upon and extends the findings of the study conducted by de Leeuw et al. (2006), which investigated the influence of estrogen on brain activation during painful heat stimulation, focusing on the affective component of pain and observed enhanced activation during the low-estrogen phase.[255] Both studies revealed significant differences in the magnitude of activation in regions associated with attention to and anticipation of pain, such as the anterior part of the anterior cingulate, cerebellum, and precuneus. These consistent findings highlight the potential role of estrogen fluctuations in modulating pain perception and emphasise the importance of considering the menstrual cycle phases when investigating the neurobiological mechanisms underlying pain experiences in women.

2.3.5 Considerations and Limitations

There are several limitations to consider when interpreting the pilot study results. The underpowered sample size is a limitation. Research suggests sample size estimates to detect a change in the participant's response due to cyclic variation on the order of 1/2 of an SD. 33 subjects would be required to allow for power > 0.80.[247] Large samples are required as there may be individual differences in how cyclic hormonal changes impact pain perception. Pain is a personal experience influenced by many factors, including previous pain experiences, as many studies have shown that previous pain predicts future pain.[293] Additionally, we did not have information about their MPP.

Another limitation relates to changes in haematocrit due to menses. In normal menstruating females, the average blood loss is 30-60ml.[294] Previous research has shown that there are significant changes in BOLD signal based on changes in haemoglobin concentration with a higher percent signal change observed with higher haemoglobin.[110] A lower signal (as seen during the mid-follicular phase) could therefore be based on lower haemoglobin levels. However, some previous work has demonstrated a minimal change in both haematocrit and haemoglobin at these menstrual cycle phases. [295] This, haemoglobin concentration may not explain the relative increased activity in the mid-luteal phase vs. the activity in the mid-follicular phase, but more research is needed before eliminating this limitation.

Lastly, pain intensity ratings may correlate with activation in sensory circuitry and may not reflect the complexity of the brain's response to a painful stimulus. It has been suggested that an NRS change of two points on the 11-point Likert scale is considered significant for pharmacological or other analgesic interventions.[296] Given this, the current approach of reporting statistical differences in NRS in menstrual cycle differences should possibly account for a similar scale. In this pilot study, we observed no significant difference in NRS ratings between the mid-follicular and mid-luteal groups but did find significant differences in the activation of pain circuitry.

2.4 Discussion

To summarise - do normal hormonal fluctuations during the menstrual cycle affect experimental pain sensitivity? I suggest the short answer is that we don't know. While some evidence suggests that hormonal fluctuations affect experimental pain sensitivity, the available data are inconclusive. Thus, further research is needed to confirm these findings.

The current scoping review revealed that the relationship between menstrual cycle hormones and experimental pain sensitivity is unclear and may be influenced by various factors. Among these factors is the type of pain stimulus employed, location tested on the body, definition of menstrual phases, and method for confirming menstrual phases. Thus, the present findings suggest that controlling for the menstrual cycle should be essential in pain research studies until sufficient evidence suggests otherwise. By doing so, we better understand how hormonal fluctuations impact pain, we may avoid potential confounding effects of menstrual cycle hormones on experimental pain results, and we may advance our understanding of pain mechanisms. However, it is important to acknowledge that the quantity and precision of data collected varied across the studies, and the reliability of the specific measures employed differed. Based on the scoring review results, I recommend the following to improve our general understanding of the impact of hormonal fluctuations on pain perception: standardization of methods, inclusion of hormonal profiles, sample diversity, and inclusion of psychological and social factors.

Clinicians should consider menstrual phase-related pain sensitivity when developing pain management plans for female patients. This may involve adjusting medication dosages or therapies during certain menstrual phases. Explore the potential use of hormonal interventions, such as hormone replacement therapy or hormonal contraceptives, in managing pain conditions, particularly for women with chronic pain. Education and encouraging a multidisciplinary approach to pain management, involving pain specialists, gynecologists, and psychologists, will also significantly help to address both physical and psychological aspects of pain during different menstrual phases.

The pilot study showed no significant difference in NRS ratings between the mid-follicular and mid-luteal groups but did find significant differences in the activation of pain circuitry. These findings open intriguing avenues for future research and have notable clinical implications. Firstly, further investigations could delve deeper into the hormonal modulation of pain sensitivity, exploring the underlying mechanisms and intricate relationships between estrogen levels and pain perception during different menstrual phases. Longitudinal studies involving a larger and more diverse population would enhance our understanding of this relationship. Additionally, neuroimaging research could expand to pinpoint specific brain regions and networks responsible for altered pain sensitivity during various menstrual phases. Lastly, future studies should further investigate differences in pain perception throughout the menstrual cycle by using a standardised operational definition and methods for identifying menstrual cycle phases, using varied methods of assessing pain, applying the painful stimuli in multiple locations, measuring both thresholds and tolerances and including high-powered sample sizes.

On a clinical front, healthcare professionals might consider incorporating knowledge of menstrual cycle-related variations in pain sensitivity into personalised pain management plans for female patients. For conditions where pain is a significant issue, hormonal interventions targeting specific menstrual phases may be explored as part of treatment strategies. However, careful evaluation of the risks and benefits would be essential. Moreover, patient education about potential pain fluctuations

across menstrual phases and providing psychological support for those experiencing cyclic pain sensitivity could significantly enhance the overall quality of care. Ultimately, an interdisciplinary approach, involving gynaecologists, pain specialists, and neuroscientists, could lead to a more comprehensive and effective approach to managing pain in women, accounting for both hormonal and neural factors.

Limitations within this research is sample bias, as many studies primarily focus on individuals with regular menstrual cycles and may not account for those with irregular cycles or underlying medical conditions affecting hormone levels. Additionally, the influence of pregnancy on pain perception, a significant hormonal change experienced by some individuals, has not been explored in this context. Furthermore, while I have discussed the variations in pain sensitivity across menstrual phases, we haven't delved into the potential effectiveness of different pain management treatments during these phases. Future research could benefit from addressing these gaps in understanding, considering a more diverse range of participants, including those with irregular cycles, and pregnancy-related hormonal changes, and exploring the efficacy of various pain management strategies.

In summary, addressing the complexities of pain sensitivity across menstrual phases requires continued research efforts, standardised methodologies, and a holistic approach in clinical practice. It's crucial to recognise that pain perception is influenced by a combination of biological, hormonal, psychological, and genetic factors, and a comprehensive understanding of these factors will lead to more effective pain management strategies for women.

2.4.1 Connection to the Next Chapter

Most importantly for this thesis, the scoping review and pilot study results informed the recruitment strategy for the study described in Chapter 3. The recruitment strategy was to only test participants during days 2-10 of their menstrual cycle if they were not taking hormonal contraception, which would help to control for the hormonal fluctuations during the menstrual cycle. Additionally, guided

by these results, the study described in Chapter 3 included a series of questions related to their menstrual history.

Chapter 3

The Pain-Brain Connection: Insights into the Complexities of Dysmenorrhea and Endometriosis

"You are not your disease. You are not the pain. You are not the surgery. You are not the medication. You are not your diagnosis. You are not a statistic. You are a human being."

Shane Koyczan

Anti-bullying advocate and my first favorite spoken word poet.

3.0 Overview

This study, Principal Investigator Dr Christine Sieberg, employed a mixed-method cross-sectional study design to investigate the relationships between, dysmenorrhea, endometriosis-related pain, pain inhibition, functional connectivity, pain catastrophising, resiliency, and adverse childhood and recent experiences. Despite the high prevalence of dysmenorrhea and endometriosis-related pain, there is limited understanding of the connections between these factors and their impact on the brain and nervous system. The underlying hypothesis suggests that pain drives brain and nervous system alterations, while psychological and psychosocial factors amplify pain. The protocol for the study was not registered or published, but the results are planned to be submitted for publication in 2023.

My responsibilities for the current project were multifaceted. It began with assisting Dr Sieberg with the grant application, which involved a meticulous review of the funding requirements, a thorough analysis of the project scope and objectives, and a strategic plan for achieving the desired outcomes. Once the funding was awarded, I prepared and maintained all ethics applications, ensuring that all research activities complied with ethical standards at Boston Children's Hospital. All the hypotheses presented in this chapter originated from my own research and analysis.

To collect the data for the project, I worked closely with a team of dedicated Research Assistants, providing them with guidance, support, and training as needed. I also oversaw the data collection process, ensuring that all data was collected accurately and efficiently and that any issues or discrepancies were promptly resolved. Once the data was collected, I was responsible for processing and analysing it using various statistical tools and techniques. This involved cleaning and organising the data, conducting descriptive and inferential analyses, and presenting the findings in a clear and concise manner to our team and at national and international conferences.

3.1 Introduction

Chapter 1 described chronic pain as a multifaceted sensory and emotional experience involving intricate interactions between the peripheral nervous system, CNS, and cognitive processes.[8,9] Understanding the mechanisms underlying pain perception and processing is crucial for developing effective pain management strategies, especially in the context of young women experiencing dysmenorrhea and endometriosis-related pain. Despite the prevalence, there are still gaps in our understanding of these conditions, especially regarding the relationships between various factors and their impact on the brain and nervous system.

These factors together may provide valuable insights into the complexities of dysmenorrhea and endometriosis-related pain, such as improving care, personalised interventions, and better outcomes for individuals living with these conditions. These factors include pain inhibition, functional

connectivity, pain catastrophising, resiliency, and adverse childhood and recent experiences, which are interconnected and can influence each other. For example, pain catastrophising may impact pain inhibition mechanisms, which in turn affects pain perception.[161,297] By studying these factors together, we can unravel the complex interplay between them and identify potential mechanisms that contribute to the experience of pain.

Thus, based on the existing literature, it is highly plausible to hypothesise that endometriosis-related pain drives significant alterations in the brain and nervous system and that psychological and psychosocial factors amplify the pain.[187,298–300] However, the precise mechanisms, underlying reasons, and the full extent of these interactions remain largely unknown, presenting an intriguing area for further research.

This study investigated four primary objectives in individuals with endometriosis-related pain, dysmenorrhea, and no pain. First, we aimed to assess group differences in pain during menstruation, length of period, pain level on the day of the visit, and the use of hormonal oral contraception, as these factors can contribute uniquely to dysmenorrhea or endometriosis-related pain.[81,301] When compared to non-pain participants, participants with pain were expected to show different baseline pain and lower pain thresholds for moderate/severe pain.

Second, I examined psychological and psychosocial variables, including pain catastrophising, adverse childhood experiences, adverse recent experiences, and resiliency. Increased pain catastrophising was hypothesised to amplify pain perception and negative psychological outcomes for the participants with pain. Participants who have experienced adverse childhood experiences or adverse recent experiences were hypothesised to have higher pain levels, increased pain catastrophising, altered pain inhibition mechanisms, and disrupted functional connectivity. Additionally, it was hypothesised that high levels of pain catastrophising disrupt homeostasis and contribute to the brain's response to stress, trauma, and pain.[302–305] Higher levels of resiliency are associated with better psychological well-being and pain management, as resiliency may play a role in moderating the impact of pain on

psychological outcomes and coping mechanisms.

Third, pain inhibition using an OA task was compared between women with and without chronic pain. We hypothesised that endometrial lesions are not the sole driver of pain and that the pain itself may contribute to the development of attenuated pain inhibition, thus any participant with pain (dysmenorrhea or endometriosis-related pain) will show an attenuated OA response when compared to pain-free controls.

Lastly, I aimed to shed light on the role of the prefrontal and somatosensory cortices in pain response among women with and without pain. Functional connectivity of ROIs at rest and during an OA task were compared between groups with and without pain. Alterations in resting-state and OA task functional connectivity were hypothesised in the prefrontal and somatosensory brain regions for the groups with pain. The prefrontal cortex is implicated in the cognitive and emotional aspects of pain, while the somatosensory cortex plays a role in processing the sensory aspects of pain, such as its location, intensity, and quality. Increased stimulation in these regions is expected to lead to increased activity and recruitment of oxygenated blood to the ROI.[306,307] It was also hypothesised that individuals reporting higher levels of stress and trauma would exhibit altered brain function in pain-processing regions.

The participants in this study completed a battery of questionnaires and rated their pain while undergoing an fNIRS brain scan. The assessment of pain inhibition was designed to activate different brain regions involved in pain processing, which was measured by changes in functional connectivity. This approach may provide insights into the underlying neural mechanisms of pain behaviour and inhibition. Furthermore, the study explored the relationship between changes in pain sensitivity and psychological and psychosocial variables, such as pain catastrophising and adverse life experiences, which have not been extensively studied in individuals with dysmenorrhea or endometriosis-related pain. Filling this knowledge gap will offer valuable insights into the role of psychophysiological factors in developing and exacerbating these conditions. This novel approach may facilitate the

development of improved preclinical models and more effective treatment strategies, including integrating positive psychology and trauma-informed care.

3.2 Methods

Institutional Ethics Review Boards approved this study for research at Boston Children's Hospital, and all participants provided informed consent.

3.2.1 Participant Selection

Participants were recruited for two different study components: completing questionnaires alone or completing questionnaires along with OA testing and an fNIRS brain scan. The questionnaire-only condition involved a relatively short completion time of approximately 25 minutes. However, the fNIRS + OA task required a longer time commitment of approximately two hours. This extended duration necessitated a higher participant reimbursement to compensate for their time and effort. Due to budget constraints, fewer participants could complete the fNIRS + OA task, resulting in a smaller sample size for that particular component of the study.

For the participants who completed questionnaires only, the goal was to recruit and test the maximum number of participants with surgically confirmed endometriosis and age-matched controls without acute or chronic pain within two years (April 2021 to April 2023). The fNIRS + OA subgroup of the study aimed to recruit 16 participants with surgically confirmed endometriosis and 16 age-matched controls without acute or chronic pain. Research assistants and I contacted and screened potential participants. There were specific criteria for participants with endometriosis and the control group. Four inclusionary criteria were applied to all participants, centring around sex, age, menstrual cycles, and ability to provide informed consent.

First, participants needed to report being assigned female at birth, as endometriosis is a female-specific condition. As for age, participants were required to be between 18-44 years old. This age range was selected because it typically covers the reproductive years of women, during which they

may experience unique health concerns related to menstruation, pregnancy, and childbirth. Also, limiting the age range may decrease the chances of recruiting more participants to reach statistical power.

Participants completed the study visit on any day of their menstrual cycle if they were using hormonal contraceptives. For participants not using hormonal contraceptives, the study was completed between days 2 and 10 of their menstrual cycle. This was selected because the results reported in Chapter 2 suggested that participants may be most sensitive to heat pain during the follicular phase. Recruiting participants during the follicular phase allows for greater consistency in the menstrual cycle phase across the study sample. This helped minimise the potential confounding effects of hormonal fluctuations and other cycle-related factors that may vary between individuals.

Lastly, participants were required to be able to read and understand English to be able to provide written informed consent. Unfortunately, our study team did not have access to translators.

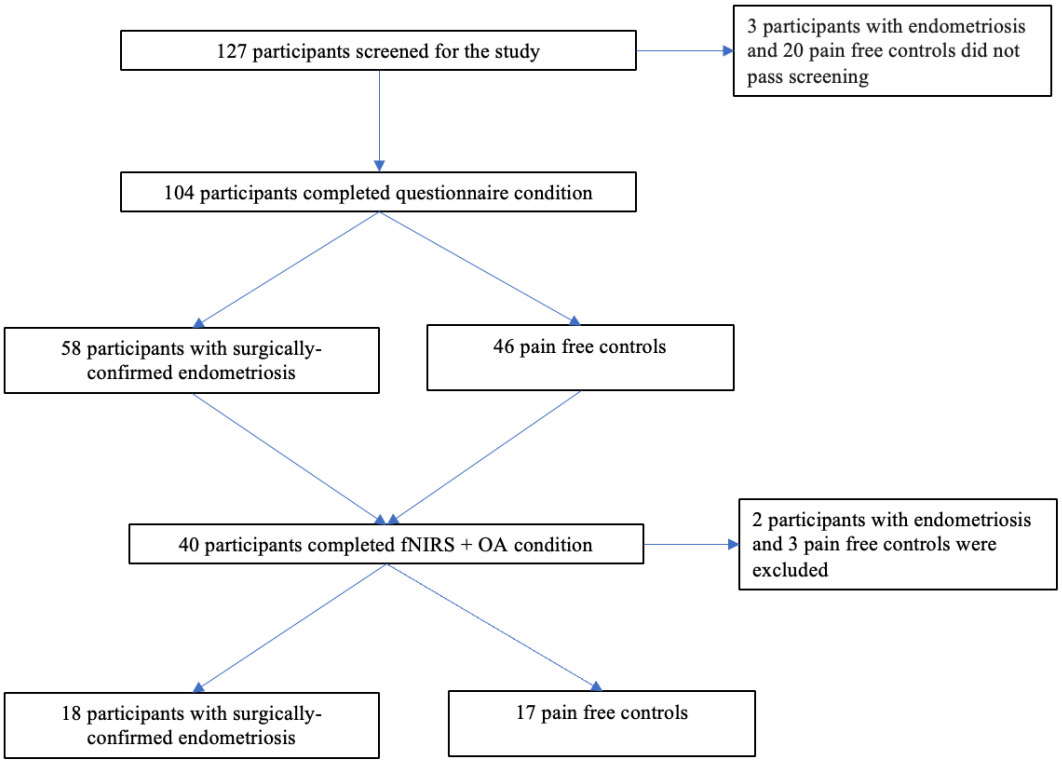
Participants with endometriosis were required to provide medical records showing they had undergone laparoscopic surgery to confirm their diagnosis of endometriosis. As the introduction mentioned, endometriosis presents various symptoms; some women are asymptomatic. To try to create a homogenous sample, all participants in the endometriosis group had their diagnosis surgically confirmed. Many participants reported multiple pain conditions, which was expected as comorbidities are often found in this patient sample.[308] To be included in this study, participants needed to report their endometriosis-related pain starting before their other pain conditions and rate their endometriosis-related pain higher than any other comorbid condition.

Participants in the control group were required to complete a health screening questionnaire via email. They were asked several questions about their health history and were excluded if they endorsed any of the following: acute pain conditions (pain less than 3 months), a history of chronic

pain (pain remaining for longer than 3 months), diagnosis of endometriosis or dysmenorrhea (severe and frequent menstrual cramps during menstruationn), use any opioid analgesics, significant medical history (*e.g.,* surgeries, concussions, migraines, traumatic brain injuries, chronic conditions, psychiatric diagnoses), and if they had ever had a hysterectomy or oophorectomy. Given the high prevalence of psychiatric diagnoses in participants with endometriosis[309] and the general community,[310] participants with a psychiatric diagnosis were included if they had a diagnosis but were not on any medications.

A total of 127 participants were screened, and 104 were deemed eligible and included in data analysis for the questionnaires only component of the study. Three with endometriosis and 20 pain free controls were excluded. For those with endometriosis, one was excluded for lack of endometriosis surgical records, one for reporting a hysterectomy, and one for reporting medications for a psychiatric condition. For those in the pain free group, three were excluded for reporting an acute pain condition, 15 for reporting a significant medical history, and four reported taking medications for psychiatric conditions. A subgroup of 40 participants completed the fNIRS + OA task, and 35 were included in the data analysis (Figure 14). These 40 participants were randomly selected from the larger group of 104 participants.

Figure 14. Flowchart of Participants Include in the Study



Two participants with endometriosis and three pain free controls were excluded from the fNIRS + OA Subgroup because of poor fNIRS signal quality. fNIRS data were excluded if we couldn't obtain reliable NIRS measures in the initial signal test. A quick signal test was performed on the participant before the actual recording session. If the signal-to-noise ratio of the fNIRS data was very low, it is difficult to extract meaningful information from the signal. This can be caused by several factors, including poor probe placement, low light intensity, or excessive movement by the participant.

For the five participants in this study, the poor signal quality is most likely due to faulty optodes producing low light intensity and the participant's dark or thick hair. During an fNIRS testing, near-infrared light is shone onto the scalp, and the resulting signal is measured by detectors placed on the head. However, if the light encounters hair, it can scatter in different directions, making it harder to measure the signal accurately.[109,311] Hair can also absorb some of the light that is being shone onto

the scalp. This can reduce the amount of light that reaches the brain and affect the fNIRS signal's accuracy. Hair can also create a gap between the scalp and the optodes (light emitters and detectors) that are used to measure the fNIRS signal.

After originally assessing the sample as two groups, surgically confirmed endometriosis vs pain free controls, we discovered there were actually several pain free participants who were not truly pain free, despite the extensive medical history screening. 46% of the Questionnaire Only Group and 65% of the pain free controls in the fNIRS + OA Subgroup of the study reported symptoms of dysmenorrhea, which was defined as a pain rating of at least 4 out of 10 during menstruation.[312] Although they had not received a formal diagnosis, we created a third group. Participants were then grouped into the following categories: no pain, dysmenorrhea, and endometriosis-related pain (Table 11).

Table 11. Group Distribution, *n*, %

Groups	**Questionnaires Only Group** (*n* = 104)	**fNIRS + OA Subgroup** (*n* = 35)
No pain	27, 26%	6, 17%
Dysm	22, 21%	11, 32%
Endo	55, 53%	18, 51%

Abbreviations. Dysm, dysmenorrhea; Endo, endometriosis; fNIRS, functional near-infrared spectroscopy; OA, offset analgesia

The no pain group included participants who reported ≤ 3 out of 10 pain during menstruation and denied experiencing any other acute or chronic pain. However, eight no pain participants reported a history of headaches. Two participants with a surgically confirmed diagnosis of endometriosis reported no pain during menstruation and did not report chronic pelvic pain, therefore, were included in the no-pain group. For the fNIRS + OA Subgroup, all participants with endometriosis reported pain.

The endometriosis-related pain group included participants who reported ≥ 4 out of 10 MPP or chronic pelvic pain AND had received a surgically confirmed diagnosis of endometriosis.

Lastly, the dysmenorrhea group included any participant without endometriosis who reported dysmenorrhea ≥ 4 out of 10 pain during menstruation. As this finding was unexpected, unfortunately, we did not ask the appropriate questions to assess their menstrual-related pain. For example, we could have asked if they sought treatment for their MPP and asked about the frequency, duration, intensity, and location of the menstrual-related pain.

The decision to split the sample in this study into either two groups or three groups presents both advantages and disadvantages. Initially, having two groups—surgically confirmed endometriosis versus pain-free controls—offers simplicity in study design and data analysis, making it easier to establish a direct association between endometriosis and the variables of interest. However, this binary categorisation oversimplifies the complex nature of pain experiences, potentially masking important variations within the "pain-free" group, as was later discovered. Creating three groups, including a "dysmenorrhea" group for individuals reporting MPP, brings increased precision and acknowledges the variability in pain experiences, providing a more nuanced understanding of how endometriosis and dysmenorrhea are related.

Nevertheless, this approach introduces complexity in data analysis and may necessitate larger sample sizes. Furthermore, it highlights the importance of collecting comprehensive data, such as the frequency, duration, intensity, and location of menstrual-related pain, to ensure the validity of findings within the newly created subgroups.

3.2.2 Procedure

Testing was completed in the Biobehavioral Pain Innovations Lab at Boston Children's Hospital in Boston, MA, USA with a minimum of three researchers present. The order of the study visit was as follows: self-report demographics and psych questionnaires, fNIRS resting state brain scan, individual test temperature of 7 out of 10 pain scores (fNIRS cap was removed), OA task training, and OA task testing.

This order of testing was deliberate. Participants completed the questionnaires before the fNIRS + OA task. Resting-state imaging is often performed before task-based brain scanning to examine the intrinsic functional connectivity of the brain in the absence of any specific task or stimulus. This can provide important baseline information about how different brain regions communicate and can help identify networks of brain regions involved in specific cognitive processes. By performing resting-state imaging first, we obtained a baseline measure of the functional connectivity of the brain before any potential changes due to a task or stimulus are introduced. Also, resting-state imaging can help identify potential sources of noise or artefacts in the data, which can be useful for quality control. By identifying and removing sources of noise or artefacts, we could improve the quality of subsequent task-based scans and increase the sensitivity of their analyses.

3.2.2.1 Demographics and Psych Questionnaires

A health screening form was used to assess the overall general health of the participant. This included questions about their basic demographics (*e.g.,* race, ethnicity, age, work status), and health history (*e.g.,* previous surgeries, comorbid conditions. To characterise menstrual cycles, participants were asked their age at menarche, their description of their menstrual cycles, the length of their cycles, and pain during menstruation. Participants were also asked to rate their pain on the day of the study visit using an NRS scale of 0 to 10. The same scale was used in the previous chapter, see Figure 12.

Next, participants completed the following self-report questionnaires measuring pain catastrophising, adverse childhood experiences, recent traumatic experiences, and resiliency.

Pain Catastrophising Scale (PCS)[313,314] was used to measure levels of pain catastrophising. The scale consists of 13 items designed to measure cognitions associated with the experience of pain (*e.g.,* "*When I am in pain, I become afraid that the pain will get worse*," "*When I am in pain, I become afraid that the pain will get worse*"). Participants were asked to indicate how likely they were to have

these thoughts when they were experiencing pain, using a 5-point scale ranging from 0 (“Not at all”) to 4 (“All the time”). Subscales were scored for rumination, magnification, and helplessness. Item responses were summed to calculate a PCS total score and each subscale score, with high scores reflecting more significant pain catastrophising or subscale levels. There are two clinical reference scores suggested for an adult sample. Low pain catastrophising was defined as scores between 0 and 29 and high was defined as scores 20 and greater.

The Childhood Traumatic Events Scale (CTES)[315] assessed six domains of stressful or traumatic events that may have occurred during the participant’s childhood (before age 17). The six domains include the death of a family member or a very close friend, parental divorce or separation, traumatic sexual experience (*e.g.,* raped, molested), victim of violence (*e.g.,* child abuse, mugged, assaulted), being extremely ill or injured, and other major upheavals. For each question, the participant is asked their age at the time of the event, their perceived intensity, and if they could confide in others. Responses were summed, with high scores indicating greater burden and confide scores.

Similarly, the Recent Traumatic Events Scale (RTES)[315] was used to assess the same domains as the CTES, however, the timeframe is within the last three years as opposed to before the age of 17. The RTES also asks about separation/divorce from a spouse or significant other instead of the CTES question about parent separation. The RTES also includes a domain related to life changes (*e.g.,* moving houses). Again, for each question, the participant is asked their age at the time of the experience, their perceived intensity, and if they could confide in others. Responses were summed, with high scores indicating greater burden and confide scores.

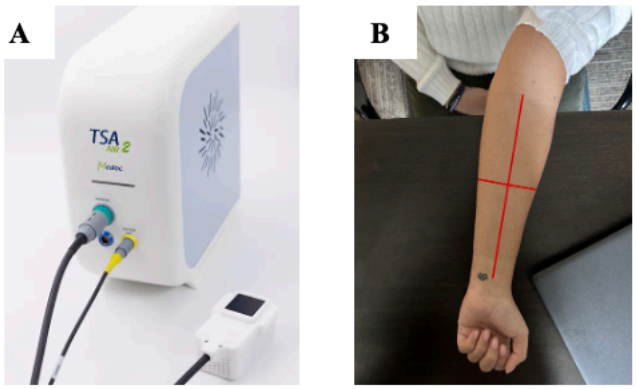
Connor-Davidson Resilience Scale 10 (CD-RISC-10)[316,317] was used to measure the participant’s resilience. Each item is scored on a 5-point Likert scale ranging from 0 (not true at all) to 4 (true nearly all the time), with higher scores indicating greater resilience. Example items include "*I can*

adapt when changes occur" and "*I can deal with whatever comes my way*." Responses were summed, with high scores indicating greater resilience (range is 0 to 40).

3.2.2.2 Pain Inhibition- OA

OA was defined and described in Chapter 1. We collaborated with pain inhibition and OA method experts, Dr Martucci, Dr Coghill and Dr Borsook, to create an OA paradigm to fit this study design and population of interest.[129,133,134,318–323] A TSA Neuroanalyzer 2 was used to administer the temperature. The entire thermode surface (30x30mm) was placed in contact with the skin on the surface of the non-dominant forearm and secured by a researcher (Figure 15). The baseline temperature was 32° C, and the maximum allowed temperature was 48° C. Simultaneously, participants continuously rated their pain using an NRS scale of 0 to 10. To capture their pain rating, the computer screen was recorded.

Figure 15. TSA Neuroanalyzer 2 was Used to Test OA Responses on the Surface of the Non-dominant Forearm.*



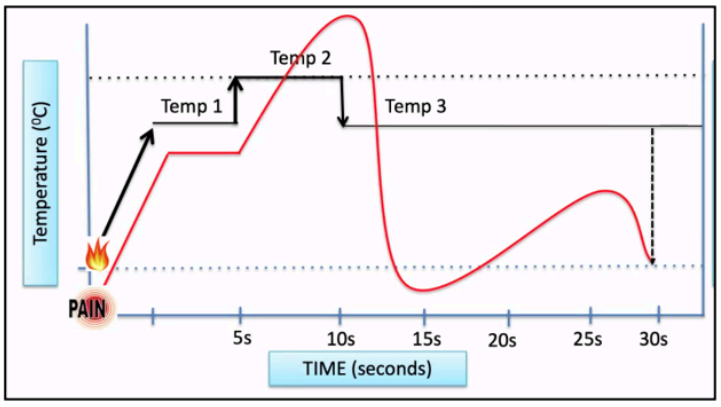
*The forearm was divided into four quadrants to ensure each OA trail was not tested on activated nerve fibres.

Once the temperature needed to elicit a pain response of 7 out of 10 on the NRS was identified for the participant, they would complete an OA Training at the corresponding temperature. This was needed to train participants on how to rate short, painful stimuli with a virtual pain scale, as it is important before having them rate the more complex/longer OA stimulus paradigms. It was expected that most

people would have a bit of a learning curve when learning how to rate their pain continuously. We used 32 stimuli for training – each 5 seconds duration – ranging from 35° C to 48° C for training using the continuous NRS to rate "real-time" pain. This was completed directly before the participant completed the OA task.

OA is typically measured using a paradigm that involves a brief and intense noxious stimulus followed by a less intense ongoing stimulus. This is called an offset block. First, the participant rates their initial pain intensity or unpleasantness. This is shown as Temp 1 in Figure 16. Next, a brief increase of 1°C is applied to the same area of the participant's body (for this study, the non-dominant forearm). This is shown as Temp 2 in Figure 16. Immediately after the intense stimulus, the temperature returns to Temp 1. This is shown as Temp 3 in Figure 16. The red line shown in Figure 16 represents the participant's continuous pain intensity or unpleasantness rates throughout the test duration. Variations of the OA paradigm exist, and specific details of the measurement procedure vary across studies.

Figure 16. Offset Block Used within OA Paradigm



We used a 3-temperature OA paradigm with three blocks: offset, constant, and control. These three blocks were randomised in presentation order to create four blocks (Table 12). Conditions E and F are highlighted in red because they were excluded from the presentation rotation. If the control block was

presented first, it could create expectations that the temperature would drop dramatically after it increases, leading to unwanted adaption effects.

Table 12. OA Block Randomisation in Presentation Order to Create Four Blocks

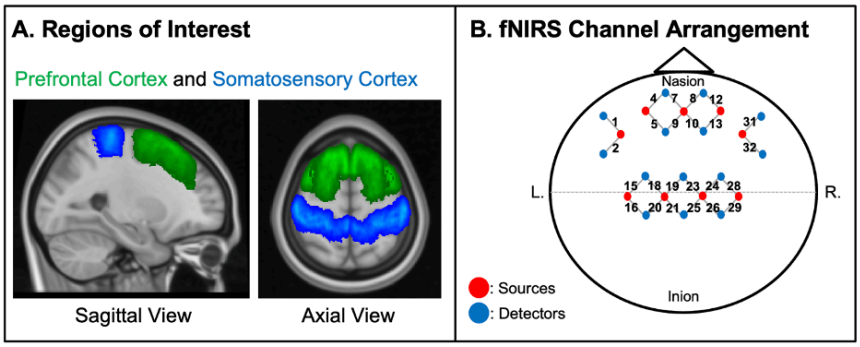
Condition	First block	Second block	Third block
A	Offset	Control	Constant
B	Offset	Constant	Control
C	Constant	Control	Offset
D	Constant	Offset	Control
E	Control	Offset	Constant
F	Control	Constant	Offset

3.2.2.3 fNIRS Data Acquisition

fNIRS was defined and described in Chapter 1. For this study, fNIRS was selected as the neuroimaging method for several reasons. It was readily available at our institution, making scheduling convenient even during the COVID-19 pandemic when the radiology department was closed for research studies. Secondly, fNIRS is a non-invasive and relatively affordable technique that is well-suited for studying cortical activity during the OA task. Finally, given the budget constraints, we could not conduct more expensive scans like MRI, supporting the decision to use fNIRS.

A TechEn CW 7 fNIRS system was used to collect fNIRS brain scans, which included nine sources (emitting at 690 and 830 nm), 23 detectors, and 33 channels. The sources and detectors are coupled to fibre optics, with each emitting fibre and detector constituting one optode; the optodes are 1-3mm in diameter, allowing them to be easily inserted through the hair to make optical contact with the scalp. The light passes through the participant's scalp onto the brain surface and returns, with some attenuation, to the detector optodes. The returning light yields concentrations of blood oxygenation levels, which are used in the analysis. (Figure 17).

Figure 17. Regions of Interest and fNIRS Channel Arrangement

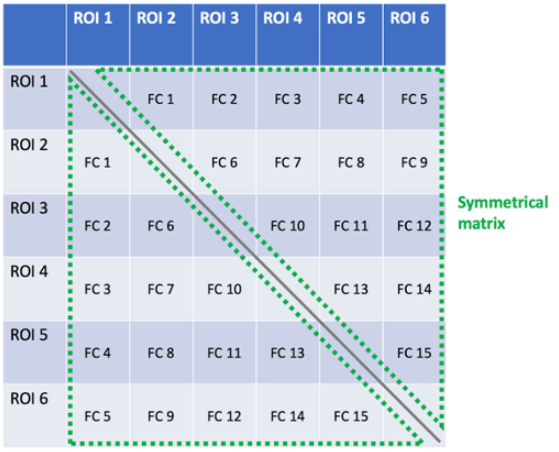


A. Regions of interest including bilateral prefrontal (green) and somatosensory cortices (blue).
B. fNIRS channel arrangement (L: left; R: right; Lateral prefrontal cortices: channels 1, 2, 31, 32; Medial prefrontal cortices: channels 4, 5, 7, 8, 9, 10, 12, 13; Somatosensory cortices: channels 15, 16, 18, 19, 20, 21, 23, 24, 25, 26, 28, 29).

3.2.2.4 Determining ROIs for this Study

The somatosensory cortex plays a key role in processing sensory information related to touch, temperature, and pain.[324] Specifically, the lateral somatosensory cortex is responsible for processing pain information originating from the body's periphery, while the medial somatosensory cortex is involved in processing information related to the location and intensity of painful stimuli. Both the lateral and medial prefrontal cortices work in conjunction with other brain regions to integrate and coordinate cognitive and emotional information, facilitating adaptive behaviour and decision-making in various contexts. Their interactions with other regions, including the somatosensory cortex, are essential for processing pain and integrating it into cognitive and emotional frameworks. Therefore, for the purpose of fNIRS measurements, we focused on the prefrontal and somatosensory brain regions known to be involved in pain processing and inhibition. These regions were further divided into six regions of interest (ROIs) as follows: ROI 1: Left lateral prefrontal cortex, ROI 2: Left medial prefrontal cortex, ROI 3: Right medial prefrontal cortex, ROI 4: Right lateral prefrontal cortex, ROI 5: Left lateral somatosensory cortex, and ROI 6: Right lateral somatosensory cortex. Figure 18 provides a visual representation of the locations of these ROIs and their corresponding functional connectivity.

Figure 18. Functional Connectivity Locations by ROIs



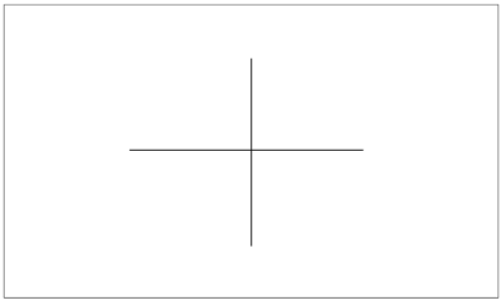
Abbreviations. ROI, region of interest; FC, functional connectivity

In summary, these ROIs were selected because the prefrontal cortex has been shown to play a crucial role in pain's cognitive and emotional aspects, including the perception of pain intensity, the modulation of pain, and the experience of negative affective states associated with pain.[306,307] The medial prefrontal cortex, in particular, is known to be involved in affective and evaluative aspects of pain processing, such as pain anticipation, appraisal, and emotion regulation.[306,307] The lateral prefrontal cortex is involved in executive functions such as attention, working memory, and decision-making, which are also known to be involved in pain perception and modulation.[325]

3.2.2.4 Resting state – fNIRS

After completing the questionnaires, the participant was seated comfortably in a chair with the fNIRS cap placed on their head, facing a computer screen showing a fixation cross (Figure 19). The participants were instructed to sit in the chair for 10 minutes to measure their baseline brain activity. They were informed that a cross would appear on the computer screen and to try to focus on this cross. If their mind started to wander or focus on one specific thought, they were instructed to bring their attention back to the cross. They were asked not to move, fall asleep, or talk.

Figure 19. Fixation Cross Shown to All Participants During the Resting State Brain Scan



3.2.2.5 OA – fNIRS

Once the questionnaires, 10-minute resting state, 7 out of 10 test temperatures, and OA training have been completed, the last component of the study visit was to complete the OA task (Figure 20). This included four trials (A-D), each with three blocks.

Figure 20. Study Setup for fNIRS + OA Task



3.2.3 Statistical Analyses

An a priori power analysis was conducted using G*Power version 3.1. Statistical analyses were performed using SPSS software ver. 28.0 (IBM, Armonk, NY, USA). fNIRS data pre-processing was completed using the toolbox HOMER2 24 implemented in Matlab (Mathworks, MA, USA).

Statistical power is a critical factor to consider when deciding whether to categorize participants into two or three groups. In the case of two groups, where surgically confirmed endometriosis with pain-free controls were compared, statistical power have higher statistical power and enhances the ability to identify true effects, if they exist. On the other hand, when opting for three groups, which include endometriosis, dysmenorrhea, and no-pain categories, I am decreasing the statistical power and thus will include multiple statistical comparisons, which could increase the risk of Type I errors.

Although there were overall aims and specific hypotheses, most of the analyses were exploratory. Therefore, I will refrain from making strong conclusions from the results. Additionally, *p*-value corrections will not be included. Instead, the best outcome and models will be used to suggest a second experiment to replicate the findings.

3.2.3.1 Data Distribution and Outliers

Before proceeding with statistical analyses used in this chapter (Analysis of Variance [ANOVA], one-way ANOVA, unpaired two-sample t-tests, and Pearson's correlation analyses) the normality of data distribution was tested using the Shapiro-Wilk test. None of the data analysed within this chapter deviated significantly from normality ($p > 0.05$).

All assumptions were thoroughly assessed for the moderation models, including Mahalanobis, Cook's and Leverage tests. Including an interaction term in the models introduced the issue of multicollinearity, which occurs when independent variables in a model are correlated. Perfect collinearity is observed when the correlation coefficient between two variables is +/- 1.0. Although the correlation coefficient between the independent variables (*e.g.,* CTES and MPP) was found to be 0.38, indicating a moderate correlation, it did not pose a significant concern.

One participant with endometriosis exhibited outlier characteristics, displaying high pain and adverse childhood and recent experience scores. Despite this outlier observation, the participant was kept in the analysis considering the limitations in statistical power and sample size. Regarding the number of bootstraps, we opted for 1000 iterations. Heteroskedasticity-consistent standard errors were employed to accommodate the presence of heteroskedastic residuals, allowing for a model-fitting process that addresses this heterogeneity.

3.2.3.2 Demographics and Psych Questionnaires

Descriptive statistics were used to summarise the characteristics of the sample, broken down by group. Descriptive statistics and inferential statistics were used to analyse the self-report questionnaires Means and SDs were calculated for each questionnaire for each of the three groups. The frequencies and percentages of the clinical cut-offs were calculated for the PCS scale.

One-way ANOVAs assessed differences between participants with endometriosis, no pain, and dysmenorrhea on their PCS, CTES, RTES, and CD-RISC questionnaires. For PCS, group differences for the three subscales (magnification, rumination, and helplessness) were assessed.

3.2.3.3 Pain Inhibition – OA

The magnitude of OA is typically expressed as a percentage or numerical difference. It represents the degree to which the ongoing stimulus produces a larger-than-expected reduction in pain perception following the intense stimulus. There are four ways to calculate the OA responses, including the difference in pain ratings (subtract the pain rating after Temp 3 from the pain at Temp 1), ratio of pain ratings (divide the pain rating at Temp 1 by the pain rating at Temp 3), absolute change in pain (subtract the pain rating after Temp 2 from the Temp 1 pain rating) and percentage change in pain ratings (divide the difference in pain ratings by the pain rating before the Temp 2, and then multiply by 100).

Studies may use different methods to calculate OA responses depending on the specific research question and the available data. We chose the fourth method to calculate the OA response (Equation 2).

Equation 2. OA Percentage Change in Pain Ratings:

$$\Delta OA = [(\text{Max VAS Temp 2} - \text{Min VAS Temp 3}) \div \text{Max VAS Temp 2}] \times 100$$

The fourth method to calculate the OA response was chosen because it provides a percentage change in pain ratings. This can be a useful metric for comparing and interpreting the magnitude of OA across different individuals or experimental conditions. By dividing the difference in pain ratings by the pain rating before Temp 2 and multiplying it by 100, the resulting value represents the percentage change in pain perception from the pre-stimulus baseline (Temp 1). This percentage change allows for a standardised and easily interpretable measure of the extent of OA. Using a percentage change can be particularly beneficial when comparing OA responses across individuals with different baseline pain levels (Temp 1). It provides a relative measure of the magnitude of pain reduction, accounting for individual differences in pain sensitivity or perception. Thus, this method was chosen to facilitate a clearer understanding and comparison of OA responses within the research context.

To assess for differences across OA trials (A vs B vs C vs D), an ANOVA with repeated measures for the three groups (no pain, dysmenorrhea, and endometriosis) were assessed. As there were no differences between trials, the median of the four scores was calculated, which was used for all other analyses. Next, one-way ANOVA was used to compare the median OA scores for the three groups.

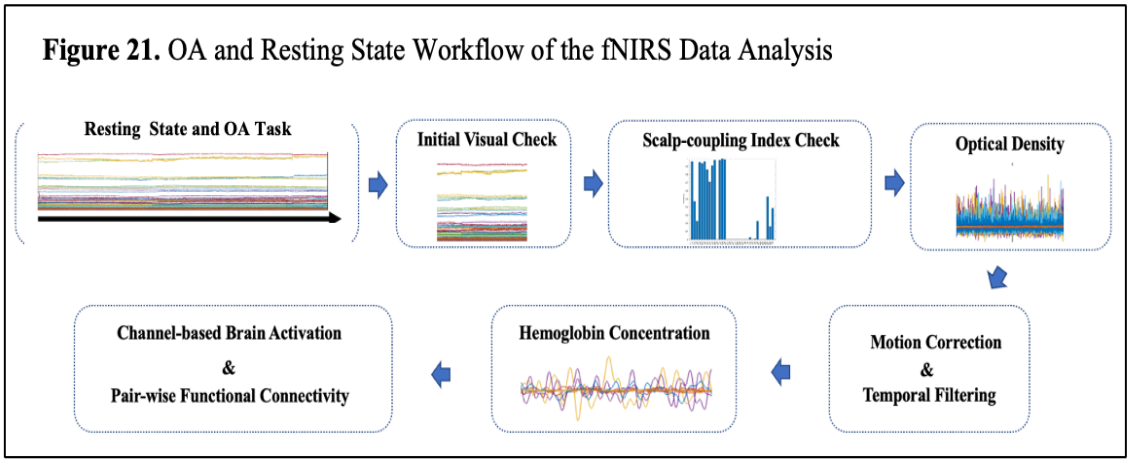
3.2.3.4 fNIRS during Resting and OA

Raw optical signals were first converted into optical density changes. Motion artefacts were identified using the automatic detection function in HOMER2. When needed, a targeted principal component analysis was performed to correct the motion artefacts in the signal. The optical density changes

underwent a third-order Butterworth low-pass filter with a cut-off frequency of 0.5Hz to remove the high-frequency noises (*e.g.* heartbeats).

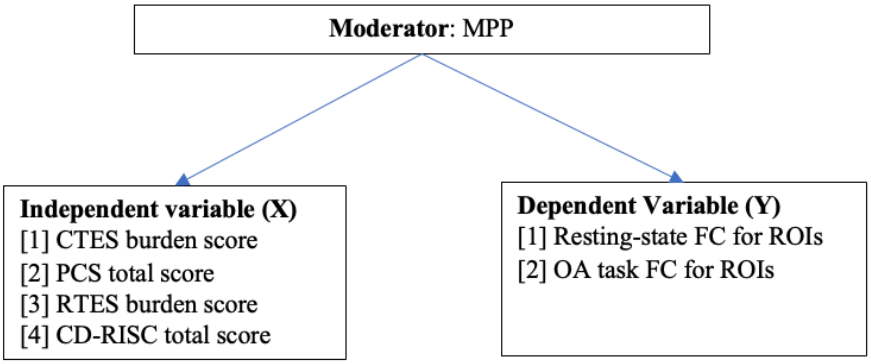
Next, the filtered optical density time courses were transformed into HbO and HbR concentration changes using the MBLL (Equation 1). The concentration changes in total haemoglobin (HbT) were be obtained by a direct sum of the HbO and HbR changes (HbT = HbO + HbR). For each of the normal fNIRS channels, removed the extracerebral contaminations from the signal with an ordinary least-square approach by including the time course of a short distance channel with the highest correlation with that of the normal channel as a regressor. A polynomial regressor was added in the model to remove the signal drifts. The physiological noise and drift-corrected HbO, HbR and HbT concentration change time courses were reconstructed simultaneously from the least-square estimation.

An analysis of the power spectral density was performed using a sliding window approach with the window size ranging from 50s to 200s. The power spectral density of each sub-band will be averaged first across frequencies within the band and then across all fNIRS channels (excluding short separations). Repeating this procedure at each second will produce fractional power spectral density (power spectral density of a sub-band divided by the sum of the power spectral density of the five sub-bands) time course that depict the power change of each sub-band during the recording session. The recorded haemoglobin was converted to concentration change time courses to the frequency domain using a Fast Fourier Transform to perform frequency analysis. The fNIRS data analysis workflow is summarised in Figure 21.



Group comparisons of regional cortical activation magnitude and pair-wise FC between ROIs were conducted using one-way ANOVAs. Moderation models were used to examine the relationship between the psychological variables and brain activity for each of the 15 functional connectivity locations, specifically when experiencing higher levels of MPP (Figure 22). While a mediation model could have been used to explore this relationship, it would primarily assess whether the psychological variables are associated with brain activity, potentially attributing it to pain during menstruation. While we acknowledge the existing relationship between the psychological variables, it remains unclear how this relationship manifests when MPP varies between low and high levels. To categorise the pain levels as low, medium, and high, we designated the MPP as the moderator (M) to observe the corresponding slopes within each group.

Figure 22. Moderation Models to Examine The Relationship Between The Psychological Variables and Brain Activity for Each of the 15 Functional Connectivity Locations



Abbreviations. MPP, menstrual phase pain; CTES, childhood traumatic events scale; PCS, pain catastrophising scale; RTES, recent traumatic events scale; CD-RISC, connor-davidson resilience scale; FC, functional connectivity; ROIs regions of interest

The PROCESS v4.2 logistic regression path analysis tool developed by Dr Andrew Hayes[326] was used to conduct the moderation analysis. This modified SPSS code facilitates regression analyses incorporating various combinations of mediators, moderators, and covariates. Additionally, the Johnson-Neyman technique[327] within the toolbox was employed, which is a robust alternative to ANCOVA when the assumption of homogeneity of regression slopes is violated. By using this technique, we obtained supplementary insights into the region of insignificance and its associated impact.

3.3 Results

3.3.1 All Participants Who Completed Questionnaires, Including the fNIRS + OA Subgroup

3.3.1.1 Demographics and Psych Questionnaires

Table 13 displays the demographics and Table 14 displays the health history of all participants (n = 104) who completed the questionnaires. A comparison of the age of the three groups did not yield any

significant differences, as indicated by an ANOVA analysis ($F(2, 101) = 2.42$, $p = 0.09$). This is important as I want to ensure I am comparing individuals at similar developmental brain stages.

For the days during the menstrual phase, a one-way ANOVA revealed there was a significant group difference detected ($F(2, 79) = 6.88$, $p = 0.002$). Tukey's HSD Test for multiple comparisons found that the mean length of the menstrual phase was significantly different between the no pain and the endometriosis groups ($p = 0.003$, 95% C.I. = [-2.98, -0.52]), as well as the endometriosis-related pain and dysmenorrhea group ($p = 0.03$, 95% C.I. = [.93, 2.71]), with the endometriosis participants showing longer menstrual phases (4.7 vs 6.4 days). However, no significant difference existed between the no pain and dysmenorrhea groups ($p = 0.83$, 95% C.I. = [-1.81, 1.10]).

The use of hormonal contraception did not differ significantly between the groups, as indicated by a chi-square test ($X2(2) = 0.552$, $p = 0.76$).

Table 13. Demographics for All Participants Who Completed Questionnaires, Including the fNIRS + OA Subgroup, Mean (SD) or *n*, %

		No Pain (*n* = 27)	**Endo** (*n* = 55)	**Dysm** (*n* = 22)	**Total** (*n* = 104)
Age min - max		25.7 (5.5) 18 - 41	28.3 (7.5) 18 - 42	25.1 (6.3) 18 - 42	27.0 (6.8) 18 - 42
Race	White	20, 74%	47, 86%	11, 50%	78, 75%
	Asian	4, 15%	3, 5%	7, 32%	14, 13%
	Black	1, 4%	2, 4%	1, 4%	4, 4%
	Other/mixed	2, 7%	3, 5%	3, 14%	8, 8%
Ethnicity	Hispanic	3, 11%	3, 6%	5, 23%	11, 11%
	Non-Hispanic	24, 89%	52, 95%	17, 77%	93, 89%
Education	High School	4, 15%	7, 13%	2, 9%	13, 13%
	College	18, 67%	36, 66%	15, 68%	69, 66%
	Graduate School	4, 15%	9, 16%	3, 14%	16, 15%
	Did Not Report	1, 3%	3, 5%	2, 9%	6, 6%
Work Status	Full-time Student	6, 22%	15, 27%	`9, 40%	30, 29%
	Employed	20, 74%	36, 66%	13, 60%	69, 66%
	Unemployed	1, 4%	2, 4%	-	3, 3%
	Did Not Report	-	2, 4%	-	2, 2%

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dysm, dysmenorrhea.

Table 14 Health data for All Participants Who Completed Questionnaires, Including the fNIRS + OA Subgroup, Mean (SD) or *n*, %

		No Pain (*n* = 27)	**Endo** (*n* = 55)	**Dysm** (*n* = 22)	**Total** (*n* = 104)
Menstrual cycle description	Regular periods	17, 62%	16, 29%	17, 77%	50, 48%
	Irregular periods	4, 15%	14, 25%	3, 14%	21, 20%
	Surgery stopped periods	1, 4%	1, 2%	-	1, 1%
	Medication stopped periods	4, 15%	23, 42%	-	29, 28%
	Other	1, 4%	1, 2%	2, 9%	3, 3%
Menstrual cycle pain	Dysmenorrhea				
	Yes	-	30, 54%	20, 91%	50, 48%
	No	22, 82%	1, 2%	-	24, 23%
	Do not menstruate	5, 18%	24, 44%	2, 9%	30, 29%
	Age period started	12.5 (1.5)	11.9 (1.3)	12.5 (2.2)	12.3 (1.8)
	Age ranges if unsure	*n* = 14	*n* = 22	*n = 7*	*n* = 43
	10-12 years	9, 33%	14, 64%	2, 29%	25, 58%
	13-15 years	4, 15%	8, 36%	4, 57%	16, 37%
	16 years+	1, 4%	-	1, 14%	2, 5%
	Days during period	4.7 (1.0)	6.4 (2.6)	5.1 (0.9)	5.6 (2.1)
	MPP	1.7 (1.1)	6.9 (2.5)	4.7 (1.7)	5.2 (3.0)
	Min, max (scale of 0-10)	0 - 3	0 - 10	0 – 8	0 - 10
Hormonal contraception	Yes	19, 70%	39, 72%	14, 64%	72, 69%
	No	8, 30%	15, 28%	8, 36%	31, 30%
Comorbidities					
	Fibromyalgia	-	2, 4%	-	2, 2%
	IBS	3, 11%	18, 33%	1, 5%	22, 21%
	PCOS	2, 7%	2, 4%	1, 5%	4, 4%
	Autism	-	1, 2%	-	1, 1%
	Headaches	8, 30%	37, 67%	6, 32%	51, 52%
	Anxiety	5, 19%	31, 56%	8, 36%	44, 42%
	Depression	3, 11%	19, 35%	5, 23%	27, 26%
	PTSD	-	5, 9%	1, 5%	6, 6%
	Personality/mood disorder	1, 4%	5, 9%	1, 5%	7, 7%
	ADHD	2, 3%	1, 2%	-	2, 2%
	Eating disorder	1, 4%	1, 2%	-	2, 2%

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dysm, dysmenorrhea; IBS, irritable bowl syndrome; PCOS, polycystic ovary syndrome; OCD, obsessive compulsive disorder; ADHD, attention deficit hyperactivity disorder; MPP, menstrual phase pain

Table 15 presents the results for psych-related questionnaires CTES, RTES, CD-RISC, and PCS.

Table 15. Questionnaire for All Participants Who Completed Questionnaires (fNIRS + OA Subgroup Included)

		No Pain (*n* = 27)	**Endo** (*n* = 55)	**Dysm** (*n* = 22)	**Total** (*n* = 104)
PCS	High	1, 4%	9, 17%	1, 5%	11, 11%
	Low	26, 96%	45, 83%	21, 95%	92, 89%
	Total Score [mean (SD)]	7.7 (9.0)	18.3 (11.3)	6.8 (8.3)	13.1 (11.5)
	Helplessness	2.4 (3.5)	7.8 (5.6)	2.2 (3.6)	5.5 (5.5)
	Rumination	3.6 (4.2)	6.0 (4.1)	3.5 (4.1)	4.8 (4.3)
	Magnification	1.7 (2.1)	4.4 (2.9)	3.1 (3.0)	3.0 (2.9)
CTES	Experienced an ACE				
	Yes	15, 56%	46, 84%	14, 64%	75, 72%
	No	12, 44%	9, 16%	8, 36%	29, 28%
	Quantity of ACEs				
	Avg ACE	0.7 (0.8)	1.6 (1.1)	0.9 (0.8)	1.2 (1.1)
	No ACE	12, 44%	9, 16%	8, 36%	29, 28%
	One ACE	11, 41%	21, 38%	10, 46%	42, 40%
	Two ACEs	3, 11%	14, 26%	3, 14%	20, 19%
	Three ACE	1, 4%	7, 13%	1, 5%	9, 9%
	Four ACEs	-	4, 7%	-	4, 4%
	Burden Score (mean [SD])	2.7 (3.5)	8.1 (6.8)	3.4 (4.6)	5.7 (6.2)
	Confide Score (mean [SD])	2.3 (3.3)	4.4 (5.1)	3.5 (4.9)	3.7 (4.7)
		No Pain (*n* = 27)	**Endo** (*n* = 55)	**Dysm** (*n* = 21)	**Total** (*n* = 103)
RTES	Experienced ARE				
	Yes	23, 85%	43, 78%	11, 52%	77, 75%
	No	4, 15%	12, 22%	10, 48%	26, 25%
	Quantity of AREs				
	Avg ARE	1.3 (0.8)	1.8 (1.3)	0.9 (1.0)	1.5 (1.2)
	No ARE	4, 15%	12, 22%	10, 48%	26, 75%
	One ARE	14, 52%	10, 18%	6, 29%	30, 29%
	Two AREs	7, 26%	5, 27%	3, 14%	25, 24%
	Three AREs	2, 7%	14, 26%	2, 9%	18, 17%
	Four AREs	-	4, 7%	-	4, 4%
	Burden Score (mean [SD])	3.9 (3.1)	9.7 (6.2)	6.8 (6.0)	7.6 (6.0)
	Confide Score (mean [SD])	5.6 (5.5)	9.6 (5.2)	7.0 (5.8)	8.0 (1.2)
		No Pain (*n* = 21)	**Endo** (*n* = 51)	**Dysm** (*n* = 19)	**Total** (*n* = 91)
CD- RISC	Low	8, 30%	29, 57%	13, 68%	50, 55%
	Moderate	8, 30%	13, 26%	2, 9%	23, 25%
	High	5, 19%	9, 18%	4, 21%	18, 17%
	Total Score [mean (SD)]	29.9 (4.4)	26.8 (6.2)	27.7 (4.9)	27.7 (5.7)

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dsym, dysmenorrhea; CTES, childhood traumatic events scale; ACEs, adverse childhood experiences; RTES, recent traumatic events scale; AREs, adverse recent experiences; CD-RISC, connor-davidson resilience scale; PCS, pain catastrophising scale

Table 16 presents the results of the one-way ANOVAS for psych-related questionnaires CTES, RTES, CD-RISC, and PCS.

Table 16. One-Way ANOVA Results

Measure	Groups Compared	F-Value	P-Value	Tukey's HSD Results	Mean Comparison	Effect Direction
PCS Total Score	No Pain vs Endo vs Dysm	14.9	< 0.001			
	No pain vs Endo			p < 0.001, 95% C.I. = -16.25, -4.83	7.7 vs 18.3	Endo
	Endo vs Dysm			p < 0.001, 95% C.I. = 5.33, 17.59	18.3 vs 6.8	Endo
	No Pain vs Dysm			p = 0.95, 95% C.I. = -6.04, 7.88	7.7 vs 6.8	No differences
Helplessness - PCS Subscale	No Pain vs Endo vs Dysm	17.3	< 0.001			
	No pain vs Endo			p < 0.001, 95% C.I. = -16.25, -4.83	2.4 vs 7.8	Endo
	Endo vs Dysm			p < 0.001, 95% C.I. = 2.81, 8.56	7.8 vs 2.2	Endo
	No Pain vs Dysm			p < 0.98, 95% C.I. = -8.11, -2.75	2.4 vs 2.2	No differences
Rumination - PCS Subscale	No Pain vs Endo vs Dysm	4.4	0.02			
	No pain vs Endo			p = 0.05, 95% C.I. = -4.65, -0.02	3.6 vs 6.0	Endo
	Endo vs Dysm			p = 0.05, 95% C.I. = 0.23, 4.99	6.0 vs 3.5	Endo
	No Pain vs Dysm			p = 0.99, 95% C.I. = -2.65, 2.99	3.6 vs 3.5	No differences
Magnification - PCS Subscale	No Pain vs Endo vs Dysm	18.3	< 0.001			
	No pain vs Endo			p < 0.001, 95% C.I. = -4.19, -1.36	1.7 vs 4.4	Endo
	Endo vs Dysm			p < 0.001, 95% C.I. = 1.74, 4.78	4.4 vs 3.1	Endo
	No Pain vs Dysm			p < 0.78, 95% C.I. = -1.24, 2.21	1.7 vs 3.1	No differences
Quantites of ACEs	No Pain vs Endo vs Dysm	7.7	0.001			
	No pain vs Endo			p = 0.002, 95% C.I. = -1.38, -0.26	0.7 vs 1.6	Endo
	Endo vs Dysm			p = 0.02, 95% C.I. = 0.10, 1.30	1.6 vs 0.9	Endo
	No Pain vs Dysm			p = 0.90, 95% C.I. = -0.81, 0.56	0.7 vs 0.9	No differences
CTES Burden Score	No Pain vs Endo vs Dysm	10.4	< 0.001			
	No pain vs Endo			p = 0.12, 95% C.I. = -1.14, 0.10	2.7 vs 8.1	Endo
	Endo vs Dysm			p = 0.004, 95% C.I. = 1.29, 8.13	8.1 vs 3.4	Endo
	No Pain vs Dysm			p = 0.91, 95% C.I. = -4.55, 3.23	2.7 vs 3.4	No differences
CTES Confide Score	No Pain vs Endo vs Dysm	1.9	0.15			
Quantities of AREs	No Pain vs Endo vs Dysm	5.8	0.004			
	No pain vs Endo			p < 0.001, 95% C.I. = -8.15, -4.85	1.3 vs 1.8	Endo
	Endo vs Dysm			p = 0.004, 95% C.I. = 0.25, 1.61	1.8 vs 0.9	Endo
	No Pain vs Dysm			(p = 0.43, 95% C.I. = -0.37, 1.17	1.3 vs 0.9	No differences

RTES Burden Score	No Pain vs Endo vs Dysm	5.1	0.009			
	No pain vs Endo			p = 0.008, 95% C.I. = -7.22, -0.90	3.9 vs 9.7	Endo scores
	Endo vs Dysm			p = 0.29, 95% C.I. = -1.52, 6.76	9.7 vs 6.8	No differences
	No Pain vs Dysm			p = 0.73, 95% C.I. = -5.92, 3.05	3.9 vs 6.8	No differences
RTES Confide Score	No Pain vs Endo vs Dysm	8.6	< 0.001			
	No pain vs Endo			p < 0.001, 95% C.I. = -9.18, -2.44	5.6 vs 9.7	Endo
	Endo vs Dysm			p = 0.26, 95% C.I. = -1.50, 7.31	9.7 vs 6.8	No differences
	No Pain vs Dysm			p = 0.32, 95% C.I. = -7.68, 1.87	5.6 vs 6.8	No differences
Resiliency	No Pain vs Endo vs Dysm	2.2	0.12			

Abbreviations. Endo, endometriosis-related pain; Dsym, dysmenorrhea; CTES, childhood traumatic events scale; ACEs, adverse childhood experiences; RTES, recent traumatic events scale; AREs, adverse recent experiences; CD-RISC, connor-davidson resilience scale; PCS, pain catastrophising scale

3.3.2 fNIRS + OA Subgroup Only

3.3.2.1 Demographics and Psych Questionnaires

Table 17 shows the demographics and Table 18 shows the health history for the subgroup of participants (*n* =35) who completed the fNIRS + OA tasks. Similarly to the larger sample of questionnaire only participants, a comparison of the age of the three groups did not yield any significant differences, as indicated by an ANOVA analysis ($F(2, 32) = 2.27$, $p = 0.12$).

For the length of the menstrual phase (days), a one-way ANOVA revealed there were no significant group differences detected ($F(2, 23) = 0.52$, $p = 0.60$).

The pain threshold of 7 out of 10 pain on the NRS (used for the OA testing) for all groups were similar, with 44.4º C for the endometriosis group and 44.9º C for no pain group and 44.7º C for the dysmenorrhea group (Figure 23). A comparison of 7 out of 10º C of the three groups did not yield any significant differences, as indicated by an ANOVA analysis ($F(2, 32) = 0.12$, $p = 0.88$). Also, a comparison of pain rating on day of the study visit between the three groups did not yield any significant differences, as indicated by an ANOVA analysis ($F(2, 32) = 1.73$, $p = 0.19$).

Table 17. Demographics for the fNIRS + OA Subgroup, Mean (SD) or *n*, %

		No Pain (*n* = 6)	**Endo** (*n* = 18)	**Dysm** (*n* = 11)	**Total** (*n* = 35)
Age					
min-max		23.5 (5.0) 19 - 33	26.5 (6.2) 18 - 38	22.5 (2.8) 18 – 28	24.7 (5.4) 18 - 38
Handedness	Right	6, 100%	12, 67%	9, 81%	27, 77%
	Left	-	6, 33%	2, 18%	8, 23%
Race					
	White	3, 50%	16, 87%	8, 73%	27, 77%
	Asian	2, 33%	1, 6%	2, 18%	5, 14%
	Black	1, 17%	-	1, 9%	2, 6%
	Other/mixed	-	1, 6%	-	1, 3%
Ethnicity					
	Hispanic	-	-	1, 9%	1, 3%
	Non-Hispanic	6, 100%	18, 100%	10, 91%	34, 97%
Education					
	High School	-	4, 22%	2, 18%	6, 17%
	College	5, 83%	9, 50%	6, 55%	20, 57%
	Graduate School	-	5, 28%	1, 9%	6, 17%
	Did Not Report	1, 17%	-	2, 18%	3, 9%
Work status					
	Full-time Student	5, 28%	5, 28%	6, 55%	12, 34%
	Employed	12, 67%	12, 67%	5, 45%	22, 63%
	Unemployed	-	-	-	-
	Did Not Report	1, 6%	1, 6%	-	1, 3%

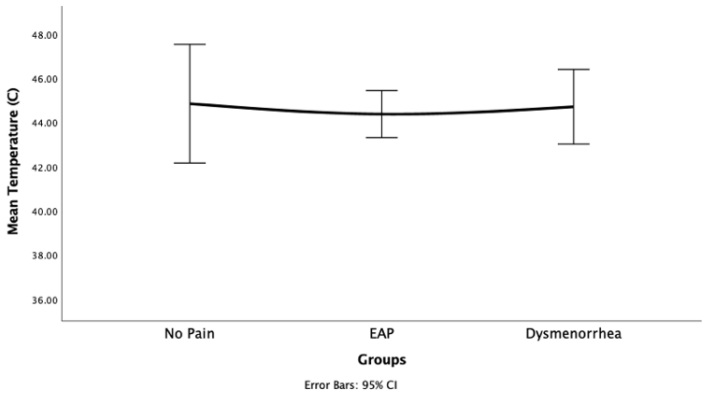
Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dsym, dysmenorrhea;

Table 18. Health Data – fNIRS + OA Subgroup, Mean (SD) or *n*, %

		No Pain (*n* = 6)	**Endo** (*n* = 18)	**Dysm** (*n* = 11)	**Total** (*n* = 35)
7/10 pain thresholds (C°)		44.9 (2.6) 41.1 – 48.0	44.4 (2.1) 39.8 - 48.0	44.7 (2.5) 39.8 – 47.0	44.6 (2.3) 39.8 – 48.0
Menstrual cycle description	Regular periods	4, 67%	5, 28%	10, 91%	19, 54%
	Irregular periods	1, 17%	5, 28%	1, 9%	7, 20%
	Surgery stopped periods	-	-	-	-
	Medication stopped periods	1, 17%	8, 44%	-	9, 26%
	Other	-	-	-	-
Menstrual cycle variables	Dysmenorrhea				
	Yes	-	17, 95%	11, 100%	21, 60%
	No	6, 100%	-	-	5, 14%
	Did not report	-	1, 6%	-	9, 26%
	Age of first menses*	13.3 (1.9)	11.8 (1.6)	13.4 (3.0)	12.6 (2.3)
	Age ranges if unsure	*n* = 4	*n* = 7	*n* = 3	*n* = 14
	10-12 years	3, 75%	5, 71%	1, 33%	9, 26%
	13-15 years	-	2, 29%	1, 33%	3, 9%
	16 years+	1, 25%	-	1, 33%	2, 6%
	Menstrual phase length (days)	4.7 (0.6)	5.5 (2.4)	5.4 (0.9)	5.3 (1.6)
	Pain level on day of study visit (scale of 0-10)	1.0 (2.0) 0 - 5 1.5 (1.4)	1.7 (1.9) 0 - 7 8.0 (1.6)	0.5 (1.6) 0 - 5 4.7 (1.0)	2.2 (2.0) 0 - 7 5.79 (2.8)
	MPP (scale of 0-10)	0 – 3	5 – 10	4 – 7	0 - 10
Hormonal contraception	Yes	4, 67%	14, 78%	8, 73%	26, 74%
	No	2, 33%	4, 22%	3, 27%	9, 26%
Comorbidities					
	Fibromyalgia	-	-	-	-
	IBS	-	4, 22%	-	4, 11%
	PCOS	2, 33%	1, 6%	-	3, 9%
	Autism	-	-	-	-
	Headaches	1, 17%	14, 78%	5, 45%	20, 57%
	Anxiety	1, 17%	9, 50%	3, 27%	13, 37%
	Depression	1, 17%	6, 33%	3, 27%	10, 29%
	PTSD	-	1, 6%	1, 9%	2, 6%
	Personality/mood disorder	-	2, 11%	1, 9%	3, 9%
	ADHD	-	-	-	-
	Eating disorder	1, 17%	-	-	1, 3%

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dysm, dysmenorrhea; IBS, irritable bowl syndrome; PCOS, polycystic ovary syndrome; OCD, obsessive compulsive disorder; ADHD, attention deficit hyperactivity disorder

Figure 23. Individual Pain Temperature Used in the OA Paradigm Across the Three Groups



Abbreviations. EAP, endometriosis-associated pain; OA, offset analgesia

Table 19 shows the results for the following questionnaires: CTES, RTES, CD-RISC, and PCS.

Table 19. Pain Catastrophising, Adverse Childhood Experiences, Adverse Recent Experiences, and Resiliency Data for the fNIRS + OA Subgroup

		No Pain (*n* = 6)	**Endo** (*n* = 18)	**Dysm** (*n* = 11)	**Total** (*n* = 35)
PCS	High	-	4, 22%	-	4, 11%
	Low	6, 100%	13, 72%	11, 100%	30, 86%
	Total Score [mean (SD)]	10.0 (11.6)	19.0 (12.2)	6.4 (6.3)	13.3 (11.8)
	Helplessness	4.3 (5.7)	8.5 (5.8)	1.5 (1.6)	5.5 (5.6)
	Rumination	4.3 (5.0)	6.1 (4.4)	3.5 (4.0)	5.0 (4.4)
	Magnification	1.3 (1.2)	4.4 (2.8)	1.3 (1.8)	2.9 (2.7)
CTES	Experienced an ACE				
	Yes	2, 33%	14, 78%	9, 82%	25, 71%
	No	4, 67%	4, 22%	2, 18%	10, 29%
	Quantity of ACEs				
	Avg ACE	0.3 (0.5)	1.1 (0.8)	1.1 (.70)	1.0 (0.8)
	No ACE	4, 67%	4, 22%	2, 18%	10, 29%
	One ACE	2, 33%	9, 50%	6, 55%	17, 47%
	Two ACEs	-	4, 22%	3, 27%	7, 20%
	Three ACE	-	1, 6%	-	1, 29%
	Burden Score (mean [SD])	0.3 (0.8)	5.7 (5.3)	3.9 (4.1)	4.2 (4.8)
	Confide Score (mean [SD])	-	2.4 (2.8)	3.8 (3.1)	2.4 (2.9)
RTES	Experienced ARE				
	Yes	6, 100%	14, 78%	6, 55%	26, 74%
	No	-	4, 22%	5, 45%	9, 26%
	Quantity of AREs				
	Avg AREs	1.8 (1.0)	1.7 (1.2)	0.9 (1.0)	1.5 (1.2)
	No ARE	-	4, 22%	5, 46%	9, 26%
	One ARE	3, 50%	4, 22%	3, 27%	10, 29%
	Two AREs	1, 17%	5, 28%	2, 18%	8, 23%
	Three AREs	2, 33%	4, 22%	1, 9%	7, 20%

	Four AREs	-	1, 6%	-	1, 3%
	Burden Score (mean [SD])	5.3 (4.3)	8.8 (6.8)	5.5 (6.0)	7.2 (6.1)
	Confide Score (mean [SD])	7.0 (7.2)	6.9 (5.5)	5.7 (4.3)	6.6 (5.5)
		No Pain (n = 2)	**Endo** (n = 16)	**Dysm** (n = 9)	**Total** (n = 35)
CD- RISC	Low	1, 50%	9, 50%	5, 46%	15, 43%
	Moderate	-	5, 28%	2, 18%	7, 20%
	High	1, 50%	2, 11%	2, 18%	5, 14%
	Total Score [mean (SD)]	32 (7.1)	27.2 (5.0)	28.2 (5.0)	27.9 (5.0)

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dysm, dysmenorrhea; PCS, pain catastrophising; ACEs, adverse childhood experiences, AREs, adverse recent experiences; CD-RISC, connor-davison resiliency scale

Table 20 shows the one-way ANOVA results for the following questionnaires: CTES, RTES, CD-RISC, and PCS.

Table 20. Results for One-Way ANOVAS

Measure	Groups Compared	F-Value	P-Value	Tukey's HSD Results	Mean Comparison	Effect Direction
PCS Total Score	No Pain vs Endo vs Dysm	5.13	0.01			
	No Pain vs Endo			$p = 0.20$, 95% C.I. = -21.36, 3.36	10.0 vs 19.0	No differences
	Endo vs Dysm			$p = 0.01$, 95% C.I. = 2.57, 22.70	19.0 vs 6.4	Endo
	No Pain vs Dysm			$p = 0.78$, 95% C.I. = -9.57, 16.84	10.0 vs 6.4	No differences
Helplessness - PCS Subscale	No Pain vs Endo vs Dysm	5.13	0.01			
	No Pain vs Endo			$p = 0.18$, 95% C.I. = -9.77, 1.50	4.3 vs 8.5	No differences
	Endo vs Dysm			$p = 0.002$, 95% C.I. = 2.33, 11.52	8.5 vs 1.5	Endo
	No Pain vs Dysm			$p = 0.50$, 95% C.I. = -3.23, 8.81	4.3 vs 1.5	No differences
Rumination - PCS Subscale	No Pain vs Endo vs Dysm	7.12	0.31			
Magnification - PCS Subscale	No Pain vs Endo vs Dysm	7.83	0			
	No Pain vs Endo			$p = 0.02$, 95% C.I. = -5.76, -0.39	1.3 vs 4.4	Endo
	Endo vs Dysm			$p = 0.004$, 95% C.I. = 0.95, 5.33	4.4 vs 1.3	Endo
	No Pain vs Dysm			$p = 0.99$, 95% C.I. = -2.81, 2.93	1.3 vs 1.3	No differences
Quantites of ACEs	No Pain vs Endo vs Dysm	2.62	0.09			
CTES Burden Score	No Pain vs Endo vs Dysm	3.24	0.05			
	No Pain vs Endo			$p = 0.04$, 95% C.I. = -10.63, -.15	0.3 vs 5.7	Endo
	Endo vs Dysm			$p = 0.55$, 95% C.I. = -2.44, 6.06	5.7 vs 3.9	No differences
	No Pain vs Dysm			$p = 0.28$, 95% C.I. = -9.21, 2.06	0.3 vs 3.9	No differences
CTES Confide Score	No Pain vs Endo vs Dysm	3.91	0.03			

	No Pain vs Endo			p = 0.16, 95% C.I. = -5.51, 0.73	0.0 vs 2.4	No differences
	Endo vs Dysm			*p* = 0.36, 95% C.I. = -3.96, 1.10	2.4 vs 3.8	No differences
	No Pain vs Dysm			*p* = 0.02, 95% C.I. = -7.18, -0.46	0.0 vs 3.8	Dysm
Quantities of AREs	No Pain vs Endo vs Dysm	1.9	0.17			
RTES Burden Score	No Pain vs Endo vs Dysm	0.98	0.39			
RTES Confide Score	No Pain vs Endo vs Dysm	0.11	0.9			
Resiliency	No Pain vs Endo vs Dysm	0.83	0.45			

Abbreviations. SD, standard deviation; Endo, endometriosis-related pain; Dysm, dysmenorrhea; PCS, pain catastrophising; ACEs, adverse childhood experiences, AREs, adverse recent experiences; CD-RISC, connor- davison resiliency scale

3.3.2.2 Pain Inhibition – OA

A one-way ANOVA revealed no significant differences in the scores between the four trials (Trial A, $F(2,32) = 3.146$, $p = 0.06$; Trial B, $F(2,32) = 2.146$, $p = 0.13$; Trial C, $F(2,32) = 2.164$, $p = 0.12$; Trial D, $F(2,32) = 0.057$, $p = 0.95$) within the three groups. As there were no differences, we calculated the median OA score to compare between the three groups (Table 21).

Table 21. OA Results

		No Pain (*n* = 6)	**Endo** (*n* = 18)	**Dysm** (*n* = 11)	**Total** (*n* = 35)
OA	Median (IQR)	54.2 (65.5)	67.1 (40.1)	89.0 (16.7)	81.87 (41.7)
	Min - max	16.7 - 100	16.7 - 100	63.1 - 100	16.7 – 100

Abbreviations. OA, offset analgesia; SD, standard deviation

A significant difference in the median OA score was found between the three groups, as determined by an ANOVA analysis ($F(2, 32) = 3.70$, $p = 0.04$). However, posthoc Tukey's test failed to detect significant differences between any of the pairs of groups, meaning that there were no significant differences between any two groups after accounting for the multiple comparisons. In other words,

while the overall ANOVA test suggests that there are differences between groups, these differences may not be statistically significant enough to be detected when comparing individual pairs of groups using posthoc tests. This may be due to several factors, such as small sample sizes, high group variability, or lack of power in the posthoc tests. The lack of significant differences between any two groups does not invalidate the overall significant ANOVA finding, as it still suggests that there are differences between the groups as a whole.

For exploratory analyses, three additional one-way ANOVAs assessed potential group differences in OA responses among participants with and without adverse childhood and recent experiences, and participants with high and low pain catastrophising scores. No significant differences were detected (adverse childhood experiences, $F(2,32) = 2.79$, $p = 0.08$; adverse recent experiences, $F(2,32) = 2.32$, $p = 0.11$; and pain catastrophising, $F(2,32) = 2.39$, $p = 0.11$).

3.3.2.3 Brain Imaging - fNIRS

3.3.2.3.1 Resting State Results

Resting-state functional connectivity was compared between groups using a one-way ANOVA, which revealed that there was a statistically significant difference in the location FC13 between at least two groups ($F(2, 32) = 4.98$, $p = 0.01$). Tukey's HSD Test for multiple comparisons found that the mean functional connectivity value of location FC13 significantly differed between the no pain and endometriosis groups ($p = 0.01$, 95% C.I. = [0.08, 0.61]). However, there were no significant differences between the no pain and the dysmenorrhea groups.

3.3.2.3.1.1 Pain Catastrophising

To assess if pain catastrophising would impact the relationship when MPP is higher, moderation analyses were conducted for each FC location at resting state. Of the 15 moderation models, the only significant results were for resting state location FC7 (between ROI 2 and 4).

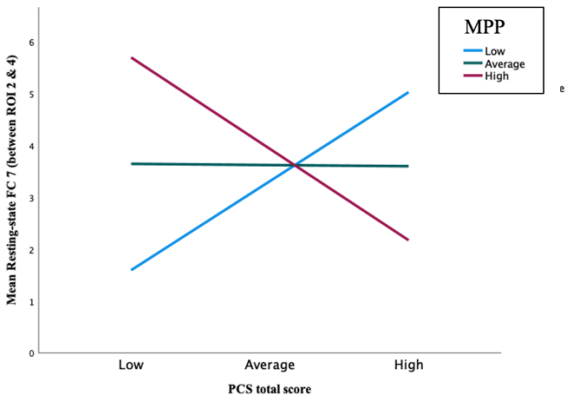
For location FC7, the overall model was significant, with MPP, PCS total score, and their interaction, predicting brain activity better than chance, with 25% of the variance due to the three predictors ($F(3, 29) = 2.98$, $p = 0.05$, $R^2 = 0.25$). As Table 22 shows, the PCS total score nor MPP was significantly related to location FC7. However, the interaction PCS total score*MPP significantly moderated the overall relationship. This interaction is illustrated in Figure 24.

Table 22. Moderation Model – Results for Pain Catastrophising, Resting State Location FC7, and MPP

Predictor	***β***	***p***	**95% CI**	
PCS Total Score	-0.002	0.98	-0.13,	0.13
MPP	0.11	0.70	-0.47	0.69
PCS x MPP*	-0.05	0.03	-0.10,	-0.01

*$p \leq 0.05$

Figure 24. Significant Interaction Between Pain Catastrophising and MPP



Abbreviations. MPP, menstrual phase pain; PCS, pain catastrophising scale; ROI, region of interest; FC, functional connectivity

The interaction was probed by testing the conditional effects of PCS total score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 23, PCS total score was not significantly related to resting-state location FC7 when MPP was one SD below the mean and when at the mean but was significantly related when MPP was one SD above the mean ($p = 0.02$).

Table 23. Resting FC7 - Conditional Effects of Pain Catastrophising at Three Levels of MPP

Levels of MPP	β	***p***	**95% CI**	
One *SD* below mean	0.14	0.20	-0.08	0.37
At the mean	-0.002	0.98	-0.13,	0.13
One *SD* above mean*	-0.15	0.02	-0.27,	-0.02

*$p \leq 0.05$

The Johnson-Neyman technique showed that the relationship between PCS total score and MPP was significant when MPP was greater than 2.15 points above the mean (β = -0.11, t(29) = -2.05, p = 0.05), but not significant with lower values of MPP. Therefore, as pain increases, the relationship between PCS total score and the activity for resting location FC7 becomes increasingly positive with the highest pain score (10 out 10) (β = -0.23, t(29) = -2.75, p = 0.01). In summary, when participants reported about 8 out of 10 pain, PCS total score, and resting location FC7 are significantly related (β = -0.11, t(29) = -2.05, p = 0.05).

3.3.2.3.1.2 Adverse Childhood Experiences

Next, the impact of adverse childhood experiences on MPP and resting-state functional connectivity was assessed. Moderation models were conducted to assess if MPP, CTES burden score, and their interaction predicted resting-state functional connectivity better than chance. Of the 15 moderation models, the only significant results were for resting state location FC13 (between ROI 4 and 5) and FC7 (between ROI 2 and 4).

For FC13, between ROI 4 and 5, the overall model was significant, with MPP, CTES burden, and their interaction predicting brain activity better than chance, with 28% of the variance due to the three predictors (F(3, 30) = 6.39, p = 0.002, R^2 = 0.28). As Table 24 shows, CTES burden score significantly related to FC13, as well as the interaction CTES burden score*MPP significantly moderated the overall relationship. This interaction is illustrated in Figure 25.

Table 24. Moderation Model – Results for Adverse Childhood Experiences, Resting State Location FC13, and MPP				
Predictor	**β**	**p**	**95% CI**	
CTES Burden Score*	-0.17	0.04	-0.34,	0.004
MPP	-0.18	0.26	-0.49,	0.13
CTES x MPP*	0.07	0.02	0.01	0.12
*$p \leq 0.05$				

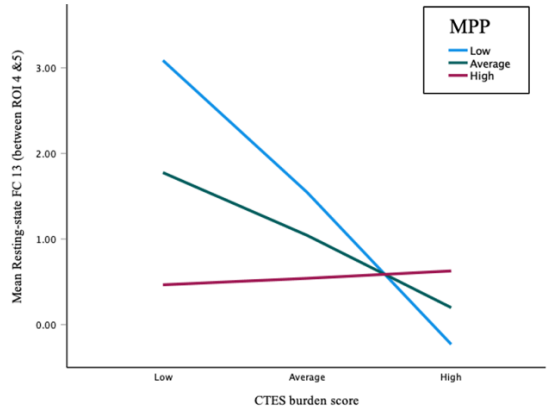


Figure 25. Significant Interaction between ACEs and MPP for Resting Location FC13.

Abbreviations. ACEs, adverse childhood experiences; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of CTES burden score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 25, CTES burden score was significantly related to resting-state FC13 when MPP was one SD below the mean ($p = 0.01$) and when at the mean ($p = 0.04$), but was not significantly related when MPP was one SD above the mean.

Table 25. Resting FC13 - Conditional Effects of ACEs at Three Levels of MPP				
Levels of MPP	β	*p*	95% CI	
One SD below mean*	-0.36	0.01	-0.65,	-0.08
At the mean*	-0.17	0.04	-0.34,	-0.004
One SD above mean	0.02	0.81	-0.13,	0.17
*$p \leq 0.05$				

The Johnson-Neyman technique showed that the relationship between CTES burden score and MPP was significant when MPP was less than 0.21 points below the mean (β = -0.16, t(30) = -2.00, p = 0.05), but not significant with higher values of MPP. Therefore, as pain decreases, the relationship between CTES burden score and the activity for location FC13 becomes increasingly significant with the lowest pain score (0 out 10) (β = -0.56, t(30) = -2.67, p = 0.01). In summary, when participants reported about 5.5 out of 10 pain, CTES burden score, and resting location FC13 were significantly related (β = -0.16, t(30) = -2.00, p = 0.05).

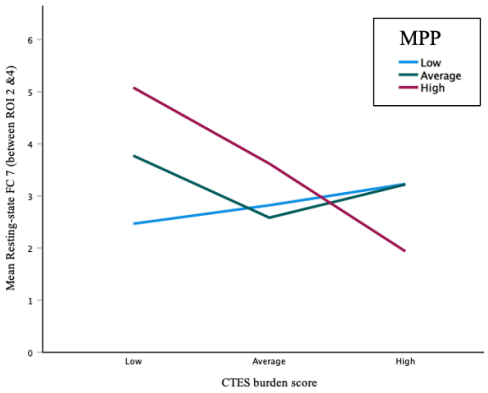
For FC7, the overall model was significant, with MPP, CTES burden, and their interaction predicting brain activity better than chance, with 18% of the variance due to the three predictors (F(3, 30) = 5.66, p = 0.003, R^2 = 0.18). As Table 26 shows, CTES burden score nor MPP significantly related to location FC7. However, the interaction CTES burden score*MPP significantly moderated the overall relationship. This interaction is illustrated in Figure 26.

Table 26. Moderation Model – Results for Adverse Childhood Experiences, Resting State Location FC7, and MPP

Predictor	**β**	**p**	**95% CI**	
CTES Burden	-0.13	0.20	-0.33,	0.07
MPDP	0.14	0.55	-0.34,	0.62
CTES Burden x MPP*	-0.08	0.03	-0.14,	-0.01

*$p \leq .05$

Figure 26. Significant Interaction between ACEs and MPP for Resting Location FC7.



Abbreviations. CTES, childhood traumatic events scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of CTES burden score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 27, CTES burden score was not significantly related to resting-state location FC7 when MPP was one SD below the mean and when at the mean but was significantly related when MPP was one SD above the mean ($p < 0.001$).

Table 27. Resting FC7 – Conditional Effects of CTES Burden Score at Three Levels of MPP

MPP	**β**	**p**	**95% CI**	
One SD below mean	0.08	0.64	-0.27,	0.44
At the mean	-0.13	0.20	-0.33,	0.07
One SD above mean**	-0.34	< 0.001	-0.053,	0.367

*$p \leq 0.05$, ** $p \leq 0.001$

The Johnson-Neyman technique showed that the relationship between CTES burden score and MPP was significant when MPP was greater than 0.64 points above the mean ($\beta = 0.17$, t(30) = -2.04, $p = 0.05$), but not significant with lower values of MPP. Therefore, as pain increases, the relationship between CTES burden score and the activity for resting location FC7 becomes increasingly significant with the highest pain score (10 out 10) ($\beta = -0.45$, t(30) = -3.94, $p < 0.001$). In summary, when

participants reported about 6.5 out of 10 pain, CTES burden score and resting location FC7 were significantly related ($\beta = 0.17$, t(30) = -2.04, $p = 0.05$).

3.3.2.3.1.3 Adverse Recent Experiences

Next, the impact of adverse recent experiences on MPP and resting-state FC was assessed. Moderation models were conducted to assess if MPP, RTES burden score, and their interaction predicted resting-state FC better than chance. None of the 15 moderation models were significant ($p > 0.05$).

3.3.2.3.1.4 Resiliency

Next, the impact of resiliency on MPP and resting-state FC was assessed. Moderation models were conducted to assess if MPP, CD-RISC total score, and their interaction predicted resting-state FC better than chance. None of the 15 moderation models were significant ($p > 0.05$).

3.3.2.3.2 OA Task Results

OA task functional connectivity were compared between groups using a one-way ANOVA, which revealed no significant difference (F(2, 32) = 4.98, $p = 0.10$).

3.3.2.3.2.1 Pain Catastrophising

Moderation analyses were conducted for each FC location to assess if pain catastrophising would impact the relationship when MPP was higher. Of the 15 moderation models, the only significant results were for OA location FC10 (between ROI 3 and 4) and location FC13 (between ROI 4 and 5).

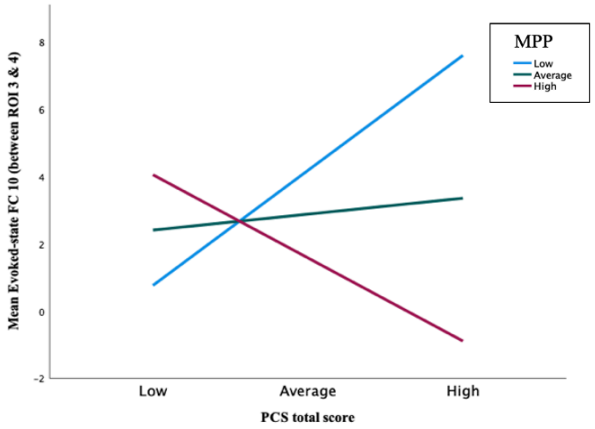
For FC10, the overall model was significant, with MPP, PCS total score, and their interaction, predicting brain activity better than chance, with 26% of the variance due to the three predictors (F(3, 29) = 5.00, $p = 0.006$, $R^2 = 0.26$). As Table 28 shows, PCS total score nor MPP is significantly related to location FC10. However, the interaction PCS total score*MPP significantly moderated the overall relationship. This interaction is illustrated in Figure 27.

Table 28. Moderation Model – Results for Pain Catastrophising, OA Task Location FC10, and MPP

Predictor	β	p	95% CI	
PCS	0.04	0.59	-0.11,	0.19
MPP	-0.67	0.25	-1.3	0.34
PCS x MPP*	-0.09	0.02	-0.16,	-0.02

*$p \leq 0.05$

Figure 27. Significant Interaction between Pain Catastrophising and MPP for OA Task Location FC10.



Abbreviations. PCS, pain catastrophising scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of PCS total score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 29, PCS total score was significantly related to OA Task location FC10 when MPP was one SD below the mean ($p = 0.05$), but not significantly related at the mean nor one SD above the mean.

Table 29. OA Task FC10 – Conditional Effects of Pain Catastrophising at Three Levels of MPP

Levels of MPP	β	p	95% CI	
One SD below mean*	0.29	0.05	0.004,	0.58
At the mean	0.04	0.59	-0.12	0.19
One SD above mean	-0.21	0.06	-0.42,	0.01

*$p \leq 0.05$

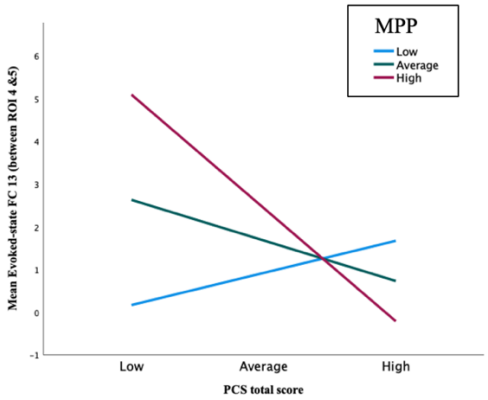
The Johnson-Neyman technique showed that the relationship between PCS total score and MPP was significant when MPP was either 2.5 points below the mean (β = 0.26, t(29) = 2.02, p = 0.05) or 3 points above the mean (β =3.1, t(29) = -2.04, p = 0.05), but not significant with values outside of that range of MPP. Therefore, when pain is less than 3 and more than 9 pain rating on a pain scale of 0 to 10, the relationship between the PCS total score and the activity of OA Task location FC10 was significant.

For FC13, between ROI 4 and 5, the overall model was significant, with MPP, PCS total score, and their interaction, predicting brain activity better than chance, with 23% of the variance due to the three predictors (F(3, 29) = 2.98, p = 0.05, R^2 = 0.23). As Table 30 shows, PCS total score nor MPP significantly related to OA Task FC13, however, the interaction PCS total score* MPP significantly moderated the overall relationship. This interaction is illustrated in Figure 28.

Table 30. Moderation Model – Results for Pain Catastrophising, OA Task Location FC13, and MPP

Predictor	**β**	**p**	**95% CI**	
PCS	-0.08	0.20	-0.20,	0.04
MPP	0.27	0.25	-0.20,	0.74
PCS x MPP*	-0.05	0.03	-0.10	-0.005
*$p \leq 0.05$				

Figure 28. Significant Interaction between Pain Catastrophising and MPP for OA Task Location FC13.



Abbreviations. PCS, pain catastrophising scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of PCS total score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 31, PCS total score was not significantly related to OA task location FC13 when MPP was one standard deviation below the mean and when at the mean but was significantly related when MPP was one standard deviation above the mean ($p < 0.008$).

Table 31. OA Task FC13 – Conditional Effects of Pain Catastrophising at Three Levels of MPP

Levels of MPP	**β**	***p***	**95% CI**	
One SD below mean	0.06	0.56	-0.13,	0.26
At the mean	-0.80	0.20	-0.33,	0.07
One SD above mean*	-0.22	0.008	-0.38,	0.06

*$p \leq 0.05$

The Johnson-Neyman technique showed that the relationship between PCS total score and MPP was significant when MPP was greater than 0.82 points above the mean ($\beta = -0.82$, t(29) = -2.05, $p = 0.05$), but not significant with lower values of MPP. Therefore, as pain increases, the relationship between PCS total score and the of OA Task location FC13 becomes increasingly significant with the higher pain score (10 out 10), $\beta = -0.20$, t(29) = -2.92, $p = 0.007$. In summary, when participants

reported about 6.6 out of 10 pain, CTES burden score, and OA Task location FC13 are significantly related (β = -0.82, t(29) = -2.05, p = 0.05).

3.3.2.3.2.2 Adverse Childhood Experiences

Moderation analyses were conducted for each FC location to assess if adverse childhood experiences would impact the relationship when MPP is higher. Of the 15 moderation models, the only significant results were for OA task location FC12 (between ROI 3 and 6).

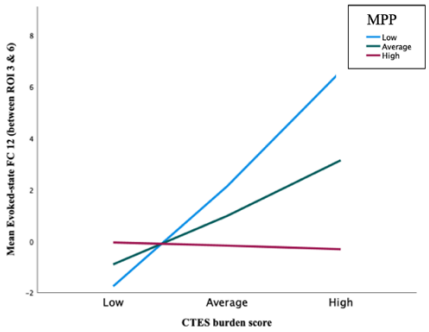
For FC12, the overall model was significant, with MPP, CTES burden, and their interaction predicting brain activity better than chance, with 18% of the variance due to the three predictors (F(3, 30) = 6.86, p = 0.001, R^2 = 0.18). Table 32 shows that CTES burden score, MPP, and the interaction CTES burden score*MPP is significantly related to OA Task location FC12. This interaction is illustrated in Figure 29.

Table 32 Moderation Model – Results for ACEs, OA Task Location FC12, and MPP

Predictor	**β**	**p**	**95% CI**	
CTES Burden	0.44	0.25	-0.32,	1.2
MPP	-0.40	0.33	-1.2,	0.43
CTES Burden x MPP	-0.17	0.45	-0.61,	0.27

Abbreviations.

Figure 29. Insignificant Interaction between ACEs and MPP for OA Task Location FC12.



Abbreviations. CTES, childhood traumatic events scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of CTES burden score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 33, CTES burden score was significantly related to OA Task location FC12 when MPP was one SD below the mean (p = 0.001), but not at the mean or one SD above the mean.

Table 33. OA FC12 - Conditional Effects of Adverse Childhood Events at Three Levels of MPP

Levels of MPP	**β**	***p***	**95% CI**	
One SD below mean*	0.92	0.01	0.25,	1.58
At the mean	0.44	0.25	-0.32,	1.21
One SD above mean	-0.03	0.98	-2.00,	1.94

*$p \leq 0.05$

The Johnson-Neyman technique showed that the relationship between CTES burden score and MPP was significant when MPP was between 4 points below the mean (β = 1.09, t(30) = 2.04, p = 0.05) and 0.6 points below the mean (β =.54, t(30) = 2.04, p = 0.05), but not significant with values outside of that range of MPP. Therefore, when pain is within the range of 1.8 and 5.2 rating on the pain scale of 0 to 10, the relationship between the CTES burden score and the activity for OA task location FC12.

3.3.2.3.2.3 Adverse Recent Experiences

To assess if adverse recent experiences would impact the relationship when MPP is higher, moderation analyses were conducted for each FC location. Of the 15 moderation models, the only significant results were for OA location FC12 (between ROI 3 and 6).

For FC12, the overall model was significant, with MPP, RTES burden, and their interaction predicting brain activity better than chance, with 31% of the variance due to the three predictors ($F(3, 20) = 4.25$, $p = 0.02$, $R^2 = 0.31$.) As Table 34 shows, RTES burden score, MPP, nor the interaction RTES burden score*MPP significantly related to OA Task location FC12. This interaction is illustrated in Figure 30.

Table 34 Moderation Model – Results for AREs, OA Task Location FC12, and MPP

Predictor	**β**	**p**	**95% CI**	
RTES burden score	.26	.10	.30,	.57
MPP	.24	.32	-.1.2,	.74
RTES x MPP	-.01	.80	-.61,	.08

Abbreviations

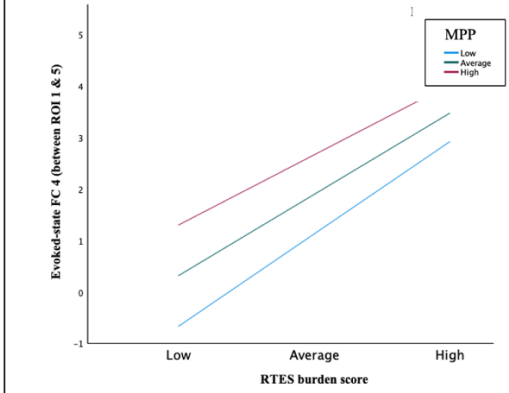


Figure 30. Insignificant Interaction between recent adverse experiences and MPP for OA Task Location FC12.

Abbreviations. RTES, recent traumatic events scale; MPP, menstrual phase pain; FC, functional connectivity; ROI, region of interest

The interaction was probed by testing the conditional effects of RTES burden score at three levels of MPP, one SD below the mean, at the mean, and one SD above the mean. As shown in Table 35, the

RTES burden score was significantly related to OA FC12 when MPP was one SD above the mean (p = 0.03), but not at the mean or one SD below the mean.

Table 35. OA FC12 - Conditional Effects of Adverse Recent Experiences at Three Levels of MPP

Levels of MPP	**β**	***p***	**95% CI**	
One SD below mean	0.29	0.29	-0.30,	0.85
At the mean	0.26	0.10	-0.05,	0.57
One SD above mean*	0.22	0.03	0.02,	0.43

*$p \leq .05$

The Johnson-Neyman technique showed that the relationship between RTES burden score and MPP was significant when MPP was 1 point above the mean (β =0.25, t(20) = 2.09, p = 0.05) but insignificant with lower values. Therefore, when pain is 6.8 or a higher rating on the pain scale of 0 to 10, the relationship between the RTES burden score and the activity between OA task location ROI 3 and 6 is significant.

3.3.2.3.2.4 Resiliency

A one-way ANOVA compared resilience characteristics and OA FC locations between groups, which revealed no significant difference (p > 0.05).

3.4 Conclusion

This study hypothesized that dysmenorrhea and endometriosis-related pain affect the functional connectivity of brain regions involved in pain processing. This effect may be amplified by adverse psychological and psychosocial factors. The results of the study supported this hypothesis, more so for the endometriosis vs dysmenorrhea participants, leading to the conclusion that the null hypothesis was not rejected. Additionally, altered endogenous pain inhibition mechanisms in women with dysmenorrhea and endometriosis-related pain were hypothesized to contribute to pain chronification. Similarly, the results of the study supported this hypothesis, leading to the conclusion that the null hypothesis was not rejected.

The control group consisted of individuals without existing pain or pain diagnoses. However, the control group surprisingly had 60% reporting dysmenorrhea rated as moderate pain or higher. The findings revealed that 62% of the pain group and 77% of the dysmenorrhea group had regular periods, whereas only 29% of the endometriosis group had regular periods. This difference could be attributed to 44% of endometriosis-related pain participants taking medication that stops their periods, which is a common treatment approach for dysmenorrhea or suspected endometriosis. The dysmenorrhea group may not have sought treatment as they did not report dysmenorrhea during screening. Still, follow-up questions about menstrual-related pain revealed that they did, in fact, have pain considered as dysmenorrhea.

The study had three primary objectives. First, it aimed to assess group differences in MPP, length of period, pain level on the day of the visit, and the use of hormonal oral contraception, as these factors can contribute uniquely to dysmenorrhea or endometriosis-related pain. Second, it examined psychological and psychosocial variables, including pain catastrophising, adverse childhood experiences, adverse recent experiences, and resiliency. Lastly, for the subgroup of participants who completed the fNIRS + OA task, the objective was to compare pain inhibition and to compare functional connectivity of ROIs at rest and pain inhibition testing.

The results for all participants who completed the questionnaires indicated no significant age differences between the three groups. The pain-free group had a significantly shorter menstrual phase than the endometriosis-related pain group and the dysmenorrhea group. Additionally, the pain-free group reported significantly lower pain than the endometriosis-related pain group and the dysmenorrhea group. There were no significant differences in the use of hormonal contraception between the groups.

Psychological questionnaires revealed several significant group differences. The pain-free group had significantly lower pain catastrophising scores than the endometriosis-related pain group and the

dysmenorrhea group. Significant group differences were also found for helplessness and magnification scores, with the pain-free group having significantly lower scores than the endometriosis-related pain group and the dysmenorrhea group.

Regarding adverse childhood experiences, the pain-free group had significantly fewer adverse childhood experiences compared to the endometriosis-related pain group. At the same time, there was no significant difference between the pain-free group and the dysmenorrhea group. There were no significant group differences in the CTES burden score, or CTES confide score.

For adverse recent experiences, the pain-free group had significantly fewer adverse recent experiences than the endometriosis-related pain group and the dysmenorrhea group. The endometriosis-related pain group had significantly higher RTES burden scores than the dysmenorrhea group. At the same time, there was no significant difference between the pain-free group and the other two groups. The endometriosis-related pain group also had significantly lower RTES confide scores than the pain-free group, with no significant difference between the pain-free and dysmenorrhea groups.

No significant differences were found in resiliency scores among the three groups.

The fNIRS + OA Subgroup analysis showed no significant age differences among the three groups. There were no significant group differences in pain ratings during the OA Task. However, there was a significant group difference in pain inhibition, with the pain-free group demonstrating more significant pain inhibition than the endometriosis-related pain group and the dysmenorrhea group.

Regarding the OA Subgroup questionnaires, the findings highlight the presence of differences in pain catastrophising and certain aspects of adverse experiences among the groups being studied. However, no significant differences in resilience or other variables indicated that these factors may not be strongly associated with pain status.

For resting-state functional connectivity, the pain-free group exhibited stronger functional connectivity between the prefrontal and somatosensory ROIs than the endometriosis-related pain group and the dysmenorrhea group. During the OA task, the pain-free group also showed stronger functional connectivity between these regions than the other two groups. These findings are consistent with previous research highlighting the involvement of these brain regions in pain processing and modulation.

Additionally, the study revealed associations between functional brain imaging measures and pain functioning measurements. Pain ratings, pain catastrophising scores, and burden scores related to stress and trauma were found to be significantly associated with specific functional connectivity patterns in the prefrontal and somatosensory brain regions. These associations suggest that psychological factors and stress-related experiences influence both the subjective experience of pain and the underlying neural activity in pain-processing networks. These results contribute to our understanding of MPP neural mechanisms and provide insights into the complex interplay between psychological factors, brain activity, and pain perception.

3.5 Discussion

Results showed significant differences in pain experience, menstrual characteristics, and psychological variables between the pain-free group, the endometriosis-related pain group, and the dysmenorrhea group. The pain-free group generally reported lower pain levels, shorter menstrual phases, and lower scores on pain catastrophising, adverse childhood experiences, and recent adverse experiences compared to the other two groups. The fNIRS + OA Subgroup analysis revealed differences in pain inhibition and functional connectivity between the prefrontal and somatosensory regions, with the pain-free group demonstrating more potent pain inhibition and functional connectivity during the OA task. These findings provide insights into the neural and psychological factors associated with MPP and may contribute to a better understanding of dysmenorrhea and endometriosis-related pain.

3.5.1 Considerations and Limitations

There are several considerations and limitations to be acknowledged. The limitations include potential endometriosis misdiagnosis in control participants, brief self-report measures that may be affected by recall bias, controversies surrounding the self-report questionnaires, and potential confounds of long-term medication use on pain response and brain activity.

The participants in the dysmenorrhea group may have endometriosis, as their condition was not disconfirmed through surgery. As we do not know the underlying cause of dysmenorrhea in participants included in this study, we assumed they are reporting primary dysmenorrhea. However, this is a major limitation of the study and its findings. The pain associated with secondary dysmenorrhea, reported in the participants with endometriosis within this study, may be more severe and persistent than that of primary dysmenorrhea.[38,301] It may also accompany other symptoms such as heavy bleeding, irregular periods, or pain during sex. [38,301]

The participants were recruited from one USA city, and it is important to replicate the study with larger and more diverse samples to ensure the robustness of the results. The study used a cross-sectional design, which limits the ability to establish causal relationships between variables. Longitudinal studies are needed to examine the temporal dynamics of MPP and explore the potential predictive factors of pain severity and persistence. The reliance on self-report measures for assessing pain, psychological variables, and menstrual characteristics introduces the possibility of recall bias or subjective interpretation. Objective measures, such as physiological assessments or clinical evaluations, could enhance the validity and reliability of the findings.

In the context of chronic pain in women, the use of measures, such as the CD-RISC-10 used in Chapters 3 and 4, and other resilience scales has faced criticism regarding what they truly measure. Some argue that these measures are capturing coping strategies rather than resilience per se.[328,329] When assessing resilience in the context of chronic pain, it becomes essential to disentangle coping strategies from resilience factors to gain a more comprehensive understanding of how individuals

navigate the complexities of chronic pain management and adaptation.[222] Future research should focus on differentiating the specific components of coping and resilience to elucidate their distinct contributions to the experiences of women living with chronic pain and inform targeted interventions for improving their well-being.

3.5.2 Summary

This study investigated differences in pain experience, menstrual characteristics, psychological variables, and neural correlates among a pain-free group, an endometriosis-related pain group, and a dysmenorrhea group. The findings suggest that the pain-free group generally reported lower pain levels, shorter menstrual phases, and lower scores on pain catastrophising and adverse childhood experiences compared to the other two groups. The subgroup analysis using fNIRS during an experimental pain task revealed differences in pain inhibition and functional connectivity between the prefrontal and somatosensory regions, with the pain-free group demonstrating stronger pain inhibition and functional connectivity. However, several limitations should be considered, including the small sample size and cross-sectional design. Future research should address these limitations and further explore the complex interplay between psychological, physiological, and neural factors contributing to the pain.

Chapter 4

Assessing the Stability of Pain Catastrophising in a Longitudinal Community Sample of Adolescents: Can it Predict Chronic Pain and Dysmenorrhea?

"Adolescence is a border between childhood and adulthood. Like all borders, it's teeming with energy and fraught with danger."

Dr Mary Pipher

American clinical psychologist and author.

4.0 Overview

The final experiment, Principal Investigator Professor Elaine Fox, is a longitudinal study that examined pain catastrophising among male and female adolescents in a community sample at three different time points. The overarching hypothesis was that pain catastrophising scores increase with age. Additionally, high levels of pain catastrophising were expected to predict general chronic pain development in males and females, as well as dysmenorrhea in female adolescents. The current study's protocol was published in 2017,[330] and multiple data-driven manuscripts have been published.[331–333] The hypotheses and data I describe within this chapter have not been published.

My responsibilities for the current study included data processing and analysis using various statistical tools and techniques. This involved cleaning and organising the data, conducting descriptive and inferential analyses, and presenting the findings clearly and concisely at national and international conferences. All the hypotheses presented in this chapter originated from my own research and analysis.

4.1 Introduction

4.1.1 Age and Sex Differences in Pain Catastrophising

Around the age of 12 or 13, during puberty, sex differences in pain perception and responses start to become more apparent.[334] Females tend to have a lower pain threshold and tolerance than males. This difference may be influenced by factors such as genetic and hormonal variations, anatomical differences, and the activation of pain-related brain regions.

The hormonal changes that occur during puberty may contribute to sex differences in pain.[335] Estrogen, as described in Chapter 2, has been associated with increased pain sensitivity and enhanced responsiveness to painful stimuli.[23,244] Sociocultural and psychological factors also contribute to sex differences in pain perception. Social expectations and gender roles can influence how pain is expressed and perceived.[335–337] For example, adolescent girls may be more encouraged to seek help and express their pain, while adolescent boys may be socialised to be more stoic and downplay their pain.[337] Understanding sex differences in pain in adults as well as adolescents is an ongoing area of research. Moreover, females tend to report higher levels of pain catastrophising when compared to males.[338] This difference seems more prominent with specific types of pain, such as fibromyalgia,[172] sickle cell disease,[339] and migraine headaches.[340] Several pain conditions impact only females, such as dysmenorrhea or endometriosis, and have shown worse functional disability with higher pain catastrophising.[341]

In adult populations, several studies have found age and sex differences in pain catastrophising.[150,342] Generally, older adults report lower pain catastrophising levels than younger adults. However, the magnitude of this effect may depend on the type of pain and other factors such as health status and

functional limitations.[150,151,343–345] For example, older adults with knee osteoarthritis[346] and chronic low back pain[347] reported lower levels of pain catastrophising than younger patients. Although less research has been conducted in adolescent samples, evidence also suggests that this trend holds, with older adolescents reporting lower levels of pain catastrophising than younger adolescents.[348] Taken together, the evidence suggests that younger adolescent participants may catastrophise at higher levels. However, more research in large, diverse samples of adolescents is needed to fully understand the nature and extent of age differences in pain catastrophising across different pain populations and age groups, specifically for adolescents with and without chronic pain.

4.1.2 Pain Catastrophising in Adolescents

Measuring pain catastrophising levels is useful for assessing adolescents with chronic pain. It may provide valuable information for developing effective interventions to manage their pain and improve their quality of life. Similar to studies on adults, several studies on paediatric pain catastrophising in chronic pain samples suggest it is a common and significant predictor of pain intensity and severity, pain related-disability, psychological distress, and decreased quality of life.[342,345,348–350]

4.1.3 Pain Catastrophising and Dysmenorrhea

Research on pain catastrophising and dysmenorrhea is limited, but some studies have suggested similar results to other pain conditions.[351,352] One study of 187 women with primary dysmenorrhea (menstrual cramps not caused by an underlying condition[38]) found that those with higher levels of pain catastrophising reported greater MPP intensity and pain-related disability.[341] The study also found that pain catastrophising mediated the relationship between MPP intensity and disability, suggesting that negative thoughts and feelings about pain may contribute to the experience of disability and impairment in daily activities.

Another study of 189 adolescent females with dysmenorrhea found that those who scored higher in pain catastrophising also reported higher levels of anxiety and depression.[351] This suggests that pain

catastrophising may be associated with not only the physical experience of MPP but also emotional distress and is a relevant factor to consider in understanding the experience of MPP in females.

As described in Chapter 1, 25–70% of chronic pelvic pain cases are caused by endometriosis, and symptoms of endometriosis most often begin during adolescence.[97,98] Further exploring this relationship and determining whether interventions targeting pain catastrophising can effectively reduce adolescent dysmenorrhea and related disability could possibly improve treatment options and long-term outcomes for these children.

4.1.4 Do Resiliency and Childhood Experiences Impact Pain Catastrophising?

Also discussed in Chapter 1, adverse childhood experiences refer to potentially traumatic events that can occur during childhood, such as abuse, neglect, or household dysfunction. Research has suggested a link between pain catastrophising and adverse childhood experiences.[353,354] Specifically, individuals who report adverse childhood experiences may be more likely to engage in pain catastrophising behaviours and experience greater pain intensity and disability.[206] Additionally, the relationship between adverse childhood experiences and pain catastrophising may be mediated by factors such as anxiety, depression, and post-traumatic stress disorder.[206]

While most research on life experiences has focused on adverse childhood experiences, some evidence suggests that positive childhood experiences may play a protective role against pain catastrophising. For example, a study found that individuals who reported higher positive events were less likely to engage in pain catastrophising behaviours and reported lower pain intensity and disability.[353] Taken together, positive childhood experiences may provide individuals with a sense of self-efficacy and resilience to help them cope with pain.

Similarly, another study found that individuals with more positive childhood experiences had lower pain catastrophising and perceived stress levels and higher levels of positive affect.[355] Researchers hypothesise that positive childhood experiences might help to build emotional and social resources

that can be used to cope with pain and other stressors. While more research is needed to fully understand the relationship between pain catastrophising and positive childhood experiences, these studies suggest that positive childhood experiences may protect against pain catastrophising and associated negative outcomes. Thus, investigating the relationship between pain catastrophising and adverse/positive childhood experiences could provide important information for adolescents at risk for developing chronic pain.

Although most studies investigating pain catastrophising include patients with chronic pain, it may be important to measure pain catastrophising in a pain-free sample for two reasons. The first key reason is to establish a baseline level of pain catastrophising to compare with individuals experiencing acute and chronic pain. This may lead to a better understanding of pain catastrophising on types of pain and the potential effects of interventions aimed at reducing pain catastrophising. This information may identify those who could benefit from treatments to reduce pain catastrophising, such as cognitive behavioural therapy or acceptance and commitment-based therapy.[106,162]

The second key reason is to identify risk factors for developing chronic pain and potentially intervene early to prevent or minimise the impact of pain. Research has shown that individuals with high levels of pain catastrophising are at greater risk for developing chronic pain conditions.[149,151,152] Assessing when levels increase may help predict who will develop chronic pain later in adolescence or adulthood.

Therefore, measuring pain catastrophising in a community sample (included with and without pain) may offer valuable insights into the development and effects of pain catastrophising, potentially informing interventions to mitigate its negative impact on health outcomes. This is the first longitudinal study to assess pain catastrophising over time in an adolescent sample specifically.

The current study's primary aims were to investigate whether pain catastrophising remains stable at ages 12, 14, and 16 years. We hypothesised that pain catastrophising scores would decrease for

adolescents with and without pain as age increased. This hypothesis is consistent with what is found in the published literature on pain catastrophising and age in older adults.

Next, we assessed if high levels of pain catastrophising at age 12 were predictors of chronic pain development at ages 14 and 16. Specifically for females, we hypothesised that increased pain catastrophising at age 14 would predict dysmenorrhea at ages 14 and 16. This study also examined the relationship between adverse and positive childhood experiences and characteristics of resiliency and pain catastrophising. We hypothesised that high resiliency and an increased number of positive childhood experiences would negatively correlate with decreased pain catastrophising score and fewer adverse childhood experiences and would positively correlate with a reduced pain catastrophising score.

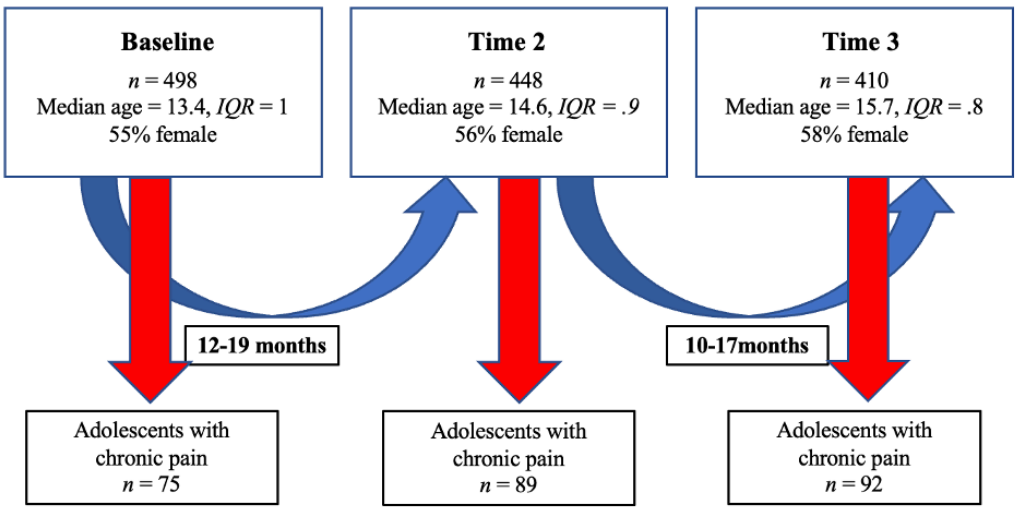
4.2 Methods

Institutional Ethics Review Boards approved this study for research at the University of Oxford. All participants provided informed consent.

4.2.1 Participant Selection

The study recruitment goal was to follow a large sample of over 500 adolescents for four years and test the participants when they were approximately 12 (Baseline), 14 (Time Point 2) and 16 (Time Point 3) years old, as shown in Figure 31.

Figure 31. Study Design



A sample size of 500 is considered highly powered for detecting even small effects in validated self-report psychological questionnaires.[356] A large sample size also allowed for the participant dropout with each assessment age. Research assistants recruited participants through their schools in southern England who emailed head teachers and psychology teachers describing the study aims.

The study included participants who were between 12 and 16 years of age, enrolled in a participating secondary school in England, and fluent in English. These inclusionary criteria were kept relatively broad to recruit a sample accurately representing the community, making the results more generalisable to the larger population. Participants with psychiatric, neurological, or learning conditions that could limit their participation were excluded at the parent or guardian's discretion.

4.2.2 Procedure

Testing was completed at the participant's schools or the Department of Experimental Psychology, University of Oxford. Each of the three assessment time points included two sessions lasting one hour each. Participants completed test sessions in small groups in computer labs and were asked to conduct

assessments in exam conditions, therefore being silent and not looking at another participant's computer screen. Participants completed a battery of self-report questionnaires and provided demographic and health-related information.

4.2.3 Demographics, Health History, and Self-report Questionnaires

For demographic data, participants reported their age, gender, race, and SES. SES was determined from an average score for their parent's highest level of education by categorising into six groups: secondary school, vocational/technical school, some college, bachelor's degree, master's degree, and doctoral degree. Parental education is a reliable indicator of SES, as education affects income and occupation while also being a source of parents' values and communicative styles.[357]

For health history, participants were asked if they had felt any aches or pains lasting longer than three months.[7] This was used to categorise participants as having no pain or chronic pain. This was chosen because chronic pain is widely defined as pain persisting for at least three to six months or beyond the average healing time for a given injury or condition.[7] Participants who endorsed pain lasting longer than three months were then asked to select all locations they felt pain from the following list: head, neck, throat, ear, back, joints, hands/arms, legs/feet, menstrual, stomach, and all over the body. They were allowed to select multiple locations. Participants were groups into three groups: the entire sample, participants with no pain, and participants with chronic pain.

The psychological and psychosocial questionnaires measured pain catastrophising, anxiety, depression, resiliency, positive childhood experiences, and adverse childhood experiences. All questionnaires assessed in this study were compared to published norms, if available.

The PCS,[313,358] the same questionnaire that was described in Chapter, was used to measure pain catastrophising. Item responses were summed to calculate a PCS total score, with high scores reflecting more significant levels of pain catastrophising. There are three clinical reference points

suggested for a paediatric chronic pain sample: low (0–14), moderate (15- 25), and high (26 and greater) catastrophising.[358]

The Child Adolescent Survey of Experiences – Child Version (CASE - C)[359] was used to assess life events, which consists of 38 life events relevant to children and adolescents (*e.g.,* "*My parents split up*", "*I went on a special holiday*"). Participants are asked to indicate whether each event happened to them during the past 12 months, and if so, they are asked to rate the event using a 6-point scale (1 = "Really bad," 2 = "Quite bad", 3 = "A little bad," 4 = "A little good", 5 = "Quite good," 6 = "Really good"). They were allowed to include two more life events, which they were asked to rate using the same scale. The questionnaire generated four scores: (1) The number of positive childhood experiences, which was computed as the number of events experienced and rated as either really good, quite good, or a little good by the participant. (2) Positive childhood experience impact score, which was the sum of the impact ratings for all life events rated as having a positive impact. (3) The number of adverse childhood experiences was computed as the number of events experienced and rated as really bad, quite bad, or a little bad by the participant. Lastly, (4) adverse childhood experiences impact score was the sum of the impact ratings for all life events rated as having a negative impact.

The CD-RISC-SF, [316,317] same questionnaire was used in Chapter 3, was used to assess characteristics of resilience. The responses were summed to produce a total score, with high scores indicating greater resilience (range is 0 to 40).

The Revised Child Anxiety and Depression Scale short form (RCADS-SF)[360] measure was used to assess characteristics of anxiety and depression. The scale includes 25 items of internalising symptoms. Participants were asked how often each item happens to them using a 4-point scale ranging from 0 ("Never") to 3 ("Always"). Depression was assessed with 10 items (*e.g.,* "*I feel sad or empty*," "*Nothing is much fun anymore*"), and anxiety was assessed with 15 items (*e.g.,* "*I feel scared if I have to sleep on my own*," "*I worry that something bad will happen to me*"). Scores were

calculated by summing the item responses for the anxiety and depression subscales separately, leading to a score ranging from 0 to 45 for anxiety and 0 to 30 for depression. Higher scores indicate a higher level of anxiety or depression.

The same questionnaire, CD-RISC-10,[316,317] to measure characteristics of resiliency that was used in Chapter 3 was used in this study. Responses were summed, with high scores indicating greater resilience.

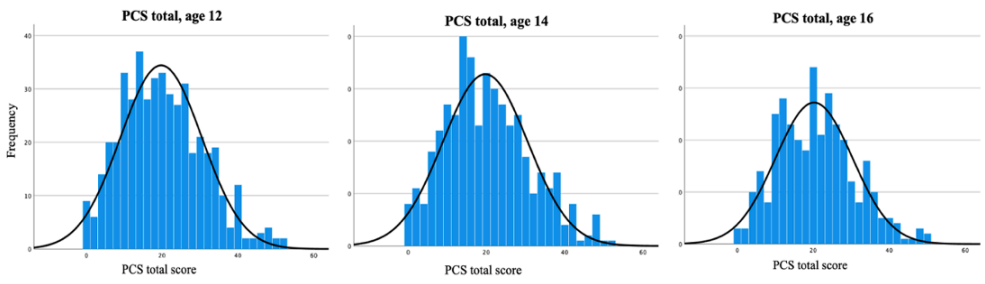
4.2.4 Statistical Analyses

Statistical analyses were performed using SPSS software ver. 28.0 (IBM, Armonk, NY, USA).

4.2.4.1 Data Distribution and Outliers

The data distribution for each self-report questionnaire was assessed using histograms and the Kolmogorov-Smirnov Tests.[361] While the histogram visually indicates the data's distribution, the Kolmogorov-Smirnov test compares the empirical distribution of the data to the theoretical distribution, making it a more robust test for normality. Interestingly, the histograms of the data appeared relatively normal, as shown in Figure 32 using PCS scores as an example.

Figure 32. Histograms of PCS Total Scores Across The Three Timepoints Show Normally Distributed Data



Abbreviations. PCS, pain catastrophising scale

However, the Kolmogorov-Smirnov Test for normality produced a *p*-value below 0.05, which means that there is enough evidence to reject the null hypothesis that the sample is normally distributed. This could indicate some departures from normality in the data, such as skewness, heavy tails, or outliers. The Kolmogorov-Smirnov test statistic D, critical values, and power are impacted by sample size.[362] As the sample size increases, the test becomes more sensitive to small departures from normality. This means that with a large sample size, the Kolmogorov-Smirnov test may detect even minor deviations from normality that would not be detected with a smaller sample size.

The Tukey Method[363] was used to identify outliers in the dataset. The method is based on the IQR, which is the range of values between the 25th and 75th percentiles of the data. Any extreme outliers identified were replaced with the median for that variable to avoid a missing data point.

After assessing the data distribution and identifying outliers, parametric statistical tests were used for all comparisons. The median scores within the results are reported instead of means, as the median is a good measure of central tendency and is less sensitive to outliers and skewed data.[364]

4.2.4.2 Demographics, Health History, and Self-report Questionnaires

The analysis plan included eight steps. To begin, the participant attrition rate was calculated across the three time points by dividing the number of missing participants from each time point by the number of participants in that time point and multiplying by 100 to get the percentage. Independent samples t-tests assessed if gender, age, SES, or race impacted participant dropout.

The second step included summarising the participant demographics and health data. Medians and IRQs were calculated for age and SES for the entire sample, chronic pain, and no-pain groups for each time point. The frequencies and percentages were calculated for gender, race, pain locations, and number of pain sites. One-way ANOVAs with repeated measures were used to compare the participant's ages across the three time points.

The third step included scoring the psych questionnaires. The self-report questionnaires assessed pain catastrophising, anxiety, depression, positive childhood experiences, adverse childhood experiences, and resiliency. Medians and IQRs were calculated for each questionnaire for the entire sample and both the chronic pain and the no-pain groups. The frequencies and percentages of the clinical cut-offs were calculated for the PCS scale.

The fourth step included comparing questionnaire scores to published norms, when available, using a one-sample t-test. Norms provide a contextualisation for making sense of the results and assist in identifying outliers, which may warrant further investigation or consideration.

The fifth step examined the effects of time and gender on questionnaire scores. A 3 x 2 ANOVA was conducted to examine the effects of time (baseline, Time Point 2, Time Point 3) and gender (male, female) on questionnaire scores. The dependent variables, questionnaire scores, met the normality assumptions and variance homogeneity.

The sixth step examined the relationship between chronic pain status and pain catastrophising levels over time while controlling for several covariates. Given the inconsistency of chronic pain presence across the three time points (*e.g.,* participants endorsing no pain at Baseline and Time Point 3 but experiencing chronic pain at Time Point 2), conducting an ANOVA would not be appropriate for this assessment. Therefore, to analyse the data across time, linear mixed-effects models were employed. Compared to an ANOVA, linear mixed-effects models are a more flexible and powerful approach for analysing repeated measures or longitudinal data as they account for within-subject dependencies and individual-level differences. Using this method, we aimed to gain a more nuanced understanding of the relationship between variables. Thus, eight separate linear mixed-effects models were conducted to analyse the relationship between chronic pain status and pain catastrophising levels over time while controlling for several covariates. The covariates included gender, positive childhood experiences, adverse childhood experiences, life event impact scores, anxiety, depression, and resiliency. By

including these covariates in the analysis, we aimed to account for their potential influence on the observed associations and enhance the validity of the results.

The seventh step examined the relationship of questionnaire scores with pain catastrophising. A Pearson's correlation was conducted to assess the relationship of childhood events, resiliency, anxiety, and depression with pain catastrophising.

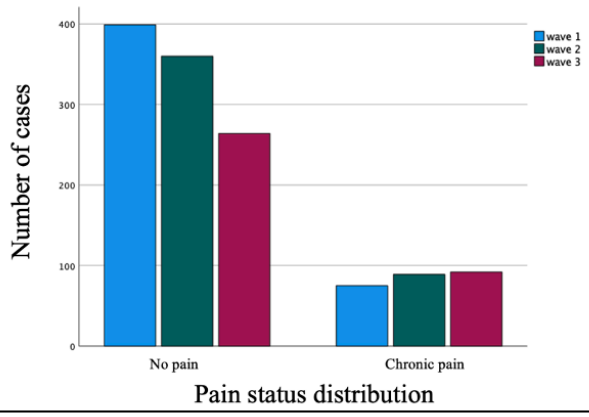
The eighth step assessed if high pain catastrophising at age 12 predicted chronic pain and dysmenorrhea at ages 14 and 16 using logistic regression analysis. This analysis predicted the *likelihood* of a binary outcome as a function of the values of the continuous predictor. The continuous measure of PCS was used as the predictor variable and the chronic pain variable at Time Point 2 and Time Point 3 as the outcome variables.

4.3 Results

4.3.1 Attrition Rate Across Study Visits (Step 1)

A total of 314 participants completed all three time points. For the entire sample, the attrition rate was 11% for time 2 and 9% for time 3. This is considered a relatively low attrition rate, with 27% reported by similar studies.[365] While the sample size decreased across time points, the incidence of chronic pain increased (Figure 33). Of the participants retained versus lost, an independent samples t-test showed a main effect of gender, with greater retention of female participants ($t(496) = 2.4$, $p = 0.007$, $d = 0.22$). Age, SES, and race did not affect participant dropout ($p > 0.05$).

Figure 33. Pain Group Distribution Across Baseline, Time Point 2 and Time Point 3.



In examining the attrition patterns of the study, I wanted to consider both the extremes of dropout and the potential factors contributing to it. To ensure the robustness of our findings and account for potential biases introduced by attrition, sensitivity analyses were conducted. These analyses aimed to assess whether the results remained consistent when accounting for the participants who dropped out. Additionally, it's worth mentioning that some participants may have moved away during the course of the study, which could have contributed to attrition. While I didn't explicitly examine this aspect in the analysis, it's a potential factor to consider when interpreting the attrition rates and their implications for the generalisability of the findings. Furthermore, gender had a significant impact on retention, with a higher retention rate observed among female participants, while age, SES, and race did not significantly affect participant dropout ($p > 0.05$). These findings shed light on the factors influencing attrition in this study, allowing for a more comprehensive understanding of the research outcomes.

4.3.2 Demographics and Health Data (Step 2)

See Table 36 for a summary of demographics health data for the entire sample and those with and without chronic pain. When comparing the participant's ages across each time point, statistically significant differences were detected ($F(1.4, 554.3) = 19425.0$, $p < 0.001$).

Table 36. Demographics and Health History

Baseline		**No Pain** (*n* = 399)	**Chronic Pain** (*n* = 75)	**Total** (*n* = 498)
Age [Median (IQR)]		13.4 (1)	13.5 (.8)	13.3 (.9)
Gender, Female [*n,* %]		291, 55%	43, 57%	275, 55%
SES [Median (IQR)]		4.0 (1.5)	4.0 (2.0)	4.0 (1.5)
Race [%]	*White*	76%	84%	77%
	African/Caribbean	2%	3%	2%
	East Asian	2%	0%	2%
	South Asian	5%	1%	5%
	Arab/Middle East	2%	0%	1%
	Mixed	6%	5%	6%
	Unknown/Did not report	8%	7%	8%
Time 2		**No Pain** (*n* = 360)	**Chronic Pain** (*n* = 89)	**Total** (*n* = 448)
Age [Median (IQR)]		14.6 (1)	14.4 (.7)	14.6 (0.9)
Gender, Female [*n,* %]		181, 51%	65, 73%	249, 56%
SES [Median (IQR)]		4 (1.0)	3.5 (1.6)	4. (1.5)
Race [%]	*White*	76%	84%	7%
	African/Caribbean	2%	2%	3%
	East Asian	2%	1%	2%
	South Asian	5%	2%	5%
	Arab/Middle East	1%	1%	1%
	Mixed	7%	3%	6%
	Did not report	8%	6%	8%
Time 3		**No Pain** (*n* = 264)	**Chronic Pain** (*n* = 92)	**Total** (*n* = 410)
Age [Median (IQR)]		15.7 (1)	15.6 (1)	15 (.7)
Gender, Female [*n,* %]		163, 63%	70, 76%	239, 58%
SES [Median (IQR)]		4 (1.5)	4 (1)	4 (1.5)
Race [%]	*White*	76%	78%	77%
	African/Caribbean	3%	3%	3%
	East Asian	3%	1%	2%
	South Asian	5%	4%	4%
	Arab/Middle East	1%	0%	1%
	Mixed	6%	4%	6%

Did not report	7%	9%	8%

Participants with chronic pain were asked to report their pain location and the number of pain sites (Table 37). At Baseline, the mean number of pain sites reported was 3.6. The mean number of pain sites for Time Points 2 and 3 was 4.2.

Female adolescents were asked if they experienced dysmenorrhea. At Baseline, dysmenorrhea was reported in 25% (n = 19) of participants. At Time Point 2, 53% (n = 47) of participants reported dysmenorrhea. Lastly, at Time Point 3, 34% (n = 31) of participants reported dysmenorrhea. The largest percentage increase between ages 12 and 14, increasing by 28%. It decreased by 19% for adolescents at age 16.

Table 37. Pain Locations for Chronic Pain Participants (Males and Females), *n, %*

Baseline (n = 75)				
Pain Location			Number of Pain Sites	
	Head	32, 43%	*1*	19, 25%
	Neck	20, 27%	*2*	9, 12%
	Throat	24, 32%	*3*	14, 19%
	Ear	17, 23%	*4*	11, 15%
	Back	35, 47%	*5*	6, 8%
	Joints	27, 36%	*6*	6, 8%
	Hands/arms	19 35%	*7*	4, 5%
	Legs/feet	40, 53%	*8*	3, 4%
	Stomach	28, 37%	*9*	2, 3%
	All over body	5, 7%	*10*	1, 1%
			11	0, 0%
Time Point 2 (*n* = 89)				
Pain Location			Number of Pain Sites	
	Head	52, 58%	*1*	16, 18%
	Neck	28, 32%	*2*	12, 14%
	Throat	27, 30%	*3*	14, 16%
	Ear	17, 19%	*4*	11, 12%
	Back	41, 46%	*5*	11, 12%
	Joints	44, 49%	*6*	4, 5%
	Hands/arms	30, 34%	*7*	6, 7%
	Legs/feet	47, 53%	*8*	6, 7%
	Stomach	34, 38%	*9*	4, 5%
	All over body	10, 11%	*10*	3, 3%
			11	1, 2%
Time Point 3 (*n* = 92)				
Pain Location			Number of Pain Sites	
	Head	58, 63%	*1*	11, 12%
	Neck	25, 27%	*2*	14, 15%
	Throat	36, 39%	*3*	15, 16%
	Ear	17, 19%	*4*	15, 16%
	Back	45, 49%	*5*	8, 9%
	Joints	40, 44%	*6*	10, 11%
	Hands/arms	31, 34%	*7*	3, 3%
	Legs/feet	46, 50%	*8*	5, 5%
	Stomach	38, 41%	*9*	6, 7%
	All over body	13, 14%	*10*	4, 4%
			11	1, 1%

4.3.3 Questionnaire Scores (Step 3)

4.3.3.1 Scores for Pain Catastrophising

The PCS score medians and IQRs for the entire sample, no pain group, and chronic pain group across the three time points are shown in Table 38. The PCS total scores and subscale scores are described, as well as the group breakdowns for the clinical cut-offs: low catastrophisers were scores between 0-

14, moderate catastrophisers were scores between 15-25, and high catastrophisers were scores between 26-52.[358]

Table 38. Pain Catastrophising Results, *Median (IQR)*

Baseline	**No Pain** (*n* = 393)	**Chronic Pain** (*n* = 68)	**Total** (*n* = 464)
PCS Total	18 (15)	19 (15)	19 (15)
Low [n, %]	149, 13%	18, 25%	167, 36%
Moderate [n, %]	136, 35%	30, 42%	166, 36%
High [n, %]	108, 28%	23, 32%	131, 28%
PCS Helplessness	6 (7)	7 (7)	6 (7)
PCS Rumination	3 (4)	4 (4)	4 (4)
PCS Magnification	9 (6)	9 (6)	9 (6)
Time Point 2	**No Pain** (*n* =356)	**Chronic Pain** (*n* = 89)	**Total** (*n* =445)
PCS Total	18 (14)	21 (18)	19 (15)
Low [n, %]	129, 36%	30, 34%	159, 36%
Moderate [n, %]	130, 37%	32, 36%	162, 36%
High [n, %]	97, 27%	27, 30%	124, 28%
PCS Helplessness	6 (7)	8 (9)	6 (7)
PCS Rumination	3 (3)	3 (5)	3 (3)
PCS Magnification	9 (6)	9 (7)	9 (6)
Time Point 3	**No Pain** (*n* = 256)	**Chronic Pain** (*n* = 90)	**Total** (*n* = 346)
PCS Total	19 (14)	21 (16)	20 (15)
Low [n, %]	89, 35%	25, 28%	114, 33%
Moderate [n, %]	93, 36%	37, 41%	130, 26%
High [n, %]	74, 29%	28, 31%	102, 21%
PCS Helplessness	6 (8)	8 (9)	7 (8)
PCS Rumination	3 (3)	3 (3)	3 (3)
PCS Magnification	9 (6)	10 (5)	10 (6)

4.3.3.2 Scores for Adverse and Positive Childhood Experiences

The CASE-C generated four scores: the number of positive childhood experiences, the positive childhood experiences impact score, the number of adverse childhood experiences, and the adverse childhood experiences impact score. See Table 39 for the median scores for the entire sample and participants with and without pain.

Table 39. Results from Child Adolescent Survey of Experiences – Child Version (CASE –C), *Median (IQR)*

Baseline	**No Pain** (*n* = 394)	**Chronic Pain** (*n* = 73)	**Total** (*n* = 489)
Number of PCEs	7 (4)	7 (5)	7 (4)
PCEs Impact Score	17 (10)	17 (10)	17 (10)
Number of ACEs*	5 (5)	12 (13)	5 (6)
ACEs Impact Score	10 (11)	25 (13)	10 (12)
Time Point 2	**No Pain** (*n* = 356)	**Chronic Pain** (*n* =89)	**Total** (*n* = 447)
Number of PCEs	6 (4)	6 (3)	6 (4)
PCEs Impact Score	15 (10)	15 (8)	15 (10)
Number of ACEs*	5 (5)	5 (6)	5 (5)
ACEs Impact Score*	9 (10)	10 (14)	9 (11)
Time Point 3	**No Pain** (*n* = 261)	**Chronic Pain** (*n* = 92)	**Total** (*n* = 390)
Number of PCEs	6 (3)	6 (4)	6 (4)
PCEs Impact Score	13 (8)	14 (11)	13 (9)
Number of ACEs**	5 (6)	6 (5)	5 (6)
ACEs Impact Score**	8 (10)	13 (7)	10 (11)

*$p < .05$, ** $p < .001$

4.3.3.3 Scores for Resiliency

The CD-RISC-SF provides one overall resiliency score, with higher scores reflecting higher resiliency (range is 0 to 40). The medians and IQRs for scores at each time point are presented in Table 40.

Table 40. Results from Connor Davidson – Resiliency Scale – Short Form, *Median (IQR)*

Baseline	**No Pain** (*n* = 391)	**Chronic Pain** (*n* = 74)	**Total** (*n* = 478)
CD-RISC-SF Total Score	25 (10)	20 (13)	25 (10)
Time Point 2	**No Pain** (*n* = 353)	**Chronic Pain** (*n* = 87)	**Total** (*n* = 445)
CD-RISC-SF Total Score	23 (11)	23 (11)	23 (10)
Time Point 3	**No Pain** (*n* = 257)	**Chronic Pain** (*n* = 89)	**Total** (*n* = 357)
CD-RISC-SF Total Score	25 (10)	23 (12)	24 (10)

4.3.3.4 Scores for Anxiety and Depression

The RCADS-SF produced a score for depression (range of 0 to 30) and anxiety (range of 0 to 45). For anxiety and depression, there was a consistent increase in Time Point 2 (Table 41)

Table 41. Results for Revised Child Anxiety and Depression Scale short form (RCADS-SF), *Median (IQR)*

Baseline	**No Pain** (*n* = 397)	**Chronic Pain** (*n* = 74)	**Total** (*n* = 501)
Anxiety	11 (10)	14 (9)	12 (10)
Depression	7 (6)	8 (6)	7 (5)
Time Point 2	**No Pain** (*n* = 356)	**Chronic Pain** (*n* = 89)	**Total** (*n* = 447)
Anxiety	13 (10)	15 (4)	13 (11)
Depression	8 (8)	11 (9)	9 (8)
Time Point 3	**No Pain** (*n* = 261)	**Chronic Pain** (*n* = 92)	**Total** (*n* = 390)
Anxiety	12 (10)	14 (14)	12 (11)
Depression	9 (8)	11 (9)	9 (9)

**p < .05, ** p < .001*
IQR = Interquartile range

4.3.4 Comparison to Published Norms (Step 4)

4.3.4.1 Pain Catastrophising

A one-sample t-test was conducted to determine whether the mean score on the PCS at each time point differed from a published study that reported a population mean of 22 for a paediatric pain sample.[314,349,358] The chronic pain group at Baseline reported a mean PCS score of 22.41, SD = 12.10. Unsurprisingly, the test did not reveal a significant difference between the sample and published population mean ($t(70) = 0.29$, $p = 0.39$). The same was true for Time Point 2 (mean = 21.57, SD = 12.14, $t(88) = -0.33$, $p = 0.37$) and Time Point 3 (mean = 21.2, SD =, 10.01, $t(89) = 0.23$, $p = 0.23$) when compared to the published population mean of 22.

Similarly, a one-sample t-test was conducted to determine whether the pain-free group's mean score on the PCS at each time point differed from the published population mean of 19.52 for a paediatric pain-free sample.[342] The no-pain group at Baseline reported a mean PCS score of 19.05, SD = 10.19. The test did not reveal a significant difference between the sample mean and the population mean ($t(392) = -0.92$, $p = 0.18$). The same was true for both Time Point 2 (mean = 19.13, SD = 10.33, $t(355) = -0.70$, $p = 0.24$) and Time Point 3 (mean = 19.69, SD =, 10.02, $t(255) = 0.27$, $p = 0.40$) compared to the published norm of 19.52.

4.3.4.2 Adverse and Positive Childhood Experiences

For children 12 years and older, the published norms for the number of positive childhood experiences are a mean of 5.69, SD = 2.72.[366] For the current sample, the mean number of positive childhood experiences for Baseline was 6.9 (SD = 3.0), Time Point 2 was 6.5 (SD = 3.1), and Wave 3 was 6.1 (SD = 2.8). Interestingly, there were significant differences for Baseline ($t(307) = 2.3$, $p = 0.01$) and Time Point 3 ($t(313) = -2.15$, $p = .002$), but not for Time Point ($t(314) = -.20$, $p = 0.42$).

For the number of adverse childhood experiences, the mean is 2.69, SD =2.53. For our sample, the mean number of adverse childhood experiences for Baseline was 5.29 (SD = 3.7), Time Point 2 was 5.52 (SD = 3.9), and Time Point 3 was 5.1 (SD = 3.5). There were significant differences for Baseline ($t(307) = 12.2$, $p < 0.001$) , Time Point 2 ($t(313) = 12.5$, $p < 0.001$), and Time Point 3 ($t(313) = 12.1$, $p < 0.001$).

For the positive childhood experience impact score, the mean is 14.37 (SD = 6.64). For our sample, the mean number of positive childhood experience impact score for Baseline was 16.72 (SD = 7.4), Time Point 2 was 15.44 (SD = 7.0), and Time Point 3 was 14.8 (SD = 7.2). Interestingly, there were significant differences for Baseline ($t(307) = 5.6$, $p < 0.001$) and Time Point 2 ($t(313) = 2.7$, $p = 0.004$). Time Point 3 did not show significant differences ($t(313) = 1.0$, $p = 0.16$).

For the adverse childhood experiences impact score, the mean published norm for adolescents is 4.89 (SD = 5.23). For our sample, the mean adverse childhood experience impact score for Baseline was 11.81 (SD = 8.85), Time Point 2 was 11.54 (SD = 9.0), and Time Point 3 was 10.81 (SD = 8.0). Interestingly, there were significant differences for Baseline 1 ($t(307) = 13.7$, $p < 0.001$), Time Point 2 ($t(313) = 13.73$, $p < 0.001$), and Time Point 3 ($t(313) = 13.0$, $p < 0.001$).

4.3.4.3 Resiliency

Currently, published norms for the CD-RISC-SF 10-item version exist for (1) a community sample of 190 adolescents between 12 – 16 years in Singapore who reported a mean score of 27.88[367] and (2) 10 juvenile males ages 14-17 from the USA who reported a mean score of 33.5, SD = 18.4[368]There are no available norms specifically for children with chronic pain or a sample of schoolchildren in England.

Since there are no norms for the CD-RISC-SF 10-item version for English schoolchildren, especially longitudinally and for those with chronic pain, publishing these results could benefit the paediatric resiliency literature. The normative data can provide a benchmark for resilience levels in schoolchildren in the UK, which can be used to identify areas where targeted interventions may be necessary. Researchers can use these normative values to compare resilience levels in different populations or examine resilience changes over time. The CD-RISC -SF questionnaire is just one tool for assessing resilience and should be used in conjunction with other clinical and psychosocial

assessments. Interpreting the questionnaire's results should be done in the context of the adolescent's specific circumstances and experiences.

4.3.4.4 Anxiety

The overall normative mean score for anxiety was 12.15 (SD = 6.53). Interestingly, for the current samples' anxiety and depression scores, there were significant differences for all time points. In the current sample, participants reported higher anxiety for each time point when compared to the published norms. Baseline anxiety, $t(494) = 2.54$, $p = 0.006$ (mean of 13 vs 12); Time Point 2 anxiety, $t(446) = 5.37$, $p < 0.001$ (mean of 14 vs 12); Time Point 3 anxiety, $t(389) = 4.31$, $p < 0.001$ (mean of 14 vs 12).

4.3.4.5 Depression

The overall normative mean score for depression is 8.24 (SD = 4.46). The Baseline was significantly lower than the published norm, but Time Points 2 and 3 were significantly higher than the published norm. Baseline depression, $t(494) = -2.43$, $p = 0.008$ (mean of 7 vs 8); Time Point 2 depression, $t(446) = 3.74$, $p < 0.001$ (mean of 9 vs 8); Time Point 3 depression, $t(389) = 5.52$, $p < 0.001$ (mean of 10 vs 8).

4.3.5 Effects of Time and Gender Questionnaire Scores (Step 5)

4.3.5.1 Pain Catastrophising

To assess PCS over three time points, eight linear mixed-effects models were conducted to examine the relationship between pain status and pain catastrophising levels over time while controlling for several covariates. The covariates included gender, number of positive childhood experiences, number of adverse childhood experiences, life event impact scores, anxiety, depression, and resiliency.

The results from the linear mixed-effects model showed that chronic pain was a significant predictor of PCS in the following seven models, (1) Resiliency; B = 2.03, SE = 0.69, t = 2.94, $p = 0.003$; (2) Number of positive childhood experiences; B = 2.24, SE = 0.68, t = 3.24, $p = 0.001$; (3) The positive

childhood experiences impact score; B = 2.25, SE = 0.68, t = 3.30, $p < 0.001$; (4) Number of adverse childhood experiences; B = 2.26, SE = 0.68, t = 3.32, $p < 0.001$; (5) The adverse childhood experience impact score; B = 2.28, SE = 0.68, t = 3.34, $p < 0.001$; (6) Anxiety; B = 2.17, SE = 0.68, t = 3.18, $p = 0.002$; (7) Depression; B = 2.18, SE = 0.68, t = 3.20, $p = 0.001$.

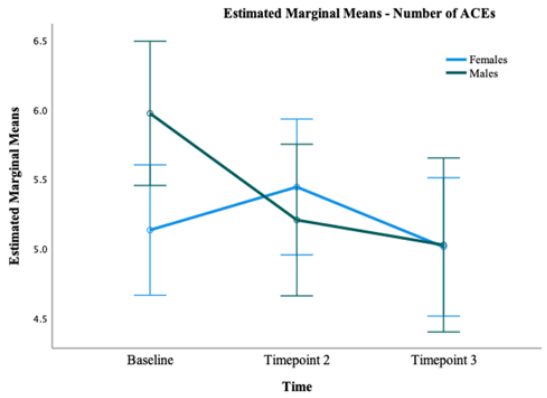
In the eighth model, controlling for gender, the analysis revealed a significant main effect of chronic pain on PCS scores (F(1,1141) = 8.81, $p = 0$ .003). This finding indicated that the chronic pain group participants had higher PCS scores than those in the no pain group. Moreover, there was a significant time effect (F(1,608) = 3.82, $p = 0.05$), which suggests that PCS scores increased over time, even after adjusting for gender. Interestingly, the analysis did not reveal a significant interaction effect between pain and time (F(1,763) = 2.10, $p = 0.15$) or gender and time (F(1,442) = 1.77, $p = 0.16$). These results indicate that the relationship between pain, gender, and PCS scores did not change over time.

This suggests that the association between pain and PCS score is robust to the influence of the covariates. In other words, even when controlling for the covariates, the pain significantly affects the PCS scores. This strengthens the evidence that the relationship between pain and the PCS score is real and not simply due to the influence of other variables.

4.3.5.2 Adverse and Positive Childhood Experiences

There was no significant main effect time for the quantity of adverse childhood experiences (F(2, 1370) = 1.945, $p = 0.14$, $\eta 2 = 0.003$) The main effect of gender was also insignificant (F(1, 1370) = *0.879*, $p = 0.35$, $\eta 2 = 0.001$). There was an insignificant interaction effect (F(2, 1270) = 2.386, $p = 0.09$, $\eta 2 = 0.004$). These results indicate that the number of adverse childhood experiences did not vary significantly across time and gender (Figure 34).

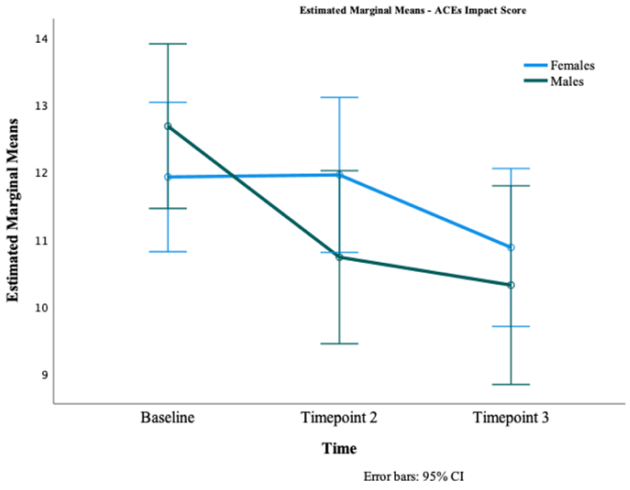
Figure 34. Number of Adverse Childhood Experiences Across Time and Gender



Abbreviations. ACEs, adverse childhood experiences

The adverse childhood experiences impact score had a significant main effect of time (F(2, 1318) = 3.642, p = 0.03, η2 = 0.005). Post hoc tests using the Bonferroni correction revealed that the adverse childhood experience impact score at Baseline (M = 12.27, SD = 9.89) were significantly higher than at Time Point 3 (M = 10.66 SD = 7.96, p = .03), indicating a decrease in adverse childhood experience impact score as participants aged. There were no differences between Baseline and Time Points 2 or Times Points 2 and 3. The main effect of gender was insignificant (F(1, 1318) = *0.438*, p = 0.51, η2 = 0.001). There was an insignificant interaction effect (F(2, 1318) = 0.002 , p = 0.25, η2 = 0.002). These results indicate that the adverse childhood experience impact score varied across time but not gender.

Figure 35. Adverse Childhood Experiences Impact Score Across Time and Gender



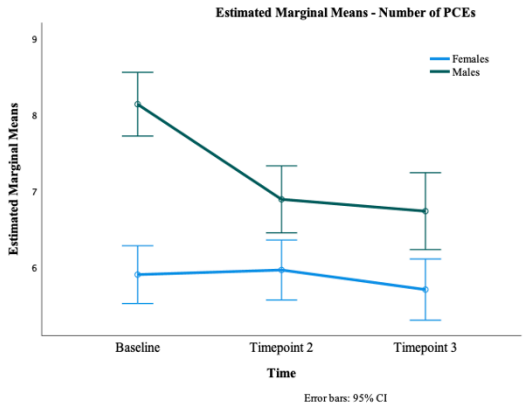
Abbreviations. ACEs, adverse childhood experiences

A 3 x 2 ANOVA was conducted to examine the effects of time (Baseline, Time Point 2, Time Point 3) and gender (male, female) on the number of positive childhood experiences. There was a significant main effect of time on the number of positive childhood experiences ($F(2, 1320) = 7.60$, $p < 0.001$, $\eta 2 = 0.011$). Post hoc tests using the Bonferroni correction revealed that the number of positive childhood experiences at Baseline ($M = 6.9$, $SD = 3.3$) was significantly higher than at Time Point 2 ($M = 6.38$, $SD = 3.3$, $p = .03$) and Time Point 3 ($M = 6.1$, $SD = 3.0$, $p < .001$), indicating a decrease in the number of positive childhood experiences as participants aged. There were no differences between Time Points 2 and 3. The main effect of Gender was also significant ($F(1, 1320) = 62.48$, $p < .001$, $\eta 2 = 0.045$). Male participants ($M = 7.3$, $SD = 3.7$) reported more positive childhood experiences than female participants ($M = 3.78$, $SD = 0.92$).

Furthermore, there was a significant interaction effect between time and gender ($F(2, 1320) = 6.07$, $p = 0.002$, $\eta 2 = 0.009$). Simple effects analyses were conducted to probe the interaction effect. These analyses revealed that the decrease in the number of positive childhood experiences from Baseline to Time Point 2 ($p < 0.001$) and Baseline to Time Point 3 ($p < 0.001$) was significant only for males compared to females ($p = 0.71$).

These results indicate that the number of positive childhood experiences varied significantly across time and gender. The number of positive childhood experiences decreased over time for both males and females, males consistently reported a higher number of positive childhood experiences than females across all time points (Figure 36).

Figure 36. Number of Positive Childhood Experiences Across Time and Gender



Abbreviations. PCEs, positive childhood experiences

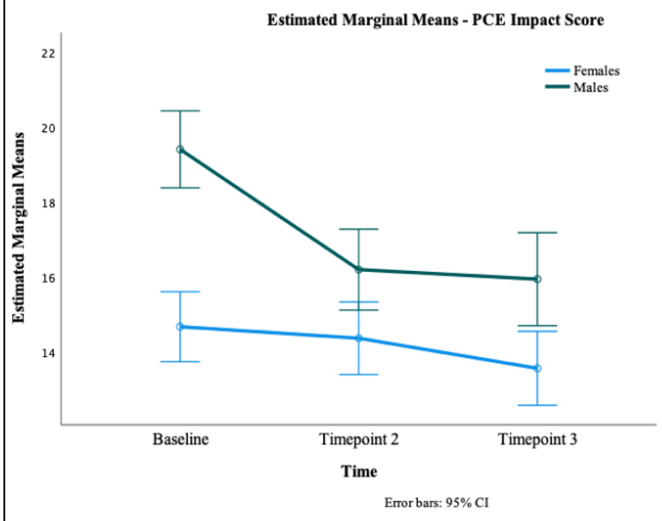
There was a significant main effect of time on the positive childhood experience impact score ($F(2, 1318) = 10.48$, $p < 0.001$, $\eta 2 = 0.016$). Post hoc tests using the Bonferroni correction revealed that the positive childhood experience impact score at Baseline ($M = 16.8$, $SD = 8.4$) were significantly higher than at Time Point 2 ($M = 15.2$, $SD = 7.8$, $p = 0.04$) and Time Point 3 ($M = 14.5$, $SD = 7.5$, $p < 0.001$), indicating a decrease in positive childhood experience impact score as participants aged. There were no differences between Time Points 2 and 3. The main effect of gender was also significant ($F(1, 1318) = 47.60$, $p < 0.001$, $\eta 2 = 0.034$). Male participants ($M = 17.37$, $SD = 9.12$) exhibited a higher positive childhood experience impact score compared to female participants ($M = 14.23$, $SD = 7.00$).

Furthermore, there was a significant interaction effect between time and gender ($F(2, 1318) = 4.53$, $p = 0.01$, $\eta 2 = 0.007$). Simple effects analyses were conducted to probe the interaction effect. These

analyses revealed that the decrease in positive childhood experience scores from Baseline to Time Point 2 ($p < 0.001$) and Baseline to Time Point 3 ($p < 0.001$) was significant only for males.

These results indicate that the positive childhood experience scores varied significantly across time and gender. The positive childhood experience scores decreased over time for both males and females but were only significant for males.

Figure 37. Positive Childhood Experiences Impact Score Across Time and Gender



Abbreviations. PCEs, positive childhood experiences

4.3.5.3 Resiliency

There was a significant main effect of time for CD-RISC score ($F(2, 1270) = 3.712$, $p = 0.03$, $\eta 2 = 0.006$). The main effect of gender was also significant ($F(1, 1270) = 33.36$, $p < 0.001$, $\eta 2 = 0.026$). Male participants ($M = 25.45$, $SD = 6.79$) exhibited a higher CD-RISC score than female participants ($M = 23.03$, $SD = 7.74$). There was an insignificant main effect of time for the CD-RISC score ($F(2, 1270) = 0.208$, $p = 0.81$, $\eta 2 = 0.001$). These results indicate that the resiliency scores varied significantly across time and gender. The resiliency decreased over time for both males and females but were only significant for males.

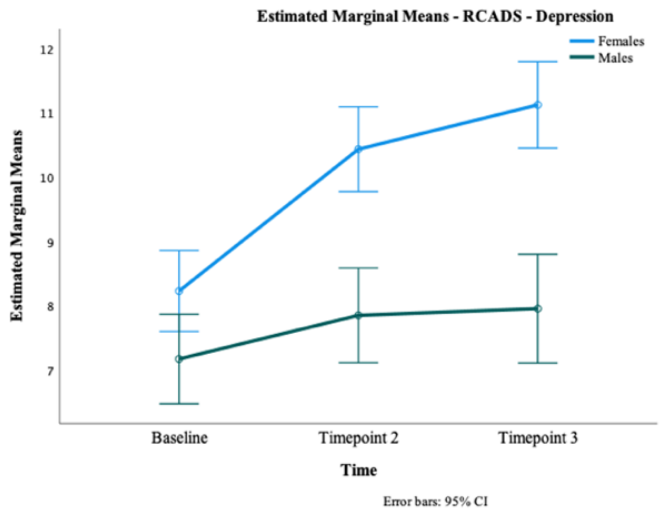
4.3.5.4 Anxiety

For anxiety, there was no significant main effect of time ($F(2, 1326) = 2.708$, $p = 0.07$, $\eta 2 = 0.004$). The main effect of gender was significant ($F(1, 1326) = 93.770$, $p < 0.001$, $\eta 2 = 0.066$). Male participants (M = 11.41, SD = 6.29) exhibited a higher anxiety score than female participants (M = 15.24, SD = 7.77). There was an insignificant interaction effect ($F(2, 1326) = 0.814$, $p = 0.44$, $\eta 2 = 0.001$). These results indicate that the anxiety varied across gender but not time.

4.3.5.5 Depression

For depression, there was a significant main effect of time ($F(2, 1326) = 14.911$, $p < 0.001$, $\eta 2 = 0.022$). Post hoc tests using the Bonferroni correction revealed that the depression score at Time Point 1 (M = 7.75, SD = 4.48) was significantly lower than at Time Point 2 (M = 9.28, SD = 5.90, $p < 0.001$) and Time Point 3 (M = 9.90, SD = 5.77, $p < 0.001$) indicating an increase in depression score as participants aged. There were no differences between Time Points 2 and 3. The main effect of gender was significant ($F(1, 1326) = 58.98$, $p < 0.001$, $\eta 2 = 0.043$). Male participants (M = 7.61, SD = 4.82) exhibited a higher depression score than female participants (M = 9.86, SD = 5.77). There was significant interaction effect ($F(2, 1326) = 4.690$, $p = 0.009$, $\eta 2 = 0.007$). Simple effects analyses were conducted to probe the interaction effect. These analyses revealed that the increase in depression scores from Baseline to Time Point 2 ($p < 0.001$) and Baseline to Time Point 3 ($p < 0.001$) was significant only for females.

Figure 38. Depression Scores Across Time and Gender



Abbreviations. ACEs, adverse childhood experiences

4.3.6 Other Psych Questionnaire Relationship with Pain Catastrophising (Step 6)

4.3.6.1 Adverse and Positive Childhood Experiences

The relationship between of positive childhood experiences, adverse childhood experiences, and pain catastrophising was assessed. First, a Pearson correlation coefficient was computed to assess the linear relationship between the number of positive childhood experiences and pain catastrophising. The relationship was not statistically significant ($p > 0.05$), suggesting that the observed correlation may have occurred due to random chance.

A Pearson correlation coefficient was computed to assess the linear relationship between the positive childhood experience impact score and pain catastrophising (Table 42). Positive childhood experience impact score at Baseline and PCS total score at Time Point 3 had a statistically significant linear relationship ($r = -0.11$, $p < 0$ .05).

Table 42. Correlation Coefficients Between the PCE Impact Scores and Pain Catastrophising Scores.

	PCS B	PCS T2	PCS T3
PCE Impact Score B	-0.03	-0.07	-0.10
PCE Impact Score T2	-0.2	-0.06	-0.09
PCE Impact Score T3	-0.11*	-0.08	-0.10

*Correlation significance level, ≤ 0.05 (2-tailed).
Abbreviations. PCE, positive childhood experience; PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

A Pearson correlation coefficient was also computed to assess the linear relationship between the number of adverse childhood experiences and pain catastrophising. There was a significant relationship at each time point (Table 43).

Table 43. Correlation Coefficients Between the Number of ACEs and Pain Catastrophising Scores

	PCS B	PCS T2	PCS T3
Number of ACEs B	0.17**	0.12*	0.12*
Number of ACEs T2	0.10*	0.21**	0.15**
Number of ACEs T3	0.15*	0.18**	0.26**

*Correlation significance level, ≤ 0.05 (2-tailed).
*Correlation significance level, ≤ 0.001 (2-tailed).
Abbreviations. ACE, adverse childhood experience; PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

Lastly, a Pearson correlation coefficient was also computed to assess the linear relationship between the adverse childhood experience impact score and pain catastrophising. There was a significant relationship at each time point (Table 44).

Table 44. Correlation Coefficients Between the ACEs Impact Score and Pain Catastrophising Scores

	PCS B	PCS T2	PCS T3
ACE Impact Score B	0.22**	0.12**	0.13*
ACE Impact Score T2	0.17*	0.25**	0.19**
ACE Impact Score T3	0.15**	0.20**	0.31**

*Correlation significance level, ≤ 0.05 (2-tailed).
*Correlation significance level, ≤ 0.001 (2-tailed).
Abbreviations. ACE, adverse childhood experience; PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

4.3.6.2 Resiliency

Next, the relationship between resiliency and pain catastrophising was examined. A Pearson correlation coefficient assessed the linear relationship between CD-RISC-SF total score and pain catastrophising. There was a significant relationship at each time point (Table 45).

Table 45. Correlation Coefficients Between the Resiliency and Pain Catastrophising Scores

	PCS B	PCS T2	PCS T3
Resiliency B	-0.36**	-0.41**	-0.25**
Resiliency T2	-0.27**	-0.35**	-0.28**
Resiliency T3	-0.17**	-0.31**	-0.32**

*Correlation significance level, ≤ 0.05 (2-tailed).
*Correlation significance level, ≤ 0.001 (2-tailed).
Abbreviations. PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

4.3.6.3 Anxiety

The relationship between anxiety and pain catastrophising was examined. A Pearson correlation coefficient assessed the linear relationship between RCADS-SF anxiety score and pain catastrophising. There was a significant relationship at each time point (Table 46).

Table 46. Correlation Coefficients Between the Anxiety and Pain Catastrophising Scores

	PCS B	PCS T2	PCS T3
Anxiety B	0.41**	0.24**	0.22**
Anxiety T2	0.27**	0.46**	0.35**
AnxietyT3	0.20**	0.33**	0.44**

*Correlation significance level, ≤ 0.05 (2-tailed).
*Correlation significance level, ≤ 0.001 (2-tailed).
Abbreviations. PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

4.3.6.4 Depression

Next, the relationship between depression and pain catastrophising was examined. A Pearson correlation coefficient assessed the linear relationship between RCADS-SF depression score and pain catastrophising. There was a significant relationship at each time point (Table 47).

Table 47. Correlation Coefficients Between the Depression and Pain Catastrophising Scores

	PCS B	PCS T2	PCS T3
Depression B	0.31**	0.18**	0.18**
Depression T2	0.28**	0.36**	0.24**
Depression T3	0.21**	0.30**	0.33**

*Correlation significance level, ≤ 0.05 (2-tailed).
*Correlation significance level, ≤ 0.001 (2-tailed).
Abbreviations. PCS, pain catastrophising scale; B, baseline; T2, time point 2; T3, time point 3

4.3.7 Pain Catastrophising Predicting Chronic Pain and Dysmenorrhea (Step 7)

A logistic regression was performed to ascertain the effects of PCS total score, positive childhood experiences, adverse childhood experiences, resiliency, anxiety, and depression from Baseline on the likelihood that adolescents will report chronic pain versus no pain at all at Time Point 3. The logistic

regression model was not statistically significant ($\chi^2(9, n = 314) = 4.349$, $p = 0.89$). The model only explained 2.1% (Nagelkerke R2) of the variance in pain and correctly classified 74.3% of cases.

Next, dysmenorrhea was specifically assessed. Again, logistic regression was used to ascertain the effects of PCS total score, positive childhood experiences, adverse childhood experiences, resiliency, anxiety, and depression from Baseline on the likelihood that female adolescents will report dysmenorrhea pain versus no dysmenorrhea at Time Point 3. The logistic regression model was statistically significant ($\chi^2(8, n = 314) = 14.858$, $p = 0.05$). The model only explained 9.5% (Nagelkerke R2) of the variance in pain and correctly classified 66.2% of cases.

4.4 Conclusions

This study used a longitudinal design to investigate pain catastrophising in male and female adolescents at three different time points. The main objectives were to assess the stability of pain catastrophising across different age groups, explore its association with chronic pain development and dysmenorrhea in females, and examine the relationship between pain catastrophising and childhood experiences, resiliency, depression, and anxiety.

The study had a relatively low attrition rate, with a higher retention rate for female participants than male participants. The increase in the chronic pain group over time, despite a decrease in the overall sample size, may be attributed to gender differences in pain prevalence among adolescents. The sample primarily consisted of White individuals, which limits the generalisability of the findings to more diverse populations.

The results regarding the location and number of pain sites in participants with chronic pain increased over time. Dysmenorrhea in female adolescents also exhibited significant changes, with a substantial increase between ages 12 and 14 and a subsequent decrease at age 16. This finding emphasises the need for increased awareness and understanding of endometriosis symptoms in adolescents, as early symptom onset is associated with delayed diagnosis and adverse impacts on quality of life.[100,369]

The mean pain catastrophising scores did not significantly differ from the published population means at any of the three time points for both the chronic pain and the no-pain groups. Anxiety and depression were measured using the RCADS-SF questionnaire, and participants reported higher scores in these domains at all time points compared to the published norms.

The number of positive childhood experiences decreased significantly as participants aged, while the number of adverse childhood experiences remained relatively high throughout the study. The number of adverse childhood experiences did not vary significantly across time and gender. However, the adverse childhood experience impact score showed a significant decrease as participants aged, while the number of positive childhood experiences varied significantly across time but not gender. Additionally, for resiliency, the findings showed no significant differences in mean resiliency scores across the three time points.

Linear mixed-effects models were conducted to assess the effects of time and gender on the questionnaire scores. The results indicated that chronic pain significantly predicted pain catastrophising scores, even when controlling for various covariates. This suggests a robust association between pain and pain catastrophising, unaffected by other variables.

The logistic regression analysis conducted to assess chronic pain did not yield statistically significant results, indicating that the examined factors (pain catastrophising, childhood experiences, resiliency, anxiety, and depression) were not predictive of reporting general chronic pain. However, the model was significant for dysmenorrhea, indicating that high pain catastrophising at age 14 was predictive of reporting dysmenorrhea at age 16.

The study sheds light on several critical findings with significant clinical implications and directions for future research. Firstly, our investigation revealed that pain catastrophising exhibited a troubling trend of escalation over time, irrespective of gender and pain status. Furthermore, I observed a

consistent association between pain catastrophizing scores and pain status, a correlation that persisted even when we controlled for various covariates. These findings underscore the importance of addressing pain catastrophizing as a dynamic and independent factor in pain management, necessitating further exploration into its underlying mechanisms and potential interventions.

Turning our attention to childhood experiences, I found intriguing patterns in adverse childhood experiences and positive childhood events. Notably, the number of adverse childhood experiences remained relatively stable across time and gender, suggesting a persistent burden that merits targeted intervention efforts. Conversely, the impact score of these adverse childhood experiences exhibited a temporal variation, declining gradually over time, an encouraging sign that interventions may have a positive influence on individuals who have experienced adversity. Surprisingly, the data unveiled a gender-related disparity in the experience of positive childhood events, with males reporting more such events as time elapsed. This gender divergence warrants further investigation to understand its underlying causes and implications for well-being.

Delving deeper into mental health, our study illuminated trends in resilience, anxiety, and depression. Resilience scores exhibited a consistent decrease over time, with males experiencing a more pronounced decline, raising questions about potential gender-specific resilience-building strategies. Anxiety levels, on the other hand, primarily differed by gender, with females consistently reporting higher anxiety scores. This disparity underscores the need for gender-tailored mental health interventions. Finally, the study highlighted an alarming increase in depression symptoms with age, particularly pronounced in females. This alarming trend necessitates urgent attention to the mental health needs of aging populations, especially among women.

In conclusion, this study has unveiled a complex interplay of factors affecting pain, childhood experiences, and mental health, with implications for clinical practice and future research. The dynamics of pain catastrophizing, the persistence of adverse childhood experiences, gender disparities in positive childhood events, and the evolving patterns of resilience, anxiety, and depression all

present exciting avenues for further investigation and the development of targeted interventions to improve the well-being of individuals across the lifespan.

Overall, this study provides valuable insights into the relationship between chronic pain, pain catastrophising, childhood experiences, resilience, anxiety, and depression in adolescents. The findings suggest the need for targeted interventions to address this population's pain catastrophising and adverse childhood experiences. Additionally, the study highlights the importance of considering individual circumstances and experiences when interpreting the questionnaire results.

4.5 Discussion

Based on the literature, it was hypothesised that pain catastrophising scores would decrease with age. It was also expected that elevated pain catastrophising scores at an earlier age would predict chronic pain and dysmenorrhea in subsequent years. Lastly, it was hypothesised that higher resiliency and fewer positive childhood events would negatively correlate with pain catastrophising, while more adverse childhood experiences would be positively correlated.

While more research is needed to understand the relationship between pain catastrophising and adverse childhood experiences fully, it is clear that these two factors are closely intertwined and can have a significant impact on an individual's pain experience. Healthcare professionals should be aware of this connection and to consider a patient's history of adverse childhood experiences when developing treatment plans for chronic pain.

Regarding the relationship between positive and adverse childhood events, resiliency, and pain catastrophising, the mean number of positive childhood events remained stable. In contrast, the mean number of adverse childhood events slightly decreased over time. Significant differences were observed between time points for all variables except positive events at Time Point 2. These findings suggest that both positive and negative life events may influence adolescents' experience of pain,

highlighting the importance of considering both adverse and positive childhood experiences when assessing and treating chronic pain.

Furthermore, the study found stable pain catastrophising scores across adolescence for both males and females, indicating consistency in this aspect of the pain experience. However, none of the examined factors (pain catastrophising, childhood experiences, resiliency, anxiety, and depression) were statistically significant predictors of chronic pain at Time Points 2 or 3. Pain catastrophising did predict dysmenorrhea at Time Point 3. The results suggest that assessing an adolescent's environment and its impact may be more predictive of chronic pain than pain catastrophising itself. The study's design and findings have implications for developing more effective treatments for adolescent chronic pain and other pain conditions that commonly arise during adolescence.

This study investigated the stability of pain catastrophising over time and its predictive value for chronic pain and dysmenorrhea in adolescents. The findings hold implications for early diagnosis and treatment of conditions such as endometriosis, which commonly emerge during adolescence but are typically diagnosed in adulthood. The results can inform future research studies and personalised interventions for adolescents with chronic pain conditions.

In conclusion, this study underscores the importance of developing early interventions targeting negative thought patterns associated with chronic pain in adolescents. The findings highlight the influence of an adolescent's environment and childhood experiences on their pain experiences, suggesting that these factors may be better predictors of chronic pain than pain catastrophising alone. The study contributes novel insights into the relationship between pain catastrophising, childhood experiences, and adolescent pain outcomes.

4.5.1 Considerations and Limitations

It is important to acknowledge the study's limitations. These include the use of self-report measures, which may introduce bias or recall inaccuracies. Additionally, the study design does not establish

causality, and unmeasured factors could influence the observed relationships. The generalisability of the findings is limited due to the specific geographic region and the focus on specific types of pain and treatments.

Furthermore, females were not diagnosed with dysmenorrhea. The exclusion of females with diagnosed dysmenorrhea from the study means I did not investigate or gather data on this specific group of individuals. This exclusion is a limitation of the study because it narrows the scope of the research. It might limit the generalisability of the findings to a broader population, as the experiences and factors influencing individuals with dysmenorrhea could differ significantly from those without this condition.

4.5.2 Summary

Despite stable pain catastrophising scores across adolescence, the examined factors did not significantly predict chronic pain but did predict dysmenorrhea at Time Point 3. This suggests the need for further research to identify additional factors that may contribute to these pain outcomes in adolescents. The findings have important implications for healthcare professionals, emphasising the importance of considering both positive and adverse childhood experiences when assessing and treating chronic pain in adolescents. It also highlights the need for increased awareness and understanding of endometriosis symptoms in adolescents to facilitate early diagnosis and improve quality of life. This study contributes valuable knowledge to the field of adolescent chronic pain and informs the development of more effective interventions and treatments for this population. Further research is needed to expand our understanding of the complex factors influencing adolescent pain outcomes and improve their overall pain management and well-being.

Chronic pain in adolescents carries a significant burden, impacting their physical, emotional, and social well-being. It disrupts daily activities, sleep patterns, and can have long-term consequences into adulthood. Consequently, there's a pressing need to find effective treatments and interventions to alleviate their suffering and enhance their overall quality of life. The "so what" factor in this context is

that understanding the factors contributing to chronic pain and dysmenorrhea in adolescents isn't merely an academic pursuit—it has practical implications for healthcare professionals. By identifying these factors, healthcare professionals can tailor their assessment and treatment strategies more effectively. For example, if adverse childhood experiences are linked to chronic pain, a holistic approach addressing both physical and psychological aspects become essential.

Chapter 5
Discussion

"Life is not easy for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something, and that this thing must be attained."

Professor Marie Salomea Skłodowska–Curie

Physicist and chemist who conducted pioneering research on radioactivity, and the first woman to win a Nobel Prize.

5.0 Overview

The research presented in this thesis makes a case for the importance of the intricate relationships between life experiences during development, emotional functioning, and biological consequences of pain, all of which contribute to the development and maintenance of chronic pain. Manipulating these factors may have a causal influence on pain experiences, but research in this area is still in its infancy. The three experimental chapters addressed distinct but related scientific gaps. Each chapter employed a unique methodology and examined a different population, assessing the relationship between chronic pain using a neuro-biopsychosocial model.

5.1 Summary of Results

A multimodal approach that combines multiple measures is often used to assess pain in clinical research to capture the complex and multidimensional nature of pain experiences. I described my research as "innovative mixed methods" to assess pain in adolescents and adults. The innovative nature of this approach lies in integrating mixed methods and applying technology in studying pain in adolescent and adult women. By combining different research approaches and incorporating advanced techniques such as fNIRS and OA, which have not been previously applied to young women with dysmenorrhea or endometriosis, we are introducing new and cutting-edge methods to pain assessment. This combination represents a significant advancement in the field and has the potential to contribute novel findings to the understanding and management of pain in this population.

I proposed several hypotheses using the neuro-biopsychosocial model for chronic pain, specifically, dysmenorrhea and endometriosis-related pain. The research within this thesis delved into various aspects of pain, including biological, psychological, and emotional factors, offering a comprehensive approach to understanding and managing pain in specific populations. The three experimental chapters address distinct but related scientific gaps. Each employs a unique methodology and examines a different population, assessing the relationship between chronic pain using a neuro-biopsychosocial model.

General Overarching Thesis Themes

- Investigating the intricate connections between life experiences, emotional well-being, and the biological effects of pain in dysmenorrhea and endometriosis-related pain.
- Introducing innovative methods for pain assessment in adolescent girls and adult women with dysmenorrhea and endometriosis-related pain.
- Investigating psychological factors, including pain catastrophising, anxiety, and depression, as they may play a crucial role in pain perception and developing chronic pain in adolescents.

Within Chapter 2, I sought to test the hypothesis that fluctuations in sex hormones during the menstrual cycle significantly impact pain perception. I specifically tested if estrogen modulated heat pain sensitivity, and if its interaction with the central nervous system alters pain perception.

The results suggested there is some evidence suggests that hormonal fluctuations affect experimental pain sensitivity, the available data are inconclusive. Thus, further research is needed to confirm these findings. Additionally, the pilot study showed no significant difference in NRS ratings between the mid-follicular and mid-luteal groups but did find significant differences in the activation of pain circuitry.

More specifically, the scoping review revealed that the relationship between menstrual cycle hormones and experimental pain sensitivity is unclear and may be influenced by various factors. Among these factors is the type of pain stimulus employed, location tested on the body, definition of menstrual phases, and method for confirming menstrual phases. Thus, the present findings suggest that controlling for the menstrual cycle should be essential in pain research studies until sufficient evidence suggests otherwise. By doing so, we better understand how hormonal fluctuations impact pain, we may avoid potential confounding effects of menstrual cycle hormones on experimental pain results, and we may advance our understanding of pain mechanisms. However, it is important to acknowledge that the quantity and precision of data collected varied across the studies, and the reliability of the specific measures employed differed. Based on the scoring review results, I recommend the following to improve our general understanding of the impact of hormonal fluctuations on pain perception: standardization of methods, inclusion of hormonal profiles, sample diversity, and inclusion of psychological and social factors.

In summary, addressing the complexities of pain sensitivity across menstrual phases requires continued research efforts, standardized methodologies, and a holistic approach in clinical practice. It's crucial to recognize that pain perception is influenced by a combination of biological, hormonal,

psychological, and genetic factors, and a comprehensive understanding of these factors will lead to more effective pain management strategies for women.

Most importantly for this thesis, the scoping review and pilot study results informed the recruitment strategy for the study described in Chapter 3. The recruitment strategy was to only test participants during days 2-10 of their menstrual cycle if they were not taking hormonal contraception, which would help to control for the hormonal fluctuations during the menstrual cycle. Additionally, guided by these results, the study described in Chapter 3 included a series of questions related to their menstrual history.

Within Chapter 3, results showed significant differences in pain experience, menstrual characteristics, and psychological variables between the pain-free group, the endometriosis-related pain group, and the dysmenorrhea group. The pain-free group generally reported lower pain levels, shorter menstrual phases, and lower scores on pain catastrophising, adverse childhood experiences, and recent adverse experiences compared to the other two groups. The fNIRS + OA Subgroup analysis revealed differences in pain inhibition and functional connectivity between the prefrontal and somatosensory regions, with the pain-free group demonstrating more potent pain inhibition and functional connectivity during the OA task. These findings provide insights into the neural and psychological factors associated with MPP and may contribute to a better understanding of dysmenorrhea and endometriosis-related pain.

Within Chapter 4, it was hypothesised that pain catastrophising scores would decrease with age. It was also expected that elevated pain catastrophising scores at an earlier age would predict chronic pain and dysmenorrhea in subsequent years. Lastly, it was hypothesised that higher resiliency and fewer positive childhood events would negatively correlate with pain catastrophising, while more adverse childhood experiences would be positively correlated.

While more research is needed to understand the relationship between pain catastrophising and adverse childhood experiences fully, it is clear that these two factors are closely intertwined and can have a significant impact on an individual's pain experience. Healthcare professionals should be aware of this connection and to consider a patient's history of adverse childhood experiences when developing treatment plans for chronic pain.

Despite stable pain catastrophising scores across adolescence, the examined factors did not significantly predict chronic pain but did predict dysmenorrhea at Time Point 3. This suggests the need for further research to identify additional factors that may contribute to these pain outcomes in adolescents. The findings have important implications for healthcare professionals, emphasising the importance of considering both positive and adverse childhood experiences when assessing and treating chronic pain in adolescents. It also highlights the need for increased awareness and understanding of endometriosis symptoms in adolescents to facilitate early diagnosis and improve quality of life. This study contributes valuable knowledge to the field of adolescent chronic pain and informs the development of more effective interventions and treatments for this population. Further research is needed to expand our understanding of the complex factors influencing adolescent pain outcomes and improve their overall pain management and well-being.

Chronic pain in adolescents carries a significant burden, impacting their physical, emotional, and social well-being. It disrupts daily activities, sleep patterns, and can have long-term consequences into adulthood. Consequently, there's a pressing need to find effective treatments and interventions to alleviate their suffering and enhance their overall quality of life. By identifying these factors, healthcare providers can tailor their assessment and treatment strategies more effectively. For example, if adverse childhood experiences are linked to chronic pain, a holistic approach addressing both physical and psychological aspects become essential.

Taken together, these results provide a comprehensive exploration of the neuro-biopsychosocial model in the context of chronic pain in adolescent girls and young women. They shed light on the

complex interplay between life experiences, emotional functioning, biological mechanisms, and psychosocial variables. The findings underscore the significance of considering multiple dimensions in pain research and clinical interventions, aiming for a realistic and holistic approach to understanding and managing chronic pain.

By synthesising the insights from these chapters, we gain a deeper understanding of the big picture: chronic pain is a multifaceted phenomenon influenced by a combination of genetic, environmental, psychological, and social factors. This knowledge paves the way for future research and interventions targeting specific components of the neuro-biopsychosocial model, aiming to alleviate the burden of chronic pain and improve the well-being of individuals affected by these conditions.

5.2 Clinical Relevance

The research presented in this study holds significant clinical relevance as it has the potential to inform and enhance clinical practices in managing chronic pain. Understanding the modifiable factors influencing pain is crucial for developing effective interventions and treatment strategies.

Clinicians should consider menstrual phase-related pain sensitivity when developing pain management plans for female patients. This may involve adjusting medication dosages or therapies during certain menstrual phases. Clinicians could also explore the potential use of hormonal interventions, such as hormone replacement therapy or hormonal contraceptives, in managing pain conditions, particularly for women with chronic pain. Similarly, clinicians should educate female patients about the potential variations in pain sensitivity across menstrual phases. This can help them better manage their pain and understand why pain levels may fluctuate. Clinicians could also encourage a multidisciplinary approach to pain management, involving pain specialists, gynaecologists, and psychologists, to address both physical and psychological aspects of pain during different menstrual phases. For conditions where pain is a significant issue, hormonal interventions targeting specific menstrual phases may be explored as part of treatment strategies.

Clinicians can improve pain assessment and management by adopting a comprehensive biopsychosocial approach. This approach may involve tailoring treatments based on menstrual cycle phases, addressing psychological factors like pain catastrophising, and providing support and interventions targeting life events. One key implication is the importance of targeting adverse life events during development to prevent the onset and persistence of chronic pain. Identifying risk factors such as pain catastrophising and adverse childhood experiences allows clinicians to identify individuals at risk and implement preventive strategies to mitigate the development and progression of chronic pain conditions.

Ultimately, this research has the potential to enhance the effectiveness of clinical interventions and improve the quality of life for individuals living with chronic pain. Addressing dysmenorrhea and endometriosis as public health concerns is important, as untreated cases can lead to infertility and other serious health complications.[41] A multifaceted approach is required, including education, early diagnosis and management, and policies that support menstrual health and well-being.

5.2.1 Possible Treatments

Pain catastrophising as it is a potentially modifiable risk factor for chronic pain. Treatment for pain catastrophising typically involves cognitive-behavioural therapy, acceptance and commitment therapy, and multimodal treatment that combines cognitive-behavioural therapy and exercise.[162,370–373] These treatments have the goal of helping individuals learn to identify and challenge negative thoughts and develop coping strategies to manage their pain more effectively.[106,162] Although no definitive intervention exists, the research suggests that these three approaches have reasonable evidence of effectiveness. However, these treatments have been effective for improving chronic pain outcomes in adolescents but have not been used to specifically target pain catastrophising.[374,375]

5.2.2 Trauma-informed Care

Trauma-informed care is an effective approach that integrates trauma-informed principles into clinical practices, creating a supportive and empathetic environment that addresses the potential impact of

trauma on pain experiences and overall well-being.[198,206,376] It recognises the widespread impact of trauma and aims to understand and address the unique needs and experiences of individuals who have experienced trauma. By implementing trauma-informed care, healthcare professionals can create a safe, supportive, and empowering healthcare environment that promotes healing and resilience.[227]

Trauma-informed care would acknowledge the higher prevalence of traumatic experiences among these patients in the context of dysmenorrhea or endometriosis-related pain.[216] It recognises the interconnectedness of trauma and pain experiences and provides compassionate, patient-centred care that addresses their complex needs. By integrating trauma knowledge and principles into clinical practice, healthcare professionals can enhance the well-being and outcomes of patients with chronic pain.

Exploring the relationships between psychological, and psychosocial factors, and pain experiences may have implications for developing more effective management strategies for endometriosis-related pain and dysmenorrhea. By understanding how these factors interact with painful experiences and underlying brain processes, researchers may identify novel targets for interventions, such as incorporating positive psychology or trauma-informed care in treatment plans. The successful implementation of trauma-informed care may require adequate resources and training. Lack of resources and limited access to specialised care can hinder the delivery of trauma-informed care, highlighting the need for systemic support and allocation of resources to ensure its effective implementation.

In conclusion, trauma-informed care offers a compassionate and patient-cantered approach that recognises the impact of trauma on pain experiences. By integrating trauma knowledge into clinical practice and considering the complex needs of individuals who have experienced trauma, healthcare professions can enhance patient well-being and outcomes. Further research into the relationships between trauma, psychological factors, and pain experiences can guide the development of more

effective management strategies, benefiting individuals with endometriosis-related pain and dysmenorrhea.

5.3 Strengths and Weaknesses

The thesis exhibits several notable strengths. First, it undertakes a comprehensive exploration of factors related to chronic pain in adolescent and young adult females. This encompasses various dimensions, including life experiences, emotional functioning, and the biological consequences of pain. By considering these multifaceted aspects, the thesis offers a holistic understanding of the complex nature of chronic pain. Second, the thesis employs a mixed-methods design, integrating objective and subjective pain measurement methods. This combination allows for a more nuanced and comprehensive analysis of the topic. By triangulating data from different sources, the validity and reliability of the findings are enhanced. Third, the thesis demonstrates the integration of advanced techniques and technologies that have not been previously used in the study of pain in this population. By incorporating these innovative methods, the research expands the boundaries of knowledge in the field and opens up new possibilities for pain assessment and management. Lastly, including a longitudinal study design provides valuable insights into the development of chronic pain, specifically focusing on dysmenorrhea in female adolescents. By examining patterns and changes over time, this longitudinal perspective strengthens the understanding of the long-term implications of pain experiences.

However, the thesis also exhibits some weaknesses that should be considered. Firstly, the research primarily focuses on adolescent and young adult females experiencing pain associated with endometriosis and dysmenorrhea. While this specific population is crucial to study, the findings may have limited generalisability to other populations or types of chronic pain. Secondly, small sample sizes in Chapters 2 and 3 can impose limitations on statistical power and reduce the generalisability of the findings. Therefore, it is important to interpret the results with caution. Another weakness is relying heavily on self-report measures to assess pain, emotional functioning, and other variables. While self-report measures are commonly used in pain research, they are subject to biases and may

not always accurately reflect participants' experiences or behaviours. Lastly, the research area itself is in its infancy. Limited existing literature and established theoretical frameworks may restrict the depth of the discussion and the ability to draw strong conclusions from the findings.

The limitations include potential endometriosis misdiagnosis in control participants. These brief self-report measures may be affected by recall bias, controversies surrounding the self-report questionnaires, and potential confounds of long-term medication use on pain response and brain activity.

The participants in the dysmenorrhea group may have endometriosis, as their condition was not disconfirmed through surgery. As we do not know the underlying cause of dysmenorrhea in participants included in this study, we assumed they are reporting primary dysmenorrhea. However, this is a major limitation of the study and its findings. The pain associated with secondary dysmenorrhea, reported in the participants with endometriosis within this study, may be more severe and persistent than that of primary dysmenorrhea.[38,301] It may also accompany other symptoms such as heavy bleeding, irregular periods, or pain during sex. [38,301]

These include the use of self-report measures, which may introduce bias or recall inaccuracies. Additionally, the study design does not establish causality, and unmeasured factors could influence the observed relationships. The generalisability of the findings is limited due to the specific geographic region and the focus on specific types of pain and treatments.

Furthermore, females were not diagnosed with dysmenorrhea. Dysmenorrhea is a medical term for painful menstrual cramps experienced by some individuals during their menstrual cycles. It is a common gynaecological condition and is often characterized by abdominal pain and discomfort. The exclusion of females with diagnosed dysmenorrhea from the study means that the study did not investigate or gather data on this specific group of individuals. This exclusion can be a limitation of the study because it narrows the scope of the research. It might limit the generalisability of the

findings to a broader population, as the experiences and factors influencing individuals with dysmenorrhea could differ significantly from those without this condition.

There are a few limitations that applied to all the studies I conducted. This includes sample bias and lack of knowledge on past pregnancies and pain treatments tried. Sample bias may have influenced the outcomes, as many studies primarily focus on individuals with regular menstrual cycles and may not account for those with irregular cycles or underlying medical conditions affecting hormone levels. Additionally, the influence of pregnancy on pain perception, a significant hormonal change experienced by some individuals, has not been explored in this context. Furthermore, while we've discussed the variations in pain sensitivity across menstrual phases, we haven't delved into the potential effectiveness of different pain management treatments during these phases. Future research could benefit from addressing these gaps in understanding, considering a more diverse range of participants, including those with irregular cycles, and pregnancy-related hormonal changes, and exploring the efficacy of various pain management strategies.

The participants were recruited from one USA city, and it is important to replicate the study with larger and more diverse samples to ensure the robustness of the results. The study used a cross-sectional design, which limits the ability to establish causal relationships between variables. Longitudinal studies are needed to examine the temporal dynamics of MPP and explore the potential predictive factors of pain severity and persistence. The reliance on self-report measures for assessing pain, psychological variables, and menstrual characteristics introduces the possibility of recall bias or subjective interpretation. Objective measures, such as physiological assessments or clinical evaluations, could enhance the validity and reliability of the findings.

In the context of chronic pain in women, the use of measures, such as the CD-RISC-10 used in Chapters 3 and 4, and other resilience scales has faced criticism regarding what they truly measure. Some argue that these measures are capturing coping strategies rather than resilience per se.[328,329] When assessing resilience in the context of chronic pain, it becomes essential to disentangle coping

strategies from resilience factors to gain a more comprehensive understanding of how individuals navigate the complexities of chronic pain management and adaptation.[222] Future research should focus on differentiating the specific components of coping and resilience to elucidate their distinct contributions to the experiences of women living with chronic pain and inform targeted interventions for improving their well-being.

Nevertheless, despite these weaknesses, the thesis's integration of mixed methods, innovative techniques, and comprehensive exploration of factors contributing to chronic pain in adolescent and young adult females adds a valuable contribution to the field. The identified strengths outweigh the weaknesses and provide a strong foundation for future research and development of more effective treatment strategies for this population.

5.4 Future Directions

The findings from these chapters highlight the need for further research in several areas to expand our understanding of chronic pain and improve its management. Some key areas include further exploration of the underlying mechanisms involved in the relationship between hormonal fluctuations, pain sensitivity, and pain modulation during the menstrual cycle is warranted. Investigating the neurobiological pathways and molecular mechanisms that mediate these relationships can provide valuable insights into the complex interplay between hormones and pain processing.

This could be accomplished by exploring the role of genetic and epigenetic factors in pain sensitivity across menstrual phases, as these factors may interact with hormonal fluctuations. One method would be using neuroimaging techniques to investigate the neural mechanisms underlying menstrual phase-related pain sensitivity. This can provide insights into brain regions involved in pain modulation. Incorporate patient-reported outcomes, such as pain diaries and quality of life assessments, in both research and clinical practice to capture the subjective experience of pain.

The pilot neuroimaging I conducted produced findings that also opened intriguing avenues for future research and have notable clinical implications. Firstly, further investigations could delve deeper into the hormonal modulation of pain sensitivity, exploring the underlying mechanisms and intricate relationships between estrogen levels and pain perception during different menstrual phases. Longitudinal studies involving a larger and more diverse population would enhance our understanding of this relationship. Additionally, neuroimaging research could expand to pinpoint specific brain regions and networks responsible for altered pain sensitivity during various menstrual phases. Future studies should further investigate differences in pain perception throughout the menstrual cycle by using a standardised operational definition and methods for identifying menstrual cycle phases, using varied methods of assessing pain, applying the painful stimuli in multiple locations, measuring both thresholds and tolerances and including high-powered sample sizes.

Moreover, conducting longitudinal studies that track pain experiences and outcomes over extended periods can shed light on the trajectories of dysmenorrhea and endometriosis-related pain. Qualitative methods and longitudinal study designs can provide deeper insights. These studies can help identify critical developmental periods, risk factors, and protective factors that influence the transition from acute to chronic pain and the persistence or remission of pain conditions. Future research could also focus on developing and evaluating interventions targeting the identified risk factors and protective factors associated with chronic pain. Investigating the effectiveness of interventions that address pain catastrophising, promote resilience, and address adverse childhood experiences can help develop evidence-based interventions to prevent or manage chronic pain in adolescent girls and young women.

Advancing research on personalised medicine approaches in chronic pain management is essential. Understanding the individual differences in pain sensitivity, pain modulation mechanisms, and psychological factors can contribute to tailoring treatment plans and interventions based on specific patient characteristics. Incorporating genetic, epigenetic, and biomarker data into pain management strategies may further enhance personalised approaches. Similarly. encouraging multidisciplinary collaboration among researchers, clinicians, and healthcare professionals is crucial for advancing

chronic pain research. Collaboration across disciplines such as neuroscience, psychology, gynaecology, and pain medicine can facilitate a comprehensive understanding of the complex nature of chronic pain and promote the development of integrated treatment approaches.

Future directions should include developing and implementing health promotion strategies and public health initiatives to prevent chronic pain. This includes raising awareness about the role of life experiences, and psychological factors in pain development, and promoting resilience, positive coping strategies, and early interventions to mitigate the risk of chronic pain. By pursuing these future directions, researchers can deepen our understanding of the mechanisms underlying chronic pain, develop targeted interventions, and advance personalised approaches to pain management. Ultimately, these efforts can improve the quality of life for individuals affected by chronic pain and reduce the burden of these conditions on individuals and healthcare systems.

5.5 Potential Implications of This Research

Several potential implications include clinical practice suggestions and public health initiatives to manage chronic pain. Healthcare professionals could benefit from understanding the intricate interactions between environmental, psychological, and biological factors involved in chronic pain. Incorporating a neuro-biopsychosocial approach, clinicians could develop personalised treatment plans that address the specific needs of individuals experiencing chronic pain. This may involve considering the menstrual cycle phase in pain assessment and management for women, integrating psychological interventions to target pain catastrophising and enhance resilience, and recognising the impact of adverse childhood experiences on pain outcomes.

Identifying potential risk factors for chronic pain and dysmenorrhea development during adolescence has important implications for preventive strategies. Public health initiatives and educational programs can raise awareness about the influence of life events, early-life experiences, and psychological factors on pain outcomes. Implementing preventive measures that promote resilience,

provide social support, and address adverse childhood experiences may reduce the incidence and impact of chronic pain conditions.

The research underscores the importance of adopting a holistic approach in pain management. By considering the interplay between biological, psychological, and social factors, healthcare professionals can develop comprehensive treatment plans that address the multidimensional aspects of chronic pain. This approach may involve integrating pharmacological interventions with psychological therapies, promoting self-management strategies, and supporting individuals across the lifespan.

Additionally, we may be able to inform policy-making and healthcare system improvements. Recognising the multifaceted nature of chronic pain, policymakers can allocate resources to support research initiatives and develop guidelines that emphasise the integration of biopsychosocial approaches in pain management. Additionally, healthcare systems can prioritise the training and education of healthcare professionals in understanding and addressing the complex factors contributing to chronic pain, ensuring that comprehensive and patient-centred care is provided.

5.6 Concluding Remarks

The findings highlight the importance of considering multiple dimensions in pain research and clinical practice. They emphasise the need for a comprehensive and holistic approach that integrates neuro, biological, psychological, and social factors in assessing, managing, and preventing chronic pain. This approach recognises that pain is not solely a physiological phenomenon but is influenced by various factors, including hormonal fluctuations, psychological variables, early-life experiences, and individual differences.

The clinical relevance of this research lies in its potential to inform evidence-based interventions and improve pain management outcomes. By understanding the relationships between these factors, healthcare professionals can develop personalised treatment plans tailored to the specific needs of

individuals experiencing chronic pain. Additionally, the findings have implications for preventive strategies, public health initiatives, and policy-making, highlighting the importance of early intervention, resilience-building, and addressing adverse childhood experiences.

Mechanistic studies exploring the underlying biological pathways and molecular mechanisms can deepen our understanding of the complex interactions involved in female chronic pain. Longitudinal studies tracking pain experiences over extended periods can provide insights into the trajectories of pain conditions and factors influencing their persistence or remission. Intervention development, personalised medicine approaches, and multidisciplinary collaboration are key areas with great potential for advancing women's health patient outcomes.

In conclusion, the research presented in these chapters underscores the need for a comprehensive, multidimensional approach to chronic pain in adolescent girls and young women. By considering the intricate relationships between biological, psychological, and social factors, we can better understand pain mechanisms, develop targeted interventions, and enhance the well-being of individuals living with chronic pain. By continuing to explore these avenues and translating research findings into clinical practice and public health initiatives, we can make significant strides in improving the lives of women affected by chronic pain.

References

1. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007;133(4):581-624. doi:10.1037/0033-2909.133.4.581
2. Wilson AC, Holley AL, Stone A, Fales JL, Palermo TM. Pain, Physical, and Psychosocial Functioning in Adolescents at Risk for Developing Chronic Pain: A Longitudinal Case-Control Stusdy. *Journal of Pain*. 2020;21(3-4):418-429. doi:10.1016/j.jpain.2019.08.009
3. Caes L, Dick B, Duncan C, Allan J. The Cyclical Relation Between Chronic Pain, Executive Functioning, Emotional Regulation, and Self-Management. *J Pediatr Psychol*. 2021;46(3):286-292. doi:10.1093/jpepsy/jsaa114
4. Liossi C, Howard RF. Pediatric chronic pain: Biopsychosocial assessment and formulation. *Pediatrics*. 2016;138(5). doi:10.1542/peds.2016-0331
5. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *The Lancet*. 2021;397(10289):2082-2097. doi:10.1016/S0140-6736(21)00393-7
6. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*. 2016;6(6). doi:10.1136/BMJOPEN-2015-010364
7. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976-1982. doi:10.1097/J.PAIN.0000000000001939
8. Russo CM, Brose WG. Chronic pain. *Annu Rev Med*. 1998;49:123-133. doi:10.1146/ANNUREV.MED.49.1.123
9. Fillingim RB. Individual differences in pain: Understanding the mosaic that makes pain personal. *Pain*. 2017;158(4):S11-S18. doi:10.1097/J.PAIN.0000000000000775
10. Abdallah CG, Geha P. Chronic Pain and Chronic Stress: Two Sides of the Same Coin? *Chronic Stress (Thousand Oaks)*. 2017;1. doi:10.1177/2470547017704763
11. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. *J Pain Res*. 2016;9:457. doi:10.2147/JPR.S105892
12. Bonezzi C, Fornasari D, Cricelli C, Magni A, Ventriglia G. Not All Pain is Created Equal: Basic Definitions and Diagnostic Work-Up. *Pain Ther*. 2020;9(Suppl 1):1. doi:10.1007/S40122-020-00217-W
13. Martucci KT, Ng P, MacKey S. Neuroimaging chronic pain: what have we learned and where are we going? *Future Neurol*. 2014;9(6):615. doi:10.2217/FNL.14.57
14. Werner A, Steihaug S, Malterud K. Encountering the continuing challenges for women with chronic pain: recovery through recognition. *Qual Health Res*. 2003;13(4):491-509. doi:10.1177/1049732302250755
15. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: A consensus report. *Pain*. 2007;132(Suppl 1):S26. doi:10.1016/J.PAIN.2007.10.014
16. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *BJA: British Journal of Anaesthesia*. 2013;111(1):52. doi:10.1093/BJA/AET127

17. Paller CJ, Campbell CM, Edwards RR, Dobs AS. Sex-Based Differences in Pain Perception and Treatment. *Pain Med*. 2009;10(2):289. doi:10.1111/J.1526-4637.2008.00558.X
18. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *The journal of pain : official journal of the American Pain Society*. 2009;10(5):447. doi:10.1016/J.JPAIN.2008.12.001
19. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinire M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception - Part 1: Are there really differences between women and men? *Pain*. 2012;153(3):602-618. doi:10.1016/j.pain.2011.11.025
20. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2013;53(8):1278-1299. doi:10.1111/HEAD.12150
21. Wolfe F, Walitt B, Perrot S, Rasker JJ, Häuser W. Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PLoS One*. 2018;13(9):e0203755. doi:10.1371/JOURNAL.PONE.0203755
22. Gobina I, Villberg J, Välimaa R, et al. Prevalence of self-reported chronic pain among adolescents: Evidence from 42 countries and regions. *Eur J Pain*. 2019;23(2):316-326. doi:10.1002/EJP.1306
23. Craft RM. Modulation of pain by estrogens. *Pain*. 2007;132 Suppl 1(SUPPL. 1):S3. doi:10.1016/J.PAIN.2007.09.028
24. Marcus DA. Interrelationships of neurochemicals, estrogen, and recurring headache. *Pain*. 1995;62(2):129-139. doi:10.1016/0304-3959(95)00052-T
25. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017;124(10):1501-1512. doi:10.1111/1471-0528.14640
26. Arumugam K, Lim JMH. Menstrual characteristics associated with endometriosis. *Br J Obstet Gynaecol*. 1997;104(8):948-950. doi:10.1111/J.1471-0528.1997.TB14357.X
27. Pieretti S, di Giannuario A, di Giovannandrea R, et al. Gender differences in pain and its relief. *Ann Ist Super Sanita*. 2016;52(2):184-189. doi:10.4415/ANN_16_02_09
28. Apkhazava M, Kvachadze I, Tsagareli, Chakhnashvili M. SEX DIFFERENCES IN RESPONSE TO EXPERIMENTALLY INDUCED PAIN. *Georgian Med News*. 2019;(287):119-124. https://pubmed.ncbi.nlm.nih.gov/30958302/. Accessed October 24, 2020.
29. The Lancet Child & Adolescent Health. Normalising menstruation, empowering girls. *Lancet Child Adolesc Health*. 2018;2(6):379. doi:10.1016/S2352-4642(18)30143-3
30. Period pain: Overview. August 2019. https://www.ncbi.nlm.nih.gov/books/NBK279324/. Accessed June 14, 2023.
31. Plodeck V, Sommer U, Baretton GB, et al. Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). *International Journal of Molecular Sciences 2021, Vol 22, Page 10554*. 2021;22(19):10554. doi:10.3390/IJMS221910554
32. Marian S, Hermanowicz-Szamatowicz K. Endometriosis–a decade later–still an enigmatic disease. What is the new in the diagnosis and treatment? *Gynecological Endocrinology*. 2020;36(2):104-108. doi:10.1080/09513590.2019.1675045
33. Itani R, Soubra L, Karout S, Rahme D, Karout L, Khojah HMJ. Primary Dysmenorrhea: Pathophysiology, Diagnosis, and Treatment Updates. *Korean J Fam Med*. 2022;43(2):101-108. doi:10.4082/KJFM.21.0103

34. Ju H, Jones M, Mishra G. The Prevalence and Risk Factors of Dysmenorrhea. *Epidemiol Rev*. 2014;36(1):104-113. doi:10.1093/EPIREV/MXT009
35. Petraglia F, Bernardi M, Lazzeri L, Perelli F, Reis FM. Dysmenorrhea and related disorders. *F1000Research 2017 6:1645*. 2017;6:1645. doi:10.12688/f1000research.11682.1
36. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhoea. *BMJ*. 2006;332(7550):1134-1138. doi:10.1136/BMJ.332.7550.1134
37. Harada T. Dysmenorrhea and Endometriosis in Young Women. *Yonago Acta Med*. 2013;56(4):81. /pmc/articles/PMC3935015/. Accessed August 10, 2022.
38. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: a critical review. *Hum Reprod Update*. 2015;21(6):762-778. doi:10.1093/HUMUPD/DMV039
39. Zhao S, Wu W, Kang R, Wang X. Significant Increase in Depression in Women With Primary Dysmenorrhea: A Systematic Review and Cumulative Analysis. *Front Psychiatry*. 2021;12:1313. doi:10.3389/FPSYT.2021.686514/BIBTEX
40. Sahin N, Kasap B, Kirli U, Yeniceri N, Topal Y. Assessment of anxiety-depression levels and perceptions of quality of life in adolescents with dysmenorrhea. *Reprod Health*. 2018;15(1):1-7. doi:10.1186/S12978-018-0453-3/TABLES/4
41. Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004;364(9447):1789-1799. doi:10.1016/S0140-6736(04)17403-5
42. Tanbo T, Fedorcsak P. Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. *Acta Obstet Gynecol Scand*. 2017;96(6):659-667. doi:10.1111/aogs.13082
43. Macer ML, Taylor HS. Endometriosis and Infertility. A Review of the Pathogenesis and Treatment of Endometriosis-associated Infertility. *Obstet Gynecol Clin North Am*. 2012;39(4):535-549. doi:10.1016/j.ogc.2012.10.002
44. Kobayashi H, Yamada Y, Morioka S, Niiro E, Shigemitsu A, Ito F. Mechanism of pain generation for endometriosis-associated pelvic pain. *Arch Gynecol Obstet*. 2014;289(1):13-21. doi:10.1007/S00404-013-3049-8
45. Moradi Y, Shams-Beyranvand M, Khateri S, et al. A systematic review on the prevalence of endometriosis in women. *Indian J Med Res*. 2021;154(3):446. doi:10.4103/IJMR.IJMR_817_18
46. Acién P, Velasco I. Endometriosis: A Disease That Remains Enigmatic. *ISRN Obstet Gynecol*. 2013;2013:1-12. doi:10.1155/2013/242149
47. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. 2014. doi:10.1093/humupd/dmu025
48. McNamara HC, Frawley HC, Donoghue JF, et al. Peripheral, Central, and Cross Sensitization in Endometriosis-Associated Pain and Comorbid Pain Syndromes. *Frontiers in Reproductive Health*. 2021;3:729642. doi:10.3389/FRPH.2021.729642
49. Zarbo C, Brugnera A, Dessì V, et al. Cognitive and Personality Factors Implicated in Pain Experience in Women With Endometriosis: A Mixed-Method Study. *Clinical Journal of Pain*. 2019;35(12):948-957. doi:10.1097/AJP.0000000000000757
50. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: A qualitative study. *BMC Womens Health*. 2014;14(1). doi:10.1186/1472-6874-14-123
51. Zarbo C, Brugnera A, Frigerio L, et al. Behavioral, cognitive, and emotional coping strategies of women with endometriosis: a critical narrative review. *Arch Womens Ment Health*. 2018;21(1). doi:10.1007/s00737-017-0779-9

52. Augoulea A, Lambrinoudaki I, Christodoulakos G. Thoracic endometriosis syndrome. *Respiration*. 2008;75(1):113-119. doi:10.1159/000105102
53. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2016;9(3):257-264. doi:10.1161/CIRCOUTCOMES.115.002224
54. Ek M, Roth B, Ekström P, Valentin L, Bengtsson M, Ohlsson B. Gastrointestinal symptoms among endometriosis patients-A case-cohort study. *BMC Womens Health*. 2015;15(1). doi:10.1186/s12905-015-0213-2
55. Fritzer N, Haas D, Oppelt P, et al. More than just bad sex: Sexual dysfunction and distress in patients with endometriosis. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2013;169(2):392-396. doi:10.1016/j.ejogrb.2013.04.001
56. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: Costs and quality of life of women with endometriosis and treated in referral centres. *Human Reproduction*. 2012. doi:10.1093/humrep/des073
57. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: A multicenter study across ten countries. *Fertil Steril*. 2011;96(2). doi:10.1016/j.fertnstert.2011.05.090
58. Sperschneider ML, Hengartner MP, Kohl-Schwartz A, et al. Does endometriosis affect professional life? A matched case-control study in Switzerland, Germany and Austria. *BMJ Open*. 2019;9(1). doi:10.1136/bmjopen-2017-019570
59. De Graaff AA, D'hooghe TM, Dunselman GAJ, et al. The significant effect of endometriosis on physical, mental and social wellbeing: Results from an international cross-sectional survey. *Human Reproduction*. 2013;28(10):2677-2685. doi:10.1093/humrep/det284
60. Culley L, Law C, Hudson N, et al. The social and psychological impact of endometriosis on women's lives: A critical narrative review. *Hum Reprod Update*. 2013;19(6):625-639. doi:10.1093/humupd/dmt027
61. Hemmert R, Schliep KC, Willis S, et al. Modifiable life style factors and risk for incident endometriosis. *Paediatr Perinat Epidemiol*. 2019;33(1):19-25. doi:10.1111/ppe.12516
62. Alimi Y, Iwanaga J, Loukas M, Tubbs RS. The Clinical Anatomy of Endometriosis: A Review. *Cureus*. 2018;10(9). doi:10.7759/cureus.3361
63. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). *International Journal of Molecular Sciences 2021, Vol 22, Page 10554*. 2021;22(19):10554. doi:10.3390/IJMS221910554
64. Chantalat E, Valera MC, Vaysse C, et al. Estrogen Receptors and Endometriosis. *International Journal of Molecular Sciences 2020, Vol 21, Page 2815*. 2020;21(8):2815. doi:10.3390/IJMS21082815
65. Maddern J, Grundy L, Castro J, Brierley SM. Pain in Endometriosis. *Front Cell Neurosci*. 2020;14:335. doi:10.3389/FNCEL.2020.590823/BIBTEX
66. Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet*. 2010;27(8):441-447. doi:10.1007/s10815-010-9436-1
67. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. *BMJ*. 2022;379. doi:10.1136/BMJ-2022-070750
68. Bontempo AC, Mikesell L. Patient perceptions of misdiagnosis of endometriosis: results from an online national survey. *Diagnosis (Berl)*. 2020;7(2):97-106. doi:10.1515/DX-2019-0020

69. Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: A randomized, placebo-controlled trial. *Fertil Steril*. 2004;82(4):878-884. doi:10.1016/j.fertnstert.2004.03.046
70. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: A multivariate analysis of over 1000 patients. *Human Reproduction*. 2007;22(1):266-271. doi:10.1093/humrep/del339
71. Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. *Endocr Rev*. 2019;40(4):1048-1079. doi:10.1210/ER.2018-00242
72. Mu F, Harris HR, Rich-Edwards JW, et al. A Prospective Study of Inflammatory Markers and Risk of Endometriosis. *Am J Epidemiol*. 2018;187(3):515-522. doi:10.1093/AJE/KWX272
73. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2017;9(6):7204-7218. doi:10.18632/ONCOTARGET.23208
74. Zheng P, Zhang W, Leng J, Lang J. Research on central sensitization of endometriosis-associated pain: a systematic review of the literature . *J Pain Res*. 2019;12:1447-1456. doi:10.2147/JPR.S197667
75. Yan H, Shi J, Li X, et al. Oral gonadotropin-releasing hormone antagonists for treating endometriosis-associated pain: a systematic review and network meta-analysis. *Fertil Steril*. 2022;118(6):1102-1116. doi:10.1016/J.FERTNSTERT.2022.08.856
76. Armour M, Smith CA, Steel KA, MacMillan F. The effectiveness of self-care and lifestyle interventions in primary dysmenorrhea: A systematic review and meta-analysis. *BMC Complement Altern Med*. 2019;19(1):1-16. doi:10.1186/S12906-019-2433-8/FIGURES/7
77. Donatti L, Malvezzi H, Azevedo BC De, Baracat EC, Podgaec S. Cognitive Behavioral Therapy in Endometriosis, Psychological Based Intervention: A Systematic Review. *Revista Brasileira de Ginecologia e Obstetricia*. 2022;44(3):295-303. doi:10.1055/S-0042-1742406/ID/BR210197-28
78. Hsu AL, Khachikyan I, Stratton P. Invasive and noninvasive methods for the diagnosis of endometriosis. *Clin Obstet Gynecol*. 2010;53(2):413-419. doi:10.1097/GRF.0B013E3181DB7CE8
79. Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JMN. Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev*. 2020;2020(10). doi:10.1002/14651858.CD011031.PUB3
80. Zanelotti A, Decherney AH. Surgery and Endometriosis. *Clin Obstet Gynecol*. 2017;60(3):477-484. doi:10.1097/GRF.0000000000000291
81. Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, Diagnosis and Clinical Management. *Curr Obstet Gynecol Rep*. 2017;6(1):34-41. doi:10.1007/s13669-017-0187-1
82. Period pains: Can anti-inflammatory drugs help? August 2019. https://www.ncbi.nlm.nih.gov/books/NBK279323/. Accessed April 19, 2023.
83. Faramarzi M, Salmalian H. Association of psychologic and nonpsychologic factors with primary dysmenorrhea. *Iran Red Crescent Med J*. 2014;16(8). doi:10.5812/IRCMJ.16307
84. Facchin F, Barbara G, Dridi D, et al. Mental health in women with endometriosis: searching for predictors of psychological distress. *Human Reproduction*. 2017;32(9):1855-1861. doi:10.1093/HUMREP/DEX249
85. Lamvu G, Soliman AM, Manthena SR, Gordon K, Knight J, Taylor HS. Patterns of Prescription Opioid Use in Women With Endometriosis: Evaluating Prolonged Use,

Daily Dose, and Concomitant Use With Benzodiazepines. *Obstetrics and Gynecology*. 2019;133(6):1120-1130. doi:10.1097/AOG.0000000000003267
86. Madsen AM, Stark LM, Has P, Emerson JB, Schulkin J, Matteson KA. Opioid knowledge and prescribing practices among obstetrician-gynecologists. *Obstetrics and Gynecology*. 2018;131(1):150-157. doi:10.1097/AOG.0000000000002407
87. Chiuve SE, Kilpatrick RD, Hornstein MD, et al. Chronic opioid use and complication risks in women with endometriosis: A cohort study in US administrative claims. *Pharmacoepidemiol Drug Saf*. 2021;30(6):787-796. doi:10.1002/PDS.5209
88. O'Hara R, Rowe H, Fisher J. Self-management in condition-specific health: A systematic review of the evidence among women diagnosed with endometriosis. *BMC Womens Health*. 2019;19(1):1-19. doi:10.1186/S12905-019-0774-6/TABLES/3
89. Perquin CW, Hazebroek-Kampschreur AAJM, Hunfeld JAM, et al. Pain in children and adolescents: A common experience. *Pain*. 2000. doi:10.1016/S0304-3959(00)00269-4
90. Roth-Isigkeit A, Thyen U, Stoven H, Schwarzenberger J, Schmucker P. Pain among children and adolescents: restrictions in daily living and triggering factors.[Erratum appears in Pediatrics. 2005 Apr;115(4):1118]. *Pediatrics*. 2005;115(2):e152-62. doi:https://dx.doi.org/10.1542/peds.2004-0682
91. Stanford EA, Chambers CT, Biesanz JC, Chen E. The frequency, trajectories and predictors of adolescent recurrent pain: A population-based approach. *Pain*. 2008;138(1):11-21. doi:10.1016/J.PAIN.2007.10.032
92. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain*. 2011;152(12):2729-2738. doi:10.1016/J.PAIN.2011.07.016
93. Miró J, Roman-Juan J, Sánchez-Rodríguez E, Solé E, Castarlenas E, Jensen MP. Chronic Pain and High Impact Chronic Pain in Children and Adolescents: A Cross-Sectional Study. *Journal of Pain*. 2023;0(0). doi:10.1016/j.jpain.2022.12.007
94. Eccleston C, Jordan AL, Crombez G. The impact of chronic pain on adolescents: A review of previously used measures. *J Pediatr Psychol*. 2006. doi:10.1093/jpepsy/jsj061
95. Eccleston C, Wastell S, Crombez G, Jordan A. Adolescent social development and chronic pain. *European Journal of Pain*. 2008;12(6):765-774. doi:10.1016/j.ejpain.2007.11.002
96. Simons LE, Claar RL, Logan DL. Chronic pain in adolescence: Parental responses, adolescent coping, and their impact on adolescent's pain behaviors. *J Pediatr Psychol*. 2008;33(8):894-904. doi:10.1093/jpepsy/jsn029
97. Sieberg CB, Lunde CE, Borsook D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review. *Neurosci Biobehav Rev*. 2020;108:866-876. doi:10.1016/J.NEUBIOREV.2019.12.004
98. Dowlut-McElroy T, Strickland JL. Endometriosis in adolescents. *Curr Opin Obstet Gynecol*. 2017;29(5):306-309. doi:10.1097/GCO.0000000000000402
99. Benagiano G, Guo SW, Puttemans P, Gordts S, Brosens I. Progress in the diagnosis and management of adolescent endometriosis: an opinion. *Reprod Biomed Online*. 2018;36(1):102-114. doi:10.1016/j.rbmo.2017.09.015
100. Gallagher JS, DiVasta AD, Vitonis AF, Sarda V, Laufer MR, Missmer SA. The Impact of Endometriosis on Quality of Life in Adolescents. *Journal of Adolescent Health*. 2018. doi:10.1016/j.jadohealth.2018.06.027
101. Laufer MR. Current approaches to optimizing the treatment of endometriosis in adolescents. In: *Gynecologic and Obstetric Investigation*. Vol 66. Gynecol Obstet Invest; 2008:19-27. doi:10.1159/000148027

102. Agarwal A, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. *Indian J Community Med*. 2010;35(1):159-164. doi:10.4103/0970-0218.62586
103. Zannoni L, Giorgi M, Spagnolo E, Montanari G, Villa G, Seracchioli R. Dysmenorrhea, absenteeism from school, and symptoms suspicious for endometriosis in adolescents. *J Pediatr Adolesc Gynecol*. 2014;27(5):258-265. doi:10.1016/j.jpag.2013.11.008
104. Sachedina A, Todd N. Dysmenorrhea, endometriosis and chronic pelvic pain in adolescents. *JCRPE Journal of Clinical Research in Pediatric Endocrinology*. 2020;12(Suppl 1):7-17. doi:10.4274/jcrpe.galenos.2019.2019.S0217
105. Missmer SA, Tu FF, Agarwal SK, et al. Impact of Endometriosis on Life-Course Potential: A Narrative Review. *Int J Gen Med*. 2021;Volume 14:9-25. doi:10.2147/ijgm.s261139
106. Day MA, Thorn BE, Burns JW. The Continuing Evolution of Biopsychosocial Interventions for Chronic Pain. *J Cogn Psychother*. 2012;26(2):114-129. doi:10.1891/0889-8391.26.2.114
107. Glover GH. Overview of Functional Magnetic Resonance Imaging. *Neurosurg Clin N Am*. 2011;22(2):133. doi:10.1016/J.NEC.2010.11.001
108. Hillman EMC. Coupling Mechanism and Significance of the BOLD Signal: A Status Report. *Annu Rev Neurosci*. 2014;37:161. doi:10.1146/ANNUREV-NEURO-071013-014111
109. Chen WL, Wagner J, Heugel N, et al. Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. *Front Neurosci*. 2020;14:724. doi:10.3389/FNINS.2020.00724/BIBTEX
110. Hidalgo-Lopez E, Mueller K, Harris TA, Aichhorn M, Sacher J, Pletzer B. Human menstrual cycle variation in subcortical functional brain connectivity: a multimodal analysis approach. *Brain Struct Funct*. 2020;225(2):591-605. doi:10.1007/s00429-019-02019-z
111. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. *Neuroimage*. 2011;55(1):8-23. doi:10.1016/j.neuroimage.2010.11.049
112. O'Reilly JX, Woolrich MW, Behrens TEJ, Smith SM, Johansen-Berg H. Tools of the trade: Psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci*. 2012;7(5):604-609. doi:10.1093/scan/nss055
113. Rohr CS, Okon-Singer H, Craddock RC, Villringer A, Margulies DS. Affect and the brain's functional organization: a resting-state connectivity approach. *PLoS One*. 2013;8(7). doi:10.1371/JOURNAL.PONE.0068015
114. Garland EL. Pain Processing in the Human Nervous System: A Selective Review of Nociceptive and Biobehavioral Pathways. *Prim Care*. 2012;39(3):561. doi:10.1016/J.POP.2012.06.013
115. Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain*. 2013;154(9):1807-1819. doi:10.1016/J.PAIN.2013.05.047
116. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006;10(1):77. doi:10.1016/J.EJPAIN.2005.02.003
117. Braun M, Bello C, Riva T, et al. Quantitative Sensory Testing to Predict Postoperative Pain. *Curr Pain Headache Rep*. 2021;25(1). doi:10.1007/S11916-020-00920-5
118. Treede RD. The role of quantitative sensory testing in the prediction of chronic pain. *Pain*. 2019;160 Suppl 1(1):S66-S69. doi:10.1097/J.PAIN.0000000000001544

119. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain*. 2006;123(3):231-243. doi:10.1016/j.pain.2006.01.041
120. Perl ER. Pain mechanisms: A commentary on concepts and issues. *Prog Neurobiol*. 2011;94(1):20-38. doi:10.1016/J.PNEUROBIO.2011.03.001
121. Shimo K, Ogawa S, Niwa Y, et al. Inhibition of current perception thresholds in A-delta and C fibers through somatosensory stimulation of the body surface. *Scientific Reports 2022 12:1*. 2022;12(1):1-6. doi:10.1038/s41598-022-18016-y
122. Campero M, Baumann TK, Bostock H, Ochoa JL. Human cutaneous C fibres activated by cooling, heating and menthol. *J Physiol*. 2009;587(23):5633-5652. doi:10.1113/JPHYSIOL.2009.176040
123. Mitsi V, Zachariou V. Modulation of pain, nociception, and analgesia by the brain reward center. *Neuroscience*. 2016;338:81-92. doi:10.1016/J.NEUROSCIENCE.2016.05.017
124. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*. 2014;8(2):143-151. doi:10.1097/SPC.0000000000000055
125. Martucci KT, Ng P, MacKey S. Neuroimaging chronic pain: what have we learned and where are we going? *Future Neurol*. 2014;9(6):615-626. doi:10.2217/FNL.14.57
126. Martucci KT, Mackey SC. Imaging Pain. *Anesthesiol Clin*. 2016;34(2):255-269. doi:10.1016/J.ANCLIN.2016.01.001
127. Kobinata H, Ikeda E, Zhang S, Li T, Makita K, Kurata J. Disrupted offset analgesia distinguishes patients with chronic pain from healthy controls. *Pain*. 2017;158(10):1951-1959. doi:10.1097/j.pain.0000000000000989
128. Ligato D, Petersen KK, Mørch CD, Arendt-Nielsen L. Offset analgesia: The role of peripheral and central mechanisms. *European Journal of Pain*. 2018;22(1):142-149. doi:10.1002/EJP.1110
129. Lunde CE, Szabo E, Holmes SA, Borsook D, Sieberg CB. Commentary: Novel Use of Offset Analgesia to Assess Adolescents and Adults with Treatment Resistant Endometriosis-Associated Pain. *J Pain Res*. 2020;13:2775-2782. doi:10.2147/JPR.S276135
130. Szikszay TM, Adamczyk WM, Luedtke K. The magnitude of offset analgesia as a measure of endogenous pain modulation in healthy participants and patients with chronic pain: A systematic review and meta-analysis. *Clinical Journal of Pain*. 2019;35(2):189-204. doi:10.1097/AJP.0000000000000657
131. Ibancos-Losada MDR, Osuna-Pérez MC, Castellote-Caballero MY, Díaz-Fernández Á. Conditioned Pain Modulation Effectiveness: An Experimental Study Comparing Test Paradigms and Analyzing Potential Predictors in a Healthy Population. *Brain Sciences 2020, Vol 10, Page 599*. 2020;10(9):599. doi:10.3390/BRAINSCI10090599
132. Hermans L, Calders P, Oosterwijck J Van, Verschelde E, Bertel E, Meeus M. Systematic Review An Overview of Offset Analgesia and the Comparison with Conditioned Pain Modulation: A Systematic Literature Review. *Pain Physician*. 2016;19:307-326. www.painphysicianjournal.com. Accessed June 18, 2020.
133. Nahman-Averbuch H, Martucci KT, Granovsky Y, Weissman-Fogel I, Yarnitsky D, Coghill RC. Distinct brain mechanisms support spatial vs temporal filtering of nociceptive information. *Pain*. 2014;155(12):2491-2501. doi:10.1016/j.pain.2014.07.008
134. Martucci KT, Eisenach JC, Tong C, Coghill RC. Opioid-independent mechanisms supporting offset analgesia and temporal sharpening of nociceptive information. *Pain*. 2012;153(6):1232-1243. doi:10.1016/j.pain.2012.02.035

135. Niesters M, Hoitsma E, Sarton E, Aarts L, Dahan A. Offset analgesia in neuropathic pain patients and effect of treatment with morphine and ketamine. *Anesthesiology*. 2011;115(5):1063-1071. doi:10.1097/ALN.0b013e31822fd03a
136. Petersen KK, Simonsen O, Olesen AE, Mørch CD, Arendt-Nielsen L. Pain inhibitory mechanisms and response to weak analgesics in patients with knee osteoarthritis. *European Journal of Pain (United Kingdom)*. 2019;23(10):1904-1912. doi:10.1002/ejp.1465
137. Niesters M, Proto P, Aarts L, Sarton E, A D, Dahan A. Tapentadol Potentiates Descending Pain Inhibition in Chronic Pain Patients With Diabetic Polyneuropathy - PubMed. *Br J Anaesth*. 2014.
138. Suzan E, Treister R, Pud D, Haddad M, Eisenberg E. The effect of hydromorphone therapy on psychophysical measurements of the descending inhibitory pain systems in patients with chronic radicular pain. *Pain Medicine (United States)*. 2015;16(1):168-175. doi:10.1111/pme.12565
139. Maurer AJ, Lissounov A, Knezevic I, Candido KD, Knezevic NN. Pain and sex hormones: a review of current understanding. *Pain Manag*. 2016;6(3):285-296. doi:10.2217/PMT-2015-0002
140. Kenshalo DR. Changes in the cool threshold associated with phases of the menstrual cycle. *J Appl Physiol*. 1966;21(3):1031-1039. doi:10.1152/jappl.1966.21.3.1031
141. Herren RY. The effect of high and low female sex hormone concentration on the two-point threshold of pain and touch and upon tactile sensitivity. *J Exp Psychol*. 1933;16(2):324-327. doi:10.1037/h0074301
142. Aloisi AM, Bonifazi M. Sex hormones, central nervous system and pain. *Horm Behav*. 2006;50(1):1-7. doi:10.1016/j.yhbeh.2005.12.002
143. Vincent K, Tracey I. Hormones and Their Interaction with the Pain Experience. *http://dx.doi.org/101177/204946370800200206*. 2008;2(2):20-24. doi:10.1177/204946370800200206
144. Chen Q, Zhang W, Sadana N, Chen X. Estrogen receptors in pain modulation: cellular signaling. *Biology of Sex Differences 2021 12:1*. 2021;12(1):1-10. doi:10.1186/S13293-021-00364-5
145. Coronel MF, Raggio MC, Adler NS, De Nicola AF, Labombarda F, González SL. Progesterone modulates pro-inflammatory cytokine expression profile after spinal cord injury: Implications for neuropathic pain. *J Neuroimmunol*. 2016;292:85-92. doi:10.1016/J.JNEUROIM.2016.01.011
146. Talbot K, Madden VJ, Jones SL, Moseley GL. The sensory and affective components of pain: are they differentially modifiable dimensions or inseparable aspects of a unitary experience? A systematic review. *Br J Anaesth*. 2019;123(2):e263-e272. doi:10.1016/j.bja.2019.03.033
147. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *J Pain*. 2016;17(9 Suppl):T70-T92. doi:10.1016/J.JPAIN.2016.01.001
148. Edwards RR, Calahan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. *Nat Rev Rheumatol*. 2011;7(4):216-224. doi:10.1038/NRRHEUM.2011.2
149. Miller MM, Meints SM, Hirsh AT. Catastrophizing, pain, and functional outcomes for children with chronic pain: a meta-analytic review. *Pain*. 2018;159(12):2442. doi:10.1097/J.PAIN.0000000000001342
150. Ruscheweyh R, Nees F, Marziniak M, Evers S, Flor H, Knecht S. Pain catastrophizing and pain-related emotions: influence of age and type of pain. *Clin J Pain*. 2011;27(7):578-586. doi:10.1097/AJP.0B013E31820FDE1B

151. Leung L. Pain Catastrophizing: An Updated Review. *Indian J Psychol Med*. 2012;34(3):204. doi:10.4103/0253-7176.106012
152. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother*. 2009;9(5):745. doi:10.1586/ERN.09.34
153. Lee H, Hübscher M, Moseley GL, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*. 2015;156(6):988-997. doi:10.1097/J.PAIN.0000000000000146
154. Trost Z, Strachan E, Sullivan M, Vervoort T, Avery AR, Afari N. Heritability of Pain Catastrophizing and Associations with Experimental Pain Outcomes: A Twin Study. *Pain*. 2015;156(3):514. doi:10.1097/01.J.PAIN.0000460326.02891.FC
155. Kim J, Loggia ML, Cahalan CM, et al. The somatosensory link in fibromyalgia: functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. *Arthritis Rheumatol*. 2015;67(5):1395-1405. doi:10.1002/ART.39043
156. Lazaridou A, Kim J, Cahalan CM, et al. Effects of Cognitive-Behavioral Therapy (CBT) on Brain Connectivity Supporting Catastrophizing in Fibromyalgia. *Clin J Pain*. 2017;33(3):215-221. doi:10.1097/AJP.0000000000000422
157. Schreiber KL, Loggia ML, Kim J, Cahalan CM, Napadow V, Edwards RR. Painful After-Sensations in Fibromyalgia are Linked to Catastrophizing and Differences in Brain Response in the Medial Temporal Lobe. *J Pain*. 2017;18(7):855-867. doi:10.1016/J.JPAIN.2017.02.437
158. Grundström H, Larsson B, Arendt-Nielsen L, Gerdle B, Kjølhede P. Pain catastrophizing is associated with pain thresholds for heat, cold and pressure in women with chronic pelvic pain. *Scand J Pain*. 2020;20(3):635-646. doi:10.1515/SJPAIN-2020-0015
159. RS R, MR P, JE B. Psychological factors and chronic pelvic pain in women: a comparative study with women with chronic migraine headaches. *Health Care Women Int*. 2011;32(8). doi:10.1080/07399332.2011.555829
160. McPeak AE, Allaire C, Williams C, Albert A, Lisonkova S, Yong PJ. Pain Catastrophizing and Pain Health-Related Quality-of-Life in Endometriosis. *Clinical Journal of Pain*. 2018;34(4):349-356. doi:10.1097/AJP.0000000000000539
161. Petrini L, Arendt-Nielsen L. Understanding Pain Catastrophizing: Putting Pieces Together. *Front Psychol*. 2020;11. doi:10.3389/FPSYG.2020.603420
162. Burns JW, Day MA, Thorn BE. Is reduction in pain catastrophizing a therapeutic mechanism specific to cognitive-behavioral therapy for chronic pain? *Transl Behav Med*. 2012;2(1):22. doi:10.1007/S13142-011-0086-3
163. Malfliet A, Coppieters I, Van Wilgen P, et al. Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. *Eur J Pain*. 2017;21(5):769-786. doi:10.1002/EJP.1003
164. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron*. 2008;59(2):195-206. doi:10.1016/J.NEURON.2008.06.030
165. Haour F. Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation*. 2005;12(4):195-200. doi:10.1159/000085651
166. Meagher MW, Arnau RC, Rhudy JL. Pain and emotion: effects of affective picture modulation. *Psychosom Med*. 2001;63(1):79-90. doi:10.1097/00006842-200101000-00010
167. Rhudy JL, Williams AE, McCabe KM, Nguyên MAT v., Rambo P. Affective modulation of nociception at spinal and supraspinal levels. *Psychophysiology*. 2005;42(5):579-587. doi:10.1111/J.1469-8986.2005.00313.X

168. Campbell CM, Edwards RR. Mind–body interactions in pain: the neurophysiology of anxious and catastrophic pain-related thoughts. *Transl Res*. 2009;153(3):97. doi:10.1016/J.TRSL.2008.12.002
169. Brown CA, El-Deredy W, Jones AKP. When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *Eur J Neurosci*. 2014;39(4):663-672. doi:10.1111/EJN.12420
170. Loggia ML, Berna C, Kim J, et al. The lateral prefrontal cortex mediates the hyperalgesic effects of negative cognitions in chronic pain patients. *J Pain*. 2015;16(8):692-699. doi:10.1016/J.JPAIN.2015.04.003
171. Yang S, Chang MC. Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States. *International Journal of Molecular Sciences 2019, Vol 20, Page 3130*. 2019;20(13):3130. doi:10.3390/IJMS20133130
172. Gracely RH, Geisser ME, Giesecke T, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*. 2004;127(Pt 4):835-843. doi:10.1093/BRAIN/AWH098
173. Galambos A, Szabó E, Nagy Z, et al. A systematic review of structural and functional MRI studies on pain catastrophizing. *J Pain Res*. 2019;12:1155-1178. doi:10.2147/JPR.S192246
174. Severeijns R, Vlaeyen J, van den Hout M, Weber W. Pain Catastrophizing Predicts Pain Intensity, Disability, an... : The Clinical Journal of Pain. *Clin J Pain*. 2001;17(2):165-172. https://journals.lww.com/clinicalpain/Abstract/2001/06000/Pain_Catastrophizing_Predicts_Pain_Intensity,.9.aspx. Accessed March 11, 2023.
175. Sullivan MJL, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain*. 2001;17(1):52-64. doi:10.1097/00002508-200103000-00008
176. Lunde CE, Sieberg CB. Walking the Tightrope: A Proposed Model of Chronic Pain and Stress. *Front Neurosci*. 2020;14:270. doi:10.3389/fnins.2020.00270
177. Thompson OJ, Powell-Roach K, Taylor JL, Terry EL, Booker SQ. Pain catastrophizing: A patient-centered approach to assessment. *Nursing (Brux)*. 2022;52(4):26-30. doi:10.1097/01.NURSE.0000823252.50782.45
178. Adams VJ, Walker B, Jepson D, et al. Measurement Characteristics and Clinical Utility of the Pain Catastrophizing Scale in Individuals Experiencing Low Back Pain. *Arch Phys Med Rehabil*. 2017;98(11):2350-2351. doi:10.1016/j.apmr.2017.03.005
179. Webster F, Connoy L, Longo R, et al. Patient Responses to the Term Pain Catastrophizing: Thematic Analysis of Cross-sectional International Data. *J Pain*. 2023;24(2). doi:10.1016/J.JPAIN.2022.10.001
180. Zhang L, Losin EAR, Ashar YK, Koban L, Wager TD. Gender Biases in Estimation of Others' Pain. *Journal of Pain*. 2021;22(9):1048-1059. doi:10.1016/j.jpain.2021.03.001
181. Casale R, Atzeni F, Bazzichi L, et al. Pain in Women: A Perspective Review on a Relevant Clinical Issue that Deserves Prioritization. *Pain Ther*. 2021;10(1):287. doi:10.1007/S40122-021-00244-1
182. Tiller JWG. Depression and anxiety. *Med J Aust*. 2013;199(S6):S28-S31. doi:10.5694/MJA12.10628
183. Koller D, Pathak GA, Wendt FR, et al. Epidemiologic and Genetic Associations of Endometriosis With Depression, Anxiety, and Eating Disorders. *JAMA Netw Open*. 2023;6(1):e2251214-e2251214. doi:10.1001/JAMANETWORKOPEN.2022.51214

184. Sepulcri R de P, Amaral VF do. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2009;142(1):53-56. doi:10.1016/j.ejogrb.2008.09.003
185. Laganà AS, La Rosa VL, Rapisarda AMC, et al. Anxiety and depression in patients with endometriosis: Impact and management challenges. *Int J Womens Health*. 2017;9:323-330. doi:10.2147/IJWH.S119729
186. Khandker M, Brady SS, Vitonis AF, MacLehose RF, Stewart EG, Harlow BL. The influence of depression and anxiety on risk of adult onset vulvodynia. *J Womens Health*. 2011;20(10):1445-1451. doi:10.1089/jwh.2010.2661
187. Coxon L, Horne AW, Vincent K. Pathophysiology of endometriosis-associated pain: A review of pelvic and central nervous system mechanisms. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:53-67. doi:10.1016/j.bpobgyn.2018.01.014
188. Vachon-Presseau E. Effects of stress on the corticolimbic system: implications for chronic pain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):216-223. doi:10.1016/j.pnpbp.2017.10.014
189. Zajacova A, Grol-Prokopczyk H, Zimmer Z. Sociology of Chronic Pain. *J Health Soc Behav*. 2021;62(3):302-317. doi:10.1177/00221465211025962
190. Nelson S, Simons LE, Logan D. The Incidence of Adverse Childhood Experiences (ACEs) and Their Association with Pain-related and Psychosocial Impairment in Youth with Chronic Pain. *Clinical Journal of Pain*. 2018;34(5):402-408. doi:10.1097/AJP.0000000000000549
191. Krantz TE, Andrews N, Petersen TR, et al. Adverse Childhood Experiences among Gynecology Patients with Chronic Pelvic Pain. *Obstetrics and Gynecology*. 2019;134(5):1087-1095. doi:10.1097/AOG.0000000000003533
192. Dennis CH, Clohessy DS, Stone AL, Darnall BD, Wilson AC. Adverse Childhood Experiences in Mothers With Chronic Pain and Intergenerational Impact on Children. *Journal of Pain*. 2019;20(10). doi:10.1016/j.jpain.2019.04.004
193. Schrepf A, Naliboff B, Williams DA, et al. Adverse childhood experiences and symptoms of urologic chronic pelvic pain syndrome: A multidisciplinary approach to the study of chronic pelvic pain research network study. *Annals of Behavioral Medicine*. 2018;52(10):865-877. doi:10.1093/abm/kax060
194. Lampe A, Doering S, Rumpold G, et al. Chronic pain syndromes and their relation to childhood abuse and stressful life events. *J Psychosom Res*. 2003;54(4):361-367. doi:10.1016/S0022-3999(02)00399-9
195. Vachon-Presseau E, Roy M, Martel MO, et al. The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. *Brain*. 2013;136(3):815-827. doi:10.1093/brain/aws371
196. Meltzer-Brody S, Leserman J, Zolnoun D, Steege J, Green E, Teich A. Trauma and posttraumatic stress disorder in women with chronic pelvic pain. *Obstetrics and Gynecology*. 2007;109(4):902-908. doi:10.1097/01.AOG.0000258296.35538.88
197. Richter-Levin G, Sandi C. Title: "Labels Matter: Is it stress or is it Trauma?" *Translational Psychiatry 2021 11:1*. 2021;11(1):1-9. doi:10.1038/s41398-021-01514-4
198. Goddard A. Adverse Childhood Experiences and Trauma-Informed Care. *Journal of Pediatric Health Care*. 2021;35(2):145-155. doi:10.1016/J.PEDHC.2020.09.001
199. Screening for Adverse Childhood Experiences | ACEs Aware – Take action. Save lives. https://www.acesaware.org/screen/screening-for-adverse-childhood-experiences/. Accessed November 30, 2020.
200. Groenewald CB, Murray CB, Palermo TM. Adverse childhood experiences and chronic pain among children and adolescents in the United States. *Pain Rep*. 2020;5(5). doi:10.1097/PR9.0000000000000839

201. Herzog JI, Schmahl C. Adverse Childhood Experiences and the Consequences on Neurobiological, Psychosocial, and Somatic Conditions Across the Lifespan. *Front Psychiatry*. 2018;9(SEP):420. doi:10.3389/FPSYT.2018.00420
202. Zarse EM, Neff MR, Yoder R, Hulvershorn L, Chambers JE, Chambers RA. The adverse childhood experiences questionnaire: Two decades of research on childhood trauma as a primary cause of adult mental illness, addiction, and medical diseases. *Cogent Med*. 2019;6(1). doi:10.1080/2331205x.2019.1581447
203. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: Integrating the potential role of stress response systems into a biopsychosocial model. *Psychosom Med*. 2005;67(5):783-790. doi:10.1097/01.psy.0000181276.49204.bb
204. Talbot NL, Chapman B, Conwell Y, et al. Childhood sexual abuse is associated with physical illness burden and functioning in psychiatric patients 50 years of age and older. *Psychosom Med*. 2009;71(4):417-422. doi:10.1097/PSY.0b013e318199d31b
205. Nicol AL, Sieberg CB, Clauw DJ, Hassett AL, Moser SE, Brummett CM. The Association Between a History of Lifetime Traumatic Events and Pain Severity, Physical Function, and Affective Distress in Patients With Chronic Pain. *Journal of Pain*. 2016;17(12):1334-1348. doi:10.1016/j.jpain.2016.09.003
206. Tidmarsh L V., Harrison R, Ravindran D, Matthews SL, Finlay KA. The Influence of Adverse Childhood Experiences in Pain Management: Mechanisms, Processes, and Trauma-Informed Care. *Frontiers in Pain Research*. 2022;3:91. doi:10.3389/FPAIN.2022.923866
207. Feldmann M, Hein HJ, Voderholzer U, et al. Cognitive Change and Relaxation as Key Mechanisms of Treatment Outcome in Chronic Pain: Evidence From Routine Care. *Front Psychiatry*. 2021;12:1287. doi:10.3389/FPSYT.2021.617871/BIBTEX
208. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr Physiol*. 2016;6(2):603-621. doi:10.1002/CPHY.C150015
209. Sachs-Ericsson NJ, Sheffler JL, Stanley IH, Piazza JR, Preacher KJ. When Emotional Pain Becomes Physical: Adverse Childhood Experiences, Pain, and the Role of Mood and Anxiety Disorders. *J Clin Psychol*. 2017;73(10):1403-1428. doi:10.1002/jclp.22444
210. Harris HR, Wieser F, Vitonis AF, et al. Early life abuse and risk of endometriosis Is there an association between physical and sexual abuse occurring in childhood or adolescence and risk of laparoscopically-confirmed endometriosis? *Human Reproduction*. 2018;33(9):1657-1668. doi:10.1093/humrep/dey248
211. Liebermann C, Kohl Schwartz AS, Charpidou T, et al. Maltreatment during childhood: A risk factor for the development of endometriosis? *Human Reproduction*. 2018;33(8):1449-1458. doi:10.1093/humrep/dey111
212. Harrison V, Rowan K, Mathias J. Stress reactivity and family relationships in the development and treatment of endometriosis. *Fertil Steril*. 2005;83(4):857-864. doi:10.1016/j.fertnstert.2004.10.033
213. Schliep KC, Mumford SL, Johnstone EB, et al. Sexual and physical abuse and gynecologic disorders. *Human Reproduction*. 2016;31(8):1904-1912. doi:10.1093/humrep/dew153
214. Harrop-Griffith J, Katon W, Walker E, Holm L, Russo J, Hickok L. The association between chronic pelvic pain, psychiatric diagnoses, and childhood sexual abuse. *Obstetrics and Gynecology*. 1988;71(4):589-594. doi:10.1016/0020-7292(89)90597-3
215. Hawks L, Woolhandler S, Himmelstein DU, Bor DH, Gaffney A, McCormick D. Association between Forced Sexual Initiation and Health Outcomes among US

Women. *JAMA Intern Med*. 2019;179(11):1551-1558. doi:10.1001/JAMAINTERNMED.2019.3500
216. Moussaoui D, Joseph K, Grover SR. Short review on adverse childhood experiences, pelvic pain and endometriosis. *J Gynecol Obstet Hum Reprod*. 2023;52(6):102603. doi:10.1016/J.JOGOH.2023.102603
217. Sonu S, Post S, Feinglass J. Adverse childhood experiences and the onset of chronic disease in young adulthood. *Prev Med (Baltim)*. 2019;123:163-170. doi:10.1016/j.ypmed.2019.03.032
218. Chang X, Jiang X, Mkandarwire T, Shen M. Associations between adverse childhood experiences and health outcomes in adults aged 18–59 years. *PLoS One*. 2019;14(2). doi:10.1371/journal.pone.0211850
219. Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. *Front Psychiatry*. 2018;9(SEP):420. doi:10.3389/fpsyt.2018.00420
220. Clemens V, Bürgin D, Eckert A, et al. Hypothalamic-pituitary-adrenal axis activation in a high-risk sample of children, adolescents and young adults in residential youth care – Associations with adverse childhood experiences and mental health problems. *Psychiatry Res*. 2020;284. doi:10.1016/j.psychres.2020.112778
221. Daines CL, Hansen D, Novilla MLB, Crandall AA. Effects of positive and negative childhood experiences on adult family health. *BMC Public Health*. 2021;21(1):1-8. doi:10.1186/S12889-021-10732-W/TABLES/2
222. Gentili C, Rickardsson J, Zetterqvist V, Simons LE, Lekander M, Wicksell RK. Psychological Flexibility as a Resilience Factor in Individuals With Chronic Pain. *Front Psychol*. 2019;10. doi:10.3389/FPSYG.2019.02016
223. Finan PH, Garland EL. The Role of Positive Affect in Pain and its Treatment. *Clin J Pain*. 2015;31(2):177. doi:10.1097/AJP.0000000000000092
224. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. *Eur J Psychotraumatol*. 2014;5. doi:10.3402/EJPT.V5.25338
225. Wu G, Feder A, Cohen H, et al. Understanding resilience. *Front Behav Neurosci*. 2013;7(JANUARY 2013). doi:10.3389/FNBEH.2013.00010
226. Roeckner AR, Oliver KI, Lebois LAM, van Rooij SJH, Stevens JS. Neural contributors to trauma resilience: a review of longitudinal neuroimaging studies. *Translational Psychiatry 2021 11:1*. 2021;11(1):1-17. doi:10.1038/s41398-021-01633-y
227. Helmreich I, Kunzler A, Chmitorz A, et al. Psychological interventions for resilience enhancement in adults. *Cochrane Database Syst Rev*. 2017;2017(2). doi:10.1002/14651858.CD012527
228. Kim D, Chae Y, Park HJ, Lee IS. Effects of Chronic Pain Treatment on Altered Functional and Metabolic Activities in the Brain: A Systematic Review and Meta-Analysis of Functional Neuroimaging Studies. *Front Neurosci*. 2021;15. doi:10.3389/FNINS.2021.684926
229. Teicher MH, Tomoda A, Andersen SE. Neurobiological consequences of early stress and childhood maltreatment: Are results from human and animal studies comparable? In: *Annals of the New York Academy of Sciences*. Vol 1071. Blackwell Publishing Inc.; 2006:313-323. doi:10.1196/annals.1364.024
230. ML G, U R. Grant Report on the Effects of Childhood Maltreatment on Neurocircuitry in Adolescent Depression. *J Psychiatr Brain Sci*. 2020;5. doi:10.20900/jpbs.20200016
231. Riem MME, Alink LRA, Out D, van Ijzendoorn MH, Bakermans-Kranenburg MJ. Beating the brain about abuse: Empirical and meta-analytic studies of the association

between maltreatment and hippocampal volume across childhood and adolescence. *Dev Psychopathol*. 2015;27(2):507-520. doi:10.1017/S0954579415000127
232. Vasic V, Schmidt MHH. Resilience and vulnerability to pain and inflammation in the hippocampus. *Int J Mol Sci*. 2017;18(4). doi:10.3390/ijms18040739
233. Liu N, Huo J, Li Y, et al. Changes in brain structure and related functional connectivity during menstruation in women with primary dysmenorrhea. *Quant Imaging Med Surg*. 2023;13(2):1071-1082. doi:10.21037/QIMS-22-683/COIF)
234. As-Sanie S, Kim J, Schmidt-Wilcke T, et al. Functional Connectivity Is Associated with Altered Brain Chemistry in Women with Endometriosis-Associated Chronic Pelvic Pain. In: *Journal of Pain*. Vol 17. Churchill Livingstone Inc.; 2016:1-13. doi:10.1016/j.jpain.2015.09.008
235. As-Sanie S, Harris RE, Napadow V, et al. Changes in regional gray matter volume in women with chronic pelvic pain: A voxel-based morphometry study. *Pain*. 2012;153(5):1006-1014. doi:10.1016/j.pain.2012.01.032
236. Szabo E, Chang YHC, Shulman J, et al. Alterations in the structure and function of the brain in adolescents with new daily persistent headache: A pilot MRI study. *Headache*. 2022;62(7):858-869. doi:10.1111/HEAD.14360
237. Martucci KT, MacKey SC. Neuroimaging of Pain: Human Evidence and Clinical Relevance of Central Nervous System Processes and Modulation. *Anesthesiology*. 2018;128(6):1241. doi:10.1097/ALN.0000000000002137
238. Holmes SA, Upadhyay J, Borsook D. Delineating conditions and subtypes in chronic pain using neuroimaging. *Pain Rep*. 2019;4(4):e768. doi:10.1097/pr9.0000000000000768
239. Tandon HK, Stratton P, Sinaii N, Shah J, Karp BI. Botulinum toxin for chronic pelvic pain in women with endometriosis: a cohort study of a pain-focused treatment. *Reg Anesth Pain Med*. 2019;44(9):886-892. doi:10.1136/RAPM-2019-100529
240. Iacovides S, Avidon I, Baker FC. Does pain vary across the menstrual cycle? A review. *Eur J Pain*. 2015;19(10):1389-1405. doi:10.1002/EJP.714
241. Reed BG, Carr BR. *The Normal Menstrual Cycle and the Control of Ovulation*. MDText.com, Inc.; 2000. http://www.ncbi.nlm.nih.gov/pubmed/25905282. Accessed April 5, 2021.
242. Arafah M, Rashid S, Akhtar M. Endometriosis: A Comprehensive Review. *Adv Anat Pathol*. 2021;28(1):30-43. doi:10.1097/PAP.0000000000000288
243. Pope CJ, Oinonen K, Mazmanian D, Stone S. The hormonal sensitivity hypothesis: A review and new findings. *Med Hypotheses*. 2017;102:69-77. doi:10.1016/J.MEHY.2017.03.012
244. Amandusson Å, Blomqvist A. Estrogenic influences in pain processing. *Front Neuroendocrinol*. 2013;34(4):329-349. doi:10.1016/J.YFRNE.2013.06.001
245. Martin VT. Ovarian hormones and pain response: A review of clinical and basic science studies. *Gend Med*. 2009;6(PART 2):168-192. doi:10.1016/J.GENM.2009.03.006
246. Athnaiel O, Cantillo S, Paredes S, Knezevic NN. The Role of Sex Hormones in Pain-Related Conditions. *Int J Mol Sci*. 2023;24(3). doi:10.3390/IJMS24031866
247. de Tommaso M. Pain perception during menstrual cycle. *Curr Pain Headache Rep*. 2011;15(5):400-406. doi:10.1007/s11916-011-0207-1
248. Vincent K, Tracey I. Sex hormones and pain: the evidence from functional imaging. *Curr Pain Headache Rep*. 2010;14(5):396-403. doi:10.1007/S11916-010-0139-1
249. Sherman JJ, Leresche L. CALL FOR PAPERS Sex and Gender Differences in Pain and Inflammation Does experimental pain response vary across the menstrual cycle? A

methodological review. *Am J Physiol Regul Integr Comp Physiol*. 2006;291:245-256. doi:10.1152/ajpregu.00920.2005.-The
250. Riley JL, Robinson ME, Wise EA, Price D. A meta-analytic review of pain perception across the menstrual cycle. *Pain*. 1999;81(3):225-235. doi:10.1016/S0304-3959(98)00258-9
251. Fillingim RB, Maixner W, Girdler SS, et al. Ischemic but not thermal pain sensitivity varies across the menstrual cycle. *Psychosom Med*. 1997;59(5):512-520. doi:10.1097/00006842-199709000-00008
252. Tassorelli C, Sandrini G, Proietti Cecchini A, Nappi RE, Sances G, Martignoni E. Changes in nociceptive flexion reflex threshold across the menstrual cycle in healthy women. *Psychosom Med*. 2002;64(4):621-626. doi:10.1097/01.PSY.0000021945.35402.0D
253. Hellström B, Anderberg UM. Pain perception across the menstrual cycle phases in women with chronic pain. *Percept Mot Skills*. 2003;96(1):201-211. doi:10.2466/PMS.2003.96.1.201
254. Soderberg K, Sundstrom Poromaa I, Nyberg S, Backstrom T, Nordh E. Psychophysically determined thresholds for thermal perception and pain perception in healthy women across the menstrual cycle. *Clin J Pain*. 2006;22(7):610-616. doi:10.1097/01.AJP.0000210904.75472.63
255. De Leeuw R, Albuquerque RJC, Andersen AH, Carlson CR. Influence of estrogen on brain activation during stimulation with painful heat. *J Oral Maxillofac Surg*. 2006;64(2):158-166. doi:10.1016/J.JOMS.2005.10.006
256. Ring C, Veldhuijzen van Zanten JJCS, Kavussanu M. Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. *Biol Psychol*. 2009;81(3):189-191. doi:10.1016/J.BIOPSYCHO.2009.04.004
257. Tousignant-Laflamme Y, Marchand S. Excitatory and inhibitory pain mechanisms during the menstrual cycle in healthy women. *Pain*. 2009;146(1-2):47-55. doi:10.1016/j.pain.2009.06.018
258. Rezaii T, Hirschberg AL, Carlström K, Ernberg M. The influence of menstrual phases on pain modulation in healthy women. *J Pain*. 2012;13(7):646-655. doi:10.1016/J.JPAIN.2012.04.002
259. Bartley EJ, Rhudy JL. Comparing pain sensitivity and the nociceptive flexion reflex threshold across the mid-follicular and late-luteal menstrual phases in healthy women. *Clin J Pain*. 2013;29(2):154-161. doi:10.1097/AJP.0B013E31824C5EDB
260. Veldhuijzen DS, Keaser ML, Traub DS, Zhuo J, Gullapalli RP, Greenspan JD. The role of circulating sex hormones in menstrual cycle-dependent modulation of pain-related brain activation. *Pain*. 2013;154(4):548-559. doi:10.1016/j.pain.2012.12.019
261. Rhudy JL, Bartley EJ, Palit S, et al. Do sex hormones influence emotional modulation of pain and nociception in healthy women? *Biol Psychol*. 2013;94(3):534-544. doi:10.1016/J.BIOPSYCHO.2013.10.003
262. Bartley EJ, Palit S, Kuhn BL, et al. Natural variation in testosterone is associated with hypoalgesia in healthy women. *Clin J Pain*. 2015;31(8):730-739. doi:10.1097/AJP.0000000000000153
263. Vincent K, Stagg CJ, Warnaby CE, Moore J, Kennedy S, Tracey I. "Luteal analgesia": Progesterone dissociates pain intensity and unpleasantness by influencing emotion regulation networks. *Front Endocrinol (Lausanne)*. 2018;9(JUL). doi:10.3389/fendo.2018.00413
264. Teepker M, Peters M, Vedder H, Schepelmann K, Lautenbacher S. Menstrual variation in experimental pain: correlation with gonadal hormones. *Neuropsychobiology*. 2010;61(3):131-140. doi:10.1159/000279303

265. Krunic J, Mladenovic I, Radovic I, Stojanovic N. Changes in pulp sensitivity across the menstrual cycle in healthy women and women with temporomandibular disorders. *J Oral Rehabil*. October 2020:joor.13116. doi:10.1111/joor.13116
266. Bartley EJ, Palit S, Kuhn BL, et al. Nociceptive processing in women with Premenstrual Dysphoric Disorder (PMDD): The role of menstrual phase and sex hormones. *Clinical Journal of Pain*. 2015;31(4):304-314. doi:10.1097/AJP.0000000000000112
267. Veldhuijzen DS, Meeker TJ, Bauer D, Keaser ML, Gullapalli RP, Greenspan JD. Brain responses to painful electrical stimuli and cognitive tasks interact in the precuneus, posterior cingulate cortex, and inferior parietal cortex and do not vary across the menstrual cycle. *Brain Behav*. 2022;12(6). doi:10.1002/BRB3.2593
268. Piroli A, Mattei A, Carta G, et al. Influence of the Menstrual Cycle Phase on Pain Perception and Analgesic Requirements in Young Women Undergoing Gynecological Laparoscopy. *Pain Pract*. 2019;19(2):140-148. doi:10.1111/PAPR.12727
269. Iacovides S, Baker FC, Avidon I, Bentley A. Women with dysmenorrhea are hypersensitive to experimental deep muscle pain across the menstrual cycle. *J Pain*. 2013;14(10):1066-1076. doi:10.1016/J.JPAIN.2013.04.010
270. Klatzkin RR, Mechlin B, Girdler SS. Menstrual cycle phase does not influence gender differences in experimental pain sensitivity. *European Journal of Pain*. 2010;14(1):77-82. doi:10.1016/J.EJPAIN.2009.01.002
271. Kowalczyk WJ, Sullivan MA, Evans SM, Bisaga AM, Vosburg SK, Comer SD. Sex differences and hormonal influences on response to mechanical pressure pain in humans. *J Pain*. 2010;11(4):330-342. doi:10.1016/J.JPAIN.2009.08.004
272. Stening K, Eriksson O, Wahren LK, Berg G, Hammar M, Blomqvist A. Pain sensations to the cold pressor test in normally menstruating women: comparison with men and relation to menstrual phase and serum sex steroid levels. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(4). doi:10.1152/AJPREGU.00127.2007
273. Sherman J, Leresche L, Mancl L, Huggins K, Sage JC, Dworkin S. Cyclic effects on experimental pain response in women with temporomandibular disorders. *J Orofac Pain*. 2005.
274. Drobek W, Schoenaers J, De Laat A. Hormone-dependent fluctuations of pressure pain threshold and tactile threshold of the temporalis and masseter muscle. *J Oral Rehabil*. 2002;29(11):1042-1051. doi:10.1046/J.1365-2842.2002.00988.X
275. Straneva PA, Maixner W, Light KC, Pedersen CA, Costello NL, Girdler SS. Menstrual cycle, beta-endorphins, and pain sensitivity in premenstrual dysphoric disorder. *Health Psychology*. 2002;21(4):358-367. doi:10.1037/0278-6133.21.4.358
276. Bajaj P, Arendt-Nielsen L, Bajaj P, Madsen H. Sensory changes during the ovulatory phase of the menstrual cycle in healthy women. *European Journal of Pain*. 2001;5(2):135-144. doi:10.1053/EUJP.2001.0236
277. Cimino R, Farella M, Michelotti A, Pugliese R, Martina R. Does the Ovarian Cycle Influence the Pressure-Pain Threshold of the Masticatory Muscles in Symptom-Free Women? *J Orofac Pain*. 2000;14(2):105-111.
278. Hellström B, Lundberg U. Pain perception to the cold pressor test during the menstrual cycle in relation to estrogen levels and a comparison with men. *Integr Physiol Behav Sci*. 2000;35(2):132-141. doi:10.1007/BF02688772
279. Hapidou EG, Rollman GB. Menstrual cycle modulation of tender points. *Pain*. 1998;77(2):151-161. doi:10.1016/S0304-3959(98)00087-6
280. Pfleeger M, Straneva PA, Fillingim RB, Maixner W, Girdler SS. Menstrual cycle, blood pressure and ischemic pain sensitivity in women. A preliminary investigation.

International Journal of Psychophysiology. 1997;27(2):161-166. doi:10.1016/S0167-8760(97)00058-5

281. Giamberardino MA, Berkley KJ, Iezzi S, De Bigontina P, Vecchiet L. Pain threshold variations in somatic wall tissues as a function of menstrual cycle, segmental site and tissue depth in non-dysmenorrheic women, dysmenorrheic women and men. *Pain*. 1997;71(2):187-197. doi:10.1016/S0304-3959(97)03362-9
282. Kuczmierczyk AR, Adams HE, Calhoun KS, et al. Pain responsivity in women with premenstrual syndrome across the menstrual cycle. *Percept Mot Skills*. 1986;63(2 Pt 1):387-393. doi:10.2466/PMS.1986.63.2.387
283. Veith JL, Anderson J, Slade SA, Thompson P, Laugel GR, Getzlaf S. Plasma beta-endorphin, pain thresholds and anxiety levels across the human menstrual cycle. *Physiol Behav*. 1984;32(1):31-34. doi:10.1016/0031-9384(84)90065-9
284. Tedford WH, Warren DE, Flynn WE. Alteration of shock aversion thresholds during the menstrual cycle. *Percept Psychophys*. 1977;21(2):193-196. doi:10.3758/BF03198725/METRICS
285. Vollert J, Trewartha N, Kemkowski D, et al. Conditioned pain modulation and offset analgesia: Influence of sex, sex hormone levels and menstrual cycle on the magnitude and retest reliability in healthy participants. *European Journal of Pain*. 2022;26(9):1938-1949. doi:10.1002/EJP.2014
286. Amodei N, Nelson-Gray RO. Reactions of dysmenorrheic and nondysmenorrheic women to experimentally induced pain throughout the menstrual cycle. *J Behav Med*. 1989;12(4):373-385. doi:10.1007/BF00844930/METRICS
287. Campbell JN, Meyer RA. Mechanisms of Neuropathic Pain. *Neuron*. 2006;52(1):77. doi:10.1016/J.NEURON.2006.09.021
288. Mihm M, Gangooly S, Muttukrishna S. The normal menstrual cycle in women. *Anim Reprod Sci*. 2011;124(3-4):229-236. doi:10.1016/j.anireprosci.2010.08.030
289. Woolrich MW, Behrens TEJ, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage*. 2004;21(4):1732-1747. doi:10.1016/J.NEUROIMAGE.2003.12.023
290. FEAT - FslWiki. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT. Accessed June 29, 2023.
291. Popescu V, Battaglini M, Hoogstrate WS, et al. Optimizing parameter choice for FSL-Brain Extraction Tool (BET) on 3D T1 images in multiple sclerosis. *Neuroimage*. 2012;61(4):1484-1494. doi:10.1016/J.NEUROIMAGE.2012.03.074
292. Isensee F, Schell M, Pflueger I, et al. Automated brain extraction of multisequence MRI using artificial neural networks. *Hum Brain Mapp*. 2019;40(17):4952. doi:10.1002/HBM.24750
293. Brown TT, Lee W. The FUTUREPAIN study: Validating a questionnaire to predict the probability of having chronic pain 7-10 years into the future. *PLoS One*. 2020;15(8):e0237508. doi:10.1371/JOURNAL.PONE.0237508
294. Heavy periods: Overview. May 2017. https://www.ncbi.nlm.nih.gov/books/NBK279294/. Accessed April 19, 2021.
295. Vellar OD. Changes in Hemoglobin Concentration and Hematocrit During the Menstrual Cycle: *I. A Cross-sectional Study*. *Acta Obstet Gynecol Scand*. 1974;53(3):243-246. doi:10.3109/00016347409162164
296. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*. 2011;63(S11):S240-S252. doi:10.1002/ACR.20543

297. Goodin BR, McGuire L, Allshouse M, et al. Associations Between Catastrophizing and Endogenous Pain-Inhibitory Processes: Sex Differences. *Journal of Pain*. 2009;10(2):180-190. doi:10.1016/j.jpain.2008.08.012
298. Howard FM. Endometriosis and Mechanisms of Pelvic Pain. *J Minim Invasive Gynecol*. 2009;16(5):540-550. doi:10.1016/j.jmig.2009.06.017
299. Adams L, Turk D. Psychosocial Factors and Central Sensitivity Syndromes. *Curr Rheumatol Rev*. 2015;11(2):96-108. doi:10.2174/1573397111666150619095330
300. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):168-182. doi:10.1016/j.pnpbp.2018.01.017
301. McKenna KA, Fogleman CD. Dysmenorrhea. *Am Fam Physician*. 2021;104(2):164-170. https://www.aafp.org/pubs/afp/issues/2021/0800/p164.html. Accessed June 29, 2023.
302. McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. *Brain Res*. 2000;886(1-2):172-189. doi:10.1016/S0006-8993(00)02950-4
303. McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci*. 2001;933:265-277. doi:10.1111/J.1749-6632.2001.TB05830.X
304. Elman I, Borsook D, Volkow ND. Pain and suicidality: insights from reward and addiction neuroscience. *Prog Neurobiol*. 2013;109:1-27. doi:10.1016/J.PNEUROBIO.2013.06.003
305. Elman I, Borsook D. Common Brain Mechanisms of Chronic Pain and Addiction. *Neuron*. 2016;89(1):11-36. doi:10.1016/J.NEURON.2015.11.027
306. Wang C, Bao C, Gao J, Gu Y, Dong XW. Pain modulates neural responses to reward in the medial prefrontal cortex. *Hum Brain Mapp*. 2020;41(5):1372-1381. doi:10.1002/HBM.24882
307. Ong WY, Stohler CS, Herr DR. Role of the Prefrontal Cortex in Pain Processing. *Molecular Neurobiology 2018 56:2*. 2018;56(2):1137-1166. doi:10.1007/S12035-018-1130-9
308. Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. Epidemiology of endometriosis and its comorbidities. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2017. doi:10.1016/j.ejogrb.2016.04.021
309. Pope CJ, Sharma V, Sharma S, Mazmanian D. A Systematic Review of the Association Between Psychiatric Disturbances and Endometriosis. *Journal of Obstetrics and Gynaecology Canada*. 2015;37(11):1006-1015. doi:10.1016/S1701-2163(16)30050-0
310. Meyer C, Rumpf HJ, Hapke U, John U. Impact of psychiatric disorders in the general population: satisfaction with life and the influence of comorbidity and disorder duration. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(6):435-441. doi:10.1007/S00127-004-0755-3
311. Rahman MA, Siddik AB, Ghosh TK, Khanam F, Ahmad M. A Narrative Review on Clinical Applications of fNIRS. *Journal of Digital Imaging 2020 33:5*. 2020;33(5):1167-1184. doi:10.1007/S10278-020-00387-1
312. de Arruda GT, Driusso P, Rodrigues JC, de Godoy AG, Avila MA. Numerical rating scale for dysmenorrhea-related pain: a clinimetric study. *Gynecol Endocrinol*. 2022;38(8):661-665. doi:10.1080/09513590.2022.2099831
313. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. *Psychol Assess*. 1995;7(4):524-532. doi:10.1037/1040-3590.7.4.524

314. Crombez G, Bijttebier P, Eccleston C, et al. The child version of the pain catastrophizing scale (PCS-C): A preliminary validation. *Pain*. 2003;104(3):639-646. doi:10.1016/S0304-3959(03)00121-0
315. Pennebaker JW, Susman JR. Disclosure of traumas and psychosomatic processes. *Soc Sci Med*. 1988;26(3):327-332. doi:10.1016/0277-9536(88)90397-8
316. Connor KM, Davidson JRT. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82. doi:10.1002/DA.10113
317. *Connor-Davidson Resilience Scale (CD-RISC) © Manual*.
318. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol*. 2002;87(4):2205-2208. doi:10.1152/jn.00730.2001
319. Martucci KT, Yelle MD, Coghill RC. Differential effects of experimental central sensitization on the time-course and magnitude of offset analgesia. *Pain*. 2012;153(2):463-472. doi:10.1016/J.PAIN.2011.11.010
320. Yelle MD, Rogers JM, Coghill RC. Offset analgesia: A temporal contrast mechanism for nociceptive information. *Pain*. 2008;134(1-2):174-186. doi:10.1016/j.pain.2007.04.014
321. Yelle MD, Oshiro Y, Kraft RA, Coghill RC. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. *Journal of Neuroscience*. 2009;29(33):10264-10271. doi:10.1523/JNEUROSCI.4648-08.2009
322. Borsook D, Becerra LR. Breaking down the barriers: fMRI applications in pain, analgesia and analgesics. *Mol Pain*. 2006;2:30. doi:10.1186/1744-8069-2-30
323. Borsook D, Edwards R, Elman I, Becerra L, Levine J. Pain and analgesia: the value of salience circuits. *Prog Neurobiol*. 2013;104:93-105. doi:10.1016/J.PNEUROBIO.2013.02.003
324. Vierck CJ, Whitsel BL, Favorov O V., Brown AW, Tommerdahl M. Role of primary somatosensory cortex in the coding of pain. *Pain*. 2013;154(3):334-344. doi:10.1016/J.PAIN.2012.10.021
325. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology*. 2022;47(1):72-89. doi:10.1038/S41386-021-01132-0
326. Igartua JJ, Hayes AF. Mediation, Moderation, and Conditional Process Analysis: Concepts, Computations, and Some Common Confusions. *Span J Psychol*. 2021;24(6):e49. doi:10.1017/SJP.2021.46
327. D'Alonzo KT. The Johnson-Neyman procedure as an alternative to ANCOVA. *West J Nurs Res*. 2004;26(7):804-812. doi:10.1177/0193945904266733
328. Denckla CA, Cicchetti D, Kubzansky LD, et al. Psychological resilience: an update on definitions, a critical appraisal, and research recommendations. *Eur J Psychotraumatol*. 2020;11(1):1822064. doi:10.1080/20008198.2020.1822064
329. Windle G, Bennett KM, Noyes J. A methodological review of resilience measurement scales. *Health Qual Life Outcomes*. 2011;9:8. doi:10.1186/1477-7525-9-8
330. Booth C, Songco A, Parsons S, et al. The CogBIAS longitudinal study protocol: cognitive and genetic factors influencing psychological functioning in adolescence. *BMC Psychol*. 2017;5(1). doi:10.1186/S40359-017-0210-3
331. Booth C, Songco A, Parsons S, Heathcote LC, Fox E. The CogBIAS longitudinal study of adolescence: cohort profile and stability and change in measures across three waves. *BMC Psychol*. 2019;7(1). doi:10.1186/S40359-019-0342-8
332. Songco A, Booth C, Spiegler O, Parsons S, Fox E. Anxiety and Depressive Symptom Trajectories in Adolescence and the Co-Occurring Development of Cognitive Biases:

Evidence from the CogBIAS Longitudinal Study. *J Abnorm Child Psychol*. 2020;48(12):1617. doi:10.1007/S10802-020-00694-9
333. Lim MC, Parsons S, Goglio A, Fox E. Anxiety, stress, and binge eating tendencies in adolescence: a prospective approach. *J Eat Disord*. 2021;9(1). doi:10.1186/S40337-021-00444-2
334. Schmitz AK, Vierhaus M, Lohaus A. Pain tolerance in children and adolescents: sex differences and psychosocial influences on pain threshold and endurance. *Eur J Pain*. 2013;17(1):124-131. doi:10.1002/J.1532-2149.2012.00169.X
335. Forbes EE, Dahl RE. Pubertal Development and Behavior: Hormonal Activation of Social and Motivational Tendencies. *Brain Cogn*. 2010;72(1):66. doi:10.1016/J.BANDC.2009.10.007
336. Blakemore SJ, Burnett S, Dahl RE. The role of puberty in the developing adolescent brain. *Hum Brain Mapp*. 2010;31(6):926. doi:10.1002/HBM.21052
337. Chaplin TM. Gender and Emotion Expression: A Developmental Contextual Perspective. *Emot Rev*. 2015;7(1):14. doi:10.1177/1754073914544408
338. Sullivan MJL, Tripp DA, Santor D. Gender differences in pain and pain behavior: The role of catastrophizing. *Cognit Ther Res*. 2000;24(1):121-134. doi:10.1023/A:1005459110063/METRICS
339. Bakshi N, Lukombo I, Shnol H, Belfer I, Krishnamurti L. Psychological Characteristics and Pain Frequency Are Associated With Experimental Pain Sensitivity in Pediatric Patients With Sickle Cell Disease. *J Pain*. 2017;18(10):1216-1228. doi:10.1016/J.JPAIN.2017.05.005
340. Mortazavi Nasiri FS, Pakdaman S, Dehghani M, Togha M. The Relationship between Pain Catastrophizing and Headache-Related Disability: The Mediating Role of Pain Intensity. *Japanese Psychological Research*. 2017;59(4):266-274. doi:10.1111/JPR.12162
341. Li R, Kreher DA, Gubbels AL, et al. Dysmenorrhea catastrophizing and functional impairment in female pelvic pain. *Frontiers in Pain Research*. 2023;3:220. doi:10.3389/FPAIN.2022.1053026
342. Bell T, Mirman JH, Stavrinos D. Pain, Pain Catastrophizing, and Individual Differences in Executive Function in Adolescence. *https://doi.org/101080/0273961520181441028*. 2018;48(1):18-37. doi:10.1080/02739615.2018.1441028
343. Dong HJ, Gerdle B, Bernfort L, Levin LÅ, Dragioti E. Pain Catastrophizing in Older Adults with Chronic Pain: The Mediator Effect of Mood Using a Path Analysis Approach. *Journal of Clinical Medicine 2020, Vol 9, Page 2073*. 2020;9(7):2073. doi:10.3390/JCM9072073
344. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J*. 2014;14(11):2639-2657. doi:10.1016/J.SPINEE.2014.03.003
345. Fisher E, Heathcote LC, Eccleston C, Simons LE, Palermo TM. Assessment of pain anxiety, pain catastrophizing, and fear of pain in children and adolescents with chronic pain: A systematic review and meta-analysis. *J Pediatr Psychol*. 2018;43(3):314-325. doi:10.1093/jpepsy/jsx103
346. Somers TJ, Keefe FJ, Pells JJ, et al. Pain Catastrophizing and Pain-Related Fear in Osteoarthritis Patients: Relationships to Pain and Disability. *J Pain Symptom Manage*. 2009;37(5):863-872. doi:10.1016/j.jpainsymman.2008.05.009
347. Sirbu E, Onofrei RR, Szasz S, Susan M. Predictors of disability in patients with chronic low back pain. *Archives of Medical Science*. 2023;19(1):94-100. doi:10.5114/AOMS.2020.97057

348. Engel JM, Wilson S, Tran ST, Jensen MP, Ciol MA. Pain Catastrophizing in Youths With Physical Disabilities and Chronic Pain. *J Pediatr Psychol*. 2013;38(2):192. doi:10.1093/JPEPSY/JSS103
349. Feinstein AB, Sturgeon JA, Darnall BD, et al. The Impact of Pain Catastrophizing on Outcomes: A Developmental Perspective across Children, Adolescents and Young Adults with Chronic Pain. *The journal of pain : official journal of the American Pain Society*. 2017;18(2):144. doi:10.1016/J.JPAIN.2016.10.009
350. Perry M, Sieberg CB, Young EE, et al. The Potential Role of Preoperative Pain, Catastrophizing, and Differential Gene Expression on Pain Outcomes after Pediatric Spinal Fusion. *Pain Management Nursing*. 2020. doi:10.1016/j.pmn.2020.05.007
351. Payne LA, Rapkin AJ, Lung KC, Seidman LC, Zeltzer LK, Tsao JCI. Pain Catastrophizing Predicts Menstrual Pain Ratings in Adolescent Girls with Chronic Pain. *Pain Medicine*. 2016;17(1):16-24. doi:10.1111/PME.12869
352. Walsh TM, LeBlanc L, McGrath PJ. Menstrual pain intensity, coping, and disability: the role of pain catastrophizing. *Pain Med*. 2003;4(4):352-361. doi:10.1111/J.1526-4637.2003.03039.X
353. Sansone RA, Watts DA, Wiederman MW. Childhood Trauma and Pain and Pain Catastrophizing in Adulthood: A Cross-Sectional Survey Study. *Prim Care Companion CNS Disord*. 2013;15(4):26816. doi:10.4088/PCC.13M01506
354. MacDonald TM, Fisk JD, Bernstein CN, et al. The association between childhood maltreatment and pain catastrophizing in individuals with immune-mediated inflammatory diseases. *J Psychosom Res*. 2021;145:110479. doi:10.1016/J.JPSYCHORES.2021.110479
355. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: Perspectives on comprehensive modeling of individual pain adaptation topical collection on psychiatric management of pain. *Curr Pain Headache Rep*. 2013;17(3):1-9. doi:10.1007/S11916-012-0317-4/METRICS
356. Brysbaert M. How many participants do we have to include in properly powered experiments? A tutorial of power analysis with reference tables. *J Cogn*. 2019;2(1):1-38. doi:10.5334/JOC.72/METRICS/
357. Sohr-Preston SL, Scaramella L V., Martin MJ, Neppl TK, Ontai L, Conger R. Parental Socioeconomic Status, Communication, and Children's Vocabulary Development: A Third-Generation Test of the Family Investment Model. *Child Dev*. 2013;84(3):1046-1062. doi:10.1111/CDEV.12023
358. Pielech M, Ryan M, Logan D, Kaczynski K, White MT, Simons LE. Pain catastrophizing in children with chronic pain and their parents: proposed clinical reference points and reexamination of the Pain Catastrophizing Scale measure. *Pain*. 2014;155(11):2360-2367. doi:10.1016/J.PAIN.2014.08.035
359. Allen JL, Rapee RM, Sandberg S. Child and Adolescent Survey of Experiences--Child and Parent Versions. *APA PsycTests*. 2012. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft37480-000. Accessed March 22, 2023.
360. Ebesutani C, Reise SP, Chorpita BF, et al. The Revised Child Anxiety and Depression Scale-Short Version: scale reduction via exploratory bifactor modeling of the broad anxiety factor. *Psychol Assess*. 2012;24(4):833-845. doi:10.1037/A0027283
361. Berger VW, Zhou Y. Kolmogorov–Smirnov Test: Overview. *Wiley StatsRef: Statistics Reference Online*. September 2014. doi:10.1002/9781118445112.STAT06558
362. Sawilowsky SS. New Effect Size Rules of Thumb. *Journal of Modern Applied Statistical Methods*. 2009;8(2):26. doi:10.22237/jmasm/1257035100

363. Exploratory Data Analysis. *The Concise Encyclopedia of Statistics*. 2008:192-194. doi:10.1007/978-0-387-32833-1_136
364. Manikandan S. Measures of central tendency: Median and mode. *https://doi.org/104103/0976-500X83300*. 2011;2(3):214-215. doi:10.4103/0976-500X.83300
365. Teague S, Youssef GJ, Macdonald JA, et al. Retention strategies in longitudinal cohort studies: a systematic review and meta-analysis. *BMC Med Res Methodol*. 2018;18(1). doi:10.1186/S12874-018-0586-7
366. Allen JL, Rapee RM, Sandberg S. Assessment of maternally reported life events in children and adolescents: A comparison of interview and checklist methods. *J Psychopathol Behav Assess*. 2012;34(2):204-215. doi:10.1007/S10862-011-9270-5/METRICS
367. Lim ML, Broekman BFP, Wong CMJ, Wong ST, Ng TP. The development and validation of the Singapore Youth Resilience Scale (SYRESS).
368. Jones S, Joyal CC, Cisler JM, Bai S. Exploring Emotion Regulation in Juveniles Who Have Sexually Offended: An fMRI Study. *https://doi.org/101080/1053871220161259280*. 2016;26(1):40-57. doi:10.1080/10538712.2016.1259280
369. Corte L Della, Di Filippo C, Gabrielli O, et al. The burden of endometriosis on women's lifespan: A narrative overview on quality of life and psychosocial wellbeing. *Int J Environ Res Public Health*. 2020;17(13):1-17. doi:10.3390/ijerph17134683
370. Buhrman M, Nilsson-Ihrfelt E, Jannert M, Ström L, Andersson G. Guided internet-based cognitive behavioural treatment for chronic back pain reduces pain catastrophizing: a randomized controlled trial. *J Rehabil Med*. 2011;43(6):500-505. doi:10.2340/16501977-0805
371. Schütze R, Rees C, Smith A, Slater H, Campbell JM, O'Sullivan P. How Can We Best Reduce Pain Catastrophizing in Adults With Chronic Noncancer Pain? A Systematic Review and Meta-Analysis. *J Pain*. 2018;19(3):233-256. doi:10.1016/J.JPAIN.2017.09.010
372. Jotwani ML, Wu Z, Lunde CE, Sieberg CB. The missing mechanistic link: Improving behavioral treatment efficacy for pediatric chronic pain. *Frontiers in pain research (Lausanne, Switzerland)*. 2022;3. doi:10.3389/FPAIN.2022.1022699
373. Gilliam WP, Schumann ME, Cunningham JL, et al. Pain catastrophizing as a treatment process variable in cognitive behavioural therapy for adults with chronic pain. *European Journal of Pain*. 2021;25(2):339-347. doi:10.1002/EJP.1671
374. Wicksell RK, Olsson GL, Hayes SC. Psychological flexibility as a mediator of improvement in Acceptance and Commitment Therapy for patients with chronic pain following whiplash. *European Journal of Pain*. 2010;14(10):1059.e1-1059.e11. doi:10.1016/J.EJPAIN.2010.05.001
375. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: A randomized controlled multicenter trial. *Pain*. 2016;157(1):174-185. doi:10.1097/J.PAIN.0000000000000348
376. Levy-Carrick NC, Lewis-O'Connor A, Rittenberg E, Manosalvas K, Stoklosa HM, Silbersweig DA. Promoting Health Equity Through Trauma-Informed Care. *Fam Community Health*. 2019;42(2):104-108. doi:10.1097/FCH.0000000000000214

Appendices

Appendix A - Acronyms in Alphabetical Order

Acronym	Definition
ANOVA/ANCOVA	Analysis of Variance/ Analysis of covariance
BOLD	Blood Oxygen Level Dependent
CASE - C	The Child Adolescent Survey of Experiences – Child Version
CD-RISC -SF	Connor-Davidson Resilience Scale Short Form
CNS	Central Nervous System
CTES	Childhood Traumatic Events Scale
FMRIB	Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
HbO	Oxygenated Haemoglobin
HbR	Deoxygenated Haemoglobin
HbT	Total Haemoglobin
LH	Luteinising Hormone
MBLL	Modified Beer-Lambert Law
MPP	Menstrual Phase Pain
MRI/fMRI	Magnetic Resonance Imaging/Functional Magnetic Resonance Imaging
NIRS/fNIRS	Near-Infrared Spectroscopy/Functional Near-Infrared Spectroscopy
NRS	Numeric Rating Scale
OA	Offset Analgesia
PCS	Pain Catastrophising Scale
QST	Quantitative Sensory Testing
RCADS-SF	Revised Child Anxiety and Depression Scale Short Form
ROI	Region of Interest
RTES	Recent Traumatic Events Scale
SES	Socioeconomic Status

Appendix B - Academic Achievements and Contributions

Conferences

Oral Presentations

Chapter 3

[1] Assessing Inhibitory Pain Mechanisms and Neural Activity in Patients with Endometriosis-Associated Pain. Society for Functional Near-infrared Spectroscopy, October 2022

[2] Exploring The Role of Childhood Trauma on Pain Modulation for People With Endometriosis. European Pain School, June 2022

Poster Presentations

Chapter 2

[1] **Lunde, CE.,** Holmes, SA., Sieberg, CB., Borsook, D. Pilot Study: Brain Regions Related to Thermal Pain Differences During Menstrual Phases. International Association for the Study of Pain, Toronto, ON. August 2022

Chapter 3

[2] **Lunde, CE**., Wu, Z., Szabo, E., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Assessing Pain Modulation and Childhood Trauma in People with Endometriosis. Judah Folkman Research Day, Harvard Medical School. June 2022

[3] **Lunde, CE.,** Wu, Z., Szabo, E., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Assessing Pain Modulation and Childhood Trauma in People With Endometriosis. Versus Arthritis 4th Annual Pain Research in the UK Conference July 2022

[4] **Lunde, CE**., Wu, Z., Szabo, E., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Exploring the role of childhood trauma on descending pain inhibition in people with endometriosis using functional near-infrared spectroscopy. International Association for the Study of Pain, Toronto, ON. August 2022

[5] **Lunde, CE**., Kim, A., Szabo, E., Holmes, SA., Borsook, D., Sieberg, CB. Endometriosis-Associated Pain and Adverse Childhood Events: Is Resiliency the Missing Puzzle Piece? International Pelvic Pain Society. October 2022

[6] **Lunde, CE**., Kim, A., Szabo, E., Holmes, SA., Borsook, D., Sieberg, CB. Assessing Inhibitory Pain Mechanisms and Neural Activity in Patients with Endometriosis-Associated Pain. Society for Functional Near-infrared Spectroscopy. October 2022

[7] **Lunde, CE**., Szabo, E., Wu, Z., Karunakaran, K., Kim, A., Holmes, SA., Borsook, D., Sieberg, CB. Does Offset Analgesia Vary as A Function of Adverse Childhood Events and Resilience? Society for Neuroscience. November 2022

Co-authored Posters

[1] Wu, Z., **Lunde, CE.,** Karunakaran, K., Kim, A., Holmes, SA., Sieberg, CB. Altered resting-state functional connectivity between prefrontal and somatosensory cortex after pain response in healthy adults: A pilot functional near-infrared spectroscopy study. International Association for the Study of Pain, Toronto, ON, August 2022

[2] Szabo, E., Kim, A., **Lunde, CE.,** Missmer, S. Borsook, D., Sieberg, CB., Holmes, SA. Endometriosis and migraine: Exploring structural brain alterations in two comorbid pain disorders. International Association for the Study of Pain, Toronto, ON, August 2022

[3] Demetriou, L., Krassowski, M., Mendes, P., Garbut, K., Vitonis, A., Wilkins, E., Coxon, L., Arendt-Nielsen, L., Aziz, Q., Birch, J., Horne, A., Hoffmann. A., Humnelshoj, L., **Lunde, CE.,** Meijlink, J., Perro, D., Pogatzki-Zahn, E., Sieberg, CB., Treede, R., Becker, C., Cruz, F., Missmer, S., Zondervan, K., Nagel, J., Vincent, K. Exploring pelvic pain and quality of life profiles in the Translational Research in Pelvic Pain (TRiPP) cohort. International Association for the Study of Pain, Toronto, ON, August 2022

[4] Perro, D., Demetriou, L., Coxon, L., Krassowski, M., Mendes, P., **Lunde, CE.,** Garbut, K., Vitonis, A., Arendt-Nielsen, L., Aziz, Q., Birch, J., Horne, A., Hoffmann. A., Humnelshoj, L., ., Meijlink, J., Pogatzki-Zahn, E., Sieberg, CB., Treede, R., Becker, C., Cruz, F., Missmer, S., Zondervan, K., Nagel, J., Vincent, K. Widespread pain is associated with poor psychological health, sleep quality, fatigue, and pain catastrophizing in women with chronic pelvic pain: A TRiPP study. International Association for the Study of Pain, Toronto, ON, August 2022

[5] Demetriou, L., Coxon, L., Perro, D., Abreu Mendes, P., **Lunde, CE.,** Garbutt, K., Krassowski1, M., Vitonis, A., Arendt-Nielsen, L., Aziz, Q., Birch, J., Horne, A., Hoffman, A., Hummelshoj, L., Meijlink, J., Pogatzki-Zahn, E., Sieberg, CB., Treede, R., Becker, C., Cruz, F., Missmer, S., Zondervan, K.,, Nage, J.,Vincent, K. Understanding fatigue in chronic pelvic pain patients: a translational research in pelvic pain (TRiPP) study. International Association for the Study of Pain, Toronto, ON, August 2022

[6] Coxon, L., Lugt, C., Perro, D., **Lunde, CE.,** Ferreira Gomes, J., Charrua Cordeiro, A., Abreu Mendes, P., Birch, J., Meijlink, J., Humnelshoj, L., Hoffmann, A., Aziz, Q., Arendt-Nielsen, L., Pogatzki-Zahn, E., Vollert, J., Krassowski, M., Evans, E., Treede, R., Demetriou, L., Missmer, S., Horne, A., Sieberg, CB., Cruz, F., Nagel, J., Vincent, K. Have you ever had a flare of your symptoms? Clinically important findings from under-explored FLARES in chronic pelvic pain. International Association for the Study of Pain, Toronto, ON. August 2022

[7] Coxon, L., Tan, E., Perro, D., **Lunde, CE.,** Ferreira Gomes, J., Charrua Cordeiro, A., Abreu Mendes, P., Birch, J., Meijlink, J., Humnelshoj, L., Hoffmann, A., Aziz, Q., Arendt-Nielsen, L., Pogatzki-Zahn, E., Vollert, J., Krassowski, M., Evans, E., Treede, R., Demetriou, L., Missmer, S., Horne, A., Sieberg, CB., Cruz, F., Nagel, J., Vincent, K. What drinking water tells us about bladder sensitivity in chronic pelvic pain. International Association for the Study of Pain, Toronto, ON., August 2022

[8] Perro, D., Krassowski, M., Coxon, L., **Lunde, CE.,** Ferreira Gomes, J., Charrua Cordeiro, A., Abreu Mendes, P., Arendt-Nielsen, L., Aziz, Q., Birch, J., Demetriou, L., Garbutt, K., Horne, A., Hoffman, A., Hummelshoj, L., Meijlink, J., Pogatzki-Zahn, E., Sieberg, CB., Treede, R., Vitonis, A., Vollert, J., Becker, C., Cruz, F., Missmer, S., Zondervan, K., Nagel, J., Vincent, K. on behalf

of the TRiPP Consortium. Is conditioned pain modulation (CPM) a useful paradigm in women? A TRiPP study. International Association for the Study of Pain, Toronto, ON, August 2022

[9] Sieberg, CB., Szabo, E., **Lunde, CE.,** Kim, A., Missmer, SA., Borsook, D., Holmes., SA. Elucidating the neural underpinnings of co-morbid endometriosis and migraine: A pilot fMRI investigation. International Pelvic Pain Society, October 2022

[10] Wu, Z., Jotwani, ML., **Lunde, CE.,** Sieberg, CB. Utilizing fNIRS to investigate effects of varied thermal increasing rates on offset analgesia hemoglobin responses. Poster presentation at Society for Functional Near-infrared Spectroscopy, October 2022

[11] Jotwani, ML., Wu, Z., **Lunde, CE.,** Sieberg, CB. Utilizing fNIRS to explore the relationship between pain catastrophizing and neural activity in post-surgical pain: A pilot investigation. Society for Neuroscience, November 2022.

[12] Wu, Z., Campos, AI., Jotwani, ML., **Lunde, CE.,** Sieberg, CB. Investigating adaptation using a thermal pain calibration paradigm in healthy volunteers using functional near-infrared spectroscopy. International Conference on Neuroscience and Brain Disorders, November 2022.

[13] Wu, Z., Campos, AI., Jotwani, ML., **Lunde, CE.,** Holmes, SA., Sieberg, CB. Investigating adaptation of thermal pain stimulations during offset analgesia paradigms in healthy volunteers using neuroimaging measures. US Association for the Study of Pain, April 2023

[14] Campos, AI., WU, Z., Jotwani, ML., **Lunde, CE.,** Holmes, SA., Sieberg, CB. Investigating adaptation using a thermal pain calibration paradigm in healthy volunteers using functional near-infrared spectroscopy. Harvard Psychiatry Research Day, March 2023

[15] Coxon, L., Perro, D., Demetriou, L., Horne, A., **Lunde, CE.,** Gomes, JF., Cordeiro, AC., Mendes, PA., Birch, J., Meijlink, J., Hummelshoj, L., Hoffmann, A., Aziz, A., Arendt-Nielsen, L., Pogatzki-Zahn, E., Vollert, J.,, Krassowski, M.,, Evans, E., Treede, RD., Missmer, SA., Sieberg, CB.,, Cruz, F., Nagel, J., Vincent, K .How many treatments do people with chronic pelvic pain try? Results from the Translational Research in Pelvic Pain (TRiPP) study. World Congress on Endometriosis, May 2023

[16] Coxon, L., Krassowski, M., Vollert, J.,, Rahmioglu, N., Abreu Mendes, P., Arendt-Nielsen, L., Aziz, O., Becker, C., Birch, J., Cordeiro, AC., Demetriou, L., DePari1, M., Evans, E., Ferreira Gomes, J., Garbutt, K., Hoffmann, A., Horne, A., Hummelshoj, L., **Lunde, CE.,** Meijlink, J., Obendorf, M., Perro, D., Pogatzki-Zahn, E., Sasamoto, N., Terry, K., ,Vitonis, A., , Treede, RD., , Missmer, SA., Zondervan, KT., Cruz, F., Sieberg, CB., Nagel, J., Vincent, K.. How quantitative sensory testing (QST) can help us stratify in endometriosis-associated pain: results from the Translational Research in Pelvic Pain (TRiPP) study. World Congress on Endometriosis, May 2023

[17] Love, V., Coxon, L., Perro, D., Demetriou, L., Horne, A., **Lunde, CE.,** Gomes, JF., Cordeiro, AC., Mendes, PA., Birch, J., Meijlink, J., Hummelshoj, L., Hoffmann, A., Aziz, A., Arendt-Nielsen, L., Pogatzki-Zahn, E., Vollert, J.,, Krassowski, M.,, Evans, E., Treede, RD., Missmer, SA., Sieberg, CB.,, Cruz, F., Nagel, J., Vincent, K. Investigating the relationship between pain features and reproductive outcomes in women with chronic pelvic pain. European Society of Human Reproduction and Embryology, June 2023

[18] Holmes SA., Kim J., Comptdaer G., Szabo E., **Lunde CE.,** Borsook D., Sieberg CB. Evaluating the brain regions implicated in descending pain modulation and their role in endometriosis associated pain: An fMRI study applying offset analgesia. Canadian Pain Society, 2023

[19] Holmes SA., Szabo E., Kim J., Comptdaer G., **Lunde CE.,** Borsook D., Sieberg CB. Frequency component analysis in persons with surgically confirmed endometriosis: CNS-based approach. Organization for Human Brain Mapping, July 2023

[20] Szabo E., Kim J., Comptdaer G., **Lunde CE.,** Borsook D., Sieberg CB., Holmes SA. Alterations in resting-state low-frequency fluctuation in patients with surgically confirmed endometriosis. Organization for Human Brain Mapping, July 2023

[21] Holmes SA., Szabo E., Kim J., Comptdaer G., **Lunde CE.,** Borsook D., Sieberg CB. Functional brain alterations in patients with endometriosis with and without migraine comorbidity: A resting-state fMRI study. Organization for Human Brain Mapping, July 2023

[22] Jotwani, ML., Szabo E., Kim J., Comptdaer G., **Lunde CE.,** Sieberg CB., Holmes SA. Exploring structural regional brain changes between persons with endometriosis and healthy volunteers: A pilot investigation. University of Toronto, Centre for the Study of Pain – Human Pain Seminar Series Symposium Day, February 2023

Peer-Reviewed Journal Articles

** Co-first author*

[1] Wu, Z., Jotwani, MJ., **Lunde, CE**., Christino, MA., Borsook, B, Sieberg, CB. Altered Connectivity and Pain in Young Adult Females After Orthopedic Surgery: A Pilot fNIRS Study. Pain Reports, May 2023 (under review)

[2] **Lunde, CE.,** Wu, Z., Reinecke, A., Sieberg, CB. The Application of Cognitive Behavioural Therapy for Adolescent Patients with Endometriosis: A Topical Review. Submitted to Cognitive & Behavioral Practice, June 2023 (under review)

[3] **Lunde, CE**., Sieberg, CB., Silva, K., Borsook, D., Ullrich, N., Manley, P., Moulton, E. The Long-Term Impact of Cerebellar Tumor Resection on Executive Functioning, Anxiety, and Fear of Pain: Mixed Methodology. Applied Neuropsychology: Child, June 2023 (under review)

[4] Kim, AJ., Szabo, E., **Lunde, CE**., Comptdaer, G., Zurakowski, D.,. Sieberg, CB., Holmes, SA. (2023) Quantitative Sensory Testing in a Magnetic Resonance Environment: Considerations for Thermal Sensitivity and Patient Safety. Frontiers in Pain Research

[5] Sieberg, CB., **Lunde, CE**., Shafrir, AL., Meints, SM., Madraswalla, M., Huntley, D., Olsen, H., Wong, C., DiVasta, AD., Missmer, SA., Sethna, N. (2023) Quantitative Somatosensory Testing of the Abdomen: Establishing Reference Values across Developmental Age and Biological Sex. PAIN

[6] Coxon, L., Vollert, J., Perro, D., **Lunde, CE**., Ferreira-Gomes, J., Charrua, A., Abreu-Mendes, P., ...Vincent, K. (2023) Comprehensive Quantitative Sensory Testing (QST) Shows Altered Sensory Function in Women with Chronic Pelvic Pain: Results from the Translational Research in Pelvic Pain (TRiPP) Study. PAIN

[7] Demetriou, L., Krassowski, M., Mendes, PA., Garbutt, K., Vitonis, AF., Wilkins, E., Coxon, L., Arendt-Nielsen, L., Aziz, Q., Birch, J., Horne, AW., Hoffman, AW., Hummelshoj, L., **Lunde, CE**., ... Vincent, K. (2023) Clinical Profiling of Specific Diagnostic Subgroups of Women with Chronic Pelvic Pain. Frontiers in Reproductive Health

[8] Sieberg, CB., **Lunde, CE**., Wong, C., Manganella, J., Starkweather, AR., Sethna, N., Perry-Eaddy, MA. (2022) Pilot Investigation of Somatosensory Functioning And Pain Catastrophising In Pediatric Spinal Fusion Surgery. Pain Management Nursing

[9] ***Lunde, CE**., *Szabo, E., Holmes, S., Borsook, D., Sieberg, CB. (2020) Commentary: Novel use of Offset analgesia to Assess Adolescents and Adults with Treatment Resistant Endometriosis-associated Pain. Journal of Pain Research

[10] **Lunde, CE**., Sieberg, CB. Walking the Tightrope: A Proposed Model of Chronic Pain and Stress (2020). Frontiers in Neuroscience

[11] Sieberg, CB, **Lunde, CE**., Borsook, D. (2020) Endometriosis and Pain in the Adolescent- Striking Early to Limit Suffering: A Narrative Review. Neuroscience and Biobehavioral Reviews

[12] Gagnon, H., **Lunde, CE.,** Wu, Z., Novais, E, Borsook, D., Sieberg. (2023) CB Exploring Medical Comorbidities in Adolescent and Young Adults with Hypermobile Ehlers Danlos Syndrome with a Surgical History vs Not: A Preliminary Investigation. Childrens,

[13] Donovan, E., Wolfson, A., Serbic, D., Fisher, E., **Lunde, CE**., Rice, C., Trosen, O., Sieberg. US And UK College Students' Experience Living With Chronic Pain: A Qualitative Analysis. International Journal of Adolescent Medicine and Health, May 2023 (under review)

[14] **Lunde, CE**., Fisher, E., Serbic, D., Donovan, E., Sieberg, CB. (2022) Cutting the Cord? Parenting Emerging Adults with Chronic Pain. Paediatric and Neonatal Pain

[15] Jotwani ML., Wu Z., **Lunde CE**., Sieberg CB. (2022) The Missing Mechanistic Link: Improving Behavioral Treatment Efficacy for Pediatric Chronic Pain. Frontiers in Pain Research

[16] ***Lunde, CE**., *Spigel, R., Gordon, C, Sieberg, CB. (2021) Beyond the Binary: Sexual and Reproductive Health Considerations for Transgender and Gender Expansive Adolescents. Frontiers in Reproductive Health

[17] Demetriou, L., Cox, E., **Lunde, CE**., Becker, C. M., Invitti, A. L., Martínez-Burgo, B., Kvaskoff, M., Garbutt, K., Evans, E., Fox, E., Zondervan, K. T., & Vincent, K. (2021). The Global Impact Of COVID-19 on the Care of People with Endometriosis. Frontiers in Global Women's Health

[18] Demetriou L., Becker C., Martínez-Burgo B., Invitti, A., Kvaskoff, M., Shah, R., Evans, E., **Lunde, CE**., Cox, E., Garbutt, K., Zondervan, K., Fox, E., Vincent, K. (2021) Stressful Experiences Impact on Pain, Fatigue and Mental Health in People with Endometriosis: A Questionnaire Study During the COVID-19 Pandemic. Authorea Preprints

[19] Pielech, M., **Lunde, CE**., Becker, S., Vowles, K., Sieberg, CB. (2020) Comorbid Chronic Pain and Opioid Misuse in Youth: Knowns, Unknowns, and Implications for Behavioral Treatment. The American Psychologist

[20] Lisenbee, J., **Lunde, CE**., Shih S., Dahl, A., (2020) Series 1: A Guide to Preconception Health Considerations. Society of Behavioral Medicine: Healthy Living (sbm.org/healthy-living).

Appendix C - Chapter 2 Scoping Review Results

Table 6. Chapter 2 Scoping Review Results

In Text Citation	Year	Pain Stimuli	Sample	Phases Studied and Definitions	Phase Validation	Results
[141]	1933	Tactile sensitivity (forearm)	5, no pain	(1) Premenstrual: 5 days before menses (2) Intermenstrual: day 2 of menses (1) Postmenstrual: 3 days after end of menses	Self-report	No difference between phases studied
[284]	1977	Shock aversion (finger)	28, no pain	(1) Menstrual: days 1-7 (2) Postmenstrual: days 8-14 (3) Ovulatory: days 15-21 (4) Premenstrual: days 21	Self-report	Increased pain sensitivity during the postmenstrual phase
[283]	1984	Electric shock (wrist) and cold pressor task (hand)	16, no pain	(1) Menstrual: days 2-4 (2) Follicular: days 8-10 (3) Ovulatory: LH surge (4) Luteal: days 6-8 post ovulation (5) Premenstrual: days 11-13 post ovulation	BBT and diary. Blood testing for estradiol and progesterone for half of the participants	No difference between phases studied
[282]	1986	Pressure (finger)	11, PMS diagnosis 10, no PMS	(1) Intermenstrual: days 7 - 22 (2) Premenstrual: days 24 - 28	Self-report	PMS higher sensitivity for inter and premenstrual phases
[286]	1989	Pressure (arm and finger)	55, chronic pain 12, no pain	(1) Premenstrual: 4 days prior to the onset of menses (2) Intermenstrual: days 12 – 16 following onset of menses	Self-report	No difference between phases studied
[281]	1997	Electrical stimulation (abdomen-rectus abdominisleft and right)	10, chronic pain 10, no pain	(1) Menstrual: days 2–6, (2) Periovulatory: days 12–16 (3) Luteal: days 17–22 (4) Premenstrual: days 25–28	Self-report	Pain group was always higher, but for no pain, sensitivity was lowest during the luteal phase
[280]	1997	Ischemic pain (arm)	11, no pain	(1) Follicular: days 4-9 (2) Mid-late luteal: days 5-10 after ovulation	Self-report and LH testing	Increased sensitivity during luteal phase
[251]	1997	Thermal and ischemic pain (arm)	11, no pain	(1) Postmenstrual: days 5 to 8 (2) Ovulatory: within 24 hours of the LH surge (3) Mid-to-late luteal: 1 to 9 days before onset of menses	Diary, blood testing for estradiol and progesterone, and LH testing	Decreased ischemic pain sensitivity during the mid-follicular phase

[279]	1998	Pressure (13 body points)	66, no pain	(1) Menstrual: days 1-7 (2) Follicular: days 8-14 (3) Early luteal phase: days 15-21 (4) Late luteal phase: days 22-28	Self-report	Increased sensitivity during the follicular phase in normally menstruating females but not for women on OC
[278]	2000	Cold pressor task (hand)	22, no pain	(1) Menstrual: days 2-4 (2) After ovulation: days 20-24	Self-report	Decreased sensitivity after ovulation
[277]	2000	Pressure (masticatory muscles).	18, no pain	(1) Menstrual: 1st day of menses (2) Follicular: days 5-9 (3) Ovulation: days 12-16 (4) Luteal: days 19-23	Pelvic ultrasonographic screening	Most sensitive during ovulation
[276]	2001	PPT, Pinch pain, HPT, and TT (abdomen, lower back, thigh and arm)	15, no pain	(1) Menstrual: days 1–6 (2) Ovulatory: days 12–16 (3) Luteal: days 17–22 (4) Premenstrual: days 25–28	LH testing	Most sensitive to heat and pressure during ovulation
[275]	2002	Ischemic pain stimulus (arm)	27, chronic pain; 27, no pain	(1) Follicular: days 4–9 (2) Luteal: days 8–12	LH testing	Increased sensitivity during luteal phase in chronic pain patients only
[252]	2002	Nociceptive flexion reflex	14, no pain	(1) Follicular: days 8–10 from menstruation (2) Luteal: days 6–8 from ovulation	BBT	Increased sensitivity during follicular phase
[274]	2002	Pressure and tactile pain	10, NOC 8, OC	(1) Follicular: days 5 - 12, (2) Luteal: days 16 – 27 (3) Perimenstrual: days 28 – 3	Self-report	Increased pressure pain during the menstrual, and decreased during the follicular phases only for women taking OC
[253]	2003	Questionnaires	20, chronic pain	(1) Menstrual: days 1-5 (2) Follicular: days 6-11 (3) Periovulatory: days 12-16 (4) Luteal: days 17-23 (5) Premenstrual: days 24-28	Self-report	Increased sensitivity during the menstrual and premenstrual phases

[273]	2005	Pressure and ischemic pain (arm)	18, NOC with chronic pain 25, OC with chronic pain 25, NOC without pain 26, OC without pain	*NOC:* (1) Menstrual: within 3 days of menses (2) Ovulation: within 2 days of receiving a positive ovulation test (3) Mid-luteal: 7 - 8 days after ovulation (4) Late luteal: 12 - 14 days after the positive ovulation *OC:* (1) Menstruation: days 1-3 (2) Ovulation: days 12 - 14 (3) Mid-luteal: days 19 – 21 (4) Late luteal: days 26 - 28.	Self-report and LH testing	Highest in intensity during the menses and mid-luteal phases and lowest during the ovulatory and late luteal
[254]	2006	Thermal pain	19, no pain	(1) Follicular: days 3-5 post menses (2) Late follicular: postmenstrual days 11-13 (3) Mid-luteal: postovulatory days 7-9	Blood testing for estradiol and progesterone	Increased sensitivity during the follicular and mid-luteal phases only for cold pain
[255]	2006	Thermal pain (masseter muscle)	9, no pain	(1) Follicular: days 2-3 after the onset of menses (2) Luteal: days 11-12 after the onset of menses	Blood testing for estradiol and progesterone	No difference between phases studied
[272]	2007	Cold pressor test (left hand)	16, no pain	(1) Follicular: estrogen levels 80 - 590 pmol/l (2) Ovulation: estrogen levels 200 - 1200 pmol/l, (3) Luteal: estrogen levels 130 - 780 pmol/l.	Self-report and blood testing for estradiol and progesterone	Increased sensitivity during the late luteal phase
[256]	2009	Venipuncture and intravenous catheterization pain	12, no pain	(1) Follicular: days 4–9 (2) Luteal: days 19–25	Blood testing for estradiol and progesterone	Increased sensitivity during luteal phase

[257]	2009	Thermal pain (cold and heat) and CPM	32, no pain	(1) Menstrual: days 1–3 (2) Ovulation: days 12–14 (3) Luteal: days 19–23	Blood testing for estradiol and progesterone	No difference for thermal pain, but did report more pain inhibition during ovulatory phase
[271]	2010	Mechanical pressure	21, NOC 17, OC	(1) Menstrual: days 2 - 5 (2) Follicular: days 6 - 10 (3) Ovulatory: days 13 - 15 (4) Luteal: days 19 - 24 (5) Late luteal: days 25 - 28	Blood testing for estradiol and progesterone and self-report	NOC decreased sensitivity during the menstrual and late luteal phases
[270]	2010	Thermal and ischemic pain.	49, no pain	(1) Early follicular: days 2–5 (2) Late follicular: days 7–12 (3) Luteal: days 8–12 after LH test	LH testing	No difference between phases studied
[258]	2012	Mechanical pressure and CPM (masseter muscle)	36, no pain	(1) Early follicular: days 3 - 5 (2) Mid-luteal: days 7 - 8 days after ovulation (3) Ovulatory: 4 – 48 hours after detection of the LH surge	LH testing	No difference between phases studied
[269]	2013	Deep muscle pain (lower back and forearm)	12, chronic pain 9, no pain	(1) Menstruation: days 1–2 (2) Follicular: days 11–13 (3) Luteal: days 17–22	Blood testing for estradiol and progesterone	No difference between phases studied
[259]	2013	Mechanical, electrocutaneous, ischemia, pain	41, no pain	mid-follicular: days 5 to 8 late-luteal: days 9 to 11 d after ovulation	Self-report, BBT, and LH testing	No difference between phases studied
[260]	2013	Pressure	15, no pain	(1) Menstrual: days 2-4 (2) Mid-follicular: days 6-8 (3) Peri-ovulatory: day 14 (4) Mid-luteal: 7 days after ovulation	Blood testing for estradiol and progesterone	Increased sensitivity to pressure during follicular phase
[261]	2013	Nociceptive flexion reflex	40, no pain	(1) Mid-follicular: days 5–8 (2) Ovulatory: within 48 h following LH surge (3) Late- luteal: days 1–6 prior to menses	Saliva testing for estradiol and progesterone	No. However, estradiol was associated with weaker emotional modulation of nociceptive pain. Emotional modulation of pain was

						decreased during the ovulatory and late-luteal phases
[262]	2015	Electrocutaneous and ischemia threshold /tolerance	40, no pain	(1) Mid-follicular: days 5 - 8 (2) Ovulatory: 2 days following LH surge (3) Late-luteal: days:1 - 6 preceding menses."	Saliva testing for estradiol and progesterone	No difference between phases studied
[266]	2015	electrocutaneous and ischemic stimuli, and the nociceptive flexion reflex threshold	14 pain and 14 non-pain	mid-follicular: days 5 to 8 following menses onset ovulatory: 2 days following a positive LH surge late-luteal: days 1 to 6 preceding menses (or 9 to 11 d postpositive LH surge)."	Saliva testing for estradiol and progesterone, LH testing, and self-report over 3 months	No difference between phases studied
[263]	2018	Noxious thermal	10, no pain	(1) Preovulation: days 10-12 (2) Premenstrual: days 20-22 (3) Menstrual: days 1-2	Blood testing for estradiol and progesterone and LH testing	Decreased pain sensitivity during the luteal phase
[264]	2019	Cold, heat, pressure and electrical current	24, no pain	(1) Follicular: days 1–14 (2) Ovulatory: day 14 (3) Luteal: days 15-28	Saliva testing for estradiol and progesterone	Increased sensitivity after menstruation. Specifically, cold pain sensitivity peaked during the follicular phase. Pressure and electrical pain peaked during the luteal phase
[268]	2019	Venipuncture	60, no pain during surgery	(1) Follicular: days 6 -12 (2) Luteal: days 20 - 24	Self-report	Increased sensitivity during the luteal phase
[265]	2020	Electric and cold stimuli (mandibular lateral incisors)	24, no pain 23, chronic pain	(1) Menstrual: days 1-5 (2) Follicular: days 6-11 (3) Periovulatory: days 12-16 (4) Luteal: days 17-23 (5) Premenstrual: days 24-28	LH testing	Higher pain sensitivity to cold pain during menstrual phase in females with and without pain

[285]	2022	CPM and OA on the forearm	30, no pain	follicular, ovulation, and luteal phases not defined	LH testing	No difference between phases studied
[267]	2022	Electrical pulses (dorsum of the left foot)	15, no pain	(1) Menstrual: days 2–4 after menses onset (2) Mid-follicular: days 6–8 after menses onset (3) Ovulatory: within 1 day of LH surge (4) Mid-luteal: 7 days after ovulation	Blood testing for estradiol and progesterone	No difference between phases studied

Abbreviations. BBT, basal body temperature; PMS, premenstrual syndrome; LH, luteinising hormone; PPT, pressure pain threshold; PiPT, pinch pain threshold; HPT, heat pain threshold; TT, tactile threshold, CPM, conditioned pain modulation; OA, offset analgesia; OC, oral contraceptive; NOC, no oral contraceptive