MASTERARBEIT | MASTER'S THESIS

Titel | Title

The fluctuations of perceived pain intensity over the menstrual cycle and the influence of stress in everyday life

verfasst von | submitted by

Rebekka Sattelberger BSc

angestrebter akademischer Grad | in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien | Vienna, 2024

Studienkennzahl lt. Studienblatt | Degree programme code as it appears on the student record sheet:	UA 066 840
Studienrichtung lt. Studienblatt | Degree programme as it appears on the student record sheet:	Masterstudium Psychologie
Betreut von | Supervisor:	Univ.-Prof. Dr. Urs Markus Nater
Mitbetreut von | Co-Supervisor:	Nida Ali BSc (Hons) MSc PhD

Acknowledgment

I want to thank Dr. Nida Ali and Prof. Urs M. Nater for the opportunity to work on this project and for all the support and helpful feedback. I would like to acknowledge Dr. Nida Ali especially for entrusting me with responsibility for this project and providing such valuable guidance. Furthermore, I would like to thank everyone who supported me during this process, proofread, or gave me advice. I really appreciate it.

Abstract

Pain is inherently unpleasant and can be a source of great distress. Research on fluctuations in pain intensity over the menstrual cycle has been inconsistent so far. While research on experimentally induced pain leans towards no fluctuations over the menstrual cycle, there are substantial indications for several clinical pain conditions that pain intensity fluctuates across the menstrual cycle. In phases with low estrogen concentrations (perimenstrual phase, mid-follicular phase) pain seems to be more intense compared to phases with higher estrogen concentrations. A reason for the inconsistent findings in the literature could be that moderating factors like stress have rarely been accounted for as stress can be an exacerbating factor for pain. This thesis therefore investigates whether the acute perception of pain intensity fluctuates over the menstrual cycle and whether stress moderates the relationship between the menstrual cycle and perceived pain intensity. The study was conducted over a whole menstrual cycle, using Ecological Momentary Assessment (EMA). Participants (N=36) indicated every day if they had experienced pain, their perceived pain intensity, and if they had experienced stress. Our results suggest that pain fluctuates over the menstrual cycle, with the perimenstrual phase having significantly higher and the mid-follicular phase having marginally significantly higher pain intensity compared to the periovulatory phase. Additionally, pain also occurred significantly more often during the perimenstrual and mid-follicular phases. While we were not able to find support for stress as a moderator for this relationship, it was a significant predictor for the occurrence of pain.

Keywords: pain perception, pain intensity, menstrual cycle, perceived stress

Table of Contents

Introduction

Pain is a phenomenon that everyone experiences now and then and that can become a source of great distress. Given the unpleasant experience of pain, there is a lot of research on the topic. However, the findings on sex differences are inconsistent. The female[1] hormonal cycle might be a possible factor contributing to the inconsistent findings as hormone levels may affect pain sensitivity (Sherman & LeResche, 2006; Bartley & Fillingim, 2013). Other factors possibly contributing to these inconsistencies are the rarely accounted for exacerbating factors of pain experience in everyday life. Because stress can aggravate pain intensity (White et al., 2014) it is one of the factors that should receive particular attention. Therefore, this thesis aims to explore if the perception of acute pain intensity in everyday life fluctuates over the menstrual cycle phases and to assess if daily perceived stress influences the relationship between the menstrual cycle phase and perceived pain intensity. At the beginning, the current state of research on pain will be presented. Subsequently, the state of research on fluctuations in pain across the menstrual cycle will be explained followed by the research status on stress and the interactions of pain, stress, and the menstrual cycle. The resulting research questions and hypotheses will be introduced and the methods that were used for the exploration of these questions will be outlined. This will be followed by the results and finally, the results will be interpreted and discussed and the limitations of the study as well as implications will be reported.

Theoretical Background

Pain

Pain can serve as an important warning and protection mechanism but can also result in severe suffering and even disease (Institute of Medicine et al., 2011). The International Association for the Study of Pain (IASP) defines pain as follows:

> An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. (Raja et al., 2020, p.2)

Pain receptors can be stimulated by damage of nerve tissue, stimulation of free nerve endings, or excessive stimulation for example, and upon stimulation they elicit physical pain (VandenBos, 2007). The reactions vary tremendously between individuals and the experience

[1] The terms *female* and *woman* are used in this paper to describe all persons who are assigned the biological sex "female".

of pain is a very personal one for several reasons (Fillingim, 2017; Raja et al., 2020). Biological, psychosocial, psychological, and social factors, training in pain response, and previous experience all contribute to individual differences in pain and pain responses (Fillingim, 2017, Raja et al., 2020, VandenBos, 2007). These biopsychosocial influences interact with each other in complex ways to result in the pain experience (Fillingim, 2017). Psychosocial factors like stress and pain catastrophizing additionally interact with genetic factors to influence pain (Fillingim, 2017). When pain is induced via a standardized experimental stimulus, the subjective pain reports may vary dramatically (Fillingim, 2017). All these factors contribute to the differences in pain perception of individuals. These differences are also visible in the clinical environment when patients' reports following the same surgical procedure vary greatly (Fillingim, 2017). To fully understand someone's response to and perception of pain, all the interactions between biological factors, psychological factors, and sociocultural context need to be looked at (Gatchel et al., 2007). Consequently, there is a need to gain a deeper understanding of the complex mechanisms leading to the differences in pain experience between people.

One of the mechanisms of pain experience is how a (painful) stimulus is signaled to the brain. The nerve endings, that signal the information to the brain that body tissue is being damaged or at risk of being damaged are called nociceptors (Bear et al., 2020). The activation of nociceptors can lead to conscious pain experience (Bear et al., 2020). Nociceptors can fire continually while pain comes and goes and pain can be severe even when nociceptors are not active (Bear et al., 2020). When talking about pain, nociception and pain must be distinguished from each other. While nociception describes the stimulation of nerves, which then provide information about potential tissue damage to the brain, pain is the subjective perception, resulting from transduction, transmission, and modulation of sensory information (Gatchel et al., 2007). Pain involves multiple two-way communication pathways in the central nervous system that communicate from the site of the pain to the brain and vice versa (Institute of Medicine et al., 2011), and can be classified as acute or chronic pain.

Acute Pain

Acute pain is defined as pain, lasting for a short time and with a sudden onset (Institute of Medicine et al., 2011). It appears usually in relation to a specific injury or illness and goes away when the underlying cause is removed (Institute of Medicine et al., 2011). If pain lasts over a longer period, it can become chronic.

Chronic Pain

Chronic pain is a global health problem, and affected persons can suffer severely from the pain itself and the consequences (Tan et al., 2020). Pain is described as chronic pain when it is persistent or recurrent for a period that lasts longer than 3 months (Treede et al., 2015). Between one-third and one-half of the population of the UK for example are affected by chronic pain (Fayaz et al., 2016). With an aging population, this figure will likely increase in the years to come (Institute of Medicine et al., 2011). Consequently, a deeper understanding of pain experience is an issue of high priority in medical and psychological research. Also, research on the prevention and treatment of pain is of high public interest and is a step towards improving life quality for many.

With pain being such an important research field, the question of how to effectively measure an experience like pain is essential.

Pain Measurement

Because pain is a subjective and very personal experience, pain assessment is a challenging endeavor (Fillingim, 2017). As direct measurement of pain is impossible, researchers must rely on individuals' self-report (Fillingim, 2017).

When assessing pain in an experimental environment, a pain stimulus is needed. This stimulus should be reproducible and strong enough to evoke a pain response that is measurable while being moderate enough to reveal differences between individuals (Sherman & LeResche, 2006). It should also be similar to pain in everyday life and theoretically precise (Sherman & LeResche, 2006). Examples of pain stimuli that are often used are the cold pressor test, electrical stimuli, pressure pain, thermal heat stimuli, and ischemic pain (Riley et al., 1998). Because these different pain stimuli activate a range of different mechanisms (Sherman & LeResche, 2006), comparisons between the pain outcome elicited by different pain stimuli might be methodologically inadequate. Moreover, in pain research, it is important to differentiate between experimentally induced pain and clinical pain.

Several factors that influence differences in pain perception need to be kept in mind when researching pain. One of these factors is sex differences, which will be further discussed in the following section.

Sex Differences in Pain

In comparison to men, women seem to suffer a greater amount of pain during their lifetime (Craft, 2007). Paradoxically, most studies on experimental pain have been performed exclusively on male participants (Tan et al., 2020). Most of the clinical pain disorders appear more often in women than in men, especially during the reproductive years (Martin, 2009).

These sex differences in pain are influenced by a range of biopsychosocial mechanisms like sex hormones, endogenous opioid function, genetic factors, pain coping, catastrophizing, and gender roles (Bartley & Fillingim, 2013). From a biological viewpoint, sex differences are attributed to the organizational and activational effects of gonadal steroid hormones (Craft, 2007). When studying sex differences, it is therefore of great importance to account for the ovarian cycle and reproductive status of females (Becker et al., 2005). The changes in the concentrations of reproductive hormones across menstrual cycle phases may affect pain in women (Tan et al., 2020). Additionally, beliefs about masculinity and femininity seem to play a role in pain responses which may lead to distorted pain reports, especially as expression of pain is more accepted in women (Bartley & Fillingim, 2013). This shows the importance of further research on the fluctuations of pain perception over the menstrual cycle. It is crucial to shed light on the question of which role the menstrual cycle plays in female pain perception and for sex differences in pain experience. Understanding the basic mechanisms of the menstrual cycle is therefore a key to being able to investigate these questions properly.

Pain Experience across the Menstrual Cycle

The Menstrual Cycle

The menstrual cycle starts with the first day of menses and ends with the day before the subsequent bleeding onset and is on average 28 days long (Schmalenberger et al., 2021). It is a natural process, allowing fertilization and pregnancy, which repeats monthly from the first menstrual bleed during puberty to menopause (Schmalenberger et al., 2021). The plasma concentrations of the main ovarian hormones are subject to cycle-related changes (Tan et al., 2020). Estrogen and Progesterone are the primary female reproductive steroids and are derived from cholesterol, secreted by the ovaries, circulate in the bloodstream, and cross the blood-brain barrier (Edler Schiller et al., 2018). There are different kinds of the hormone estrogen. The three main naturally occurring estrogens are called estradiol (E2), estrone, and estriol (Coelingh Bennik, 2008). During the premenopausal part of a woman's life, estradiol, which is mainly secreted by the ovaries, is the predominant estrogen (Coelingh Bennik, 2008). The menstrual cycle phases are characterized by the predictable fluctuations of estradiol (E2) and progesterone (P4) (Schmalenberger et al., 2021).

The menstrual cycle starts with the onset of menses, where the proliferated endometrium is shed, followed by the day of ovulation when the dominant follicle releases oocyte (Schmalenberger et al., 2021). This phase is called the follicular phase and during this phase, the P4 levels remain low and E2 rises through the mid-follicular phase and spikes dramatically just before ovulation (Schmalenberger et al., 2021). The luteal phase starts the

day after ovulation and ends the day before menses. During this phase the remains of the dominant follicle are transformed into the corpus luteum, which then again produces P4 and E2, letting the luteal phase begin with gradually rising P4 and E2 levels (Schmalenberger et al., 2021). In the mid-luteal phase, there is a peak in P4 and a secondary peak in E2 (Schmalenberger et al., 2021). These two phases have been used a lot in menstrual cycle research. The phases can be further divided for more accuracy. Schmalenberger et al. (2021) recommend using the following cycle phases to differentiate between the menstrual cycle phases: mid-follicular, perimenstrual, mid-luteal, and periovulatory. The mid-luteal phase is characterized by a primary peak in P4 and a secondary peak in E2 levels (Schmalenberger et al., 2021). The perimenstrual phase has active withdrawal in E2 and P4 levels and takes place during the last days of the luteal phase and the beginning of the follicular phase, including the onset of menses (Schmalenberger et al., 2021). It is also the time in which up to 50% of females experience primary dysmenorrhea (Dawood, 2006). Dysmenorrhea is a condition occurring during or before menstruation, which is characterized by pain in the lower abdomen (Fang et al., 2023). The mid-follicular phase is characterized by a slight rise in E2 levels and very low P4 levels (Schmalenberger et al., 2021). The periovulatory phase takes place at the end of the follicular phase and the beginning of the luteal phase and it includes ovulation (Schmalenberger et al., 2021). It has a steep increase, primary peak, and subsequent fall in E2 levels, while P4 levels start to slightly increase (Schmalenberger et al., 2021). Even though there has been a lot of research on the menstrual cycle, studies have not been able to adopt consistent methods to operationalize the menstrual cycle, which has resulted in inconsistent results and confusion in the literature (Schmalenberger et al., 2021). Sherman and LeResche (2006) report that at least nine different terms have been used in the research to define the menstrual cycle phases.

To investigate the effect that the menstrual cycle can have on pain perception it is necessary to also consider how gonadal hormones relate to pain experiences.

Pain and Gonadal Hormones

Animal studies showed that estradiol and progesterone seem to have pronociceptive as well as antinociceptive effects on pain and how they work is complex and probably depends on hormone interactions (Iacovides et al., 2015). In humans, according to Martin (2009), ovarian hormones have effects on several mechanisms that increase or decrease pain reactivity. These effects include inflammation, affective states, stress responses, modulatory pain systems, and afferent sensory systems (Martin, 2009). Ring et al. (2009) also infer from their research that gonadal hormones do influence the pain experience in healthy women.

They found correlations between increases in estradiol and progesterone and pain increases (Ring et al., 2009). Stening et al. (2007) found that pain sensations caused by noxious tonic cold stimulation are influenced by changes in the serum concentration of gonadal hormones across the menstrual cycle.

Progesterone seems to play a role in migraines in the luteal phase of the menstrual cycle (Martin et al., 2005). However, more research has been conducted on estrogens in relation to pain experiences and they appear to have an especially important role in pain perception. Estrogens play a part in the modulation of a variety of systems in the body, which makes the estrogenic modulation of pain highly complex (Craft, 2007). They produce pronociceptive effects as well as antinociceptive effects. In consequence, the effect of estrogen also depends on which systems of the body are involved in the type of pain at interest in a given research question (Craft, 2007). Looking at the activational effects of gonadal hormones, most of the research points towards estrogens as key modulators of pain (Craft, 2007). A study by Aloisi et al. (2007) looked at the effects of hormone treatment and found that male-to-female subjects suffered more pain than female-to-male subjects, with about half of the female-to-male subjects who suffered from chronic pain before treatment even experiencing a reduced number of painful episodes. This also points towards effects of sex hormones on pain experience.

It is common knowledge that many women experience pain during or right before menstruation. Therefore, the phenomenon of dysmenorrhea will be explained further in the next section.

Dysmenorrhea

Up to 50% of menstruating females experience painful menstrual cramps (called primary dysmenorrhea) without any evident pathology to account for them (Dawood, 2006). These cramps cause significant disruption in the quality of life (Dawood, 2006). While by now it is scientifical consensus, that dysmenorrhea is a pain that appears in dependence of the menstrual cycle phase, literature about other pains that are experienced in everyday life is far more inconsistent and unanimous.

As previously mentioned, pain can be researched in multiple ways. One way to research pain is to use painful stimuli in an experimental setting.

Experimentally Induced Pain

Numerous animal studies suggest that gonadal steroids may play an important role in the female response to painful stimuli (Sherman & LeResche, 2006). In humans, a large body of research on pain experience is conducted as experimental studies using pain stimuli to

induce pain. Experimental stimuli commonly used in experimental pain studies are electrical stimuli, pressure pain, thermal heat stimuli ischemic pain (Riley et al., 1998), and the cold pressor test (Tousignant-Laflamme & Marchand, 2009; Stening et al., 2007). Stening et al. (2007) found reduced pain thresholds for the cold pressure test during the late luteal phase in comparison with the early follicular phase. Fillingim et al. (1997) found less ischemic pain sensitivity in the mid-follicular phase compared to the ovulatory and mid-to-late luteal phase but no variation in thermal pain responses across all menstrual cycle phases. Ring et al. (2009) did not find any differences in pain ratings between the follicular and luteal phases regarding venipuncture and intravenous catheterization pain. However, there was a positive correlation between increases in estradiol, progesterone and the pain ratings indicating that these gonadal hormones influence the pain experience. De Barbosa et al. (2013) didn't find significant variation in pain thresholds between menstrual cycle phases in women using electrical current as a pain stimulus. Tousignant-Laflamme and Marchand (2009) also did not find differences in mean pain intensity, pain threshold, and pain tolerance across different menstrual cycle phases using two tonic heat pain stimulations and the cold pressor test as pain stimuli.

All this research shows that the findings on experimentally induced pain across the menstrual cycle are contradictory and not easily comparable because of the different pain stimuli and different operationalization of the menstrual cycle phases. Previously conducted meta-analyses shed more light on this issue. Riley et al. (1999) concluded from their meta-analysis that experimentally induced pain varies across the menstrual cycle with the follicular phase having the highest thresholds compared to later phases. In line with that, Riley et al. (1998) found that pain sensitivity was highest during the luteal phase. Martin (2009) also reports that there are modest effects of the menstrual cycle phase on experimental pain sensitivity. In the majority of studies Martin (2009) looked at, the pain thresholds and tolerance times varied during different phases of the menstrual cycle in healthy women pre-menopause. Taken all research together, most studies find that experimentally induced pain does not vary across menstrual cycle phases (Tousignant-Laflamme & Marchand, 2009). Several other meta-analyses and reviews have been conducted over the years, with the more recent publications leaning toward no significant fluctuations of pain perception over the different menstrual cycle phases in experimental pain studies. Sherman and LeResche (2006) as well as Iacovides et al. (2015) both conclude from their meta-analysis that the findings are mostly ambiguous, and research has so far not been able to draw clear conclusions on the question of whether the menstrual cycle phase influences the perception of pain intensity. Tan et al. (2020) explain the confusion in the literature and the contradicting findings with the

methodological variations between the studies such as the definition of menstrual phases and the differences in the experimental pain stimuli. The various applied pain stimuli being used contribute to the inconsistencies in the outcomes across studies (Iacovides et al., 2015).

Sherman and LeResche (2006) report a range of reasons for the inconsistent findings. They mention the differences in the sampled populations, the timing of experimental sessions across the menstrual cycle, the different used pain stimuli in experimental studies, the nomenclature for the identification and the description of different cycle phases, and the measured outcomes. It becomes apparent that there is enormous variability in the way the menstrual cycle is operationalized. This shows the need for better operationalization of the menstrual cycle and more comparable studies on pain perception.

While the experimental approach provides important insights, there remains the question of generalizability as the experience of pain in an experimental setting and the naturally occurring experience of pain possibly might work in different ways. That is why the research on clinical pain is so important. Especially as the results found on the fluctuations of pain perception across the menstrual cycle in individuals with clinical pain conditions differ from the research in experimental settings.

Clinical Pain

The fact that clinical pain disorders are more prevalent in women may be explained by the fluctuation in ovarian hormones over the menstrual cycle, which may affect the perception of pain (Martin, 2009). Craft (2007) reports substantial evidence for the involvement of estrogen in migraine, temporomandibular disorders, and arthritis. Moreover, Tan et al. (2020) also report that research has found variability in the severity of pain over the menstrual cycle in a range of chronic pain conditions. This includes Migraine, temporomandibular disorders, fibromyalgia, rheumatoid arthritis, and irritable bowel syndrome (Tan et al., 2020). Martin et al. (2005) also found that headache in female migraine patients was different among different menstrual cycle phases.

Hellström and Anderberg (2003) found that women with chronic pain experienced their pain as significantly higher during the premenstrual and menstrual phases compared to the mid-menstrual cycle and ovulatory phases. Hellström and Anderberg (2003) found this to be consistent with other study results that also found less pain sensitivity in phases associated with high estrogen.

During the menstrual interval of the menstrual cycle, migraine headaches are more severe and frequent than during the mid-luteal or mid-cycle phases (Martin et al., 2005). Linstra et al. (2021) compared women with menstrually-related migraine (MRM) and women

without MRM in their pain response to trigeminal and non-trigeminal painful stimuli. They found that women without MRM and women with MRM significantly differentiated in the changes across the menstrual cycle. Whereas trigeminal pain increased during the mid-luteal phase compared to the early-follicular phase in women without MRM it stayed low throughout the cycle in women with MRM (Linstra et al., 2021). Women with irritable bowel syndrome (IBS) often experience increased IBS symptoms during menses, including worsening abdominal pain and bloating (Houghton et al., 2002). Temporomandibular disorders are pain conditions regarding the temporomandibular joint and the muscles of mastication (LeResche et al., 2003). LeResche et al. (2003) found that temporomandibular pain is highest in phases of low estrogen. Yet, there might also be an association between increased pain and rapid estrogen change (LeResche et al., 2003).

Across menstrual cycle phases, clinical pain intensity seems to be most severe in phases that are characterized by low estrogen levels (Iacovides et al., 2015; Martin, 2009). Sherman and LeResche (2006) state in their meta-analysis that temporomandibular pain, migraine, and also possibly tension-type headache occur more often and are experienced more intensely in times of low estrogen or when estrogen fluctuates rapidly. A large amount of research shows more severe pain in phases with low estrogen like the early follicular and late luteal phase (Martin, 2009).

While some research points towards menstrual cycle effects in clinical pain conditions, other studies do not find fluctuations across the menstrual cycle. Alonso et al. (2004) for example, did not find any menstrual cycle effects in female fibromyalgia patients. This shows the need for more research in the field of clinical pain.

As we have covered clinical pain and experimentally induced pain, to complete the picture, the next section will address acute pain in everyday life in healthy individuals.

Pain in Everyday Life in Healthy Individuals

There has been a lot of research on experimentally induced pain in healthy individuals and a lot of research on patients with clinical pain conditions. Understanding the disruptive effects of not experimentally induced pain in healthy subjects has only recently emerged as a research area (Anderson et al., 2021). Self-reported acute pain in the everyday life of healthy individuals has rather been neglected in research so far. This leaves a gap for important exploration of non-experimental pain mechanisms in healthy individuals.

Due to the confusion in the literature about menstrual cycle effects on pain intensity, it is of great relevance to look at moderating factors that might influence whether healthy

women experience fluctuations in the perception of pain intensity over the menstrual cycle. An especially important one of these possible moderators is stress.

Pain and Stress

Stress

Stress is a component of everyday life and can influence many experiences. It can even function as an exacerbating factor for pain (Fischer et al., 2016, White et al., 2014). The APA Dictionary of Psychology defines stress as follows:

> A state of physiological or psychological response to internal or external stressors (VandenBos, 2007, p.898).

Stress is an important physiological response, which is a great necessity for the survival of a species (Lupien et al., 2018). When we speak of stress in everyday life we sometimes mean the cause of stress (a stressor) and sometimes mean the physiological consequences of a stressor or the psychological stress reaction (Nater et al., 2020). There is a multitude of potentially stress-inducing situations but not every individual will respond with a stress reaction (Nater et al., 2020). If a stressor evokes a stress reaction, it is the result of a complex interaction of different factors and objective values of the stressor interacting with the subjective assessments of an individual (Nater et al., 2020). In the stress response, physiological systems interact in a complex network that can lead to a wide range of effects when it is disturbed (Nater, 2018).

Chronic exposure to stress can have negative effects (Lupien et al., 2018). Stress can set off physical ailments but can also influence disease symptomology, the severity of an illness, and the prognosis (Nater et al., 2020). Severely stressful life events as well as smaller daily life stressors lead to wear and tear on the body, which can be summarized as “allostatic load” (McEwen, 2006). Stress hormones protect the body in the short run but longer exposure to allostatic load can lead to changes in the body and even result in disease (McEwen, 2006).

The two major stress-response systems are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) (Strahler et al., 2017). Stress increases the activity of the HPA axis and the ANS. The following release of biological substances like cortisol and adrenaline leads to physiological changes in the body which prepare the organism for a stressor and coping with the stressor (Nater et al., 2020). Short-term and long-term stress have different regulatory mechanisms (Russell & Lightman, 2019). When acute stress is experienced, cortisol levels rise and when stress becomes chronic, cortisol levels stay elevated

(Russell & Lightman, 2019). While acutely elevated cortisol levels have a beneficial effect in triggering a fight-or-flight response, chronic exposure to stress and therefore elevated cortisol levels, become maladaptive (Russell & Lightman, 2019).

As mentioned before, stress should be investigated more thoroughly as an influencing factor for the relationship between the menstrual cycle phase and perceived pain intensity. Therefore, the next section introduces some findings on the interactions between stress and pain.

How Stress and Pain Interact

Stress can be a powerful exacerbating factor for pain intensity (White et al., 2014) and there has been increased recognition of the fact that psychological factors like emotional stress can influence pain experience (Gatchel et al., 2007). Fibromyalgia (FMS) is a clinical condition characterized by widespread body pain (Fitzcharles & Yunus, 2012). Stress has been discussed as an influence factor in fibromyalgia (FMS) for some time (Fitzcharles & Yunus, 2012). Fischer et al. (2016) conducted a diary study and found that higher stress was associated with higher reported pain levels in women with FMS. This affirms the exacerbating effect of stress at least in FMS patients. White et al. (2014) were able to show that higher PSS (Perceived Stress Scale) scores are associated with higher pain intensity in older adults. Stress-decreasing methods are even being discussed as pain-management strategies. Smith et al. (2018) for example investigated relaxation techniques like yoga, mindfulness, music listening, etc. for pain management in labour. On the other hand, it is important to note, that the experience of pain itself can create stress (Institute of Medicine et al., 2011).

Because stress has been shown to aggravate pain in several studies and the menstrual cycle seems to influence pain perception, the next section will explore the complex relationships between all three variables.

Pain, Stress, and the Menstrual Cycle

Gonadal hormones can be altered by environmental stimuli like chronic exposure to a stressor like psychological distress and this alteration can ultimately result in ovarian dysfunction (Aloisi & Bonifazi, 2006). However, in the complex interactions between stress and gonadal hormones the direction of influence varies (Aloisi & Bonifazi, 2006). Interpretations should therefore be approached very carefully. The changing sex steroids during the female menstrual cycle might influence the HPA axis and autonomic activity (Strahler et al., 2017).

Animal as well as human studies show that the secretion of gonadal steroids can be altered by stress and glucocorticoids (Becker et al., 2005). The response of an organism to a

stressful challenge is largely influenced by modifications of the HPA axis and corresponding changes in circulating levels of glucocorticoids (Whirledge & Cidlowski, 2010). Increased levels of glucocorticoids are necessary to evoke a stress response and glucocorticoids have effects on gonadal function at multiple Hypothalamic-pituitary-gonadal (HPG) axis levels (Whirledge & Cidlowski, 2010). The HPG axis regulates the menstrual cycle (Edler Schiller et al., 2018). This underlines the role that stress can play in influencing the menstrual cycle. Strahler et al. (2017) also recommend controlling for the menstrual cycle phase when working with stress biomarkers like cortisol or alpha amylase. Becker et al. (2005) recommend always accounting for the possible impact of stress when studying sex differences. The impact stress and stress hormones can have on physiology and behavior are immense (Becker et al., 2005). Because moderating factors like stress have not been studied thoroughly enough, the interactions between stress, menstrual cycle, and pain should be examined further. As most studies on stress are conducted in artificial laboratory settings and leave the question of generalizability open, it is of great importance to study stress in everyday life (Nater, 2018). For example women with irritable bowel syndrome (IBS) often experience increased IBS symptoms during menses, including worsening of abdominal pain (Houghton et al., 2002). We know that IBS is a condition in which stress can play an important role. IBS is an example of a condition in which multiple factors interact to trigger the condition (Nater et al., 2020).

To conclude, the literature on pain perception over the menstrual cycle phases is quite inconsistent with research on experimentally induced pain pointing towards no effects, and research on clinical pain pointing towards more pain in phases that are characterized by low estrogen. Additionally, stress has been shown to aggravate pain in several studies and there are complicated interactions between gonadal hormones and stress which means that stress might influence the relationship between the menstrual cycle phase and pain intensity. The next section will introduce the research questions and hypotheses, that have been derived from the examined literature.

Research Questions and Hypotheses

The goals of this thesis are to investigate if the perception of acute pain intensity fluctuates over the menstrual cycle and to assess if daily perceived stress moderates these fluctuations over the menstrual cycle.

As women seem to suffer from more pain during their lifetime than men (Craft, 2007) and pain is an inherently unpleasant feeling, it is important to investigate the role of influence factors like the menstrual cycle in the female pain experience. Due to the inconsistency of the

literature on the existence of menstrual cycle effects on pain perception, it is of great relevance to further investigate if pain intensity fluctuates over the menstrual cycle. As laid out before, most of the research on clinical pain points towards fluctuations in the perception of pain intensity over the menstrual cycle (Tan et al., 2020; LeResche et al, 2003; Martin, 2009), and the research on experimental pain perception leans toward no effects (Sherman & LeResche, 2006). As we are interested in the acute pain experience of healthy individuals in everyday life, we assume fluctuations in the acute pain perception over the menstrual cycle in the natural non-experimental setting of our study. This leads to the following research question and corresponding hypotheses.

1. **Question:** Does the perception of pain intensity fluctuate over the menstrual cycle?
   Hypothesis 1: The perception of pain intensity fluctuates over the menstrual cycle.

The main body of research that does find fluctuations in pain perception over the menstrual cycle points towards the phases with low estrogen as the ones with the highest pain perception (Martin, 2009). Therefore, we hypothesize that the participants will experience pain most intensely during the perimenstrual phase and the mid-follicular phase compared to phases with higher estrogen levels like the mid-luteal phase and the periovulatory phase.

> **Hypothesis 2:** Pain is experienced most intensely during phases with low estrogen like the perimenstrual, and mid-follicular phases compared to the mid-luteal and periovulatory phases.

Potential moderators like stress are rarely considered in the research. However, research points towards stress as an exacerbating factor for pain intensity (White et al., 2014; Fischer et al., 2016). It is therefore important to investigate if the daily stress experienced in everyday life influences the perception of pain intensity or even moderates the relationship between pain intensity and cycle phase as an exacerbating factor for pain. This gives rise to the following research question.

2. **Question:** Does daily perceived stress moderate the fluctuations in perceived pain intensity over the menstrual cycle?

Because of the pain-exacerbating effects that stress seems to entail (White et al., 2014; Fischer et al., 2016), we assume that daily perceived stress influences the relationship between the menstrual cycle phase and the perceived pain intensity in a way that more daily perceived stress experience leads to more fluctuations in the perceived pain intensity.

> **Hypothesis 1:** Women who experience more daily perceived stress show more fluctuations in perceived pain intensity over the menstrual cycle.

It is expected that more experience of daily perceived stress is also associated with a more intense pain experience.

> **Hypothesis 2:** Women who experience more daily perceived stress, also experience more intense pain over the menstrual cycle than women who experience less daily perceived stress.

The methods for investigation of our research questions will be introduced in the following section.

Method

Study Design

This project is part of a broader study characterizing the amylase awakening response[2]. The study uses Ecological Momentary Assessment (EMA) to require data over the course of 30 days for men and one menstrual cycle for women. The study is structured as follows. If participants are eligible, they take part in two lab appointments: One at the beginning of participation and one at the end. In the approximately 30 days of testing in between the lab appointments, they take 3 saliva samples every morning in 15-minute intervals starting at awakening. Additionally, they answer a morning and an evening questionnaire. The aimed for sample size consists of 45 men and 45 women. Because the research interest of this thesis was aimed at the menstrual cycle, only the female participants were included in the analysis.

[2] Because the project is part of a broader study with other students writing their thesis on different aspects of the project, similarities in parts of the thesis might be the result.

Study Procedure

Between February 2023 and April 2024, 36 females completed the study. The participants were mostly recruited via Flyers (Appendix 1) and a mailing list. To determine eligibility, participants took part in a phone screening which took approximately 15 minutes. In case of eligibility, the participants were invited to a 45-minute lab appointment, where they received all information on the Ecological Momentary Assessment (EMA) part of the study, gave their consent to participation, and filled out a Unipark questionnaire. They also received 90 Salicaps and straws. Salicaps are small plastic containers in which the saliva samples are stored. The saliva was collected into the Salicap via a straw. To ensure the correct sample-giving procedure the participants did a supervised test run of giving a saliva sample. They received a study phone (if needed) with the movisens app (movisensXS, Version 1.5.23 (movisens GmbH, Karlsruhe, Germany)) installed or the app was installed on their phone. They were introduced to the movisens app (movisensXS, Version 1.5.23 (movisens GmbH, Karlsruhe, Germany)) and guided through the morning and evening questionnaires. The female participants let the study team know via E-mail or text message when they started their period and received a QR code enabling them to start with the EMA part of the study the day after they started their period. Every day of participation participants gave three saliva samples in the morning and answered a short questionnaire every morning and every evening. To make sure that a whole menstrual cycle was captured the participants completed 30 days to 35 days of testing depending on the average length of their menstrual cycle. Because the cycle length can fluctuate within persons, participants were provided with material for a few additional days. After completing the 30 days to 35 days of testing, the participants returned to the lab for another 45-minute lab appointment where they handed in all study materials and filled out another Unipark questionnaire. Participants received a compensation of 100€ once they had completed participation.

Sample

The sample consists of 36 healthy women[3] aged 18 to 35. All participants were fluent in German. Exclusion criteria were pregnancy, breastfeeding, smoking or drug use, chronic pain, chronic physical or psychological disorders, use of hormonal contraception, and an irregular menstrual cycle. Two participants had to be excluded because they had barely answered any of the movisens questionnaires which left us with 34 participants at the time of data analysis.

[3] Participants were included as *women* if they answered the question: “Was ist Ihr biologisches Geschlecht” which translates to “What is your biological sex?” with “weiblich” which translates to “female”.

Measurements

Perceived Pain Intensity

Participants were asked about their pain experience in the morning assessment as well as the evening assessment. The morning assessment included the following question: “Haben Sie gerade Schmerzen?” which translates to “Do you experience pain at the moment?”. If participants answered with “yes”, they were asked: “Welche Art von Schmerz?“ which translates to “What kind of pain?”. Furthermore, they were asked to indicate how intense the perceived pain was: „Wie stark sind die Schmerzen?“ which translates to “How strong is the pain?”. This question could be answered on a scale of 1 to 10 with 1 being the lowest pain intensity and 10 being the highest pain intensity. The participants could enter up to three different kinds of pain and the related pain intensity. In the evening assessment participants were asked the same questions as in the morning questionnaire: “Haben Sie gerade Schmerzen?”, „Was für eine Art von Schmerz“ and „Wie stark sind die Schmerzen?“. They were again able to indicate up to three different kinds of pain with related pain intensity. Additionally, they were asked: “Haben Sie im Laufe des Tages Schmerzen erlebt?“ which translates to „Did you experience pain during this day?”. If they indicated that they had experienced pain during the day they were asked which kind of pain they had experienced but not how strong the pain intensity during the day had been. Pain intensity was only inquired about when participants experienced pain at the time of assessment. Because participants who reported chronic pain or chronic pain conditions in the phone screening were excluded from the study, it can be assumed that all reported pain can be defined as acute pain. A new variable for acute pain intensity was created for analysis using the information from morning and evening assessments to create one value for each day. On most days participants experienced only one kind of pain. In the rare case that different pains were reported on the same day the first reported pain was used for analysis assuming that this would be the most prominent pain for the participant. When they reported different intensities for the same pain at different assessment time points the highest pain intensity was used.

Menstrual Cycle Phase

The cycle phases were determined using the forward-count and backward-count methods as recommended by Schmalenberger et al. (2021). The position within an individual’s menstrual cycle can be approximated using the start date of the preceding cycle and the start date of the following cycle (Schmalenberger et al., 2021). As recommended by Schmalenberger et al. (2021), the menstrual cycle was divided into the following four phases: mid-luteal phase, mid-follicular phase, perimenstrual phase, and periovulatory phase. To

determine the mid-luteal phase the backward-count method was used because we had no information about the actual day of ovulation. This meant that days -9 until -5 before the onset of subsequent menses were determined as the days of the mid-luteal phase. When participants had not indicated the onset of their subsequent menses, no mid-luteal phase was determined, and missing data was the result. The perimenstrual phase was determined by counting backward and forward from menstrual onset. Day -3 until day +2 were determined as the days of the perimenstrual phase. By using the counting method, the days when perimenstrual symptoms are expected to be the highest are included while avoiding progressing into the follicular phase (Schmalenberger et al., 2021). The mid-follicular phase was determined using the forward-count method, determining the mid-follicular phase as the phase between day +4 and day +7. The periovulatory phase was determined using the backward-count approach, defining the periovulatory phase as the days -15 to -12 before the onset of menses. When participants did not indicate their menses onset, the periovulatory phase could not be determined.

Daily Perceived Stress (PSS-4 Short Version)

Daily perceived stress was assessed via the movisens questionnaire using the short version of the Perceived Stress Scale (PSS) by Cohen et al. (1983). The PSS measures the degree to which situations in one's life are appraised as stressful (Cohen et al., 1983). Cronbach's alpha of the PSS-4 ranges from .60 to .82 in different studies that look at the psychometrics of the PSS (Lee, 2012). The four items were assessed every day in the evening assessment. They rated the item on a Likert scale ranging from 0 (never) to 4 (often). The original items were formulated assessing stress experience over the last month and were adjusted for the study to ask about the day. Examples of the items are: "Wie oft hatten Sie heute das Gefühl, wichtige Dinge in Ihrem Leben nicht beeinflussen zu können?" which translates to "How often have you had the feeling today that you cannot influence important things in your life?" or „Wie oft haben Sie sich heute sicher im Umgang mit Ihren persönlichen Aufgaben und Problemen gefühlt?" which translates to „How often have you felt confident in dealing with your personal challenges and problems today?".

Despite daily perceived stress being the stress measure of interest in this thesis, the chronic stress scores were included in the model as a covariate to control for the potential influence chronic stress experience could have.

Covariates

As mentioned before, several factors can influence pain experience (Fillingim, 2017, Raja et al., 2020, VandenBos, 2007). Many of the other variables, controlled for in the study

would make for interesting research questions and could also influence pain. However, in the motivation to keep the model interpretable in a straightforward manner, we decided to keep the covariates in this thesis to a minimum. This led to chronic stress being our only accounted-for covariate.

Chronic stress as a covariate. Chronic stress was assessed using the 12-Item-Screening-Skala (SSCS) from the Trier Inventar zum chronischen Stress (TICS) (Schulz et al., 2004), which is a global measure of experienced stress. The internal consistencies (Cronbach's alpha) of the TICS lie between .84 and .91 (M = .87) (Schulz et al., 2004). The participants filled out the SSCS in the Unipark survey which was part of the second in-lab appointment. The SSCS includes several items which are rated on a Likert scale. An example of an item is item 6: "Erfahrung, dass alles zu viel ist, was ich zu tun habe" which translates to „Experience that everything I have to do is too much". Another example would be item 2: „Ich bemühe mich vergeblich, mit guten Leistungen Anerkennung zu erhalten" which translates to „I struggle without success to gain acknowledgment for my good performance". The answers are given on a Likert scale ranging from 0 (never) to 4 (very often).

Analysis

For data preparation and a big part of the descriptive statistics, SPSS Statistics Version 29.0.0.0 (241) by IBM was used. Multilevel Modeling was used for the main data analysis. This was done using R Statistics 4.3.3 by R Foundation for Statistical Computing, 2023. The following R packages were used for the analysis: lme4 Version 1.1-35.2 (Bates et al., 2024), dplyr Version 1.1.4 (Wickham et al., 2023), ggplot2 Version 3.5.0 (Wickham et al., 2024), lmerTest (3.1-3) (Kuznetsova et al., 2020).

To avoid multicollinearity issues when computing interaction terms, the continuous variables for perceived daily stress and chronic stress were grand-mean centered. Grand-mean centering also allows the interpretation of the intercept to refer to the predicted pain intensity for persons with average stress levels instead of zero stress levels. In the first step of the analysis, we looked at the null model and computed the Intracorrelation Coefficient (ICC). Then the model was built stepwise, adding parameters one by one making it gradually more complex, and comparing each model to the previous one using the log-likelihood test. The model was fitted in seven steps.

Statistical Model

The Multilevel model is structured in a way that level 1 is the days/observations that are nested within participants (level 2).

Linear mixed model (LMM). We started fitting the model, beginning with the null model. The full model included pain intensity as the continuous outcome variable and cycle phase, daily perceived stress, chronic stress (covariate) as well as the interaction between cycle phase and daily perceived stress as fixed effects. A random intercept for each participant was included in each model, to account for the variability between participants. Additional random effects for the full model included daily perceived stress and cycle phase for which we allowed random slopes to account for the possibility of the effects of pain intensity and menstrual cycle phase on pain intensity to vary across participants. When fitting the model, we started with the null model and gradually added parameters until arriving at the full model. We added variable by variable, finishing with the addition of the random slopes. Each model was compared to the previous model using the log-likelihood test. The estimation method used was Restricted Maximum Likelihood (REML).

The full model was formulated as follows.

$$\text{Pain intensity}_i = b_0 + b_1 \cdot \text{mid-luteal phase}_i + b_2 \cdot \text{perimenstrual phase}_i + b_3 \cdot \text{mid-follicular phase}_i + b_4 \cdot \text{daily perceived stress}_i + b_5 \cdot \text{chronic stress (covariate)}_i + b_6 \cdot \text{mid-luteal phase} \cdot \text{daily perceived stress}_i + b_7 \cdot \text{perimenstrual phase} \cdot \text{daily perceived stress}_i + b_8 \cdot \text{mid-follicular phase} \cdot \text{daily perceived stress}_i + e_i$$

i … person 1 to n
person as random intercept
random slopes for daily perceived stress and cycle phase
e … residuals

Generalized linear mixed model (GLMM). Over the course of the analysis, it became apparent that pain was occurring rather rarely. Because the model requirements for a linear model were therefore not met and the data was not suitable for the planned analysis the originally planned model was supplemented by a generalized linear mixed model with logit link. In consequence, a dichotomous outcome variable was created, that reflected if pain had been experienced that day or not. To gain the most information about the research interest and to be able to draw the most accurate conclusions, it was decided to look at both models.

In the alternative model, Maximum Likelihood (ML) was used because of the dichotomous outcome variable. The model with pain occurrence as the binary outcome

variable was fitted with all variables like the original model, only exchanging the outcome variable. Model comparisons were started with the null model and gradually parameters were added making the model more complex, comparing each model to the previous model, using the log-likelihood test.

The full model with pain occurrence as the binary outcome variable was formulated as follows.

$$P(Pain_i) = 1 / (1 + \exp(-(b_0 + b_1 \cdot \text{mid-luteal phase}_i + b_2 \cdot \text{perimenstrual phase}_i + b_3 \cdot \text{mid-follicular phase}_i + b_4 \cdot \text{daily perceived stress}_i + b_5 \cdot \text{chronic stress (covariate)}_i + b_6 \cdot \text{mid-luteal phase} \cdot \text{daily perceived stress}_i + b_7 \cdot \text{perimenstrual phase} \cdot \text{daily perceived stress}_i + b_8 \cdot \text{mid-follicular phase} \cdot \text{daily perceived stress}_i))$$

i … person 1 to n
person as random intercept
random slopes for daily perceived stress and cycle phase

Data Cleaning

Of the sample of 36 women, two women had to be excluded because of missing data in the movisens questionnaires. Some evening questions had to be removed because the participants answered them only the next morning after giving saliva and after answering the morning assessment which made those answers not usable for us. The variables for daily perceived stress and chronic stress (covariate) were grand-mean centered. In some cases, participants had ended their participation before the next onset of their menses which made it impossible to determine the menstrual cycle phases that need backward-counting. In those cases, missing values were the result. Participants were allowed to enter up to 3 kinds of pain in the morning and the evening assessment which led to a challenge in data preparation. On some days participants experienced multiple kinds of pain. Since multiple kinds of pain were only indicated in a small number of cases, the first reported pain and the highest corresponding pain intensity level were used assuming that that was the most prominent experienced pain to the participant.

Results

Descriptive Statistics

The 34 female participants were between 19 and 30 years old and had a mean age of 23.23 (*SD* = 2.40). The shortest cycle length in the sample was 23 days and the longest was 33 days. The mean cycle length was 27.42 (*SD* = 2.73) days. The participants completed between 25 to 36 days of testing. On average, they completed 31 days of testing. This resulted in a total of 1058 observations (days). Out of these 1058, pain was experienced on 91 of the observations. 457 of the 1058 measurement time points fell into the relevant cycle phases. This meant that on average 14 testing days would fall into the relevant menstrual cycle phases. Leaving 40 occasions of perceived pain intensity within the relevant periods of the defined menstrual cycle phases. Table 1 shows an overview of the days falling into the menstrual cycle phases on which pain was experienced or not experienced. Table 2 shows the descriptive statistics of perceived pain intensity for the different menstrual cycle phases. When looking at Table 2, it becomes apparent that the mean pain intensity was highest during the perimenstrual phase, closely followed by the mid-follicular phase. The mid-luteal phase has a lower mean pain intensity than those two phases and the periovulatory phase has the lowest mean pain intensity of all four phases. The descriptive statistics for perceived pain intensity, daily perceived stress, and chronic stress (covariate) are summarized in Table 3.

Table 1

Overview of Days per Cycle Phase on which Pain Occurred/Did not Occur

	Pain	No pain	Total
Mid-luteal phase	9 (7.1%)	118 (92.9%)	127
Perimenstrual phase	14 (12.7%)	96 (87.3%)	110
Mid-follicular phase	14 (11.4%)	109 (88.6%)	123
Periovulatory phase	3 (3.1%)	94 (96,9%)	97
Total	40 (8.8%)	417 (91.22%)	457

Note. 34 participants observed over an average of 14 days (days within the relevant cycle phases).

Table 2

Descriptive Statistics for Perceived Pain Intensity over Menstrual Cycle Phases

Cycle phase	n	Min	Max	Mean	SD
Mid-luteal phase	127	0	8	0.28	1.15
Perimenstrual phase	110	0	10	0.61	1.86
Mid-follicular phase	123	0	8	0.53	1.59
Periovulatory phase	97	0	5	0.13	0.77
Total	457				

Note. n = number of days that fell into this cycle phase; Min = Minimum; Max = Maximum; SD = Standard deviation.

Table 3

Descriptive Statistics of the Variables Perceived Pain Intensity, Daily Perceived Stress, and Chronic Stress

	n	Min	Max	Mean	*SD*
Perceived Pain Intensity	1058	0	10	0.35	1.26
Daily Perceived Stress	929	0	14	5.02	3.10
Chronic Stress (covariate)	34	5	38	22.63	9.71

Note. n = number of observations or number of participants, Min = Minimum, Max = Maximum, SD = Standard deviation.

Exploratory Data Analyses

Figure 1 shows how often a certain kind of pain was experienced during the different menstrual cycle phases. On 66 days, participants indicated what kind of pain they had experienced. The indicated pains were distributed as follows: Head (17), lower abdomen (17), abdomen (11), back (6), muscle ache (4), throat (3), period (2). All other reported pains only occurred on one occasion (exhaustion pain, heart, knee, ankle, upper arm, calves). 40 of these reported pain experiences fell into the relevant menstrual cycle phases.

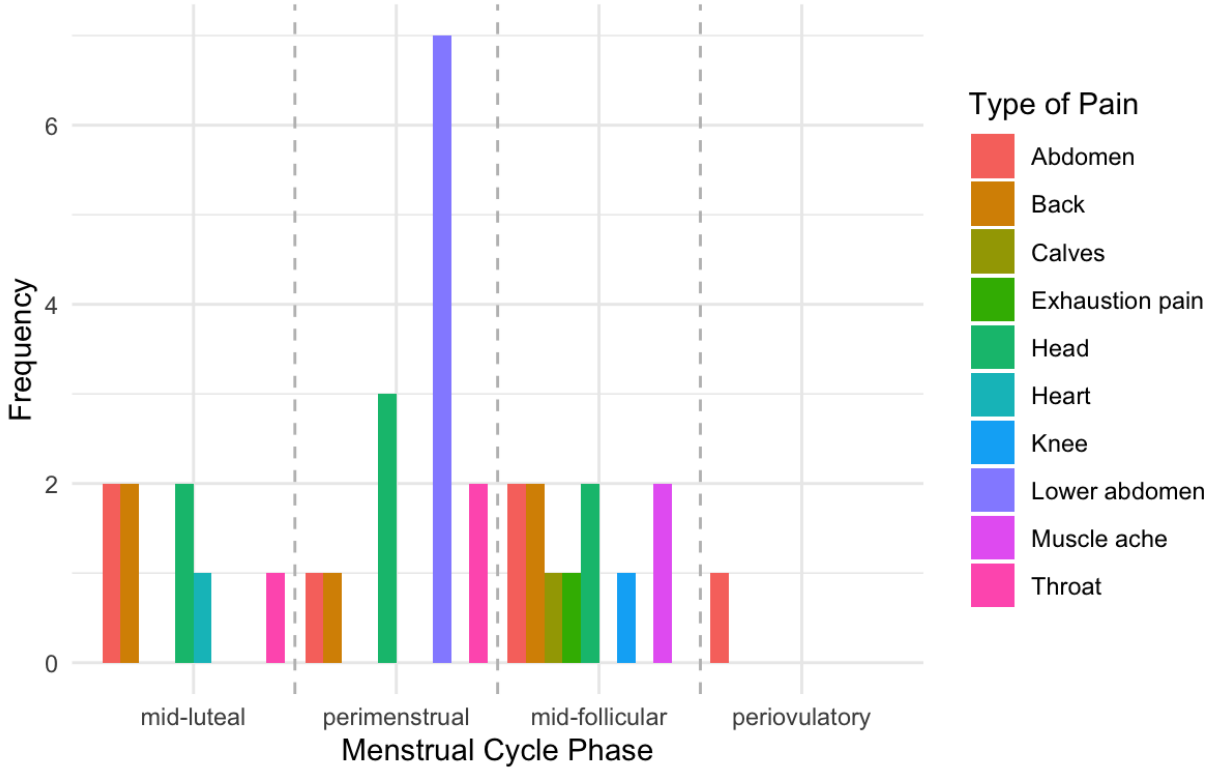


Figure 1.

Frequency of Pain Types during Menstrual Cycle Phases

Looking at the distribution of pain intensity, a problem for the planned analysis became apparent quite quickly. Out of 1058 observations, participants experienced pain only on 91 occasions. This left only 40 occasions of perceived pain intensity within the relevant periods of the defined menstrual cycle phases. As a result, the value for perceived pain intensity was 0 at most measurement time points. The distribution of the experienced pain intensity is visualized in Figure 2. Figure 3 visualizes the experienced pain intensity per person. Looking at Figures 2 and 3 it becomes clear, that pain intensity is not normally distributed and therefore a linear model is not the right fit. This distribution is not suited for the estimation of mean values as practiced in the linear model. Figure 3 shows that the rare occurrence of pain does not mean that only a few women perceive pain. However, it appears that the majority of women perceive pain but only at a few measurement time points.

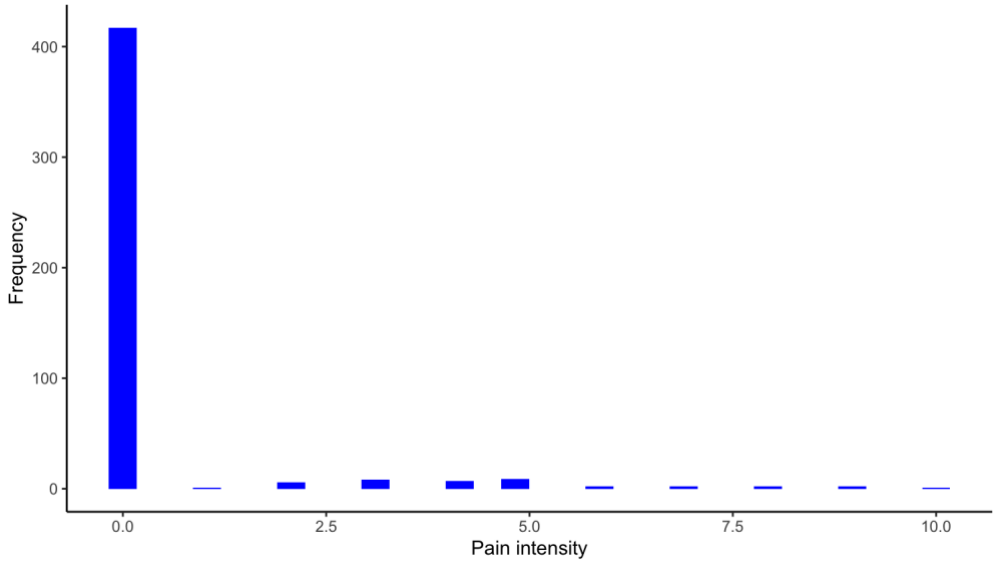


Figure 2.

Distribution of the Experienced Pain Intensity

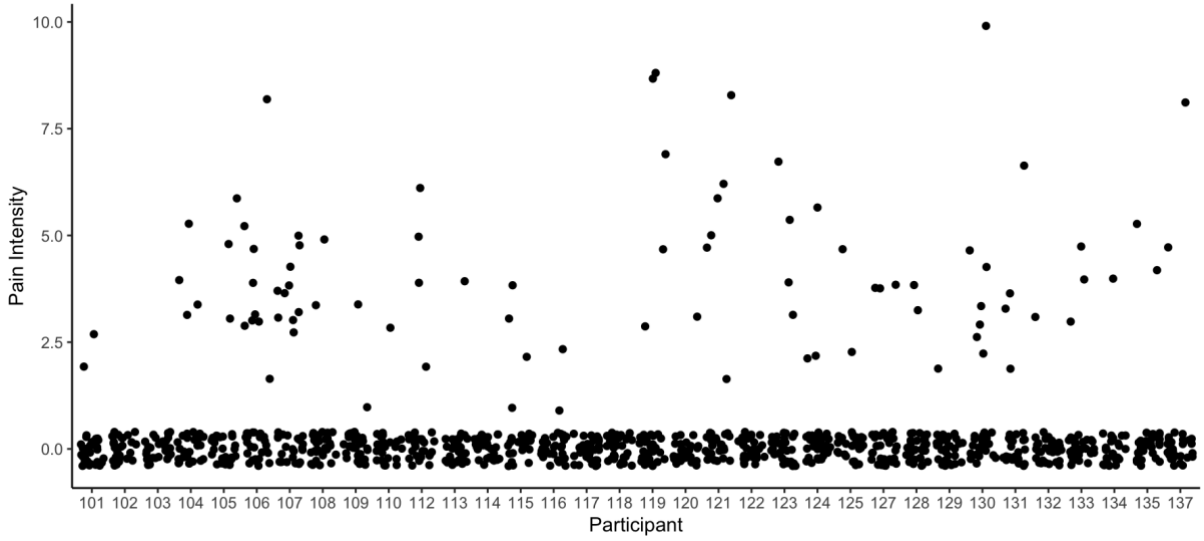


Figure 3.

Perceived Pain Intensity across all Observations Separated by Participant

Note. Participants are numbered starting with 101=1, 102=2, etc.; the dots are jittered to make the ones who are in the same place visible, so they don't sit on top of each other.

Multilevel Modeling of Pain Intensity and Pain Occurrence

Plotting the standardized residuals of the linear mixed model against the predicted values (see Figure 4) shows that we can assume homoscedasticity but there is severe skewness of the residuals.

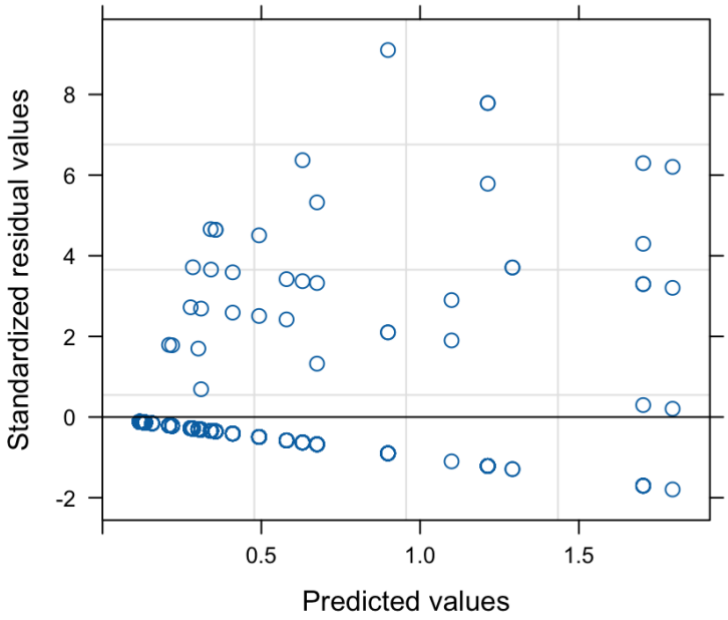


Figure 4.

Plot of the Standardized Residuals of the Linear Mixed Model against the Predicted Values

Two models were fitted. The originally planned model with the continuous outcome variable perceived pain intensity and the alternative model with the dichotomous outcome variable pain occurrence. Regarding the linear mixed model, the intraclass correlation coefficient (ICC) which was calculated for the null model (model 1) was 0.145, meaning that 14.5% of the variability in pain intensity is due to differences between participants. In the next step, the model was fitted, starting with the null model, and then adding variables until arriving at the full model. Model 2 achieved the best fit with a marginally significant log-likelihood test for the comparison between model 1 and model 2. Model 2 had pain intensity as the continuous outcome variable and included only the cycle phase as a fixed effect and the participant as a random effect. One can find the log-likelihood tests for all model comparisons in Table 4.

Regarding the generalized linear mixed model, the ICC calculated for the null model (model 1) was 0.264, meaning, that 26.4% of the variability in pain occurrence was due to differences between participants. The alternative model with pain occurrence as the binary outcome variable was fitted with all variables like the original model, only exchanging the outcome variable. In this case, model 3 had the best fit. This meant the model included pain occurrence as the outcome variable, the predictor variables cycle phase and daily perceived stress as fixed effects, and the participants as a random effect with freely varying intercept.

Table 4

Log-Likelihood-Tests for all Models

M	Model change (added parameter)	npar	AIC	BIC	LogLik	Deviance	χ^2	*df*	p-value
Continuous Outcome Variable: Pain Intensity									
1		3	1608.8	1621.2	-801.39	1602.8			
2	Cycle phase[1]	6	1607.0	1631.7	-797.50	1595.0	7.78	3	.051 .
2		6	1607.0	1631.7	-797.50	1595.0			
3	PSS score[1]	7	1608.1	1637.0	-797.04	1594.1	0.91	1	.341
3		7	1608.1	1637.0	-797.04	1594.1			
4	SSCS score (covariate) [1]	8	1609.2	1642.2	-796.60	1593.2	0.89	1	.345
4		8	1609.2	1642.2	-796.60	1593.2			
5	Interaction[1]	11	1614.5	1659.9	-796.25	1592.5	0.7	3	.874
5		11	1614.5	1659.9	-796.25	1592.5			
6	PSS score[2]	13	1616.7	1670.3	-795.36	1590.7	1.77	2	.413
7	Cycle phase[2]	Non-convergence							
Binary Outcome Variable: Pain Occurrence									
1		2	266.90	275.15	-131.45	262.90			
2	Cycle phase[1]	5	264.33	284.95	-127.17	254.33	8.57	3	0.036 *
2		5	264.33	284.95	-127.17	254.33			
3	PSS score[1]	6	262.44	287.19	-125.22	250.44	3.9	1	.048 *
3		6	262.44	287.19	-125.22	250.44			
4	SSCS score (covariate) [1]	7	263.62	292.50	-124.81	249.62	0.81	1	.367
5	Interaction[1]	Non-convergence							
6	PSS score[2]	Non-convergence							
7	Cycle phase[2]	Non-convergence							

Note. M = Model, npar = number of parameters, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, LogLik = Log-Likelihood, χ^2 = chi-squared, *df* = degrees of freedom, [1] = fixed effect predictor, [2] = random slope, PSS = Perceives Stress Scale, SCSS = Screening Scale for Chronic Stress, * = significant, . = marginally significant.

The interaction between the cycle phase and daily perceived stress did not significantly improve the model with pain intensity as the outcome variable or the model with pain occurrence as the outcome variable. Therefore, the interaction was not included in the models with the best fit. The covariate chronic stress did also not significantly improve the model and was therefore not further included in the analysis.

The estimates for the model with the continuous outcome variable pain intensity (see Table 5) indicate that pain intensity tends to be significantly higher during the perimenstrual phase compared to the periovulatory phase. Pain intensity also tends to be marginally significantly higher during the mid-follicular phase compared to the periovulatory phase.

Table 5

Estimates for Continuous Outcome Variable of Pain Intensity using Linear Mixed Model

Predictors	***b***	***SE***	***t***	***p***
Intercept	0.21	0.17		
Reference=periovulatory phase				
Mid-follicular phase	0.36	0.18	1.93	.055 .
Mid-luteal phase	0.17	0.18	0.94	.346
Perimenstrual phase	0.48	0.19	2.59	.010 *
Random intercept	Variance			
Participant	0.29			

Note. b = Regression Coefficient or fixed effect estimate, SE = Standard Error, t = t-value, p = p-value, . $p < .100$, * $p < 0.050$.

The estimates for the model with pain occurrence as a binary outcome variable (see Table 6) show significant coefficients for the perimenstrual phase and the mid-luteal phase compared to the periovulatory phase. Additionally, daily perceived stress also seems to be a significant predictor of pain occurrence.

Table 6

Estimates for Binary Outcome Variable of Pain Occurrence Using Generalized Mixed Model with Logit Link Function

Predictors	***b***	***SE***	***z***	***p***
Intercept	-3.77	0.65		
Reference=periovulatory phase				
Mid-follicular phase	1.43	0.68	2.09	.037 *
Mid-luteal phase	0.98	0.70	1.39	.163
Perimenstrual phase	1.62	0.68	2.39	.017 *
Daily perceived stress	0.14	0.07	2.01	.045 *
Random intercept	Variance			
Participant	0.93			

Note. b = Regression Coefficient or fixed effect estimate, SE = Standard Error, z = z-value, p = p-value, * $p < 0.050$.

Regarding the first research question “Does the perception of pain intensity fluctuate over the menstrual cycle?”, both, the model with pain intensity as a continuous outcome variable (see Table 5) and the model with pain occurrence as a binary outcome variable (see Table 6) provide strong support for hypothesis 1, which states that pain intensity fluctuates over the menstrual cycle. Both models also provide support for hypothesis 2, which states that pain is experienced most intensely during phases with low estrogen like the perimenstrual, and mid-follicular phase compared to the mid-luteal and periovulatory phase. Significant and marginally significant results in the model with pain intensity as a continuous outcome variable (see Table 5) indicate that pain intensity is significantly higher in phases with lower estrogen like the mid-follicular and the perimenstrual phase. The significant coefficients for the mid-follicular and perimenstrual phase compared to the periovulatory phase in the model with pain occurrence as a binary outcome variable (see Table 6), suggest that pain occurs more often in those phases.

Regarding the second research question “Does daily perceived stress moderate the fluctuations in perceived pain intensity over the menstrual cycle?”, the interaction between the cycle phase and daily perceived stress did not significantly improve the model and was therefore not included in either of the final models. Consequently, we cannot make statements about daily perceived stress as a moderator of the relationship between the menstrual cycle

phase and pain. We therefore didn't find an indication, that daily perceived stress moderates the relationship between cycle phase and pain occurrence or cycle phase and pain intensity. The alternative model with pain occurrence as a binary outcome variable, however, shows support for daily perceived stress being a significant predictor of pain occurrence.

In the following, the results will be interpreted and discussed in light of the current state of research, and the limitations and implications of this thesis will be reported.

Discussion

The goal of this thesis was to investigate if the perception of pain intensity fluctuates over the menstrual cycle and if stress moderates the relationship between the menstrual cycle phase and perceived pain intensity. The results showed that pain intensity was significantly higher during the perimenstrual compared to the periovulatory phase and marginally significantly higher in the mid-follicular phase compared to the periovulatory phase. Additionally, pain occurred significantly more often during the perimenstrual phase and the mid-follicular phase compared to the periovulatory phase. Daily perceived stress did not significantly improve the model and was therefore not further investigated as a moderator for the relationship between the menstrual cycle phase and pain intensity. It was however found to be a significant predictor for the occurrence of pain.

Fluctuations of Perceived Pain Intensity and Pain Occurrence over the Menstrual Cycle

In research question one it was investigated if the perception of pain intensity fluctuates over the menstrual cycle. Correspondingly, the first hypothesis stated that the perception of pain intensity fluctuates over the menstrual cycle. In line with the research by Tan et al. (2020), Martin et al. (2005), Hellström and Anderberg (2003), and Houghton et al. (2002), who report fluctuations in clinical pain conditions over the menstrual cycle, our data provides support for this hypothesis. We found significant differences in the occurrence of pain over the menstrual cycle phases, meaning that the coefficients in MLM were significant for the perimenstrual phase and the mid-follicular phase in the alternative model with pain occurrence as the binary outcome variable. Additionally, we found the data showed significant coefficients for the perimenstrual phase and marginally significant coefficients for the mid-follicular phase compared to the periovulatory phase in MLM for our original model with pain intensity as the continuous outcome variable. This indicates that the occurrence of pain as well as the intensity of pain perception significantly fluctuates over the menstrual cycle. These findings also match the conclusions regarding experimentally induced pain in the meta-analyses of Riley et al. (1999) and Martin (2009) concerning the existence of fluctuations.

This is also in line with the researchers that find fluctuations in experimentally induced pain such as Stening et al. (2007) or Fillingim et al. (1997). However, their conclusions regarding which phases are characterized by more pain occurrence and more pain intensity, do not match ours.

The larger body of research on experimentally induced pain contradicts our results because most research on experimentally induced pain does not find fluctuations over the menstrual cycle (Tousignant-Laflamme & Marchand, 2009). Comparability of our results and the results from experimental studies is questionable because pain mechanisms can severely differentiate between different kinds of pain (Sherman and LeResche, 2006), and we did not experimentally induce pain in our study. The differences between the findings on experimentally induced pain and clinical pain could potentially be explained by the broad range of different mechanisms that underly the different kinds of pain as mentioned by Sherman and LeResche (2006). It can be assumed that all pain which was experienced by the participants was naturally occurring pain. Therefore it is plausible that our results are much more in line with the research on clinical pain perception, which finds fluctuations in pain perception over the menstrual cycle (Tan et al., 2020). Also, a range of different operationalization methods and phasing procedures have been applied to measure and compare menstrual cycle phases. This has resulted in difficulties in interpretation and comparability (Sherman & LeResche, 2006, Schmalenberger et al., 2021) that also make it more challenging to compare our results to previous research. Future research should try to operationalize the menstrual cycle sensibly and think of comparability between studies. Additionally, because the sample size was only moderate and the measurement time points on which pain was experienced were not that many in comparison to all recorded measurement time points, the interpretations must be made very cautiously.

Our data analysis also provided support for the second hypothesis which posited that pain is experienced most intensely during phases with low estrogen like the perimenstrual, and mid-follicular phase compared to the mid-luteal and periovulatory phase. We found significant coefficients for the perimenstrual phase as well as marginally significant coefficients for the mid-follicular phase in the model with pain intensity as the outcome variable when comparing them to the periovulatory phase. Additionally, in the model with pain occurrence as the binary outcome variable, during the perimenstrual phase and the mid-follicular phase, tends to arise significantly more often compared to the periovulatory phase. This is in line with the research on the effect of estrogen on the perception of pain intensity but should be interpreted with caution since estrogenic pain modulation is highly complex and

estrogen produces both nociceptive and antinociceptive effects (Craft, 2007). Additionally, the effect of pain perception is likely dependent on many different systems involved in a particular type of pain (Craft, 2007).

Regarding the different kinds of pain, pain in the lower abdomen occurred more often during the perimenstrual phase than during any other phase which makes sense because pain in the lower abdomen is a symptom of dysmenorrhea (Fang et al., 2023) which occurs during or proceeding menstruation. The perimenstrual phase encompasses menses and the few days before menses onset which means that more occurrence of pain in the lower abdomen is in line with the previous research.

As some research on pain conditions finds fluctuations across menstrual cycle phases (Tan et al., 2020) and other research does not (Alonso et al., 2004), maybe certain types of pain are related to menstrual cycle phases while other types of pain do not interact with the menstrual cycle. There might be differences regarding fluctuations of pain over the menstrual cycle depending on the kind of pain. To answer this question more research that looks at healthy individuals and their everyday pain experiences is needed.

The Influence of Stress

Regarding the second research question, the goal of this thesis was to investigate if stress is a moderator of the relationship between the menstrual cycle phase and the perception of pain intensity. It was expected that stress would have a moderating effect on the relationship. As the interaction between daily perceived stress and cycle phase did not significantly improve the model, it was not included in the final model, and we were therefore not able to find support for a moderating effect of daily perceived stress on the relationship between pain intensity and menstrual cycle phase. A possible explanation for why we did not find support for this could be that we did not account for possible covariates that might have stress-decreasing effects like physical activity or relaxation methods. We did however find support for daily perceived stress as a predictor for pain occurrence in the model with pain occurrence as a binary outcome variable, which corresponds with the research by White et al. (2014) and Fischer et al. (2016) who found stress to be an exacerbating factor for pain. This is further evidence for the hypothesis that stress plays an important role in pain experience and should be the subject of future research. Stress might influence pain in more complex ways than we accounted for in our model. It should not be neglected that stress might work as an exacerbating factor for pain in some cases and might have no effect in other cases. Additionally, as mentioned by the Institute of Medicine et al. (2011) the experience of pain is inherently unpleasant, can be a great stressor, and could therefore evoke stress itself. These

complex interactions and interdependencies give reason to caution when interpreting the results but also indicate that more research is needed.

The results of this thesis bear important implications for future research as well as for the treatment and prevention of pain but the thesis also has some limitations which will be addressed in the following.

Limitations and Implications

Because the study was already fully developed and set up to start when the research questions for this thesis were developed, they had to be developed within an already set up study, which can be argued is methodologically flawed.

In terms of operationalization, because pain measurement is highly subjective and reliant on self-report (Fillingim, 2017), a limitation of the study lies in the subjective nature of the answers that the participants gave in their rating of pain intensity. It cannot be determined if participants have similar reference frames, and different people would therefore assign different numbers to the same pain stimulus. As explained in the methods section, when assessing pain experience, participants were asked about their experienced pain intensity at assessment time. Additionally, they were asked if they had experienced pain during the day. The acute pain intensity however was only assessed for pains experienced at the time of assessment and not for the pains which had occurred between the assessment times. Because of the nature of the research question and the pain assessment already in place, a new pain variable was created from the available data from both assessment time points. This approach posits a limitation and means that some data was lost. Future research should have a more systematic approach to measuring perceived pain intensity.

Additionally, there is a question of comparability when looking at all the kinds of pain that participants experience over the course of a menstrual cycle. Since different kinds of pain can have different underlying mechanisms (Sherman & LeResche, 2006), it might be problematic to treat them all the same or generalize from one pain to another kind of pain. It is, on the contrary, necessary to differentiate the pain that females experience in a more nuanced manner. More research on the pain experience of healthy women in everyday life is needed to understand which kinds of pain fluctuate in which ways over the menstrual cycle and what influence factors play a role in the perception and occurrence of different kinds of pain. If participants report “back pain” it cannot be inferred what caused the pain. This calls for an approach in which people describe their pain in more detail. Potentially a lot more information on the pain and its context, perception, and underlying mechanisms is needed to be able to sufficiently differentiate between pains. Also, information about the time of day

when the pain was experienced and knowledge about the cause or origin of the pain perception could play important roles. An important further step would be to look at the different kinds of pain, their causes, and how they vary across the menstrual cycle individually.

Regarding the operationalization of the menstrual cycle, as no ovulation tests were carried out in the study, we cannot say whether ovulation occurred during participation. To classify the cycle phases more accurately, ovulation tests would be helpful. It is another of the limitations of our study that plasma concentrations of estrogen and progesterone were not measured. In this thesis, we only assume that estrogen was low in specific phases because we know that it usually behaves this way, but we did not account for it. With the menstrual cycle only being a rough index of the hormonal profile it can be argued that it would be a methodological improvement to directly measure ovarian hormones (Becker et al., 2005) The determination of estrogen and progesterone levels is crucial to further explore the relationship between pain and gonadal hormones. For future studies, it is advisable to investigate the role of estrogen and progesterone further as well as their interactions. It would be very beneficial to conduct a similar study, which assesses exact estrogen and progesterone concentrations across the different menstrual cycle phases.

To keep the model well interpretable and because there were issues with non-convergence in some of the more complex versions of the model, we decided to keep the covariates to a minimum, only including chronic stress as a covariate. Thereby we might have missed confounding effects. Future studies should therefore include more covariates. Several covariates should be controlled for when doing so. Age for example was not included as a covariate because the participants were between 19 and 30 years old, which we did not expect to have a big influence. Future studies however should include age as a covariate especially when investigating a broader age range. Other covariates that could potentially influence pain perception were not accounted for in this thesis but should be included in future studies because of possible confounding effects. Also, other potentially stress-influencing factors like relaxation methods as mentioned by Smith et al. (2018) were not included as covariates in this thesis, but future research should investigate their relationship to pain, stress, and the menstrual cycle.

Since the study was still going on when analyses for this thesis were started, not the full potential of sample size could be used and only the participants that had been tested until that time were included in the analysis, which resulted in a moderate sample size. Also, the women generally did not experience a lot of pain in our sample. Only on 91 out of 1058

occasions did participants experience pain. To draw better conclusions and regarding that healthy individuals usually do not experience great amounts of pain in everyday life, the moderate sample size of 36 participants should be increased in future studies on pain in everyday life.

Another methodological limitation is, that because pain intensity was not normally distributed, the analysis had to be adjusted. However, with both MLM models taken together, a lot of useful information has been gained.

Because the study required a large commitment from the participants, interfered with their usual morning routine, and was time-consuming, compliance could have possibly decreased over time. A possible indication for less compliance is the cases in which participants indicated that they had experienced pain but then did not indicate what kind of pain and how intensely the pain had been experienced.

Regarding future research, another step in making sense of the research that has been conducted so far would be an EMA project with an experimental pain condition. A project of this sort, using the methods for measuring the menstrual cycle phases recommended by Schmalenberger et al. (2021) could shed more light on the different findings between experimentally induced pain and clinical pain. The recommended operationalization of the menstrual cycle by Schmalenberger et al. (2021), differs from the operationalization of most studies because there has not been a consensus on operationalization so far. This leads to some issues when comparing the study results to other research and is one of the reasons for the inconsistent findings in the literature. Because decades of research have not managed to adopt consistent research methods for the operationalization of the menstrual cycle (Schmalenberger et al., 2021), it is of great importance to conduct further research and contribute to making menstrual cycle research more comparable. This is not only important for further research but also for improving medical aid for females experiencing pain.

Since stress also seems to play an important role in pain conditions, for example in FMS (Fischer et al., 2016), future research should further explore the relationship between acute pain experience and perceived stress levels in the everyday life of people with and without pain conditions.

In terms of clinical implications, if stress is a predictor for pain occurrence as our results indicate, it would make sense to try to minimize stress in more vulnerable menstrual cycle phases if pain is expected during this time. Stress-reducing techniques like relaxation, yoga, etc. could be used as interventions for people experiencing pain as discussed for women in labour by Smith et al. (2018).

If the perception of pain intensity fluctuates across the menstrual cycle as our results indicate, it would make sense to plan treatments and prevention methods accordingly. This could mean different intensities of treatment or prevention measures between more vulnerable and less vulnerable phases. It could even mean different dosages of pain medication for individuals in different phases might be sensible. For painful medical treatments, it might be a helpful adjustment for the patients to plan the treatment for less sensitive menstrual cycle phases. If more intense pain in certain cycle phases is “normal”, this knowledge might help research and additionally might help individuals understand their own pain experience better and consequently might also help patients to cope better with their pain.

Conclusion

This thesis provides substantial support for the hypothesis that the perception of pain intensity as well as the occurrence of pain fluctuates over the menstrual cycle with the perimenstrual phase and the mid-luteal phase being the most vulnerable menstrual cycle phases which could be explained by the low estrogen concentration during these phases. To improve the treatment and prevention of pain in women, more research on the relationship between pain intensity and menstrual cycle phases is needed. The role of daily perceived stress remained unclear in this thesis, but indications were found, that daily perceived stress might be a predictor of pain occurrence. A better understanding of the interactions between acute pain experience, the menstrual cycle, and daily perceived stress would be a step towards improved prevention and treatment of pain-, and stress-related illness in women and better pain-coping strategies for healthy females dealing with pain in everyday life. Especially the mechanisms in which gonadal hormones interact with pain and stress should be the focus of future research.

References

Aloisi, A. M., Bachiocco, V., Constantino, A., Stefani, R., Ceccarelli, I., Bertaccini, A., & Meriggiola, M. C. (2007). Cross-sex hormone administration changes pain in transsexual women and men. *Pain, 132*, 60-67. https://doi.org/10.1016/j.pain.2007.02.006

Aloisi, A. M., & Bonifazi, M. (2006). Sex hormones, central nervous system and pain. *Hormones and Behavior*, *50*, 1–7. https://doi.org/10.1016/j.yhbeh.2005.12.002

Alonso, C., Loevinger, B. L., Muller, D., & Coe, C. L. (2004). Menstrual cycle influences on pain and emotion in women with fibromyalgia. *Journal of Psychosomatic Research, 57*, 451-458. https://doi.org/10.1016/j.jpsychores.2004.05.003

Anderson, S. R., Witkin, J. E., Bolt, T., Llabre, M. M., Ashton-James, C. E., & Reynolds Losin, E. A. (2021). Modeling neural and self-reported factors of affective distress in the relationship between pain and working meomory in healthy individuals. *Neuropsychologia*, *153*. https://doi.org/10.1016/j.neuropsychologia.2021.107766

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anesthesia*, *111*(1), 52–58. https://doi.org/10.1093/bja/aet127

Bates, D., Maechler, M., Bolker, B., Walker, S., Christensen, R. H. B., Singmann, H., Dai, B., Scheipl, F., Grothendieck, G., Green, P., Fox, J., Bauer, A., Krivitzky, P. N., Tanaka, E., & Jagan, M. (2024). *lme4: Linear Mixed-Effects Models using 'Eigen' and S4* (1.1-35.4) [Computer software].

Bear, M., Connors, B., & Paradiso, M. A. (2020). *Neuroscience: Exploring the brain* (4th ed.). Jones & Bartlett Learning, LLC.

Becker, J. B., Arnold, A. P., Berkley, K. J., Blaustein, J. D., Eckel, L. A., Hampson, E., Herman, J. P., Marts, S., Sadee, W., Steiner, M., Taylor, J., & Young, E. (2005). Strategies and methods for research on sex differences in brain and behavior. *Endocrinology*, *146*(4), 1650–1673. https://doi.org/10.1210/en.2004-1142

Coelingh Bennik, H. J. T. (2008). Reprint of Are all estrogens the same? *Maturitas*, *61*(1–2), 195–201. https://doi.org/10.1016/j.maturitas.2003.11.009

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of Perceived Stress. *Journal of Health and Social Behavior*, *24*(4), 385–396. https://doi.org/10.2307/2136404

Craft, R. M. (2007). Modulation of pain by estrogens. *Pain*, *132*, 3–12. https://doi.org/10.1016/j.pain.2007.09.028

Dawood, Y. M. (2006). Primary dysmenorrhea: Advances in pathogenesis and management. *Obstetrics and Gynecolgy*, *108*(2), 428–441. https://doi.org/10.1097/01.AOG.0000230214.26638.0c

De Barbosa, M., De Oliveira, E. C., & Nunes, F. R. (2013). Evaluation of sensitivity, motor and pain thresholds across the menstrual cycle through medium-frequency transcutaneous electrical nerve stimulation. *Clinics, 68*(7), 901-908. https://doi.org/10.6061/clinics/2013(07)03

Edler Schiller, C., Johnson, S. L., Abate, A. C., Schmidt, P. J., & Rubinow, D. R. (2018). Reproductive steroid regulation of mood and behavior. *Comprehensive Physiology*, *6*(3), 1135–1160. https://doi.org/10.1002/cphy.c150014

Fang, X., Liu, H., Wang, M., & Wang, G. (2023). Scientific knowledge graph of dysmenorrhea: A bibliometric analysis from 2001 to 2021. *Journal of Pain Research*, *16*, 2883–2897. https://doi.org/10.2147/JPR.S418602

Fayaz, A., Croft, P., Langford, R. M., Donaldson, L. J., & Jones, G. T. (2016). Prevalence of chronic pain in the UK: A systematic review and meta-analysis of population studies. *BMJ Open*, *6*, 1–12. https://doi.org/10.1136/bmjopen-2015-010364

Fillingim, R. B., Maixner, W., Girdler, S. S., Light, K. C., Harris, M. B., Sheps, D. S., & Mason, G. A. (1997). Ischemic but not thermal pain sensitivity varies across the menstrual cycle. *Psychosomatik Medicine, 59*(5), 512-520. https://doi.org/10.1097/00006842-199709000-00008

Fillingim, R. B. (2017). Individual differences in pain: Understanding the mosaic that makes pain personal. *Pain*, *158*, 11–18. https://doi.org/10.1097/j.pain.0000000000000775

Fischer, S., Doerr, J. M., Strahler, J., Mewes, R., Thieme, K., & Nater, U. M. (2016). Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome—The role of cortisol and alpha-amylase. *Psychoneuroendocrinology*, *63*, 68–77. https://doi.org/10.1016/j.psyneuen.2015.09.018

Fitzcharles, M., & Yunus, M. B. (2012). The clinical concept of fibromyalgia as a changing paradigm in the past 20 years. *Pain Research and Treatment*, *2012*, 184835–184838. https://doi.org/10.1155/2012/184835

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future dircetions. *Psychological Bulletin*, *133*(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

Hellström, B., & Anderberg, U. M. (2003). Pain perception across the menstrual cycle phases in women with chronic pain. *Perceptual and Motor Skills, 96*, 201-211. https://doi-

org/10.2466/pms.2003.96.1.201

Houghton, L. R., Jackson, N., & Whorwell, P. J. (2002). The menstrual cycle affects rectal sensitivity in patients with irritable bowel syndrome but not healthy volunteers. *Gut*, *50*(4), 471–474. https://doi.org/10.1136/gut.50.4.471

Iacovides, S., Avidon, I., & Baker, F. C. (2015). Does pain vary across the menstrual cycle? A review. *European Journal of Pain*, *19*, 1389–1405. https://doi.org/10.1002/ejp.714

Institute of Medicine, Board on Health Sciences Policy, & Committee on Advancing Pain Research, Care, and Education (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education, and reserach*. The National Academies Press.

Kuznetsova, A., Brockhoff, P. B., Christensen, R. H. B., & Jensen, S. P. (2020). *lmerTest: Tests in Linear Mixed Effects Models* (3.1-3) [Computer software].

Lee, E. (2012). Review of the psychometric evidence of the perceived stress scale. *Asian Nursing Research*, *6*(4), 121–127. https://doi.org/10.1016/j.anr.2012.08.004

LeResche, L., Mancl, L., Sherman, J. J., Gandara, B., & Dworkin, S. F. (2003). Changes in temporomandibular pain and other symptoms across the menstrual cycle. *Pain*, *106*, 253–261. https://doi.org/10.1016/j.pain.2003.06.001

Linstra, K. M., Ibrahimi, K., van Casteren, D. S., Wermer, M. J. H., Terwindt, G. M., & Maassen VanDenBrink, A. (2021). Pain perception in women with menstrually-related migraine. *Cephalalgia*, *41*(3), 417–421. https://doi.org/10.1177/0333102420966977

Lupien, S. J., Juster, R., Raymond, C., & Marin, M. (2018). The effect of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Frontiers in Neuroendocrinology*, *49*, 91–105. https://doi.org/10.1016/j.yfrne.2018.02.001

Martin, V. T. (2009). Ovarian hormones and pain response: A review of clinical and basic science studies. *Gender Medicine*, *6*, 168–192. https://doi.org/10.1016/j.genm.2009.03.006

Martin, V. T., Wernke, S., Mandell, K., Ramadan, N., Kao, L., Bean, J., Liu, J., Zoma, W., & Rebar, R. (2005). Defining the relationship between ovarian hormones and migraine headache. *Headache*, *45*, 1190–1201. https://doi.org/10.1111/j.1526-4610.2005.00242.x

McEwen, B. S. (2006). Protective and damaging effects of stress mediators: Central role of the brain. *Dialogues Clinical Neuroscience*, *8*(4), 367–381. https://doi.org/10.31887/DCNS.2006.8.4/bmcewen

Nater, U. M. (2018). The multidiemensionality of stress and its assessment. *Brain, Behavior,*

and Immunity, *73*, 159–160. https://doi.org/10.1016/j.bbi.2018.07.018

Nater, U. M., Ditzen, B., & Ehlert, U. (2020). Psychosomatische und stressabhängige körperliche Beschwerden [Psychosomatic and stress-related physical complaints]. In J. Hoyer & S. Knappe (Eds.), *Klinische Psychologie & Psychotherapie* (2nd ed.). Springer.

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F., Mogil, J. S., Ringkamp, M., Sluka, K., Song, X.-J., Stevens, B., Sullivan, M., Tutelman, P., Ushida, T., & Vader, K. (2020). The Revised IASP definition of pain: Concepts, challenges, and compromises. *Pain*, *161*(9), 1976–1982. https://doi.org/10.1097/j.pain.0000000000001939

Riley, J. L., Robinson, M. E., Wise, E. A., Myers, C. D., & Fillingim, R. B. (1998). Sex differences in the perception of noxious experimental stimuli: A meta-analysis. *Pain*, *74*, 181–187. https://doi.org/10.1016/S0304-3959(97)00199-1

Riley, J. L., Robinson, M. E., Wise, E. A., & Price, D. D. (1999). A meta-analytic review of pain perception across the menstrual cycle. *Pain, 81*(3), 225-235. https://doi.org/10.1016/S0304-3959(98)00258-9

Ring, C., Veldhuijzen van Zanten, J. J. C. S., & Kavussanu, M. (2009). Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. *Biological Psychology*, *81*(3), 189–191. https://doi.org/10.1016/j.biopsycho.2009.04.004

Russell, G., & Lightman, S. (2019). The human stress response. *Nature Reviews.Endocrinology*, *15*(9), 525–534. https://doi.org/10.1038/s41574-019-0228-0

Schmalenberger, K. M., Tauseef, H. A., Barone, J. C., Owens, S. A., Lieberman, L., Jarczok, M. N., Girdler, S. S., Kiesner, J., Ditzen, B., & Eisenlohr-Moul, T. A. (2021). How to study the menstrual cycle: Practical tools and recommendations. *Psychoneuroendocrinology*, *123*, 1–12. https://doi.org/10.1016/j.psyneuen.2020.104895

Schulz, P., Schlotz, W., & Becker, P. (2004). *Trier Inventar zum chronischen Stress (TICS)*. Hogrefe.

Sherman, J. J., & LeResche, L. (2006). Does experimental pain response vary across the menstrual cycle? A methodological review. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *291*(2), 245–256. https://doi.org/10.1152/ajpregu.00920.2005

Smith, C., Levett, K., Collins, C., Dahlen, H., & Suganuma, M. (2018). Relaxation techniques for pain management in labour. *Chochrane Database of Systematic Reviews, 2018.*

https://doi.org/10.1002/14651858.CD009514.pub2

Stening, K., Eriksson, O., Wahren, L., Berg, G., Hammar, M., & Blomqvist, A. (2007). Pain sensations in the cold pressor test in normally menstruating women: Comparison with men and relation to menstrual phase and serum sex steroid levels. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 293*(4), 1711-1716. https://doi.org/10.1152/ajpregu.00127.2007

Strahler, J., Skoluda, N., Kappert, M. B., & Nater, U. M. (2017). Simultaneous measurement of salivary cortisol and alpha-amylase: Application and recommendations. *Neuroscience and Biohehavioral Reviews*, *83*, 657–677. http://dx.doi.org/10.1016/j.neubiorev.2017.08.015

Tan, B., Philipp, M., Hill, S., Muhamed, A. M. C., & Mündel, T. (2020). Pain across the menstrual cycle: Considerations of hydration. *Frontiers in Physiology*, *11*, 1–8. https://doi.org/10.3389/fphys.2020.585667

Tousignant-Laflamme, Y., & Marchand, S. (2009). Excitatory and inhibitory pain mechanisms during the menstrual cycle in healthy women. *Pain*, *146*, 47–55. https://doi.org/10.1016/j.pain.2009.06.018

Treede, R., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup., N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., …Wang, S. (2015). A classification of chronic pain for ICD-11. *Pain, 156*(6), 1003-1007. http://dx.doi.org/10.1097/j.pain.0000000000000160

VandenBos, G. R. (Ed.). (2007). *APA Dictionary of Psychology* (1st ed.). American Psychological Association.

Whirledge, S., & Cidlowski, J. A. (2010). Glucocorticoids, stress and fertility. *Minerva Endocrinology*, *35*(2), 109–125.

White, R. S., Jiang, J., Hall, C. B., Katz, M. J., Zimmermann, M. E., Sliwinski, M., & Lipton, R. B. (2014). Higher Perceived Stress Scale scores are associated with higher pain intensity and pain interference levels in older adults. *Journal of the American Geriatrics Society*, *62*(12), 2250–2356. https://doi-org/10.1111/jgs.13135

Wickham, H., Chang, W., Henry, L., Pedersen, T. L., Takahashi, K., Wilke, C., Woo, K., Yutani, H., Dunnington, D., & van den Brand, T. (2024). *ggplot2: Create elegant data visualisations using the grammar of graphics* (3.5.1) [Computer software].

Wickham, H., François, R., Henry, L., Müller, K., & Vaughan, D. (2023). *dplyr: A grammar of data manipluation* (1.1.4) [Computer software].

Tables

Figures

Abbreviations

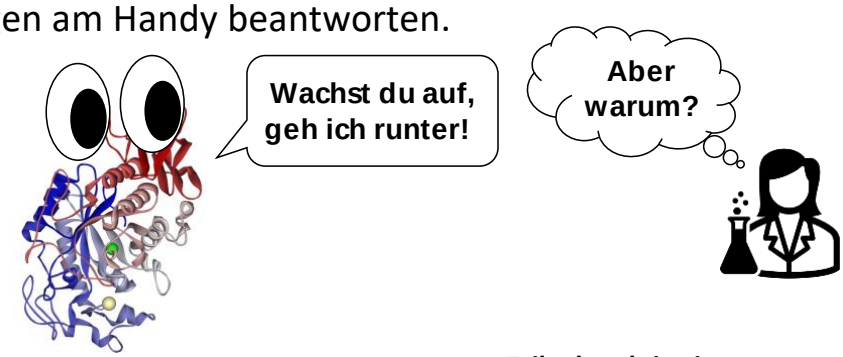
ANS	autonomic nervous system
EMA	ecological momentary asessment
E2	estrogen
FMS	fibromyalgia syndrome
HPA	hypothalamus-pituitary-adrenal
HPG	hypothalamus-pituitary-gonadal
IBS	irritable bowel syndrome
ICC	intracorrelation coefficient
MLM	multilevel modeling
MRM	menstrually related migraine
PSS	Perceived Stress Scale
P4	Progesterone
SCSS	Screening Scale for Chronic Stress

Appendix 1: Recruitment Flyer

universität wien

ProbandInnen gesucht für Studie zu „Messung von Stress im Speichel“!

Für eine psychologische Studie suchen wir aktuell gesunde Teilnehmerinnen und Teilnehmer. Die Studie untersucht die Bedeutung der Morgenaufwachreaktion von Alpha-Amylase, einem Verdauungsenzym im Speichel, das bei Stress ansteigt. Die Studie findet bei Ihnen zuhause im Alltag statt. Für die Dauer eines Monats oder eines Menstruationszyklus würden Sie innerhalb der ersten 30 Minuten nach dem Aufwachen drei Speichelproben sammeln und Fragen am Handy beantworten.



Aufwand und Entschädigung

- Für die Dauer von 30 Tagen bei Männern/einem Menstruationszyklus bei Frauen: Speichelproben (3x pro Tag) und Fragebögen (morgens und abends)
- Beantworten von Fragen zu Stress, Stimmung, Lifestyle und Menstruation.
- Aufwandsentschädigung von 100€

Teilnahmekriterien

- Regelmäßiger Menstruationszyklus, keine
- hormonelle Verhütung
- Derzeit nicht schwanger und nicht stillend
- Kein Unter oder Übergewicht , keine
- körperlichen oder psychischen Erkrankungen .
- Fließende Deutschkenntnisse
- 18 35 Jahre alt
- Kein regelmäßiger Nikotinkonsum

Bei Interesse Email an

studya45@univie.ac.at

Projektleitung: Univ.-Prof. Dr. Urs Nater (urs.nater@univie.ac.at)
Nida Ali, MSc BSc (Hons) PhD
Nadine Skoluda, Dipl.-Psych. Dr. rer. nat.
Universität Wien – Fakultät für Psychologie – Klinische Psychologie des Erwachsenenalters – Stress & Health Lab

Abstract

Pain is inherently unpleasant and can be a source of great distress. Research on fluctuations in pain intensity over the menstrual cycle has been inconsistent so far. While research on experimentally induced pain leans towards no fluctuations over the menstrual cycle, there are substantial indications for several clinical pain conditions that pain intensity fluctuates across the menstrual cycle. In phases with low estrogen concentrations (perimenstrual phase, mid-follicular phase) pain seems to be more intense compared to phases with higher estrogen concentrations. A reason for the inconsistent findings in the literature could be that moderating factors like stress have rarely been accounted for as stress can be an exacerbating factor for pain. This thesis therefore investigates whether the acute perception of pain intensity fluctuates over the menstrual cycle and whether stress moderates the relationship between the menstrual cycle and perceived pain intensity. The study was conducted over a whole menstrual cycle, using Ecological Momentary Assessment (EMA). Participants (N=36) indicated every day if they had experienced pain, their perceived pain intensity, and if they had experienced stress. Our results suggest that pain fluctuates over the menstrual cycle, with the perimenstrual phase having significantly higher and the mid-follicular phase having marginally significantly higher pain intensity compared to the periovulatory phase. Additionally, pain also occurred significantly more often during the perimenstrual and mid-follicular phases. While we were not able to find support for stress as a moderator for this relationship, it was a significant predictor for the occurrence of pain.

Keywords: pain perception, pain intensity, menstrual cycle, perceived stress

Zusammenfassung

Schmerz ist ein von Natur aus unangenehmes Gefühl und kann Quelle von großem Leidensdruck sein. Die Studienergebnisse zu Schwankungen der Schmerzintensität über den Menstruationszyklus sind bisher inkonsistent. Während Forschung zu experimentell induziertem Schmerz größtenteils zum Schluss kommt, dass Schmerz über den Menstruationszyklus nicht schwankt, zeigt sich in verschiedenen klinischen Schmerzstudien, dass die wahrgenommene Schmerzintensität über den Menstruationszyklus schwankt. In Zyklusphasen mit niedrigeren Östrogenkonzentrationen (perimenstruelle Phase, mittlere Follikelphase) im Vergleich zu Phasen mit höheren Östrogenkonzentrationen scheint Schmerz häufig intensiver wahrgenommen zu werden. Ein Grund für die inkonsistenten Ergebnisse in der Literatur könnte sein, dass moderierende Faktoren wie Stress selten miteinbezogen wurden, da Stress ein verschlimmernder Faktor für Schmerz sein kann. Daher untersucht diese Arbeit die Fragen, ob die Wahrnehmung von Schmerzintensität über den Menstruationszyklus schwankt und ob Stress die Beziehung zwischen dem Menstruationszyklus und der wahrgenommenen Schmerzintensität moderiert. Die Studie wurde unter Verwendung von Ecological Momentary Assessment (EMA) über einen kompletten Menstruationszyklus durchgeführt. Die Teilnehmerinnen (N = 36) gaben jeden Tag an, ob sie Schmerzen erlebt hatten, wie intensiv der Schmerz war und ob sie Stress erlebt hatten. Unsere Ergebnisse implizieren, dass die Schmerzintensität über den Menstruationszyklus schwankt, da die Schmerzintensität unserer Teilnehmerinnen während der perimenstruellen Phase und der mittleren Follikelphase signifikant höher war, verglichen mit der periovulatorischen Phase. Zusätzlich trat Schmerz signifikant häufiger während der perimenstruellen und mittleren Follikelphase auf. Während wir keine Hinweise auf Stress als Moderator für die Beziehung zwischen Zyklusphase und wahrgenommener Schmerzintensität finden konnten, war Stress ein signifikanter Prädiktor für das Auftreten von Schmerzen.

Stichworte: Schmerzwahrnehmung, Schmerzintensität, Menstruationszyklus, Stressempfinden