THE

Cycle-Brain *Guide*

samphire neuroscience

Dear *reader,*

For too long, women have been told their symptoms aren't real or that hormonal treatments are their only option. As a neuroscientist, I've witnessed firsthand how the medical establishment has failed to investigate the crucial connection between hormonal cycles and brain function, despite clear evidence that women disproportionately bear the burden of many mental health conditions.

Our story began in the halls of Oxford University, where I came for my PhD in Neuroscience after years of studying neuroscience at Harvard University and working as an emergency medic on the frontlines of mental health emergencies. My research in advanced depression treatments revealed a startling gap: while we had sophisticated neurotechnology for various conditions, very few psychiatrists or clinicians ever considered the role of the menstrual cycle, giving birth or approaching menopause as an important factor in addressing women's health needs, and there was so little research for women's cyclical health challenges, and how to treat them. This realisation sparked our mission to revolutionise women's health by applying cutting-edge brain stimulation technology to menstrual health, because we all deserve to have more than one (hormonal) treatment option for our health.

What we're up *against*

The status quo has been unacceptable:

- A medical system that dismisses women's experiences
- Limited research into female-specific health conditions
- A persistent belief that hormonal treatments are the only solution and skepticism about whether women's health challenges even warrant innovative solutions

Our *vision*

At Samphire, we envision a world where women:

- Have complete agency over their bodies and health choices
- Receive treatment based on rigorous scientific evidence
- Can access innovative, non-hormonal solutions for their health challenges and never have to choose between their natural cycles and their quality of life

Fundamentally, we know that if **women are in charge of their own bodies**, the world will be a better place. Our role is to make science and evidence-based therapeutics accessible as an option alongside those that have dominated the discourse for far too long. Together, we're proving that women's health deserves better than the status quo. We're showing that when we apply serious science to women's health challenges, we can create transformative solutions that work with our bodies, not against them.

With determination,

Emile Radyte

CEO, Samphire Neuroscience

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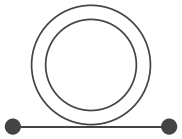

Disclaimer

Throughout our communications, we use the word women to include all people experiencing menstrual-related issues, including but not limited to all people assigned female at birth.

CHAPTER 1

The Connection Between the *Brain* and the *Menstrual Cycle*

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CHAPTER 1

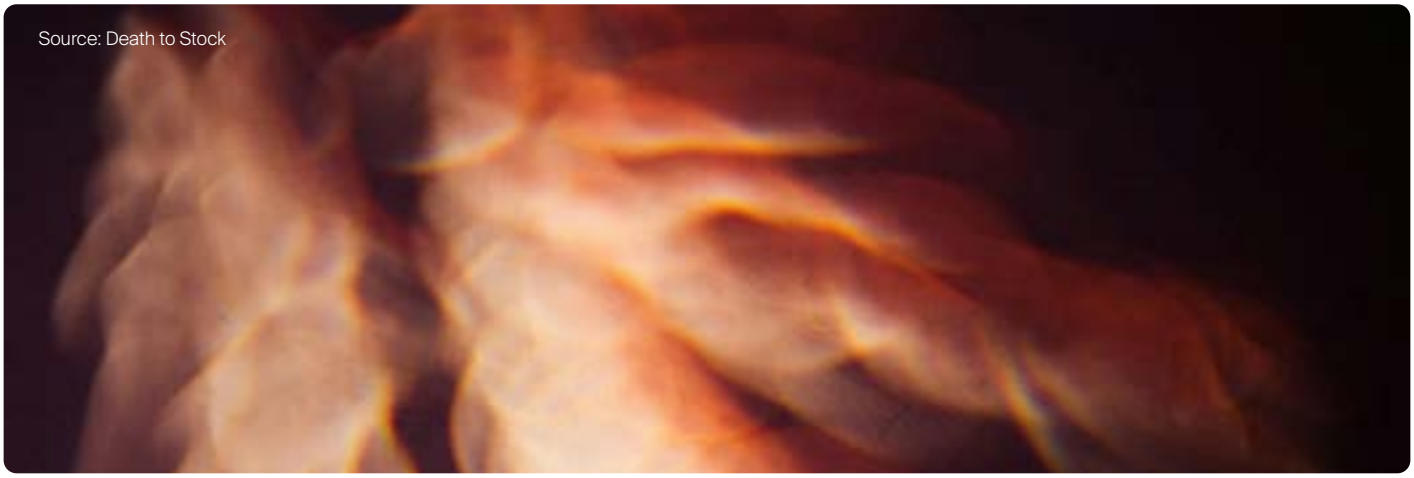
The Connection Between the *Brain* and the *Menstrual Cycle*

The human brain is an enigma. For centuries, the prevailing belief was that the adult brain was immutable to change. The concept of neuroplasticity—the brain's ability to change functionally or structurally—was thought to stop by the age of 25. However, today, we know that is just not the case.

Over 50 years of clinical research has shown that a number of factors like stress, hormones, and learning can change the structure and function of the brain. These changes can include new connections between brain cells, growth of new neurons, and even changes in how genes are read and used. For example, stress can cause neurons in the hippocampus - a brain area involved in memory and stress regulation - to shrink and lose connections. However, in most cases these effects can be reversed once the stress subsides (Fuchs & Flügge, 2014).

But there's another factor at play when women of reproductive age are involved - the menstrual cycle. Recent studies have shown that the mature brain undergoes functional and structural changes on a monthly basis, driven by hormonal fluctuations.

These discoveries underscore the importance of developing more brain-based solutions to optimise wellbeing. Our approach centres on understanding the intricate connections between hormonal fluctuations and brain function throughout the menstrual cycle. By focusing on the brain, we can explore targeted treatments and strategies that address symptoms more precisely, potentially reducing the need for systemic chemical or hormonal interventions.


Source: Death to Stock

Your Cycle

Before we dive into the connection between the brain and your cycle, it's important to understand the physiological, hormonal and symptomatic changes you might experience in each phase (Reed & Carr, 2000).

01 Menstruation

Menstruation is the cyclical, orderly shedding of the uterine lining, responding to hormonal interactions from the hypothalamus and pituitary glands in your brain, and the ovaries of your reproductive system. This phase typically lasts between four to six days, but commonly ranges from two to eight days, and involves the shedding of blood, mucus, and cells from the uterine lining. Most researchers would consider it to be a sub-phase of the follicular phase based on its hormone profile.

Hormonal changes: Both oestrogen and progesterone levels are low at the start of menstruation.

Common symptoms: Abdominal cramps, bloating, breast tenderness, fatigue, mood swings, headaches, back pain, and digestive issues like diarrhoea or constipation.

02 The Follicular Phase

The follicular phase starts on the first day of menstruation and lasts until ovulation, spanning approximately 13 to 14 days. This phase is characterised by the development of ovarian follicles. The pituitary gland in your brain releases follicle-stimulating hormone (FSH) to stimulate the growth of several of these follicles, with one typically maturing into an egg.

Hormonal changes: Rising levels of FSH and oestrogen.

Common symptoms: Increased energy levels, a more positive mood, and clearer skin. Changes in discharge, which becomes clearer and more stretchy.

03 Ovulation

Ovulation occurs approximately 10-12 hours after the luteinising hormone (LH) peak and lasts about 16 to 32 hours. A mature egg is released from an ovary and travels down a fallopian tube towards the uterus. The LH surge is initiated by a dramatic rise in oestrogen produced by the follicle.

Hormonal changes: A peak in LH and oestrogen levels just before ovulation.

Common symptoms: Mild pelvic or lower abdominal pain (known as mittelschmerz), an increase in body temperature, and heightened libido. Some women may also experience light spotting or changes in their discharge, which becomes more slippery and elastic.

04 The Luteal Phase

Following ovulation, the luteal phase is relatively constant in all women, with a duration of 14 days. A temporary collection of cells called the corpus luteum forms on your ovary from the remnants of the follicle and secretes progesterone and a small amount of oestrogen. These hormones cause the uterine lining to thicken in anticipation of a fertilised egg. If pregnancy does not occur, the corpus luteum degenerates, leading to a drop in progesterone levels and the onset of menstruation.

Hormonal changes: High levels of progesterone and a small amount of oestrogen. If fertilisation has not occurred, both hormone levels drop sharply towards the end of this phase.

Common symptoms: Premenstrual syndrome (PMS) symptoms such as mood swings, irritability, bloating, breast tenderness, and fatigue. Some may also experience acne flare-ups, changes in appetite, and difficulty sleeping.

How Hormonal Fluctuations Affect your Brain

More and more studies are finding a link between hormonal fluctuations during the menstrual cycle and the brain's structure and function, indicating that our brains are "more plastic" during certain phases. With a few key findings collated and summarised below, you can deep dive into each by clicking through to each paper.

Neuroplasticity

Hormonal fluctuations during the menstrual cycle significantly impact neuroplasticity. Research, including studies by Barth et al. (2016), has shown that hippocampal plasticity varies with the menstrual cycle, particularly noting increased brain connectivity with rising oestrogen levels before ovulation. The connection between oestrogen and brain health is further supported by studies on early menopause, which demonstrate a heightened risk of neuronal loss and increased vulnerability to Alzheimer's disease due to reduced oestrogen levels (Scheyer et al., 2018).

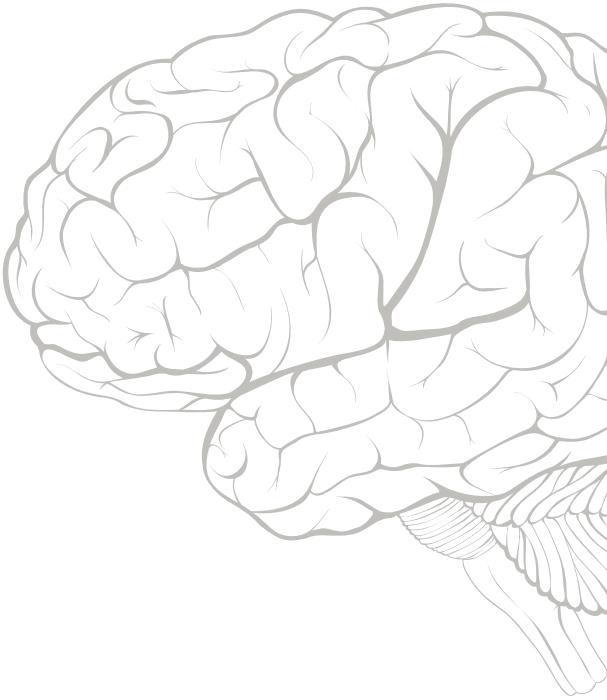
At the molecular level, research shows a correlation between oestrogen and increased neuronal plasticity, partly due to higher levels of neurotrophic factors like Brain-derived Neurotrophic Factor (BDNF), a key indicator of neuroplasticity (Zhou et al., 2005; Brinton, 2009).

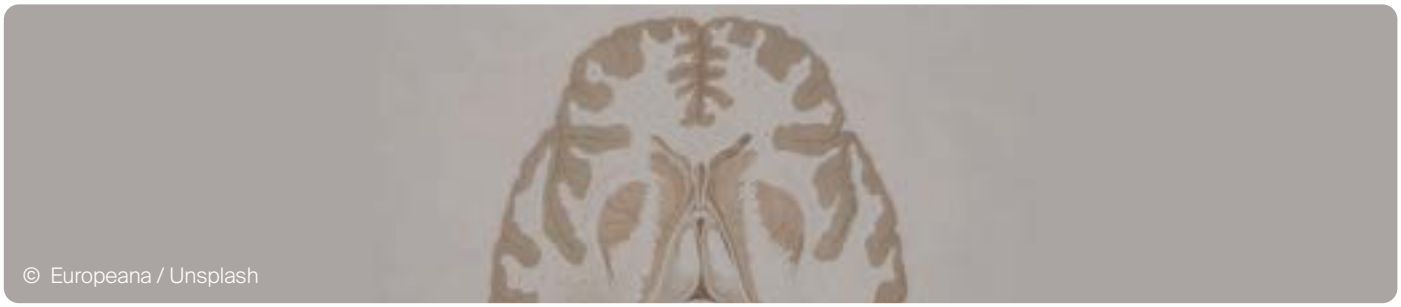
Memory and sensory processing

A recent longitudinal study by Zsido and colleagues found that changes in hippocampal subregions are closely tied to fluctuations in ovarian hormones. Increased oestrogen levels have been linked to the expansion of the parahippocampal cortex, crucial for memory encoding and retrieval, while elevated progesterone levels have been associated with increased volume in the perirhinal cortex, important for processing sensory information and memory (Zsido et al., 2023).

Brain structure

Research from the University of California at Santa Barbara indicates that follicle-stimulating hormone (FSH) and other ovarian hormones affect cortical thickness across the brain. This study observed that progesterone levels during the luteal phase can lead to variations in cortical thickness in different regions, suggesting a complex relationship between hormones and brain structure (Rizor et al., 2023).





Pain

Hormonal fluctuations, particularly in oestrogen levels, significantly impact pain perception in the brain. Research indicates that the highest instances of pain correlate with periods of low or rapidly declining oestrogen levels. Oestrogen interacts with various neural pathways including serotonergic, noradrenergic, dopaminergic, and endogenous opioid systems, which are crucial for pain modulation. Studies have shown that steady oestrogen levels are associated with reduced pain perception, while abrupt changes can exacerbate pain symptoms in conditions such as fibromyalgia, migraines, and tension headaches (Vincent & Tracey, 2008; Manolagas & Kousteni, 2001; Hernandez-Leon et al., 2018; Athnaiel et al., 2023).

Mood

Ovarian hormones have a huge impact on your mood. Studies in both people and animals have shown that fluctuations in these hormones can make women more prone to depression and anxiety. Oestrogen, in particular, helps regulate mood by boosting serotonin levels and keeping it active in the brain for longer. This explains why changes in oestrogen levels can really affect how you feel, highlighting its crucial role in mood regulation. Interestingly, women with premenstrual dysphoric disorder (PMDD - discussed further in Chapter 2) don't have lower hormone levels but are very sensitive to normal hormonal changes during their menstrual cycle (Stefaniak et al., 2023; Kundakovic & Rocks, 2022).

Your Cycle-Brain Connection

There's a lot of scientific evidence on how the main reproductive hormones impact our brain. First, we'll look at this evidence and then we'll take one of the most recent studies to explore the impact of the menstrual cycle on the major brain networks.

Reproductive hormones and your brain

	Chemical impacted	Oestrogen	Progesterone
Neurotransmitter	Glutamate (learning and memory)	↑	↓
	GABA (calming)	↓	↑
	Dopamine (reward and motivation)	↑	↓
	Serotonin (mood regulation)	↑	↓

As we saw in Your Cycle, the ovarian hormones oestrogen and progesterone are the powerhouses behind your menstrual cycle. As oestrogen and progesterone levels fall and are at their lowest right before your period begins, women often report negative changes in their mood, energy levels, and motivation during menstruation (Del Río et al., 2018)

However, as you enter your follicular phase and head toward ovulation, rising oestrogen levels can make you feel invincible and you may experience a boost in mood and cognitive abilities. That's because oestrogen plays a pivotal role in modulating brain function: enhancing learning, memory, mood, and emotional regulation. It does a lot of this by regulating the release and sensitivity of neurotransmitters - chemicals that allow neurons to communicate with each other throughout the body (Del Río et al., 2018).

Specifically, oestrogen impacts:

- Glutamate: As the main excitatory neurotransmitter in the brain, glutamate is essential for proper brain function. By boosting the release and sensitivity of this neurotransmitter, oestrogen increases and strengthens connections between brain cells, which is crucial for learning and memory. This is why you may feel as though you have a better memory, sharper focus, and improved cognitive abilities during the follicular phase (Adams et al., 2004; Riedel, Platt & Micheau, 2003; Schwartz, Sachdeva & Stahl, 2012; Morris et al., 1986).

- Gamma-aminobutyric acid (GABA): Glutamate is also needed for making another neurotransmitter in your brain called gamma-aminobutyric acid (GABA). Also known as the "calming" neurotransmitter, GABA plays a crucial role in regulating brain activity and maintaining emotional balance. By inhibiting the release and sensitivity of GABA, oestrogen actually decreases the calming effects of this neurotransmitter. Whilst in theory, this

should make you feel more anxious, it means that even more glutamate and dopamine are produced making you feel in control in your follicular and ovulatory phases (Murphy et al., 1998; Barth, Villringer & Sacher, 2015; Sieghart & Sperk, 2002).

- **Dopamine:** Oestrogen also boosts the production and release of dopamine, a neurotransmitter involved in reward and motivation. It also makes dopamine receptors more sensitive, meaning that during the follicular phase, you may feel more motivated, happy, and focused, with a reduced risk of feeling depressed or anxious (Sealfon & Olanow, 2000; Del Río et al., 2018; Daniel, Sulzer & Hulst, 2006).

- **Allopregnanolone:** Changes in allopregnanolone (ALLO) levels throughout the menstrual cycle significantly affect mood, especially in women with PMDD. ALLO interacts with GABA receptors in the brain to promote calmness and manage stress. However, in those with PMDD, the GABA receptors can struggle to adapt, leading to mood swings, anxiety, and irritability when ALLO levels change over the cycle. This indicates that managing ALLO levels and its interaction with GABA receptors can help control mood issues, especially in those with PMDD (Hantsoo & Epperson, 2020).

- **Serotonin:** Despite being wrongly referred to as 'the happy hormone', serotonin is actually a neurotransmitter that regulates mood. Oestrogen affects serotonin receptors and reuptake mechanisms, increases the production of serotonin and helps serotonin neurons fire more effectively, further enhancing mood. These higher serotonin levels, and associated improved receptor function, can lead to the feeling of a more positive mood, reduced anxiety, and greater emotional stability (Portas, Bjorvatn & Ursin, 2000; Bethea et al., 2002; Del Río et al., 2018).

On the other hand, most people associate the luteal phase with feelings of sedation or depression - common impacts of rising progesterone levels. In fact, progesterone has almost the exact opposite effects on the listed neurotransmitters:

- **Glutamate:** Progesterone inhibits glutamate release in the brain, particularly in the prefrontal cortex (we'll come back to the PFC in the next chapter). This inhibition reduces neuronal excitability and decreases glutamate receptor efficiency, leading to a calming effect on the brain. As a result, you may experience a decrease in cognitive sharpness and memory performance during the luteal phase. but this mechanism may help in maintaining overall brain stability and preventing overstimulation (Schwartz, Sachdeva & Stahl, 2012; Riedel, Platt & Micheau, 2003; Del Río et al., 2018).

- **Gamma-aminobutyric acid (GABA):** Whilst you may not have felt it, the rising progesterone of the luteal phase actually increases the activity of GABA receptors, promoting the calming effects of GABA. In theory, this increased activity could lead to a reduction in anxiety and stress. However, in reality, GABAs impact on the production of dopamine and glutamate may lead to mood swings and irritability (Sieghart & Sperk, 2002; Del Río et al., 2018; Barth, Villringer & Sacher, 2015).

- **Dopamine:** Progesterone has a complex relationship with dopamine. In one part of the brain, progesterone can enhance dopamine release, improving sensorimotor functions and contributing to better coordination, whilst in another, progesterone's metabolite (allopregnanolone) can inhibit dopamine release, modulating emotional responses and reducing stress. This dual role means you might feel a mix of enhanced coordination and subdued emotional reactivity during the luteal phase (Del Río et al., 2018; Daniel, Sulzer & Hulst, 2006).

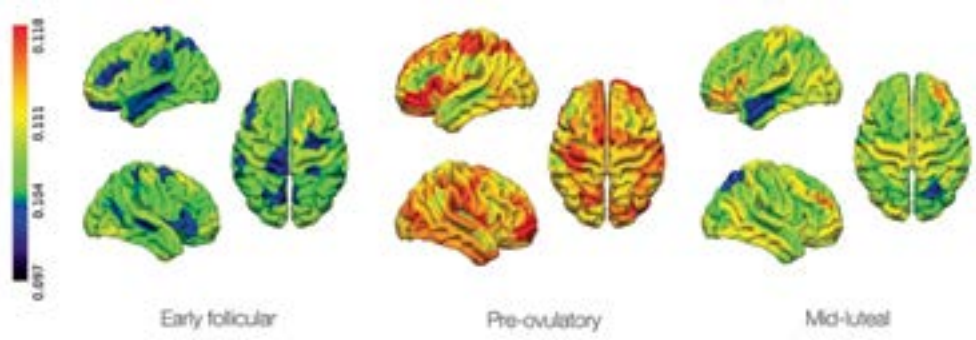
- **Allopregnanolone:** Changes in allopregnanolone (ALLO) levels throughout the menstrual cycle significantly affect mood, especially in women with PMDD. ALLO interacts with GABA receptors in the brain to promote calmness and manage stress. However, in those with PMDD, the GABA receptors can struggle to adapt, leading to mood swings, anxiety, and irritability when ALLO levels change over the cycle. This indicates that managing ALLO levels and its interaction with GABA receptors can help control mood issues, especially in those with PMDD (Hantsoo & Epperson, 2020).

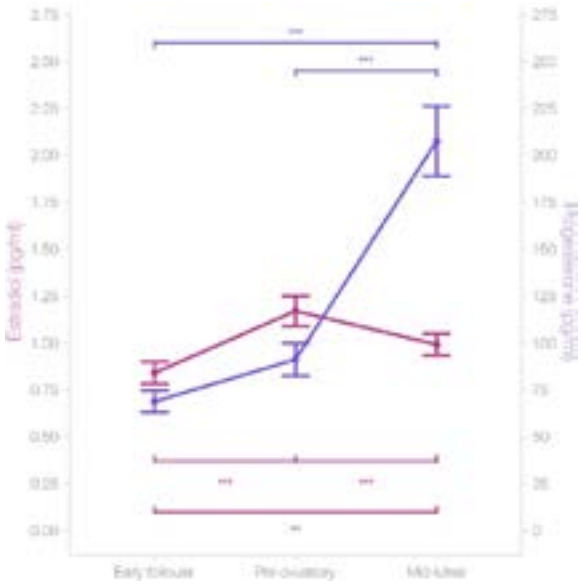
- **Serotonin:** Progesterone can reduce serotonin release in certain brain regions and increase its degradation, leading to negative effects on mood. During the luteal phase, these changes might manifest as mood swings or feelings of irritability, depending on the balance of progesterone and oestrogen in your body (Del Río et al., 2018; Barth, Villringer & Sacher, 2015).

Taking a Closer Look at Research Involving Neuroimaging

Only now scientists are beginning to use neuroimaging techniques to explore how the menstrual cycle impacts brain function. A study titled “Whole-brain dynamics across the menstrual cycle: the role of hormonal fluctuations and age in healthy women” (Avila-Varela et. al, 2024) observed brain network dynamics in 60 women during different menstrual phases.

By using MRI scans, researchers observed that brain activity varied significantly during the menstrual cycle, particularly noting that the preovulatory (follicular) phase displayed the highest variability, or metastability. This suggests that during this phase, the brain is most dynamic and adaptable, responding vividly to hormonal changes. This heightened brain dynamism suggests that during the preovulatory phase, the brain is better equipped to manage changes, potentially enhancing its ability to process emotions and cognitive tasks. We can see how this looks visually in the figure below.





Further, the study illustrated how oestrogen and progesterone influence different brain networks that affect mood, attention, and motor functions, underscoring the significant impact these hormonal fluctuations have on cognitive and emotional well-being. This sets the tone for future research exploring how these dynamic changes contribute to symptoms experienced in the luteal phase, and how we can manage them better using more targeted brain based interventions.

Avila-Varela, D.S., Hidalgo-Lopez, E., Dagnino, P.C. et al. Whole-brain dynamics across the menstrual cycle: the role of hormonal fluctuations and age in healthy women. npj Womens Health 2, 8 (2024).

Why This Matters

When it comes to managing menstrual symptoms, many of us reach for the usual suspects: painkillers like ibuprofen or hormonal contraceptives. However, these treatments do not discriminate; they affect the entire body rather than targeting the specific source of the symptoms.

These treatments also often come with a host of unwanted side effects. For instance, painkillers like ibuprofen can lead to stomach ulcers, gastrointestinal issues, and increased risk of cardiovascular problems when used long-term (FDA, 2018). Hormonal contraceptives, on the other hand, can cause mood changes, weight gain, nausea, and in some cases, contribute to depression and increased risk of certain cancers (FDA, 2023).

> Understanding the intricate connection between the brain and the menstrual cycle opens up exciting new avenues for brain-based approaches to managing menstrual symptoms without relying on drugs or hormones, and affecting only the targeted area of the body. It was this reasoning, coupled with significant clinical research exploring the connection between the menstrual cycle and the brain, that made us ask ourselves: why aren't we addressing menstrual symptoms at the level of the brain?

CHAPTER 2

The Neuroscience Behind *PMS*

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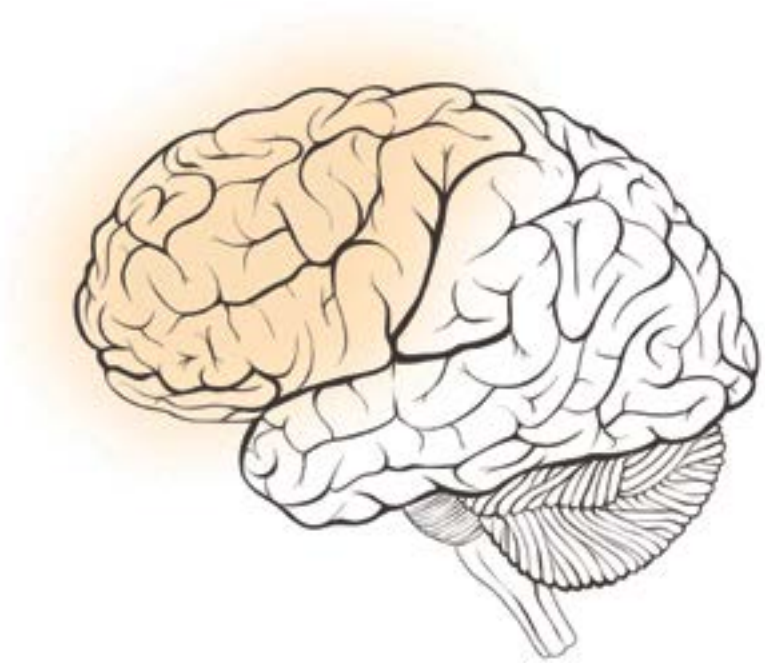
Introduction to the Prefrontal Cortex



Briefly mentioned in the last chapter, the prefrontal cortex (PFC) is a critical region located at the front part of the brain. It is involved in a wide range of complex behaviours, including planning, decision-making, problem-solving, and moderating social behaviour. The PFC is also crucial for personality development and the orchestration of thoughts and actions in accordance with internal goals.

Within the prefrontal cortex, the dorsolateral prefrontal cortex (DLPFC) plays a particularly important role. The DLPFC is essential for higher cognitive functions, such as working memory, cognitive flexibility, and planning.

Most importantly for the menstrual cycle, it is a key player in the regulation of emotions. The DLPFC helps modulate responses to emotional stimuli and stress, which is vital for maintaining emotional stability.

The DLPFC's ability to regulate emotions is essential for everyday functioning. It helps manage how we respond to stress and emotional stimuli by exerting control over other parts of the brain, including the limbic system (responsible for emotional responses). This is referred to as the top-down control mechanism and ensures that your emotional reactions are appropriate and proportional to the situation at hand (Hathaway and Newton, 2024).

Emotional Regulation During the Luteal Phase

During your luteal phase, the surge in progesterone and fluctuating oestrogen levels lead to significant changes in brain activity and mood.

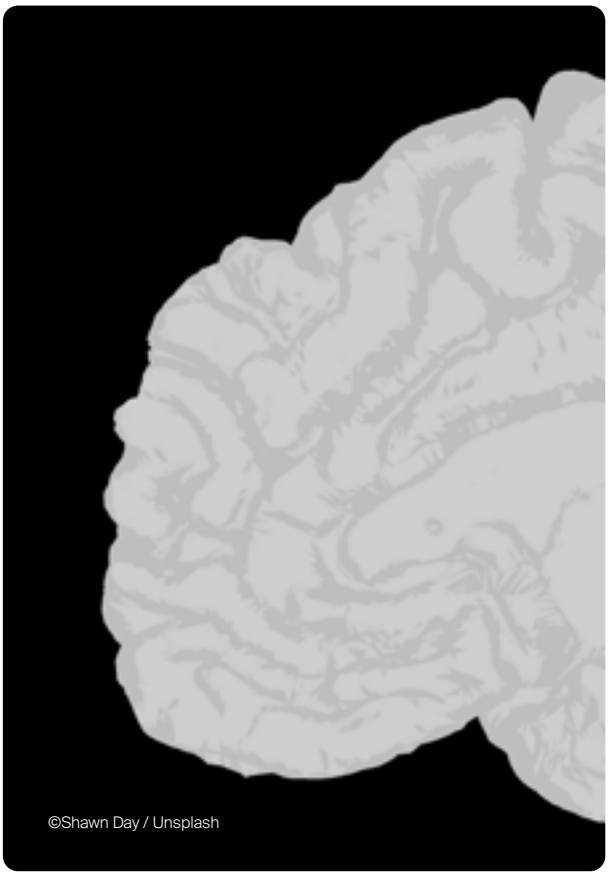
A study by Li et al. (2021), revealed that hormonal changes are not just statistical data points but have tangible effects on brain function and, by extension, mood and cognition. The prefrontal cortex, a brain region pivotal for emotional regulation and cognitive processing, becomes less responsive to emotional stimuli during this phase.

The luteal phase also triggers distinct changes in brain wave activity. Baehr et al. (2004) found that alpha waves, which are instrumental in mood regulation, exhibit notable imbalance or asymmetry during this phase. This isn't a harmless physiological shift. For women, this alpha wave asymmetry correlates with increased emotional sensitivity, mood swings, and episodes of depression.

In essence, the luteal phase isn't just a period of hormonal change but a phase where the very foundations of emotional and cognitive well-being are shaken up and recalibrated. Millions of women go through these drastic changes every single month, with little to no validation for their suffering.

Impact on Top-Down Control

The top-down control exerted by the DLPFC may be compromised during the luteal phase. This can result in diminished ability to modulate emotional responses and increased vulnerability to stress and emotional stimuli. For individuals suffering from premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD - discussed later in this chapter), the DLPFC may be underactive or functioning suboptimally. This underactivity can lead to intense and often disproportionate emotional responses, making emotional regulation particularly challenging.



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Variability in Emotional Regulation: PMS vs PMDD vs PME

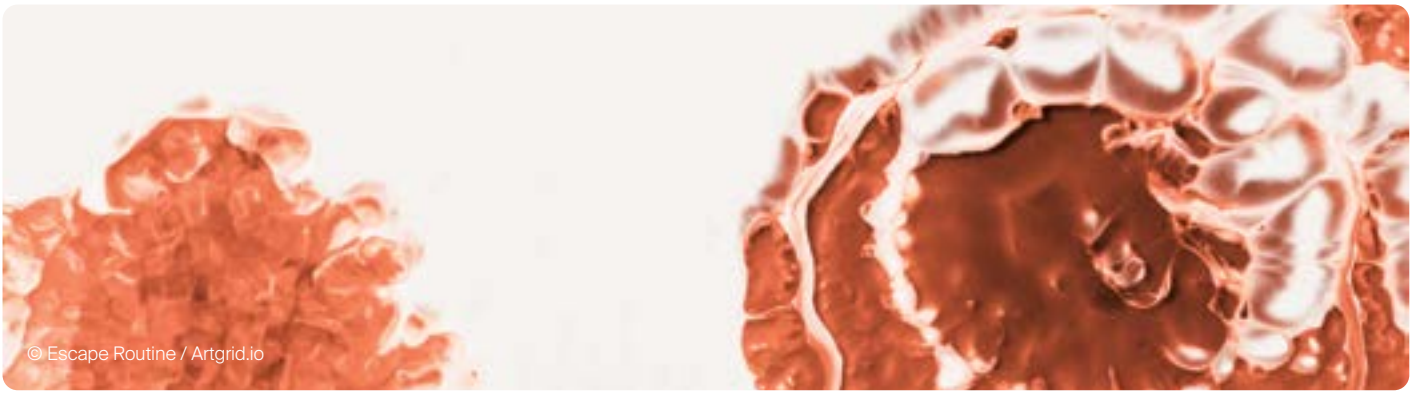
Have you ever spoken with a friend and felt like their menstrual symptoms are different to yours? That's because they are. Whilst the underlying hormonal changes may be similar across the population, the way your brain responds will be different from others. Some women experience mild emotional disturbances, but if they are severe enough to interfere with daily life, something more significant may be underlying.

01 Premenstrual Syndrome (PMS)

Premenstrual syndrome (PMS) refers to a series of physical, emotional, cognitive, and behavioural symptoms that regularly recur during the late luteal phase of each menstrual cycle, usually resolving soon after the onset of menstruation. It is estimated that up to 90% of reproductive age experience several mild-severe menstrual symptoms each month, and up to 40% of these women of reproductive age experience PMS (Matsumoto, Asakura and Hayashi, 2013).

PMS can significantly impact a woman's quality of life, affecting family relationships, work productivity, social activities, and sexual relationships. Despite its widespread impact, the exact causes of PMS remain unclear, but research points to a combination of hormonal changes, genetic factors, psychosocial influences, and central nervous system (CNS) pathways.
Changes in brain activity and connectivity have been observed during the luteal phase in women with PMS compared to those without. These neural abnormalities might be linked to the psychological changes that occur during the menstrual cycle, especially in the luteal phase. Specifically, the DLPFC may be underactive or functioning suboptimally. By targeting and supporting this area, intense emotional responses experienced by those with PMS may be regulated (Rode et al., 2010; Aoki et al., 2022).

To better understand these brain activity changes, researchers use tools like resting state functional magnetic resonance imaging (RS-fMRI). This technology helps detect spontaneous brain activity and has been used to study various neuropsychiatric disorders, including PMS. By examining these brain activity patterns, scientists hope to uncover more about the neural mechanisms underlying PMS and how psychological changes may influence these processes. Understanding PMS is crucial for developing effective treatments and improving the quality of life for those affected (Liu et al., 2015)



02 Premenstrual Dysphoric Disorder (PMDD)

Premenstrual dysphoric disorder (PMDD) is a severe form of PMS affecting 5-8% of women and characterised by significant mood disturbances including depression, irritability, and anxiety (Mishra, Elliott and Marwaha, 2024).

Despite its significant impact, women often wait an average of 20 years for an accurate PMDD diagnosis (Osborn et al., 2020). This lengthy process is due to several unique challenges:

1 **Lack of Biomarker Based Tests:** The absence of biomarker-based diagnostic tests for PMDD, such as blood tests or imaging scans, mean that diagnosis is made through the observation and recording of symptoms over several menstrual cycles.

2 **Cyclical Nature:** PMDD symptoms are linked to the menstrual cycle, typically appearing during the luteal phase and easing with the onset of menstruation. For many women, a biphasic pattern of PMDD is seen, with symptoms being much worse every other month. This cyclical pattern makes diagnosis difficult because symptoms are transient and inconsistent. Symptoms must be observed and recorded over several menstrual cycles to identify a consistent PMDD pattern, which can be time-consuming and impractical.

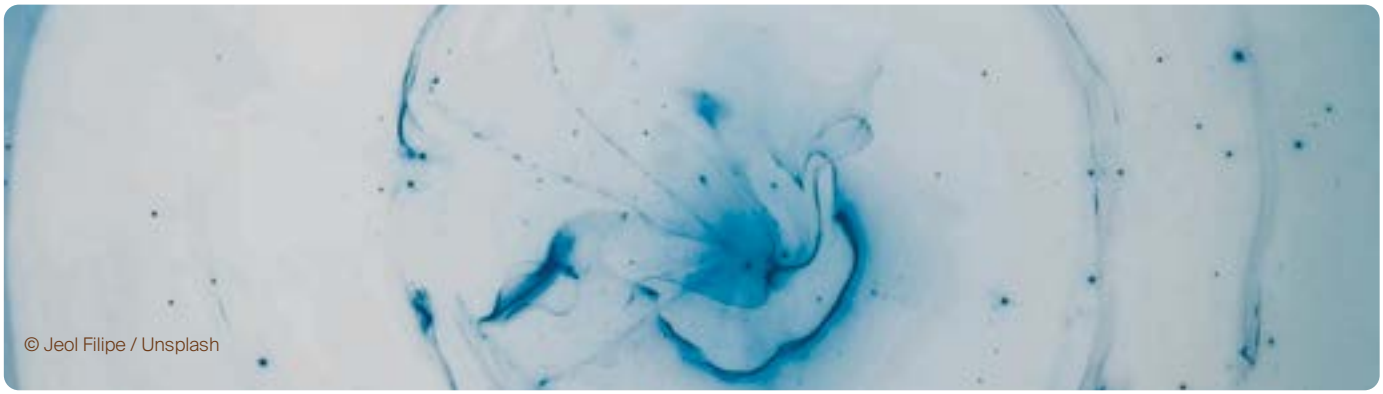
3 **Similarity to Other Mood Disorders:** PMDD shares many symptoms with other mood disorders (such as Major Depressive Disorder and Generalised Anxiety Disorder), including mood swings, irritability, and depressive episodes. This overlap often results in misdiagnosis or the assumption that PMDD symptoms are simply an intensification or a “milder version” of an existing mood disorder.

4 **Reliance on Self-Reported Symptoms:** Diagnosing PMDD primarily depends on the patient’s self-reported symptoms, which means they are highly subjective. Cognitive and emotional fluctuations throughout the menstrual cycle can lead to recall bias and inconsistent symptom recording, further complicating the diagnosis (Mishra, Elliott and Marwaha, 2024).

The link between PMDD and depression is particularly strong, as both conditions share similar symptoms and can profoundly impact daily functioning. Research suggests that individuals with PMDD may have an increased sensitivity to hormonal changes, leading to pronounced mood swings and depressive episodes during the luteal phase. Let’s take a look at the clinical study below, which visually illustrates how real these changes in the brain are:

Baehr et al. (2004) tracked the mood of five women with PMDD over two of their menstrual cycles. The results showed that outside of their PMDD-affected luteal phase (the time leading up to their period), their mood scores were significantly higher and indicated no depression. However, during their PMDD-luteal phase, their mood scores dropped dramatically, well below the threshold that is considered to be depressive (58% PCT). This suggests that these women experienced depressive symptoms specifically during the phase before their period.

Imaging and stimulation of the brain represent future breakthroughs in the improved diagnosis and treatment of PMDD, respectively. For instance, Baller et al. (2013) used functional MRI (fMRI) and PET scans to show that PMDD patients exhibited greater DLPFC activation than those without PMDD. This correlated with PMDD severity, symptom duration, and onset age - highlighting the validity of DLPFC dysfunction as a risk factor for PMDD. That’s why stimulating the DLPFC, without acting on the rest of the body, offers an approach to rebalance the brain fluctuations experienced during the menstrual cycle - without the side effects.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03 Premenstrual Exacerbation (PME)

Premenstrual Exacerbation (PME) is the premenstrual worsening of symptoms associated with an existing mental health condition, such as major depressive disorder (MDD) or generalised anxiety disorder (GAD). Approximately 60% of women with mood disorders suffer with PME . It's not just about feeling a bit more emotional or moody—it's a significant intensification of symptoms that can derail your routine, making treatment harder and prolonging illness.

Research into PME is notably flawed as many studies don't differentiate between PME and PMDD - even Google's algorithm will search for PMDD when you are looking for information on PME. However, unlike PMDD, PME involves symptoms that are present throughout the entire menstrual cycle but become more severe in the premenstrual phase. Distinguishing PME from PMDD is crucial for effective treatment, as PME requires continuous management of the underlying disorder with additional attention to the premenstrual exacerbation of symptoms.

When it comes to treatment, the options are currently, unfortunately, based on this limited research. Some small studies suggest that increasing antidepressant or mood stabiliser doses during the luteal phase could help manage PME in depression and bipolar disorders. Oral contraceptives are also often prescribed, despite the fact that there is limited evidence for their efficacy with PME, and they could interact negatively with other medications vital for existing condition management (Kuehner and Nayman, 2021).

CHAPTER 3

The Neuroscience Behind *Menstrual Pain*

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Introduction to Pain: Beyond a Symptom

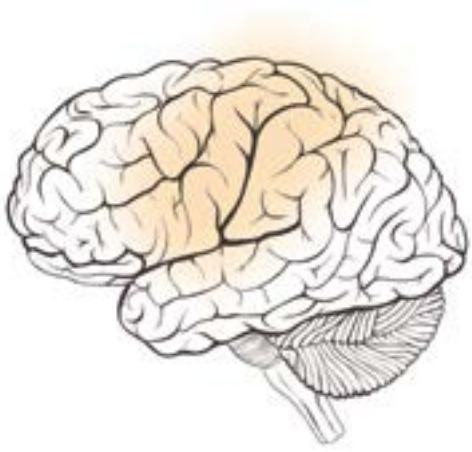
Pain is not just a symptom. It's a complex experience deeply influenced by biological, psychological, and social factors. Pain is also notoriously difficult to measure - and the most widely adopted tools rely on the subjective reports of sufferers. This approach is inherently flawed, as it rests on the perceived credibility of the person reporting the pain—leading to a historical oversight of women's pain experiences. The gender pain gap serves as a clear testament to this issue. The most common treatment for pain - a chemical painkiller in the form of a pill - also hasn't evolved much since the 1980s. Yet chronic pain continues to be the most significant and silent epidemic, affecting more than 28 million adults in the UK alone. The medical world finds pain frustrating, if not painful - its indescribability and subjective nature make it particularly difficult to treat. In fact, for decades our framing of pain was linear, and it was thought to be no more than a direct sensory response to a painful physical stimulus. Today we know that pain is far more complex and intricate than this.

The Role of the Motor Cortex, *Insula* and Amygdala

The motor cortex (M1) , insula and amygdala are critical brain regions involved in the perception and modulation of pain. The motor cortex, primarily responsible for planning, controlling, and executing voluntary movements, also plays a role in the modulation of chronic pain by indirectly modulating the activity of the posterior insula. Studies suggest that disruptions in the motor cortex can contribute to central sensitisation: a condition where the central nervous system (CNS) is in a heightened state of reactivity; lowering the pain-perception threshold.

This pain perception threshold is understood to be encoded in the posterior insula, a brain region deep in the brain that is challenging to access directly.

Research has also shown that motor cortex stimulation can alleviate chronic pain, suggesting its role in modulating pain signals **downstream and reaching the source of pain perception, such as the insula.** The amygdala, known for its role in processing emotions, **especially fear,** also plays a significant part in how pain is perceived and experienced. It is involved in the emotional response to pain and can influence pain sensitivity and chronic pain development. Research indicates that individuals with chronic pain conditions often exhibit altered amygdala activity, underscoring the emotional and psychological dimensions of pain.



Why is Pain Notoriously Hard to Measure?

Pain's subjectivity makes it notoriously difficult to measure. Traditional pain assessment tools rely on self-reporting, which is inherently subjective and influenced by various factors, including individual pain thresholds, emotional states, and cultural backgrounds. This reliance on subjective reports has led to significant challenges in accurately diagnosing and treating pain, particularly in women, whose pain experiences have historically been underestimated or dismissed.

In recent years, a growing number of scientists have begun finding ways to capture pain in quantifiable ways in order for us to better understand it and its underlying mechanisms. Their findings, especially in the realm of neuroimaging, reveal a complex relationship between pain and the neural networks that process how it is perceived (Davis, 2011). Such research underscores that pain is not just a sensory experience, but also an emotional and cognitive one - and definitely one that varies significantly among individuals (Raja et al., 2021). Neuroimaging has also revealed patterns of similarity between individuals diagnosed with similar pain conditions, allowing researchers to draw connections between brain regions and their role in pain perception (Damascelli et al., 2022).

Pain Sensitivity Threshold During Menstruation

During and before menstruation, many women experience a lowered pain sensitivity threshold. Hormonal fluctuations, particularly the decrease in oestrogen levels, are believed to contribute to this heightened sensitivity. This means that women may feel pain more intensely during their menstrual cycle, affecting their overall pain experience and management.

However, as with a lot of women's health, this is an area of research that has historically been underserved. Iacovides et al. (2015) compiled a review of 42 studies relating to pain sensitisation in the menstrual phase and found that the current body of research does not paint a clear picture on whether the menstrual cycle affects pain sensitivity, but 64% of studies did find variations in pain across the cycle. Limitations of these studies were largely due to differences in experimental pain stimuli used, the definition of menstrual phases, not measuring hormonal levels alongside the pain documentation, or simply not confirming ovulation had taken place (Sherman & LeResche, 2006).

Central Nervous System Sensitisation in Women with Primary Dysmenorrhea

45-95% of women of reproductive age experience primary dysmenorrhea (painful periods without an underlying cause) and may have a heightened sensitivity to all types of pain due to central nervous system sensitisation. Tavares de Arrude et al. (2022) found that central sensitivity symptoms (CSS) occur in 50% of all women and are more prevalent in women with dysmenorrhoea. CSS are associated with cycle irregularity, presence of dysmenorrhoea since adolescence and gynaecological diseases. This condition involves an increased response to pain stimuli, not just during menstrual periods but throughout the entire menstrual cycle. Central sensitisation implies that the nervous system undergoes changes that amplify pain signals, leading to a generalised increase in pain sensitivity.

A 2016 commentary published in Pain Journal supports the theory that the underlying issue in primary dysmenorrhea is not merely inflammation of the uterus but rather an abnormal processing of pain by the central nervous system. The authors claim that this theory is supported by the observed comorbidity between dysmenorrhea and other pain syndromes such as irritable bowel and painful bladder syndrome, suggesting a central sensitisation to pain.

More recent research using neuroimaging helps elucidate the pain-brain relationship in women diagnosed with primary dysmenorrhea. In a study published this year, researchers Yu et. al looked at how brain function changes in women with primary dysmenorrhea by comparing brain scans from 41 women with this condition to 39 healthy women. The study found significant differences in brain connectivity, particularly in areas related to pain and emotion regulation. Specifically, women with primary dysmenorrhea showed increased brain connectivity in regions associated with pain processing and heightened anxiety levels, even when not in pain.

Of particular interest are studies that explore the relationship between primary dysmenorrhea and the motor cortex (M1). A 2016 study by Wei et al. delves into the hypothesis that brain networks responsible for pain modulation may function differently in women with primary dysmenorrhea. Using resting-state functional Magnetic Resonance Imaging (MRI), the study investigated the brain's functional connectivity during different menstrual phases, with a particular emphasis on the connectivity between the periaqueductal gray (PAG) and motor areas of the brain in women with dysmenorrhea. The findings indicated increased connectivity between the PAG and motor areas during menstruation but decreased connectivity with the default mode network during the follicular phase, suggesting abnormal or dysfunctional connectivity in the motor region of the brain in individuals with dysmenorrhea.

The ongoing research around primary dysmenorrhea and brain abnormalities is in line with studies across various chronic pain conditions, which similarly reveal disturbances in the brain's motor region (M1). Moreover, the effectiveness of Motor Cortex Stimulation in treating chronic pain, recognised as a pioneering non-pharmacological intervention, further supports this connection (DosSantos et al., 2016).

Overall, there is a considerable amount of research that suggests that treatments for primary dysmenorrhea might be more effective if they target the central nervous system directly, rather than focusing solely on alleviating inflammation—which is the common approach taken by painkillers. By addressing the root cause of pain processing anomalies in the brain, it's possible not only to reduce the physical symptoms associated with dysmenorrhea but also to mitigate the associated psychological distress, such as anxiety and depression that often accompany this condition (Pakpour et al., 2020). This shift in understanding and treatment approach could significantly improve the quality of life for those affected by primary dysmenorrhea, offering relief that is both more comprehensive and effective.

Endometriosis and Chronic Pelvic Pain

Endometriosis, characterised by the presence of endometrium-like tissue outside the uterus, can cause severe pain. It is estimated that more than 1 in 10 women live with the condition and, according to a review of 22 research papers, the average time to diagnosis is 6.6 years. However, delays varied within the study: from 6 months in a small study from Brazil, to a study in the UK showing a 27-year delay.

Chronic pelvic pain (CPP) is a persistent pain in the pelvic region that lasts more than six months and can be linked to various underlying conditions. 71-81% of those with CPP have endometriosis. Chronic pelvic pain causes neurological changes in a part of the spine, resulting in inflammation of parts of the pelvic viscera (bladder, rectum, pelvic genital organs and lower part of the urethra), exaggerated autonomic nervous system response (blood pressure, heart rate, body temperature), a lower sensory threshold and, therefore, a greater perception of pain.

Endometriosis is also associated with central sensitisation. In a study conducted by Quinta-Marques et al., 100% of patients with endometriosis reached the central sensitisation threshold, whilst just 5% of those without endometriosis did. Explanations as to why those with endometriosis and CPP are more likely to have CSS include reduced brain volume in pain-processing regions; increased resting-state connectivity between pain processing regions; and alteration of the hypothalamic-pituitary-adrenal axis (a communication channel between three parts of the brain) leading to reduced capacity to mount a stress response to painful stimuli. As seen in the primary dysmenorrhea section above, this means that endometriosis is likely more than just a localised inflammatory condition; it's also an abnormal processing of pain in the central nervous system.

Targeting the Nervous System vs. Inflammation (Painkillers)

Traditional painkillers primarily target inflammation to relieve pain. However, this approach may not be sufficient for conditions like primary dysmenorrhea, endometriosis, and CPP, where central sensitisation plays a crucial role. Targeting the nervous system directly, through methods like neuromodulation and brain stimulation, offers a promising alternative.

Studies, including those conducted by us, show promising potential of transcranial direct current stimulation (tCDS) in the amelioration of pain. In just one cycle, participants in our double-blind randomised controlled trial experienced a 53% reduction in pain symptoms - an effect likely to improve with sustained use. And unlike traditional treatments such as hormonal contraception and painkillers, brian stimulation offers a non-invasive option with zero severe side effects.

If we begin to reframe pain in relation to the brain and central nervous system, it's not hard to see that brain stimulation has a theoretical advantage when compared with traditional chronic pain treatments: It directly targets the neural networks involved in pain perception. While advancements in medical technology begin to embrace these discoveries, there is still so much to be done to truly manage pain and its underlying pathologies.

CHAPTER 4

Are Brain-Based Approaches the Future of *Menstrual Health?*

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The Problem with Pills: Hormonal Contraceptives, SSRIs, and Painkillers

You're likely aware of the most commonly available treatments for menstrual pain and mood symptoms - NSAIDs (painkillers like ibuprofen and naproxen), hormonal contraceptives, and SSRIs (antidepressants sometimes used for PMS and PMDD). But let's be real: these options are far from perfect. They often come with a long list of side effects and don't always get to the root of the problem.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly listed as the most widely used treatment for the relief of period pain. The most widely used, ibuprofen, was approved in the 1960s on the back of a trial of six men with rheumatoid arthritis that showed it was safer for long term use than its predecessor, aspirin (NHS, 2017; Connelly, 2017).

How they work: NSAIDs like ibuprofen and naproxen work by blocking an enzyme - a catalyst for a reaction in the body - called cyclooxygenase (COX). This enzyme is crucial for making substances called thromboxanes, prostaglandins, and prostacyclins, which are involved in inflammation, pain, and fever. In particular, prostaglandins are associated with an increased response to painful stimuli. By inhibiting COX, NSAIDs reduce the production of these substances, thereby relieving pain and reducing inflammation (Ghlichloo and Gerriets, 2024).

Side Effects: In general, using small doses of painkillers is safe for most people. However, commonly reported side effects are rarely spoken about, such as headaches, nausea, dizziness, and stomach issues like heartburn and constipation. For example, up to 14% of naproxen users report stomach pain, and headaches are common in about 15% of ibuprofen users. More worrying are the serious side effects. Whilst infrequently observed, long-term use can lead to gastrointestinal bleeding, ulcers, and even heart attacks or strokes - the US' Food and Drug Administration issued a formal warning of their cardiovascular impact in 2015. NSAIDs can also harm your kidneys and liver, trigger severe skin reactions or worsen asthma (FDA, 2021, 2024; Center for Drug Evaluation and Research, 2023).

Use in menstruation management: Research has shown that women with dysmenorrhea have elevated levels of prostaglandins, therefore heightening their experience of pain (Institute for Quality and Efficiency in Health Care, 2023). While NSAIDs are generally effective for managing dysmenorrhea, prolonged use can lead to adverse effects. A recent study found that 32% of women using NSAIDs for dysmenorrhea experienced gastrointestinal issues, with nausea being the most common side effect (Gobba, Kibone and Kiguba, 2024). Furthermore, approximately 18% of women with dysmenorrhea do not respond to NSAIDs, a condition known as NSAID-resistant dysmenorrhea (Oladusu, Tu and Hellman, 2018).

Hormonal Contraceptives

When women experience NSAID-resistant dysmenorrhea, or any mood/PMS-related symptoms, their next point of call is often hormonal contraceptives. The first combined oral contraceptive pill (COCP) was introduced to the US market in 1957 for the treatment of menstrual disorders. In 1960, it was approved as a contraceptive (Junod and Marks, 2002). Whilst this delay was mostly due to the social views of the time, the market has significantly grown since with many countries (including the US and UK) approving a COCP for over-the-counter use, and many other types of hormonal contraceptives are now available (Medicines and Healthcare products Regulatory Agency, 2021; FDA, 2023).

How they work: Hormonal contraceptives work for menstrual symptom management by using synthetic oestrogen and progesterones (as seen in Your Cycle) to thin the lining of the uterus, where prostaglandins are formed. This helps to decrease the uterine contractions and menstrual bleeding that contribute to pain and cramping. They may also cause amenorrhea (the absence of your period) (Chan, Yusoff Dawood and Fuchs, 1981).

Side Effects: Common problems include headaches, nausea, mood swings, and dizziness. For instance, over 10% of Yasmin (a COCP) users report headaches. Other frequent side effects are breast tenderness, abdominal pain, and fatigue, which can seriously disrupt daily life. The serious risks are more concerning. Hormonal contraceptives can increase the risk of blood clots, strokes, and high blood pressure, leading the FDA to issue warnings about pills like Yasmin. They can also cause liver disease and potentially increase the risk of liver cancer. Long-term use might lower bone density, delay fertility return, and raise the risk of breast and reproductive cancers (FDA, 2023; Center for Drug Evaluation and Research, 2019).

Use in menstruation management: For women who do not currently wish to get pregnant, hormonal contraceptives can also be used to treat dysmenorrhea. Users often report dysmenorrhea relief within several months, although efficacy studies have disputed its efficacy - a review of ten clinical trials found there to be limited evidence for pain improvement with the use of the COCPs in women with dysmenorrhoea (Wong et al., 2009). In those with endometriosis, however, hormonal contraceptives are found to have an efficacy of 60-80%, together with the potential to slow down the progression and recurrence of symptoms post-surgery (Allaire, Bedaiwy and Yong, 2023). This leads many women to use hormonal birth control alongside NSAIDs to manage pain, even though this combination has been found to increase the risk of blood clots (Lipanovic, 2023)

Whether you have or are thinking about hormonal contraception for menstrual pain-related symptom relief, we've compiled a list of key findings for each below:

Combined Contraceptive Pills: Pills containing both synthetic oestrogen and progesterone are more effective in relieving menstrual pain compared to placebos (Schroll et al., 2023). Extended-cycle pills (taken continuously or with fewer/shorter breaks) may provide better pain relief than the regular 21-day active pill cycle with a 7-day break (Edelman et al., 2014).

Progesterone-Only Pills: There has been very limited research on the impact of synthetic progesterone-only pills on menstrual pain, but using them for the treatment of endometriosis-related pain has been shown to be more effective than COCPs (Strowitzki et al., 2010; Casper, 2017).

Hormonal IUD: Progestin-releasing intrauterine devices (IUDs) are more effective in decreasing menstrual pain than no treatment or copper IUDs (Bahamondes et al., 2007; Kelekci, Kelekci and Yilmaz, 2012).

Implant: The hormonal implant, inserted under the skin and releasing progestin, has been linked to a reduction in menstrual pain over time according to several studies (Mansour et al., 2008).

Injection: Injectable contraceptives containing medroxyprogesterone acetate may reduce menstrual pain in individuals with endometriosis, performing as well as implants and other treatments (Schlaff et al., 2006; Walch et al., 2009).

Vaginal Ring: Users of the progestin-releasing vaginal ring reported less menstrual pain compared to their previous contraceptive method in one study (Roumen, op ten Berg and Hoomans, 2006).

SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are most commonly prescribed for depression, but are the first port of call for PMDD and are sometimes also prescribed for severe PMS.

How they work: It's too simplistic to say that depression and PMDD are caused by low serotonin levels, but it's thought that SSRIs work by increasing serotonin levels in the brain - although no one really knows. As we saw in Chapter 2, serotonin is a neurotransmitter that modulates mood. After transmitting its message, serotonin is usually reabsorbed by the nerve cells (known as re-uptake). SSRIs work by inhibiting this reuptake, meaning more serotonin is available to pass further messages between nearby nerve cells (Edinoff et al., 2021).

Side Effects: Just two SSRIs are approved in the US for PMDD - sertraline (brand name Zoloft) and fluoxetine (Prozac). Common problems with SSRIs include headaches, nausea, insomnia, and sexual dysfunction. For instance, 16% of Zoloft users reported headaches in clinical trials. Other frequently reported side effects in the Zoloft labelling include dry mouth, diarrhoea, increased sweating, and dizziness, which can significantly impact daily activities. More serious risks involve an increased risk of suicidal thoughts and behaviours, particularly in children, adolescents, and young adults. Additionally, there is a risk of serotonin syndrome, with symptoms such as agitation, hallucinations, and a rapid heart rate. Long-term use of SSRIs may result in weight gain, changes in appetite, and potential effects on bone density. Given these notable health risks, some women might find SSRIs less desirable for managing conditions like depression and PMDD, despite their effectiveness (FDA, 2023a, 2023b).

Use in menstruation management: SSRIs are the only type of antidepressant shown to improve PMDD and studies have suggested that they may work differently for PMDD symptoms than they do for other conditions like depression. It is hypothesised that their efficacy may be due to their ability to increase ALLO (previously discussed in Chapter 2) levels in the brain and enhance GABA receptor function, leading to a calming effect (Pearlstein and Steiner, 2008). Studies have also shown that those with PMDD may be able to take SSRIs during just their luteal phase due to the speed of change of ALLO production (Reilly et al., 2023). However, as with any other medication, not all women with PMDD will find relief from SSRIs - 60%–70% of women respond to them in comparison with about 30% of women responding to placebo (Pearlstein and Steiner, 2008).

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The Promise of Neuromodulation

At the very start of this guide, we highlighted that it was a centuries-old prevailing belief that the adult brain was immutable to change. Neuroplasticity—the brain's ability to change functionally or structurally—was thought to stop by the age of 25. However, modern clinical research has overturned this idea, revealing that the adult brain can continue to develop well into old age when stimulated by certain activities and experiences. We've also shown you that multiple recent studies have shown that the mature brain undergoes functional and structural changes on a monthly basis, influenced by menstrual cycles.

It is therefore reasonable to suggest that engaging in neuroplasticity-promoting activities could be an effective strategy to manage the physical and mental symptoms associated with menstrual cycles. However, the challenge lies in consistently integrating these practices into daily life, as they often require the development of new habits over extended periods. This is the context in which neuromodulation technologies like Nettle may offer valuable assistance.

Let's dive deeper into both the natural techniques and neuromodulatory technologies currently available for use in menstruation management.

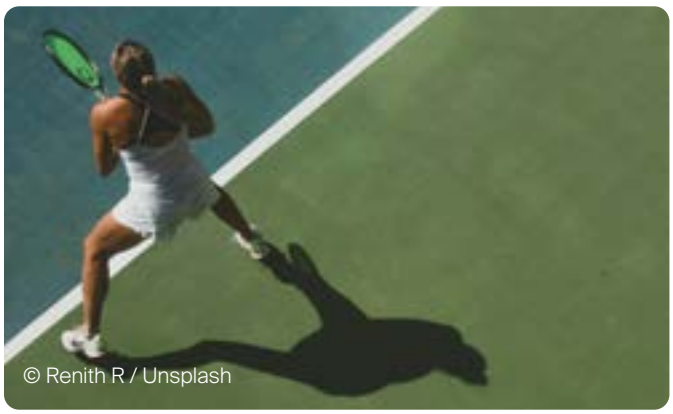
Natural *Brain-Based* Techniques

First, let's take a look at the brain-based methods backed by science that can help you manage your menstrual symptoms. We've put together the science of how these work below, but you can find how to integrate these into your cycle in Chapter 5.

01 Exercise

It's well known that exercise is good for us but, thanks to neuroimaging, scientists have been able to observe its positive effects on brain health. Specifically, researchers have revealed how exercise changes neural activity, brain structure and other indicators of neuroplasticity. For example, research by Erickson et. al found that a year of aerobic exercise can enlarge the hippocampus, a critical area for memory and learning and the first to be affected in Alzheimer's disease. Similarly, a study by Colcombe revealed six months of exercise training enhances grey and white matter volumes in areas critical for higher cognition, which are vulnerable to ageing. Beyond structural changes, a recent meta-analysis showed that physical exercise also increases neuroplasticity via neurotrophic factors and in turn leads to improvements in cognitive enhancement of learning and memory (Angevaren et al., 2008; Erickson, Gildengers and Butters, 2013; Lin, Tsai and Kuo, 2018).

However, we know that finding the motivation and energy to exercise whilst on your period can be difficult - a review of 6,812 women found that menstrual symptoms compromise their exercise participation and work capacity (Bruinvels et al., 2021). However, it has been observed that physical fitness can reduce the severity of menstrual symptoms (Kawabe et al., 2022). Therefore, the combination of exercise's impact on your brain and body means that any movement during your cycle may help you feel better during your period.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02 Meditation

The same can be said for mindfulness meditation. A group of researchers from Harvard Medical School demonstrated that when compared to no meditation, an 8-week mindfulness-based training program led to increases in the grey matter volume (tissue of the CNS that contains a high number of neurons) in several brain areas including the posterior cingulate cortex, temporal areas and cerebellum – all of which are key regions for learning, memory, and emotional regulation (Hölzel et al., 2011; Tang, Hölzel and Posner, 2015). Another study showed that long-term meditators as compared to non-meditators have a greater number of neurons within the regions responsible for attention, and self-control (Hernández et al., 2016). Moreover, evidence from a randomised controlled trial in older adults, led by a group of investigators from Boston, found that an 8-week mindfulness intervention resulted in improvements in cognitive performance and increased connectivity within the brain's network known as the default mode network (DMN), which is highly susceptible to age-related neuronal loss (Sevinc et al., 2021).

Research indicates that mindfulness and meditation significantly influence attitudes toward menstruation and alleviate premenstrual syndrome (PMS) symptoms. Evidence demonstrates that meditation can effectively reduce both physical and emotional symptoms of PMS and offers greater relief compared to similar quiet activities, such as reading (Goodale, Domar and Benson, 1990). Furthermore, meditation has shown potential in mitigating specific premenstrual physical symptoms, including pain and water retention (Lustyk et al., 2011). Given its low risk and cost, meditation may be a simple way to reduce your stress levels and any PMS symptoms this may influence.

03 Yoga

A combination of the two activities above, yoga combines postures, meditation and breathwork. It has been well documented to improve mental health and alleviate pain (Wren et al., 2011; Li and Goldsmith, 2012). Recent studies have revealed that experienced yoga practitioners have greater grey matter volume in several brain regions compared to non-practitioners, including the hippocampus, somatosensory cortices, insular cortex, cingulate cortices, parietal cortices, temporal gyrus, orbitofrontal cortex, medial prefrontal cortex, and cerebellum. These areas are associated with memory, sensory perception (including pain), emotional regulation, decision-making, and overall cognitive function (Villemure et al., 2015).

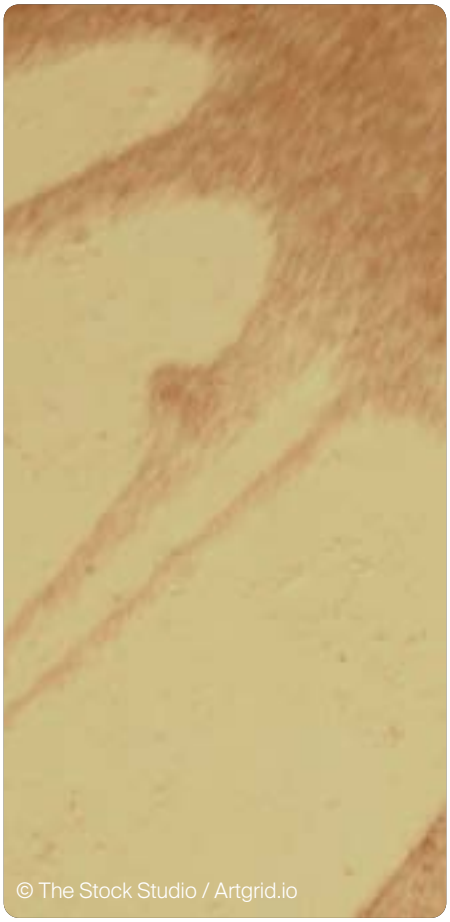
While these findings suggest a correlation, they do not establish causation due to the nature of the studies. Villemure et al. (2015) controlled for other inputs when using neuroimaging to compare age-related grey matter decline in yogis. It was found that yogis did not experience as much of a grey matter decline as non-practitioners, suggesting that yoga may protect the brain against age-related deterioration. The study also examined how yoga experience and weekly practice influenced grey matter volume; longer yoga practice was associated with increased grey matter volume in the left hemisphere, particularly in regions like the insula, frontal operculum, and orbitofrontal cortex. This indicates that yoga may promote a parasympathetic, relaxed state and positive emotions. Specifically, the combination of yoga postures and meditation was linked to larger brain areas involved in memory and body awareness, while meditation and breathing exercises were particularly beneficial for the primary visual cortex, the part of the brain responsible for processing visual information.

Whilst the research above highlights the neuroprotective prospects of yoga, there are some simple physical mechanisms by which yoga may also help. Firstly, certain poses stretch the abdomen, pelvis, and groin, which can lessen pain intensity (Vaziri et al., 2015). Increased blood flow from yoga practice may also counteract reduced uterine blood flow that can intensify cramps and the warming effect of yoga may mimic the pain relief of a heating pad (Altunyurt et al., 2005; Woodyard, 2011). Hormonally, yoga regulates cortisol levels (the stress hormone) and so may reduce uterine cramps this way as well (Thirthalli et al., 2013). Finally, the distraction provided by yoga may simply help you to focus away from pain (Campbell and McGrath, 1999) - why not give it a go?

04 Magnesium Supplements

Magnesium is the fourth most abundant mineral in the human body and is involved in more than 600 biochemical reactions in the human body, playing a key role in health, including brain function. It is fundamental for nerve signal transmission and maintaining homeostasis (a constant internal environment). Magnesium modulates neurotransmission pathways by acting as an agonist of GABA receptors (our old friend from Chapter 2), involved in reducing anxiety and promoting sleep, and inhibiting NMDA receptors to prevent neuronal overstimulation and death. Additionally, Magnesium supports the integrity of the blood-brain barrier (BBB), protecting the brain from toxins and pathogens, and enhances the production of brain-derived neurotrophic factor (BDNF), crucial for neuroplasticity, learning, and memory. Magnesium supplementation has been shown to increase BDNF levels in patients with depression and improve memory and neuroplasticity in animal models (Maier et al., 2023; Porri et al., 2021)).

Many women have an inadequate magnesium intake. This can be for many reasons, but most often it is due to the modern refinement of food leading to the loss of magnesium. Interestingly, several studies have shown that magnesium levels in women with PMS were lower than in women without. Therefore, magnesium supplementation has been proposed as a preventive and therapeutic approach for PMS, but with limited observed efficacy (Moslehi et al., 2019) Some of the risk factors for PMS, such as depressive symptoms, smoking and weight gain, have also been associated with High-sensitivity C-reactive protein (hs-CRP), an inflammatory marker. The anti-inflammatory properties of magnesium are well defined, so it is not surprising that several studies reported an association between magnesium intake and some important inflammatory markers, including hs-CRP (Porri et al., 2021).



TMS vs tDCS: What's the Difference?

There are two main types of neurostimulation available for use in menstruation management: transcranial magnetic stimulation (TMS) and tDCS (transcranial direct current stimulation).

TMS

Transcranial magnetic stimulation (TMS) modulates cortical excitability (the level of neuronal activation in a specific region of the brain) to treat various psychiatric and neurological disorders. TMS involves applying magnetic pulses to specific brain regions, with effects dependent on stimulation parameters such as frequency, intensity, and duration - high-frequency TMS increases cortical excitability, while low-frequency TMS decreases it. It is delivered using a large wire coil positioned near the scalp, generating rapidly changing magnetic pulses that induce an electric field and modulate cortical excitability (Mann and Malhi, 2024).

TMS has shown promise in treating conditions like treatment-resistant depression, PTSD, OCD, and Tourette's disorder by targeting areas that we previously mentioned in the mood (DLPFC) and pain (motor cortex) chapters of this guide. TMS has been FDA-approved for major depressive disorder (MDD) since 2008 and for chronic pain and OCD more recently. TMS' use in the treatment of PMDD has yielded promising results, despite still emerging research in the area of women's health. Studies have also explored its potential for conditions like schizophrenia, tinnitus and smoking cessation. At the time of writing, there are no known standard treatment programmes employing TMS for the management of menstrual disorders (Monteiro et al., 2024; Mann and Malhi, 2024).

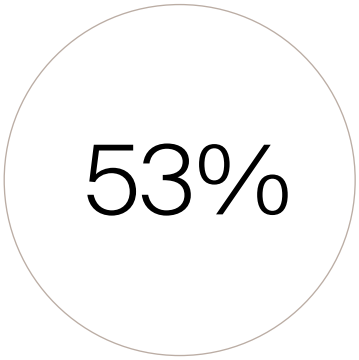
tDCS

If you've received any other content from us, you may be aware that Nettle is a transcranial Direct Current Stimulation (tDCS) device for the treatment of menstrual-related pain and mood symptoms. It is a non-invasive neuromodulation technique that alters neuronal activity through the targeted delivery of low-intensity electrical pulses to brain regions responsible for mood regulation and pain perception.

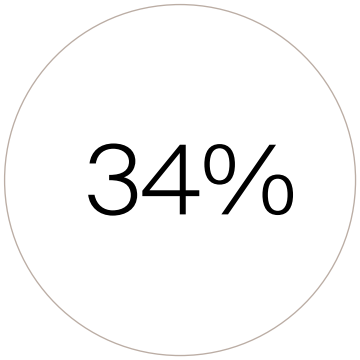
Although research in the field of tDCS is ongoing, there are promising studies that highlight its potential benefits for managing mental and physical symptoms related to menstrual cycles. For example, recently published guidelines by clinical and scientific experts in the field, and based on a meta-review of clinical studies, found that tDCS is effective for the treatment of depression. Studies also demonstrate that tDCS is a promising and safe alternative pain therapy for the treatment of chronic pain (Fregni et al., 2020; Pacheco-Barrios et al., 2020).

Interestingly, a recent study led by a group from Japan showed that a combination of neuromodulation (tDCS) with mindfulness meditation led to a significant decrease in anxiety levels following the intervention in a healthy group of individuals. This suggests promising potential in leveraging a combination of neuroplasticity tools to further enhance their effectiveness (Nishida et al., 2021).

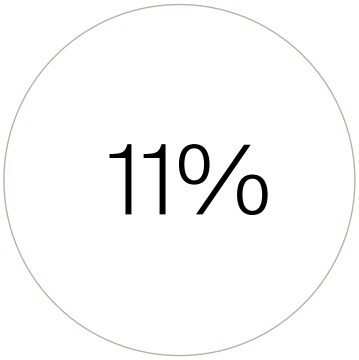
As the first tDCS device for the treatment of menstruation-related symptoms that has been approved by medical and regulatory authorities, we have and continue to conduct clinical trials into its efficacy for women's health. Using Nettle, our studies with academic partners have shown that after just one menstrual cycle (five 20 minute sessions):



72% of users reported clinically significant pain relief and the average pain symptoms reduced by 53%.



67% of users reported a clinically significant improvement in low mood and the average low mood symptoms in the PMS period improved by 34%.



67% of users reported a clinically significant improvement in average functionality, or fitness status, which improved by 11%.

It's also worth noting that 44% of participants had a diagnosis of PMDD, indicating severe mood symptoms. Furthermore, across all trials conducted, participants reported no severe side effects with the most common side effect being mild tingling during sessions that goes away with repeated use.

So Which is Better?

Both TMS and tDCS offer promising, non-invasive approaches to managing menstrual symptoms, especially when combined with other natural methods. Neither tDCS nor TMS is inherently better; they serve different purposes and have distinct applications. The choice depends on your individual needs, treatment goals, and medical advice. Here are the key differences:

01 Modality

Perhaps the clearest difference, TMS utilises a magnetic field to stimulate specific brain regions, whilst tDCS involves the application of low-level electrical currents directly to the scalp (Hameed et al., 2017).

02 Size

TMS devices are larger than tDCS devices, ranging from the size of a large microwave to a mini fridge, and are wall-powered and used in clinical settings. They require additional equipment like neuronavigation systems and EMG machines for accurate application. In contrast, tDCS devices are smaller, portable, battery-powered, and can be used at home.

03 Application

TMS is a treatment that can only be accessed in a clinic. Whilst this is only as an outpatient, you will need to physically go to the clinic several times; typically 30 to 40 times over a six to ten-week period (Mann and Malhi, 2024). In contrast, a tDCS device like Nettle can be used at home and is portable enough to be taken wherever life takes you.

04 Cost

The cost difference is one of the main reasons we built Nettle. We saw how in-clinic neurostimulation was improving the symptoms of depression and chronic pain, but also recognised just how expensive these treatments are: in-clinic costs for 30 TMS treatment sessions can cost up to £8,000. In the US, one 2009 study found that one course of TMS treatment can cost $6-12,000 but prices have likely increased since then (Simpson et al., 2009). In comparison, Nettle costs £449.

05 Efficacy

The effectiveness of TMS or tDCS depends on the intended use and specific condition being treated. TMS is established for clinical use, particularly for depression and OCD, whereas tDCS devices have been approved in the EU/UK for the treatment of dysmenorrhea and PMS, as well as major depressive disorder (MDD) (Mann and Malhi, 2024; Thomson, 2019; Radyte, 2023).

06 Adverse Effects

TMS may cause scalp twitching and discomfort, with a low risk of seizures. On the other hand, tDCS may cause mild itching and tingling under the electrodes that ceases on stopping the stimulation, with no long-term side effects. The primary difference in side effects is the higher discomfort level and seizure risk with TMS when compared to tDCS (Mann and Malhi, 2024; Matsumoto and Ugawa, 2016).

CHAPTER 5

A Neuroscientific Approach to *Cycle Syncing*

samphire
neuroscience

Cycle syncing is a practice where individuals adjust their lifestyle choices and activities to match the phases of their menstrual cycle. It's based on the idea that different phases of the cycle affect energy levels, mood and physical capabilities. By understanding and responding to these changes, people can optimise their health, productivity, and overall well-being.

Neuroscience offers unique insights into how one can tailor their lifestyles and routines according to their menstrual cycles. This is because recent research, as explained in previous chapters, has shown how hormonal fluctuations impact your brain, and therefore your physical and mental well-being. Responding to these changes and being in tune with your mind and body can reap many benefits for overall well-being. This chapter will discuss the four phases of the menstrual cycle—luteal, menstrual, follicular, and ovulatory—and provide neuroscience-backed recommendations for each to optimise physical and mental health.

Neuroscience research continues to change and improve, especially when it comes to women's bodies, brains and minds, so this reflects what we know to be true now, and we will continue updating our advice as the science and evidence help us push it forward.

Luteal Phase

Brain Activity

Imbalances in brain activity and less responsiveness in the prefrontal cortex which is responsible for emotional regulation. Increasing progesterone levels lead to increased GABA which can cause mood irregularities and anxiety.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What Research Shows

To counteract a range of mental symptoms associated with the luteal phase, integrating Yoga Nidra, a guided meditation known as "yogic sleep", can be particularly beneficial. In fact, yoga nidra practices have been shown to induce a mental state scientifically known as "non-sleep deep rest", or NSDR. A clinical study (Rani et. al, 2016) evaluated the effects of Yoga Nidra on women with menstrual disorders, comparing outcomes between those who practised Yoga Nidra alongside medication and those who only received medication. Results showed significant improvements in the Yoga Nidra group in terms of anxiety, depression, well-being, general health, and vitality. Other practices, such as gratitude meditation, visualisation and breathwork have also shown to be able to induce NSDR states, likely contributing to the improvements seen in managing menstrual symptoms.

General Recommendations

COGNITIVE

In the luteal phase, cognitive functions such as concentration and memory may be affected. You could try incorporating concentration exercises like the Pomodoro Technique to maintain focus during potentially lower concentration spans without overwhelming the brain.

THE POMODORO TECHNIQUE

1. Identify a task or tasks that you need to complete.
2. Set a timer for 25 minutes.
3. Work on a task with no distractions.
4. When the alarm sounds, take a 5-minute break.
5. Repeat the process 3 more times.
6. Take a longer 30-minute break and start again.

NUTRITION

Cravings and mood swings are common in the luteal phase due to fluctuating hormones. Consuming complex carbohydrates can help stabilise blood sugar levels, which in turn can curb cravings and mood instability.

PHYSICAL

Opt for lighter, restorative exercises like yoga, pilates or Tai Chi to match your body's lower energy level as progesterone rises and oestrogen drops. These are especially relevant for the latter half of your luteal phase. We've spoken to professional athletes, and they have also noted that trying to learn new skills during the luteal phase may lead to higher risk of injury. And while further research is needed a study did conclude that injury risk was significantly elevated during the luteal phase of the menstrual cycle among elite female professional footballers. (Barlow et al., 2024).

EMOTIONAL

The hormonal changes in the luteal phase can lead to increased susceptibility to stress and anxiety. Relaxation techniques such as meditation, deep breathing, or Yoga Nidra can help stabilise mood fluctuations, promoting a sense of calm.

Menstruation

Brain Activity

During the menstrual phase, declining levels of oestrogen and progesterone reduce serotonin levels in the brain. Serotonin is crucial for stabilising mood and regulating pain perception. This decrease in serotonin not only makes you more susceptible to feeling pain but also can contribute to mood swings or general feelings of sadness or irritability.

What Research Shows

The study "A comparison of physical activity and nutrition in young women with and without primary dysmenorrhea" (Bavil et. al, 2018) found that exercise prior to and during the early days of menstruation can alleviate symptoms of dysmenorrhea. The study found that dysmenorrhea was less prevalent in those who were more physically active, and regular exercise can reduce stress in women and thus improve blood circulation and increase the amount of endorphins and neurotransmitters. More specifically, it concluded that engaging in 30 minutes of brisk walking each day for the first three days of the menstrual period is recommended to improve blood circulation in the pelvic area, reduce the accumulation of pain-causing prostaglandins, and decrease pain duration.

General Recommendations

COGNITIVE

Hormonal fluctuations can lead to decreased concentration and cognitive abilities. During this period, prioritising lighter, less demanding tasks can help manage these effects effectively. It's also a good time to practise visualisation techniques. Imagining a positive outcome to a situation for a few minutes can enhance creativity, reduce stress, and improve mood.

NUTRITION

Focus on incorporating iron-rich foods to replenish iron lost during menstruation and sustain your energy levels. Foods like spinach, red meat, lentils, and fortified cereals are excellent sources. Iron is crucial for the production of haemoglobin, the protein in red blood cells that carries oxygen throughout the body.

PHYSICAL

Engage in gentle physical activities like walking or yoga. Opt for yoga styles that are gentle and restorative, such as Hatha or Yin Yoga. These practices involve slow movements and poses that enhance relaxation and stretching without exertion. This can help ease cramps, improve mood, and maintain flexibility.

EMOTIONAL

During the menstrual phase, it's vital to prioritise emotional well-being by allowing yourself time to rest and recharge. It's a good time to practise gratitude interventions like journaling which have been clinically proven to reduce depression, stress and increase happiness levels (O'Leary & Dockray, 2015).

Follicular Phase

Brain Activity

During the follicular phase, rising oestrogen levels boost brain connectivity and serotonin levels. This surge enhances mood, energy, and cognitive functions like memory and focus, by improving the efficiency of neural networks across the brain.

What Research Shows

Women's brains may have higher reward responsivity during the follicular phase, making goal-directed activities and positive reinforcement more effective and enjoyable. This could be a prime time for engaging in creative endeavours, socialising and meeting new people, trying new experiences, or completing tasks that offer immediate positive feedback. (Zhuang et al., 2020)

General Recommendations

COGNITIVE

The hormonal boost in oestrogen can increase neural connectivity and improve cognitive flexibility, making it a good time to tackle challenging projects or brainstorm new ideas. It could be fun to try writing flash fiction (a creative writing piece under 10 minutes) or learning a new language or instrument.

PHYSICAL

With the increase in energy levels driven by rising oestrogen, the follicular phase could be the best time for more intense physical activities, especially in the latter half. Engaging in vigorous workouts during this time can be more rewarding and less exhausting.

NUTRITION

To support the increased physical activity and cognitive demands of this phase, a balanced diet rich in protein and fibre is recommended.

EMOTIONAL

Utilise the natural boost in positivity and energy to engage in social and creative activities. An interesting study actually found that we respond better and significantly faster to happy male facial expression during the follicular phase as compared to the luteal, so this might be a good time to show gratitude to your partner or plan romantic activities (Yamazaki and Tamura, 2018).

Ovulation

Brain Activity

During the ovulation phase, the peak in oestrogen levels significantly enhances several areas of brain function. This hormonal surge boosts verbal skills and emotional intelligence, facilitating more effective communication and stronger interpersonal connections.

What Research Shows

A study called “The Impact of Menstrual Cycle Phase on Economic Choice and Rationality” (Lazzarro et al., 2016) suggests that women’s economic and social behaviours change significantly around ovulation. During ovulation, women are less loss-averse, meaning they are more willing to tolerate potential financial losses and may exhibit more risk-taking behaviours. These findings suggest the ovulation phase might be a good time to engage in activities that involve risk-taking and economic decision-making due to a decreased loss aversion, potentially maximising opportunities for economic gain.

General Recommendations

COGNITIVE

It’s a good time to tackle activities that require strong communication skills. Scheduling important meetings, presentations, or any public speaking engagements during this phase can be beneficial, as you are likely to be more articulate and persuasive.

PHYSICAL

The surge in energy that accompanies ovulation can be ideal for capitalising on physical activities. High-intensity workouts can be more effective during this time due to increased endurance and strength.

NUTRITION

To support the heightened physical and cognitive activity, incorporating foods rich in omega-3 fatty acids and healthy fats like fish, nuts and avocados can be beneficial. These nutrients support hormone balance and brain health, enhancing cognitive functions and mood stability.

EMOTIONAL

Explore deeper social interactions and new experiences to make the most of your enhanced emotional connectivity. This phase also provides an opportunity to express more empathy and understanding towards partners or close friends, potentially deepening bonds and improving communication in personal relationships.

Resources

References

All about Nettle

We’re on a mission to change the lives of historically underserved communities by delivering pioneering neuroscience and evidence-based solutions.

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