Bachelor Degree Project

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Cyclical Women:

Menstrual Cycle Effects On Mood And Neuro-Cognitive Performance

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Abstract

During roughly forty years of a woman's life-span, the fertile female human body prepares itself monthly for the possibility of pregnancy. Science has shown that the fluctuation of the sex steroids progesterone and estrogen have a crucial role in the female body's physiology, determining the menstrual cycle and its general phases. This biological dance of hormones governing the cycle influences a lot of physical, mental and cognitive aspects of life for a fertile ovulating woman. Although the question of whether these changes also affect women's cognitive performance is still unclear, some evidence has been gathered that could bring us closer to answers. Recent research findings show that this hormonal interplay might have a significant role in cognitive and psychological development - modulating brain activity, cognitive performance, higher cognition, emotional status, sensory processing, appetite and more. This thesis aims to uncover to what extent the menstrual cycle affects brain functions, neurobiology, mood, well-being and cognitive performance in menstruating cisgender women.

Keywords: menstrual cycle, estrogen, progesterone, cognition, mood

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1. Introduction

There has been increased interest among researchers on the minutiae behind the menstrual cycle during past decades. Through collected data from the medical literature and personal narratives, it has become possible to generalize enough and say that the female body presents exquisitely balanced biochemistry of hormones that create cyclical changes not only on physical but also on psychological processes in the body. It has been argued that these changes have possible measurable effects on cognitive and emotional processes for women (Farage, Osborn & MacLean, 2008). Disturbances to this highly intricate hormonal balance are associated with very specific menstrual irregularities that are beyond the scope of this thesis. This thesis will focus on the menstrual cycle of healthy women with the natural interplay between the "female" hormones, mainly estrogen and progesterone, and the central nervous system, with effects on cognitive performance.

The complexity of the female reproductive cycle shapes the life experience of more than half the human population. Increasing knowledge of its intricacy contributes to the common understanding of what differentiates the female from the male sex in humans. As Sherwin (2003: p. 135) writes, “although there are no qualitative differences in cognitive skills between the sexes, quantitative differences have been consistently found”.

There is steady evidence from well-being studies that variations in mood-regulation for women are cycle-related (Symonds, Gallagher, Thompson, & Young, 2004) and correlated with high or low levels of estrogen. Researchers disagree on whether this variation has a sufficient magnitude to manifest a change in cognitive performance (Cockerill, Wormington, & Nevill, 1994). Mappings of the biology of the menstrual cycle have shown that levels of hormones vary along with the menstrual cycle. These hormones are present in the brain and have important regulatory roles in the body.

What this thesis intends to answer is how, from a neurocognitive perspective, this variation over the menstrual cycle influences women when it comes to cognitive performance and mood. Making use of recent research in the fields of cognitive studies and neuroscience, but

also physiology and medicine, the focus here lies on the neuroendocrine system and reproductive organs, as well as their relationship to the central nervous system (CNS). This critical knowledge to be gained has the potential of adding to a deeper recognition of the specifics and similarities between the sexes. Finally, I hope that the material here presented can result in practical applications, both on the individual and societal levels, with women better equipped to live a life that respects their natural rhythms, along with policies and therapeutic strategies that support women's well-being and promote healthy aging.

I aim to examine to what extent the female menstrual cycle is a variable in cognitive performance in women. This thesis will cover the human menstrual cycle and its different components, presenting essential information of the physical changes happening within the female body on a cyclical basis. It will discuss the main brain regions associated with the menstrual cycle along with hormones and their brain receptors according to the most recent research findings. Later all previous information will be connected in a chapter dedicated to answering how cognition, mood, and well-being are affected by the menstrual cycle. The thesis will offer a brief discussion of the implications of these findings.

2. Methods

This thesis is designed as a literature review. Starting with a first systematic search for peer-reviewed research articles on the topic, I used well-established databases like Web of Science and Science Direct. To remove the risk of ending up with too many irrelevant data, the search was filtered for only neuroscience-related registers, focusing mainly on keyword's combinations such as "menstrual cycle + brain" "menstrual cycle + performance", "estrogen + mood" and so forth. A short number of articles were selected based on their suitability for the aim of this thesis.

Articles were examined on their research methods and results, inspecting their chosen experimental design and performance, attesting their fitness to the questions they propose to answer. This left me with a smaller number of research reports since only those with solid findings were selected. I compared these articles on their methods, design, and results, observing whether they related or agreed on their findings. This final step defined this thesis and brought

me closer to a relevant answer to how the menstrual cycle influences women when it comes to performance and mood.

3. The human female reproductive cycle and endocrinology

The beginning of the menstrual cycle is a naturally occurring phenomenon resulting from puberty, the onset of sexual maturity and the ability to reproduce (Gazzaniga, Heatherton & Halpern, 2016). Typically taking place between the ages eight and fourteen, menarche, or the first menstrual period, is one of the primary sex characteristics developing in the female body, and will accompany women throughout their adult lives up until menopause approaches, at about 50 years old, when new changes transform most parts of the female reproductive system once again (Dyer, 2014). The menstrual cycle is a coordinated sequence of hormonal signals and tissue responses that function to bring a ripe fertilized egg into contact with a ready uterus (Wilcox, 2010). Gathering results and observations from different studies, the epidemiologist and author Allen J. Wilcox (2010) describes the six-day fertility window in a woman's reproductive cycle. It is possible to infer that, if sperm survives for up to five days in the woman's reproductive tract and the ovum dies quickly after ovulation, one has six days per cycle in which a woman can get pregnant.

Once a girl reaches reproductive age, the hypothalamus, ovaries, and pituitary gland start secreting estrogen, progesterone and the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The rise and fall of these hormones determine the buildup and shedding of the internal layer of the uterus during the menstrual cycle, as well as the growth and release of an egg. This process makes pregnancy possible (White & Porterfield, 2013).

Each cyclical interval compresses the time needed for the ovum to mature, the reproductive tract to get prepared for receiving the fertilized ovum, the ovum to become fertilized, and pregnancy to be established. If the ovary does not receive a signal that the embryo has begun to develop, the process of gamete maturation starts anew, initiating a new cycle. Menstruation continues at cyclic intervals until menopause normally interrupted only by periods of pregnancy (Goodman, 2003).

A menstrual period starts on the first day of bleeding, also called menses, and ends on the last day before the next bleeding, which opens the next period. The menses on average lasts six days, with 90% of women having menses that last from four to seven days. Although the number of days of bleeding varies among women, it tends to remain fairly constant for a given woman. The heaviest bleeding usually occurs on the second and third days (Wilcox, 2010) In terms of duration of a cycle, Wilcox refers to the problem with textbooks' description of a typical "normal" or "standard" menstrual cycle of 28 days, with ovulation on day fourteen. Menstrual cycles are not only highly variable, but they are easily disrupted; and, by this definition, most cycles would not be normal. Making use of several studies on the topic, Wilcox explains that only 12% of cycles are 28 days long. Overall, the within-woman variance is greater than the between-women variance. Numbers can vary widely, with cycles lasting usually 21 to 45 days in young women and 21 to 35 days in adults. There is a tendency for the gradual shortening of menstrual cycles when women have their most stable menstrual patterns, which is between the ages of twenty and forty.

In the following sections, the female reproductive cycle will be described in more detail, using the common characterization of it by three cycles all working together: the ovarian, the hormonal and the menstrual, or uterine, cycle (Dyer, 2014).

3.1. The ovarian cycle and the sex hormone cycle

The ovarian cycle describes the changes occurring in the follicles: tiny fluid-filled cavities, each of which holds an immature egg cell - the oocyte (Wilcox, 2010). This cycle consists of three phases: follicular, ovulation and luteal (Silverthorn, 2013). Throughout these three phases, the ovaries secrete varying levels of the sex hormones estrogen and progesterone, and this phenomenon characterizes the sex hormone cycle.

Wilcox (2010) affirms that much of the variance in length observed among menstrual cycles is due to the follicular phase: that is, the time from bleeding to ovulation. Studies he presents show that the length of the follicular phase among women ranges from nine to 55 days: in other words, only about 1% of these menstrual cycles would be considered “standard” according to the common textbook definition.

Despite what many might think, although bleeding is a clear sign of menstruation, it is not the central reference for understanding the menstrual cycle. Rather, it is ovulation that provides the most important benchmark, since it ends the follicular phase and launches the luteal phase. It alone determines the days on which intercourse can produce a pregnancy, as endocrinologist Maurice H. Goodman (2003) affirms.

The early follicular phase corresponds to the menstrual bleeding phase and is expressed by low levels of both sex hormones (Farage et al., 2008). This low ebb of sex hormones stimulates the hypothalamus to secrete gonadotropin-stimulating hormone (GnRH). GnRH prompts the anterior pituitary gland to secrete both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The increasing levels of both these gonadotropin-hormones triggers not only follicle growth in the ovary but also the secretion of estrogen (Sherwood, 2007).

As Goodman (2003) explains, under normal circumstances, during each cyclic interval, a limited pool of follicles - the female gametes - is mobilized in the ovary, from which only one will continue through the maturation process, be released and ovulate. The follicle appears randomly on either the right or left ovary (Goodman, 2003). As these follicles grow, they produce a type of estrogen called estradiol. An increasing amount of estradiol stimulates the lining of the uterus to prepare for a possible pregnancy (Wilcox, 2010). Estrogen levels start rising rapidly, peaking in the late follicular phase, one day before ovulation (Farage et al., 2008). Also peaking around this time is LH, the physiological signal for ovulation. Its concentration in the blood rises sharply and reaches a peak about sixteen hours before ovulation (Goodman, 2003).

The ovulation stage is characterized by the maturation of the follicle as an effect of stimulation from increased blood levels of FSH, as well as the first spike in estrogen secretion (Wilcox, 2010). This first estrogen peak triggers a spike in LH levels, which in turn causes the follicle to rupture and the egg to be released, initiating ovulation (Dyer, 2014). The ovum has less than 24 hours to be fertilized after ovulation. If fertilization does not occur, it dies and a new follicle must be prepared. Coordination of these events requires two-way communication

between the pituitary and the ovaries, and between the ovaries and the reproductive tract (Goodman, 2003).

The luteal phase follows ovulation and encompasses the life cycle of the corpus luteum - a temporary endocrine structure in female ovaries, involved in the production of sex hormones. This phase is accompanied by a rapid decline in estrogen levels, ending at the beginning of the next menses. Under the influence of the gonadotropin LH, the collapsed follicle is transformed into a small swelling of yellowish tissue called the corpus luteum: “yellow body” in Latin. The corpus luteum main task is to produce progesterone, the hormone that alters the uterine lining and prepares it for pregnancy (Wilcox, 2010).

In this phase, there is a constant rise in levels of progesterone, which peaks in the mid-luteal phase, in parallel with a second estrogen peak. If fertilization doesn't occur, the corpus luteum degenerates and the end of the luteal phase sees a decline in both estrogen and progesterone levels. This loss of the proliferated endometrium - the internal lining of the uterus - is accompanied by bleeding; this cyclic vaginal discharge is called menstruation (Goodman, 2003). Both estrogen and progesterone reach baseline shortly before (Farage et al., 2008).

These changes occur regardless of whether conception has occurred. As Maner and Miller (2014) affirm, this phenomenon is consistent with the logic of error management theory: i.e., the energy costs of preparing for possible pregnancy in the absence of conception are outweighed by the reproductive costs of failing to generate the necessary environment for the growth of a fertilized egg. Thus, during the luteal phase of each menstrual cycle, a woman's body prepares itself for possible pregnancy whether or not an egg has been fertilized.

Although the rhythmic release of GnRH is controlled by the hypothalamus, the timing for this is coordinated by the ovary. The corpus luteum has a programmed life-cycle of about twelve days. A new cohort of follicles cannot arise so long as the corpus luteum remains functional. When it dies, it appears to allow follicular growth and FSH secretion in the blood once again, stimulating the growth of the next cohort of follicles. So, the ovary determines the interval between the LH surge and the emergence of the new cohort of follicles.

The length of the follicular phase may be somewhat variable, influenced by events happening outside the ovaries; but the timing of the LH surge resides in the ovary (Goodman, 2003). It is only when the developing follicle signals it is ready to ovulate with increasing blood levels of estradiol that the pituitary secretes the ovulatory spike of gonadotropin. Throughout the cycle, it is the ovary that notifies the pituitary and hypothalamus of its readiness to proceed to the next stage. Compared with the follicular phase, the luteal phase is less variable, due to the programmed death of the corpus luteum, which will involute despite continued stimulation with LH (Wilcox, 2010).

3.2 The menstrual (or uterine, or endometrial) cycle

The third cycle within human female reproduction is the uterine cycle, also known as the menstrual cycle or even the endometrial cycle. It describes the changes happening in the uterus within one cycle and can also be divided into three phases: menstruation, proliferative and secretory (or progestational) stages (Sherwood, 2007).

Day One of menstruation marks a new period. During the first five days, the endometrium sheds its functional layer, leaving the deepest layer intact. At about day six, the endometrium moves into the proliferative stage when it begins regenerating its functional layer, driven by rising estrogen levels (Sherwood, 2007). This stage of the uterine cycle is known as the proliferative phase and coincides with the follicular phase of the ovarian cycle. Endometrial growth is accompanied by increased blood flow, especially through the spiral arteries, which grow rapidly under the influence of estrogen (Goodman, 2003).

After ovulation starts the secretory stage. Increased progesterone stimulates the conversion of the functional layer of the uterus into a secretory mucus, which is more receptive to the implantation of a fertilized egg (Sherwood, 2007). This stage of the menstrual (or uterine) cycle coincides with the luteal phase of the ovarian cycle. That progesterone stimulates the function layer of the uterus into forming a secretory mucosa is consistent with its role of preparing the uterus for nurture and implantation of the newly fertilized ovum, if successful fertilization has happened. The so-called uterine milk secreted by the endometrium is thought to nourish the blastocyst until it can implant (Goodman, 2003) and develop into an embryo. The

proliferation of the endometrium is an intensive investment that cannot be sustained for long. Progesterone's production by the corpus luteum reaches its peak nine or ten days after ovulation, after which it declines, together with the corpus luteum. If implantation does not occur, the corpus luteum regresses completely over the next five or six days, at which point the production of progesterone ends. The withdrawal of hormonal support leaves the richly engorged lining of the uterus to atrophy and die. This tissue sloughs from the uterus into the vagina, producing menstrual bleeding (Wilcox, 2010).

4. Hormones and the menstrual cycle

The principal ovarian hormones are the steroids estrogen and progesterone. Their biosynthesis is intricately interwoven with events of the ovarian cycle. Also important to the female reproductive function of vertebrates are gonadotropins, secreted by the anterior pituitary and responsible for controlling gamete and sex hormone production. Together these hormones orchestrate the cyclic series of events that unfold in the ovary, pituitary, and reproductive tract each month, their action intimately connected to ovulation and transformations in the uterus (Goodman, 2003).

4.1 Sex (or ovarian) hormones

Sex steroids are part of a bigger group of hormones, the steroids, which are lipids derived from enzymatic modifications of cholesterol. They *organize* the brain, sculpting and amplifying sexual dimorphism, and then *activate* the already imprinted and sexually dimorphic brain, leading to sex-specific hormonal behaviors (Catenaccio, Mu & Lipton, 2016).

In women, the production of estrogen and progesterone occurs primarily in the ovary but also in the adrenal gland and at other locations, such as in the adipose tissue - the body fat. They are transported in plasma bound to binding proteins and act by readily penetrating target cell membranes and binding to their specific receptors. They affect DNA transcription, mRNA and protein synthesis, altering the functional response of the target cell. In this family, one finds estrogens, progesterone, and androgens (Catenaccio et al., 2016).

All the steroid hormones are produced in men and women but with varying profiles. Although androgens are primarily associated with the development and maintenance of male sex

characteristics, they also affect sexual behavior in women (Coad & Dunstall, 2012). To discuss the effects of androgens in women is beyond the scope of this thesis. However, both estrogens and progesterone will be presented in further detail, since these two hormones are intimately related to the menstrual cycle. Both estrogen and progesterone act on the female reproductive tract to prepare it for fulfilling its role in fertilization, implantation, and development of the embryo; they induce changes elsewhere that equip the female physically and behaviorally for conceiving, giving birth, and rearing the child (Goodman, 2003).

4.1.1 estrogen[1]

Estrogens are the primary hormones that, together with progesterone, are secreted by the ovaries. Their synthesis depends on the gonadotropins FSH and LH and the cooperative interplay of follicular cells (Goodman, 2003). 17$^{N}_{L}$-estradiol is the major estrogen in most mammals, referred to henceforth as estradiol (Jacobs & D´Esposito, 2011).

Among estrogen's main effects is to promote female secondary sex characteristics and to prepare the uterus for ovulation and fertilization (Coad & Dunstall, 2012). It has also vascular effects such as to increase blood flow and the creation of new blood vessels, and it has growth-promoting effects on endometrium and breasts. It primes the endometrium for progesterone action, it is mildly anabolic and increases calcification of bones. Coad and Dunstall (2012) refer to estrogen as associated with sexual behavior. Goodman (2003) affirms its protagonism to sexuality as responsible for the promotion of estrus, the period of sexual receptivity in female vertebrates animals.

Plasma concentrations of estrogen are considerably lower than those of other gonadal steroids and vary over an almost twenty-fold range during the cycle (Goodman, 2003). The liver is the principal site of metabolic decomposition of estrogens and, over time, it gradually absorbs estrogens, converting them to a soluble form that can be excreted in the bile (Martini, Nath & Bartholomew, 2012). However, it is through the kidneys that estrogenic metabolites find their primary route of excretion (Goodman, 2003).

[1] For the purpose of this thesis, the terms estradiol and estrogen will be used interchangeably. Estradiol is one type of estrogen, and “estrogen” is a category of sex hormones.

As estrogen levels decrease and menopause approaches, usually at 50 years, changes affect most parts of the female reproductive system (Dyer, 2014).

4.1.2 progesterone

The word "progesterone" comes from "pro-" (in support of), "-gest-" (gestation), and "-sterone" (steroid hormone). This sex hormone is essential to pregnancy. Progesterone in a non-pregnant woman is secreted by cells of the corpus luteum and is the chemical signal used by the ovary to convert the endometrial lining of the uterus into a richly secretory tissue that can support the fertilized egg (Wilcox, 2010).

This hormone production rate varies widely throughout a cycle. Its concentration in the blood goes from almost non-existent during the early pre-ovulatory part of the ovarian cycle to as much as 2 mg/dl after the corpus luteum has formed. Progesterone is mostly metabolized in the liver, but considerable degradation also occurs in the uterus (Goodman, 2003).

Progesterone has a moderate thermogenic effect; it may increase basal body temperature throughout the cycle. As Goodman (2003) suggests, "because the appearance of progesterone indicates the presence of a corpus luteum, a woman can readily determine when ovulation occurred, and hence the time of maximum fertility, by monitoring her temperature daily" (p.412). This is a method traditionally recommended for women wishing to conceive. However, this is not an infallible method and cannot be blindly reliable, especially not for scientific research alone since basal body temperature can easily be disrupted due to an array of causes as fewer hours of sleep and alcohol ingestion.

The finding that the pharmacological blockade of progesterone synthesis prevents ovulation indicates that this agent plays an essential role in the ovulatory process. It also affects the central nervous system (CNS) and, in addition to its effects on the regulation of gonadotropin secretion, it may produce changes in behavior or mood (Goodman, 2003).

Estrogens and progesterone usually function in conjunction, sometimes adding to or counteracting each other's effects. As Goodman (2003) explains, estrogen secretion usually precedes progesterone secretion and primes the target tissues to respond to progesterone. What estrogens do is to promote the synthesis of progesterone receptors. Without estrogen priming,

progesterone would have very limited effect. On the other hand, progesterone acts by reducing its receptors and estrogen receptors in some tissues and, by doing so, decreasing the response to estrogens (Goodman, 2003).

4.2 Gonadotropins

The gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), modulate ovarian sex hormone synthesis and secretion. Their secretion is influenced to a large measure by the same ovarian steroid hormones. FSH and LH are released from the pituitary gland under CNS control, mediated predominantly by the hypothalamus, which is in turn extensively connected to other CNS areas (Catenaccio et al., 2016).

If the connections between the anterior pituitary gland and the hypothalamus are blocked or if the arcuate nuclei of the medial basal hypothalamus are destroyed, FSH and LH secretion cease (Goodman, 2003). Some recurring environmental events, such as travel across time zones, stress, anxiety, and other effects also have an impact on reproductive function in women, presumably through neural input to the medial basal hypothalamus (Goodman, 2003).

5. The autonomic nervous system, the limbic system, and the menstrual cycle

The central nervous system (CNS) consists of the cortex and spinal cord. This complex system coordinates and integrates information which it receives from the brain, influencing the activity of all parts of the body. A part of the CNS is the autonomic nervous system (ANS), also called the visceral or motor system. The ANS is, for the most part, an unconscious control system that regulates involuntary action of visceral functions such as heart rate, digestion, respiratory rate, urination, and sexual arousal. The ANS determines which course of action one takes in terms of threat and stress, and is a part of the HPA-axis (Gazzaniga, Ivry & Mangun, 2015). As Farage and colleagues (2008) emphasize, the ANS may be an important intermediary in mood cycling that parallels hormonal changes in women, especially concerning the pre-menstrual period.

Many of the studies involving the menstrual cycle and ANS focus on a brain region that is strongly connected to the ANS and is located in the limbic system: the amygdala: small, almond-shaped structures in the medial temporal lobe adjacent to the anterior portion of the hippocampus. Since the amygdala is the most connected structure in the forebrain and contains

receptors for many different neurotransmitters and various hormones including estrogens, it has a central role in many aspects of cognition. Another important brain structure named in studies on the menstrual cycle is the hypothalamus, which links the nervous system and the endocrine system by commanding most of the production and control of hormones (Gazzaniga et al., 2015). Since it produces stimulating hormones that regulate anterior pituitary hormones, the hypothalamus affects target glands as well, as the pituitary regulates the target gland hormones (Dyer, 2014).

A comprehensive array of structures composes the limbic system in humans (Catenaccio et al., 2016). It includes both subcortical regions (olfactory bulb, thalamus, hypothalamus, amygdala, mammillary bodies, nucleus accumbens, and septum) and cortical regions (hippocampal formation, parahippocampal gyrus, insula, orbitofrontal cortex [OFC], medial prefrontal cortex [PFC] and cingulate gyrus). Areas such as the hypothalamus, amygdala and nucleus accumbens are part of the reproductive function and neuroendocrine homeostasis, whereas others such as hippocampal formation are central to many other functions, such as memory and emotional processing. The OFC and other prefrontal regions enable top-down modulation of limbic system function, with a connection to decision-making and learning (Catenaccio et al., 2016). Note that the limbic system is neither anatomically nor functionally organized as other systems in the brain, and its validity as a concept disputed among researchers (Gazzaniga et al, 2015).

Both progesterone and estrogen are thought to induce and modulate neuroplasticity, primarily by modulating dendritic spine and synapse density in areas such as the hippocampus, hypothalamus, nucleus accumbens, and amygdala. This modulation is poised to affect learning, memory, neuroendocrine state, and emotional processing, among other processes. Areas that exhibit follicular/luteal structural plasticity have been identified in the hippocampus, parahippocampal gyrus, fusiform gyrus, cingulate cortex (in particular, ACC), insula, middle frontal gyrus, thalamus and cerebellum (Catenaccio et al., 2016).

6. Menstrual cycle, hormones, and brain receptors

As Catenaccio, Wu and Lipton (2016) affirm, many structures within the CNS and ANS contain receptors for both progesterone and estrogen. The classic nuclear receptor for progesterone has been localized in the rat brain to the frontal cortex, hypothalamus, thalamus, amygdala, hippocampus, and cerebellum. The distribution of progesterone receptors is sexually dimorphic, responding to fluctuations in sex steroid levels in females and, to a lesser extent, male rats. Estradiol acts on various cells in the CNS and is responsible for certain behavioral patterns, especially in less conscious species of animals (Sherwin, 2012). Estrogen receptors (ERs) in the CNS include the nuclear ER-alpha and ER-beta nuclear receptors (Catenaccio et al., 2016). The amygdala, septum, thalamus, hypothalamus, and dentate nucleus of the cerebellum are among the areas in the rat brain showing the highest concentrations of ER messenger ribonucleic acid (mRNA) expression. Catenaccio and colleagues (2016) review studies in both other animals and humans, demonstrating expression of ER-alpha in the ventromedial nucleus of the hypothalamus and amygdala, and expression of both ER-alpha and ER-beta at high concentrations in the hippocampus, with ER-beta expression dominating in the subiculum, the most inferior component of the hippocampal formation.

Barbara Sherwin (2012) writes that the identification and mapping of ER throughout different brain structures in the 1980s found considerable concentrations of these proteins in the hypothalamus, pituitary, hippocampus, cerebral cortex, midbrain, and brainstem. These findings led to the hypothesis that estrogen helps maintain central aspects of cognition in women, with its most profound effect on the hippocampus and frontal lobe-related cognitive functions such as memory, including working memory, and learning (Sherwin, 2012). Although there are sex differences in ER concentration in the hypothalamus, overall both classic nuclear ERs are similarly widely distributed throughout the rest of the brain in adult females and males (Catenaccio et al., 2016).

Craig and Murphy (2007) write that the sex steroid estrogen is associated with the modulation of several neurotransmitter systems important to memory formation. These include the cholinergic, serotonergic and dopaminergic systems. Jacobs and D'Esposito (2011) discuss

studies that found that the estrogen estradiol enhances cortical dopamine (DA) activity and modulates glutamatergic activity; whereas GABA, the principal inhibitory neurotransmitter, has been shown to fluctuate over the menstrual cycle.

7. How cognition and mood are affected by the menstrual cycle

The mechanisms behind the processing of information in the human brain are complex and multifactorial, involving many cognitive modalities such as attention, learning, memory, pattern recognition, problem-solving, language, and motor abilities (Farage et al., 2008). There does seem to be some effect of the menstrual-cycle phase not only on function but also on the structure of the brain (Gingnell, Morell, Bannbers, Wikström, et al., 2012). Studies with menopausal women help researchers to see the possible effects of estrogen on cognitive processing, because the reduction of estrogen production, typical of this period, has considerable effects on mood, behavior, and cognition (Farage et al., 2008). A wide array of cognitive modalities has been observed in research to assess whether cognitive function varies with the menstrual cycle. Among these modalities are spatial perception in sexual dimorphism, attention and vigilance, verbal fluency, emotional face recognition, social monitoring and memory.

7.1 Cognition and the menstrual cycle

Many studies on menstrual cycle effects depend on sexual dimorphism, in particular, previous findings that conclude that adult women, on a population level, tend to perform better than men on tasks of verbal fluency, manual speed, manual coordination, and articulation. Adult men, on a population level, have been shown to perform better on tasks of spatial perception, visualization, and mental rotation, along with other spatial-temporal tasks. According to Catenaccio et al. (2016), sexual dimorphism is activated and amplified by the sex hormones, guiding sex-specific actions and behaviors. Many of the following studies explore the effects of sex hormones over the menstrual cycle, and to what extent it is possible to observe variations in cognitive performance and neurochemistry.

Broverman, Vogel, Klaiber, Majcher, and colleagues (1981) ran a series of cognitive tests to measure whether some performance variation could be observed over the menstrual cycle. Eighty-seven regularly menstruating female undergraduate students were divided into two

groups. Odd-numbered subjects were tested first on or about Day Ten of their cycle and then again on Day Twenty; even-numbered subjects were tested in the reverse sequence. Daily basal body temperature records were obtained, eliminating anovulatory cycles, natural cycles characterized by the absence of ovulation. The results support the experimental hypothesis that menstrual-cycle-related changes in estrogen affect cognitive performance. The estrogen peak occurring at mid-cycle in ovulatory women facilitates the performance of highly practiced "automatized" tasks and impairs the performance of "percepts to less obvious stimulus" tasks, compared to the performance of these tasks in the postovulatory phase.

7.1.1 Sexual dimorphism

In a study by Elizabeth Hampson (1990), an extensive battery of cognitive and motor tests was administered to women with a normal menstrual cycle at mid-luteal and menstrual phases to investigate whether women's performance changed over the menstrual cycle. Tests included spatial ability, perceptual speed, verbal fluency, articulation, manual speed/coordination, and deductive reasoning tasks. Her results confirmed changes over the menstrual cycle on a variety of manual and articulatory measures and some nonverbal/spatial tests. For the author, the results provide qualified support for the hypothesis that high levels of gonadal steroids estrogen and progesterone present at the luteal phase facilitate women's performance using skills favoring females, but are detrimental for women performing skills that favor males.

In another classic study on the menstrual cycle and cognitive performance, Cockerill, Wormington, and Nevil (1994) tested twenty-seven women on three occasions - during the premenstrual, menstrual and ovulatory phases - against a control group of twenty-seven male participants. Each testing session involved completing questionnaires and performing five timed trials on the task. What the researchers observed is that the females experienced low energy and impaired cognitive function, both premenstrually and during menstruation. However, they found no task performance variation along with menstrual-cycle phases, suggesting that cycling women had crafted effective coping strategies for physical discomfort without either mood or performance being adversely affected.

Epting and Overman (1998) tested young college women and men on three putative female-advantage tasks and three putative male-advantage tasks to check whether performance shifts could be observed with the menstrual cycle. The tests were administered twice, at six-week intervals, having women receiving the tests once during menstruation and once during the mid-luteal phase. There is persistent evidence that estrogen positively influences performance on sexually dimorphic tasks favoring females and negatively influences women's performance on tasks favoring males. Results from the study revealed a significant sex difference for five of the six tasks. However, there was no evidence that performances differed with the menstrual cycle. A possible explanation for these findings is the relationship between the sex-steroid progesterone and age: younger women might have fewer effects and therefore present less impact on the cognitive function within the menstrual cycle. Another way of seeing the results, as Epting and Overman propose, is that humans, with increased cortical-to-subcortical ratios, may be capable of overriding hormonally modulated subcortical changes by using systems that are perhaps not available to or sufficiently developed in other animals.

Celec, Mesežnikov, Ostatníková, and Hodosy (2011) tested ten healthy young female teenagers twice during their menstrual cycle to investigate the effects of the menstrual cycle on spatial abilities and general well-being. The authors wanted to check whether their results would agree with available findings. Mental rotation and spatial visualization were tested, as they are thought to be influenced by sex steroids. Well-being was used as a control measure. The results confirm that women usually experience higher well-being during the preovulatory phase. The authors did not observe any effect of the menstrual cycle on cognitive performance on mental rotation or spatial visualization tasks.

Dietrich, Krings, Neulen, Willmes, and colleagues (2001) performed a series of experiments to check one of the then currently preferred hypotheses, that the menstrual-cycle hormones modulate functional hemispheric lateralization. The authors examined six female and six male subjects with functional magnetic resonance imaging (fMRI) to determine whether cortical activation patterns associated with cognitive and motor tasks vary with the menstrual cycle. Female subjects, who did not use oral contraceptives, were scanned twice: once during the low-estrogen menses and once on the 11th/12th day of the menstrual cycle - the periovulatory

phase, which is high on estrogen levels. A word-stem completion task, a mental rotation task, and a simple motor task were performed by all subjects. The researchers found blood oxygenation level dependent (BOLD) imaging changes showing that menstrual-cycle hormones influence the overall level of cerebral hemodynamics to a much stronger degree than the activation pattern itself. No differences were seen between male and female subjects during the low-estrogen phase. During both neuropsychological tasks, blood estrogen level had a profound effect on the size but not lateralization or localization of cortical activation patterns. The female brain under estrogen showed a marked increase in perfusion in cortical areas involved in both cognitive tasks, whereas the hemodynamic effects during the motor tasks were less pronounced. What the authors could infer from these findings is that due to changing blood estrogen levels, the female brain is more susceptible to changes in cerebral hemodynamics and that these changes dramatically alter the size but not the pattern of cortical activation during the performance of cognitive tasks.

7.1.2 Emotional face recognition and social monitoring

Two important categories in many studies on menstrual cycle effects are social monitoring and emotional facial expression recognition. For example, the researchers Guapo, Graeff, Zani, Labate, and colleagues (2009) wanted to observe whether the menstrual cycle would have any effect on women's accuracy in recognizing emotional facial expressions. They carried out a study with a group of 40 healthy volunteering women and men, women being assigned depending on their phase of the menstrual cycle. The study had eleven women assigned to the early follicular group, nine women to the ovulatory group and ten women to the luteal group, plus a group of ten men. Estrogen, progesterone, and testosterone levels were assessed. The results showed that the early follicular group was more accurate perceiving angry faces than all the other groups. Sadness was better recognized by the early follicular group in comparison to the luteal group. Regarding the recognition of fearful faces, a trend to better performance and significantly higher accuracy was observed in the early follicular and ovulatory groups, compared to men. In women, estrogen negatively correlated to accuracy in perception of angry male faces. For the authors, the results suggest a specific effect of sex hormones on emotion processing independently of measurable effects on mood, at least in healthy volunteers. The results point to the need for

controlling the phases of the menstrual cycle in future studies involving emotional processing, since hormones may play a role in how accurate face recognition is. The results also highlight the importance of estrogen specifically in the recognition of negative emotions such as sadness, anger, and fear. These findings agree with earlier studies where estrogen levels have been positively related to serotonin function, and progesterone to the modulation of facial expressions.

Capacity for social monitoring might be enhanced with increased progesterone levels during the luteal phase according to Maner and Miller (2014). By social monitoring, the authors mean intensified sensitivity to signs in the social context that point out to the presence of a threat or opportunity. Earlier studies had found that when progesterone peaks during the luteal phase, women subjectively judge as more intense the emotional expressions displayed by others indicating nearby threat (e.g., disgust and fear expressions); but progesterone levels were unassociated with the perceived intensity of happy expressions. Participants completed a facial expression identification task with anger, disgust, fear, and sadness as options, as well as a visual cueing task that assessed positive and negative social stimuli. The conclusion was similar to the literature: enhanced ability to decode facial expressions in others, as well as improved attention to stimuli in the social environment, is associated with higher levels of progesterone in the luteal phase of the menstrual cycle. They propose that, similarly to what occurs around ovulation, when psychological changes appear to serve specific mating-related functions, what could happen during the luteal phase is that some of the psychological changes may serve specifically as affiliative and self-protective functions.

7.1.3 Verbal fluency and word recognition

Symonds, Gallagher, Thompson, and Young (2004) examined the relationship between changes in neurocognition and hypothalamic-pituitary-adrenal (HPA) axis function in different phases of the menstrual cycle. Fifteen healthy female volunteers, not on hormonal medication, were tested twice, during mid-follicular and late-luteal phases in a randomized, crossover design: i.e., the participants were their own controls. Mood, neurocognitive function, and basal cortisol and dehydroepiandrosterone (DHEA) were profiled. The results showed that, compared to the follicular phase, verbal fluency was impaired and reaction times reduced on a continuous

performance task in the luteal phase, without affecting overall accuracy. ‘Hedonic', or well-being measurements, scores on the UWIST-MACL scale decreased in the luteal phase. There was evidence of changes in the function of the HPA axis, with 24-hours urinary cortisol concentrations and salivary DHEA levels significantly lower during the luteal phase, contrary to the researchers' hypothesis. These results suggest that luteal-phase HPA-axis function is lower than in the follicular phase, in normally cycling women.

7.1.4 Attention and vigilance and memory

To investigate whether it is possible to find sex differences and menstrual cycle influences on attention, Pletzer, Harris, and Ortner (2017) checked three aspects of attention: sustained, selected and divided attention. Thirty-two naturally cycling women and 35 men in the control group were assessed twice on three neuropsychological attention tasks. Sessions comprised the follicular and luteal phase in menstruating women. Results showed differences in performance in tests on divided and sustained attention, with improved accuracy in the early follicular compared to the mid-luteal cycle phase. Males showed an advantage in these modalities in previous studies. When it comes to selected and sustained attention, high progesterone seems to influence learning effect; women who were in the luteal phase at the beginning of the experiment presented increased learning effect from the first session to the next. Progesterone seems to have a modulating role on menstruating women's ability to focus and sustain attention. This study suggests that whether women are in the low or high progesterone phase of their cycle will influence their attentional processing.

There is a wide array of studies focusing on the menstrual cycle and cognitive performance involving memory. Craig and Murphy (2007) review evidence that, in healthy women, the ovarian steroid estrogen affects brain regions crucial to higher cognitive function at the macroscopic, microscopic, functional and neurotransmitter level. The authors found that estrogen indeed modulates cognitive function so that hormonal therapy (HT) (or estrogen therapy [ET]) could protect women's brains against Alzheimer disease if the hormone replacement therapy was initiated during a "window of opportunity" at the onset of menopause. This

hypothesis is strongly sustained by Sherwin's (2003; 2012) findings on studies on postmenopausal women and dementia.

In a within-subject study to explore how hormonal variations affect the consolidation of emotionally-arousing information, a group of twenty-three women underwent functional magnetic resonance imaging (fMRI) twice: during the encoding of emotional and neutral stimuli in the low-hormone early follicular and the high-hormone luteal phase. Bayer, Schultz, Gamer, and Sommer (2014) found that, whereas overall recognition accuracy remained stable across cycle phases, recognition quality varied with menstrual cycle phases. Particularly recollection-based recognition memory for negative items tended to decrease from early follicular to the luteal phase. Emotional enhancement of memory (EEM) effects for both emotional and neutral stimuli were associated with higher activity in the right anterior hippocampus during early follicular compared to the luteal phase, whereas the anterior cingulate, amygdala and posterior hippocampus were found to perform valence-specific modulations; modulations of the levels of attractiveness or averseness of stimuli (Bayer, Schultz, Gamer & Sommer, 2014).

Jacobs and D'Esposito (2011) examined the effects of endogenous fluctuations in estradiol on working memory in healthy young women. As they discuss, the prefrontal cortex (PFC) is extremely sensitive to changes in levels of neurochemicals, and small fluctuations in cortical dopamine (DA) can effectively alter working memory, a PFC-dependent cognitive function essential to many human behaviors. From previous studies in other species, estradiol has been shown to enhance DA activity. So far though, no human study has adequately addressed whether the impact of estradiol on cognition occurred by way of modulating specific neurochemical systems. The authors found that, although estrogen - considered in isolation - may have unpredictable effects on cognitive performance, its influence is clarified when considered within a larger neuromodulatory framework. For Jacobs and D'Esposito (2011), understanding the relationship between estrogen and DA is essential for advancing women’s health, given the clinical prevalence of dopaminergic drugs.

Nielsen, Ahmed, and Cahill (2013) performed another study on memory and the menstrual cycle. They also tested whether sex can influence the process of encoding of memory. They aimed to test whether the ability to retain information changes throughout the menstrual cycle. The authors invited naturally cycling women and a control group of men, presenting them with a design story divided into three parts, all containing emotional or neutral elements. One week later, participants were asked general information as well as specific details from the story. What the authors could find is that, when hearing the emotional compared with neutral stories, women in their luteal phase at memory encoding show enhanced memory for details ($p < .05$), but not to global information. Such a result could not be found among women in the follicular phase. When it comes to sex influences on memory, measurements of fixation time percentage and pupil diameter changes showed no evidence to differences in attention or arousal. Similar performance was found among women on both luteal and follicular phases and men during the most arousing phase of the emotional story. As the authors note, studies have shown that female rape victims experience fewer intrusive symptoms if they are currently on hormonal contraception or have taken emergency contraception immediately after the sexual assault. Victims report significantly lower total post-traumatic stress symptom levels when taking contraceptives (Ferree et al., 2012 as cited in Nielsen, Ahmed, & Cahill, 2013), suggesting that sex-hormone levels influence memory consolidation in the post-trauma period, altering the likelihood of developing PTSD. This study points to the possibility that the menstrual-cycle phase at the time of an emotional event can affect how information is encoded in long-term memory and recalled in women. This process affects men differently and varies depending on a woman's contraceptive status.

Another study reinforces the suggestion that hormonal fluctuation during the menstrual cycle can influence memory at the time of encoding of emotional information. Pompili, Arnone, D'Amico, Federico, and Gasbarri (2016) wanted to verify the effects of estrogens in the interplay of cognition and emotion by focusing on memory processes in healthy young women. Two groups of young women in different cycle phases - a preovulatory group characterized by high levels of estrogens and low levels of progesterone, and an early follicular group characterized by low levels of both estrogens and progesterone - were presented images based on valence

(pleasant, unpleasant and neutral). Their electrophysiological event-related potential (ERP) - a measure of brain activity - in response to images were collected, being the focus on the P300 peak, which is an ERP involved in decision making, thought to express stimulus evaluation or other categorization processes. One week later, long-term memory was tested employing free recall. The intragroup analysis revealed that preovulatory women had a significantly better memory for positive images, while the follicular women showed significantly better memory for negative images. Comparison between groups revealed that women in the periovulatory phase had better memory performance for positive pictures than women in the follicular phase, while no significant differences were found for negative or neutral pictures. According to the free-recall results, the subjects in the preovulatory group showed greater P300 amplitude and shorter latency for pleasant images compared with women in the follicular group. The authors conclude that these results describe an improvement in cognitive performance for women in the preovulatory rather than follicular phase, although only after the presentation of pictures with positive emotional valence.

7.2 Mood, well-being, cognitive function, and the menstrual cycle

Some studies have shown that mood states and well-being change rapidly in women over the menstrual cycle due to several physiological mechanisms, which may also influence decision-making and cognitive ability. Studies as early as the 1930s have consistently found the highest levels of well-being and self-esteem reported on late follicular phase and around ovulation, when estrogen reaches its first peak, with negative affects (anxiety, hostility, and depression), physical discomfort and hypersensitivity to various stimuli from the mid-luteal to menstrual phase, when both estrogen and progesterone reach their lowest levels (Cockerill et al., 1994; Benedek & Rubenstein, 1939, as cited in Farage et al., 2008).

Due to its widespread presence in the brain, circulating estrogen interacts with many neurotransmitter systems such as the serotonergic and dopaminergic systems, intimately related to mood regulation (Farage et al., 2008). This interaction may contribute to the risk of suicidal behavior associated with this period of the menstrual cycle. Suicide attempts appear to correlate with those phases within the menstrual cycle when estrogen levels are at the lowest: the late

luteal and early follicular phase, or the premenstrual and bleeding phase (Saunders & Hawton, 2006, as cited in Farage et al., 2008). As Catenaccio and colleagues (2016) explain, the sex hormones estrogen and progesterone are thought to modulate dendritic spine and synapse density in areas of the brain responsible for learning, memory, neuroendocrine state, and emotional processing. A consequence of this modulation is that impairment of these functions is seen in many of the symptoms associated with menstrual cycling including irritability, impulsivity, decreased concentration, anger, and anxiety.

Van Goozen, Wiegant, Endert, Helmond and Van De Poll (1997) investigated blood levels of ovarian and adrenocortical hormones throughout one menstrual cycle of 21 healthy women, correlating this data to self-reported measurements of sexual interest, and mood. Eleven of the 21 women reported suffering from premenstrual discomfort. Such difference was also found on a hormonal level between the two groups, being estradiol levels and estradiol-progesterone ratio higher among women in the non-premenstrual discomfort group. The results showed also a significant effect of tension and sexual interest relating to the menstrual cycle. The study found a clear correlation between the menstrual-cycle phase and varying levels of testosterone. Sexual interest differed also between the two groups, having women in the non-premenstrual discomfort group sexual interest peaking in the premenstrual phase, whereas women who showed premenstrual discomfort had their sexual interest peaking at mid-cycle, in the ovulatory phase. A significant difference in self-reported fatigue - but not in the mood - was found between the groups over the menstrual cycle. These results add to previous research findings on women's sexuality, showing the crucial role played by the androgen testosterone in it. It also points to a clearer relationship between the menstrual cycle and sexuality than that between menstrual-cycle phase and mood; this study found clear evidence for tension as a visible effect of the menstrual cycle, but no variation in mood, which contradicts previous findings.

According to Bayer and colleagues (2014), it is conceivable that hormonal fluctuations could modulate the emotional enhancement of memory (EEM) effect. As the authors point out, estradiol and progesterone affect cellular mechanisms in brain areas responsible for mediating initial processing, encoding, and consolidation of emotionally arousing information. Studies with

other animal species showed that both hormones perform anxiolytic and antidepressant actions, while fMRI studies in humans revealed that estradiol and progesterone change reactivity to emotional stimuli in the amygdala, hippocampus, and medial prefrontal cortex. Corroborating this possibility is that estradiol has been shown to enhance extinction of contextual and cued fear conditioning in both other species and humans.

A recent study by Eggert, Kleinstäuber, Hiller, and Witthöft (2017) could point to a possible limitation of clinical studies measuring emotional or attentional processes in female subjects. The authors wanted to examine whether women suffering from premenstrual syndrome (PMS) show larger emotional interference compared to women in a non-PMS group. They followed 110 women over two months via online screening, telephone interviews, and daily records. Divided into two groups, 55 of these women were recruited to the PMS group and 55 to the non-PMS group. All participants completed three emotional Stroop tasks (EST) with a neutral and negative word, picture, and facial stimuli during the follicular and luteal phases of the menstrual cycle. The study found a greater emotional Stroop effect for picture and facial stimuli in the luteal phase in women with PMS, but no significant difference for word stimuli. Emotionally relevant information in pictures slowed reactions, while emotionally relevant information in faces accelerated them. For the authors, these results have an important implication for future research on emotional and attentional processes: i.e., that the influence of menstrual-cycle phase should be considered to avoid any bias of results (Eggert, et al., 2017).

A study examining amygdala reactivity in women with Premenstrual Dysphoric Disorder (PMDD) performed by Gingnell, Morell, Bannbers, Wikström, and Sundström (2012) found increased reactivity in the left amygdala in the luteal compared to the follicular phase among both women with PMDD and healthy controls: i.e., women with no symptoms of PMDD. The researchers observed no correlation with estrogen or progesterone serum concentrations. All participants were exposed to emotional faces during the mid-follicular and late luteal phases, and mean blood-oxygen-level dependence (BOLD) signal changes in the amygdala were determined using fMRI. The authors propose a correlation between progesterone levels and amygdala reactivity. Their finding is in line with prior studies of healthy women, where high progesterone serum concentrations (following oral progesterone administration in the follicular phase)

correlated significantly with amygdala reactivity. In healthy women with no artificial hormonal administration, progesterone levels are low during the follicular phase, and from the reproductive perspective negligible. The source of progesterone production during this period is most likely the adrenal glands, possibly in response to stress.

Ossewaarde, van Wingen, Rijpkema, Bäckström, et al. (2013) carried out the first study showing the structural plasticity of the amygdala associated with endogenous gonadal hormone fluctuations in humans. They wanted to investigate whether amygdala morphology changes over the menstrual cycle and whether this change explains differences in stress sensitivity and mood regulation. They tested 28 young healthy women once during the premenstrual phase and once during the late follicular phase. The women acted as their own controls during the menstrual cycle. The researchers applied magnetic resonance imaging (MRI) and analyzed the data with optimized voxel-based morphometry, which measures differences in local concentrations of brain tissue, through comparison of multiple brain images. To measure mood regulation and stress sensitivity, negative affect was assessed after participants watched strongly aversive or neutral movie clips. The results show a difference between women in the premenstrual vs. follicular phase. There was an increased density of gray-matter volume in the dorsal part of the left amygdala during the premenstrual phase compared with the late follicular phase. This increase was positively correlated with a heightened negative affect reaction to the adverse images. The number of sex hormones receptors vary over the menstrual cycle. The increased number of sex hormones receptors in the dorsal part of the left amygdala during the premenstrual phase could be behind the increased volume in gray matter. The authors cite studies observing reduced stress after a mindfulness-based stress reduction intervention, associated with a decrease in the volume of amygdala gray matter.

A recent review article on menstrual-cycle influence on cognitive function and emotion processing by Poromaa and Gingnell (2014) analyzed a set of studies comparing women and men on cognitive tasks and found that the effects of sexual dimorphism are not only small but also difficult to be replicated in further studies. The authors also found a much clearer effect of progesterone rather than estradiol concerning emotion-related changes and the menstrual cycle.

Such an effect can be explained by evidence of increased amygdala reactivity and emotional memory related to high progesterone levels.

Hengartner, Kruger, Geraedts, Tronci, Mancini, et al. (2017) explored the association between sex hormones and negative affect over the menstrual cycle. They examined estrogen, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone serum levels in association with negative affect as measured with the Positive and Negative Affect Schedule (PANAS). The scale consists of twenty items listing negative and positive emotions. These emotions can be subjectively classified based on the level of which one feels them on a scale ranging from 1 (not at all) to 5 (extremely). PANAS results and hormone assessments were collected at four consecutive time points comprising the menstrual, pre-ovulatory, mid-luteal and premenstrual phase across two cycles (n = 87 vs. n = 67 for the first and second cycles). The research team did not find that negative affect was increased pre-menstrually as hypothesized. As for associations with hormone levels, they found only one statistically significant effect, during the first cycle: a significant negative association between changes in FSH and negative affect from the preovulatory to mid-luteal phase (within-subject). The authors propose that the high stability of negative affect across the cycle reported in the study could indicate that these mood states are manifestations of a stable underlying personality trait - in this case, neuroticism. This work provides evidence that self-reported negative affect remains stable across the menstrual cycle and is not directly and uniformly related to fluctuating hormone levels. This finding supports the validity of psychological assessments of affect such as the PANAS questionnaire.

In a recent study, Mulligan, Nelson, Infantolino & Luking et al. (2018) examined whether hormone levels and variation in neural response to reward and loss across menstrual-cycle phases were associated with depressive symptoms. Subjects were tested twice, once during the follicular phase and later at the luteal phase, serving as their own controls. The experimenters tested gonadal hormones levels and measured event-related potential (ERP) recordings as a response to gain or loss, in this case, of money. Their findings indicate that hormonal fluctuations associated with the menstrual cycle may indeed relate to depressive symptoms and reward systems in the brain by altering reward sensitivity. Fluctuations in neural response to

gains - but not losses - across menstrual cycle phases were associated with greater depressive symptoms. The study used *reward positivity* as the main measurement, based on ERP response to reward. By *reward positivity*, the authors meant how strong these subjects responded to reward stimuli. Women with higher depressive symptoms showed a more observable neural response to reward; they showed reduced reward positivity to monetary gains during the luteal phase compared to the follicular phase. Reward positivity was not observed among women low in depressive symptoms. This study suggests that responsivity to reward stimuli increases in the follicular phase due to the presence of estradiol and lack of progesterone, while it is attenuated in the luteal phase, characterized by high progesterone and moderate to high estradiol.

As Pompili et al. (2016) clarify, estrogens seem to modulate not only reactions to emotional stimuli but also rewards, even though these two processes use different cerebral areas. The amygdala is essential in emotional processing, reacting to negative and positive stimuli, affecting behavior adaptively. The ventral tegmental area and nucleus accumbens modulate reward - though, as the authors explain, reward processing can activate the amygdala as well, and positive non-rewarding stimuli can activate the reward system in the brain: i.e., sometimes reward and emotional stimuli can overlap. The complex nature of positive stimuli could be helpful to explain the mixed findings on estrogens' effects on reactions to positive stimuli.

7.3 A note on methods: definition and measurement of the menstrual cycle in research

Epting and Overman (1998) raise the question of why with so many studies having been performed, research findings are so incongruent when it comes to research outcomes on the menstrual cycle and cognition. For the authors, the reason lies in the different methods. Positive findings have, in many cases, proven notoriously difficult to replicate.

Ovulation is, again, the main criterion defining a menstrual cycle (Goodman, 2003). However, as Wilcox (2010) explains, the challenge with using ovulation as the main reference point is that it is generally invisible. Even though it would be extremely useful for women as well as for researchers to know precisely when fertile days are occurring, the most one can do so far is make probabilistic statements about the likelihood of ovulation occurring. Wilcox refers to one sign proposed for helping identify ovulation: changes in basal body temperature; but, due to

individual variability, it is a weak biological marker. Another proposed marker is the changes in the amount and consistency of cervical mucus, also not highly reliable.

Broverman et al. (1981) propose among other factors explaining why studies disagree on findings the failure to precisely align the times of testing to the times of the inferred hormonal peaks. Additionally, it is necessary to eliminate anovulatory cycles from the data. Despite it being a naturally occurring phenomenon, including cycles with no ovum released would work against obtaining positive results related to menstrual cycle changes in cognitive function.

Epting and Overman (1998) found that most studies on cognition and the menstrual cycle have used one of three methods to delineate menstrual phase: counting days from menstruation, measuring basal body temperature (BBT), or directly assaying hormonal change through blood collection; noting that the first two methods are not very reliable procedures for determining hormonal levels. As they explain, many studies use young women as subjects. Evidence from women aged 18 to 41 years indicates that ovulatory progesterone displays a parabolic rise and fall with age, with peak levels occurring between the ages of 25 and 35. It is possible, the authors propose, that a critical level of progesterone or estradiol, or both, must be present for cognitive function to be affected (Epting & Overman, 1998). This could explain Herlitz, Thilers and Habib (2007) findings with a sample of 45-,50- and 55- year-old women in which they did not find any influence of menstruation on cognitive performance. They investigated semantic memory, verbal fluency, visuospatial performance, and face recognition. The problem could be the low levels of progesterone among women in those ages.

Another possible explanation for why so many studies disagree comes from cross-species comparisons of cognitive change across estrous and menstrual cycles (Epting & Overman, 1998). Several lines of evidence from other species indicate that hormonal fluctuations induce changes in neuro-anatomical function and structure within higher cognitive brain regions. At first glance, it would seem logical that similar hormonal-cognitive relationships should be found in humans, As mentioned, it is conceivable that humans, with their increased cortical-to-subcortical ratios, may be capable of overriding hormonally modulated subcortical changes by using systems that are not available or sufficiently developed in other animals. Finally, Epting and Overman (1998)

raise the possibility that cognition may not change systematically over the menstrual cycle for women as a population, and that the existence of positive findings in the literature could be due to the known bias toward öpositive findings being more likely to be published than negative ones.

Blake, Dixson, O'Deana, and Denson (2016) performed a series of tests to provide a standardized protocol for characterizing women's fertile phase. They compared the accuracy of self-report methods and counting-days procedures in estimating ovulation using data from 140 women whose fertility was verified with luteinizing hormone tests. They claim that their procedure can provide a cost-effective and pragmatic approach to predicting ovulation. They attribute conflicting results to a rather broad window for predicting ovulation, using alternative estimators for the onset of the next cycle, often removing outliers to increase the homogeneity of the sample. Their method, combining counting methods with a relatively inexpensive urine test of luteinizing hormone (LH) predicts fertility to an accuracy of 95%. The authors recommend that samples be restricted to participants whose prior cycles lasted between 25 and 35 days, instructing participants to perform daily LH tests ten to eighteen days before their next predicted menses or even every day of the cycle. The restriction on cycle length is necessary as long and short cycles may both indicate anovulation.

8. Discussion

This thesis is aware of the complexities of terms surrounding gender and sexual identity and wishes to respect the plurality of this constellation. "Woman" is a term describing identities that go far beyond the purely biological makeup of the female body. This thesis investigated studies performed with cis-gendered women with regular menstrual cycles. For the present purpose, the term "women" and "female" will be used interchangeably referring to biological sex and meaning those individuals who have a uterus and at least one ovary: a prerequisite for their bodies to menstruate naturally. Studies of transgender women, non-binary individuals with a period, post-menopausal women, women with irregular or "problematic" menstrual cycles (i.e. due to polycystic ovary syndrome (PCOS) or other diseases and pathologies) have not been explored. The exclusion of the full array of individuals who experience periods, but perhaps not

in a predictable manner, may influence the results and future research should diversify the structure of studies to include such individuals.

A body of research has mapped out the effect that different phases of the menstrual cycle have on endocrinological and neurobiological systems. Researchers such as Broverman et al., (1981), Hampson (1990), Sherwin (2003; 2012), Symonds et al. (2004), Craig and Murphy (2007), Guapo et al. (2009), Nielsen et al. (2013), Maner and Miller (2014), Bayer et al. (2014), Pompili et al. (2016) and Pletzer et al. (2017) have found that the timing of a menstrual cycle can influence cognitive outcomes, while others such as Cockerill et al. (1994), Epting and Overman (1998) and Celec et al. (2011) have not. The discrepancy in results may indicate a methodological differentiation in the measurement of effects of the menstrual cycle, as some studies (mostly newer ones) have made use of more accurate biomarkers for mapping structural and hormonal changes in the brain (Blake et al., 2016). Many studies, though are older, and changes in methods may play an important role.

In regards to the age of participants as a confounding variable, most studies focus on younger women. As discussed, the effect of sex hormones is possibly at its peak during fertile ages, between the ages of 25 and 35. While Herlitz et al. (2007) highlight the importance of exploring female sex hormones pre- and post-menopause and their influence of cognition, the age groups they used when they performed the study (45, 50 and 55) may not be indicative of overall influence of sex hormones on cognition over a lifetime; this could explain why the authors found no significant correlation in pre-and post-menopausal women and cognitive function.

Even though sex-hormones *per se* may not influence cognitive performance - as suggested by Cockerill et al. (1994), Epting and Overman (1998) and Celec et al. (2011) - it is worth noting that well-being and mood, which *are* influenced by the menstrual cycle (Ossewaarde et al., 2013; Poromaa and Gingnell, 2014; Eggert, et al., 2017; Mulligan et al., 2018) do influence cognitive performance. This may indicate that mood and well-being might be strong covariates or moderating variables in the association between cognitive performance and the menstrual cycle. Individual differences in how one copes with and perceives one's bodily -

e.g., symptoms - energy levels and tension - over the menstrual cycle might influence performance on cognitive tasks. Some women might perform more optimally during pre-ovulation while others experience distraction due to estrous peaking. This may be difficult to track with simple methods, requiring larger cohorts and the creation of individualized algorithms. Such methods could help shed more light on the true effect of the menstrual cycle as a booster or down-regulator of cognitive performance and well-being.

When it comes to sex differentiation and what is being written about it, there is a persistent cultural bias in the scientific literature that many times pass unseen, but needs attention. A brief survey of anatomy and physiology books shows a worrying pattern where it is normal to find the majority of drawings of the human body being represented by male bodies; references to "man and woman", "male and female" in this order; the female reproductive system being shown *after* the presentation and description of the male reproductive system; introduction to sex-differentiated structures, bodily functions and substances following the strict male-female order: e.g., hormone sections starting with the presentation of the “male” androgen testosterone and only later discussing estrogen and progesterone. The cultural bias toward patriarchal norms is clear (Goodman, 2003; Sherwood, 2007; Wilcox, 2010; Martini et al., 2012; White & Porterfield, 2013; Silverthorn, 2013; Dyer, 2014).

When it comes to cognitive neuroscience, it is still frequent to find no mention whatsoever of the menstrual cycle or related terminology in renowned and widely used textbooks (Gazzaniga et al., 2015; Gazzaniga et al., 2016; Lopez, Pedrotti & Snyder, 2015) - despite increased scientific interest in the phenomena. Considerable evidence points towards effects of the cycle for roughly half the earth’s population, going beyond physiology; but diagnoses related to the specifics of the female menstrual cycle only gained relevance and credibility in the DSM[2] in the current version: e.g., Premenstrual Dysphoric Disorder (PMDD) was moved from Appendix B, where it was only included for the first time in the previous edition, to the main text (see e.g., Steiner, Hartlage, Eriksson & Schmidt, 2012; Morrison, 2014).

[2] American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders.

The menstrual cycle has been systematically studied since the 1930s, but the popularity of the topic has only recently surged (Sherwin, 2003). As Broverman and colleagues (1981) stress, the issue of whether cognitive abilities vary systematically over the menstrual cycle is a legitimate concern of feminists, uneasy that findings could be used as evidence against the suitability of women for various types of employment. Science has historically asked the wrong questions when it comes to women's biology and its consequences. Biased by the idea that "changes", "variation", "diversity" and so on imply loss of ability, function or stability, fluctuation in hormonal levels in women was automatically interpreted as cognitive impairment and emotional imbalance, instead of the equal plausible enhancement of aspects of cognition or cognition as a whole. The focus of the research was, and still is many times, on "impairment", "loss" (of abilities and skills), "detrimental effects" (of change) and "moody women". The unavoidable reality is that most of the scientific mentality so has its base in limited Western, white and patriarchal cultural roots, with the history of eugenic research as an extreme case of similar biased assumptions.

Broverman and colleagues (1981) feel assured that research aims have changed. Studies like theirs aspire to test a theoretical hypothesis about whether changes observed with the menstrual cycle affect cognitive function in predictable ways, not to question women's ability to carry out tasks that require cognition. In consonance, Barbara Sherwin (2003) affirms that hormone levels are sufficient at all times to maintain cognitive functions in women, despite minor fluctuations in some cognitive abilities co-occurring with fluctuations in sex hormones over the menstrual cycle phases. While the first studies on cognition and the menstrual cycle were devoted to exploring the fitness of women in male-dominated working areas, recent research is driven by the interest in sex influences on neurobiology (Poromaa & Gingnell, 2014).

However, science still seems blind to cultural biases. Considering sexual dimorphic studies and their findings in light of how they are interpreted - which is even more visible in older studies - it is plausible to question whether women perform better on tasks of verbal fluency, manual speed, and coordination, etc, because of their biological makeup or because parents tend to read more to girls than boys (Baker & Milligan, 2016). Studies have shown that boys are allowed more to play outdoors and perform fine motor tasks, which could favor their

performance as a population on tasks of spatial perception, visualization and mental rotation (Boxberger & Reimers, 2019). This could perhaps have a strong influence on how women and men use their brains throughout their lifetime, influencing their mastery of skills later in life. Leaving this environmental aspect unseen has detrimental effects on our understanding of the results found in dimorphic studies.

Independently of whether these differences are biological or cultural - or both - for Nielsen and colleagues (2013) it is clear that failure to account for sex, menstrual cycle position, or hormonal contraceptive intake at the time of testing can lead to biased results. As they write, in the case of memory performance studies, evidence suggests that these elements might influence cognition in the encoding phase of memory processing - a concern shared by Eggert and colleagues (2017) and Guapo and colleagues (2009) when measuring emotional, attentional or perceptual processes.

This thesis did not address women that do not menstruate or transgender women. Neither did it discuss postpartum cognitive states or women who are on hormonal birth control. Studies on postmenopausal women fell outside the scope of this thesis as did those focusing on the relation between endocrine disruptors and puberty.

Future research would benefit from a common methodology that includes more precise biomarkers, such as daily hormonal assessment through salivary or urinary recollection, as the possibility of individualized algorithms that could give a more thorough understanding of the bodily function and its variations on an individual level. This information could later be compared on a broader level, allowing researchers to create a more accurate picture of hormonal influences on neurocognition.

The correlation of these findings with results from studies with different populations such as those not included in this review is also important for advances in research. This could cast light on whether hormones present similar effects despite the different body makeup from women who do not menstruate, transgender women, lactating women, men and so on.

9. Conclusion

It is already known that levels of hormones vary along the menstrual cycle. Along with this, research has also shown that these hormones are present and have important regulatory roles in the brain and the body. My aim with this literature review was to uncover to what extent the menstrual cycle affects brain functions, neurobiology, mood and cognitive performance in adult menstruating cis-gendered women. I expected to find variations in neurocognitive performance, as well as in mood and well-being levels over the menstrual cycle. This thesis presented both historical and recent scientific studies. Despite the growing popularity of the topic, researchers are still far from consensus when it comes to the relationship between cognitive performance and the hormonal variation typical of the female reproductive cycle. Findings pointing to differences in sexually dimorphic tasks are small, while those relying on the hormonal ratio variation that defines different phases of the cycle are difficult to replicate. Methods to pinpoint ovulation and, consequently, determine the right timing for measurement based on hormonal levels, are still deficient, which might account for the incongruity among research findings. Emotion-related changes that influence mood and perceived well-being are found more consistently, however, and are more clearly associated with progesterone than estrogen. Varying levels of well-being and self-esteem are more conclusively associated with the menstrual cycle, being the highest levels commonly reported in the late follicular phase and around ovulation, when estrogen reaches its first peak. Negative affect (anxiety, hostility, and depression), physical discomfort and hypersensitivity to various stimuli are associated with increased amygdala reactivity in the mid-luteal phase when progesterone reaches its highest levels, as well as the menstrual phase when both estrogen and progesterone levels reach their lowest levels.

10. References

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